Knee cartilage surgery: epidemiology, research methods and a proposal for improved surveillance

PhD thesis

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2017

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Norwegian School of Sports Sciences

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University of Oslo

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-8377-027-8

Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

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Acknowledgements

The present work was carried out during the years 2009-2017. In the beginning of this period, I was a medical student in the research program at the Faculty of Medicine at the University of Oslo (2009-2011). I continued working with the project as a PhD-student at the Oslo Sports Trauma Research Center (OSTRC), Norwegian School of Sports Sciences from March 2014. The work has been carried out in close collaboration with the Department of Orthopedics, Oslo University Hospital, Ullevål and the Department of Orthopedic Surgery, Akershus University Hospital. The project was funded through grants from the South-Eastern Norway Regional Health Authority (Helse Sør-Øst), the OSTRC and Sophies Minde.

Through these years, I have met so many smart, nice, talented and helpful people to whom I will be forever grateful.

Lars Engebretsen introduced me to this field. He has been my supervisor and an inspiration to me from the first time we met. Your capacity and knowledge seem to be without boundaries and you find solutions to any challenge or obstacle. Thank you for all pep talks and advices, both professional and private.

I am also very grateful to my co-supervisor Asbjørn Årøen. You are attentive and enthusiastic. You are like a bank of good ideas and your insight in methodology and critical thinking is impressive. I have also had the pleasure of consulting you on clinical questions, and your answers are always well reasoned. Also, thank you for the great work with reconstructing my ACL!

There are several others that in one way have been involved in the project, or as a colleague at the OSTRC and SIM:

I have had the pleasure of several conversations and discussions with Sverre Løken along the way. You are reliable and observant. You have the ability of getting an overview of any text or project, which I have learnt a lot from.

Sigmund Andersen, thank you for your consideration and support. You have the ability to see everyone around you, and I appreciate it.

Thank you for all the conversations and open doors, Roald Bahr, May Arna Risberg, Grethe Myklebust, Tone Øritsland, Christine Holm Moseid and Thor-Einar Andersen. Thank you for your help and insight in computer-related and statistical issues, Oliver Faul, Elin Kolle, Jostein Steene-Johannessen, Guri

Ranum Ekås, Guro Pauck Bernhardsen, Knut Eirik Dalene and Bjørge Herman Hansen. In addition, thanks to all other colleagues at the OSTRC and SIM for sharing both fun and challenging periods but nevertheless have made it great to come to work.

Specifically, thank you for your assistance in removing all the rocks from the boat, Julie Stang. I have learnt so much from you and I appreciate your friendship.

Finally, I would like to send my gratitude to all of my family and friends for support and patience. Thank you for all the quizzes and preps throughout the years, grandma and grandpa. And Lars (Fafakongen), my favorite person in the world. Whom I was so lucky to meet during the PhD-courses. You are my hero, my motivator, my best friend and my love.

Cathrine Nørstad Engen

Oslo, January 9th 2017

Abbreviations and definitions

ACI	Autologous chondrocyte implantation, refers to a surgical technique in cartilage repair
ACL	Anterior cruciate ligament
Clinical equipoise	The uncertainty to whether an intervention is beneficial
dGEMRIC	delayed Gadolinium-Enhanced Magnetic Resonance Imaging of cartilage
Effectiveness	Whether an intervention has effect in an uncontrolled, or real-life, setting, larger patient populations or different surgeons.
Efficacy	The effect of an intervention, or treatment, when measured under controlled settings, meaning the difference between two different techniques/instruments/medications excluding patient factors
External validity	Measures the generalizability of results from a study
FCD	Focal cartilage defect
Focal cartilage defects	Cartilage defects include a single or several focal lesions or it might constitute generalized degenerative changes within the knee. Focal lesions are either traumatic or non-traumatic and even degenerative, and some exist without causing symptoms. Cartilage injuries can be large or small, partial-thickness or full-thickness and localization might vary. They are believed to lead to a chronic osteoarthritic stage with pain and reduced function, despite demonstrated only in animal models.[1]
ICC	Intraclass correlation coefficient
ICRS	International Cartilage Repair Society
KOOS	Knee Injury and Osteoarthritis Outcome Score

K&L	Kellgren and Lawrence, refers to a radiological grading system of osteoarthritis
OAT	Osteochondral autograft, refers to a surgical technique in cartilage repair
LFC	Lateral Femoral Condyle
LTP	Lateral Tibial Plateau
MF	Microfracture, refers to a surgical technique in cartilage repair
MFC	Medial Femoral Condyle
MP	Mosaic Plasty, refers to a surgical technique in cartilage repair
MRI	Magnetic Resonance Imaging
MTP	Medial Tibial Plateau
NKLR	Norwegian Knee Ligament Register
NPR	National Patient Register
OA	Osteoarthritis
Phase-III-study	The drug/intervention is given to a larger population with an aim of confirming effectiveness and monitoring side effects. It is also comparable to other commonly known procedures at this stage, although without the gold standard comparison possible in an RCT.
Phase-IV-study	The drug/intervention is released to the free market and the effectiveness of long-term use, or long-term results, is monitored along with side effects.
PROMs	Patient reported outcome measures
ROI	Region of interest

Papers

Paper I

Engen CN, Årøen A, Engebretsen L. Incidence of knee cartilage surgery in Norway, 2008-2011. BMJ Open. 2015 Nov 30;5(11):e008423.

Paper II

Engen CN, Engebretsen L, Årøen A. Knee Cartilage Defect Patients Enrolled in Randomized Controlled Trials Are Not Representative of Patients in Orthopedic Practice. Cartilage. 2010 Oct;1(4):312-9.

Paper III

Engen CN, Løken S, Årøen A, Ho C and Engebretsen L. No degeneration found in focal cartilage defects evaluated with dGEMRIC at 12-year follow-up. Acta Orthop. 2016 Nov 24:1-9.

Paper IV

Engen CN, Årøen A, Engebretsen L. Development of a pilot cartilage surgery register. Manuscript, submitted to *BMC musculoskeletal disorders*.

Summary

Focal articular cartilage defects (FCDs) of the knee are identified in 20% of knee arthroscopies[2] and are affecting a large and severely troubled group of young, adult patients.[3] FCDs may subsequently lead to knee osteoarthritis (OA).[4-6] An obvious treatment goal is repair of the cartilage defect allowing patients to live their usual life and delay, or better still in the long run, avoid, joint replacement surgery. Existing treatments involve physical training, palliating surgical procedures, bone marrow–stimulating techniques and more advanced cartilage surgery. The results from clinical cohort studies and randomized controlled trials (RCTs) are conflicting, and no current gold-standard treatment exists. RCTs assess efficacy of interventions, but the effectiveness of cartilage surgery is unknown. Furthermore, cartilage surgery has not been compared to non-operative treatment under randomized and controlled conditions. In addition, the methodological quality of the majority of published studies is low. It is time for a comprehensive and standardized long-time follow-up of these patients, preferably through a register. However, there are some limitations and challenges that must be cleared out in advance.

The aims of the PhD-project were to outline epidemiological data of cartilage surgery in Norway and the external validity of RCTs. Furthermore, we studied the long-term effect of FCDs and biomarkers of early OA. Resolving these issues may lead to more standardized and less variations in treatment. Finally, we explored the prospects of a cartilage surgery register through a pilot.

