Prognosis and treatment of focal cartilage lesions of the knee joint

Medium- to long-term results

PhD Thesis

Svend Ulstein

2019

Department of Orthopaedic Surgery

Akershus University Hospital

Institute of Clinical Medicine

Campus AHUS

University of Oslo

To Karen, Oliver and Emil

"Either write something worth reading or
do something worth writing"

Benjamin Franklin

Table of contents

Acknowledgements

I would like to express my most sincere gratitude to some of those who have contributed in the realization of the present work:

First and foremost, to my main supervisor Jan Harald Røtterud MD, PhD at Dept. of Orthopaedic Surgery, Akershus University Hospital, for so expertly guiding all aspects of this work with unparalleled enthusiasm, wit, responsiveness, and razor-sharp scientific skills. Despite tireless hours in the trenches with me, you never lost confidence or trust in me over the years, thank you!

To my co-supervisors Professor Asbjørn Årøen at Dept. of Orthopaedic Surgery, Akershus University Hospital, and Dr. Med. Einar Andreas Sivertsen at Diakonhjemmet Hospital. Asbjørn, the pater familias of orthopaedic research at AHUS, who gave me the opportunity to do scientific work, and was my main supervisor the first couple of years. Without your indestructible enthusiasm, optimism and support, even in troublesome times, this work had never come to an end. Einar, 6-7 years ago, in the blink of an eye, you had me recruited to scientific work. In just a few hours after my stammering acceptance, you and Jan Harald had written down the project plan on a small napkin. The title, by the way, was "the easy and lazy way to a PhD"… Even though it turned out to be diametrically opposite, I have never regretted a day, thank you!

The annual spring seminars have been key in driving the projects forward, and critical in refining study methodology and in training communicative skills.

My parents and family for always supporting me, my parents-in-law for taking care of my sons while I spent an unspeakable amount of hours doing this research, or was away on scientific meetings etc. Morten Wiencke for eminent proofreading and linguistic revision of paper III and IV.

And most important, I would like to express my gratitude, love, and respect to my wife – Karen and my precious boys –Oliver and Emil. Karen, without your love, friendship, patience, and seemingly endless talent to keep so many wheels in motion, this thesis had never seen the light of day. Oliver and Emil, my miracles and endless source of inspiration, even though I doubt you will find this work particularly impressive, I hope you some day come across it, covered in dust, open it and think: *OK, maybe he wasn't all that useless!*

Svend Ulstein
Asker, November 28th 2018

Abbreviations

ACL	Anterior Cruciate Ligament
ACLR	Anterior Cruciate Ligament Reconstruction
ACI	Autologous Chondrocyte Implantation
ADL	Activities of Daily Living Function
BMI	Body Mass Index
CI	Confidence interval
CPM	Continuous Passive Motion
ECM	Extra Cellular Matrix
ICRS	International Cartilage Regeneration and Joint Preservation Society
IKDC	International Knee Documentation Committee
K&L	Kellgren & Lawrence classification of osteoarthritis
KOOS	Knee and Osteoarthritis Outcome Score
MDC	Minimal Detectable Change
MF	Microfracture technique
MIC	Minimal Important Change
MRI	Magnetic Resonance Imaging
NKLR	Norwegian National Knee Ligament Registry
OA	Osteoarthritis
OAT	Osteochondral Autologous Transplantation
OCD	Osteochondritis Dissecans
PROM(s)	Patient Reported Outcome Measure(s)
QoL	Quality of Life
RCT	Randomized Controlled Trial

SD	Standard Deviation
SKLR	Swedish National Knee Ligament Registry
Sport/Rec	Sports and Recreation
STROBE	Strengthening the reporting of observational studies in epidemiology
TKA	Total Knee Arthroplasty
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Papers included in the thesis

Paper I

Ulstein S, Årøen A, Røtterud JH, Løken S, Engebretsen L, Heir S. Microfracture technique versus osteochondral autologous transplantation mosaicplasty in patients with articular chondral lesions of the knee: a prospective randomized trial with long-term follow-up. *Knee Surg Sports Traumatol Arthrosc.* 2014;22(6):1207-1215.

Paper II

Ulstein S, Bredland K, Årøen A, Engebretsen L, Røtterud JH. No negative effect on patient-reported outcome of concomitant cartilage lesions 5-9 years after ACL reconstruction. *Knee Surg Sports Traumatol Arthrosc.* 2016;25(5):1482-1488.

Paper III

Ulstein S, Årøen A, Engebretsen L, Forssblad M, Lygre SHL, Røtterud JH. Effect of Concomitant Cartilage Lesions on Patient-Reported Outcomes After Anterior Cruciate Ligament Reconstruction: A Nationwide Cohort Study From Norway and Sweden of 8470 Patients With 5-Year Follow-up. *Orthop J Sports Med.* 2018;6(7):2325967118786219.

Paper IV

Ulstein S, Årøen A, Engebretsen L, Forssblad M, Lygre SHL, Røtterud JH. A Controlled Comparison of Microfracture, Debridement, and No Treatment of Concomitant Full-Thickness Cartilage Lesions in Anterior Cruciate Ligament-Reconstructed Knees: A Nationwide Prospective Cohort Study From Norway and Sweden of 368 Patients With 5-Year Follow-up. *Orthop J Sports Med.* 2018;6(8):2325967118787767.

Summary of thesis

Paper	Research question	Patients & methods	Main findings
I	What is the long-term outcome of microfracture (MF) and osteochondral autologous transplantation (OAT) mosaicplasty for full-thickness cartilage lesions of the knee joint, and is there a difference in the long-term outcome of these surgical techniques?	25 patients randomized to MF or OAT mosaicplasty. 10-year follow-up with patient-reported outcome measures (PROMs), muscle strength deficit measurements and radiographic evaluation.	Significant improvements in PROMs from baseline, but no difference between the two treatments in PROMs, muscle strength deficits or radiographic osteoarthritis (OA).
II	Are there differences in the medium- to long-term outcome after anterior cruciate ligament reconstruction (ACLR) in patients with and without concomitant cartilage lesions?	30 ACL-reconstructed patients with a concomitant full-thickness cartilage lesion and a matched group of 59 control patients without cartilage lesions. 5-9 year-follow-up with PROMs and radiographic evaluation.	Patients with a concomitant full-thickness cartilage lesion had similar PROMs, but had less radiographic OA compared to patients without cartilage lesions at medium- to long-term term follow-up after ACLR.
III	What are the effects of concomitant cartilage lesions on PROMs at medium term follow-up after ACL-reconstruction?	8470 ACL-reconstructed patients with 5-year follow-up with KOOS as outcome measure.	Full-thickness cartilage lesions showed significant adverse effects on the medium term outcome after ACLR.
IV	What are the effects on the medium-term PROMs of debridement or MF of concomitant cartilage lesions in the setting of ACL-reconstruction?	368 ACL-reconstructed patients treated with debridement, MF, or no surgical treatment of their concomitant full-thickness cartilage lesions. KOOS as the 5-year outcome measure.	Compared to no surgical treatment of concomitant full-thickness cartilage lesions, neither debridement nor MF had significant effects on PROMs at medium term follow-up after ACLR.

Preface

The articular cartilage of the knee joint is commonly injured, and the difficulty in treating these injuries has been recognized since the 18th Century. In 1743, physician and scientist William Hunter (1718-1783) made the observation; *"Ulcerated cartilage is a troublesome thing…once destroyed it is not repaired"*[159]. Generations of surgeons and scientists have since then struggled to find methods to repair injured cartilage.

Injury to the articular cartilage, isolated or concomitant to other intra-articular injuries, is a common cause of knee pain and dysfunction in the often young and active individual. Focal cartilage lesions may contribute to pain and disturbed joint function in the short-term, and progress to premature osteoarthritis (OA), with the inherent risk of crippling disease in the long run. Moreover, like many other musculoskeletal disorders, focal cartilage lesions may reduce quality of life, lead to loss of function, long rehabilitation periods and time off work. The patients, whose age typically is a relative contra-indication for joint arthroplasty, would obviously benefit from the availability of less radical surgical techniques to restore knee function and reduce pain. Knowledge on factors that might affect the prognosis and choice of treatment is therefore of particular interest and importance to the patient, the orthopaedic surgeon and the society.

However, the effect of isolated and concomitant focal cartilage lesions on prognosis and outcome varies greatly. Regardless of treatment, there is a wide range of severity of symptoms, from non-symptomatic to severely impaired patients. The reasons for this variance and the factors influencing them are largely unknown and remain to be determined.

The present thesis is the result of the ambition to increase the knowledge on the prognosis, factors that influence the prognosis, and the effect on outcomes of surgical treatment options for focal cartilage lesions. Firm knowledge on the prognosis and the effect of surgical treatment is necessary if the information and advice given to the focal cartilage-lesion patients are to be correct, and key in our efforts towards an evidence-based optimization of treatment strategies.

1   Introduction

1.1   Focal cartilage lesions

1.1.1   Background

The bony ends of human synovial joints are lined with a few millimetre thick hyaline articular cartilage (Fig.1). This highly specialized tissue is designed to facilitate the transfer of forces in a practically frictionless manner during intense and repetitive movement, and as an absorber of weight during static loading, throughout life[69]. However, the unique load shearing and low-friction properties come with the sacrifice of adequate self-healing ability in the case of cartilage injury or disease[43]. Injury to the cartilage might leave a permanent damage, which in turn is shown to increase shear strains and depletion of cartilage constituents at the lesion rim under compressive loading[166]. Such permanent cartilage damage, often referred to as a lesion or a defect, is associated with the predisposition of early onset OA[34, 83]. A genetic component is also proposed as a high degree of heritability in the prevalence and severity of cartilage lesions are found in offspring of families with OA history[32]. An insidious onset of pain, joint swelling and mechanical symptoms like catching or locking episodes may occur in patients with articular cartilage injury. However, a more progressive onset of symptoms may also be experienced. In some cases a history of a major knee trauma is present, but in other cases only minor, or no knee trauma is present in the anamnesis.
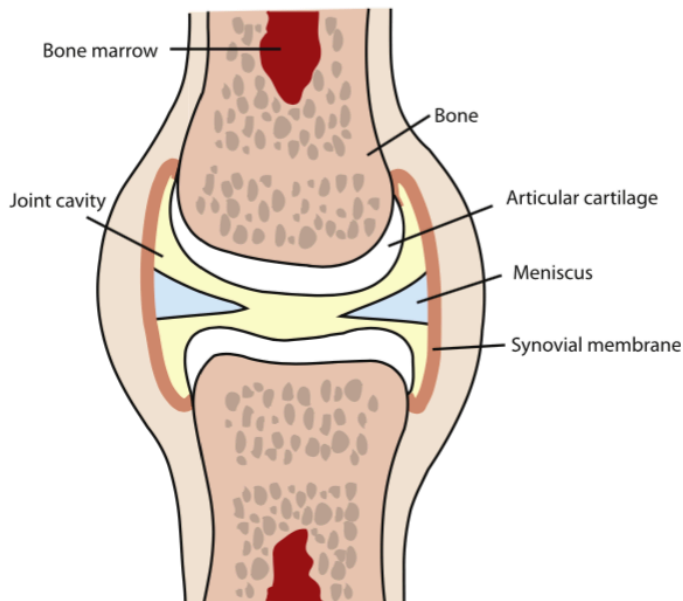
Figure 1. Schematic drawing of a synovial joint, adapted from Hunziker, E.B. et al.[69], with permission from Elsevier Ltd, ScienceDirect ®.

There is a wide spectrum of clinical manifestations, spanning from asymptomatic patients to patients that have impairments in quality of life similar to OA-patients scheduled for knee replacement[77, 65]. The symptoms can be hard to distinguish from other intra-articular injuries or pathologies, and cartilage lesions are often detected during the diagnostic process of searching for other knee injuries. Frequently, the combined diagnosis of a cartilage lesion and an anterior cruciate ligament (ACL) tear can be made[42, 128].

Consequently, the diagnosis of a focal cartilage lesion of the knee must be based on patient history, physical examination, radiological imaging like Magnetic Resonance Imaging (MRI), and arthroscopy to ensure a complete approach to the patient.

Surgical management has been the mainstay in the handling of these patients. In Norway, approximately 2500 cartilage surgeries are performed per annum[39]. In the United States, an increasing estimated annual incidence of knee cartilage surgical procedures has been reported to be approaching 300,000 in 2010 alone[98].

In general, the main treatment goal is restoration of the knee function with absence of pain, while secondary goals are return to pre-injury activity level and the prevention of subsequent premature OA development.

However, despite several decades of research efforts all over the world, the literature is inconsistent and somewhat divergent when it comes to the management of these lesions. Numerous surgical techniques and procedures, ranging from debridement to advanced cell-based techniques, have been introduced. However, no method has so far shown with certainty to be superior to others[31, 42, 50, 105]. Hence, no method can be considered as the golden standard. In addition, the previous literature has focused on comparing different surgical interventions, to a large extent circumnavigating the need for control groups and long-term follow-up. Consequently, no surgical method has been shown with certainty to be superior to rehabilitation alone. To that end, there is no consensus on effects on prognosis of focal cartilage lesions, and the optimal treatment strategy is yet to be established. Hence, the treatment of focal cartilage lesions remains a controversial challenge.

1.1.2 Cartilage composition and structure

The articular (hyaline) cartilage is composed of very few and scattered chondrocytes embedded in the extracellular matrix (ECM). Analogous to cardiomyocytes and the neurons of the central nervous system, chondrocytes remain in their allocated positions throughout life and manifest only a limited capacity to migrate to an injury site[68]. In addition to a high interstitial water content, the ECM is a complex arrangement of macromolecules including several types of collagen, proteoglycans and noncollagenous proteins, all of which the chondrocytes are responsible for synthesis and turnover[109].

Simplified, the ECM can be seen as a composite structure of collagen fibrils with intertwining proteoglycan aggregates. The collagen molecules assemble to form small fibrils and larger fibres that are cross-linked together in a finely detailed architectural arrangement that enables the tissue to resist tensile, compressive, and shear forces developed during compressive loading of the knee. In addition to several other types of collagen (V,VI,IX,X,XI and XII) collagen type II is the main constituent of hyaline cartilage (80-85%)[25]. The intertwining proteoglycan aggregates are large, complex molecules composed of several proteoglycan monomers. The proteoglycan monomers contain a core protein to which negatively charged glucosaminoglycans (GAGs) are covalently attached. The resultant high cation concentration

makes them hydrophilic and creates an osmotic pressure gradient that promotes fluid influx from the surrounding synovial fluid into the cartilage. The restrictive tensile force of the collagen network opposes the swelling of the cartilage, and in this way gives the cartilage its elasticity, resilience and viscoelastic behaviour[47]. Compressive loading of the cartilage makes fluid efflux from the ECM to the joint cavity. Upon removal of compressional load, the cartilage will regain its initial dimensions by fluid influx due to the increased osmotic pressure in the ECM. This movement of synovial fluid is also the main nutritional passage for the cartilage[161]

Articular cartilage can be divided into four zones (Fig): superficial, transitional, deep and the zone of calcified cartilage[155]. Within each zone, the cellular organization, collagen fibre architecture and content of proteoglycan and interstitial water have a highly ordered structure[109, 148]. (Fig.) The thin superficial zone forms the gliding surface of the joints. Its composition of high water content, low proteoglycan aggregate content, and densely packed collagen fibres arranged parallel to the surface, allows for low-friction motion and resistance against shear stresses. In the transitional zone, the collagen fibres are more obliquely aligned and the proteoglycan aggregate content is higher; features that are important in resisting and transferring forces. In the deep zone, in order to resist compressional forces, the larger collagen fibres are oriented perpendicular to the joint surface and the subchondral bone. The matrix has a high proteoglycan aggregate content and low water content. The tidemark demarcates the deep zone from the underlying calcified cartilage. The calcified layer is characterized by the calcification of the ECM. It plays an essential role in securing the cartilage to bone by anchoring the collagen fibrils of the deep zone to subchondral bone plate[148].

In respond to traumatic injuries or metabolically pathological conditions, the chondrocytes demonstrate only a limited ability to proliferative and alter their synthetic pattern[136]. These features, together with the avascular and aneural nature of the cartilage, make the response to injury differ from other tissues[70, 96]. The general response to injury in most human tissues or organs requires two elements; specialized cells with the ability to clean up damaged tissue, proliferation and of de-novo synthesis of new tissue, either recruited locally or by cells that have entered the injury site by blood vessels. The second requirement is vascular supply of the many bioactive agents necessary for healing. The limited healing response seen in cartilage injury is considered to be closely associated with the structural and physiological

properties of cartilage, precluding both two required elements for general response to injury[3, 68, 69, 109]. Consequently, if spontaneous cartilage healing is to take place, support from the surrounding components of the synovial joint is required. The synovial membrane, the synovial fluid, the subchondral bone plate and the subchondral bone marrow are vascularized tissue-compartments that might assist in a healing response. If an injury to the cartilage causes lesioning down trough the subchondral bone plate, the resultant bleeding fill the defect with a fibrin-clot, trapping cells and bioactive agents from blood and the bone marrow. The undifferentiated marrow-derived cells then mature and produce a reparative tissue[136]. Hence, the response of cartilage to injury depends on the depth of the injury. In superficial lesions, in which no bleeding from surrounding vascularized tissues occurs, a zone of necrosis might develop, followed by a small increase in the mitotic activity and matrix synthesis of the nearby chondrocytes[65]. As a result, spontaneous repair is limited or absent.

1.1.3 Focal cartilage lesions

According to the etiology, there are two distinct articular cartilage lesion phenotypes: degenerative lesions and focal lesions[69].

Degenerative lesions appear less demarcated and the surrounding or opposing articular surfaces are affected as well. These lesions are often part of the clinical syndrome of OA, which is one of the most common causes of pain and disability in middle-aged and older people[18]. OA is the end stage of degenerative joint disease and has multifactorial etiology. OA is often labeled "idiopathic" or "primary" when the underlying disease is unknown, and "post-traumatic" or "secondary" if it develops following distinct knee trauma or disorders.

Figure 2. Isolated focal full-thickness cartilage lesion as seen by arthroscopy, photograph by Per Henrik Randsborg MD, PhD.

This thesis focuses on focal cartilage lesions, where the term "focal" describes a well-delineated lesion with surrounding cartilage considered as macroscopically normal or nearly normal. The term "lesion" is often used as a general term covering several types of focal pathological changes of the cartilage, and therefore do not comprise an aetiological explanation. In the literature, the term "cartilage defect" is sometimes used rather than cartilage lesion. Commonly, and in this thesis, focal cartilage lesions are also referred to by the suspected cause of lesioning, i.e. trauma to the joint, or osteochondritis dissecans (OCD). OCD is a condition that primarily affects the subchondral bone, with risk for focal osteonecrosis and subsequent reabsorption, leaving the overlying cartilage it is supposed to support prone to damage[76]. If spontaneous healing does not occur, an osteochondral fragment may detach and leave a focal osteochondral defect on the joint surface. OCD can affect both juveniles and adults, but onset is typically in skeletally immature and physically active patients[76]. Moreover, distinctions are often made based on the depth of the lesion; lesions confined to the hyaline cartilage are classified according to what layers it extends to, while lesions extending down into the subchondral bone is referred to as *osteochondral lesions*. Focal cartilage lesions in knees without other substantial intra-articular injuries are in the

present thesis referred to as *isolated cartilage lesions*, and focal cartilage lesions in knees with other concurrent injuries, e.g., ACL-injury, are referred to as *concomitant cartilage lesions*.

1.1.4 Classification of focal cartilage lesions

Focal cartilage lesions of the knee joint can be classified according to their macroscopic appearance. The extent of cartilage damage can be described according to the pathological changes (blisters, cracks, fibrillation, etc.) at the joint surface and/or the size, depth and localization of the lesion. Since the introduction of a novel cartilage injury classification system by Brittberg et al. in 1998 [15], and later revised in 2003[16], which is also included in the International Cartilage Regeneration & Joint Preservation Society (ICRS) clinical cartilage injury evaluation system, the ICRS classification has gradually gained popularity in both research and clinical settings. It was developed for arthroscopic assessment and it has been shown to have good psychometric properties and correlation to histological assessment of lesion depth[36]. Since the establishment of the Norwegian National Knee Ligament Registry (NKLR) in 2004, and the Swedish National Knee Ligament Registry (SKLR) in 2005, the ICRS has been the chosen cartilage lesion classification system. The ICRS classification grades the lesions from grade 0 to grade 4, mainly according to the depth of the lesion (Fig. 3). Grade 0 is normal cartilage, grade 1 is nearly normal (superficial lesions, soft indentations, and/or superficial fissures and cracks), grade 2 is abnormal cartilage (lesions extending down to <50% of cartilage depth), grade 3 is severely abnormal (lesions extending down to >50% of cartilage depth as well as down to the calcified layer and down to, but not trough the subchondral bone), and grade 4 which is severely abnormal lesions extending just trough the subchondral bone plate or even deeper into the trabecular bone. The grade 4 lesions are often labelled *osteochondral lesions.*
As the ICRS classification system does not include lesion size or location in the knee, the treating surgeon normally measures the cartilage lesion size in cm^2 and denotes the anatomical localization in the knee.

ICRS Grade 0 - Normal

ICRS Grade 1 – Nearly Normal
Superficial lesions. Soft indentation (A) and/or superficial fissures and cracks (B)

A   B
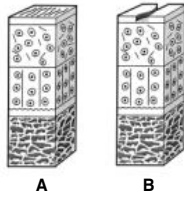
ICRS Grade 2 – Abnormal
Lesions extending down to <50% of cartilage depth

ICRS Grade 3 – Severely Abnormal
Cartilage defects extending down >50% of cartilage depth (A) as well as down to calcified layer (B) and down to but not through the subchondral bone (C). Blisters are included in this Grade (D)

A   B   C   D
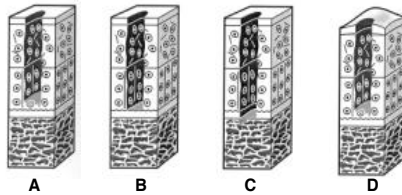
ICRS Grade 4 – Severely Abnormal

A   B
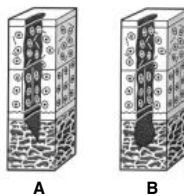
Figure 3. International Cartilage Regeneration & Joint Preservation Society (ICRS) classification system (reprinted with permission from the ICRS)

1.1.5 Prevalence, incidence and lesion characteristics

The accuracy of prevalence and incidence data depends upon the ability to detect and report the condition in an accurate manner. Even though there have been recent attempts to initiate nationwide cartilage injury registries, historically there have been none with satisfying size or coverage[40]. The exact incidence and prevalence of focal cartilage lesions is therefore not known. The reported prevalence in patients undergoing arthroscopic surgery of the knee, for any reason (symptomatic patients), ranges between 19 and 63% [26, 66, 146, 163, 168], while focal cartilage lesions deemed eligible for cartilage repair surgery by the operating surgeon are diagnosed in 5-10% of all knees subjected to knee arthroscopy[66, 168]. Based on several cross sectional MRI studies, the prevalence in the general healthy population (without OA) is reported to be 43-57 %[32]. However, the steadily increasing sensitivity of MRI makes detection of very small lesions possible, some of which may not be clinically relevant.

Cartilage injury incidence rates are commonly estimated from large registries that primarily gather data for other knee conditions, and probably only from the most severely affected patients scheduled for surgery. Hence, the true incidence rate for the whole spectrum of cartilage injuries is not established. The challenges in collecting accurate incidence data become apparent when reviewing the current literature on this subject matter as quite widespread incidence rates are reported. A mean annual cartilage surgery procedure incidence rate of 900/100,000 patients has been reported from a large United States database[98]. In England, the rates of cartilage procedures have increased steadily by a total of 1500% from 3.2/100,000 inhabitants in 1997-1998 to 51/100,000 in 2016-2017, in line with the incidence rate of 56/100,000 inhabitants that has been reported in a population-based study from Norway[1, 39].

The highest incidence of focal cartilage lesions is found in patients between 20 and 35 years old[168]. Significant geographical variations in incidence and surgical cartilage treatment have been reported. Moreover, substantial variations were reported between public and private hospitals[39].

It is a consistent finding in the literature that the cartilage lesions commonly are localized on the medial femoral condyle and the patella, accounting for 32-58% and 11-36% of the lesions, respectively [26, 66, 163, 168]. An acute traumatic onset of knee symptoms, e.g. sports injury, is reported in about 50-60%, and OCD in only 0.7-9% of cases[26, 66, 168]. 35-60% of focal

24

cartilage lesions detected by arthroscopy are categorized as full-thickness lesions, i.e. ICRS grade 3-4[66, 163, 168]. Cartilage lesion size is reported to be <2cm^2 in 45-64% of cases[66, 163]. Concomitant ACL- or meniscal injury is common, and is reported in 42-68% of patients with a focal cartilage lesion[26, 66].

1.1.6 Prognosis/Natural history of focal cartilage lesions/Non-operative treatment

In general, focal cartilage lesions can be treated non-operatively or operatively. The short-term prognosis and outcome following a large spectrum of surgical methods have been described in the literature, but the prognosis in terms of the natural history (rehabilitation alone) of focal cartilage lesions is less well described. In a study by Messner and Maletius, in which 28 athletes were evaluated 14 years after arthroscopic diagnosis of a severe focal cartilage lesion of the articular knee surface, 21 patients had been able to return to preinjury sports activity level, and 22 patients had excellent or good knee function[99]. In a 5-8 year follow-up of 84 patients with arthroscopically verified full-thickness cartilage lesions, Løken et al. found that knee function improved but remained substantially affected regardless of treatment (surgical or non-surgical). Moreover, a substantial fraction of the patients developed premature OA during the follow-up period, again regardless of treatment[93]. Shelbourne et al. found no negative effects of untreated concomitant full-thickness lesions up to 12 years postoperative in a cohort of patients treated with ACL-reconstruction[139]. In a recent randomized study, reporting on the effect of debridement versus observation of unstable cartilage lesions encountered during arthroscopy for meniscal surgery, patients with their cartilage lesion left in situ had equivalent improvements in outcome scores 1 year postoperatively[11].

It is shown, however, that at least a proportion of the cartilage-lesion patients persistently report major problems with pain and functional impairment, worse than those of ACL-deficient patients, and quality of life similar to severely affected OA- patients[65].

In the preoperative phase, when compared to patients with ACL- or meniscal tears, patients with cartilage lesions develop substantial muscle deficits, but accordingly also the largest potential for improvement by muscular training[37]. In a study by Wondrasch et al., on patients

scheduled for cartilage surgery that were enrolled in a preoperative 3-month active
rehabilitation program, clinically meaningful improvements in patient-reported outcome
measures (PROMs) were reported. Moreover, 65% of the patients postponed surgery due to
those improvements[164]. Similarly, in a study by Dozin et al., in a comparative trial aiming to
evaluate two different cartilage restoration techniques, 1/3 of the included patients declined
surgery due to relief of symptoms following a 6-month preoperative physical rehabilitation
program[33].

Generally, there is an obvious lack of adequately designed level-1 studies investigating this
subject matter, and, indeed, it remains to be demonstrated that the natural history would be
modified by any of the cartilage surgery techniques available today.

1.1.7 Operative treatment

In general, the main treatment goal is restoration of the knee function with absence of pain,
while secondary goals are return to pre-injury activity level and the prevention of subsequent
premature OA.

Ideally, to accomplish all treatment goals, a surgical method should result in the complete
restoration of articular hyaline cartilage. However, currently no such method exists. As a
consequence, the widespread spectrum of surgical techniques that has been developed over
the years all share the common secondary aims of reducing symptoms, improve knee function
and hopefully prevent OA development, rather than providing a cure.

The individual treatments offered today have in numerous published articles resulted in good
or excellent short-term effects on pain and knee function, but consistent and reproducible
evidence of durable and long lasting improvements is insufficient, and no treatment has so far
proved to reduce the risk of OA[50, 105]. Unfortunately, the majority of published studies have
low methodological quality, e.g. case series, low-quality cohort or case-control studies, with
no control group, no randomization, and only short- to midterm follow-up[49, 50, 64, 74, 105].
Hence, comparative studies with long-term follow-up are warranted, and caution is required
when interpreting the results after operative treatment in the current literature[7, 31, 50, 105].

Surgical strategies:

In addition to surgical debridement, in which mechanical (soft tissue shaver) or thermal (radiofrequecy ablation) arthroscopic resection of unstable, delaminated or fibrillated cartilage is performed to smoothen the articular surface, stabilize the edges of the lesion and thereby merely aiming to reduce symptoms, decelerate further damage to the cartilage and avoid the formation of free bodies, the current surgical strategies can be categorized into:

I) Reparative techniques; surgical techniques that take advantage of the spontaneous repair response, or "bone-marrow-stimulation techniques", e.g. "microfracture" technique. Refixation of loose cartilage fragments, e.g. in unstable OCD-lesions or traumatically induced cartilage- or osteochondral fragmentation.

II) Transplantation techniques that do not attempt to induce any cartilage repair response, but replace damaged or lost tissue with healthy articular cartilage in the form of osteochondral autografts or allografts.

III) Restorative techniques that aim to fill the lesion with neo-cartilage by induction of chondrogenesis. Various tissue cell sources are being used in efforts to obtain such chondrogenesis, the most common being autologous chondrocyte implantation (ACI).

IV) Joint surface replacement in the form of unicompartmental, bicompartmental or total knee replacement is well documented in terms of pain relief, especially in the elderly. In the younger and active population, however, less favorable results are seen[44]. Hence, joint surface replacement is not the first line of treatment for patients with focal cartilage lesions.

An overview of the currently used surgical techniques is shown in Figure 4. A more detailed description, with emphasis on the surgical techniques most commonly used, is given in the sections to follow.
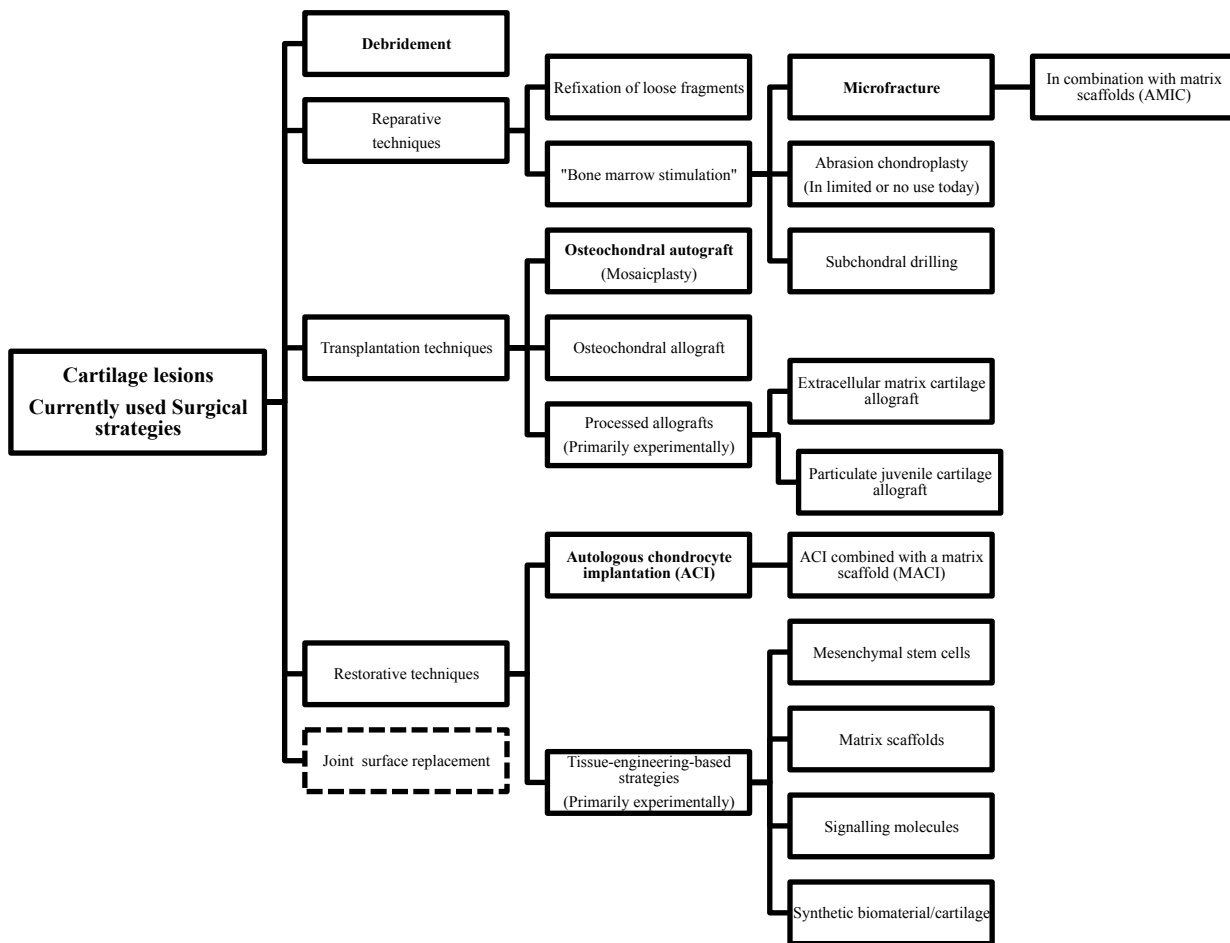
Figure 4. Summary of currently used surgical techniques in the treatment of focal cartilage lesions

Microfracture

The microfracture (MF) technique was introduced by Dr. Stedman and co-workers[123, 151] as an elaboration of other bone-marrow-stimulating techniques, like the drilling trough osteoarthritic eburnated bone, described by Pridie in 1959[72]. Since its introduction in the late 1980´s, and because of its low-cost and technical ease, it gained popularity in the coming decades, and as of today, it remains the most commonly performed cartilage procedure[49] MF, as described by Dr. Steadman, is the assessment of a full-thickness articular cartilage lesion, which is then debrided of unstable cartilage to stable, viable and perpendicular edges surrounding the defect. The calcified layer is removed and specially designed awls are used to make multiple perforations, or "microfractures", perpendicular into the subchondral bone plate. The perforations are made close together, but not so close that one breaks into another. Consequently, the microfracture holes should be approximately three to four millimeters apart (3-4 holes/cm^2). The integrity of the subchondral bone plate should be maintained. The appropriate depth has been reached when fat droplets and blood can be seen coming from the underlying bone marrow. In that way MF attempts to stimulate and recruit mesenchymal cells and blood cells to form a fibrin clot that eventually turns into a predominantly fibrocartilaginous regenerate that fills within the lesion[43, 151].
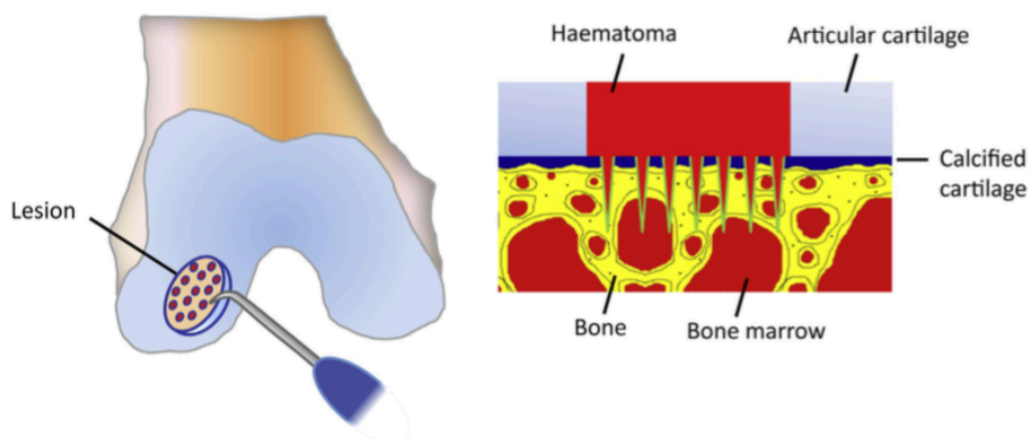
Figure 5. Schematic representation of the microfracture (MF) technique, adapted from Hunziker , E.B. et al.[69], with permission from Elsevier Ltd, ScienceDirect ®.