The results show that cartilage surgery in Norway is common and there are large variations. The external validity in RCTs on cartilage surgery is low. There are currently difficulties with long-term follow-up as we are lacking reliable biomarkers. The results from this project support the establishment of a future cartilage surgery register, although the identified challenges must be continuously handled. Together with experiences from other registers, this project will serve as valuable information for optimizing the design of a potential cartilage surgery register.

Theoretical background

Epidemiology

Knee cartilage defects are well-known after the introduction of knee arthroscopy and MRI. Arthroscopic studies have shown that FCDs within the knee occur in 19-67% of patients with painful knees.[2;7-9] Knee cartilage defects also occur in healthy subjects,[7;9] and an MRI-study including healthy subjects

found that 37% had cartilage defects.[10] Increasing age and BMI are linked to increased prevalence and severity of cartilage injuries in healthy subjects.[7;11]

A systematic review found a prevalence of 36% in athletes examined by arthroscopy, MRI or both.[12] High-level sports are linked to increased incidence of cartilage defects, although most are asymptomatic.[13] Also asymptomatic collegiate basketball players were examined with MRI and 41% had abnormal cartilage signal or a focal abnormality.[14] None of the players had meniscal abnormalities. FCDs are commonly present in the general population, in subjects with knee pain and in athletes.

Impact on health system and society

A painful knee is a common reason for seeking medical assistance, and a report shows that nearly 14% of acute consultations within the primary health services in Norway constitute diagnosis affecting the musculoskeletal system and connective tissue.[15] Data available in Statbank provided by the Statistics Norway (SSB) illustrate that more than 10% of all consultations in the specialist health services constitute patients with musculoskeletal complaints. Lærum et al. estimates the yearly total costs for this group in Norway to be 70 billion NOK (10 billion USD), whereas the cost within specialist health services is 7.7 billion NOK. These numbers position this patient population as the most expensive patient group in Norway after psychiatric disorders.[16] Other studies have shown that musculoskeletal disorders cause 21% of all years lived with disability (YLDs) on a global scale.[17]

The population of patients with diseases or injuries within the musculoskeletal system is heterogeneous. Patients with cartilage defects are often young people early in their working career and many are competing in high-performance sports. They have increased risk of repeated periods of absence from work due to sick-leave and premature working disability. Knee symptoms in younger adults lead to not only physical impairments, but also a disrupted emotional and social life, and a different way of thinking about one's body and self.[18] Knee symptoms thereby influence recreational activities as well as work and social life. The young age of this patient population leads to a higher cumulative costs over the years.

FCDs increase the risk of OA.[5;6;19] The development of OA is gradual and includes increasing pain and stiffness and reduced joint function. Knee arthroplasty is not recommended for younger patients as the prosthesis has limited durability. The development of OA depends on genetics, age, gender

(higher risk in females), previous knee injury, local mechanical factors such as unfavorable axis or increased compression and stress from obesity or systemic factors.[20] Due to the disabling clinical picture and widespread disease, a major task for both physical health and socioeconomic costs is to delay or avoid the development of OA. Therefore, there may be a potential for larger savings if research is focused on the early stage of OA development, as FCDs are central risk and prognostic factors of knee OA.

What is cartilage, and what happens with injury?

The articular cartilage protects the intraarticular joint surfaces. It is of hyaline type and contains mainly water (around 70% of weight) and proteoglycans (3-10%) embedded in a collagenous framework (15-20%). It is normally 2-4 mm thick and an MRI-study found a mean average cartilage thickness of 2.28 mm in the weight bearing areas of the femoral condyles.[21]

The cartilage structure is important for proper joint function and it has the possibility of withstanding large amounts of load as well as providing low-friction movements throughout the lifespan of a person. The water molecules are held within a collagenous framework during loading. The smooth surface results from the superficial layer where the fibers are oriented horizontally. This layer has the highest potential of deformation during compression. The middle and deeper zone have less organized collagen with obliquely and perpendicularly oriented fibrils, withstand more effectively compression, have higher content of proteoglycan and lower content of water.[22]

When trauma, infection, fractures or degeneration causes disruption of the superficial layer, the homeostasis is changed and water molecules enters the cartilage layer uncontrolled from the synovial fluid. This disrupts the distribution of loading within the cartilage. The response to injury thereby depends on the affected layer of cartilage, whether it is damage to extracellular matrix (ECM) or cells without visible disruption of the joint surface and finally whether it is a chondral or an osteochondral defect. An osteochondral lesion may present itself either as an Osteochondritis Dissecans (OCD) in subjects with open physes or as an osteochondral fracture due to trauma in adults and older patients. OCD is a separate disease where a bony fragment separates from an otherwise normal vascular bone bed.

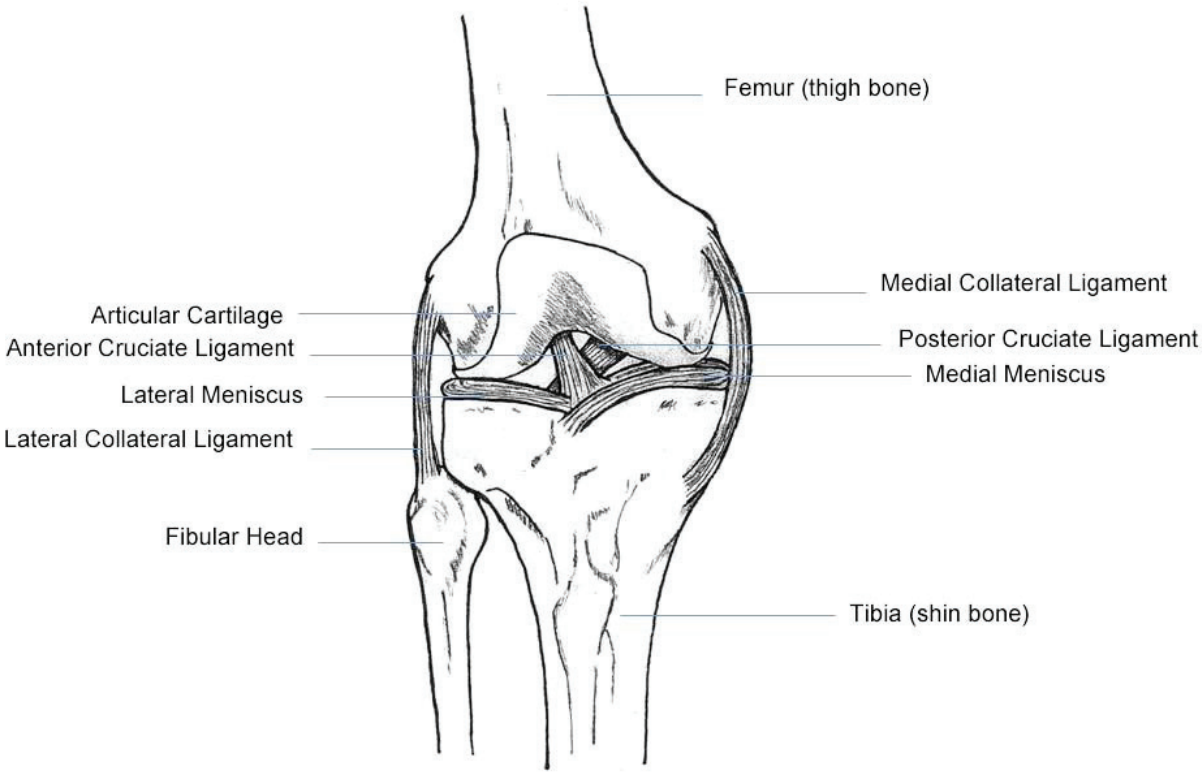

Figure 1 illustrates the anatomy of the human knee, including the articular cartilage. Adapted from Wikimedia Commons, with permission from Wikimedia commons (link: https://commons.wikimedia.org/wiki/File:Human_Knee_Anatomy.jpg).