Despite fibrocartilage formation with inferior biomechanical characteristics compared to native hyaline articular cartilage[48], several short- to mid-term follow-up studies following MF, report significant pain relief and improvement in knee function, especially in young patients with small lesions[49, 101, 150]. However, consistent and reproducible favorable clinical results, and especially in the long term, are not readily available.

In the recent years, MF has also been combined with the introduction of diverse biomaterial matrix scaffolds into the lesion, often labeled autologous matrix-induced chondrogenesis (AMIC)[9]. However, despite some indications that it may enhance the durability of the repair tissue[158], the current literature afford little evidence of any additional benefit from this combined approach[45].

Osteochondral autologous transplantation (OAT mosaicplasty)

Osteochondral autologous transplantation (OAT) involves open or arthroscopic transplantation of one or more cylindrical plugs of native articular cartilage and some of its underlying subchondral bone, harvested from the relatively less weight-bearing periphery of the articular surface into the cartilage defect, thus providing a hyaline-cartilage-covered resurfacing[63]. "Mosaicplasty" in which several osteochondral plugs are transplanted to the recipient defect creating a "mosaic" of circular profiles, is the OAT technique with the longest history. One of the obvious disadvantages of the technique is the inevitable creation of additional lesions (donor sites) within an already diseased joint, a disadvantage that is bypassed if using allografts.
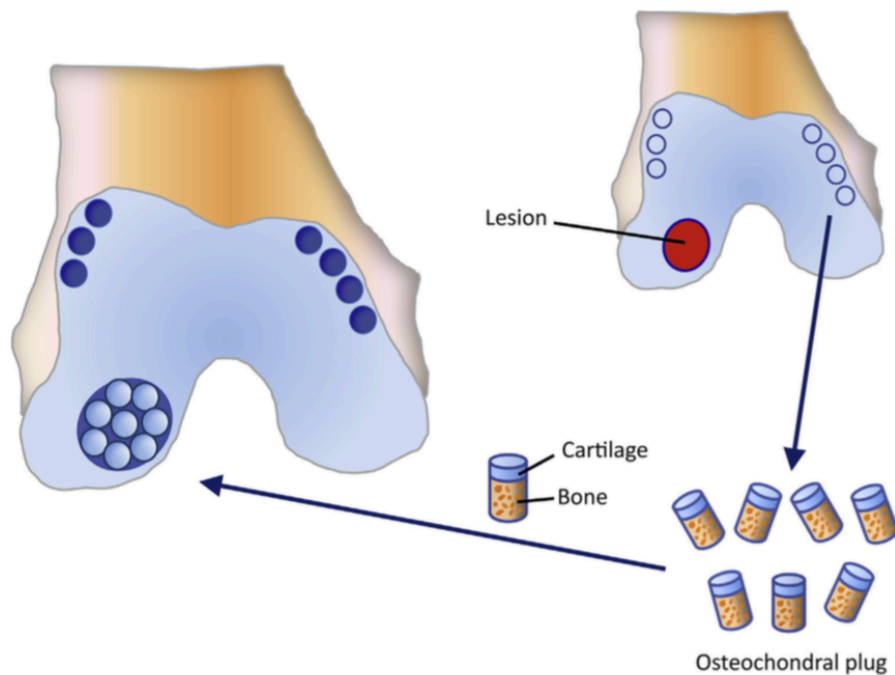
Figure . Schematic representation of the principle of Osteochondral Autologous Transplantation (OAT) moasicplasty, adapted from Hunziker , E.B. et al.[69], with permission from Elsevier Ltd, ScienceDirect ®.

It is also technically demanding to place the cylinder grafts in the perfect anatomical position relative to the native cartilage surface (height, angulation). Moreover, to maintain such perfect docking of the grafts over time, some bonding must occur between the grafts and between the grafts and the surrounding native cartilage.

Nevertheless, case series and comparative trials have reported 83–92 % good to excellent short- to midterm results following OAT mosaicplasty[21, 57, 62, 143], and there are indications that the deterioration in results over time and rate of failure is less than for MF[119, 141, 142]. However, there are very few randomized controlled trials (RCTs) comparing the long-term outcome of OAT to other surgical techniques. In a RCT by Gudas et al., athletes treated with OAT reported superior outcome- and activity scores and lower failure rates than MF-treated athletes at a mean follow-up of 10.4 years[56]. In a recently published randomized study, Solheim et al., OAT mosaicplasty resulted in significantly better clinical outcomes than MF at short, medium and long-term (minimum 15 years) follow-up[145]. On the contrary, in a RCT with ten-year follow-up comparing OAT to autologous chondrocyte implantation (ACI), the

failure rate in OAT-patients was significantly higher, and the functional outcome significantly worse than in ACI-patients[10].

Hence, firm knowledge regarding long-term outcome after OAT remains insufficient.

Autologous chondrocyte implantation

According to the ACI-technique, introduced by Brittberg et al. in 1994[14], a biopsy of healthy cartilage, arthroscopically harvested from an uninvolved area of the injured knee, is enzymatically digested to release viable chondrocytes. The chondrocytes are then expanded in culture over a few weeks to produce millions of cells. In a second procedure, the cells are then injected into the cartilage lesion and sealed under a sutured periostal flap (ACI-P), the latter subsequently refined to collagen-flaps (ACI-C) and matrix scaffolds made of biomaterials in which the chondrocytes are embedded (MACI).

The initial report by Brittberg et al. showed "hyaline-like" cartilage in 11 of 15 medial femoral condyle lesions. ACI has since then been compared to MF and OAT in several studies of varying methodological quality. According to two recent systematic reviews, ACI might produce a more durable repair tissue and favorable results in lesions greater than 4 cm^2 compared to MF[115], and successful outcomes in 82% of patients over the long-term[118]. On the other hand, Knutsen et al.[83], in a 14-15 year follow-up of a RCT comparing ACI to MF, found no difference in clinical outcomes between treatment groups. Moreover, the incidence rates of failure and OA were substantial for both treatment groups.

1.1.8 Prognostic factors and treatment selection

Even though the short-term results after cartilage surgeries are generally good, there is paucity in evidence of consistent and reproducible improvement over time. In addition to the variation among surgeons regarding indications for surgery, surgical experience and preferences, postoperative rehabilitation and assessment of the outcome[153], great variability in patient-, joint-, and lesion characteristics exists. Taken together, there are numerous, known and unknown, risk factors and predictors for the outcome after cartilage surgery.

Large and unbiased prospective cohorts are appropriate study designs when investigating prognostic factors. However, most of the proposed prognostic factors in relevance to cartilage

surgery are derived from small RCTs and case-series. Nevertheless, some prognostic factors are more consistently reported to have effect on the outcome after cartilage surgery in general. Increasing age (above 30-40 years old)[82, 85], female gender[46, 114, 144], increasing Body Mass Index (BMI)[103], previous surgery to the lesion[100, 108], increasing lesion size[57, 97, 144], lesion location other than the medial femoral condyle[61, 86, 114], and increasing time from symptoms to surgery[103, 114] are factors that have been shown to predict less favorable clinical outcome. Obviously, there are numerous additional factors that should be considered when selecting treatment for articular cartilage lesions, e.g., activity-level and the patient's prospect for adherence to the post-operative rehabilitation program, general health issues, smoking status, concomitant joint or limb injury, etc., but the effect of the majority of factors are less well investigated.

Even though some authors recommend MF for small sized lesions and OAT or chondrocyte-based restorative techniques for larger lesions, conclusive evidence to support treatment selection based solely on lesion-characteristics or patient-characteristics is not available in systematic reviews and meta-analyses of high-quality trials on this subject matter[7, 31, 50, 105, 119].

1.2   ACL injury

Injury to the anterior cruciate ligament (ACL) is one of the most common knee injuries in orthopaedic practice with an estimated annual incidence in Norway of 85 per 100 000 inhabitants in the age group 16-39 years[52]. Associated concomitant articular cartilage lesions are reported to exist in 1/3 of the cases[131]. In Norway, the annual incidence of ACL-reconstruction (ACLR) has for several years been approximately 2000, which in turn is estimated to represent about 50% of the annual incidence of ACL injury[52].

The ACL is the primary mechanical restraint to anterior tibial displacement and also an important contributor in stabilizing the internal rotation of the tibia. The knee joint works by the precise and complex interaction of the musculoskeletal- and nervous system, where proprioceptive input, including from the ACL, is the basis for neuromuscular coordination and dynamic stability throughout the range of motion[147]. Consequently, a rupture of the ACL can lead to both mechanical and dynamic joint deficiencies. The increased joint laxity and the reduced ability to recruit adequate stabilization from muscular activation can result in

combined anterior and rotational subluxations, often referred to as episodes of the knee giving away.

In addition to the short-term consequences of an unstable knee, e.g., inability to perform strenuous work and participate in sport activities, or even activities of daily life, the patients face an increased risk of developing premature OA of the knee[5, 91, 112]. Even though the mechanisms behind OA-development following an ACL injury are not fully understood[90], additional intra-articular injuries, like cartilage lesions, have been proposed to contribute in the process towards OA[75, 78, 122].

A tear of the ACL can be treated conservatively by rehabilitation alone, or by surgical reconstruction in combination with rehabilitation. Even though there is no clear consensus on which treatment alternative is best in achieving the treatment goals of restoration of knee function and stability, returning to pre-injury activity level and prevention of premature OA, surgical reconstruction is the mainstay in the treatment of young and active patients[20, 30].

1.3 ACL injury and concomitant focal cartilage lesions

1.3.1 Incidence and risk

ACL injuries are associated with other intra-articular knee injuries like meniscal tears and focal articular cartilage lesions. At the time of the initial knee injury, in which the ACL was torn, or in subsequent episodes of knee subluxations, other intra-articular structures like the meniscus and/or the articular cartilage are vulnerable for injury. Concomitant cartilage lesions might be inflicted by the impact from the femoral condyle to the tibial plateau, and the provocation of shear forces across the articular surface from the less restricted pivoting movement.

The exact incidence of concomitant focal cartilage lesions in the setting of ACL-injury is not known, but the prevalence of concomitant partial-thickness and full-thickness cartilage lesions at the time of anterior cruciate ligament reconstruction (ACLR) has been reported to be 20.2 and 6.4 %, respectively, in the Norwegian and Swedish knee ligament registries, and similar rates have been found in the USA[95, 131]. However, even with the broad diagnostic

armamentarium at hand, it is a deductive challenge for the surgeon to judge whether a cartilage lesion detected in relation to the ACL injury is a novel cartilage injury, and whether the patient´s signs and symptoms originate from that cartilage lesion or the ACL injury itself, or both. In any case, and considering the commonness of this associated injury, the orthopaedic surgeons need a well-founded information- and treatment strategy when dealing with these patients.

The risk factors for having concomitant intra-articular injuries in relation to ACL injury are assessed in numerous publications, but the significance of the diverse factors is somewhat inconsistent. However, in reports that are adequately powered, and where adjustments for relevant confounders are made; increasing age, previous knee surgery, male gender, time elapsed from ACL injury to ACLR exceeding 6-12 months and some high knee-loading pivoting sports are shown to be significant risk factors for having focal cartilage lesion at the time of ACLR[4, 54, 131].

1.3.2 Prognosis

Historically, ACLR research has probably been one of the areas within orthopaedic research with the largest number of publications, but the attention has predominantly been dedicated to the ACL injury itself. Gradually, associated injuries, like cartilage lesions, have been appreciated as important for the outcome and prognosis after ACLR[42].

The presence of a concomitant cartilage lesion at the time of ACLR is shown to be a significant predictor of premature radiographic knee OA[22, 75, 78, 88, 106]. Yet, OA usually develops gradually and the presence of radiographic OA does not always correlate well with the patients' symptoms[113]. As a consequence, measurements where the patients' own opinion and experience of the outcomes (PROMs) are recommended and has gained popularity in outcome evaluations in orthopaedic medicine[27, 107].

However, the literature is inconsistent and somewhat divergent when it comes to the effect on PROMs of such concomitant cartilage lesions. Some of the studies have found no adverse effects[4, 139, 149, 162], while others have found that concomitant cartilage lesions are associated with inferior PROMs after ACLR[24, 128, 130, 137]. However, as pointed out in a recent systematic review of the current literature on this subject matter, the majority of reports in the literature

support the clinical relevance of concomitant cartilage lesions as correlated with poorer outcome after ACLR. But the overall low level of evidence, considerable heterogeneity in patients, injuries, classification systems, surgical factors, outcome measurements, and observation periods among the different studies, made it difficult to make firm conclusions based on the included studies[42].

Hence, there is a need for large population-based studies with adequate time to follow-up. Knowledge on the prognosis after ACLR, in patients with concomitant focal cartilage lesions, is necessary if the information and advice given to the patient regarding treatment and expectations are to be optimal.

1.3.3 Treatment of concomitant cartilage lesions in the setting of ACL-Reconstruction

In general, concomitant focal cartilage lesions encountered during the diagnostic work-up of an ACL injury, or at the time of ACLR, can be managed surgically or left untreated. A third option is to delay concomitant cartilage surgery, and later assess the patients' progress and improvement during the postoperative rehabilitation program to decide if any further surgical treatment is indicated[156]. Indeed, if an unrecognized cartilage lesion is detected at the time of ACLR, some surgical techniques are not available for immediate combined surgical treatment; ACI requires a lag of several weeks between cartilage biopsy to chondrocyte implantation, and techniques using allografts rely upon graft availability.

The surgical treatment options, and the proposed factors to be considered when selecting the treatment for concomitant cartilage lesions are essentially identical to those in the setting of isolated focal cartilage lesions (Fig. 4). The reason being that the majority of publications on cartilage repair have reported on isolated cartilage lesions, and the knowledge and conclusions drawn from those studies is often generalized to patients with the combined injuries of ACL-injury and concomitant cartilage lesions. However, to infer similar disease progress and outcome is questionable considering that he ACL injury, and eventual ACLR, might substantially alter the biomechanical and biochemical properties of the knee joint, which in turn can have implications for the outcome following cartilage surgery. Hence, whether

similar outcome is to be expected following surgery of isolated and concomitant cartilage lesions is controversial.

In a recent systematic review of the current literature on the surgical management of these combined injuries, 10 isolated reports were identified, suggesting the usefulness of different procedures such as MF, OAT and ACI[42]. The majority of reports were of low-level evidence, frequently case series. Only one RCT was identified, in which OAT showed to be superior to MF or debridement, in terms of PROMs, at the 3-year follow-up. In the only study with an adequate control group where the full-thickness cartilage lesions were left untreated, MF showed adverse effects, and debridement no effects on PROMs at the 2-year follow-up[129].

In summary, there is limited evidence to guide the surgical management of concomitant cartilage lesions, and it remains to be demonstrated that the natural history would be modified by any of the cartilage surgery methods available today. Moreover, firm knowledge regarding the outcome at medium- to long-term follow-up is limited in the current literature. As such, there is a need for further comparative studies, and the inclusion of a control group where the cartilage lesion is left untreated, is essential.

2   Objectives

2.1   Overall objective

The overall objective of this PhD-project was to provide knowledge on the medium- to long-term effects on prognosis, and outcome following surgery, of focal articular cartilage lesions of the knee joint.

2.2   Specific objectives

    I.   To investigate the long-term outcome following MF versus OAT for patients with isolated cartilage lesions of the knee joint.

    II.   To investigate differences in the long-term outcome following ACLR between patients with and without concomitant full-thickness cartilage lesions.

    III.   To investigate the effect of concomitant cartilage lesions on PROMs 5 years after ACLR.

    IV.   To evaluate the relative effect of MF and debridement, compared with no surgical treatment of concomitant full-thickness cartilage lesions, on PROMs 5 years after ACLR.

3 Materials and Methods

3.1 Study design and study population

3.1.1 Paper I

In this prospective randomized trial of MF versus OAT mosaicplasty for the treatment of femoral isolated full-thickness cartilage lesions, patients were recruited from 3 orthopaedic cartilage repair centers in Norway between November 2000 and June 2006. Patients with anamnestic and clinically relevant symptoms of knee articular cartilage injury were invited to take part in an exploratory investigation that included standing radiographs of both knees (Hip-Knee-Ankle alignment, fixed 45°- flexion views, and patella-femoral skyline Merchant views), standard knee protocol MRI, and clinical knee examination (including Lysholm score, Tegner activity score and the Knee injury and Osteoarthritis Outcome Score)
Based on the results from these investigations, eligible patients that accepted to move forward with surgical treatment were informed that the final decision regarding inclusion into the study had to be based on the findings during the arthroscopic examination. Once eligibility was confirmed, and following arthroscopic debridement, randomization between MF and OAT mosaicplasty was performed in the operating room.

Inclusion criteria were:

- An arthroscopically verified cartilage- or osteochondral lesion, ICRS grade 3 or 4, located on the articulating surfaces of the femoral condyles or trochlea, with an area between 2 and 6 cm^2 (alternatively two lesions with a cumulative area between 2 and 6 cm^2), patients between 18 (epiphyseal fusion) –50 years of age, and Lysholm score < 80 and Tegner activity score <6.

Exclusion criteria were:

- Any sign of radiographic OA, a medical history of systemic disease with joint affection, (e.g. Mb. Bechterew or rheumatic disorders), major knee malalignment (>5º

as compared to the contralateral knee), pre-existing or concurrent symptomatic knee ligament injury or knee instability (with increased laxity, compared to the contralateral knee), extension deficit > 3°, flexion deficit > 5°, and cartilage lesion(s) of ICRS grade 3 or 4 located on the tibial plateau or patella, and in the case of OCD; depth more than 10 mm. And finally, patients with any impairment of the contralateral knee-function that could potentially interfere with the rehabilitation protocol were also excluded.

A total of 25 patients with a mean age of 32.3 (SD 7.7) met all of the above-mentioned criteria and were enrolled into the study between November 2000 and June 2006. 19 patients that initially were found to be eligible were not included, frequently due to findings during arthroscopic assessment, e.g. size or localization of the cartilage lesion not in accordance with the inclusion criteria, or additional grade 3-4 cartilage lesions in other localizations than the femur. Two patients declined surgery due to pregnancy, and two patients withdrew their consent at the time of surgery as they insisted on being treated with one of the surgical techniques, and thereby declining randomization.

The patients were randomized by a restricted shuffled approach in blocks of 10, allocation ratio 1:1, using sequentially numbered sealed envelopes to assign treatment. Accordingly, 14 patients were treated with OAT mosaicplasty and 11 patients with MF. The surgical principles of the MF and OAT techniques, as outlined in the introduction of the current thesis, and described by Steadman et al.[151] and Hangody et al.[63], respectively, were used throughout the study.

With the exception of a slightly larger median lesion size (3.0 cm^2; range, 2.0-6.0 versus 2.6 cm^2; range, 2.0-5.2), a shorter mean (± standard deviation, [SD]) preoperative duration of symptoms (75.8 ± 73.5 months versus 111 ± 77.3 months) and injury mechanism less frequently reported to be OCD (29% versus 55%) in the OAT-group than in the MF group, the patient characteristics in the two study groups were comparable. There were slightly more males than females in both groups with 55% males in the MF group and 57% males in the OAT group. The mean age at inclusion was 31.7 ± 8.0 years and 32.7 ± 7.8 years in the MF and OAT group, respectively.

The postoperative care and rehabilitation program was similar for all patients and included: hospitalization for minimum 5 days, continuous passive motion exercise (Kinetec®) 3–4 hours x 2/day from the first postoperative day until it was discontinued at the fifth postoperative

day. Compression and cold therapy (Aircast Knee Cryo/ Cuff®) were applied the two first days postoperatively to reduce swelling and pain. A maximum load of 15–20 kg weight bearing was encouraged the initial 6 weeks postoperatively, subsequently gradually discontinuing the crutches up to 8 weeks. From 8 weeks, progression to full weight bearing was encouraged. Physiotherapist-guided rehabilitation was initialized immediately postoperatively and was continued for a minimum of 6 months. The rehabilitation program included exercises aiming to restore full range of motion and proprioceptive neuromuscular control as soon as possible, progressing to dynamic strength exercises from 6 weeks postoperatively. Patients were generally allowed return to full activity after 6 months. However, participation in competitive contact sports or other activities that might expose the knee to pivoting forces was discouraged until 12 months postoperatively.

3.1.2 Papers II-IV

In paper II-IV, registry data made up the basis for the investigations. In paper II, additional measurements were performed at follow-up, while in paper III and IV all analyses were made solely on the basis of data reported to the registries at preoperative- and 5 years after ACLR. In paper III and IV, patients from both the Norwegian and Swedish registry databases were included, while in paper II, only patients from the Norwegian registry database were included.

The National Knee Registries
The Norwegian National Knee Ligament Registry (NKLR) was established in June 2004, and was the first national prospective surveillance system for monitoring the outcome of cruciate ligament surgery. The design and development of the NKLR has been described in the literature[51]. In January 2005, the Swedish National Knee Ligament Register (SKLR) was established. In order to facilitate collaboration, the design and methodology of collecting data is practically identical in the two registries[53]. The two national registries aggregate data from surgical procedures performed on the main knee ligaments, and prospectively monitor outcomes on a nationwide scale. Reporting to the registries are voluntary, both for the patients and the surgeons. The surgeons complete a form postoperatively, in which patient-, knee-, and

surgery-specific variables are reported to the registries. As a part of that registration, the surgeons grade concomitant cartilage lesions according to the ICRS guidelines[16, 17], the cartilage lesion size (area $\leq$2 cm^2 or >2 cm^2), and anatomical localization within the knee. In the present thesis, the ICRS classification system is used in all classifications of cartilage lesions. Moreover, a categorization of focal cartilage lesions ICRS grade 1 and 2 into *partial-thickness lesions,* and cartilage lesions ICRS grade 3 and 4 into *full-thickness lesions*, is used throughout the thesis.

The surgeons' nationwide reporting rates are found to be satisfactory, with rates above 85%[165]. Before surgery, the patients complete an informed consent form allowing for later use of their registry data (Norway only), including results on the Knee injury and Osteoarthritis Outcome Score questionnaire (KOOS)[127], which is used as the patient- reported outcome measure at preoperative, and 1 (Sweden only), 2, 5 and 10 years postoperatively.

Paper II

The study was designed as a prospective cohort study with a matched control group. A search performed among the 4849 primary ACLRs reported to NKLR by the end of 2007 identified 30 patients that met the following inclusion criteria: A full-thickness cartilage lesion (ICRS grade 3 or 4), age less than 40 years, no associated ligament or meniscus injury, no previous ipsilateral knee surgery, < 12 months from ACL injury to ACLR, and completed the preoperative KOOS questionnaire. These patients constituted the study group.

For each study patient, two control patients with an isolated ACL injury (no concomitant cartilage lesion) were included from the NKLR by the end of 2007, generating 60 control patients. Except from not having a concomitant cartilage lesion, the control patients had to meet the same inclusion criteria as the study group, and match the study patients on the criteria of age, gender, days from injury to ACLR, and type of ACL-graft. One control patient had to be excluded due to incomplete preoperative KOOS data, leaving a control group of 59 patients.

22 (73 %) of the study patients had a concomitant full-thickness cartilage lesion measuring $\leq$ 2 cm^2, and 8 (27 %) were >2 cm^2. 20 (67 %) of the cartilage lesions were located in the medial tibiofemoral compartment, 6 (20 %) in the lateral femoral compartment and 4 (13 %) in the patellofemoral compartment. 23 (77 %) patients in the study group underwent ACLR

without any simultaneous cartilage surgery. Of the remaining 7 study patients, 4 had a debridement procedure and 3 patients received MF.

At a median follow-up of 6.3 years (range, 4.9-9.1), 74 (84%) of the original 89 patients were available for follow-up. 29 study patients and 45 control patients, respectively.

The stringent matching performed at the time of inclusion was sustained during follow-up. The mean age at follow-up was 34.9 ± 6.8 years in the study group and 34.7 ± 7.4 years in the control group. The mean time elapsed from ACLR to follow-up was 6.8 ± 1.5 years for the study group, and 6.1 ± 1.3 years for the control group. The gender distribution was similar in both groups, with 28% and 29% females, respectively. Additional group characteristics, e.g., smoking status, Body mass index (BMI), and Tegner activity level, not being part of the initial matching between groups, were comparable as well.

Paper III

The study was designed as a nationwide population-based prospective cohort study, including all patients in Norway and Sweden receiving unilateral primary ACLR from January 1, 2005 through December 31, 2008. Of the total 15783 included patients, 6135 (39%) patients were registered in the NKLR and 9726 (61%) patients in the SKLR.

At a mean follow-up of 5.1 ± 0.2 years after ACLR, KOOS data were available for 8470 (54%) patients, who constituted the study group. 7313 patients were considered as lost to follow-up as they had not returned the 5-year follow-up KOOS questionnaire.

With the exception of gender and age, the baseline characteristics, including the preoperative KOOS, of the study group and those lost to follow-up (n=7313) were comparable. Patients in the study group had a median age of 27 (range 9-69) years at the time of ACLR, while patients lost to follow-up tended to be younger; median 24 (range, 8-64) years at surgery. There were 4125 (49%) females in the study group, and 2573 (35%) females amongst those lost to follow-up.

The study patients had median 9 (range 0-521) months from injury to surgery, and 2232 (26%) of them had undergone previous ipsilateral knee surgery. At the time of ACLR, 3688 (43%) study patients had concomitant meniscal lesions, and 621 (7%) had concomitant ligament (other than ACL) injury. In 6473 (76%) of the study cases, an ACL hamstring tendon graft was used, while in 1833 (22%) cases, a bone-patellar tendon-bone (BPTB) graft was used.

2248 (27%) study patients had ≥1 concomitant cartilage lesions at the time of ACLR: 1685 (20%) patients with partial-thickness lesion (ICRS grades 1-2) and 563 (7%) with full-thickness lesions (ICRS grades 3-4). The total number of partial-thickness lesions was 2825, and the total number of full-thickness lesions was 656.

Of the 1685 patients with concomitant partial-thickness cartilage lesions, 591 (35%) had >1 lesion (ICRS grades 1-2). Of the 563 patients with full-thickness cartilage lesions, 74 (13%) had >1 full-thickness cartilage lesion, and 218 patients (39%) had an associated partial-thickness cartilage lesion.

Paper IV

The study was designed as a nationwide population-based (Norway and Sweden) prospective cohort study. Of the 15783 patients included in paper III, 1012 (6.4%) had concomitant full-thickness (ICRS grade 3 or 4) cartilage lesions at the time of ACLR and made up the population of interest.

To be considered eligible for inclusion into the study, those patients also had to be registered as having received debridement, MF, or no surgery to their concomitant cartilage lesion, and completed the preoperative KOOS. Overall, 360 patients did not meet the inclusion criteria; in 239 cases due to missing preoperative KOOS data, and in 129 cases because the cartilage treatment was not reported, or reported to be other than debridement, MF or no treatment. The remaining 644 eligible patients were included into the study, consisting of 351 (54%) patients receiving no surgical treatment to their concomitant cartilage lesion, 129 (20%) patients receiving debridement, and 164 (26%) MF. Patients with >1 concomitant cartilage lesions were categorized according to the lesion with the highest ICRS grade.

At a mean follow-up of 5.1 ± 0.1 years, and mean age of 41.2 ± 10.4 years, KOOS data were available for 368 (no surgical treatment of cartilage lesion, n=203; debridement, n=70; MF, n=95) of the 644 study patients. 276 (43%) patients were considered as lost to follow-up as they did not return their 5-year follow-up KOOS questionnaire. As in the larger cohort in paper III, a higher proportion of males, and a younger mean age at ACLR, characterized patients lost to follow-up.

Except for a difference in the proportion of grade 4 lesions and the prevalence of >1 full-thickness cartilage lesions between the 3 treatments groups, there were no substantial differences in the baseline characteristics of patients available for the 5-year follow-up.

3.2   Classification of cartilage lesions

The International Cartilage Regeneration & Joint Preservation Society (ICRS) classification system for articular cartilage lesions was chosen as the arthroscopic classification tool in paper I, in line with the choice of the NKLR and the SKLR to use the ICRS as their classification tool for concomitant cartilage lesions.

The macroscopic features of the cartilage lesion, as seen by knee arthroscopy, determine the ICRS grading, and for all practical purposes, relies on the assessment of the depth of the lesion. A description of the different ICRS grades is given in the introduction of the current thesis, together with Figure 3.

In the present thesis, a dichotomization of lesions of ICRS grade I-II into *partial-thickness lesions,* and lesions grade III-IV into *full-thickness lesions*, were made. Moreover, since the ICRS does not include a description of the lesion size, the area in cm^2 is reported in paper I. In paper II-IV, registry data is used. Since the surgeons report lesion size as area ≤ 2 cm^2 or >2cm^2 to the NKLR and the SKLR, this dichotomization was also used in paper II-IV.

In addition, lesions are reported to the registries according to their anatomical localization in the knee as follows; medial patella, lateral patella, femoral trochlea, medial femoral condyle, lateral femoral condyle, medial tibial plateau and lateral tibial plateau. In the current thesis a simplified categorization into lesions of the; patella, trochlea, lateral or medial femoral condyle, and lateral or medial tibial plateau, was made.

3.3   Outcome measures

The outcome measures used in the current thesis are primarily PROMs, in which the patients' own opinion and experience of the outcomes are measured. PROMs are selected as one of the

main outcome measures in the NKLR and the SKLR, and are recommended in outcome evaluations in orthopaedic medicine[27, 107]. In paper I and II, with the intention to allow for a more comprehensive interpretation of the results, additional outcome measures were included. It has been recommended that in any studies on knee populations, the measurement of additional constructs, such as the activity level, should complement existing functional outcome instruments[58]. Moreover, due to the inherent risk of developing OA in the median- to long-term, radiographic evaluation was considered important and included in paper I and II. In the following, an outline of all outcome measures used in paper I-IV is given:

KOOS (Papers I-IV)

The Knee injury and Osteoarthritis Outcome score[127] (KOOS) is the most commonly used PROM in level I and II studies on cartilage repair[132], and is included in all 4 papers in the present thesis. KOOS is the main outcome measure in paper II-IV, and a secondary outcome measure in paper I.