Studies indicate that cartilage injury occurs after one single high impact or after several, repetitive smaller impact forces through joint instability or malalignment.[23;24] High-impact activity leads to increased degenerative changes.[25] The force and type of joint loading sufficient to cause cartilage injuries in humans is not fully understood. It is demonstrated that articular cartilage in donor knees can withstand impact loads up to 25 N/mm^2 (figure 2) without visible damage to chondrocytes or cartilage fissures.[26] Impact loads lead to a reduced content of proteoglycans in animal models, even in the absence of visible damages.[27]

1 N/mm^2 = 1 MPa = 1 000 000 Pa = 10 Bar
and
1 standard atmospheric pressure = 101325 Pa = 760 mm Hg

Figure 2 illustrates the relationships of pressure, represented by the tensile strength (newton per square meter).

Superficial cartilage defects do not heal. After 2 years the defects consist of rough and irregular surface both within the floor of the defect and the surrounding cartilage.[28] The mechanical shearing towards the area of the defect seems to induce degenerative changes. When the subchondral bone plate is affected, bleeding into the defect occurs. The bleeding supplies mesenchymal stem cells that initiate an inflammatory response. However, the repair tissue of the chondral part consists of a mixture of fibrous tissue and hyaline cartilage and normally does not fill the entire defect.[29]

An FCD may also lead to altered mechanical loading of the cartilage surrounding the defect. When an FCD occurs, the stress along the rim increases and the contact area adapts.[1] Guettler et al. studied the "threshold" defect size necessary to cause mechanical stress on the border of the defect.[32] This threshold is clinically important because it determines at what point the defect causes disruption of the adjacent cartilage and thereby provides a clinical implication of when to treat defects. They applied loading forces to cadaveric knees without defects and thereafter created increasingly larger osteochondral defects. They found that load was distributed properly through the meniscus in intact cartilage and with defects up to 8 mm in diameter. Lesions smaller than this did not affect the surrounding cartilage negatively, but when the defects had a diameter of 10 mm and above, rim stress was evident.

Table 1 summarizes some statements about FCDs and accompanying evidence.

What`s being said		*What research shows*
"FCDs may lead to joint damage and OA"		Approved in animal models for lesions over a threshold in size.[1;30] No studies in humans with healthy cartilage.
"Even small isolated defects lead to further degeneration"	-Cell death	Spontaneous repair occur in small lesions.[30;31]
		A new layer of matrix is produced and present around a year after a controlled formation of small defects in rabbit articular cartilage.[28]
	-Accelerated wear	Accelerated wear if >10 mm in diameter.[32]

This means that the surrounding cartilage and meniscus can adapt and protect the joint with defects up to 8 mm in diameter, but that surrounding structures

are affected with larger lesions. The mechanical loading depends upon defect size, depth and location within the joint. The study further noted increased stress on the medial femoral condyle (MFC), compared to the lateral femoral condyle (LFC). The intraarticular location, and whether the defect affects the weight bearing area, are important for further progress of these defects. Also, the depth of the defects is central as the penetration to the bone marrow ensures compounds for repair tissue. A defect also indirectly affects the subchondral bone so that calcification initiates and further degenerative changes with subchondral sclerosis occur.[33] To conclude, FCDs are considered progressive when present and over a certain size. They may lead to increased degeneration of both cartilage and bone.[11]

Natural history of FCDs

An isolated FCD may have an acute, chronic or acute-on-chronic onset. Approximately 50% of the patients present with a history of trauma.[34] The defects involve different depths of cartilage. FCDs occur at all ages, with gradually increasing degeneration with increasing age. The activity profiles of the patients vary from sedentary lifestyle to high-level athletes.

Articular cartilage lesions have limited capability of self-healing with normal hyaline cartilage.[30] Small defects might have some potential of spontaneous healing as it is demonstrated that 3 mm defects heal with hyaline or fibrocartilage in rabbit models.[31] Controlled FCDs develop into OA in animals.[4;30] but no such study is available in humans. Therefore, the link between an FCD and OA is not completely understood, and the penetration of the disease (which/how many patients will develop OA from their FCD) is not yet studied. It is believed that isolated FCDs eventually lead to OA.[6]

Some long-term observational studies on clinical outcome of non-operated, isolated FCDs in humans exist. Linden demonstrated that a clinically significant cartilage defect led to a higher incidence and to an earlier clinical onset of OA when compared to the general population.[35] Spahn et al. found that 30% of 115 patients with FCDs of the MFC were in need of arthroplasty 10 years after diagnosis.[36] These studies support the hypothesis of that FCDs lead to increased cartilage degeneration within the knee. However, the presence of an FCD may not lead to degeneration in all joints. A cohort of healthy subjects was examined with MRI at baseline and after 2 years by Wang et al.[6] They found that the mean cartilage defect score increased, although some patients had decreased scores (table 2). Another study performed MRI at baseline and after 2 years in a cohort of both children of

patients with total knee replacement (TKR) and randomly selected participants (mean age 45 years).[37] One third of these knees worsened while 37% actually had an improvement in cartilage defect score.

Table 2. Table adapted from Wang et al. The table illustrates the natural progression of cartilage defects over 2 years. For this purpose only baseline grade 3 and 4 were included in the table since these are the most clinically relevant defects. Of all FCDs scored as full-thickness lesions at baseline, 10 out of 22 (45%) regressed and had a lower score at follow-up, whereas 41% were no longer classified as full-thickness lesions. The grey-shaded windows are those defects with a similar or higher grade at follow-up. The authors discussed that the low number of full-thickness lesions in the cohort made ceiling-effects less likely to explain the negative association.

Baseline grade	*Follow-up grade at 2 years*				
	0	*1*	*2*	*3*	*4*
3 (n=14)	0	2	4	3	5
4 (n=5)	0	1	2	1	1

Widuchowski et al. studied patients with isolated untreated severe cartilage lesions (size 2-4 cm^2) 15 years after diagnosis, and found that clinical outcomes were comparable to the results following cartilage repair.[38] There were no statistically difference in the frequency of OA between injured and uninjured knee. Of the included patients, 39% had OA after 10-15 years, which is in the same range as the occurrence of degenerative changes after cartilage repair.[39;40] They concluded that isolated cartilage defects left with no treatment have limited influence on clinical outcomes and the development of OA. Another long-term study followed young, athletic patients after arthroscopic diagnosis (including 3 Pridie drillings and *occasional* cartilage shaving) of an isolated full-thickness FCD. The lesions were located in the weight-bearing area of the femoral or tibial condyles and were >1 cm in diameter whereas 70% were traumatic defects. They found that 92% of patients returned to pre-injury activity level and less than 50% had radiographic joint space narrowing (JSN).[41] A short-term study evaluated the feasibility of active rehabilitation in patients considered candidates for cartilage repair and found a significant improvement of knee Quality of Life subscale of Knee Injury and Osteoarthritis Outcome Score (KOOS) and the IKDC 2000.[42] These results imply that some patients may have a favorable result with a non-surgical approach. Thus, we still do not know if surgery actually is better than the natural development in preserving joint function after FCDs.

Which defects cause symptoms?