The KOOS is a patient-administered and self-explanatory questionnaire consisting of 42 questions distributed between 5 subscales covering the domains of: Pain (9 questions), other Symptoms (7 questions), Activities in Daily Living function (ADL) (17 questions), Sport and Recreation function (Sport/Rec) (5 questions) and knee-related Quality of Life (QoL) (4 questions). Based on the patient's answers, each question was assigned a score from 0 to 4, and a normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) was calculated for each subscale. All calculations of the KOOS scores of each subscale and the management of missing data were performed according to the online users guide[124]

The KOOS was designed as an extension of the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC)[8], which primarily is used to evaluate patients with OA, to assess young and active patients with knee injuries that can result in post traumatic OA, as well as patients with established post traumatic OA. Since its introduction in the 1990s, the psychometric properties have been assessed in a wide variety of knee injuries, including ACL injuries and cartilage injuries, in which it is considered to be a valid, reliable and responsive assessment instrument following non-surgical and surgical interventions over short- and long term follow-up[6, 23, 38, 127]. Moreover, population-based normative data, stratified by gender and age, are available[117].

Lysholm Knee Scoring Scale *(Paper I)*

The Lysholm scale was introduced in 1982, and later revised in 1985[92, 152]. Even though it was originally designed to evaluate outcomes of knee ligament injuries, it has been widely used for knee conditions in general. The revised scale includes 8 items: limp, support, locking, instability, pain, swelling, stair climbing and squatting. Each item is scored independently with maximum scores ranging from 5 to 25 points, and the maximum total score is 100 (a score of 100 meaning no symptoms or disability). The scoring was intended to be performed by the surgeon with the patient´s collaboration, although subsequent publications have documented patient-administration[12]. It is found to demonstrate overall acceptable psychometric performance regarding validity, reliability and responsiveness to change in the setting of cartilage injury[84]. Moreover, population-based normative data, stratified by gender and age, are available[13]. In paper I, at follow-up, the study patients completed the Lysholm questionnaire prior to the examination, followed by an individual review with the orthopaedic surgeon.

Tegner Activity Score *(Paper I and II)*

The Tegner score was developed to complement the Lysholm scale, aiming to provide a standardized method to grade work and sporting activities[152]. The rationale being that limitations in function scores (Lysholm) might be masked by a decrease in activity level. In a list of 11 items, graduated activities of daily living, recreation and sporting activities are given. The patients select the level of activity that best describes their current ability. A score of 10 represents participation in national and international elite competitive sports, whereas a score of 0 corresponds to sick leave or disability pension due to knee problems. Activity levels 6-10 can only be achieved if the patient is participating in recreational or competitive sports. Although not specifically tested in the setting of cartilage injury, it is found to demonstrate acceptable psychometric performance at the group level in the setting of other knee disorders, including ACL injury[12, 23]. In a systematic review, the ability of the Tegner score to detect change in activity levels in cartilage injury populations have been described[58]. Population-based normative data, stratified by gender and age, are available[13]. In paper I, at follow-up, the patients completed the Tegner scores prior to examination, followed by an individual review with the orthopedic surgeon. In paper II, the patients completed the Tegner scores without any involvement from the orthopaedic surgeon.

Isokinetic Muscle Strength *(Paper I)*

There are indications that the effect on knee-related muscle strength of articular cartilage injury is more pronounced than in other knee disorders, and that the resultant deficit persists for years after cartilage repair surgery[37, 94]. Accordingly, and due to the comparison of an arthroscopic surgical procedure (MF) and an open procedure, measurements of knee-related muscle strength deficits were included in paper I.

A Biodex 6000 dynamometer (Biodex Medical System Inc., Shirley, New York) was used to perform the muscle strength measurements. This device is shown to produce reliable and valid measurements of dynamic muscle function on variables related to torque, power and endurance[35]. Standardized warm-up and test protocols were performed for all patients. Two physiotherapists, both blinded to the treatment, performed the measurements. Comparison was made between the operated and the non-operated, uninvolved knee. The parameter used for analysis was peak torque/highest muscular force output (Nm) expressed as percentage deficit compared to the uninvolved leg.

Radiographic Examination *(Paper I and II)*

In both papers, the absence of radiographic OA was a prerequisite for inclusion into the study. At follow-up, radiographic examination was performed in the AP-plane with the patients standing with semi-flexed knees (paper I), or standing with normal weight bearing (paper II). The radiographs were graded independently, blinded to group assignment, by at least two orthopaedic surgeons. Grading was done according to the original Kellgren and Lawrence criteria of knee (tibiofemoral) OA; 0 normal to 4 severe (Grade 0: no OA; Grade 1: doubtful narrowing of joint space and possible osteophytic lipping; Grade 2: definite ostophytes and possible narrowing of joint space; Grade 3: multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends; Grade 4: large osteophyte, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends)[79].

In cases of inconsistency in grading between the two evaluators, radiographs were reinvestigated and consensus agreement made.

Radiographic classification of OA remains the reference standard, and the original Kellgren and Lawrence classification is the most widely used instrument to set the diagnosis of radiological OA ($\geq$ grade 2) in epidemiological and clinical settings[133]. Accordingly, OA was

defined as Kellgren and Lawrence ≥ grade 2 in the present thesis. Analyses were based upon between-group comparisons and between the involved knee and the uninvolved knee in the subjects.

Auxiliary outcome measurements (Paper I and II)

Based on reviews of the medical charts and personal interviews with all patients at follow-up, reliable data on any subsequent surgeries or reoperations during the follow-up period were available for the subjects included in paper I and II.

3.4   Statistical analyses

All statistical analyses were performed in IBM® SPSS® (Statistical Package of Social Sciences) software version 20.0 in paper I, version 22.0 in paper II, and version 24.0 in paper III and IV. The assumption of normally distributed data was checked by visual inspection of frequency distributions (histograms) and Q-Q plots in paper I and II, and by Q-Q plots and residual plots in paper III and IV. Depending on what was considered most adequate, descriptive data was presented as frequencies, as ratios, as percentages, mean and SD, or as median and range. The main results were presented with 95% confidence intervals (CIs). P-values <.05 were considered statistically significant.

3.4.1 Paper I

The sample size calculation was performed using the Altman´s nomogram, with the following assumptions: an intention to detect a difference in Lysholm score of 15 points; a predetermined power of 0.80; a level of significance of 0.05, and a standardized difference of 0.88 (Δ Lysholm score to be detected/expected SD). Accordingly, a sample size of 20 patients in each treatment group was estimated to be sufficient.
Due to the restricted number of included patients, normality was not confirmed.
Consequently, non-parametric statistical hypothesis tests were applied. Between-group

comparisons at follow-up in Lysholm score, KOOS and isokinetic muscle strength deficits were performed using Mann-Whitney *U* test. Changes in Lysholm score and KOOS from baseline to follow-up were compared between the groups using Wilcoxon signed-rank test. Changes is radiographic grading of OA were compared between the groups using Fisher´s exact test.

3.4.2 Paper II

The KOOS QoL subscale is regarded as the most sensitive when evaluating ACL-injured patients and was consequently chosen as the basis for sample size calculations[127]. To detect a change or difference in KOOS QoL of 10 points, given a power of 0.80, a level of significance of 0.05, and a SD of the difference between the two groups of 17.2 which in turn was based on the SD of the between group difference at preoperative[67, 130], 26 pairs of patients were needed at follow-up.

Within-group changes in the different KOOS subscales from baseline to follow-up, as well as between group comparisons regarding mean changes in the KOOS subscales from baseline to follow-up, were assessed using paired samples *t* –test. In cases where both control patients were available at follow-up, the KOOS data were considered as clustered and the average score used in the subsequent analyses[80]. Fisher´s exact test was used to assess the significance of the observed between-group difference in radiographic OA.

3.4.3 Paper III

The crude mean KOOS scores at follow-up were calculated and stratified by patients with concomitant partial-thickness cartilage lesions, by those with full-thickness lesions, and those without any concomitant cartilage lesions. Multivariable linear regression analyses were used to assess the possible effect on prognosis, as measured by the KOOS at 5-year follow-up, of concomitant partial-thickness and full-thickness cartilage lesions.

Initially, the factors of interest (partial-thickness- and full-thickness cartilage lesions) were included as independent variables, and the different KOOS subscales as the dependent variables, in an unadjusted regression analysis.

Next, in an adjusted multivariable regression analysis, possible predictors and confounders of patient-reported outcome, i.e., gender, age at surgery (continuous variable), previous ipsilateral knee surgery (yes/no), concomitant ligament injury (yes/no), concomitant meniscal injury (yes/no), concomitant meniscal resection (yes/no), time from injury to surgery (continuous variable), and type of ACL graft (hamstring, patellar tendon, or other), were included in the regression model together with the factors of interest as independent variables, and the different KOOS subscale scores as the dependent variables. Thus, patients with no cartilage lesions served as the reference category for the effect of partial-thickness and full-thickness cartilage lesions.

Lastly, to determine whether concomitant cartilage lesion size (>2 cm^2) was a predictor of KOOS scores 5 years after ACLR, a separate multivariable regression analysis were performed for the subset of patients with partial-thickness and full-thickness cartilage lesions. The factor of interest (lesion size >2 cm^2) was included as an independent variable together with possible predictors and confounders of patient-reported outcome, similar to the initial adjusted regression model, and each of the KOOS subscale scores as the dependent variable. Thus, patients with partial-thickness cartilage lesions ≤ 2cm^2 and patients with full-thickness cartilage lesions ≤ 2cm^2, respectively, served as the reference category for the effect of cartilage lesion size >2cm^2.

3.4.4 Paper IV

Crude mean KOOS scores at preoperative and at the 5-year follow-up were calculated and stratified by treatment of the concomitant cartilage lesions, i.e., no treatment, debridement and MF. Multivariable linear regression analyses were used to assess the possible effect on KOOS at the 5-year follow-up of surgical debridement or MF for concomitant full-thickness cartilage lesions.

In an unadjusted regression analysis, the surgical treatment of the cartilage lesions (debridement or MF) was used as the independent variable, and the different KOOS subscales scores as the dependent variable.

51

In the adjusted multivariable regression analyses, the treatment variable was included together with possible predictors and confounders of patient-reported outcome, i.e., gender, age at surgery, previous ipsilateral knee surgery, concomitant ligament injury, concomitant meniscal injury, concomitant meniscal resection, time from injury to surgery, area of cartilage lesion ($\leq 2cm^2$ or >2 cm^2), depth of cartilage lesion (ICRS grade 3 or 4), location of cartilage lesion (patella, trochlea, medial femoral condyle, lateral femoral condyle, medial tibial plateau, or lateral tibial plateau), type of ACL graft, and preoperative KOOS. Thus, patients that had not received any surgical treatment to their concomitant full-thickness cartilage lesion, served as the reference category for the effect of debridement or MF.

3.5 Ethics

In paper I, inclusion was based on an informed, written consent. Based on what was known at the time of the initiation of the study, all patients were given information regarding the diagnosis, the different treatment options, the spectrum of possible complications, the postoperative rehabilitation program, the need for supplementary follow-up with radiographic examinations and the expected prognosis following surgery or conservative treatment. Both treatment options were well documented at the time of initiation of the study, but no direct comparisons between the two techniques had been performed. Based on the knowledge at that time, there was no reason to suspect major differences in the outcome or complication rates. Patients that did not want to participate were offered the standard treatment, according to the respective institutions´ procedures. At follow-up, all patients were again asked to give their written consent, based on the extensive time expenditure to complete all additional examinations, i.e., radiographic examination, functional testing, follow-up session with the orthopaedic surgeon and completion of different patient-based questionnaires. The regional ethical committee of South Eastern Norway raised no ethical concerns; approval ID 155-00066/April 2000.

In paper II-IV, data were collected from the NKLR and SKLR and can be regarded as observational studies. Accordingly, inclusion into the studies does, by definition, not alter treatment, rehabilitation or prognosis. In paper III-IV, data from both NKLR and SKLR were used. The NKLR is approved as a national health registry by the Norwegian Data

Inspectorate. Moreover, at the time of ACLR, the patients are asked to participate in the collection of data, and if approved, they sign an informed consent form allowing for the data assembly at baseline and at 2-, 5-, and 10-year follow-up, and for the later use of these data for scientific purposes. The SKLR has no written consent form, but the registration of data is voluntary and the processing of data is protected by the Personal Data Act of Sweden. Provided patient approval, the KOOS data are completed using a web-based portal. In the current thesis, all data from the SKLR and the NKLR were made non-identifiable to all members of the research team. The regional ethical committee of South Eastern Norway raised no ethical concerns regarding paper III and IV; approval ID 2017/122.

In paper II, only data from the NKLR was used. However, additional outcome measurements were applied at follow-up, i.e., radiographic examination and additional patient-based questionnaires, as well as additional follow-up sessions with the orthopeadic surgeon. Accordingly, the patients were asked to participate, and if approved, asked to give a written consent. No ethical concerns came into view, as participation did not involve change of treatment, risk of complications or prognosis. The regional ethical committee of South Eastern Norway raised no ethical concerns; approval ID 2013/180b.

4 Summary of results

4.1 Paper I

Lysholm score and KOOS were available for all patients (25/25) at a median follow-up of 9.8 (range 4.9-11.4) years. Patients in both treatment groups reported significant improvements during follow-up. Lysholm score improved from a mean baseline score of 48.2 (95% CI, 38.2-58.2) to 69.7 (95% CI, 55.1-84.4) for MF-treated patients, while patients in the OAT mosaicplasty group improved from a mean baseline score of 49.2 (95% CI, 43.0-55.4) to 62.6 (95% CI, 52.6-72.6) at follow-up. The corresponding mean changes in Lysholm scores over time were 21.6 (95% CI, 3.7-39.4) and 13.4 (95% CI, 0.9-25.8), respectively. The between group differences in Lysholm score at follow-up and change over time were not statistically significant.

Except from in ADL, MF-treated patients reported statistically significant improvements over time in all KOOS subscales. Patients in the OAT mosaicplasty group reported significant improvements in the subscales of Sport/Rec and QoL. When comparing the change over time between the two treatment groups, no statistically significant differences were identified for any of the KOOS subscales.

Isokinetic muscle strength measurements (n = 22) revealed a statistically significant extension weakness of the affected leg of 17.6% (95% CI, 8.9-226.3), as compared to the non-injured leg, in the OAT mosaicplasty group, but no statistically significant between-group differences in muscle strength deficits were detected at follow-up.

The median Tegner activity score (n = 25) improved from 3 (range 0-4) in the MF group, and 2.5 (range 0-4) in the OAT mosaicplasty group, to 4 (range 0-9) and 3.5 (range 0-5) at follow-up, respectively.

Radiographic examination (n = 23) revealed OA (Kellgren and Lawrence $\geq$ grade 2) of the affected knee in 5 out of 11 patients in the MF group, and 2 out 12 patients in the OAT mosaicplasty group at follow-up (p = 0.193). OA of the unaffected knee was evident in 3/11 and 1/12 knees, respectively.

Reoperations, or further procedures during follow-up occurred in 6/11 (54%) patients in the MF group, and in 5/14 (36%) patients in the OAT mosaicplasty group.

4.2 Paper II

At preoperative, there were no significant differences in KOOS between patients in the study group (ACL-injury and concomitant full-thickness cartilage lesion) and patients in the control group (ACL-injury only). At the 6.3 (range 4.9-9.1) year follow-up, the study patients (n = 29) reported lower scores in all KOOS subscales compared to the control patients (n = 45), with mean between-group differences ranging from -2.6 (95% CI, -10.7 to5.5) in ADL, to -6.3 (95% CI, -21.2 to 8.6) in Sport/Rec. However, none of the observed between-group differences in KOOS scores at follow-up were statistically significant. Correspondingly, when comparing the change over time between the two groups, no statistically significant differences were detected.

Both groups reported significant improvements in KOOS scores at follow-up, the most prominent being observed in QoL with a mean change over time of 31.8 (95% CI, 21.3 to

42.3) and 33.7 (95% CI, 23.6 to 43.8) in the study group and the control group, respectively. The control group, however, reported significant improvement in all KOOS subscales, while patients in the study group did not report significant improvement in the KOOS subscales of Symptoms and ADL, with a mean change over time of 4.7 (95%CI, -3.3 to 12.7) and 5.7 (95% CI, -1.0 to 12.5), respectively.

At a median follow-up of 8.2 (range 6.4-9.8) years, and 8.4 (range 6.7-9.8) years, respectively, 19 patients from the study group and 22 patients from the control group were available for radiographic OA assessment. Radiographic OA (Kellgren and Lawrence ≥ grade 2) of the affected knee was a significant more frequent finding in the control group (12 out of 19 patients) than in the study group (21 out of 22 patients) ($p = 0.016$). The corresponding numbers for the contralateral, unaffected knee were 5 out of 19 and 9 out of 21, respectively (non-significant difference).

During the follow-up period, 7 (24%) patients in the study group, and 10 (22%) patients in the control group underwent a total of 23 subsequent surgical procedures.

4.3   Paper III

Compared to patients with partial-thickness cartilage lesions, and in particular patients without any cartilage lesions, patients with concomitant full-thickness cartilage lesions reported inferior crude mean KOOS scores at the 5-year follow-up.

Multivariable regression analyses showed that concomitant partial-thickness cartilage lesions were significantly associated with lower scores in all KOOS subscales, except from Pain and ADL: Symptoms (regression coefficient [ß], -1.1; 95% CI, -2.1 to -0.1), Sport/Rec (ß, -1.8; 95% CI, -3.2 to -0.3), and QoL (ß, -1.5; 95% CI, -2.8 to -0.1)

Full-thickness cartilage lesions were significantly associated with lower scores in all KOOS subscales: Pain (ß, -6.0; 95% CI, -7.5 to -4.5), Symptoms (ß, -6.5; 95% CI, -8.2 to -4.9), ADL (ß, -4.6; 95% CI, -5.9 to -3.3), Sport/Rec (ß, -8.1; 95% CI, -10.5 to -5.7), and QoL (ß, -8.0; 95% CI, -10.2 to -5.7)

Multivariable regression analyses showed that lesion size ($\geq 2cm^2$) was significantly associated with lower KOOS at follow-up for patients with partial-thickness cartilage lesions, while no associations between lesion size and KOOS were detected in patients with full-thickness cartilage lesions.

4.4   Paper IV

Compared with patients receiving no treatment of their concomitant full-thickness cartilage lesions, those treated with debridement reported higher crude mean KOOS scores, and those treated with MF reported lower crude mean scores, at the 5-year follow-up.

In the multivariable regression analyses, neither debridement nor MF showed significant associations with any of the KOOS subscales scores at follow-up. There were, however, based on the regression coefficients and the accompanying CI´s, a trend in both the unadjusted and adjusted analyses towards negative effects of MF in the subscales of Sport/Rec (ß, -5.0; 95% CI, -12.3 to 2.2) and QoL (ß, -5.7; 95% CI, -12.5 to 1.1).

5   Discussion

5.1   Materials and methods; methodological considerations

5.1.1 Study design and study population

Paper I

Paper I was designed as an intervention study. The two surgical interventions were compared by being randomly allocated to the participants. The randomized controlled trial (RCT) design is considered to be the gold standard for evaluating health care interventions in clinical and epidemiological research. The control group is often defined as individuals assigned to receive a placebo treatment, standard practice or no intervention[104]. In paper I, MF was considered as standard practice, or reference treatment, due to the fact that it is the most commonly performed cartilage procedure[49].

The main advantage of the RCT design is that by randomly allocating the study participants into the intervention groups, systematic between-group differences are prevented (other than

the interventions under study). In theory, by randomization, both known and unknown prognostic factors are to be evenly distributed between the intervention groups, and selection and confounding biases avoided. Hence, properly designed and conducted RCTs are considered to have high internal validity. In practice, however, during the design and conduct of a RCT, several possible methodological pitfalls might introduce bias. According to the Consolidated Standards of Reporting Trials (CONSORT) statement, which was developed to assess the quality of reporting of two-group parallel RCT designs, there are four internal validity design criteria: the randomization process, blinding of participants/assessors, comparable groups, and handling of withdrawals or dropouts in the data analyses[2].

A successful randomization depends on the generation of an unpredictable allocation sequence, and the concealment of that sequence until assignment occurs (allocation concealment)[135]. In general, simple randomization, analogous to repeated coin tossing, secures adequate unpredictability to group assignment. On the other hand, and especially in smaller RCTs, it may generate imbalance in the number of patients allocated to the intervention groups. Consequently, to achieve balance in the intervention groups, restricted randomization can be used. The most frequently used method is "blocking", e.g., after a block of every 10 participants is assigned, 5 would be allocated to each intervention group. Thus, in paper I, a restricted blocked randomization procedure was used to control the randomization as to achieve balance between groups in size. The restricted shuffled approach used in paper I is based on the apportioning of 5 prepared cards for each treatment (block size 10, allocation ratio 1:1), inserting those 10 cards into envelopes which are the shuffled, and thereby generating blocks of 10 sequentially numbered sealed envelopes to randomly assign treatment. The restricted shuffled approach is considered to adequately generate unpredictable allocation and allocation concealment[135]. However, due to the restricted rate of inclusion into the study, the sample size requirements were not fulfilled (20 patients in each intervention group). Consequently, not all envelopes were used, resulting in a sample size imbalance in the intervention groups. Using smaller block sizes could have reduced that imbalance. However, reducing the block sizes comes at the cost of reducing the unpredictability and concealment of the sequence. Although the order of interventions varies randomly within each block, small block sizes make it easier for the investigator to deduce the next treatment allocations. According to the CONSORT statement, there is strong empirical evidence that studies with

inadequate allocation concealment tend to overestimate treatment effects with as much as 30% to 40% compared to adequately designed trials[2].

Ideally, the study participants, the health care providers, and those collecting and analyzing the clinical data should be unaware of the assigned intervention. This procedure of "blinding" to treatment is considered important to prevent bias at several steps of a RCT. Blinding of patients was not an option in paper I as one of the interventions was performed by arthrotomy (OAT mosaicplasty), and the other was performed arthroscopically (MF) (large versus small incisions, respectively). Therefore, due to the possibility of varying expectations and assumptions, knowledge of group assignment might have influenced the response to treatment. To avoid observer bias, the assessors should be blinded to group assignment, i.e., the observer´s outcome assessment is influenced by the knowledge of which treatment was given. In paper I, two physiotherapists, both blinded to intervention assignment, performed the muscle strength measurements (concealed surgical cicatrix), and two independent assessors, both blinded to group assignment performed the assessment of radiographic OA. However, evaluation of patient reported outcomes (Lysholm score and KOOS), as well as data analyses were performed by unblinded assessors.

The study design and primary analysis was based on "intention-to-treat", that is, data were handled according to the original group assignment regardless of any subsequent events, e.g., additional cartilage surgeries (1 patient originally assigned to MF was subsequently treated with OAT mosaicplasty, and 2 patients with ACI). The intention-to-treat design is generally advised as it avoids bias related to non-random loss of participants[2].

When conducting clinical studies, the final study population is inevitable only a fraction of the larger, general population, for which the results and conclusions are meant to apply. The RCT design, if properly planned and conducted, affords studies with high internal validity. The external validity, or to what degree the study findings can be extrapolated to the population at large, however, varies. Systematic errors may be hidden in the process of sampling study participants and in factors influencing individual participation, ultimately resulting in what is called selection bias. Randomization of the participants into allocated interventions largely prevents selection bias. However, selection bias and external validity is related. Even though randomization protects against selection bias, it does not necessarily provide external validity. It is known that knee cartilage patients enrolled in RCTs are not representative of patients in general orthopaedic practice[41]. Both inclusion and exclusion criteria and source of recruitment

might shape the selection of study participants, as is the case in the present RCT as well. Patients were recruited from three large academic institutions with relatively high-volume of cartilage patients, and with surgeons specialized to perform these interventions. Hence, one cannot rule out that the source of recruitment does not represent standard orthopaedic practice. Moreover, the inclusion and exclusion criteria, to a large extent, narrows down the spectrum of cartilage injured patients. If available, the number of persons assessed for eligibility should be reported. It is a useful indicator of whether trial participants were likely to be representative of all eligible participants[2]. In paper I, 19 patients that initially were found eligible, were later found not to fulfill the study criteria. Considering a total sample size of 25, this elucidates the issue of external validity.

Papers II-IV

Papers II-IV in the current thesis were based on registry data. Registry data is widely used in many fields of medical research, and has increasingly been used in orthopaedic research since the development over the last decades of national arthroplasty-, and knee ligament registries in the Scandinavian countries. While RCTs provide valuable information on the effect of interventions, one important advantage of registry data is that it allows for the conduction of relatively large cohort studies, which in turn is considered to be appropriate in wide range of research settings, e.g., epidemiological research, exploring exposure-outcome associations or the natural history of disease[157].

The prospectively registered data from the NKLR and the SKLR make up the basis for the observational study design used in papers II-IV. It is shown that the patient characteristics are similar across the Scandinavian registries, and in comparison to the Luxembourg ligament registry, the UK national ligament registry and the US Kaiser Permanente registry[120] However, time from injury to surgery was longer (>6 months), and allograft was used considerably less in the Scandinavian and other European cohorts (≤1%) compared with in the US cohort (39.9%)[120].

In paper II and III the research question was strictly epidemiological by exploring the prognosis following ACLR combined with articular cartilage injury. In study IV, the observational study design was applied to explore the outcome after surgical treatment of concomitant cartilage lesions in the setting of ACLR. The application of observational design to explore the effectiveness of interventions, however, is not considered to be optimal as it

raises some interpretational difficulties related to causal inference and confounding, as will be discussed further in later segments of the current thesis. On the contrary, as opposed to a RCT design, the use of registry data is often less time consuming, less costly and, at least in the case of nationwide sampling; more representative of the population at large, and current clinical practice. This is especially relevant when the condition of interest is relatively rare, as is the case for concomitant full-thickness cartilage lesions. It has formerly been shown that knee cartilage patients enrolled in RCTs are not representative of patients in general orthopaedic practice[41].

Several methodological considerations should be taken into account when designing cohort studies. It is generally advised to follow the Strengthening the Reporting of Observational studies in epidemiology (STROBE) statement[157]. In doing so, important quality items such as selection of patients, manner of assessing exposures and outcomes and adequacy in control of confounding, are emphasized. The reporting of paper III and paper IV are performed in accordance with the STROBE statement checklist, but further elaborations are given in the following sections.

Papers II-IV are all prospective cohort studies, in which the participants are identified, exposed or non-exposed to one or several (prognostic) factors, and followed over time to evaluate the subsequent development of outcomes. What distinguishes the methodology in paper IV is that the exposures of interest are specific investigator-defined interventions (cartilage surgery) for the exposed group.

Special attention should be given to prevent or control confounding in cohort studies[157]. In confounding, the effect of the exposure of interest is, partly or wholly, mixed with the effect of another variable[73]. This other factor is called the confounding factor or confounder. A study might seem to show associations between an exposure and the risk of an outcome. In reality, the seeming association is due to the confounder, which determines the outcome but is also associated with the exposure[73]. Confounding can thus result in erroneous causal inference, i.e., a wrong assessment of the potential causal association of an exposure[157]. As confounding can mask the real effect, it needs to be prevented or subsequently corrected for. Like most types of bias, confounding can, at least to a certain degree, be prevented by proper study design. Most effectively, this is done by randomization. As randomization is not an option in cohort studies, other means of prevention can be utilized. Restriction can be used to minimize confounding, e.g., restriction by age. However, by applying many restrictions, the

external validity of the study may decrease. Hence, as the desired population sample in paper III and IV was nationwide, few restrictions were applied.

In paper II, however, quite strict restrictions were applied when sampling the exposed group. Moreover, matching was performed. By matching in pairs for potential confounders, the exposed and the unexposed group will be less likely to have differences in the distribution of known confounding factors.

In paper III and IV, the approach for controlling confounding was primarily based on statistical procedures adjusting for it, after study completion. In general this can be achieved by stratification and multivariable analyses[73], which will be discussed in later sections. By relaying on adjusting for confounding at this later stage, it is important to emphasize that this can only be performed if information on the confounding factors has been assembled during the study conduct. Hence, a priori assessments of possible confounding factors are important to adequately design cohort studies.

The process of selecting study participants is key in observational study designs. The recruitment sources and study criteria shapes this selection. As formerly mentioned, studies on cartilage injuries are often based on non-representative population samples. One of the major advantages of using data obtained from national registries is that it ensures representation from a wide spectrum of hospitals, patients, and surgeons. In paper III and IV, patients were included without restrictive inclusion or exclusion criteria. Considering that the NKLR and the SKLR are nationwide population-based registries with satisfying reporting rates[53, 165], this should contribute to representative study populations and sufficient external validity. In paper II, as mentioned before, measures were taken to avoid confounding. However, those measures, i.e., the strict inclusion and exclusion criteria and the strict matching of groups, most likely came with the cost of low external validity, and the possibility of selection bias. In order to address this issue, related research questions were subsequently applied in paper III, in which a large population based cohort made up the basis for the investigations.

In paper IV, as in paper I, the focus of interest was the medium- to long-term effect of surgical treatment of cartilage lesions. By including all patients with full-thickness cartilage lesions registered in the two national registries as having received MF, debridement, or no treatment, without restrictions other than a complete data set, some of the methodological and interpretational drawbacks related to a selected study population from paper I was avoided.

5.1.2 Classification of cartilage lesions

Both the choice of treatment in the clinical setting, and whether patients are to be included in studies, relies on the classification of the cartilage lesion. Despite several decades of extensive research efforts on the topic of cartilage injuries, no consensus exists when it comes to choosing a classification system, neither in the clinical setting, nor in research settings. Even though there are more than fifty articular cartilage injury measurement systems described in the literature, the Outerbridge and ICRS classification systems are the two most widely used when it comes to focal cartilage lesions in the knee[111].

Historically, the classification system introduced by Outerbridge[116] in 1961 has been the most widely used descriptive tool. It was originally designed to describe lesions of the patella, and not for arthroscopic use. This system divides the cartilage lesions into 4 grades (grades I trough IV), and has been found to be accurate and reliable [19]. However, Outerbridge grades II and III do not include a description of the lesion depth.

At the time of the initiation of studies II-IV, no formal validation study of the use of the ICRS classification system had been undertaken. Nevertheless, its use was recommended by the ICRS, and also applied by the two Scandinavian knee ligament registries. Recently, in a study by Dwyer et al.[36], good inter- and intraobserver reliability, as well as a high correlation with histological assessment of lesion depth was reported for the ICRS classification system. However, as in all research making use of classification, there is an inherent risk that the assessor misclassifies. Such misclassifications, e.g., classifying a cartilage lesion as ICRS grade II when in reality it is an ICRS grade III lesion, might lead to what is called misclassification bias. To what extent this might be the case in the Scandinavian registries, and if so, made by random error, or by systematic misclassification, is not known. It is reason to believe, however, that due to the findings in the formerly mentioned ICRS-validation study, the issue of misclassification bias is not a significant source of bias in papers I-IV. The dichotomization of lesion size into $\leq 2cm^2$ or $>2cm^2$ in paper II-IV, implies that some information regarding lesion size is lost, and makes more nuanced subgroup analyses difficult. Moreover, arthroscopic evaluation of lesion size is shown to be less than perfect, but provide estimates of lesion size with errors less than 25%[167]. Even though not perfect, a widely accepted universal classification system would have eased the process of comparing the findings from different studies around the world.

5.1.3 Outcome measurements

Patient-reported outcome was the main outcome measure in all papers. Lysholm score was chosen as the main outcome measure in paper I to allow for comparison with concurrent and older literature, given the wide use of the score. The rating at follow-up was patient-administered, but included a subsequent review with the orthopaedic surgeon. Even though adequate psychometric properties have been demonstrated for the Lysholm score, it is largely based on surgeon administration[23]. However, patient administration has shown not to differ from professional rating[140], and additional outcome measures were included to support the conclusions to be drawn. Additional outcome measures were also included in paper II.

It would have been beneficial to include additional outcome measures in paper III and IV as well, most importantly measures of OA development. OA, as discussed in former sections of the current thesis, and shown in paper II, is associated with both ACL-injury and cartilage lesions. Since OA most likely is on the causal pathway between the exposure (s) and the outcome, it is not considered to be a confounding variable, but an effect modifier. Information on such effect modifiers is important when interpreting the results. However, in studies with sample sizes as in papers III and IV, the costs and time expenditure would have been substantial. Moreover, to recruit patients to perform radiographic examination is difficult, and could have led to further decline in the response rates.