In a cohort of asymptomatic NBA players nearly half of the players had cartilage lesions in their knees.[43] All players with prior history of knee pain or mechanical symptoms were excluded. The localization of the defects was different from what is seen in symptomatic individuals. In clinical studies, the MFC and the patella are the most common localizations with around 50% of defects on the MFC, whereas the MFC was involved only in 10% of NBA-players. A systematic review found that 14% of athletes with FCDs were asymptomatic.[12] However, when these defects are symptomatic they seem to affect patients to the same degree as patients scheduled for total knee replacement for OA.[3]

Factors that need to be present for a defect to become symptomatic remain unknown. The different aspects of the defect itself might produce different intensities and types of symptoms. The articular cartilage has neither vascular nor nervous supply, and nerve endings are therefore not irritated until the subchondral bone is affected, meaning that there should be a full-thickness defect present in order for the defect to produce pain. Still some partial-full-thickness defects seem to cause similar symptoms. The threshold in size for symptoms to occur is unknown. Whether the defect is localized in the weight-bearing area is of clinical significance, as is the status of the surrounding cartilage.

FCDs often occur together with other types of injuries such as damage to the menisci, the ligaments, the joint capsule or intraarticular fractures. Medial meniscal tears and anterior cruciate ligament ruptures occur in 37% and 36% of cartilage injuries.[8] A focus in the literature has been cartilage injuries in combination with reconstructions of the anterior cruciate ligament (ACL). The long-term effects of isolated cartilage defects in ACL-reconstruction remains unresolved.[44;45] Studies have suggested worse prognosis with treating these patients with microfracture (MF) when compared to debridement or no treatment.[46]

To summarize, full-thickness defects larger than 2 cm^2 in the weight bearing area of the knee joint cause symptoms. However, the exact size for a defect to cause symptoms is not yet known. Some partial-thickness defects cause symptoms, as well as defects located outside the weight bearing area. This may be due to inflammatory mediators, for instance, matrix metallopeptidases (MMPs) through mitogen activated protein kinases, which influence the repair process after mechanical injury (animal models).[47;48] Inflammatory mediators are suspected to contribute to pain in knees with cartilage injuries, but their role is not fully understood.

Diagnostic challenges - arthroscopy, MRI and newer techniques

The findings from a clinical examination of a knee with an FCD are subtle and unspecific. A final and exact diagnosis is impossible without visualizing the defect. When diagnosed, the lesions are classified with different grading systems. In order to follow FCDs both with natural development and after cartilage surgery, it is necessary to have standardized grading systems. We also need biomarkers of early knee OA, as OA as an end-point requires long follow-up time.

The Outerbridge classification was previously widely used for arthroscopic assessment.[49] A study addressed the accuracy and reproducibility of the Outerbridge classification system for cartilage injuries in the knee by examining 3 cadaveric knees and found an overall accuracy rate of 68%.[50] Many sought a routinely assessment of size and location.[51] The International Cartilage Repair Society (ICRS) designed a standardized and simple classification system.[51] The system was developed to include enough information for long-term follow-up and allowing for prognostic evaluations of FCDs. It is the most widely used system. Other systems for classifying lesions on both arthroscopy and MRI exist. [52-56]

Both invasive and non-invasive procedures visualize FCDs. Although arthroscopy is the gold standard for diagnosing FCDs, there are obvious advantages of non-invasive techniques. Radiographs with Kellgren and Lawrence (K&L) protocol[57] is used for the development of OA. The method is not sensitive for FCDs or earlier degenerative changes, only for osteochondral defects with a visible bone-piece or lesions with substantial cartilage volume loss.[58] MRI detects soft tissue and is a potential tool for diagnosing and following FCDs within the knee. The advantage of MRI is that it is non-invasive and thereby allow better longitudinal follow-up of patients. MRI also enables a broader intraarticular evaluation, as opposed to histologic analysis. Additionally, not all defects are noticed on arthroscopy.[59;60] A non-invasive technique such as MRI is beneficial for subgroups of patients with FCDs undergoing an early non-surgical approach, for timing of surgical treatment and for detecting and following the lesions.

The MRI technique depends on how atoms react under the influence of a magnetic field. All atoms are oriented in one axis by an activated magnet and orients back to their original spin position when the magnetic effect is turned off. Different measures of time for the atoms to spin back result in values that are converted to a picture consisting of shades of grey. The grey-shaded

pictures represent the morphologic feature of the tissues dependent on the different MRI modalities, T1 and T2. Different tissues, and different parts of tissues, thereby yield different T1 and T2 values, dependent on how quickly the atoms spin back. A short T2 yields low signal and dark images in T2-weighted images, and a short T1 yields high signal, or bright images in T1-weighted images. The cartilage is bright in T2 and darker, although not completely dark, in T1. This means that different modalities are used according to what anatomical structure is studied. The most commonly used protocols for evaluating cartilage and FCDs are T2-weighted "fast-spin-echo" (FSE) (with or without fat suppression) and T1-weighted fat-suppressed (or water-selective excitation) spoiled gradient-echo (3D-GRE) image acquisition.[61;62] Fat-suppressed 3D-GRE has the advantage of yielding high signal intensity from cartilage and low from surrounding tissues, visualizing both thickness and surface. FSE-techniques yield low signal intensity from cartilage, whereas subchondral bone and joint fluid yields high signal intensity and the cartilage surface is visualized. The latter is also robust against artifacts in patients who have undergone previous knee surgery.

MRI gives objective and reproducible data on native cartilage and on cartilage repair tissue. The surface, signal intensity and homogeneity, subchondral lamina, osteophytes and effusion are evaluated. After repair, defect filling and integration can be evaluated. Some defects are too small to be detected[63;64] and conventional MRI is insensitive to how the surrounding cartilage reacts until gross morphologic changes occur. Although some studies have demonstrated good diagnostic accuracy, some have also demonstrated poor sensitivity. The diagnostic accuracy demonstrates large variations dependent on design and study population (table 3). The diagnostic accuracy of MRI may be satisfying when the correct technique is used.[65] The overall sensitivity for MRI is 0.74 (0.71-0.77) and specificity is 0.95 (0.94-0.95) when compared to arthroscopy, with a higher accuracy for high-grade lesions. A systematic review found that 1/3 of studies demonstrated correlation between MRI and clinical outcome and concluded that the reliability of MRI in predicting clinical outcome is lacking.[66] Additionally, it is not possible to evaluate the cartilage matrix in detail with conventional MRI-sequences. Therefore, many still rely on second-look arthroscopy. However, arthroscopy does not allow for an evaluation of deeper structures. Quantitative MRI (qMRI) allow for a detailed evaluation of different segments of the knee, including the content and quality of cartilage.

Table 3. The table demonstrates the sensitivity and specificity of different MRI-techniques.