Upon the decision to use registry data as the basis for papers II-IV, and considering that KOOS is the only PROM used in common by the Scandinavian registries, KOOS became the natural first choice. Even though the KOOS is considered to be a valid, reliable and responsive outcome measure for patients with ACL injury[23, 126, 127], and patients with cartilage lesions[6, 23, 38], it will always be a matter for discussion whether other PROMs would have been better to monitor the outcome after surgery. There are, however, no PROM designed to specifically address the combined injury of an ACL tear and a cartilage lesion. In a systematic review by Wang et al., evaluating the psychometric performance of different knee-specific PROMs, KOOS and Lysholm scale were the only to be recommended for both ACL-injury and cartilage lesions[160]. Interpretational difficulties inevitably occur when trying to measure the effect of each separate injury by one instrument. Theoretically, the effect of one injury could mask, or exaggerate the effect of the other at different time points of follow-up. Others have raised the question if KOOS is suboptimal in discriminating differences in patients who

have undergone ACLR with concomitant injuries[59]. These interpretational difficulties are, at least by part, overcome by including control patients without such combined injuries, and by using longitudinal data. The cohort in paper II is in addition to the 5-9 year follow-up included in the present thesis, followed closely with KOOS measurements at preoperative[67], and at 2-years after ACLR[130]. Correspondingly, the cohorts in paper III and IV have, in addition to the present 5-year follow-ups, been assessed at 2 years after ACLR[128, 129].

The use of individual scores for each KOOS subscale, rather than an aggregate score, is recommended in both clinical and research settings. It enhances and acknowledges the impact of different interventions on different dimensions, e.g., the sport/ recreation subscale is more important in patients with a high physical activity level, while the ADL subscale is more important in subjects with a lower physical activity level[23]. In line with previous studies, the subscales of Sport/Rec and QoL are probably the most responsive when examining the outcome after ACLR in knees with a concomitant cartilage lesion[23, 125, 128, 129].

The minimum detectable change (MDC), which is the minimum amount of change in a score that falls outside the measurement error[28], was not calculated for the population samples used in papers II-IV, but has been reported to range across the KOOS subscales from 6 to 12 for various populations with various knee disorders[23]. However, firm conclusions whether the observed changes in KOOS over time in paper II, and the observed between-group differences in paper III and IV, represent values outside measurement error, cannot be made without establishing MDC values for these populations. The MDC for the Lysholm scale has been reported as between 8.9 and 10.1 for knee injuries[23]. None of the observed within-group changes in Lysholm score over time in paper I were below these thresholds, while the observed between-group differences over time were in the range of the reported MDC. Moreover, any statistically significant differences or changes in scores in papers I-IV may not necessarily be clinically relevant or meaningful to the patients. Until recently, the minimal important change (MIC), defined as the smallest change in score considered important by patients[28], has not been established for KOOS in the setting of ACLR or cartilage lesions, or both. Historically, a change in scores of 8-10 points has been regarded as clinically important[125]. However, in a recently published study by Ingelsrud et al.[71], MIC values of 12.1 for Sport/Rec and 18.3 for QoL was detected, while the obtained MIC values for the subscales of Pain, Symptoms, and ADL, were not considered valid. In paper III and IV, the observed values for change over time for these two sub-scores were over above those MIC thresholds,

whereas the between group differences were below. The relevance of these MIC values, however, is limited when interpreting the findings in the current thesis (papers II-IV), the reasons being: a) the estimates for interpretation of meaningful improvement in KOOS scores after ACLR were applicable for follow-up periods limited to 24 months only, and b) the authors were not able to recommend estimates for interpretation of difference in mean change scores between groups of patients[71].

MIC values for the Lysholm score has not been established for any patient population[23], but a pragmatic value of 10 points have been used[12, 145].

The classification of OA (Kellgren and Lawrence) used in paper I and II, has been criticized for its low reproducibility, and for the many alternative versions of scoring criteria. However, it is shown that by using the original version, and by applying grade 2 as the cut-off point for OA, it is a useful tool to distinguish patients with- and without radiological OA[134]. Even though no objective measure of agreement was obtained, at least two independent assessors scored the radiographs in paper I and II.

5.1.4 Statistical analyses

Due to the restricted number of included patients in paper I, non-parametric statistical hypothesis tests were applied (Mann-Whitney U test, Wilcoxon signed-rank test, and Fisher´s exact test). There is always a possibility that by performing other statistical analyses, e.g., multiple regression analyses for the numerical main outcome (Lysholm score) and logistic regression for the binary secondary outcome (OA), we would have been able to detect between-group differences that were not evident with the aforementioned statistical methods. Moreover, despite adequate randomization procedures, the risk of generating imbalance in baseline variables between the treatment groups is always larger in small sample RCTs. On the other hand, adjustment for imbalance in covariates measured at baseline is only recommended if there is clear a priori evidence of variables strongly related to the outcome[81]. The differences in baseline characteristics of the study groups in paper I was considered minor, and variations in covariates with a priori evidence of relation to outcome (e.g., lesion depth and lesion size) were narrowed down by adherence to the inclusion- and exclusion criteria. Moreover, no loss to follow-up, no loss of adherence to treatment as allocated, and no

exclusions from the main analyses indicate trustworthy estimation of treatment effect, even with simple and unadjusted statistical methods.

Papers II-IV were prospective cohort studies. As mentioned in the materials and methods section, special attention should be given to avoid confounding in cohort studies. In paper II, this was mainly addressed by applying quite strict restrictions when sampling the exposed group, and by matching. By applying restrictions and by matching in pairs for potential confounders, the exposed and the unexposed group will be less likely to have differences in the distribution of known confounding factors, but we can never rule out residual confounding. Residual confounding, i.e., unknown factors that might have an effect on the outcome that is not controlled for, is relevant for the regression analyses made in paper III and IV as well. Since there are no standardized or validated sets of possible confounding variables considered to be requisite, the judgment on what possible confounding variables to be included in the regression models, had to be based on the current literature and clinical assumptions, but to a certain degree restricted by the panorama of parameters that the registries actually record.

In paper III, adjustments for the variables of preoperative KOOS and treatment of the cartilage lesions, were not performed. The reason being that they were considered as variables on the causal pathway between the exposure (cartilage lesion) and the outcome (KOOS at 5-year follow-up). Hence, adjusting for both variables could result in an underestimation of the effect of cartilage lesions and transfer the regression model to focus more on the effect of ACLR.

5.2 Discussion of main results

5.2.1 Prognosis

Medium to long-term prognosis, with focus on PROMs, was investigated in paper II and paper III. The main finding in paper II was that, 5-9 years after ACLR, patients with concomitant full-thickness cartilage lesions reported similar PROMs compared with patients without such concomitant lesions. In paper III, however, patients with concomitant cartilage

lesions (both partial-thickness and full-thickness) reported statistically significant inferior PROMs to patients without such concomitant lesions at 5-year follow-up after ACLR.

The results and conclusions in paper II and paper III can appear to be contradictory, but it is important to recognize that the population sample in paper II was only a small and selected fraction (29 ACLR study patients with concomitant full-thickness cartilage lesions, and 45 control patients with ACLR only) of the large population-based sample in paper III (563 ACLR patients with concomitant full-thickness cartilage lesions, and 6222 control patients with ACLR only). The exact reason(s) for the apparently contradictory findings is difficult to state, but there is reason to believe that the selection of study patients in paper II, which was based on quite strict inclusion criteria, may have resulted in a study cohort not directly comparable to the larger, less-restricted sampling of cohort patients in paper III. This notion is supported by the fact that study patients in paper II tended to have better mean KOOS scores at baseline, than patients with concomitant full-thickness lesions in the larger population-based cohort in paper III (ranging from a mean difference of 2.4 in QoL, to 5.4 in Symptoms). Moreover, differences in other baseline characteristics, such as time from injury to ACLR, differed substantially with mean 5.5 months versus median 18 months, respectively. As such, it is possible that the study patients in paper II represent a more active cohort, with higher knee demands.

Correspondingly, the selection of strictly matched control patients in paper II, may have led to a reference group not directly comparable to the controls in the larger cohort in paper III. Given the knowledge that KOOS differed significantly in favor of control patients in the short term evaluation of the cohort[130](median 2.1 years) in paper II, the observed convergence in KOOS scores over time certainly must have occurred after the first evaluation and up to the present 5–9-year follow-up. That convergence in KOOS scores can largely be explained by a slight deterioration of outcomes for control patients, and a continued improvement for the study patients. As outlined in paper II, a decrease in the mean between-group difference was observed in all KOOS subscales from the 2.1-year follow-up to the present 5–9-year follow-up. Whether that deterioration in KOOS for the control patients can be attributed to the significantly higher proportion of control patients developing OA at the latest follow-up, is difficult to decide, but nevertheless a clinically plausible explanation. In any case, previous literature generally does not support the finding that patients without concomitant cartilage lesions more frequently develop OA[75, 78, 88, 106]. The exact reason(s) for control patients to

more frequently develop OA at 5-9 years after ACLR is hard to decide, but is yet another indication that the measures taken to control confounding (restriction and matching) may have come with the cost of decreasing the external validity of the study. Nonetheless, it shows that, at least for a selected sub-population of patients, the outcome following ACLR in knees with concomitant cartilage lesions is not necessarily attributable to an unproportional development of OA. Moreover, it exemplifies the importance of including radiographic examinations in long-term follow-up studies investigating this subject matter.

Even though statistically significant, the observed negative effects on KOOS of concomitant partial-thickness lesions in paper III were small, and likely without major clinical significance. However, it indicates a dose-response relationship as increasing severity (ICRS) of the cartilage lesions resulted in lower KOOS scores. Another important finding in paper III was that more pronounced negative effects of concomitant cartilage lesions were found in the present 5-year follow-up than in the 2-year follow-up[128] of the cohort. That observation indicates a divergence in PROMs over time, in favor of patients without concomitant cartilage lesions.

The notion that the findings in paper III is more attributable to the population at large is supported by the findings in several recent high-level studies, in which concomitant full-thickness cartilage lesion are shown to negatively affect the medium to long-term outcome after ACLR. Shelbourne et al., in a large prospective cohort study with >10-year follow-up, showed that patients who had articular cartilage damage had statistically significantly lower subjective scores if they also had less than normal range of motion[138]; Cox et al., in a recent comprehensive level 1 cohort study of 1512 ACL- reconstructed patients with 6-year follow-up, showed that concomitant cartilage lesions (Outerbridge grades 3 and 4) were significant predictors of inferior KOOS and International Knee Documentation Committee (IKDC) scores[24]; Spindler et al., in a Multicenter Orthopaedic Outcomes Network (MOON) prospective cohort, identified concomitant lesions of varying intraarticular locations and Outerbridge grades to be significant predictors of worse IKDC, KOOS QoL, and KOOS Sport/Rec outcomes, 10 years after ACLR; Senorski et al.[60], in a 10-year risk factor analysis from the SKLR, reported that the presence of a concomitant cartilage lesion resulted in decreased KOOS Symptoms, Sport/Rec, QoL, and $KOOS_4$ (a composite score of all subscales except ADL) with odds ratio 0.64-0.80 for every 2-step increase in ICRS grade; and Risberg et al., in a prospective cohort study of 168 patients available for a 20 year follow-up, showed

that patients with combined injuries (ACLR and concomitant meniscal or cartilage injury of ICRS grade 3 or 4) reported significantly worse outcomes for all KOOS subscales, except for QoL[122]. In contrast, others have found no such associations[4, 139, 162]. There are, however, considerable heterogeneity in patients, injuries, surgical factors, outcome measurements, and length of follow-up, making it difficult to directly compare the findings from the different studies.

In the case of paper III and paper IV, the information on additional possible confounders, or effect modifiers, such as body mass index, activity level, and type of postoperative rehabilitation, was not available. These factors, together with other, unknown factors, could be a potential source of confounding, or at least be a source of modification of the measured effects. The main limitation of paper III, however, is the magnitude of loss to follow-up, and is discussed in later sections.

However, in line with the findings in paper III, and in light of the steadily increasing number of high quality studies assessing the medium to long-term effects on prognosis of concomitant full-thickness cartilage lesions, the body of evidence points towards negative effects, in terms of PROMs, of such lesions. This notion is also supported in a recent systematic review on this subject matter[42]. It must be noted, however, that the vast majority of studies are observational in design. Since associations found in observational studies do not necessarily imply causation, caution is needed when drawing conclusions. What paper III specifically adds in this context, in addition to replication of results, is to establish temporal relationship (i.e., longitudinal study design with data collection and coherent findings at several time points), and a coherent pattern of dose-response relationship (patients with no concomitant lesions vs. patients with partial thickness lesions vs. patients with full-thickness lesions), all indicators of causal inference.

In the clinical setting, the information provided by paper II and III regarding the medium to long-term prognosis for patients with this combined injury could be applied in the counseling and the information given to these patients.

5.2.2 Treatment

With focus on PROMs, medium to long-term effects of surgical treatment of focal full-thickness cartilage lesions were investigated in paper I and in paper IV. The main finding

from paper I was that the long-term outcomes, as measured by PROMs, of MF and OAT mosaicplasty for the treatment of isolated cartilage lesions, did not differ. In paper IV, the main finding was that compared to leaving the concomitant cartilage lesion untreated, neither surgical debridement nor MF showed effect on PROMs at 5-year follow-up.

In paper I, patients in both intervention groups reported statistically significant and clinically relevant improvement in Lysholm score, and in several of the KOOS subscales (except from in ADL for the MF-group, and except for in Pain, Symptoms and ADL for the OAT mosaicplasty-group) at the 9.8-year follow-up. However, no statistically significant between-group differences were detected, neither in PROMs at follow-up, nor in the change in PROMs from baseline to follow-up. These findings indicate that the two interventions do not differ in their ability to improve the patient-reported outcome at long-term. There are, however, two major limitations to that conclusion: first, due to the limited number of included patients, one might falsely affirm the null-hypothesis of no difference between the intervention groups (type II error), secondly, the lack of a non-operatively treated control group, makes any conclusions regarding the actual treatment effect difficult. Moreover, even though significant improvements in PROMs were detected in both intervention groups, the knee function scores were substantially poorer than the respective population-based normative knee function scores. Nevertheless, no patients were lost to follow-up, and the coherence in comparable results among all additional outcome measures (isokinetic muscle strength, radiographic OA, and Tegner activity score) strengthens the conclusion of no difference between the two interventions.

The reoperation rate was high in both intervention groups, 6/11 (54%) in the MF group, and 5/14 (36%) in the OAT mosaicplasty group. Moreover, all patients that underwent a second cartilage repair procedure (*n*=3) or total knee arthroplasty (*n*=1) during follow-up belonged to the MF group. One might argue that this between-group imbalance in adherence to protocol should imply performing an additional per-protocol analysis, but this was never done. Caution should be taken, however, if considering this higher re-operation rate as an indication of higher failure after MF, as the surgeon´s (and patient´s) threshold for undertaking a second cartilage procedure after MF could be different than after OAT mosaicplasty. Nevertheless, the overall high reoperation rates and wide confidence intervals derived from the two data samples indicate diversity in the long-term outcomes among the included

patients. This unpredictability of cartilage surgery is a common finding, regardless of surgical technique[10, 50, 83, 141, 144].

There are few other RCTs comparing the long-term outcome after MF and OAT mosaicplasty for isolated cartilage lesion. Gudas et al.[56], demonstrated significantly better PROMs (ICRS scores), Tegner scores, for OAT mosaicplasty patients (*n*=28) at a mean follow-up of 10.4 years. Moreover, the failure rate (11/29) and proportion of OA (14/29) was higher in the MF group than in the OAT mosaicplasty group (4/28) and (7/28), respectively. Some of the findings in that study are in line with the results from paper I, i.e., the significant improvement over time for both treatment modalities, and the tendency of more reoperations in the MF group. However, direct comparison to the findings in paper I is difficult due to the many differences in population samples and surgical factors, i.e., patients in the Gudas study were sampled from competitive athletes, whereas patients in paper I was sampled from the general population; all surgical procedures in the Gudas study were performed arthroscopically, whereas OAT mosaicplasty was performed by arthrotomy in paper I; small sized lesions $<2cm^2$ were included in the Gudas study, whereas such lesions were excluded in paper I.

Lim et al.[89], randomly assigned 109 patients to receive MF, OAT mosaicplasty, and ACI. At a mean follow-up of 5 years, 25 MF patients, 22 OAT patients, and 18 ACI patients were available for follow-up with Lysholm score and Tegner activity score. In line with the findings in paper I, all three procedures in the Lim study showed improvement over time in PROMs, but no between-group differences were detected. Moreover, the Lim study was probably underpowered as well. In contrast to paper I, the mean Lysholm scores at follow-up for the three groups were approximating the population-based normative values for the Lysholm score.

A recent systematic review and meta-analysis, largely based on the aforementioned studies and paper I, showed that for some outcome measures, i.e., activity level, failure rate and some PROMs, the OAT mosaicplasty might be superior to MF in terms of medium term results, but the authors concluded that the body of evidence was very limited[119]. Moreover, a recent systematic review and meta-analysis by the Cochrane Collaboration[50], also based on the aforementioned studies and paper I, concluded that there is insufficient evidence in the literature to draw conclusions on the relative effects of MF and OAT mosaicplasty, and that both procedures were associated with treatment failure and recurrence of symptoms.

In a recent randomized controlled trial, which was published subsequent to the aforementioned systematic reviews, Solheim et al.[145], with a study design resembling paper I, but with several more follow-up points, up to as much as minimum 15 years, found that mosaicplasty resulted in significantly better Lysholm score at short, medium and long term follow-up. Compared to the results from paper I, analogous Lysholm values for patients belonging to the MF groups are seen at baseline and at the10 year-follow-up in the two RCTs. However, the Lysholm scores at follow-up of the two OAT mosaicplasty groups differ substantially in favor of patients included in the Solheim et al. study (mean 62.6 [SD, 17.3] versus 81 [SD, 16], respectively). Of note is that the mean Lysholm score in the OAT mosaicplasty group at follow-up in paper I was below the threshold for what Solheim et al. classify as "poor result", while this was true only for 4 patients in that study. Both the former and the latter is hard to decipher, as the two studies are surprisingly similar in terms of patient demographics, study criteria, cartilage lesion characteristics, randomization procedures, surgical techniques, and postoperative rehabilitation protocol. However, paper I was a multi-center trial, whereas the other RCT was a single center trial. It is possible that the involvement of more centers and surgeons led to less consistency in the technical performance of the surgical procedure. In turn, as OAT mosaicplasty is considered to be more technically demanding than MF, it is presumptively more sensitive to variation among surgeons, in terms of outcome. Moreover, Solheim et al. reported on a larger sample size, which generally implies more confidence in the analyses. All things considered, and taking into account the long-term follow-up RCT from Gudas et al.[56] and the results from other comparative cohort studies authored by Solheim et al.[141, 142], current evidence points towards advantageous long-term outcome of OAT mosaicplasty compared to MF in the setting of isolated focal cartilage lesions. This is also supported by the findings in a large systematic review and meta-analysis investigating "return to sport" and the KOOS Sport/Rec, where OAT mosaicplasty and ostochondral allograft transplantation showed to be superior to both MF and ACI in a pooled analysis of more than 2500 patients[87].

Still, it is important to emphasize that the findings from paper I are not necessarily generalizable to the patient population in paper IV, and vice versa. The reason being that the outcome after cartilage surgery might be affected by the different setting in which these interventions are performed. Patients in paper I had isolated full-thickness cartilage lesions, i.e., no other intra-articular injuries, while patients included in paper IV had full-thickness

cartilage lesions in combination with ACL-injury/reconstruction. Even though no conclusive knowledge exists regarding any substantial differences in the outcome of cartilage surgery in these two settings, it is reasonable to assume that differences in knee joint biomechanics and biochemistry, i.e., the loss of joint stability associated with an ACL injury (regardless of ACLR or not), and the potential difference in release of factors important for the healing response, might be of importance for the outcome.

The findings in paper IV that the surgical treatment strategy of debridement or MF of concomitant full-thickness cartilage lesions in the setting of ACLR confers no benefit, in terms of PROMs, over nonoperative treatment at 5-year follow-up, could question the indications for performing these procedures. Especially considering the finding of significantly adverse effects on several of the KOOS subscales at the 2-year follow-up of the cohort[129]. Even though not statistically significant, there was a trend in the analyses toward negative effects of MF on the KOOS Sport/Rec and QoL subscales in paper I as well. Moreover, even though a formal sensitivity analysis were not performed, the robustness of the data and the comprehensive multivariable adjustments made in paper IV implies that it is very unlikely that by including more subjects or by performing further adjustments, the regression model would shift to the degree of showing beneficial effects of MF. In line with these findings, a recognition that the results after MF might deteriorate over time, and in some cases beginning only 18 months after surgery, has emerged over the last decade[85, 86, 119, 141, 142]. However, firm knowledge on the reasons for this deterioration is not readily available. The subsequent fibrocartilage formation, with inferior biomechanical and histological characteristics compared to native hyaline articular cartilage, is a plausible explanation[48]. Moreover, MF inevitably disturbs the cartilage-bone unit. This disturbance has been associated with bone overgrowth, which in turn has been associated with postoperative failure after MF[102]. However, none of these variables were available for analyses in papers I-IV. These factors could potentially have been assessed during study conduct, but only by including MRI investigations, or by performing tissue biopsies. To perform such investigations on a nation-wide scale is probably not realistic, but in selected subgroups it would potentially offer further insight into the reasons of success or failure of the different treatments.

As elaborated in former sections of the current thesis, firm conclusion cannot be made on the basis of a single study, and especially not when it is observational in design. The limitations

discussed for paper II and III are largely attributable for paper IV as well. In particular, depending on the use of definitions, large cohort studies are often subject to selection- or attrition bias. This is also the case in paper III and IV, in which the rates of loss to follow-up were substantial: 46% and 43%, respectively. In both studies, the outcome analyses were based on those available for follow-up. Hence, there is a possibility for systematic differences between responders and non-responders, namely selection- or attrition bias. Even though such bias is considered as a larger issue if introduced between study groups[110], it might limit our inference of associations made in paper III and IV. Firm information on what determines the response rate, or what patients will become responders, does not exist, but the results from a validation study of the Danish Knee Ligament Reconstruction Register showed the KOOS scores from non-responders to be comparable to non-responders, thus indicating that registry data could be valid despite a high rate of loss to follow-up[121]

However, in the analyses of baseline characteristics of responders and non-responders, time from injury to surgery in paper IV, and age and gender in paper III and IV, were identified as differentiating factors. In both papers, younger males were more likely to be non-responders. As cartilage surgery tends to be more successful in young patients with fewer long-standing cartilage lesions[29], there is a possibility that those patients lost to follow-up have affected the results. Nevertheless, those factors, together with other factors most likely to have affected the prognosis and outcome after surgery, were adjusted for in the multivariable regression analyses.

There are very few high-level studies reporting on this subject matter. The majority of studies are of low-level evidence, e.g., case series or retrospective case-control studies. In the only RCT, Gudas et al., reported significantly better PROMs (IKDC) at 3-year follow-up for OAT mosaicplasty-treated patients compared to MF or debridement[55]. Moreover, in line with findings in paper IV, no between-group differences in PROMs were detected for MF versus debridement at follow-up. The actual effect, however, of the different surgical treatments are difficult to evaluate as no control group of non-surgically treated patients were included. In fact, to the best of our knowledge, paper I represents the only clinical study where a control group of non-surgically treated patients are included. In a recently published paper by Tirico et al.[154], the research question was if ACLR affect the outcome of osteochondral allograft transplantation (OCA) at 6-year follow-up. In that study a control group of patients with OCA-only (n=62) was compared to patients receiving OCA concomitant to ACLR (n=31),

and PROMs (KOOS, IKDC) and failure rates were not affected by ACLR. These findings support the conclusion from Gudas et al. that OAT mosaicplasty, or in this case OCA, can be a viable and long lasting treatment option for full-thickness cartilage lesions in the setting of ACLR. Contrary to MF, OAT mosaicplasty does not rely on any chondrogenesis or substitutional tissue formation within the lesion. The hyaline-covered osteochondral plus largely fills the lesion as a result of the transplantation alone. Having that said, several possible pitfalls, e.g., symptoms from the donor site, less than optimal placement of the plugs, and failure of the plugs to integrate with the surrounding bone and cartilage, might prevent adequate outcome following OAT mosaicplasty as well.

Even though the results from the longitudinal follow-up of the cohort in paper IV does not support the general use of MF, and probably not debridement as well, in the setting of ACLR, there might be subgroups of patients that could benefit from these surgical procedures. This, however, remains to be proved. Adequately designed studies, with sufficient size and power, that includes control groups were the concomitant cartilage lesion is left surgically untreated, is key if we are to decipher what patients are to be given which treatment.

5.3   Future perspectives

I.   There is a need for adequately designed comparative studies, preferably with a control group where the cartilage lesion(s) are left untreated to establish whether cartilage surgery (of any modality) is superior to natural history or rehabilitation.

II.   There is a general need for further studies with long-term follow-up examining the outcome after sustaining cartilage injury and its subsequent treatment. Special emphasis should be given to monitor the development of OA. Ideally, a cartilage injury registry, similar to NKLR, should be established.

III. The Scandinavian registries allow for unique opportunities to understand and interpret factors that affect patient reported outcome after ACLR. To improve the validity of findings, they should strive to increase the response rate, especially at medium to long-term follow-up.

IV.　Further studies focusing on the specific combination of ACL-injury and cartilage injury are needed to better understand what subgroups of patients can benefit from surgical treatment of their cartilage lesion, and if so, what surgical technique(s) offer the best prognosis in different settings and in different sub-populations.

V.　Follow-up studies of the patients in papers II-IV should be conducted to investigate the long-term effects of concomitant cartilage lesions in the setting of ACLR.

6　General conclusions and clinical implications

I.　The long-term outcome for patients treated with MF or OAT for focal isolated full-thickness cartilage lesions does not differ in terms of PROMs, radiographic OA or activity level. Patients receiving both types of surgery can expect to improve in regards to general knee function, but not to the extent of the normal, uninjured population. A substantial proportion of patients can expect to be in need of subsequent surgery to their knee during the first 10 years following cartilage surgery.

II.　Patients with concomitant full-thickness cartilage lesions, regardless of lesion size, can expect to improve significantly less than patients without such lesions up to 5 years after ACLR. However, for selected patients, resembling the study population in paper II, the additional injury of a concomitant full-thickness cartilage lesion, does not necessarily lead to inferior outcome in terms of PROMs or radiographic OA, compared to patients without such lesion, 5-9 years after ACLR.

III.　The surgical treatment strategy of debridement or MF of concomitant full-thickness cartilage lesions in the setting of ACLR confers no benefit, in terms of PROMs, over nonoperative treatment at 5-year follow-up. Consequently, and considering the formerly proven adverse effects of MF at the 2-year follow up, debridement and

especially MF should be used with caution until future research has identified if there are any subgroups of patients that may benefit from these procedures. Future studies examining this subject matter should include a control group of non-operatively treated patients.

References

1.   Abram SGF, Judge A, Beard DJ, Wilson HA, Price AJ. Temporal trends and regional variation in the rate of arthroscopic knee surgery in England: analysis of over 1.7 million procedures between 1997 and 2017. Has practice changed in response to new evidence? *Br J Sports Med.* 2018.

2.   Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med.* 2001;134(8):663-694.

3.   Aroen A, Heir S, Loken S, Engebretsen L, Reinholt FP. Healing of articular cartilage defects. An experimental study of vascular and minimal vascular microenvironment. *J Orthop Res.* 2006;24(5):1069-1077.

4.   Barenius B, Forssblad M, Engstrom B, Eriksson K. Functional recovery after anterior cruciate ligament reconstruction, a study of health-related quality of life based on the Swedish National Knee Ligament Register. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(4):914-927.

5.   Barenius B, Ponzer S, Shalabi A, Bujak R, Norlen L, Eriksson K. Increased risk of osteoarthritis after anterior cruciate ligament reconstruction: a 14-year follow-up study of a randomized controlled trial. *Am J Sports Med.* 2014;42(5):1049-1057.

6.   Bekkers JE, de Windt TS, Raijmakers NJ, Dhert WJ, Saris DB. Validation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions. *Osteoarthritis Cartilage.* 2009;17(11):1434-1439.

7.   Bekkers JE, Inklaar M, Saris DB. Treatment selection in articular cartilage lesions of the knee: a systematic review. *Am J Sports Med.* 2009;37 Suppl 1:148S-155S.

8.   Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol.* 1988;15(12):1833-1840.

9.   Benthien JP, Behrens P. The treatment of chondral and osteochondral defects of the knee with autologous matrix-induced chondrogenesis (AMIC): method description and recent developments. *Knee Surg Sports Traumatol Arthrosc.* 2011;19(8):1316-1319.

10.   Bentley G, Biant LC, Vijayan S, Macmull S, Skinner JA, Carrington RW. Minimum ten-year results of a prospective randomised study of autologous chondrocyte implantation versus mosaicplasty for symptomatic articular cartilage lesions of the knee. *J Bone Joint Surg Br.* 2012;94(4):504-509.

11.   Bisson LJ, Kluczynski MA, Wind WM, et al. Patient Outcomes After Observation Versus Debridement of Unstable Chondral Lesions During Partial Meniscectomy: The Chondral Lesions And Meniscus Procedures (ChAMP) Randomized Controlled Trial. *J Bone Joint Surg Am.* 2017;99(13):1078-1085.

12. Briggs KK, Lysholm J, Tegner Y, Rodkey WG, Kocher MS, Steadman JR. The reliability, validity, and responsiveness of the Lysholm score and Tegner activity scale for anterior cruciate ligament injuries of the knee: 25 years later. *Am J Sports Med.* 2009;37(5):890-897.

13. Briggs KK, Steadman JR, Hay CJ, Hines SL. Lysholm score and Tegner activity level in individuals with normal knees. *Am J Sports Med.* 2009;37(5):898-901.

14. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med.* 1994;331(14):889-895.

15. Brittberg M PL. Introduction of an articular cartilage classification. *ICRS Newsl 1:5–8.* 1998.

16. Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. *J Bone Joint Surg Am.* 2003;85-A Suppl 2:58-69.

17. Brittberg MP, L. Introduction of an articular cartilage classification. *ICRS Newsl 1:5–8.* 1998.

18. Buckwalter JA, Mankin HJ. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. *Instr Course Lect.* 1998;47:487-504.

19. Cameron ML, Briggs KK, Steadman JR. Reproducibility and reliability of the outerbridge classification for grading chondral lesions of the knee arthroscopically. *Am J Sports Med.* 2003;31(1):83-86.

20. Chalmers PN, Mall NA, Moric M, et al. Does ACL reconstruction alter natural history?: A systematic literature review of long-term outcomes. *J Bone Joint Surg Am.* 2014;96(4):292-300.

21. Chow JC, Hantes ME, Houle JB, Zalavras CG. Arthroscopic autogenous osteochondral transplantation for treating knee cartilage defects: a 2- to 5-year follow-up study. *Arthroscopy.* 2004;20(7):681-690.

22. Claes S, Hermie L, Verdonk R, Bellemans J, Verdonk P. Is osteoarthritis an inevitable consequence of anterior cruciate ligament reconstruction? A meta-analysis. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(9):1967-1976.

23. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res (Hoboken).* 2011;63 Suppl 11:S208-228.

24. Cox CL, Huston LJ, Dunn WR, et al. Are articular cartilage lesions and meniscus tears predictive of IKDC, KOOS, and Marx activity level outcomes after anterior cruciate ligament reconstruction? A 6-year multicenter cohort study. *Am J Sports Med.* 2014;42(5):1058-1067.

25. Cremer MA, Rosloniec EF, Kang AH. The cartilage collagens: a review of their structure, organization, and role in the pathogenesis of experimental arthritis in animals and in human rheumatic disease. *J Mol Med (Berl).* 1998;76(3-4):275-288.

26. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. *Arthroscopy.* 1997;13(4):456-460.

27. Davis JC, Bryan S. Patient Reported Outcome Measures (PROMs) have arrived in sports and exercise medicine: Why do they matter? *Br J Sports Med.* 2015;49(24):1545-1546.

28. de Vet HC, Terwee CB, Ostelo RW, Beckerman H, Knol DL, Bouter LM. Minimal changes in health status questionnaires: distinction between minimally detectable change and minimally important change. *Health Qual Life Outcomes.* 2006;4:54.

29. de Windt TS, Bekkers JE, Creemers LB, Dhert WJ, Saris DB. Patient profiling in cartilage regeneration: prognostic factors determining success of treatment for cartilage defects. *Am J Sports Med.* 2009;37 Suppl 1:58S-62S.

30. Delince P, Ghafil D. Anterior cruciate ligament tears: conservative or surgical treatment? A critical review of the literature. *Knee Surg Sports Traumatol Arthrosc.* 2012;20(1):48-61.

31. Devitt BM, Bell SW, Webster KE, Feller JA, Whitehead TS. Surgical treatments of cartilage defects of the knee: Systematic review of randomised controlled trials. *Knee.* 2017;24(3):508-517.

32. Ding C, Cicuttini F, Jones G. Tibial subchondral bone size and knee cartilage defects: relevance to knee osteoarthritis. *Osteoarthritis Cartilage.* 2007;15(5):479-486.

33. Dozin B, Malpeli M, Cancedda R, et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial. *Clin J Sport Med.* 2005;15(4):220-226.

34. Drogset JO, Grontvedt T. Anterior cruciate ligament reconstruction with and without a ligament augmentation device : results at 8-Year follow-up. *Am J Sports Med.* 2002;30(6):851-856.

35. Drouin JM, Valovich-mcLeod TC, Shultz SJ, Gansneder BM, Perrin DH. Reliability and validity of the Biodex system 3 pro isokinetic dynamometer velocity, torque and position measurements. *Eur J Appl Physiol.* 2004;91(1):22-29.

36. Dwyer T, Martin CR, Kendra R, et al. Reliability and Validity of the Arthroscopic International Cartilage Repair Society Classification System: Correlation With Histological Assessment of Depth. *Arthroscopy.* 2017;33(6):1219-1224.

37. Eitzen I, Grindem H, Nilstad A, Moksnes H, Risberg MA. Quantifying Quadriceps Muscle Strength in Patients With ACL Injury, Focal Cartilage Lesions, and Degenerative Meniscus Tears: Differences and Clinical Implications. *Orthop J Sports Med.* 2016;4(10):2325967116667717.

38. Engelhart L, Nelson L, Lewis S, et al. Validation of the Knee Injury and Osteoarthritis Outcome Score subscales for patients with articular cartilage lesions of the knee. *Am J Sports Med.* 2012;40(10):2264-2272.

39. Engen CN, Aroen A, Engebretsen L. Incidence of knee cartilage surgery in Norway, 2008-2011. *BMJ Open.* 2015;5(11):e008423.

40. Engen CN, Aroen A, Engebretsen L. Development of a pilot cartilage surgery register. *BMC Musculoskelet Disord.* 2017;18(1):282.

41. Engen CN, Engebretsen L, Aroen A. Knee Cartilage Defect Patients Enrolled in Randomized Controlled Trials Are Not Representative of Patients in Orthopedic Practice. *Cartilage.* 2010;1(4):312-319.

42. Filardo G, de Caro F, Andriolo L, Kon E, Zaffagnini S, Marcacci M. Do cartilage lesions affect the clinical outcome of anterior cruciate ligament reconstruction? A systematic review. *Knee Surg Sports Traumatol Arthrosc.* 2016.

43. Frisbie DD, Oxford JT, Southwood L, et al. Early events in cartilage repair after subchondral bone microfracture. *Clin Orthop Relat Res.* 2003(407):215-227.

44. Furnes O, Espehaug B, Lie SA, Vollset SE, Engesaeter LB, Havelin LI. Failure mechanisms after unicompartmental and tricompartmental primary knee replacement with cement. *J Bone Joint Surg Am.* 2007;89(3):519-525.

45. Gao L, Orth P, Cucchiarini M, Madry H. Autologous Matrix-Induced Chondrogenesis: A Systematic Review of the Clinical Evidence. *Am J Sports Med.* 2017:363546517740575.

46. Gille J, Schuseil E, Wimmer J, Gellissen J, Schulz AP, Behrens P. Mid-term results of Autologous Matrix-Induced Chondrogenesis for treatment of focal cartilage defects in the knee. *Knee Surg Sports Traumatol Arthrosc.* 2010;18(11):1456-1464.

47. Goldring MB. Update on the biology of the chondrocyte and new approaches to treating cartilage diseases. *Best Pract Res Clin Rheumatol.* 2006;20(5):1003-1025.

48. Gomoll AH, Minas T. The quality of healing: articular cartilage. *Wound Repair Regen.* 2014;22 Suppl 1:30-38.

49. Goyal D, Keyhani S, Lee EH, Hui JH. Evidence-based status of microfracture technique: a systematic review of level I and II studies. *Arthroscopy.* 2013;29(9):1579-1588.

50. Gracitelli GC, Moraes VY, Franciozi CE, Luzo MV, Belloti JC. Surgical interventions (microfracture, drilling, mosaicplasty, and allograft transplantation) for treating isolated cartilage defects of the knee in adults. *Cochrane Database Syst Rev.* 2016;9:CD010675.

51. Granan LP, Bahr R, Steindal K, Furnes O, Engebretsen L. Development of a national cruciate ligament surgery registry: the Norwegian National Knee Ligament Registry. *Am J Sports Med.* 2008;36(2):308-315.

52. Granan LP, Engebretsen L, Bahr R. [Surgery for anterior cruciate ligament injuries in Norway]. *Tidsskr Nor Laegeforen.* 2004;124(7):928-930.

53. Granan LP, Forssblad M, Lind M, Engebretsen L. The Scandinavian ACL registries 2004-2007: baseline epidemiology. *Acta Orthop.* 2009;80(5):563-567.

54. Granan LP, Inacio MC, Maletis GB, Funahashi TT, Engebretsen L. Sport-specific injury pattern recorded during anterior cruciate ligament reconstruction. *Am J Sports Med.* 2013;41(12):2814-2818.

55. Gudas R, Gudaite A, Mickevicius T, et al. Comparison of osteochondral autologous transplantation, microfracture, or debridement techniques in articular cartilage lesions associated with anterior cruciate ligament injury: a prospective study with a 3-year follow-up. *Arthroscopy.* 2013;29(1):89-97.

56. Gudas R, Gudaite A, Pocius A, et al. Ten-Year Follow-up of a Prospective, Randomized Clinical Study of Mosaic Osteochondral Autologous Transplantation Versus Microfracture for the Treatment of Osteochondral Defects in the Knee Joint of Athletes. *Am J Sports Med.* 2012;40(11):2499-2508.

57.   Gudas R, Stankevicius E, Monastyreckiene E, Pranys D, Kalesinskas RJ. Osteochondral autologous transplantation versus microfracture for the treatment of articular cartilage defects in the knee joint in athletes. *Knee Surg Sports Traumatol Arthrosc.* 2006;14(9):834-842.

58.   Hambly K. The use of the Tegner Activity Scale for articular cartilage repair of the knee: a systematic review. *Knee Surg Sports Traumatol Arthrosc.* 2011;19(4):604-614.

59.   Hamrin Senorski E, Svantesson E, Beischer S, et al. Factors Affecting the Achievement of a Patient-Acceptable Symptom State 1 Year After Anterior Cruciate Ligament Reconstruction: A Cohort Study of 343 Patients From 2 Registries. *Orthop J Sports Med.* 2018;6(4):2325967118764317.

60.   Hamrin Senorski E, Svantesson E, Spindler KP, et al. Ten-Year Risk Factors for Inferior Knee Injury and Osteoarthritis Outcome Score After Anterior Cruciate Ligament Reconstruction: A Study of 874 Patients From the Swedish National Knee Ligament Register. *Am J Sports Med.* 2018;46(12):2851-2858.

61.   Hangody L, Dobos J, Balo E, Panics G, Hangody LR, Berkes I. Clinical experiences with autologous osteochondral mosaicplasty in an athletic population: a 17-year prospective multicenter study. *Am J Sports Med.* 2010;38(6):1125-1133.

62.   Hangody L, Fules P. Autologous osteochondral mosaicplasty for the treatment of full-thickness defects of weight-bearing joints: ten years of experimental and clinical experience. *J Bone Joint Surg Am.* 2003;85-A Suppl 2:25-32.

63.   Hangody L, Kish G, Karpati Z, Szerb I, Udvarhelyi I. Arthroscopic autogenous osteochondral mosaicplasty for the treatment of femoral condylar articular defects. A preliminary report. *Knee Surg Sports Traumatol Arthrosc.* 1997;5(4):262-267.

64.   Harris JD, Erickson BJ, Abrams GD, et al. Methodologic quality of knee articular cartilage studies. *Arthroscopy.* 2013;29(7):1243-1252 e1245.

65.   Heir S, Nerhus TK, Røtterud JH, et al. Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome score in 4 patient categories scheduled for knee surgery. *Am J Sports Med.* 2010;38(2):231-237.

66.   Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. *Arthroscopy.* 2002;18(7):730-734.

67.   Hjermundrud V, Bjune TK, Risberg MA, Engebretsen L, Aroen A. Full-thickness cartilage lesion do not affect knee function in patients with ACL injury. *Knee Surg Sports Traumatol Arthrosc.* 2010;18(3):298-303.

68.   Hunziker EB. Articular cartilage repair: basic science and clinical progress. A review of the current status and prospects. *Osteoarthritis Cartilage.* 2002;10(6):432-463.

69.   Hunziker EB, Lippuner K, Keel MJ, Shintani N. An educational review of cartilage repair: precepts & practice--myths & misconceptions--progress & prospects. *Osteoarthritis Cartilage.* 2015;23(3):334-350.

70.   Hunziker EB, Quinn TM, Hauselmann HJ. Quantitative structural organization of normal adult human articular cartilage. *Osteoarthritis Cartilage.* 2002;10(7):564-572.

71. Ingelsrud LH, Terwee CB, Terluin B, et al. Meaningful Change Scores in the Knee Injury and Osteoarthritis Outcome Score in Patients Undergoing Anterior Cruciate Ligament Reconstruction. *Am J Sports Med.* 2018;46(5):1120-1128.

72. Insall JN. Intra-articular surgery for degenerative arthritis of the knee. A report of the work of the late K. H. Pridie. *J Bone Joint Surg Br.* 1967;49(2):211-228.

73. Jager KJ, Zoccali C, Macleod A, Dekker FW. Confounding: what it is and how to deal with it. *Kidney Int.* 2008;73(3):256-260.

74. Jakobsen RB, Engebretsen L, Slauterbeck JR. An analysis of the quality of cartilage repair studies. *J Bone Joint Surg Am.* 2005;87(10):2232-2239.

75. Janssen RP, du Mee AW, van Valkenburg J, Sala HA, Tseng CM. Anterior cruciate ligament reconstruction with 4-strand hamstring autograft and accelerated rehabilitation: a 10-year prospective study on clinical results, knee osteoarthritis and its predictors. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(9):1977-1988.

76. Jones MH, Williams AM. Osteochondritis dissecans of the knee: a practical guide for surgeons. *Bone Joint J.* 2016;98-B(6):723-729.

77. Kaplan LD, Schurhoff MR, Selesnick H, Thorpe M, Uribe JW. Magnetic resonance imaging of the knee in asymptomatic professional basketball players. *Arthroscopy.* 2005;21(5):557-561.

78. Keays SL, Newcombe PA, Bullock-Saxton JE, Bullock MI, Keays AC. Factors involved in the development of osteoarthritis after anterior cruciate ligament surgery. *Am J Sports Med.* 2010;38(3):455-463.

79. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis.* 1957;16(4):494-502.

80. Kirkwood BR SJ. *Essential medical statistics 2nd edn. p368*; 2003.

81. Kirkwood BR SJ. Essential medical statistics 2nd edn. p398-406. 2003.

82. Knutsen G, Drogset JO, Engebretsen L, et al. A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. *J Bone Joint Surg Am.* 2007;89(10):2105-2112.

83. Knutsen G, Drogset JO, Engebretsen L, et al. A Randomized Multicenter Trial Comparing Autologous Chondrocyte Implantation with Microfracture: Long-Term Follow-up at 14 to 15 Years. *J Bone Joint Surg Am.* 2016;98(16):1332-1339.

84. Kocher MS, Steadman JR, Briggs KK, Sterett WI, Hawkins RJ. Reliability, validity, and responsiveness of the Lysholm knee scale for various chondral disorders of the knee. *J Bone Joint Surg Am.* 2004;86-A(6):1139-1145.

85. Kreuz PC, Erggelet C, Steinwachs MR, et al. Is microfracture of chondral defects in the knee associated with different results in patients aged 40 years or younger? *Arthroscopy.* 2006;22(11):1180-1186.

86. Kreuz PC, Steinwachs MR, Erggelet C, et al. Results after microfracture of full-thickness chondral defects in different compartments in the knee. *Osteoarthritis Cartilage.* 2006;14(11):1119-1125.

87. Krych AJ, Pareek A, King AH, Johnson NR, Stuart MJ, Williams RJ, 3rd. Return to sport after the surgical management of articular cartilage lesions in the knee: a meta-analysis. *Knee Surg Sports Traumatol Arthrosc.* 2016.

88. Li RT, Lorenz S, Xu Y, Harner CD, Fu FH, Irrgang JJ. Predictors of radiographic knee osteoarthritis after anterior cruciate ligament reconstruction. *Am J Sports Med.* 2011;39(12):2595-2603.

89. Lim HC, Bae JH, Song SH, Park YE, Kim SJ. Current treatments of isolated articular cartilage lesions of the knee achieve similar outcomes. *Clin Orthop Relat Res.* 2012;470(8):2261-2267.

90. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med.* 2007;35(10):1756-1769.

91. Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. *Arthritis Rheum.* 2004;50(10):3145-3152.

92. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. *Am J Sports Med.* 1982;10(3):150-154.

93. Løken S, Heir S, Holme I, Engebretsen L, Årøen A. 6-year follow-up of 84 patients with cartilage defects in the knee. Knee scores improved but recovery was incomplete. *Acta Orthop.* 2010;81(5):611-618.

94. Løken S, Ludvigsen TC, Hoysveen T, Holm I, Engebretsen L, Reinholt FP. Autologous chondrocyte implantation to repair knee cartilage injury: ultrastructural evaluation at 2 years and long-term follow-up including muscle strength measurements. *Knee Surg Sports Traumatol Arthrosc.* 2009;17(11):1278-1288.

95. Maletis GB, Inacio MC, Funahashi TT. Analysis of 16,192 anterior cruciate ligament reconstructions from a community-based registry. *Am J Sports Med.* 2013;41(9):2090-2098.

96. Mankin HJ. The response of articular cartilage to mechanical injury. *J Bone Joint Surg Am.* 1982;64(3):460-466.

97. Marcacci M, Kon E, Delcogliano M, Filardo G, Busacca M, Zaffagnini S. Arthroscopic autologous osteochondral grafting for cartilage defects of the knee: prospective study results at a minimum 7-year follow-up. *Am J Sports Med.* 2007;35(12):2014-2021.

98. McCormick F, Harris JD, Abrams GD, et al. Trends in the surgical treatment of articular cartilage lesions in the United States: an analysis of a large private-payer database over a period of 8 years. *Arthroscopy.* 2014;30(2):222-226.

99. Messner K, Maletius W. The long-term prognosis for severe damage to weight-bearing cartilage in the knee: a 14-year clinical and radiographic follow-up in 28 young athletes. *Acta Orthop Scand.* 1996;67(2):165-168.

100. Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. *Am J Sports Med.* 2009;37(5):902-908.

101. Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. *Am J Sports Med.* 2009;37(10):2053-2063.

102. Mithoefer K, Venugopal V, Manaqibwala M. Incidence, Degree, and Clinical Effect of Subchondral Bone Overgrowth After Microfracture in the Knee. *Am J Sports Med.* 2016;44(8):2057-2063.

103. Mithoefer K, Williams RJ, 3rd, Warren RF, et al. The microfracture technique for the treatment of articular cartilage lesions in the knee. A prospective cohort study. *J Bone Joint Surg Am.* 2005;87(9):1911-1920.

104. Moher D, Schulz KF, Altman D, Group C. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA.* 2001;285(15):1987-1991.
105. Mundi R, Bedi A, Chow L, et al. Cartilage Restoration of the Knee: A Systematic Review and Meta-Analysis of Level 1 Studies. *Am J Sports Med.* 2015.
106. Murray JR, Lindh AM, Hogan NA, et al. Does anterior cruciate ligament reconstruction lead to degenerative disease?: Thirteen-year results after bone-patellar tendon-bone autograft. *Am J Sports Med.* 2012;40(2):404-413.
107. Musahl V, Becker R, Fu FH, Karlsson J. New trends in ACL research. *Knee Surg Sports Traumatol Arthrosc.* 2011;19 Suppl 1:S1-3.
108. Nehrer S, Dorotka R, Domayer S, Stelzeneder D, Kotz R. Treatment of full-thickness chondral defects with hyalograft C in the knee: a prospective clinical case series with 2 to 7 years' follow-up. *Am J Sports Med.* 2009;37 Suppl 1:81S-87S.
109. Newman AP. Articular cartilage repair. *Am J Sports Med.* 1998;26(2):309-324.
110. Nunan D, Aronson J, Bankhead C. Catalogue of bias: attrition bias. *BMJ Evid Based Med.* 2018;23(1):21-22.
111. Oakley SP, Lassere MN. A critical appraisal of quantitative arthroscopy as an outcome measure in osteoarthritis of the knee. *Semin Arthritis Rheum.* 2003;33(2):83-105.
112. Oiestad BE, Engebretsen L, Storheim K, Risberg MA. Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. *Am J Sports Med.* 2009;37(7):1434-1443.
113. Oiestad BE, Holm I, Engebretsen L, Risberg MA. The association between radiographic knee osteoarthritis and knee symptoms, function and quality of life 10-15 years after anterior cruciate ligament reconstruction. *Br J Sports Med.* 2011;45(7):583-588.
114. Ollat D, Lebel B, Thaunat M, et al. Mosaic osteochondral transplantations in the knee joint, midterm results of the SFA multicenter study. *Orthop Traumatol Surg Res.* 2011;97(8 Suppl):S160-166.
115. Oussedik S, Tsitskaris K, Parker D. Treatment of articular cartilage lesions of the knee by microfracture or autologous chondrocyte implantation: a systematic review. *Arthroscopy.* 2015;31(4):732-744.
116. Outerbridge RE. The etiology of chondromalacia patellae. 1961. *Clin Orthop Relat Res.* 2001(389):5-8.
117. Paradowski PT, Bergman S, Sunden-Lundius A, Lohmander LS, Roos EM. Knee complaints vary with age and gender in the adult population. Population-based reference data for the Knee injury and Osteoarthritis Outcome Score (KOOS). *BMC Musculoskelet Disord.* 2006;7:38.
118. Pareek A, Carey JL, Reardon PJ, Peterson L, Stuart MJ, Krych AJ. Long-Term Outcomes after Autologous Chondrocyte Implantation: A Systematic Review at Mean Follow-Up of 11.4 Years. *Cartilage.* 2016;7(4):298-308.
119. Pareek A, Reardon PJ, Macalena JA, et al. Osteochondral Autograft Transfer Versus Microfracture in the Knee: A Meta-analysis of Prospective Comparative Studies at Midterm. *Arthroscopy.* 2016.

120. Prentice HA, Lind M, Mouton C, et al. Patient demographic and surgical characteristics in anterior cruciate ligament reconstruction: a description of registries from six countries. *Br J Sports Med.* 2018;52(11):716-722.

121. Rahr-Wagner L, Thillemann TM, Lind MC, Pedersen AB. Validation of 14,500 operated knees registered in the Danish Knee Ligament Reconstruction Register: registration completeness and validity of key variables. *Clin Epidemiol.* 2013;5:219-228.

122. Risberg MA, Oiestad BE, Gunderson R, et al. Changes in Knee Osteoarthritis, Symptoms, and Function After Anterior Cruciate Ligament Reconstruction: A 20-Year Prospective Follow-up Study. *Am J Sports Med.* 2016.

123. Rodrigo JJ SJ, Silliman JF, Fulstone HA. Improvement of full-thickness chondral defect healing in the human knee after debridement and microfracture using continuous passive motion. *Am J Knee Surg.* 1994;1994(3):109-116.

124. Roos EM. The 2012 User`s guide to: Knee injury and Osteoarthritis Outcome Score KOOS. http://www.koos.nu. 2012.

125. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes.* 2003;1:64.

126. Roos EM, Roos HP, Ekdahl C, Lohmander LS. Knee injury and Osteoarthritis Outcome Score (KOOS)--validation of a Swedish version. *Scand J Med Sci Sports.* 1998;8(6):439-448.

127. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther.* 1998;28(2):88-96.

128. Rotterud JH, Sivertsen EA, Forssblad M, Engebretsen L, Aroen A. Effect of Meniscal and Focal Cartilage Lesions on Patient-Reported Outcome After Anterior Cruciate Ligament Reconstruction: A Nationwide Cohort Study From Norway and Sweden of 8476 Patients With 2-Year Follow-up. *Am J Sports Med.* 2013;41(3):535-543.

129. Rotterud JH, Sivertsen EA, Forssblad M, Engebretsen L, Aroen A. Effect on Patient-Reported Outcomes of Debridement or Microfracture of Concomitant Full-Thickness Cartilage Lesions in Anterior Cruciate Ligament-Reconstructed Knees: A Nationwide Cohort Study From Norway and Sweden of 357 Patients With 2-Year Follow-up. *Am J Sports Med.* 2016;44(2):337-344.

130. Røtterud JH, Risberg MA, Engebretsen L, Årøen A. Patients with focal full-thickness cartilage lesions benefit less from ACL reconstruction at 2-5 years follow-up. *Knee Surg Sports Traumatol Arthrosc.* 2012;20(8):1533-1539.

131. Røtterud JH, Sivertsen EA, Forssblad M, Engebretsen L, Årøen A. Effect of gender and sports on the risk of full-thickness articular cartilage lesions in anterior cruciate ligament-injured knees: a nationwide cohort study from Sweden and Norway of 15 783 patients. *Am J Sports Med.* 2011;39(7):1387-1394.

132. Saltzman BM, Redondo ML, Beer A, et al. Wide Variation in Methodology in Level I and II Studies on Cartilage Repair: A Systematic Review of Available Clinical Trials Comparing Patient Demographics, Treatment Means, and Outcomes Reporting. *Cartilage.* 2018:1947603518809398.

133. Schiphof D, de Klerk BM, Kerkhof HJ, et al. Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis. *Ann Rheum Dis.* 2011;70(8):1422-1427.

134. Schiphof D, de Klerk BM, Kerkhof HJ, et al. Impact of different descriptions of the Kellgren and Lawrence classification criteria on the diagnosis of knee osteoarthritis. *Ann Rheum Dis.* 2011;70(8):1422-1427.
135. Schulz KF. Generation of allocation sequences in randomized trials: chance, not choice. *The Lancet.* 2002;359:515-519.
136. Shapiro F, Koide S, Glimcher MJ. Cell origin and differentiation in the repair of full-thickness defects of articular cartilage. *J Bone Joint Surg Am.* 1993;75(4):532-553.
137. Shelbourne KD, Gray T. Results of anterior cruciate ligament reconstruction based on meniscus and articular cartilage status at the time of surgery. Five- to fifteen-year evaluations. *Am J Sports Med.* 2000;28(4):446-452.
138. Shelbourne KD, Gray T. Minimum 10-year results after anterior cruciate ligament reconstruction: how the loss of normal knee motion compounds other factors related to the development of osteoarthritis after surgery. *Am J Sports Med.* 2009;37(3):471-480.
139. Shelbourne KD, Jari S, Gray T. Outcome of untreated traumatic articular cartilage defects of the knee: a natural history study. *J Bone Joint Surg Am.* 2003;85-A Suppl 2:8-16.
140. Smith HJ, Richardson JB, Tennant A. Modification and validation of the Lysholm Knee Scale to assess articular cartilage damage. *Osteoarthritis Cartilage.* 2009;17(1):53-58.
141. Solheim E, Hegna J, Inderhaug E. Long-term clinical follow-up of microfracture versus mosaicplasty in articular cartilage defects of medial femoral condyle. *Knee.* 2017;24(6):1402-1407.
142. Solheim E, Hegna J, Inderhaug E. Long-Term Survival after Microfracture and Mosaicplasty for Knee Articular Cartilage Repair: A Comparative Study Between Two Treatments Cohorts. *Cartilage.* 2018:1947603518783482.
143. Solheim E, Hegna J, Oyen J, Austgulen OK, Harlem T, Strand T. Osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee: results at 5 to 9 years. *Knee.* 2010;17(1):84-87.
144. Solheim E, Hegna J, Oyen J, Harlem T, Strand T. Results at 10 to 14years after osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee. *Knee.* 2013;20(4):287-290.
145. Solheim E, Hegna J, Strand T, Harlem T, Inderhaug E. Randomized Study of Long-term (15-17 Years) Outcome After Microfracture Versus Mosaicplasty in Knee Articular Cartilage Defects. *Am J Sports Med.* 2018;46(4):826-831.
146. Solheim E, Krokeide AM, Melteig P, Larsen A, Strand T, Brittberg M. Symptoms and function in patients with articular cartilage lesions in 1,000 knee arthroscopies. *Knee Surg Sports Traumatol Arthrosc.* 2016;24(5):1610-1616.
147. Solomonow M, Krogsgaard M. Sensorimotor control of knee stability. A review. *Scand J Med Sci Sports.* 2001;11(2):64-80.
148. Sophia Fox AJ, Bedi A, Rodeo SA. The basic science of articular cartilage: structure, composition, and function. *Sports Health.* 2009;1(6):461-468.
149. Spindler KP, Huston LJ, Wright RW, et al. The prognosis and predictors of sports function and activity at minimum 6 years after anterior cruciate ligament reconstruction: a population cohort study. *Am J Sports Med.* 2011;39(2):348-359.

150. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. *Arthroscopy.* 2003;19(5):477-484.

151. Steadman JR, Rodkey WG, Rodrigo JJ. Microfracture: surgical technique and rehabilitation to treat chondral defects. *Clin Orthop Relat Res.* 2001(391 Suppl):S362-369.

152. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res.* 1985(198):43-49.

153. Theodoropoulos J, Dwyer T, Whelan D, Marks P, Hurtig M, Sharma P. Microfracture for knee chondral defects: a survey of surgical practice among Canadian orthopedic surgeons. *Knee Surg Sports Traumatol Arthrosc.* 2012;20(12):2430-2437.

154. Tirico LEP, McCauley JC, Pulido PA, Bugbee WD. Does Anterior Cruciate Ligament Reconstruction Affect the Outcome of Osteochondral Allograft Transplantation? A Matched Cohort Study With a Mean Follow-up of 6 Years. *Am J Sports Med.* 2018;46(8):1836-1843.

155. Tyyni A, Karlsson J. Biological treatment of joint cartilage damage. *Scand J Med Sci Sports.* 2000;10(5):249-265.

156. van Duijvenbode DC, Jonkers FJ, Konst YE, van Royen BJ, Benink RJ, Hoozemans MJ. Gel-type autologous chondrocyte implantation for cartilage repair in patients with prior ACL reconstruction: A retrospective two year follow-up. *Knee.* 2016;23(2):241-245.

157. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg.* 2014;12(12):1500-1524.

158. Volz M, Schaumburger J, Frick H, Grifka J, Anders S. A randomized controlled trial demonstrating sustained benefit of Autologous Matrix-Induced Chondrogenesis over microfracture at five years. *Int Orthop.* 2017;41(4):797-804.

159. W. H. On the structure and diseases of articulating cartilages. *Philos Trans R Soc.* 1743;42(B):514-521.

160. Wang D, Jones MH, Khair MM, Miniaci A. Patient-reported outcome measures for the knee. *J Knee Surg.* 2010;23(3):137-151.

161. Wang Y, Wei L, Zeng L, He D, Wei X. Nutrition and degeneration of articular cartilage. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(8):1751-1762.

162. Widuchowski W, Widuchowski J, Koczy B, Szyluk K. Untreated asymptomatic deep cartilage lesions associated with anterior cruciate ligament injury: results at 10- and 15-year follow-up. *Am J Sports Med.* 2009;37(4):688-692.

163. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. *Knee.* 2007;14(3):177-182.

164. Wondrasch B, Aroen A, Rotterud JH, Hoysveen T, Bolstad K, Risberg MA. The feasibility of a 3-month active rehabilitation program for patients with knee full-thickness articular cartilage lesions: the Oslo Cartilage Active Rehabilitation and Education Study. *J Orthop Sports Phys Ther.* 2013;43(5):310-324.

165. Ytterstad K, Granan LP, Ytterstad B, et al. Registration rate in the Norwegian Cruciate Ligament Register: large-volume hospitals perform better. *Acta Orthop.* 2012;83(2):174-178.

166. Zevenbergen L, Gsell W, Chan DD, et al. Functional assessment of strains around a full-thickness and critical sized articular cartilage defect under compressive loading using MRI. *Osteoarthritis Cartilage.* 2018.
167. Årøen. Agreement in Arthroscopic and Arthrotomy Assessment of Full-Thickness Articular Cartilage Lesions of the Knee in a Clinical Setting in 33 Consecutive Patients.
168. Årøen A, Løken S, Heir S, et al. Articular cartilage lesions in 993 consecutive knee arthroscopies. *Am J Sports Med.* 2004;32(1):211-215.

Errata

Paper I - IV

KNEE

Microfracture technique versus osteochondral autologous transplantation mosaicplasty in patients with articular chondral lesions of the knee: a prospective randomized trial with long-term follow-up

Svend Ulstein · Asbjørn Årøen · Jan Harald Røtterud · Sverre Løken · Lars Engebretsen · Stig Heir

Abstract

Purpose   To compare long-term functional and radiological outcome following microfracture technique (MF) versus osteochondral autologous transplantation (OAT) mosaicplasty for treating focal chondral lesions of the knee.
Methods   Twenty-five patients (mean age 32.3 years, SD 7.7) with a full-thickness (International Cartilage Repair Society grade 3 or 4) chondral lesion of the articulating surface of the femur were randomized to either MF ($n = 11$) or OAT mosaicplasty ($n = 14$). At a median follow-up of 9.8 years (range 4.9–11.4), the patients were evaluated using Lysholm score ($n = 25$), Knee Injury and Osteoarthritis Outcome Score (KOOS, $n = 25$), isokinetic quadriceps measurement and hamstring strength measurement ($n = 22$) and standing radiographs ($n = 23$).

Results   There were no significant differences in Lysholm score, KOOS, isokinetic muscle strength or radiographic osteoarthritis between MF-treated patients and OAT mosaicplasty-treated patients at follow-up. Mean Lysholm score at follow-up was 69.7 [95 % confidence interval (CI), 55.1–84.4] for the MF group and 62.6 (95 % CI, 52.6–72.6) for the OAT mosaicplasty group.
Conclusion   At long-term follow-up, there were no significant differences between patients treated with MF and patients treated with OAT mosaicplasty in patient-reported outcomes, muscle strength or radiological outcome.
Level of evidence   Therapeutic study, Level II.

Keywords   Chondral lesion · Microfracture · Mosaicplasty · Long-term follow-up · Lysholm · KOOS

S. Ulstein (✉) · A. Årøen · J. H. Røtterud
Department of Orthopedic Surgery, Akershus University Hospital, 1478 Lørenskog, Norway
e-mail: svend.ulstein@ahus.no

A. Årøen · L. Engebretsen · S. Heir
Oslo Sports Trauma Research Center, Oslo, Norway

A. Årøen
Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, Lørenskog, Norway

S. Løken · L. Engebretsen
Department of Orthopaedics, Oslo University Hospital, Oslo, Norway

L. Engebretsen
Norwegian Knee Ligament Registry, Bergen, Norway

S. Heir
Department of Orthopaedic Surgery, Martina Hansens Hospital, Bærum, Norway

Introduction

Chondral or osteochondral lesions of the knee eligible for cartilage repair surgery are diagnosed in 5–10 % of all knees subjected to knee arthroscopy [1, 20] and may contribute to disability and premature osteoarthritis (OA) [29]. Furthermore, focal chondral lesions of the knee have been shown to impair quality of life similar to patients scheduled for knee replacement, even though the chondral lesion patients are 30 years younger [18].

Various cartilage repair techniques have been developed. Resurfacing techniques include abrasion arthroplasty [24], Pridie drilling [36] and microfracture technique (MF) [3, 43]. MF procedures stimulate and recruit mesenchymal cells from the subchondral bone marrow and subsequently form a fibrin clot that eventually turns into a predominantly fibrocartilaginous regenerate with inferior biomechanical characteristics compared to native hyaline articular

cartilage [11]. Despite fibrocartilage formation, several short- to mid-term follow-up studies following MF treatment of chondral lesions report significant pain relief and improvement in knee function [32, 33, 43].

Grafting and transplantation procedures, like autologous chondrocyte implantation (ACI) [6] and osteochondral autologous transplantation (OAT) mosaicplasty [16] gained popularity after introduction in the 1990s. The OAT mosaicplasty technique involves open or arthroscopic transplantation of multiple cylindrical osteochondral grafts from the relatively less weight-bearing periphery of the articular surface to the cartilage defect, thus providing a hyaline-cartilage-covered resurfacing [2, 22]. Case series and comparative trials have reported 83–92 % good to excellent short- to mid-term results following OAT mosaicplasty [8, 13, 15]. Even though MF and OAT mosaicplasty have proven to be effective in short- to mid-term follow-up studies, knowledge regarding long-term outcome remains uncertain [4, 8, 14, 32, 41, 42]. To our knowledge, there is only one prospective randomized study comparing the long-term outcomes following MF and OAT mosaicplasty [12]. Due to the limited information on the long-term outcome after these two common cartilage repair techniques, patient information and decision-making regarding treatment options is challenging for the orthopaedic surgeon.