MRI method	Author	Sensitivity / specificity
3D-GRE techniques	Tyrrell et al. (1988) [55]	36% (grade 1) and 100% (grade 2 and 3) / -
	Speer et al. (1991) [67]	15% (partial-thickness) and 41% (full-thickness) / -
	Disler et al. (1996) [63]	75-85% / 97%
	Spiers et al. (1992) [68]	18% / 100%
	Recht et al. (1993) [69]	96% / 95%
FSE-techniques	Potter et al. (1998) [70]	87-95% / 87-94%
	Bredella et al. (1999) [71]	94% / 99%
	Irie, Yamada and Inoue (2000) [72]	59.4% (grade 3) and 100% (grade 4) / -
Standard MRI	Disler et al. (1996) [63]	29-38% / 97%
	Figueroa et al. (2007) [73]	45% / 100%
MR arthrography	Kramer et al. (1994) [74]	85-87% / 100%

Early osteoarthritis

The primary changes towards a degenerated knee joint involve an interrupted cartilage structure, proliferation of chondrocytes and increased water content in the ECM. Fibrillation of the superficial layer and cracking of the matrix then occur before morphologic destruction of the cartilage. Lorenzo et al. looked at biochemical content in knees with normal cartilage, early OA and OA, and found increased relative amount of proteoglycans in early OA and an altered biochemical synthesis even in the absence of cartilage fibrillation.[75] The continuous degeneration ultimately leads to a destroyed joint and criteria for early OA are suggested.[76] To actually visualize "early OA" and identify these patients at risk of early TKR are important to implement early treatment strategies and increase future joint protection. Independent systems for sensitive evaluation of knee articular cartilage by MRI are developed, among which the most complete are the *whole-organ magnetic resonance imaging score* (WORMS)[77] and the *magnetic resonance observation of cartilage repair tissue* (MOCART).[78;79] The WORMS consist of several semi-quantitative

scores for different features for evaluating degree of degeneration within the knee. The quality after cartilage repair is evaluated by the MOCART system. Defect fill is considered to be the most important factor, and is demonstrated to correlate with clinical symptoms 2 years after MF,[80] and after MACT.[81] Also the cartilage surface, matrix thickness, volume and subchondral borders are visualized with MRI and the status following cartilage repair is evaluated with the same acquisition techniques as for native cartilage.

Delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage

The altered composition of proteoglycans[82] with reduced GAG concentration ([GAG]) occur prior to cartilage loss.[22] A disrupted cartilage can also be evaluated with newer MRI-techniques which quantify the contents of cartilage and create a "biochemical image" to evaluate the cartilage quality.[83] The delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC) is one of the newer techniques and detects areas with subtle changes even in the absence of morphological changes.[84;85]

GAGs, measured by dGEMRIC, correspond to the true [GAG] both biochemically and histologically.[86;87] The technique relies on the injection of a contrast agent that changes the relaxation rate and energy amount of cartilage. The dGEMRIC technique is validated for use in vivo,[88] for both hip and knee.[89;90]

T2 mapping

The T2 relaxation is increased in damaged cartilage.[91] T2 mapping is another method for quantifying biochemical content of cartilage. It is less time-consuming and does not require any contrast agents. For articular cartilage, the T2 relaxation time depends on the relationship between water content and collagen structure. The T2-mapping reflects water molecules and their interaction with surrounding collagen and macromolecules, thereby measuring the collagen component of ECM. It is therefore sensitive to altered hydration.[92;93]

Treatment and indication for treatment

Diagnosing FCDs can be challenging, as there are subtle symptoms and often additional injuries. This may lead to variations in both diagnosis and treatment. Improving function and symptoms and the long-term prognosis, to delay or

avoid, joint replacement surgery, are the goals when treating patients with FCDs. New surgical techniques have been developed since the first chondrocyte implantation in Sweden in 1994. Some treatment algorithms have been proposed (figure 3), based upon size and depth of lesion and age and level of activity of patient. But for the majority of this heterogeneous patient group with isolated FCDs, there is no known gold standard treatment. The role of physical training as treatment is not yet fully explored. Non-operative treatment generally consists of avoiding sports and weight bearing for 6 weeks in addition to a strict rehabilitation protocol with exercise under the control of an experienced physiotherapist. Intraarticular injections of Hyaluronic acid (HA) and platelet-rich-plasma (PRP) have an unclear role in the treatment of cartilage defects.[94] They are used more frequently in knees with cartilage degeneration or OA, although with still unresolved evidence.

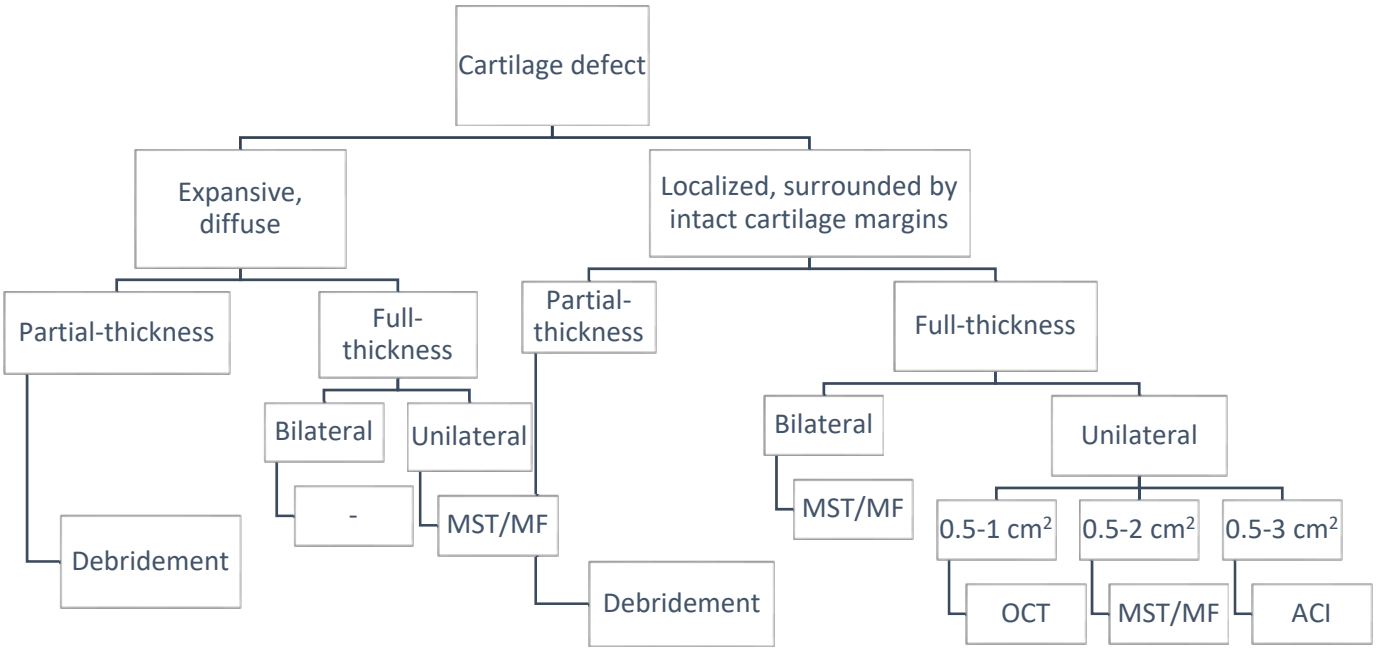

Figure 3 illustrates an example of a surgical treatment algorithm for FCDs. Figure adapted from Madry, Grün and Knutsen.[98] MST is an abbreviation for marrow-stimulating techniques, such as MF. MF or MP is mostly recommended for smaller lesions (less than 2 or 3.5 cm^2).