In the present prospective randomized study, the purpose was to compare long-term functional and radiological outcome following MF and OAT mosaicplasty for full-thickness chondral lesions of the knee. The null hypothesis was that there is no difference in patient-reported outcomes or radiographic OA between MF-treated patients and OAT mosaicplasty-treated patients at long-term follow-up.

Materials and methods

Twenty-five patients [mean age 32.3 years, standard deviation (SD) 7.7] were enroled in the study between November 2000 and June 2006. Three orthopaedic cartilage repair centres participated in the study, and experienced knee surgeons performed both the selection of the patients and the surgical procedure. Informed consent was obtained from all patients.

Inclusion criteria were an arthroscopically verified chondral or osteochondral lesion of International Cartilage Repair Society (ICRS) grade 3 or 4 [7] located on the femoral condyle or trochlea, with an area between 2 and 6 cm^2 and depth <10 mm. Additionally, the patients had to be 18–50 years of age with Lysholm score <80 and Tegner score <6.

Exclusion criteria were radiographic osteoarthritis (OA), major malalignment, major ligament injury or instability,

extension deficit >3°, flexion deficit >5° and chondral lesion(s) of ICRS grade 3 or 4 on the tibial plateau or patella. Patients were also excluded if they had contralateral impaired knee function that might influence the ability to follow the rehabilitation protocol.

Randomization between MF and OAT mosaicplasty was performed in the operating room, following arthroscopic debridement. Patients were randomized by a restricted shuffled approach [39] in blocks of 10, allocation ratio 1:1, using sequentially numbered sealed envelopes to assign treatment. The block randomization approach used ensured that all centres/surgeons performed both procedures and also ensured randomization to surgeon. Twenty-five patients were included, and in accordance with randomization, 14 patients were treated with OAT mosaicplasty and 11 patients with MF. Group characteristics at inclusion are shown in Table 1.

A total of 19 patients were excluded from the study. In most cases, this was due to findings during the arthroscopic assessment, e.g. size or localization of the chondral lesion not in accordance with the inclusion criteria or additional ICRS grade 3 or 4 chondral lesions of the tibia or patella. Two patients declined surgery due to pregnancy, and two

Table 1 Characteristics of the study groups at inclusion

	MF (n = 11)	OAT Mosaicplasty (n = 14)
Age, years[a] (n = 25)	31.7 (8.0)	32.7 (7.8)
Duration of symptoms, mos[a] (n = 24)	111.0 (77.3)	75.8 (73.5)
Gender, n (%)		
Females	5 (45)	6 (43)
Males	6 (55)	8 (57)
Right/left	7/4	8/6
Lesion localization (n = 25)		
Trochlea	0	2
Medial femoral condyle	10	10
Lateral femoral condyle	1	2
Lesion size[b] (n = 25)	2.6 (2.0–5.2)	3.0 (2.0–6.0)
Injury mechanism (n = 25)		
Gradual onset	0	4
Trauma/acute onset	5	6
Osteochondritis dissecans	6	4
ICRS classification (grade 3/4)	4/7	8/6
Previous cartilage surgery[c]	3	1
Tegner activity level score[b] (n = 23)	3 (0–4)	2.5 (0–4)

ICRS International Cartilage Repair Society

[a] Mean and (standard deviation)

[b] median and (range)

[c] Resurfacing and/or grafting and/or transplantation

patients withdrew their consent at the time of surgery as they insisted on being treated with one of the surgical techniques.

Treatment

Microfracture technique

The procedure was arthroscopic and the principles of the technique introduced by Steadman et al. [43] were used. Debridement of all damaged and unstable cartilage was performed, as to obtain stable and healthy cartilage edges. An arthroscopic awl (Linvatec) was then used to perform multiple holes ("microfractures") about 3–4 mm apart. The depth of the holes was considered appropriate when "fat-pearls" emerged from the subchondral bone.

OAT mosaicplasty

Following application of a tourniquet, the OAT mosaicplasty was performed through a medial parapatellar arthrotomy or a mini-invasive arthrotomy, depending on the lesion size and localization. Debridement was done similar to that described for MF. The OAT mosaicplasty procedure was performed as described by Hangody et al. [16] by obtaining small cylindrical osteochondral grafts (3.5, 4.5 or 6.6 mm in diameter) from the minimal weight-bearing periphery of the femoral condyles and transplanting them "press-fit" to recipient tunnels in the prepared lesion site (Acufex®, Smith&Nephew). At the end of the procedure, the knee was moved through a full range of motion to check the stability of the osteochondral plugs.

For both techniques, one dose of prophylactic antibiotics was administrated intravenous in advance of the procedure, followed by two dosages postoperatively. Intra-articular Bupivacaine (Marcain®) was installed at the end of the procedure.

Postoperative care

All patients were hospitalized for a minimum of 5 days. Continuous passive motion (Kinetec®) 3–4 h × 2/day was started the first postoperative day and continued for four days. Cold therapy and compression (Aircast Knee Cryo/Cuff®) were applied the two first days postoperatively to reduce swelling and pain.

Rehabilitation

The rehabilitation programme was similar for both groups. The programme used was based on the principles and recommendations of Hangody and Steadman [17, 43]. A maximum load of 15–20 kg weight bearing was allowed the initial 6 weeks postoperatively, following gradually discontinuing of the crutches up to 8 weeks. From 8 weeks, progression to full weight bearing was encouraged. Physiotherapist-guided rehabilitation was initialized immediately postoperatively and was continued for a minimum of 6 months. The rehabilitation programme included exercises aiming to restore full range of motion and proprioceptive neuromuscular control as soon as possible, progressing to dynamic strength exercises from 6 weeks postoperatively. Patients were generally allowed return to full activity after 6 months. However, participation in competitive contact sports or other activities that may expose the knee to pivoting forces was discouraged until 12 months postoperatively.

Outcome measures

All outcome measures were obtained both at baseline and follow-up, except for isokinetic muscle strength measurements, which were performed only at follow-up. In addition to the outcome measures, all patients were also questioned about any additional surgical procedures to the knee during the follow-up period.

Lysholm score

The primary outcome measure was the Lysholm score [44], which is an 8-item (limp, support, locking, instability, pain, swelling, stair climbing and squatting) questionnaire. The total score is the sum of each response to the 8 items, of a possible score of 100 (100 = no symptoms or disability) The Lysholm score is validated for patients with cartilage injuries [26], and age and gender-specific population-based reference data have been established [5]. At follow-up, the Lysholm questionnaire was completed by the patients prior to the examination [21].

The Knee Injury and Osteoarthritis Outcome Score (KOOS)

The KOOS is a self-reported assessment tool consisting of 42 questions distributed between 5 separately scored subscales: pain, other symptoms, activities of daily living (ADL), function in sport and recreation (Sport/Rec) and knee-related quality of life (QoL). Each subscale score is converted to a 0 (worst)–100 (best) scale. The KOOS is considered as a valid, reliable and responsive questionnaire for patients with chondral lesions of the knee [10, 38]. Age and gender-specific population-based reference data of the KOOS have been established [35]. A difference or change of 10 points or more in either of the subscales is considered

as clinically relevant [10, 37]. At follow-up, the KOOS questionnaire was completed by the patients prior to the examination.

Isokinetic muscle strength

Isokinetic quadriceps and hamstring muscle strength tests were performed at follow-up. It has previously been shown that muscular strength deficits in various knee disorders are associated with a poorer outcome, and two recently published studies found highly significant side-to-side differences in knee-related muscle strength in ACI-treated patients [27, 30]. In addition, since this is a comparative study between an arthroscopic and an open procedure, muscle strength assessments were considered relevant. Muscle strength was measured using a Biodex 6000 dynamometer (Biodex Medical System Inc., Shirley, New York). This device gives reliable and valid measurements of dynamic muscle function on variables related to torque, power and endurance [9]. Before testing, the patients did 10-min warm-up on a stationary bike. The test protocol consisted of five repetitions at an angular velocity of 60°/s in a concentric mode. Two physiotherapists, both blinded to the treatment, performed the measurements. Comparison was made between involved and uninvolved knee. The parameter used for analysis was peak torque/highest muscular force output (Nm) expressed as percentage deficit compared to the uninjured leg.

Radiographs

Radiographs were performed in the AP-plane with the patients standing with semi-flexed knees. Evaluation and grading of anonymized radiographs were done according to the original Kellgren and Lawrence criteria [23] of knee OA (0 normal to 4 severe). The grading was done by three of the authors (SU, AÅ and SL) by consensus agreement.

The study was approved by the Regional Ethical Committee of South-Eastern Norway, University of Oslo, ID 155-00066.

Statistical analysis

The sample size required to detect a difference in Lysholm score of 15 between groups was estimated by using the Altman nomogram. In addition to the predetermined power (0.80) and level of significance (0.05), the estimation is based on the calculation of the standardized difference, i.e. the difference in Lysholm score to be detected divided by the expected SD. Based on previous studies [40], the SD was expected to be 17, giving a standardized difference of $15/17 = 0.88$. Using these figures, the Altman's nomogram revealed that 20 patients in each treatment group would be sufficient.

SPSS software version 20 (Chicago, IL, USA, 2006) was used for statistical analysis. Lysholm, KOOS and isokinetic muscle strength deficits compared to uninjured leg at follow-up were compared between the treatment groups using Mann–Whitney U test. Changes in Lysholm and KOOS from baseline to follow-up were compared using Wilcoxon signed rank test. Changes in radiographic appearance according to Kellgren–Lawrence classification were compared between the two groups using Fishers exact test. Level of significance was defined as $p \leq 0.05$.

Results

At a median follow-up of 9.8 years (range 4.9–11.4 years), all patients (25/25) reported Lysholm score and KOOS. One patient had moved abroad, and another was not available for examination in the outpatient clinic. However, these patients were contacted by postal mail and telephone, and returned their questionnaires.

Mean Lysholm score for patients treated with MF and OAT mosaicplasty at baseline and at follow-up are shown in Fig. 1. No significant differences in mean Lysholm score were detected between MF-treated patients and OAT mosaicplasty-treated patients at follow-up (n.s.), or in mean change from baseline to follow-up (Table 2). MF-treated patients scored 48.2 (95 % CI, 38.2–58.2) preoperatively
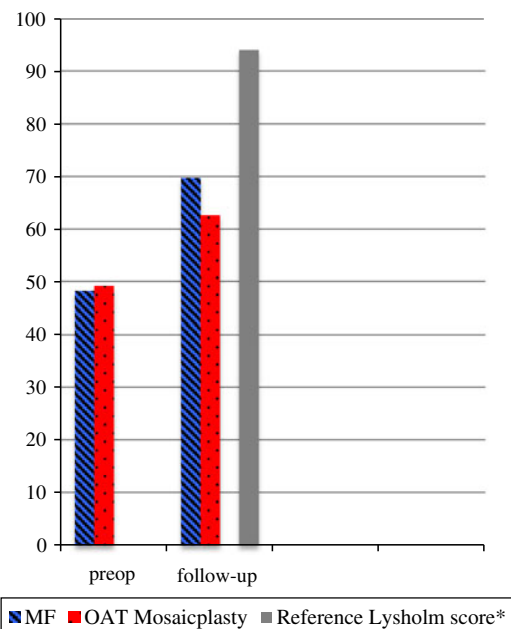

Fig. 1 Mean Lysholm score for patients treated with MF ($n = 11$) and OAT mosaicplasty ($n = 14$) at preoperative and follow-up. *Lysholm score acquired from a normal, healthy population as a standard point of reference for the injured or postsurgical knee, as described by Briggs, K.K. et al., Am J Sports Med, 2009

Table 2 Mean change in Lysholm score and Knee Injury and Osteoarthritis Outcome Score from preoperative to follow-up, and mean difference in change over time between the MF group and OAT mosaicplasty group

	MF Change over time Mean (95 % CI)	OAT Mosaicplasty Change over time Mean (95 % CI)	MF vs OAT mosaicplasty Change over time Mean difference (95 % CI)	*p* value
Lysholm	21.6 (3.7–39.4)	13.4 (0.9–25.8)	8.2 (−11.7 to 28.1)	n.s
KOOS Pain	20.6 (2.8–38.3)	11.8 (−2.8 to 26.4)	8.8 (−12.7 to 30.3)	n.s
KOOS Symptoms	17.4 (2.6–32.2)	8.5 (−3.5 to 20.6)	8.9 (−8.9 to 26.7)	n.s
KOOS ADL	13.0 (−3.8 to 29.8)	7.5 (−4.3 to 19.3)	5.5 (−13.4 to 24.4)	n.s
KOOS Sport/Rec	32.4 (13.3–51.6)	41.3 (23.7–58.9)	−8.9 (−33.4 to 15.7)	n.s
KOOS QoL	34.6 (15.1–54.0)	25.0 (10.6–39.3)	9.6 (−12.7 to 31.9)	n.s

Change over time = follow-up minus preoperative

Mean difference = mean change over time in MF group minus mean change over time in OAT mosaicplasty group

CI confidence interval, *p* level of significance, *ADL* activities in daily living, *Sport/Rec* function in sport and recreation, *QoL* knee-related quality of life

and OAT mosaicplasty-treated patients 49.2 (95 % CI, 43.0–55.4). The mean Lysholm score at follow-up in the MF group was 69.7 (95 % CI, 55.1–84.4) compared to 62.6 (95 % CI, 52.6–72.6) in the OAT mosaicplasty group. The increase in Lysholm score from baseline to follow-up was significant for both groups (Table 2).

The KOOS profiles with mean scores at inclusion and at follow-up for the MF group and the OAT mosaicplasty group are shown in Fig. 2. There were no significant differences between the two groups in any of the KOOS subscales at follow-up or in the changes from baseline to follow-up (Table 2). The increase in KOOS from baseline to follow-up within the treatment groups was significant for all subscales except for ADL in the microfracture group, and pain, symptoms and ADL in the OAT mosaicplasty group (Table 2).

Isokinetic muscle strength measurements (*n* = 22) of the knee extensors and flexors at follow-up are shown in Table 3. There were no significant differences between the MF group and OAT mosaicplasty group in mean strength deficit of the affected knee. A significant mean extension strength deficit of the affected knee, compared to the unaffected, was detected in the OAT mosaicplasty group.

Twenty-three patients performed radiographic examination at follow-up. No patient had radiological signs of osteoarthritis of any knee at inclusion. Osteoarthritis was defined as Kellgren–Lawrence ≥2 and was detected in the affected knee in 5 of 11 patients in the MF group and 2 of 12 in the OAT mosaicplasty group at follow-up (*p* = 0.193). Osteoarthritis in the unaffected leg was detected in 3 of 11 knees in the MF group and in 1 of 12 knees in the OAT mosaicplasty group.

Mean body mass index (BMI) at follow-up was 28.2 (SD 4.2) for patients treated with MF and 27.9 (SD 3.8) in the OAT mosaicplasty group.
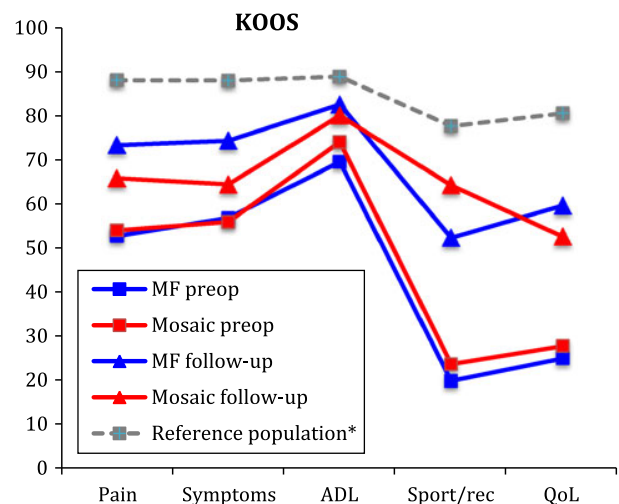

Fig. 2 Knee Injury and Osteoarthritis Outcome Score (KOOS) at inclusion and follow-up for the MF group and the OAT mosaicplasty group. *Reference population as described by Paradowski et al. [35] BMC Musculoskelet Disord

Reoperations and additional surgical procedures during follow-up are outlined in Table 4.

Discussion

The main finding of the present study is that the long-term outcomes following MF and OAT mosaicplasty for treating focal chondral lesions of the knee are comparable. The evidence in this material is not sufficient to reject the study hypothesis that there is no difference between the two alternative treatments. However, the small number of included patients makes any firm conclusions regarding the hypothesis testing difficult. Due to less eligible patients for

Table 3 Muscle strength measurements expressed as peak torque in Nm [mean (95 % CI)]

	MF (n = 10)			OAT mosaicplasty (n = 12)			p value
	Injured leg	Contralateral leg	% deficit	Injured leg	Contralateral leg	% deficit	
Extension peak torque 60°/s	159.4 (104.2–214.5)	179.3 (128.0–230.7)	7.1 (−22.1–36.3)	164.5 (132.8–196.1)	199.4 (165.4–233.5)	17.6 (8.9–26.3)	n.s
Flexion peak torque 60°/s	88.3 (57.1–119.4)	99.9 (73.6–126.1)	13.5 (−4.8–31.9)	92.7 (70.9–114.4)	98.9 (81.4–116.4)	6.7 (−7.3–20.7)	n.s

% Deficit = strength deficit of the operated knee in percentage, compared to contralateral leg

p values refer to Mann–Whitney nonparametric test used to analyse differences in strength deficit between the two treatment groups (MF vs. OAT mosaicplasty)

n.s non-significant

Table 4 Reoperations and additional surgical procedures during follow-up

	MF (n = 11)	OAT mosaicplasty (n = 14)
Procedures	6	5
ACI	2	
OAT mosaicplasty	1	
Open wedge osteotomy		1
Removal of loose body	1	
Diagnostic arthroscopy/debridement	1	4
Scheduled to TKA	1	

ACI autologous chondrocyte implantation, TKA total knee arthroplasty

the study than expected, the duration of the inclusion period was extended up to 5 years. Still only 25 patients were enroled in the study. However, no patients were lost to follow-up.

Reoperations occurred in 6/11 patients (54 %) in the MF group and in 5/14 patients (36 %) in the OAT mosaicplasty group. Even though non-significant, all knees that underwent a second cartilage repair procedure (n = 3) or a total knee arthroplasty (n = 1) belonged to the MF group. It should also be noted that a significant reduction in extension force of the affected leg, compared to the unaffected, was found in the OAT mosaicplasty group, even though a mini-invasive arthrotomy was used when possible.

Both treatment groups reported significant improvement in Lysholm score and in several of the KOOS subscales from baseline to follow-up at 9.8 years. However, the mean Lysholm score and KOOS at follow-up were considerably lower than in the reference population [5, 35], which indicates that the long-term patient-reported outcomes are modest for both treatments. In addition, the wide confidence intervals indicate diversity among the patients, which however, is not an uncommon finding in long-term follow-up studies on cartilage repair [4, 45]. The unpredictability of these two cartilage repair methods has been found in standardized controlled animal studies as well [19].

To our knowledge, there are only two other clinical studies comparing MF and OAT mosaicplasty [12, 28]. In the only randomized trial, the OAT mosaicplasty-treated patients scored significantly higher on the ICRS outcome scores and Tegner scores compared to the MF-treated patients at a mean follow-up of 10.4 years [12]. Furthermore, the failure rate and the decrease in sports activity were significantly higher for the MF group. Although our study did not demonstrate any significant difference regarding reoperations, the trend was that reoperations occur more often in the MF group. However, comparison between the studies is difficult due to differences in study

populations, surgical techniques and the use of other outcome measures. Gudas et al. included competitive or well-trained athletes, whereas the present study did not exclude non-athletes. Several studies indicate that both OAT mosaicplasty and MF provide favourable outcome in small lesions [4, 8, 25, 31, 34]. The fact that relatively small-sized lesions <2 cm^2 were included and that lesions >4 cm^2 were excluded in the Gudas study might in part explain the apparently better results at follow-up in that study compared to the present study. Another difference between these two studies is that in the Gudas study, all OAT mosaicplasty patients were treated arthroscopically, whereas in the current study an arthrotomy was performed in all mosaicplasty procedures.

In a recent retrospective, comparative study, Krych et al. [28] showed that both MF and OAT mosaicplasty-treated patients reported significant improvements in knee function and activity level at 5-year follow-up. No significant differences were detected between the two groups regarding knee function, but the mosaicplasty group maintained a superior level of activity compared to those treated with MF. The main findings of that study are in line with those of the present study, but the validity of the conclusions in the study of Krych et al. is limited by the study design, since it allows for selection bias. The unevenly distributed number of patients with previous cartilage surgery, and osteochondritis dissecans, should also be accounted for in the study by Krych et al.

There are few long-term follow-up studies following MF for treating chondral lesions of the knee. In a systematic review by Mithoefer et al. [32] only 5 studies reported a follow-up of 5 years or more, and the reports on the durability of the initial functional improvement were conflicting. The present study shows that functional improvement after MF is to be expected as long as 9.8 years after surgery.

The long-term outcome following OAT mosaicplasty in the present study supports the findings from other studies on OAT mosaicplasty, indicating acceptable long-term clinical outcome given the appropriate indication for surgery, a limitation being the defect size [12, 14, 41].

The main limitation of this study is the small number of included patients, which may lead to a false affirmation of the null hypothesis (type II error). On the other hand, the follow-up of 100 % for the main outcome (Lysholm score), and the high follow-up (88–100 %) and uniformity of comparable results between the two groups in the additional broad spectrum of outcome measures, strengthens the validity of the conclusion. Other limitations of the study are lack of a mid-term evaluation and the incompleteness of the preoperative strength measurements.

In the light of the limited information in current literature on the topic of long-term comparison between MF and OAT mosaicplasty, there is a need for further RCTs and a future cartilage repair registry in order to monitor and assess the cartilage repair procedures in use. The results from the current study might help the orthopaedic surgeon in the preoperative decision-making and in informing the patient what to expect concerning long-term outcome following these two cartilage repair techniques.

Conclusion

At long-term follow-up, there were no significant differences between patients treated with MF and patients treated with OAT mosaicplasty in patient-reported outcomes, muscle strength or radiological outcome. Both MF-treated as well as OAT mosaicplasty-treated patients reported improved knee function compared to the preoperative level. However, compared to a reference population, inferior patient-reported knee function was found in both treatment groups at follow-up.

References

1. Årøen A, Løken S, Heir S, Alvik E, Ekeland A, Granlund OG, Engebretsen L (2004) Articular cartilage lesions in 993 consecutive knee arthroscopies. Am J Sports Med 32(1):211–215
2. Barber FA, Chow JC (2001) Arthroscopic osteochondral transplantation: histologic results. Arthroscopy 17(8):832–835
3. Benthien JP, Behrens P (2011) The treatment of chondral and osteochondral defects of the knee with autologous matrix-induced chondrogenesis (AMIC): method description and recent developments. Knee Surg Sports Traumatol Arthrosc 19(8):1316–1319
4. Bentley G, Biant LC, Vijayan S, Macmull S, Skinner JA, Carrington RW (2012) Minimum ten-year results of a prospective randomised study of autologous chondrocyte implantation versus mosaicplasty for symptomatic articular cartilage lesions of the knee. J Bone Jt Surg Br 94(4):504–509
5. Briggs KK, Steadman JR, Hay CJ, Hines SL (2009) Lysholm score and Tegner activity level in individuals with normal knees. Am J Sports Med 37(5):898–901
6. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L (1994) Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med 331(14):889–895
7. Brittberg M, Winalski CS (2003) Evaluation of cartilage injuries and repair. J Bone Jt Surg Am 85-A(Suppl 2):58–69

8. Chow JC, Hantes ME, Houle JB, Zalavras CG (2004) Arthroscopic autogenous osteochondral transplantation for treating knee cartilage defects: a 2- to 5-year follow-up study. Arthroscopy 20(7):681–690

9. Drouin JM, Valovich-mcLeod TC, Shultz SJ, Gansneder BM, Perrin DH (2004) Reliability and validity of the Biodex system 3 pro isokinetic dynamometer velocity, torque and position measurements. Eur J Appl Physiol 91(1):22–29

10. Engelhart L, Nelson L, Lewis S, Mordin M, Demuro-Mercon C, Uddin S, McLeod L, Cole B, Farr J (2012) Validation of the Knee Injury and Osteoarthritis Outcome Score subscales for patients with articular cartilage lesions of the knee. Am J Sports Med 40(10):2264–2272

11. Frisbie DD, Oxford JT, Southwood L, Trotter GW, Rodkey WG, Steadman JR, Goodnight JL, McIlwraith CW (2003) Early events in cartilage repair after subchondral bone microfracture. Clin Orthop Relat Res 407:215–227

12. Gudas R, Gudaite A, Pocius A, Gudiene A, Cekanauskas E, Monastyreckiene E, Basevicius A (2012) Ten-year follow-up of a prospective, randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint of athletes. Am J Sports Med 40(11):2499–2508

13. Gudas R, Stankevicius E, Monastyreckiene E, Pranys D, Kalesinskas RJ (2006) Osteochondral autologous transplantation versus microfracture for the treatment of articular cartilage defects in the knee joint in athletes. Knee Surg Sports Traumatol Arthrosc 14(9):834–842

14. Hangody L, Dobos J, Balo E, Panics G, Hangody LR, Berkes I (2010) Clinical experiences with autologous osteochondral mosaicplasty in an athletic population: a 17-year prospective multicenter study. Am J Sports Med 38(6):1125–1133

15. Hangody L, Fules P (2003) Autologous osteochondral mosaicplasty for the treatment of full-thickness defects of weight-bearing joints: ten years of experimental and clinical experience. J Bone Jt Surg Am 85-A(Suppl 2):25–32

16. Hangody L, Rathonyi GK, Duska Z, Vasarhelyi G, Fules P, Modis L (2004) Autologous osteochondral mosaicplasty. Surgical technique. J Bone Jt Surg Am 86(Suppl 1):65–72

17. Hangody L, Vasarhelyi G, Hangody LR, Sukosd Z, Tibay G, Bartha L, Bodo G (2008) Autologous osteochondral grafting—technique and long-term results. Injury 39(Suppl 1):S32–S39

18. Heir S, Nerhus TK, Røtterud JH, Løken S, Ekeland A, Engebretsen L, Årøen A (2010) Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of Knee Injury and Osteoarthritis Outcome Score in 4 patient categories scheduled for knee surgery. Am J Sports Med 38(2):231–237

19. Heir S, Årøen A, Løken S, Holme I, Engebretsen L, Reinholt FP (2012) Cartilage repair in the rabbit knee: mosaic plasty resulted in higher degree of tissue filling but affected subchondral bone more than microfracture technique: a blinded, randomized, controlled, long-term follow-up trial in 88 knees. Knee Surg Sports Traumatol Arthrosc 20(2):197–209

20. Hjelle K, Solheim E, Strand T, Muri R, Brittberg M (2002) Articular cartilage defects in 1,000 knee arthroscopies. Arthroscopy 18(7):730–734

21. Hoher J, Bach T, Munster A, Bouillon B, Tiling T (1997) Does the mode of data collection change results in a subjective knee score? Self-administration versus interview. Am J Sports Med 25(5):642–647

22. Horas UP, Pelinkovic D, Herr G, Aigner T, Schnettler R (2003) Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint. J Bone Jt Surg Am 85-A(2):185–192

23. Kellgren JH, Lawrence JS (1957) Radiological assessment of osteo-arthrosis. Ann Rheum Dis 16(4):494–502

24. Kim HK, Moran ME, Salter RB (1991) The potential for regeneration of articular cartilage in defects created by chondral shaving and subchondral abrasion. An experimental investigation in rabbits. J Bone Jt Surg Am 73(9):1301–1315

25. Knutsen G, Engebretsen L, Ludvigsen TC, Drogset JO, Grontvedt T, Solheim E, Strand T, Roberts S, Isaksen V, Johansen O (2004) Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. J Bone Jt Surg Am 86-A(3):455–464

26. Kocher MS, Steadman JR, Briggs KK, Sterett WI, Hawkins RJ (2004) Reliability, validity, and responsiveness of the Lysholm knee scale for various chondral disorders of the knee. J Bone Jt Surg Am 86-A(6):1139–1145

27. Kreuz PC, Muller S, Erggelet C, von Keudell A, Tischer T, Kaps C, Niemeyer P, Hirschmuller A (2012) Is gender influencing the biomechanical results after autologous chondrocyte implantation? Knee Surg Sports Traumatol Arthrosc

28. Krych AJ, Harnly HW, Rodeo SA, Williams RJ 3rd (2012) Activity levels are higher after osteochondral autograft transfer mosaicplasty than after microfracture for articular cartilage defects of the knee: a retrospective comparative study. J Bone Jt Surg Am 94(11):971–978

29. Løken S, Heir S, Holme I, Engebretsen L, Årøen A (2010) 6-Year follow-up of 84 patients with cartilage defects in the knee. Knee scores improved but recovery was incomplete. Acta Orthop 81(5):611–618

30. Løken S, Ludvigsen TC, Hoysveen T, Holm I, Engebretsen L, Reinholt FP (2009) Autologous chondrocyte implantation to repair knee cartilage injury: ultrastructural evaluation at 2 years and long-term follow-up including muscle strength measurements. Knee Surg Sports Traumatol Arthrosc 17(11):1278–1288

31. Magnussen RA, Dunn WR, Carey JL, Spindler KP (2008) Treatment of focal articular cartilage defects in the knee: a systematic review. Clin Orthop Relat Res 466(4):952–962

32. Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR (2009) Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. Am J Sports Med 37(10):2053–2063

33. Mithoefer K, Williams RJ III, Warren RF, Potter HG, Spock CR, Jones EC, Wickiewicz TL, Marx RG (2005) The microfracture technique for the treatment of articular cartilage lesions in the knee. A prospective cohort study. J Bone Jt Surg Am 87(9):1911–1920

34. Panics G, Hangody LR, Balo E, Vasarhelyi G, Gal T, Hangody L (2011) Osteochondral autograft and mosaicplasty in the football (Soccer) athlete. Cartilage 3(1 Suppl):25S–30S

35. Paradowski PT, Bergman S, Sunden-Lundius A, Lohmander LS, Roos EM (2006) Knee complaints vary with age and gender in the adult population. Population-based reference data for the Knee injury and Osteoarthritis Outcome Score (KOOS). BMC Musculoskelet Disord 7:38

36. Pridie KH (1959) A method of resurfacing osteoarthritic knee joints. In: Proceedings of the British orthopaedic association. J Bone Joint Surg Br 41:618–9

37. Roos EM, Lohmander LS (2003) The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes 1:64

38. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD (1998) Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self-administered outcome measure. J Orthop Sports Phys Ther 28(2):88–96

39. Schulz KF (2002) Generation of allocation sequences in randomized trials: chance, not choice. The Lancet 359:515–519

40. Solheim E (1999) Mosaikkplastikk ved leddbruskskader i kne. Tidsskr Nor Laegeforen 119:4022–4025

41. Solheim E, Hegna J, Oyen J, Harlem T, Strand T (2013) Results at 10 to 14 years after osteochondral autografting (mosaicplasty) in articular cartilage defects in the knee. Knee 20(4):287–290

42. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG (2003) Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. Arthroscopy 19(5):477–484

43. Steadman JR, Rodkey WG, Briggs KK (2002) Microfracture to treat full-thickness chondral defects: surgical technique, rehabilitation, and outcomes. J Knee Surg 15(3):170–176

44. Tegner Y, Lysholm J (1985) Rating systems in the evaluation of knee ligament injuries. Clin Orthop Relat Res 198:43–49

45. Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP, Tig/Act, Group EXTS (2011) Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. Am J Sports Med 39(12):2566–2574

II

Effect of Concomitant Cartilage Lesions on Patient-Reported Outcomes After Anterior Cruciate Ligament Reconstruction

A Nationwide Cohort Study From Norway and Sweden of 8470 Patients With 5-Year Follow-up

Svend Ulstein,*[†‡§] MD, Asbjørn Årøen,[†‡§] MD, PhD, Lars Engebretsen,[§‖¶] MD, PhD,
Magnus Forssblad,[#**] MD, PhD, Stein Håkon Låstad Lygre,[††‡‡] MSc, PhD,
and Jan Harald Røtterud,[†‡§] MD, PhD
Investigation performed at the Department of Orthopedic Surgery,
Akershus University Hospital, Lørenskog, Norway

Background: The effect of concomitant focal cartilage lesions on patient-reported outcomes after anterior cruciate ligament reconstruction (ACLR) remains to be determined.

Purpose: To evaluate the effect of concomitant partial-thickness (International Cartilage Repair Society [ICRS] grades 1-2) and full-thickness (ICRS grades 3-4) cartilage lesions on patient-reported outcomes 5 years after ACLR.

Study Design: Cohort study; Level of evidence, 2.