The treatment options concerning the depth of the defect have been non-operative treatment for ICRS grade 1 lesions. Prevention of progression is the main goal for grade 2 lesions, and simple debridement might reduce symptoms. Small (<1.5 cm^2) partial-thickness lesions are thought to be non-progressive.[95] More aggressive cartilage therapy is suggested for lesions

where more than 50% of the cartilage thickness is affected. Some algorithms suggest marrow-stimulating procedures and osteochondral autograft (OAT) for smaller defects, whereas autologous chondrocyte implantation (ACI) is recommended for larger defects.[96] A study comparing early cartilage repair of the knee with none or late cartilage repair showed better results for early cartilage repair in goats.[97] This supports early cartilage repair to prevent the cartilage from negative influence by the altered matrix metabolism. Delayed surgery in humans leads to increased development of OA.[34]

Non-operative therapy, active rehabilitation and training

The literature in non-operative treatment of FCDs mainly focuses on rehabilitation after surgery. However, many cartilage injuries are treated without surgery. Training has a positive effect on meniscal injuries when compared to arthroscopic surgery.[99] An identical study including randomization of active rehabilitation or training has not been performed for patients with FCDs. Training leads to neuromuscular effects with potential of modifying the loading of the joint. A study found increased GAG content after training.[100]

Still, morphological changes or changes in the biochemical status of cartilage are not demonstrated after 12 weeks of neither strength training or 12 months of high-intensity training.[101;102] Furthermore a study found a positive effect on bone but no effect on cartilage after progressively high-impact training in women aged 50-66 years.[102] The previously mentioned study evaluating the feasibility of active rehabilitation in subjects scheduled for cartilage repair showed a significant improvement of patient reported outcome measures (PROMs) after 2 years.[42] 64% of the patients postponed their surgery after 3 months of rehabilitation exercise. These findings support a further exploration of how non-operative treatment approaches affect the articular cartilage and the long-term prognosis. Exercise and activity modification are chondroprotective when knee OA is established.[103] Adjusted knee loading in well-adapted and highly trained extremities may reduce expected symptoms in some patients also with early degenerative changes and FCDs. We do not know yet how to identify patients who will benefit from training.

Prognostic factors in surgery

Single defects less than 4 cm^2 and located on the MFC are defined as *simple* lesions whereas larger defects on the MFC and defects located on the trochlea, tibia or patella together with multifocal defects are *complex*.[104]

Kissing lesions and early degenerative changes are considered to be salvage cases. Examples on prognostic factors are lesion etiology, size, depth, location, patient age, BMI, activity level and the different treatment modalities. The role of the depth is outlined in previous sections.

Age of the patient is highly relevant as certain surgical techniques should not be used in patients <50 years since there are demonstrated poorer results for older patients.[105] Other studies have identified better results for even younger patients.[40;106-108]

Location of the defects seems to affect the clinical presentation, treatment and prognosis. The location of an FCD is reported in accordance to the affected area and the ICRS have made a mapping system dividing the knee joint into 6 different parts; MFC, LFC, patella, trochlea, medial tibial plateau (MTP) and lateral tibial plateau (LTP). Most clinical studies report FCDs to be most common on the MFC and patella[7;8;34;70;109-111] or LFC[112] and uncommon on the tibia.[24] Lesions on the MFC have the best outcome after treatment in most studies.[41;107;113] The LFC is the most favorable one in others, although lesions occur more frequently here in younger patients.[114;115] Lesions on the femoral condyles show more improvement when treated with ACI than lesions on the patellae and trochlea.[116] Tibial lesions have poorer results and Mandelbaum have warned against using ACI and mosaic plasty (MP) on these defects.[24]

Size is an established prognostic factor in FCDs.[24] Lesions less than 2 cm^2 are classified as small, 2-10 cm^2 as moderate, and lesions more than 10 cm^2 as large. The size influence on the prognosis and small lesions on the femoral condyle have the best potential[41] whereas moderate and large lesions are more likely to develop into OA.[24] Recommendations of when to treat FCDs have ranged from 1.0 cm^2 to 1.6 cm^2.[110;117-119] Some utilize a cut-off at 4 cm^2,[40;120;121] whereas others suggest 2 cm^2 as the indication for cartilage repair.[106;120]

Based on size, there is no difference in clinical outcome in the natural history of FCDs in association with ACL-reconstruction (range 0.5 cm^2 to 6.5 cm^2).[122] However patients with sizes larger than 6 cm^2 have inferior results compared to patients with smaller defects 2-4 years after surgery for isolated FCDs.[123] Also, patients with lesions less than 2 cm^2 have a higher return-to-sports rate.[34]

Debut may be acute, chronic or acute on chronic. Approximately 40-50% of patients included in clinical studies have traumatic lesions.[110] The German Cartilage Registry includes degenerative lesions more frequently than

traumatic and posttraumatic lesions.[124] Acute lesions may have an increased potential for a good outcome, although no statistically significant difference between degenerative and other lesions was found after osteochondral allografting.[125] Acute injuries are also more common in younger patients, which is an individual prognostic factor. A systematic review of ACI and a clinical study on MF found that young patients with a short duration of symptoms do best.[80;126] Longer time periods from debut until treatment seems to worsen the outcome, as previously demonstrated for delayed ACL-surgery.[127]

Previous surgery is present in 20-28% of patients.[2;128] However, up to 83% and 94% of patients have prior surgery to the index lesion performed, including diagnostic arthroscopy.[110;129] Previous surgery with bone marrow stimulating techniques may complicate the current treatment as the subchondral bone plate is disrupted. In a study population where 37% had prior cartilage surgery, previous surgery was not identified as a poor prognostic factor.[130] Also, previous surgery did not seem to influence the 3 year clinical outcome in a register study on ACI.[131] Other studies have demonstrated the opposite, previous surgery seems to yield a poor outcome with the use of Hyalograft C autograft as only 7% of patients operated on primary indications experienced graft failure versus 81% of the patients operated for secondary indications.[132] ACI after previous marrow-stimulating techniques yields poorer results than ACI as a first-line treatment.[104;133] Also, prior surgery correlate negatively with return to sports after MF.[34]

Increasing age,[134] low activity level,[135] and high BMI[80] are negative prognostic factors for cartilage repair. In a cohort of athletes treated with MF, they found size to be a more important prognostic factor than age.[113] The best results are achieved in young patients,[34;120] with a single lesion less than 2 cm^2 on the MFC.[136;137] Patients with an acute history of trauma and a short period of symptoms prior to treatment and no previous surgery have better results.[34;120;135] However, there is still insufficient knowledge about the importance of each parameter`s role for the prognosis. Many of these factors are identified through RCTs, which is not suited for that purpose. A large, unbiased prospective cohort enables a more comprehensive evaluation of the prognostic factors.