Methods: All patients who underwent unilateral primary ACLR registered in the Norwegian and Swedish National Knee Ligament Registries from 2005 to 2008 (n = 15,783) were included in the study. At 5-year follow-up, 8470 (54%) patients completed the Knee injury and Osteoarthritis Outcome Score (KOOS). Multivariable linear regression models were used to estimate the effect of concomitant partial-thickness and full-thickness cartilage lesions on patient-reported outcomes (KOOS) 5 years after ACLR.

Results: Compared with no concomitant cartilage lesions, both partial-thickness and full-thickness cartilage lesions were indicators of statistically significant adverse effects on the KOOS in the adjusted regression analysis at 5-year follow-up after ACLR.

Conclusion: ACL-injured patients with concomitant cartilage lesions reported worse outcomes and less improvement than those without cartilage lesions 5 years after ACLR.

Keywords: knee; anterior cruciate ligament (ACL); reconstruction; cartilage lesions; KOOS

Anterior cruciate ligament (ACL) injuries are associated with articular focal cartilage lesions. In reports from large, prospectively collected ACL cohorts such as the Norwegian National Knee Ligament Registry (NKLR), the Swedish National Knee Ligament Registry (SKLR), and the Kaiser Permanente Anterior Cruciate Ligament Reconstruction Registry in the United States, concomitant cartilage lesions were present in 27% and 23% of ACL reconstructions (ACLRs), respectively.[16]

Even though the presence of a cartilage lesion at the time of ACLR is known to be a significant predictor of premature radiographic knee osteoarthritis,[6,13-15,17] the previous literature is inconsistent and somewhat divergent when it comes to the effect on patient-reported outcomes. Some of the studies have found no adverse effects of concomitant cartilage lesions on patient-reported outcomes after ACLR,[2,25-28] while others have found that concomitant cartilage lesions are associated with inferior patient-reported outcomes.[7,21,23,24] Firm knowledge on the short- and long-term prognosis after ACLR in patients with these combined injuries is necessary if the information and advice given to the patient regarding treatment and expectations are to be optimal. Hence, there is a need for large population-based studies evaluating that subject matter.

The primary objective of the present prospective, nationwide population-based study was to evaluate the effect of concomitant focal partial-thickness (International Cartilage Repair Society [ICRS] grades 1-2) and full-thickness

(ICRS grades 3-4) cartilage lesions on patient-reported outcomes as measured by the Knee injury and Osteoarthritis Outcome Score (KOOS) 5 years after ACLR.

METHODS

NKLR and SKLR

After obtaining approval from the institutional review board of Akershus University Hospital and the Regional Ethical Committee of South-Eastern Norway, University of Oslo, data were assembled from the NKLR and the SKLR. The NKLR was established in June 2004 and the SKLR in January 2005, with the main objective to register all surgical procedures performed on knee ligaments and to prospectively monitor outcomes on a nationwide scale.[10,11] The Swedish registry was based on the Norwegian registry, and there are no major cross-cultural differences in the data between the 2 countries.[11] In both registries, the surgeons' reporting rates are found to be satisfactory, with reporting rates above 85%.[1,11]

As a part of the immediate postoperative registration of patient-, knee-, and surgery-specific variables, the surgeons grade concomitant focal cartilage lesions according to the ICRS guidelines.[4,5] Cartilage lesion size is reported as area $<2 \, cm^2$ or $\geq 2 \, cm^2$. Concomitant cartilage lesions are treated at the discretion of the surgeon with, in descending order of frequency, no treatment, debridement, microfracture, or various other surgical techniques.

The KOOS is used as the patient-reported outcome measure in both the NKLR and SKLR. The questionnaire consists of 42 questions distributed between 5 separately scored subscales: Pain, Symptoms, Activities of Daily Living (ADL), Sport and Recreation (Sport/Rec), and Knee-Related Quality of Life (QoL); it is considered to be a valid, reliable, and responsive assessment tool for patients with ACL and cartilage injuries.[3,8,20] Data assembly is voluntary, and patients complete an informed consent form before surgery, allowing for later use of their registry data, including the KOOS questionnaire.

Patients

The current study is a longitudinal 5-year follow-up of a nationwide population-based cohort consisting of all patients who underwent unilateral primary ACLR between
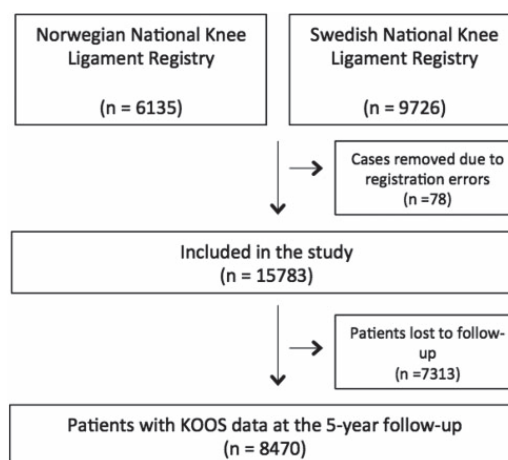

Figure 1. Flowchart of the patients during inclusion (2005-2008) and follow-up. KOOS, Knee injury and Osteoarthritis Outcome Score.

January 1, 2005, and December 31, 2008, and who were registered in the NKLR or SKLR. During this time frame, a total of 15,783 patients were prospectively registered. This patient cohort has previously been described in a study on the incidence and risk of full-thickness cartilage lesions in ACL-injured knees[22] and a study reporting on 2-year outcomes after ACLR in patients with concomitant meniscal and cartilage lesions.[23]

At a mean (±SD) follow-up of 5.1 ± 0.2 years and with a mean patient age of 33.8 ± 10.6 years, KOOS data were received from 8470 (54%) of the 15,783 patients. Of these, 3573 (42%) patients were from the Norwegian registry and 4897 (58%) patients from the Swedish registry. Patient flow during inclusion and follow-up is shown in Figure 1, and baseline characteristics at the time of ACLR for the patients included in the study cohort and for patients lost to follow-up are shown in Table 1. With the exception of sex and age, the baseline characteristics of the study population and those lost to follow-up were comparable. The patients available for follow-up tended to be older and to have a higher proportion of women compared with patients lost to follow-up.

In the present study, patients were categorized as having no concomitant cartilage lesion, partial-thickness cartilage lesions (ICRS grades 1-2), or full-thickness cartilage lesions (ICRS grades 3-4). Patients with more than 1 concomitant

*Address correspondence to Svend Ulstein, MD, Department of Orthopedic Surgery, Akershus University Hospital, Sykehusveien 25, 1478 Lørenskog, Norway (email: svend.ulstein@ahus.no).

†Department of Orthopedic Surgery, Akershus University Hospital, Lørenskog, Norway.

‡Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

§Oslo Sports Trauma Research Center, Norwegian School of Sport Sciences, Oslo, Norway.

‖Department of Orthopaedic Surgery, Oslo University Hospital, Oslo, Norway.

¶Norwegian Cruciate Ligament Register, Bergen, Norway.

#Capio Artro Clinic, Stockholm, Sweden.

**Stockholm Sports Trauma Research Center, Karolinska Institutet, Stockholm, Sweden.

††Norwegian Arthroplasty Register, Department of Orthopedic Surgery, Haukeland University Hospital, Bergen, Norway.

‡‡Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway.

TABLE 1
Baseline Characteristics at the Time of ACL Reconstruction for Patients in the Study Cohort and Patients Lost to Follow-up[a]

	Study Cohort (n_1)	Lost to Follow-up (n_2)
Age at surgery, y, median (range), ($n_1 = 8470$; $n_2 = 7306$)	27 (9-69)	24 (8-64)
Time from injury to surgery, mo, median (range) ($n_1 = 8178$; $n_2 = 7072$)	9 (0-521)	9 (0-400)
Female sex ($n_1 = 8470$; $n_2 = 7313$)	4125 (49)	2573 (35)
Previous ipsilateral knee surgery ($n_1 = 8470$; $n_2 = 7313$)	2232 (26)	1914 (26)
Concomitant ligament injury[b] ($n_1 = 8470$; $n_2 = 7313$)	621 (7)	493 (7)
Concomitant meniscal lesion ($n_1 = 8470$; $n_2 = 7313$)	3688 (43)	3156 (43)
Concomitant cartilage lesion ($n_1 = 8470$; $n_2 = 7313$)	2248 (27)	1910 (26)
ACL graft ($n_1 = 8470$; $n_2 = 7313$)		
Hamstring tendon	6473 (76)	5762 (79)
Bone–patellar tendon–bone	1833 (22)	1383 (19)
Other/unknown	164 (2)	168 (2)
Preoperative KOOS value, mean ± SD		
Pain ($n_1 = 6070$; $n_2 = 4877$)	74.7 ± 17.6	73.9 ± 18.0
Symptoms ($n_1 = 6089$; $n_2 = 4893$)	71.4 ± 18.0	70.2 ± 18.0
Activities of Daily Living ($n_1 = 6062$; $n_2 = 4866$)	83.8 ± 17.4	82.9 ± 17.5
Sport and Recreation ($n_1 = 6031$; $n_2 = 4864$)	42.3 ± 27.1	41.8 ± 27.1
Knee-Related Quality of Life ($n_1 = 6067$; $n_2 = 4878$)	34.2 ± 18.2	33.5 ± 18.2

[a]Data are shown as n (%) unless otherwise indicated. ACL, anterior cruciate ligament; KOOS, Knee injury and Osteoarthritis Outcome Score.
[b]Medial collateral ligament, lateral collateral ligament, posterior cruciate ligament, or posterolateral corner.

cartilage lesion were categorized according to the lesion with the highest ICRS grade. The baseline characteristics as stratified by these categories are shown in Table 2. At baseline, it was a consistent finding that some of the between-group differences (age at surgery, time from injury to surgery, previous ipsilateral knee surgery, concomitant ligament and meniscal injury, meniscal resection, and cartilage lesion size $\geq 2\,cm^2$) were more pronounced with increasing depth (higher ICRS grade) of the cartilage lesion.

Statistical Analysis

SPSS software (version 24.0; IBM) was used for all statistical analyses. *P* values <.05 were considered statistically significant. Crude mean KOOS scores and standardized regression coefficients are presented with 95% CIs. Crude mean KOOS scores at 5-year follow-up were estimated and stratified by patients with partial-thickness cartilage lesions, those with full-thickness cartilage lesions, and those without any concomitant cartilage lesions.

Multivariable linear regression was used to assess the possible impact on prognosis, as measured by the KOOS at 5-year follow-up, of concomitant partial-thickness and full-thickness cartilage lesions. The results are presented both unadjusted and adjusted for possible confounding from sex, age at surgery (continuous variable), previous ipsilateral knee surgery (yes/no), concomitant ligament injury (yes/no), concomitant meniscal injury (yes/no), concomitant meniscal resection (yes/no), time from injury to surgery (continuous variable), and type of ACL graft (hamstring, patellar tendon, or other). In all regression analyses, the no concomitant cartilage lesion category was used as the reference for the effect of partial-thickness and full-thickness cartilage lesions. Cartilage lesion–specific

characteristics such as area and location were not included as independent variables in the multivariable regression analysis for the reason that controlling for these variables would shift the regression model to focus on the effect of ACLR instead of the concomitant cartilage lesion.

To determine whether cartilage lesion size ($<2\,cm^2$ or $\geq 2\,cm^2$) was a significant predictor of KOOS scores at 5 years after ACLR, separate multivariable regression analyses were performed for the subsets of patients with partial-thickness cartilage lesions and full-thickness cartilage lesions. The factor of interest (lesion size $\geq 2\,cm^2$) in these additional analyses was included as an independent variable together with sex, age at surgery (continuous variable), previous ipsilateral knee surgery (yes/no), concomitant ligament injury (yes/no), concomitant meniscal injury (yes/no), concomitant meniscal resection (yes/no), time from injury to surgery (continuous variable), and type of ACL graft (hamstring, patellar tendon, or other). Cartilage lesion area $<2\,cm^2$ was used as a reference for the effect of lesion size on KOOS scores at 5-year follow-up.

RESULTS

Of the 8470 patients available for follow-up at 5 years, 2248 (27%) had ≥ 1 concomitant cartilage lesions at the time of ACLR: 1685 (20%) patients with ≥ 1 partial-thickness cartilage lesions (ICRS grades 1-2) and 563 (7%) patients with ≥ 1 full-thickness cartilage lesions (ICRS grades 3-4). There were a total of 2825 partial-thickness cartilage lesions and 656 full-thickness cartilage lesions. Of the 1685 patients with concomitant partial-thickness cartilage lesions, 591 (35%) had >1 cartilage lesion (ICRS grades 1-2). Of the 563 patients with full-thickness cartilage lesions, 74 (13%) had >1 full-thickness cartilage lesion, and 218

TABLE 2
Baseline Characteristics by Cartilage Status at the Time of ACL Reconstruction[a]

	Study Cohort (N = 8470)		
	No Cartilage Lesions (n = 6222)	Partial-Thickness Cartilage Lesions (n = 1685)	Full-Thickness Cartilage Lesions (n = 563)
Age at surgery, y, median (range)	25 (9-69)	32 (13-67)	37 (14-66)
Time from injury to surgery, mo, median (range)	8 (0-361)	13 (0-430)	18 (0-521)
Female sex	3143 (50)	730 (43)	252 (45)
Previous ipsilateral knee surgery	1347 (22)	635 (38)	250 (44)
Concomitant ligament injury[b]	398 (6)	156 (9)	67 (12)
Concomitant meniscal lesion	2468 (40)	893 (53)	327 (58)
Meniscal resection	1608 (26)	652 (39)	253 (45)
ACL graft			
Hamstring tendon	4728 (76)	1307 (78)	438 (78)
Bone–patellar tendon–bone	1356 (22)	361 (21)	116 (21)
Other/unknown	138 (2)	17 (1)	9 (1)
Area			
<2 cm^2	NA	1048 (62)	248 (44)
≥ 2 cm^2	NA	573 (34)	310 (55)
Not reported	NA	64 (4)	5 (1)
Location			
Patella	NA	393 (14)	67 (10)
Trochlea	NA	149 (5)	45 (7)
Medial femoral condyle	NA	1099 (39)	344 (52)
Lateral femoral condyle	NA	356 (13)	82 (13)
Medial tibial plateau	NA	411 (14)	66 (10)
Lateral tibial plateau	NA	417 (15)	52 (8)
Preoperative KOOS value, mean ± SD			
Pain	75.6 ± 17.1	73.6 ± 18.5	69.8 ± 19.4
Symptoms	72.0 ± 17.8	70.4 ± 18.1	67.9 ± 19.0
Activities of Daily Living	84.8 ± 16.8	81.9 ± 18.4	78.4 ± 19.2
Sport and Recreation	43.6 ± 26.9	39.7 ± 27.1	36.1 ± 27.1
Knee-Related Quality of Life	34.8 ± 18.0	33.1 ± 18.3	31.0 ± 18.7

[a]Data are shown as n (%) unless otherwise indicated. ACL, anterior cruciate ligament; KOOS, Knee injury and Osteoarthritis Outcome Score; NA, not applicable.
[b]Medial collateral ligament, lateral collateral ligament, posterior cruciate ligament, or posterolateral corner.

TABLE 3
Crude KOOS Scores by Cartilage Status at 5-Year Follow-up After Anterior Cruciate Ligament Reconstruction[a]

	No Cartilage Lesions (n = 5981-6199)	Partial-Thickness Cartilage Lesions (n = 1609-1684)	Full-Thickness Cartilage Lesions (n = 510-562)
Pain	86.2 (85.8-86.6)	85.3 (84.5-86.1)	79.7 (78.0-81.4)
Symptoms	79.7 (79.2-80.1)	79.3 (78.4-80.2)	74.2 (72.5-75.6)
Activities of Daily Living	92.1 (91.7-92.4)	90.6 (89.8-91.3)	86.0 (84.4-87.5)
Sport and Recreation	70.6 (69.9-71.2)	68.4 (67.1-69.6)	61.6 (59.2-64.0)
Knee-Related Quality of Life	67.2 (66.6-67.8)	66.3 (65.1-67.4)	60.0 (57.8-62.2)

[a]Data are shown as mean (95% CI). KOOS, Knee injury and Osteoarthritis Outcome Score.

patients (39%) had an associated partial-thickness cartilage lesion.

The crude mean KOOS scores at 5-year follow-up for patients with no concomitant cartilage lesions, patients with partial-thickness cartilage lesions, and patients with full-thickness cartilage lesions are outlined in Table 3. Compared with patients with partial-thickness cartilage lesions, and in particular patients without any cartilage lesions, patients with full-thickness cartilage lesions reported inferior crude mean values on all of the KOOS subscales at 5-year follow-up. Except for lower scores on the KOOS subscales of ADL and Sport/Rec, patients with partial-thickness cartilage lesions reported equal crude mean KOOS scores at follow-up compared with patients without any cartilage lesions.

The results from the multivariable regression analysis with the unadjusted and adjusted effects of

TABLE 4
Unadjusted and Adjusted Regression Analyses of the Associations Between KOOS Subscales and Partial-Thickness
and Full-Thickness Cartilage Lesions at 5-Year Follow-up After Anterior Cruciate Ligament Reconstruction[a]

KOOS Subscale	n	Partial-Thickness Cartilage Lesions			Full-Thickness Cartilage Lesions		
		β	95% CI	P Value	β	95% CI	P Value
Pain							
Unadjusted	8425	−0.9	−1.8 to −0.1	.040	−6.6	−8.0 to −5.1	<.001
Adjusted	8091	−0.8	−1.7 to 0.1	.084	−6.0	−7.5 to −4.5	<.001
Symptoms							
Unadjusted	8445	−0.4	−1.4 to 0.6	.400	−5.5	−7.0 to −3.9	<.001
Adjusted	8107	−1.1	−2.1 to −0.1	.042	−6.5	−8.2 to −4.9	<.001
Activities of Daily Living							
Unadjusted	8425	−1.5	−2.3 to −0.7	<.001	−6.1	−7.3 to −4.9	<.001
Adjusted	8088	−0.7	−1.5 to 0.0	.067	−4.6	−5.9 to −3.3	<.001
Sport and Recreation							
Unadjusted	8100	−2.2	−3.6 to −0.8	.002	−8.9	−11.2 to −6.7	<.001
Adjusted	7779	−1.8	−3.2 to −0.3	.018	−8.1	−10.5 to −5.7	<.001
Knee-Related Quality of Life							
Unadjusted	8356	−0.9	−2.2 to 0.4	.170	−7.2	−9.3 to −5.1	<.001
Adjusted	8026	−1.5	−2.8 to −0.1	.033	−8.0	−10.2 to −5.7	<.001

[a]KOOS, Knee injury and Osteoarthritis Outcome Score.

TABLE 5
Adjusted Regression Analysis of the Associations Between KOOS Subscales and Cartilage Lesion Size
at 5-Year Follow-up After Anterior Cruciate Ligament Reconstruction[a]

KOOS Subscale	Partial-Thickness Cartilage Lesions ≥2 cm²				Full-Thickness Cartilage Lesions ≥2 cm²			
	n	β	95% CI	P Value	n	β	95% CI	P Value
Pain	1561	−1.9	−3.7 to −0.1	.045	524	−0.7	−4.2 to 2.8	NS
Symptoms	1562	−2.3	−4.3 to −0.4	.019	526	−0.1	−3.6 to 3.5	NS
Activities of Daily Living	1561	−1.7	−3.3 to −0.1	.046	524	−0.7	−3.9 to 2.6	NS
Sport and Recreation	1494	−3.2	−6.0 to −0.4	.026	479	−4.2	−9.3 to 0.1	NS
Knee-Related Quality of Life	1543	−2.0	−4.6 to 0.6	NS	515	−2.0	−6.6 to 2.6	NS

[a]KOOS, Knee injury and Osteoarthritis Outcome Score; NS, not significant.

partial-thickness cartilage lesions and full-thickness cartilage lesions on each of the KOOS subscales are shown in Table 4. In the unadjusted analysis, with patients without concomitant cartilage lesions as the reference, partial-thickness cartilage lesions were significantly associated with inferior scores on all KOOS subscales except for Symptoms and QoL. In the adjusted analysis, partial-thickness cartilage lesions showed significant associations with inferior scores at follow-up on all KOOS subscales except for Pain and ADL. Full-thickness cartilage lesions were significantly associated with inferior scores on all KOOS subscales in both the unadjusted and the adjusted analyses.

As shown in Table 5, the subgroup multivariable regression analysis of patients with partial-thickness cartilage lesions (n = 1685), lesion size ≥2 cm² was significantly associated with inferior scores at 5-year follow-up on all KOOS subscales except for QoL. In the corresponding subgroup analysis of patients with full-thickness cartilage lesions (n = 563), no significant associations between lesion size and the KOOS subscales were detected (Table 5).

DISCUSSION

The main finding of the present study was that compared with patients with no concomitant cartilage lesions, those with cartilage lesions reported significantly inferior outcomes, as measured by the KOOS, at 5-year follow-up after ACLR. To date, this is the largest multivariable modeling of midterm outcomes in patients with this combined injury.

Both partial-thickness and full-thickness cartilage lesions were indicators of statistically significant adverse effects on the KOOS in the adjusted regression analysis. The minimal clinically important difference for the KOOS in the current population is not established, but a clinically meaningful difference or change in the KOOS score of at least 8 points is often used.[19] Though statistically significant, the observed adverse effects of partial-thickness cartilage lesions were small and likely without major clinical significance. However, the observed negative adjusted effects of full-thickness cartilage lesions were larger, with −8.1 and −8.0 points for the 2 most responsive KOOS subscales, Sport/Rec and QoL,

respectively. This is in line with the results from a recent comprehensive level 1 cohort study of 1512 ACL-reconstructed patients with 6-year follow-up by Cox et al,[7] in which concomitant cartilage lesions of Outerbridge grades 3 to 4 were a significant predictor of reduced KOOS and International Knee Documentation Committee (IKDC) scores. In contrast, in the only other level 1 prognostic study with >5 years' follow-up of these combined injuries, no negative effect of concomitant full-thickness cartilage lesions on the KOOS was detected 5 to 9 years after ACLR.[27] This diversity in the reported effects of concomitant cartilage lesions on patient-reported outcomes after ACLR is illustrative of the current literature on this subject matter, as some have found an association between cartilage lesions and patient-reported outcomes,[7,21,23,24] while others have found no such association.[2,25-28] As pointed out in a recent systematic review, considerable heterogeneity in patients, injuries, surgical factors, outcome measurements, and observation periods exists among the different reports, making it difficult to directly compare the findings from these studies.[9]

When comparing the adjusted negative effects of full-thickness cartilage lesions at the current 5-year follow-up with 2-year follow-up of this cohort,[23] with effect differences ranging from –1.7 to –2.7, more pronounced adverse effects of full-thickness cartilage lesions were found on all KOOS subscales at the 5-year follow-up. Consequently, not only did ACLR, in the short term, fail to restore knee function to the same level as patients without full-thickness cartilage lesions, but the divergence in knee function also seems to evolve with time, at least up to 5 years after surgery.

Aside from controlling for the variables included in the multivariable regression analysis, the current study design did not allow for an assessment on the reasons for this relative deterioration in patient-reported outcomes over time. However, the limited functional competence and durability of repair tissue after spontaneous or surgical cartilage repair are well known.[12] Moreover, others have shown that there is an increased risk of osteoarthritis associated with these cartilage lesions.[13,14] The subgroup analysis on the impact of lesion size on KOOS scores at 5-year follow-up indicates that lesions ≥ 2 cm^2 can predict inferior outcomes for patients with partial-thickness cartilage lesions. On the contrary, there was no significant association between lesion size and patient-reported outcomes 5 years after ACLR in patients with full-thickness cartilage lesions. However, firm conclusions regarding the effect of lesion size cannot be drawn from these results, as some information is lost in the dichotomization of lesion size into <2 cm^2 and ≥ 2 cm^2. In particular, exact information about small (<1 cm^2) and large (>4 cm^2) lesions would allow for more nuanced subgroup analyses.

The observational study design has limitations, as is the case with the current study. The main limitation of this study is the rate of loss to 5-year follow-up (46%), with the potential of introducing attrition bias. Although the baseline characteristics of the study cohort and those lost to follow-up were comparable in the majority of the reported variables, patients lost to follow-up were younger and had a higher proportion of men than the patients available for follow-up. On the other hand, those factors, together with other factors most likely to have affected the prognosis and outcome after surgery, were adjusted for in the multivariable regression analysis. Moreover, in a validation study from the Danish Knee Ligament Reconstruction Registry, the KOOS values from nonresponders were equivalent to those from responders, indicating that registry data could be valid despite a high rate of loss to follow-up.[18] Another limitation is the use of the KOOS as the only outcome measure. Additional outcome measures, such as radiographic assessments of osteoarthritis and activity level scores, could have reduced the potential risk of unmeasured predictors and confounders as well as potentially shed some light on the reasons for the findings of the current study. None of these additional parameters were recorded in either the NKLR or SKLR during the current study period. However, the reasons for choosing the KOOS as the patient-reported outcome measure in the registries, and its limitations, are carefully outlined and discussed in the previous literature.[10]

The main strengths of the present study are that patients from nationwide population-based registries were included, without restrictive inclusion or exclusion criteria, ensuring a large sample size and the representation of a wide range of patients, hospitals, and surgeons. This should in turn provide results that are applicable to a large group of orthopaedic patients and practices. In addition, the validity of the findings is strengthened by the comprehensive adjustment for predictors and confounders in the analyses. However, when using regression models to examine exposure-outcome associations, it is often a matter for discussion whether the appropriate confounders have been controlled for. As there are no standardized or validated sets of possible confounding variables considered to be requisite when developing such regression models, the choice of possible confounders in this study was based on the current literature, clinical assumptions, and available parameters recorded by the 2 national registries. Possible confounding variables such as smoking status, body mass index, and energy of the initial trauma were not included.

In summary, the main finding in the present study, that concomitant full-thickness cartilage lesions were an indicator of significant adverse effects on patient-reported outcomes 5 years after ACLR, should be taken into account and assist in counseling patients with this combined injury regarding the midterm prognosis after ACLR. Moreover, the results highlight the need for further research emphasizing the improvement of current treatment algorithms for patients with these combined injuries. In addition, future studies should distinguish the cartilage lesion depth, as this variable is significantly associated with patient-reported outcomes.

CONCLUSION

ACL-injured patients with concomitant full-thickness cartilage lesions reported worse outcomes and less improvement

than those without cartilage lesions 5 years after ACLR. There were no effects of lesion size on patient-reported outcomes in patients with full-thickness cartilage lesions. Concomitant partial-thickness cartilage lesions had statistically significant adverse effects on patient-reported outcomes at 5-year follow-up, but this finding may not be clinically significant. Cartilage lesion size ≥ 2 cm^2 was a significant predictor of inferior patient-reported outcomes at 5-year follow-up in patients with partial-thickness lesions.

ACKNOWLEDGMENT

REFERENCES

1. Ahlden M, Samuelsson K, Sernert N, Forssblad M, Karlsson J, Kartus J. The Swedish National Anterior Cruciate Ligament Register: a report on baseline variables and outcomes of surgery for almost 18,000 patients. *Am J Sports Med*. 2012;40(10):2230-2235.
2. Barenius B, Forssblad M, Engstrom B, Eriksson K. Functional recovery after anterior cruciate ligament reconstruction: a study of health-related quality of life based on the Swedish National Knee Ligament Register. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(4):914-927.
3. Bekkers JE, de Windt TS, Raijmakers NJ, Dhert WJ, Saris DB. Validation of the Knee injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions. *Osteoarthritis Cartilage*. 2009;17(11):1434-1439.
4. Brittberg M, Peterson L. Introduction of an articular cartilage classification. *ICRS Newsletter*. 1998;1:5-8.
5. Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. *J Bone Joint Surg Am*. 2003;85(suppl 2):58-69.
6. Claes S, Hermie L, Verdonk R, Bellemans J, Verdonk P. Is osteoarthritis an inevitable consequence of anterior cruciate ligament reconstruction? A meta-analysis. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(9):1967-1976.
7. Cox CL, Huston LJ, Dunn WR, et al. Are articular cartilage lesions and meniscus tears predictive of IKDC, KOOS, and Marx activity level outcomes after anterior cruciate ligament reconstruction? A 6-year multicenter cohort study. *Am J Sports Med*. 2014;42(5):1058-1067.
8. Engelhart L, Nelson L, Lewis S, et al. Validation of the Knee injury and Osteoarthritis Outcome Score subscales for patients with articular cartilage lesions of the knee. *Am J Sports Med*. 2012;40(10):2264-2272.
9. Filardo G, de Caro F, Andriolo L, Kon E, Zaffagnini S, Marcacci M. Do cartilage lesions affect the clinical outcome of anterior cruciate ligament reconstruction? A systematic review. *Knee Surg Sports Traumatol Arthrosc*. 2017;25(10):3061-3075.
10. Granan LP, Bahr R, Steindal K, Furnes O, Engebretsen L. Development of a national cruciate ligament surgery registry: the Norwegian National Knee Ligament Registry. *Am J Sports Med*. 2008;36(2):308-315.
11. Granan LP, Forssblad M, Lind M, Engebretsen L. The Scandinavian ACL registries 2004-2007: baseline epidemiology. *Acta Orthop*. 2009;80(5):563-567.
12. Hunziker EB, Lippuner K, Keel MJ, Shintani N. An educational review of cartilage repair: precepts & practice—myths & misconceptions—progress & prospects. *Osteoarthritis Cartilage*. 2015;23(3):334-350.

13. Janssen RP, du Mee AW, van Valkenburg J, Sala HA, Tseng CM. Anterior cruciate ligament reconstruction with 4-strand hamstring autograft and accelerated rehabilitation: a 10-year prospective study on clinical results, knee osteoarthritis and its predictors. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(9):1977-1988.
14. Keays SL, Newcombe PA, Bullock-Saxton JE, Bullock MI, Keays AC. Factors involved in the development of osteoarthritis after anterior cruciate ligament surgery. *Am J Sports Med*. 2010;38(3):455-463.
15. Li RT, Lorenz S, Xu Y, Harner CD, Fu FH, Irrgang JJ. Predictors of radiographic knee osteoarthritis after anterior cruciate ligament reconstruction. *Am J Sports Med*. 2011;39(12):2595-2603.
16. Maletis GB, Granan LP, Inacio MC, Funahashi TT, Engebretsen L. Comparison of community-based ACL reconstruction registries in the U.S. and Norway. *J Bone Joint Surg Am*. 2011;93(suppl 3):31-36.
17. Murray JR, Lindh AM, Hogan NA, et al. Does anterior cruciate ligament reconstruction lead to degenerative disease? Thirteen-year results after bone-patellar tendon-bone autograft. *Am J Sports Med*. 2012;40(2):404-413.
18. Rahr-Wagner L, Thillemann TM, Lind MC, Pedersen AB. Validation of 14,500 operated knees registered in the Danish Knee Ligament Reconstruction Register: registration completeness and validity of key variables. *Clin Epidemiol*. 2013;5:219-228.
19. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1:64.
20. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee injury and Osteoarthritis Outcome Score (KOOS): development of a self-administered outcome measure. *J Orthop Sports Phys Ther*. 1998;28(2):88-96.
21. Røtterud JH, Risberg MA, Engebretsen L, Årøen A. Patients with focal full-thickness cartilage lesions benefit less from ACL reconstruction at 2-5 years follow-up. *Knee Surg Sports Traumatol Arthrosc*. 2012;20(8):1533-1539.
22. Røtterud JH, Sivertsen EA, Forssblad M, Engebretsen L, Årøen A. Effect of gender and sports on the risk of full-thickness articular cartilage lesions in anterior cruciate ligament-injured knees: a nationwide cohort study from Sweden and Norway of 15 783 patients. *Am J Sports Med*. 2011;39(7):1387-1394.
23. Rotterud JH, Sivertsen EA, Forssblad M, Engebretsen L, Aroen A. Effect of meniscal and focal cartilage lesions on patient-reported outcome after anterior cruciate ligament reconstruction: a nationwide cohort study from Norway and Sweden of 8476 patients with 2-year follow-up. *Am J Sports Med*. 2013;41(3):535-543.
24. Shelbourne KD, Gray T. Minimum 10-year results after anterior cruciate ligament reconstruction: how the loss of normal knee motion compounds other factors related to the development of osteoarthritis after surgery. *Am J Sports Med*. 2009;37(3):471-480.
25. Shelbourne KD, Jari S, Gray T. Outcome of untreated traumatic articular cartilage defects of the knee: a natural history study. *J Bone Joint Surg Am*. 2003;85(suppl 2):8-16.
26. Spindler KP, Huston LJ, Wright RW, et al. The prognosis and predictors of sports function and activity at minimum 6 years after anterior cruciate ligament reconstruction: a population cohort study. *Am J Sports Med*. 2011;39(2):348-359.
27. Ulstein S, Bredland K, Aroen A, Engebretsen L, Rotterud JH. No negative effect on patient-reported outcome of concomitant cartilage lesions 5-9 years after ACL reconstruction. *Knee Surg Sports Traumatol Arthrosc*. 2016;25(5):1482-1488.
28. Widuchowski W, Widuchowski J, Koczy B, Szyluk K. Untreated asymptomatic deep cartilage lesions associated with anterior cruciate ligament injury: results at 10- and 15-year follow-up. *Am J Sports Med*. 2009;37(4):688-692.