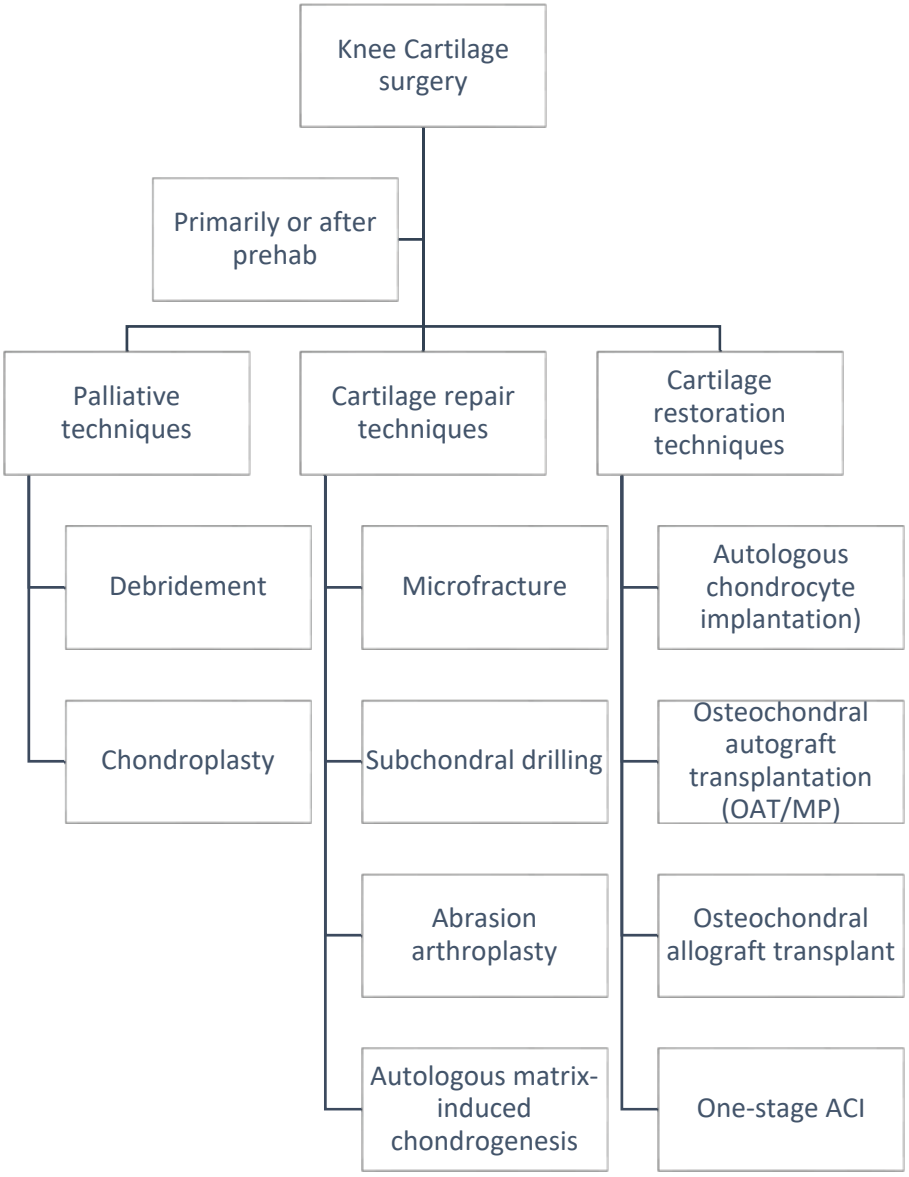

Figure 4 illustrates an overview of the existing treatment modalities.

Surgery

Several different surgical techniques exist and they can be divided into 3 groups based on their role as palliative, reparative or restorative techniques (figure 4). There is a general agreement that symptomatic full-thickness defects larger than 2 cm^2 in an otherwise stable and healthy knee could be treated with cartilage surgery. Good results from clinical studies support surgery for defects over this size, however we are not aware of any original research supporting cartilage surgery over non-surgical treatment. Some of the smaller lesions are operated and some larger lesions undergo non-operative treatment. In this section, I will first present the commonly used

surgical techniques together with some clinical results, mainly from cohort studies, before a summary of the existing evidence with results from RCTs.

Palliating techniques

Palliative techniques include chondroplasty, debridement or smoothening of the defect. The defect is not repaired and although the loading might be removed from the defect itself, it is probably redistributed to the surrounding cartilage. Still, the most commonly performed surgical procedure for FCDs is debridement.[138] Debridement is effective for smaller cartilage lesions within the knee as a first-line treatment.[139] Dozin et al. found that 30% of the patients in their study improved after initial debridement, and received no further treatment.[140] Further, Meissner et al. demonstrated good results after minimally treatment of knees in patients <40 years of age, diagnosed with Outerbridge grade 2 and 3 defects.[41]

The results indicate that these techniques result in symptomatic relief and that some patients experience little symptoms from the initial defect also for the long-term follow-up. The role in joint preservation is not clear and we do not know which patients who will benefit from palliating techniques only.

Reparative techniques

The subchondral bone plate between the defect and the bone marrow is penetrated allowing bone marrow and blood to enter the defect. This results in a fibrin clot. The clot initializes healing and the formation of articular cartilage, but the repair tissue is disorganized and resembles fibrocartilage more than hyaline cartilage.[93;106]

In MF the subchondral bone plate is penetrated with small awls making holes around 3 mm apart within the defect.[141] Patients experience improvement after 2-12 years whereas 20% report no benefit from the procedure.[136] The PROMs increase postoperatively in both general patients[106;107;142] and in athletes.[113] Thereafter comes a plateau after 12-24 months[80;143;144] or even a slight decline after 18-60 months.[107;145] Scores 11 years postoperatively, however, remain higher than prior to operation.[136] A BMI >30 is linked to inferior outcome.[80] There is better outcome in patients younger than 30-40 years.[40;106;107] A systematic review of MF demonstrated effective short-term results and insufficient data to conclude on the long-term outcome.[146] Reported survival

rates are around 75% but no studies have demonstrated a clear advantage of MF.[40]

Restorative techniques

Autologous transplantation - autologous chondrocyte implantation and matrix-associated autologous chondrocyte transplantation

In ACI, the chondrocytes are isolated from a less weight-bearing area of the knee and grown in cell cultures before they are implanted within the cartilage defect in a two-step procedure. In first generation ACI the cells are covered by a periosteal flap, whereas newer techniques include scaffolds where the chondrocytes are seeded and the scaffolds are implanted. Advances have led to different variations of solutions with scaffolds, matrices and 3D-systems for these procedures. The variety ranges from autologous periosteum to second generation xenograft tissue (porcine-derived type I/type III collagen cover) or third-generation biosynthetic scaffolds.[147] These are matrix-associated autologous chondrocyte transplantation (MACT), and the harvested chondrocyte are grown and cultivated on a 3D polymer scaffold. Recent advances have led to the possibility of performing ACI as a single-step procedure.[148] Histologic findings after transplantation techniques include partially hyaline-like repair tissue.[118;149] There are some disadvantages with these techniques as they require a long rehabilitation period. In the postoperative phase some complications, such as hypertrophy and arthrofibrosis, may occur. Hypertrophy, together with graft detachment have been related to the periosteal flap in first generation procedures[121] but seems to have been overcome with newer techniques.

ACI[118] is indicated for larger ($2cm^2$-$12cm^2$) full-thickness defects or for smaller defects where previous surgery with MF or MP has failed.[150] One study found better outcome with ACI over abrasion techniques in 50 patients.[151] Good to excellent results are demonstrated at both short-term and medium to long-term follow-up in 60-90% of patients in clinical observational studies,[40;96;139;150;152;153] and in one RCT including ACI.[110] A systematic review from 2011 with ACI as one of the interventions found good short-term outcomes.[126] One of the first long-term (10-20 years follow-up) case series found that 92% of patients were satisfied and would have done the ACI again.[130] These excellent long term results are still not reproduced to the same extent by other research groups, but one prospective cohort study found that less than 7% of all operated

patients had a complete failure 10 years after operation, although 45% had radiographic signs of OA.[134]

Studies on newer ACI-techniques demonstrate around 75% improvement in clinical scores after 5 and 10 years.[132;154] An RCT comparing first-generation ACI with MACT found no statistically significant differences.[155] However, the quality of research including MACT is considered to be low with mainly case series and studies with short to mid-term follow-up periods.[156] We are still lacking information to conclude precisely on results from the different techniques and to identify the patients who will benefit from ACI-techniques.