IV

Original Research

A Controlled Comparison of Microfracture, Debridement, and No Treatment of Concomitant Full-Thickness Cartilage Lesions in Anterior Cruciate Ligament– Reconstructed Knees

A Nationwide Prospective Cohort Study From Norway and Sweden of 368 Patients With 5-Year Follow-up

Svend Ulstein,*[†‡§] MD, Asbjørn Årøen,[†‡§] MD, PhD, Lars Engebretsen,[§||¶] MD, PhD, Magnus Forssblad,[#**] MD, PhD, Stein Håkon Låstad Lygre,[††‡‡] MSc, PhD, and Jan Harald Røtterud,[†‡§] MD, PhD
Investigation performed at the Department of Orthopedic Surgery, Akershus University Hospital, Lørenskog, Norway

Background: The effect of microfracture (MF) or surgical debridement of concomitant full-thickness cartilage lesions in anterior cruciate ligament–reconstructed knees on patient-reported outcomes remains to be determined.

Purpose: To evaluate the effect of debridement or MF compared with no surgical treatment of concomitant full-thickness cartilage lesions on patient-reported outcomes 5 years after anterior cruciate ligament reconstruction (ACLR).

Study Design: Cohort study; Level of evidence, 2.

Methods: Included in this study were 644 patients who were registered in the Norwegian and the Swedish National Knee Ligament Registries from 2005 to 2008 as having undergone unilateral primary ACLR and having a concomitant full-thickness cartilage lesion (International Cartilage Repair Society [ICRS] grades 3-4). Of these patients, 129 were treated with debridement, 164 were treated with MF, and 351 received no surgical treatment simultaneously with ACLR. At 5-year follow-up, 368 (57%) patients completed results on the Knee injury and Osteoarthritis Outcome Score (KOOS). Multivariable linear regression was used to estimate the effect of surgical debridement or MF of concomitant full-thickness cartilage lesions on patient-reported outcomes 5 years after ACLR.

Results: Compared with no surgical treatment, there were no unadjusted or adjusted effects of debridement or MF of concomitant full-thickness cartilage lesions on KOOS scores at 5-year follow-up.

Conclusion: Compared with leaving concomitant full-thickness cartilage lesions untreated at the time of ACLR, debridement and MF showed no effect on patient-reported outcomes 5 years after surgery.

Keywords: knee; anterior cruciate ligament (ACL); reconstruction; cartilage lesions; debridement; microfracture; KOOS

Anterior cruciate ligament (ACL) injuries are commonly associated with focal cartilage lesions. In reports from large, sprospectively collected ACL cohorts, such as the Norwegian and Swedish National Knee Ligament Registries (NKLR and SKLR, respectively), concomitant full-thickness cartilage lesions (International Cartilage Repair Society [ICRS] grades 3-4) were present in 7% of ACL reconstructions (ACLRs).[23] In addition to being a significant predictor of later osteoarthritis of the knee joint,[6,15] a full-thickness cartilage lesion at the time of ACLR has been shown to have significant adverse effects on patient-reported outcomes.[7,23]

Previous literature has focused on comparing different surgical interventions, to a large extent circumnavigating the need for control groups and long-term follow-up.[18] To

1

that end, very little is known regarding the natural history of concomitant focal cartilage lesions.

There is a lack of knowledge regarding to what extent surgical interventions affect these lesions. Various surgical treatment options, ranging from debridement to advanced cell-based techniques, exist.[17] In addition to leaving the cartilage lesion untreated, debridement and microfracture (MF) are the most commonly used surgical treatment options.[10] However, only 1 randomized study[14] and 1 prospective cohort study[24] on the issue of ACLR with concomitant treatment of cartilage lesions have been published.[14,24] Hence, there is insufficient evidence to support any surgical gold-standard treatment option.

The primary objective of the present 5-year follow-up after ACLR was to evaluate the effect of surgical debridement or MF as compared with no surgical treatment of concomitant full-thickness cartilage lesions on patient-reported outcomes.

METHODS

NKLR and SKLR

After obtaining approval from the Regional Committee for Medical Research Ethics of South-Eastern Norway, University of Oslo, data were assembled from the NKLR and SKLR. The 2 national registries aggregate data from all surgical procedures performed on knee ligaments and prospectively monitor outcomes on a nationwide scale.[12,13] There are no major differences in the collection of data between the 2 countries, and in both registries, the surgeons' reporting rates are found to be satisfactory, with rates above 85%.[1,13]

The surgeons report patient-, knee-, and surgery-specific variables to the registries. As a part of that registration, the surgeons grade concomitant focal cartilage lesions according to the ICRS guidelines.[4,5] Cartilage lesion size is reported as area <2 cm^2 or ≥ 2 cm^2. The treating surgeon determines the treatment of concomitant cartilage lesions.

Before surgery, the patients complete an informed consent form allowing for later use of their registry data, including results on the Knee injury and Osteoarthritis Outcome Score (KOOS), which is used as the patient-reported outcome measure. The KOOS questionnaire consists of 42 questions distributed between 5 separately scored subscales: Pain, Symptoms, Activities of Daily Living (ADL), Sport and Recreation (Sport/Rec), and Knee-Related Quality of Life (QoL). It is established as a valid, reliable, and responsive assessment tool for patients with ACL and cartilage injuries.[2,9,22]

Patients

The current study is a longitudinal 5-year follow-up of a nationwide population-based cohort consisting of all patients who underwent unilateral primary ACLR between January 1, 2005, and December 31, 2008, and who were registered in the NKLR or SKLR with a concomitant ICRS grade 3 or 4 cartilage lesion. A total of 1012 patients were prospectively registered. This patient cohort has previously been described in a study on the effects of surgical debridement or MF of concomitant full-thickness cartilage lesions on 2-year patient-reported outcomes.[24]

Apart from having a full-thickness cartilage lesion and completing the KOOS preoperatively, eligible patients had to be registered as undergoing no treatment, debridement, or MF of the cartilage lesion. Patients with more than 1 concomitant cartilage lesion were categorized according to the lesion with the highest ICRS grade. Overall, 368 patients did not meet the inclusion criteria because of missing preoperative KOOS data (n = 239) or because the treatment of the cartilage lesion was not reported or was reported as other than no treatment, debridement, or MF (n = 129). Of the 644 patients who fulfilled the inclusion criteria, 351 (54%) received no surgical treatment of their cartilage lesion at the time of ACLR, 129 (20%) were treated with debridement, and 164 (26%) were treated with MF.

At a mean follow-up of 5.1 ± 0.1 years, KOOS data were available for 368 (57%) of the included patients, who had a mean age of 41.2 ± 10.4 years. There were 276 (43%) patients who did not return their 5-year follow-up KOOS questionnaire and were considered lost to follow-up. Patient flow during inclusion and follow-up is shown in Figure 1, and baseline characteristics at the time of ACLR for the patients available for follow-up and those lost to follow-up are shown in Table 1. Patients lost to follow-up tended to be younger, and a higher proportion of them were male. Except for a difference in the proportion of grade 4 lesions and the prevalence of >1 full-thickness cartilage lesions, there were no substantial differences between these groups in baseline characteristics.

*Address correspondence to Svend Ulstein, MD, Department of Orthopedic Surgery, Akershus University Hospital, Sykehusveien 25, 1478 Lørenskog, Norway (email: svend.ulstein@ahus.no).

†Department of Orthopedic Surgery, Akershus University Hospital, Lørenskog, Norway.
‡Institute of Clinical Medicine, University of Oslo, Oslo, Norway.
§Oslo Sports Trauma Research Center, Norwegian School of Sport Sciences, Oslo, Norway.
‖Department of Orthopaedic Surgery, Oslo University Hospital, Oslo, Norway.
¶Norwegian Cruciate Ligament Register, Bergen, Norway.
#Capio Artro Clinic, Sophiahemmet, Stockholm, Sweden.
**Stockholm Sports Trauma Research Center, Karolinska Institutet, Stockholm, Sweden.
††Norwegian Arthroplasty Register, Haukeland University Hospital, Bergen, Norway.
‡‡Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway.
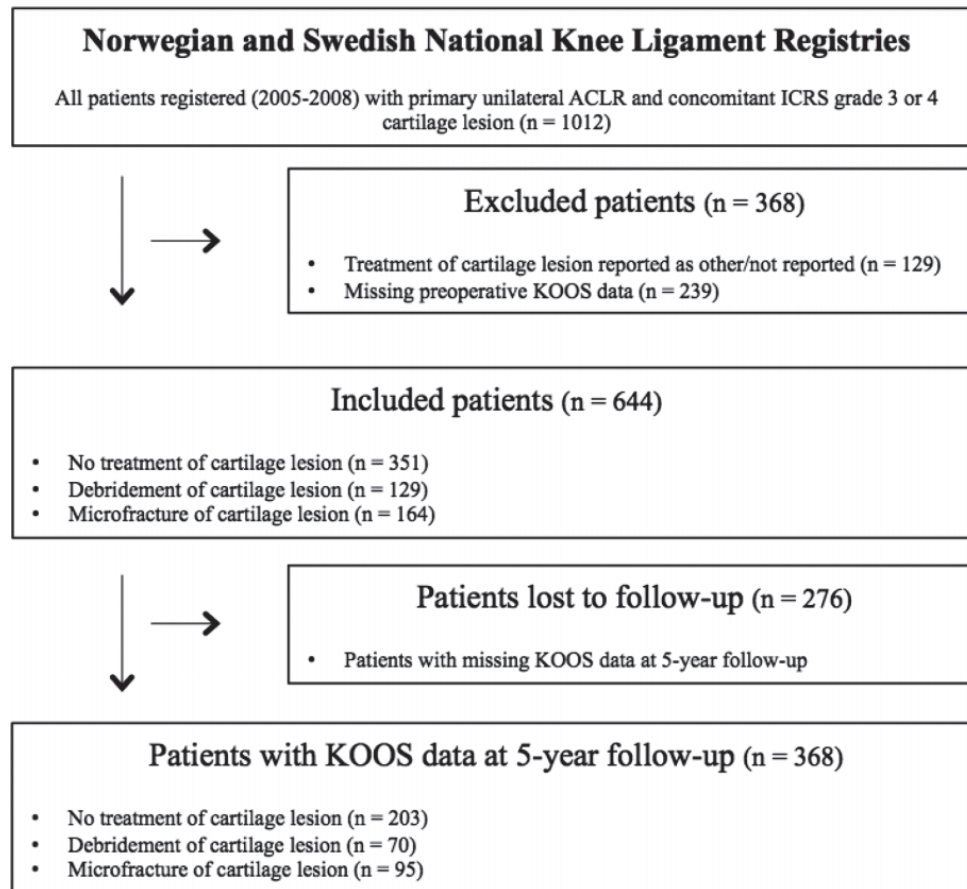
Figure 1. Flowchart of the patients during inclusion and follow-up. ACLR, anterior cruciate ligament reconstruction; ICRS, International Cartilage Repair Society; KOOS, Knee injury and Osteoarthritis Outcome Score.

Statistical Analysis

SPSS software version 24.0 (IBM) was used for all statistical analyses. P values $<.05$ were considered statistically significant. Crude mean KOOS scores and standardized regression coefficients are presented with 95% CIs.

Crude mean KOOS scores preoperatively and at 5-year follow-up were estimated and stratified by treatment (ie, no treatment, debridement, or MF) of concomitant cartilage lesions. Multivariable linear regression was used to assess the possible impact on 5-year follow-up KOOS scores of surgical debridement or MF for concomitant full-thickness cartilage lesions. No surgical treatment of full-thickness cartilage lesions was used as a reference in all regression analyses. Results are presented as both unadjusted and adjusted for possible confounding from sex, age at surgery (continuous variable), previous ipsilateral knee surgery (yes/no), concomitant ligament injury (yes/no), concomitant meniscal injury (yes/no), concomitant meniscal resection (yes/no), time from injury to surgery (continuous variable), area of cartilage lesion ($<2\,\mathrm{cm}^2$ or $\geq 2\,\mathrm{cm}^2$), depth of cartilage lesion (ICRS grade 3 or 4), location of cartilage lesion (patella, trochlea, medial femoral condyle, lateral femoral condyle, medial tibial plateau, or lateral tibial plateau), type of ACL graft (hamstring, patellar tendon, or other), and preoperative KOOS subscale scores (continuous variable).

RESULTS

Of the 368 patients available for follow-up at 5 years, 203 (55%) patients received no surgical treatment of their full-thickness cartilage lesion at the time of ACLR, 70 (19%) were treated with debridement, and 95 (26%) were treated with MF. The crude mean KOOS scores for the 3 study groups (ie, no treatment, debridement, and MF) are shown in Table 2. Figure 2 illustrates the changes in mean KOOS scores from preoperatively to 5-year follow-up for the 3 study groups. The results for the unadjusted and adjusted effects of debridement and MF on each of the KOOS subscales at 5-year follow-up are shown in Table 3. With no treatment of concomitant cartilage lesions as the reference, there were no significant effects of debridement or MF detected in the unadjusted or adjusted regression analyses on any of the KOOS subscales at 5-year follow-up. However, based on the 95% CIs, there was a trend in both the

TABLE 1
Baseline Characteristics at the Time of ACL Reconstruction[a]

	Patients Available at Follow-up (n = 368)			
	No Treatment (n = 203)	Debridement (n = 70)	Microfracture (n = 95)	Patients Lost to Follow-up (n = 276)
Age at surgery, median (range), y	37 (14-59)	37 (15-64)	35 (15-62)	32 (15-55)
Time from injury to surgery, median (range), mo	16 (0-348)	18 (1-260)	21 (1-482)	14 (0-359)
Female sex, n (%)	96 (47)	26 (37)	46 (48)	71 (26)
Previous ipsilateral knee surgery, n (%)	102 (50)	22 (31)	30 (32)	98 (36)
Concomitant ligament injury,[b] n (%)	21 (10)	8 (11)	9 (10)	19 (7)
Concomitant meniscal lesion, n (%)	110 (54)	46 (65)	61 (64)	165 (60)
Meniscal resection, n (%)	85 (42)	41 (59)	48 (50)	121 (44)
ACL graft, n (%)				
Hamstring tendon	152 (75)	53 (76)	76 (80)	216 (78)
Bone–patellar tendon–bone	48 (24)	14 (20)	19 (20)	54 (20)
Other/unknown	3 (1)	3 (4)	0 (0)	6 (2)
>1 full-thickness cartilage lesions (ICRS grades 3-4), n (%)	36 (18)	9 (13)	3 (3)	30 (11)
Depth (ICRS grade 4), n (%)	42 (21)	8 (11)	51 (54)	69 (25)
Area, n (%)				
<2 cm^2	94 (46)	24 (34)	57 (60)	123 (45)
≥2 cm^2	107 (53)	46 (66)	38 (40)	145 (52)
Not reported	2 (1)	0 (0)	0 (0)	8 (3)
Location, n (%)				
Patella	11 (5)	6 (9)	1 (1)	18 (6)
Trochlea	16 (8)	3 (4)	4 (4)	10 (4)
Medial femoral condyle	128 (63)	53 (76)	78 (82)	195 (71)
Lateral femoral condyle	27 (13)	7 (10)	7 (7)	35 (13)
Medial tibial plateau	6 (3)	1 (1)	3 (3)	6 (2)
Lateral tibial plateau	15 (7)	0 (0)	2 (2)	12 (4)
Preoperative KOOS score, mean ± SD				
Pain	70.0 ± 19.4	70.7 ± 18.9	68.5 ± 18.5	69.9 ± 19.6
Symptoms	68.0 ± 19.3	68.4 ± 18.1	66.2 ± 19.2	66.8 ± 18.6
ADL	78.2 ± 19.1	80.2 ± 17.5	77.4 ± 19.5	77.7 ± 20.1
Sport/Rec	38.1 ± 28.7	38.6 ± 27.0	30.0 ± 24.2	36.0 ± 27.6
QoL	30.8 ± 19.0	32.6 ± 16.6	28.6 ± 17.5	30.9 ± 18.5

[a]ACL, anterior cruciate ligament; ADL, Activities of Daily Living; ICRS, International Cartilage Repair Society; KOOS, Knee injury and Osteoarthritis Outcome Score; QoL, Knee-Related Quality of Life; Sport/Rec, Sport and Recreation.
[b]Medial collateral ligament, lateral collateral ligament, posterior cruciate ligament, or posterolateral corner.

TABLE 2
Crude KOOS Scores by Treatment of Cartilage Lesions at 5-Year Follow-up
After Anterior Cruciate Ligament Reconstruction[a]

KOOS Subscale	No Treatment (n = 203)	Debridement (n = 70)	Microfracture (n = 95)
Pain	81.5 (79.0-84.1)	82.1 (77.7-86.5)	78.5 (74.6-82.5)
Symptoms	75.1 (72.4-77.9)	78.0 (73.0-83.0)	73.4 (69.6-77.2)
ADL	87.5 (85.1-89.6)	89.5 (85.5-93.5)	85.2 (81.4-88.9)
Sport/Rec	63.2 (59.2-67.3)	68.2 (62.0-74.5)	57.5 (51.9-63.0)
QoL	61.6 (58.0-65.1)	65.7 (58.9-72.6)	55.6 (50.8-60.4)

[a]Values are shown as mean (95% CI). ADL, Activities of Daily Living; KOOS, Knee injury and Osteoarthritis Outcome Score; QoL, Knee-Related Quality of Life; Sport/Rec, Sport and Recreation.

unadjusted and the adjusted analyses toward negative effects of MF on the KOOS Sport/Rec and QoL subscales.

DISCUSSION

The main finding of the present study is that, compared with patients who received no surgical treatment of their concomitant full-thickness cartilage lesion at the time of ACLR, surgical debridement and MF had no effect on patient-reported outcomes as measured by the KOOS at 5-year follow-up. To date, this is the largest multivariable model assessing the midterm outcomes of the surgical treatment of these concomitant injuries and the only study to have included a control group with the cartilage lesion left untreated.
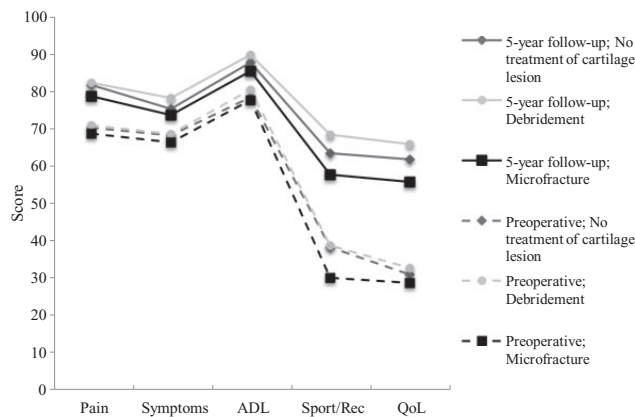
Figure 2. Profiles of mean Knee injury and Osteoarthritis Outcome Score values of patients undergoing no treatment, debridement, or microfracture of concomitant full-thickness cartilage lesions preoperatively and at 5-year follow-up after anterior cruciate ligament reconstruction. ADL, Activities of Daily Living; QoL, Knee-Related Quality of Life; Sport/Rec, Sport and Recreation.

The findings from the present 5-year longitudinal follow-up indicate a loss of magnitude of the adverse effects of MF over time, as significant negative effects of MF on KOOS scores were observed at 2-year follow-up in the same cohort.[24] Nevertheless, there was a trend in the analyses toward negative effects of MF on the KOOS Sport/Rec and QoL subscales in the present study as well, thus adding support to the view that there should be a restrictive use

of MF as a first-line treatment of full-thickness cartilage lesions in the setting of ACLR. Compared with the 2-year follow-up of the current cohort, the crude mean KOOS Sport/Rec and QoL subscores improved for all 3 patient categories, but no significant between-group differences in change over time were observed.

In the only randomized study on the concomitant treatment of cartilage lesions in the setting of ACLR, Gudas et al[14] compared the 3-year patient-reported outcomes after debridement, MF, and osteochondral autograft transfer (OAT). Those authors reported significantly better outcomes, as measured by the International Knee Documentation Committee (IKDC) form, in patients treated with OAT than in patients treated with MF or debridement. Moreover, no differences were detected between patients treated with MF and debridement.[14] However, the absence of a control group of patients with the cartilage lesion left untreated in that study makes it difficult to evaluate the actual effect of MF or debridement.

Despite an emerging recognition that the results after MF deteriorate over time,[16,20] it remains the most commonly performed cartilage procedure.[11,18] In addition to the inferior biochemical and histological properties associated with the resultant fibrocartilaginous repair tissue, more recently, subchondral bone overgrowth has been suggested as another factor in the deterioration of knee function seen in some patients after MF.[19] However, the current observational study design does not allow for assessments regarding those aforementioned factors. Even if debridement usually is understood as a removal of unstable or loose flaps of cartilage to leave stable edges of the lesion, the potential of variation and diversity during surgery is

TABLE 3
Unadjusted and Adjusted Regression Analyses of the Associations Between KOOS Subscales
and Treatment of Cartilage Lesions at 5-Year Follow-up After ACL Reconstruction[a]

KOOS Subscale	n	Debridement[b]			Microfracture[b]		
		β	95% CI	*P* Value	β	95% CI	*P* Value
Pain							
Unadjusted	367	0.6	−4.6 to 5.7	.83	−3.0	−7.6 to 1.6	.20
Adjusted	346	−1.0	−5.9 to 3.9	.69	−1.7	−6.2 to 2.8	.46
Symptoms							
Unadjusted	368	2.9	−2.5 to 8.3	.30	−1.7	−6.5 to 3.1	.49
Adjusted	348	2.2	−3.2 to 7.6	.42	0.3	−4.7 to 5.4	.90
ADL							
Unadjusted	367	2.1	−2.7 to 6.8	.40	−2.3	−6.6 to 2.0	.30
Adjusted	346	0.2	−4.3 to 4.7	.93	−1.8	−6.0 to 2.3	.39
Sport/Rec							
Unadjusted	338	5.0	−2.7 to 12.8	.20	−5.7	−12.7 to 1.2	.10
Adjusted	319	2.9	−5.0 to 12.8	.46	−5.0	−12.3 to 2.2	.17
QoL							
Unadjusted	361	4.1	−2.9 to 11.2	.25	−6.0	−12.3 to 0.4	.06
Adjusted	341	1.8	−5.5 to 9.1	.62	−5.7	−12.5 to 1.1	.10

[a]Adjusted for sex, age, previous ipsilateral knee surgery, time from injury to surgery, concomitant ligament injury, concomitant meniscal lesion, meniscal resection, type of ACL graft, area of cartilage lesion, depth (International Cartilage Repair Society) of cartilage lesion, location of cartilage lesion, and preoperative KOOS scores. ACL, anterior cruciate ligament; ADL, Activities of Daily Living; β, regression coefficient; KOOS, Knee injury and Osteoarthritis Outcome Score; QoL, Knee-Related Quality of Life; Sport/Rec, Sport and Recreation.
[b]No treatment of cartilage lesions used as the reference.

present. There are indications that aggressive, deep removal of the calcified cartilage layer represents a significant risk factor for subchondral bone overgrowth.[19] As subchondral bone overgrowth has been associated with postoperative failure after MF, one might hypothesize that this phenomenon might play a role in the postoperative course after debridement as well. Nevertheless, when compared with no treatment of full-thickness cartilage lesions, debridement showed no effect on KOOS scores at 2-year and 5-year follow-up in the current cohort. That finding is in line with the findings in a recent randomized controlled trial demonstrating no benefit of debridement of chondral lesions encountered during arthroscopic partial meniscectomy.[3] However, as pointed out in a recent systematic review,[10] considerable heterogeneity in patients, injuries, surgical factors, outcome measurements, and observation periods exists among the different reports, making it difficult to directly compare the findings from these studies.

The observational study design has limitations, as is the case in the present study as well. The main limitation of the present study is the rate of loss to 5-year follow-up (43%), with the potential of introducing attrition bias. Even though the baseline characteristics of the study cohort and those lost to follow-up were comparable in the majority of the reported baseline variables, patients lost to follow-up were younger, had a higher proportion of men, and had a shorter time from injury to surgery than the patients available for follow-up. As cartilage surgery tends to be more successful in young patients with fewer long-standing cartilage lesions, there is a possibility that those patients lost to follow-up have affected the results.[8] On the other hand, those factors, together with other factors most likely to have affected the prognosis and outcomes after surgery, were adjusted for in the multivariable regression analyses. Moreover, in a validation of the Danish Ligament Reconstruction Register, the KOOS scores from nonresponders were comparable with those of responders, thus indicating that registry data could be valid despite a high rate of loss to follow-up.[21] Other limitations are the lack of randomization and the use of the KOOS as the only outcome measure. Supplementary outcome measures, such as radiographic assessments of osteoarthritis and activity level scales, would have strengthened the present study and reduced the potential risk of unmeasured predictors and confounders. Randomization would have reduced the potential risk of uneven distribution of such hidden confounders and predictors.

The main strengths of the present study are the large sample size and the inclusion of a control group of patients with the concomitant cartilage lesion left untreated. Thus, we were able to investigate the actual treatment effect of debridement and MF on patient-reported outcomes. Moreover, the inclusion of patients from nationwide population-based registries ensures the representation of a wide range of patients, hospitals, and surgeons. This should in turn provide results that are relevant to most clinical settings. Finally, the comprehensive adjustment for predictors and confounders in the analyses should provide valid estimates of the effect of the different surgical treatment options. However, it will often be a matter of discussion whether the appropriate confounders have been controlled for. There are no standardized or validated sets of possible confounding variables considered to be requisite, so the included variables had to be based on the current literature, clinical assumptions, and available parameters recorded by the 2 national registries. Possible confounding variables such as smoking status, body mass index, and energy of the initial trauma were not included in the current regression model. However, because of the even distribution of patients lost to follow-up between the groups, the demographic similarities between the groups, and the comprehensive adjustment for possible confounders in the regression analyses, it is not likely that additional adjustments would alter the results substantially. At least, it is highly unlikely that the results would be altered to the extent that they would demonstrate a beneficial effect of MF.

In summary, the findings in the present study should be taken into account and assist patient counseling and decision making regarding the surgical treatment of concomitant cartilage lesions. The findings in the present study suggest that the concomitant treatment of full-thickness cartilage lesions with MF or debridement does not show the anticipated effect on patient-reported outcomes at midterm follow-up after ACLR. More research is needed to optimize the clinical management of these combined injuries and, in addition to including a control group with the cartilage lesion left untreated, should focus on identifying whether there are any subgroups of patients that benefit from debridement or MF.

CONCLUSION

Compared with leaving concomitant full-thickness cartilage lesions untreated at the time of ACLR, debridement and MF showed no effect on patient-reported outcomes at 5-year follow-up. Taking into account the fact that MF showed significant adverse effects on KOOS scores at 2-year follow-up in the current cohort,[24] MF should probably be used with caution in the setting of ACLR.

ACKNOWLEDGMENT

REFERENCES

1. Ahlden M, Samuelsson K, Sernert N, Forssblad M, Karlsson J, Kartus J. The Swedish National Anterior Cruciate Ligament Register: a report on baseline variables and outcomes of surgery for almost 18,000 patients. *Am J Sports Med*. 2012;40(10):2230-2235.
2. Bekkers JE, de Windt TS, Raijmakers NJ, Dhert WJ, Saris DB. Validation of the Knee injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions. *Osteoarthritis Cartilage*. 2009;17(11):1434-1439.

3. Bisson LJ, Kluczynski MA, Wind WM, et al. Patient outcomes after observation versus debridement of unstable chondral lesions during partial meniscectomy: the Chondral Lesions And Meniscus Procedures (ChAMP) randomized controlled trial. *J Bone Joint Surg Am*. 2017;99(13):1078-1085.

4. Brittberg M, Peterson L. Introduction to an articular cartilage classification. *ICRS Newsletter*. 1998;1:5-8.

5. Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. *J Bone Joint Surg Am*. 2003;85-A (suppl 2):58-69.

6. Claes S, Hermie L, Verdonk R, Bellemans J, Verdonk P. Is osteoarthritis an inevitable consequence of anterior cruciate ligament reconstruction? A meta-analysis. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(9):1967-1976.

7. Cox CL, Huston LJ, Dunn WR, et al. Are articular cartilage lesions and meniscus tears predictive of IKDC, KOOS, and Marx activity level outcomes after anterior cruciate ligament reconstruction? A 6-year multicenter cohort study. *Am J Sports Med*. 2014;42(5):1058-1067.

8. de Windt TS, Bekkers JE, Creemers LB, Dhert WJ, Saris DB. Patient profiling in cartilage regeneration: prognostic factors determining success of treatment for cartilage defects. *Am J Sports Med*. 2009;37 (suppl 1):58S-62S.

9. Engelhart L, Nelson L, Lewis S, et al. Validation of the Knee injury and Osteoarthritis Outcome Score subscales for patients with articular cartilage lesions of the knee. *Am J Sports Med*. 2012;40(10):2264-2272.

10. Filardo G, de Caro F, Andriolo L, Kon E, Zaffagnini S, Marcacci M. Do cartilage lesions affect the clinical outcome of anterior cruciate ligament reconstruction? A systematic review. *Knee Surg Sports Traumatol Arthrosc*. 2017;25(10):3061-3075.

11. Goyal D, Keyhani S, Lee EH, Hui JH. Evidence-based status of microfracture technique: a systematic review of level I and II studies. *Arthroscopy*. 2013;29(9):1579-1588.

12. Granan LP, Bahr R, Steindal K, Furnes O, Engebretsen L. Development of a national cruciate ligament surgery registry: the Norwegian National Knee Ligament Registry. *Am J Sports Med*. 2008;36(2):308-315.

13. Granan LP, Forssblad M, Lind M, Engebretsen L. The Scandinavian ACL registries 2004-2007: baseline epidemiology. *Acta Orthop*. 2009;80(5):563-567.

14. Gudas R, Gudaite A, Mickevicius T, et al. Comparison of osteochondral autologous transplantation, microfracture, or debridement techniques in articular cartilage lesions associated with anterior cruciate ligament injury: a prospective study with a 3-year follow-up. *Arthroscopy*. 2013;29(1):89-97.

15. Janssen RP, du Mee AW, van Valkenburg J, Sala HA, Tseng CM. Anterior cruciate ligament reconstruction with 4-strand hamstring autograft and accelerated rehabilitation: a 10-year prospective study on clinical results, knee osteoarthritis and its predictors. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(9):1977-1988.

16. Krych AJ, Pareek A, King AH, Johnson NR, Stuart MJ, Williams RJ 3rd. Return to sport after the surgical management of articular cartilage lesions in the knee: a meta-analysis. *Knee Surg Sports Traumatol Arthrosc*. 2017;25(10):3186-3196.

17. Makris EA, Gomoll AH, Malizos KN, Hu JC, Athanasiou KA. Repair and tissue engineering techniques for articular cartilage. *Nat Rev Rheumatol*. 2015;11(1):21-34.

18. Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. *Am J Sports Med*. 2009;37(10):2053-2063.

19. Mithoefer K, Venugopal V, Manaqibwala M. Incidence, degree, and clinical effect of subchondral bone overgrowth after microfracture in the knee. *Am J Sports Med*. 2016;44(8):2057-2063.

20. Pareek A, Reardon PJ, Macalena JA, et al. Osteochondral autograft transfer versus microfracture in the knee: a meta-analysis of prospective comparative studies at midterm. *Arthroscopy*. 2016;32(10):2118-2130.

21. Rahr-Wagner L, Thillemann TM, Lind MC, Pedersen AB. Validation of 14,500 operated knees registered in the Danish Knee Ligament Reconstruction Register: registration completeness and validity of key variables. *Clin Epidemiol*. 2013;5:219-228.

22. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee injury and Osteoarthritis Outcome Score (KOOS): development of a self-administered outcome measure. *J Orthop Sports Phys Ther*. 1998;28(2):88-96.

23. Rotterud JH, Sivertsen EA, Forssblad M, Engebretsen L, Aroen A. Effect of meniscal and focal cartilage lesions on patient-reported outcome after anterior cruciate ligament reconstruction: a nationwide cohort study from Norway and Sweden of 8476 patients with 2-year follow-up. *Am J Sports Med*. 2013;41(3):535-543.

24. Rotterud JH, Sivertsen EA, Forssblad M, Engebretsen L, Aroen A. Effect on patient-reported outcomes of debridement or microfracture of concomitant full-thickness cartilage lesions in anterior cruciate ligament-reconstructed knees: a nationwide cohort study from Norway and Sweden of 357 patients with 2-year follow-up. *Am J Sports Med*. 2016;44(2):337-344.