Mesenchymal cells and other cell-based techniques

Mesenchymal stem cells were used for cartilage defects in rabbits in 1994.[157] Mesenchymal stem cells have a potential for producing more hyaline cartilage compared to mature cartilage cells. Certain growth factors can be used to induce cell growth and chondrogenesis.[158] There are currently not enough evidence to conclude on the overall result of cartilage repair with mesenchymal stem cells.

There are also other less studied surgical treatment options. Autologous matrix-induced chondrogenesis (AMIC) combines MF with ChondroGide® (GeistlichPharma AG, Wolhusen, Switzerland). Interim analyses in an RCT comparing AMIC to MF for isolated cartilage defects demonstrated similar increases in defect filling 2 years after operation.[159] An FDA phase II RCT compared Neocart (an autologous cartilage tissue implant) with MF and found significantly better clinical scores in patients treated with Neocart after 2 year follow-up.[160]

Osteochondral transplants

Autologous osteochondral transplantation is a one-step procedure with the incorporation of an osteochondral plug into a defect with surrounding healthy cartilage. The plug is harvested from a non-weight bearing area within the knee, and donor-site morbidity in the long-term is a yet unresolved question. MP refers to the transplantation of one or several plugs into a large defect. The long-term outcome from a cohort study of MP showed improved subjective scores and good survival of the grafts on MRI.[161] The outcomes from clinical studies after 3 years follow-up are good and one randomized study found better results for OAT after 3 and 10 years when compared to MF.[39;106;162] A

study comparing MP with ACI in defects with mean size around 4 cm^2 found equal results after 2 years, but a higher failure rate for MP after 10 years (17% vs 55%).[110] Another study found clinical improvements in both groups after 2 years, whereas the histological findings demonstrated more fibrocartilage in the ACI-group.[96]

It is also possible to use osteochondral grafts from a donor, although it is not available everywhere. The technique is single-staged with a fresh allograft that contains hyaline articular cartilage and is shaped to match the defect identically. The technique is appropriate for treatment of very large chondral or osteochondral defects (4-20 cm^2) and after failure of previous treatment.[125] The survival rate is >80% after 10 years.[125;163]

Cartilage surgery for degenerative lesions

Degenerative cartilage is believed to have even less regenerative potential than healthy cartilage. The distinction between an acute focal lesion and a degenerative focal lesion is sometimes challenging as the development from acute defects to a degenerative lesion may be seen as a continuum. Cartilage defects should be surrounded by healthy cartilage in order to optimize the implantation process of the graft and prevent negative influence from cytokines in a surrounding degenerative milieu.[97] The surrounding cartilage depicts the quality of the remaining cartilage within the joint. There is a presence of inhibitory factors in the synovial fluid of chronic lesions as opposed to stimulating factors with acute lesions.[164] Still, promising results are demonstrated in mid-term (2-5 years) follow-up of isolated degenerative lesions treated with MF[165] and ACI,[135] and also for the treatment of early OA with ACI.[111] The latter study performed by Minas et al. followed 153 patients for 11 years after ACI for early stage OA. They concluded that they were able to delay the need for joint replacement as 92% of patients were functioning well after 5 years.

Rehabilitation and return to sports

An important factor for a good outcome after an FCD is the rehabilitation protocol. The role of rehabilitation alone is not fully understood.[42] The effect of exercise on articular cartilage is positive,[100] although high-intensity loading leads to injuries and degenerative changes.[25] The rehabilitation program depends on individual factors and reflects the 3 healing phases of cartilage. It begins with protection and activation allowing full active ROM and protected

weight-bearing for up to 6 weeks,[166] thereafter progressive joint loading and finally functional restoration of the joint, including a sports specific rehabilitation in athletes.[119] The length of each phase depends on the treatment choice as well as lesion and patient factors. Generally, there is a longer protection phase immediately after treatment compared to any other orthopedic surgery.

A study with early and accelerated weight bearing after cartilage repair showed good clinical outcomes without negative effects on the graft.[167] Also, the postoperative knee function score improved in patients who participated in sports after ACI compared to those that did not participate in sports after rehabilitation.[166] Rehabilitation after cartilage surgery is a research field of its own with increasing evidence concerning both rehabilitation alone, prehabilitation and post-surgical rehabilitation.

As these defects cause both pain and reduced function, the return to sport after treatment is an important outcome for athletes. Return to sports is normally not allowed until minimum a year after treatment. Some athletes are able to return to sports without surgery, but not all.[41] Only 7 of 28 patients still performed activity at their preinjury level at final follow-up although many returned to sports. For that study, the average follow-up was 14 years, and a decline in activity profile due to age must also be accounted for. There are mainly 3 different surgical options to consider when treating athletes, whereas a non-surgical approach is the fourth. MF is a technique with good short- to medium-term results but with a clinical deterioration seen after 2 years.[119] Still long-term outcomes are better than baseline.[107;113] Especially the rehabilitation after ACI is long and demanding.[168] OAT seems to lead to a higher rate of return to sports in young and active patients and has a shorter rehabilitation period.[39] Brophy et al. found that players in the National Football League (NFL) undergoing surgical treatment with MF instead of debridement for an FCD had slower return to sports, however biased with regards to lesion size.[169]

Table 4 demonstrates the return rates after different surgical techniques. Good and excellent rating was found in 67% after MF, 82% after ACI and 93% after OAT in a review.[126] The patients treated with OAT had the smallest defect sizes. The return rate to overall sports was 73%, whereas the return to preinjury sport level was 68%. The continuation of sports participation was further explored, and was found to be higher for the patients who underwent ACI.

Table 4. Summary of the return to sports from different surgical techniques.

Technique	*Return to sports*	*Time*	*Comment*
Chondroplasty	67%[170]	8.2 months	Average age 28 years and most lesions 1-2 cm^2. 35% of players had a concomitant MF performed and were less likely to return
MF	44%-77% [34;113;120;142;146;171]	8 +/- 1 months[34]	The study with the lowest return rate had on average larger lesions than the study with the best rate (4.9 cm^2 vs 3.8 cm^2)
ACI	33%-96% [34;128]	18 +/- 4 months[34]	Dependent on lesion size
OATS	91%-93% [106;142]	7 +/- 2 months[34]	Mean size 2 cm^2
MP	63% (90% <30 years and 23% >30 years)[172]	Not specified	26.5 months average follow up

Summarized outcome for surgery, current evidence

The concern that no clinical studies have included a control group of untreated patients was addressed already in 1996 in a critical review by Messner et al.[117] Studies both on the natural development of FCDs and the result from surgery exist. However, the risk of selection bias between these typically small studies is high. The patients in natural history studies are more likely to experience fewer symptoms and constitute smaller lesions. The results are therefore not comparable to clinical studies including surgery. The lack of a control group in an RCT means that we do not know how the outcomes after surgery differ from either natural history or rehabilitation alone. An ongoing multicenter RCT addresses this by comparing both MF and ACI with a non-operatively treated group.[173;174]

The overall results for reparative techniques demonstrate that around 70% of patients improve over a period of 10 years, although histological and radiological findings show varying results with evidence of degenerative changes. The majority of the patients undergoing cartilage repair regain good function and experience less symptoms after 2-5 years.[110;145;175;176] However, several studies find these initial good results to be followed by a clinical deterioration.[34;106;145] The patients reduce their activity level and some do not improve, or even experience worsening of symptoms and a decreased

function.[44;177-179] This deterioration in prognosis is observed also in patients treated non-surgically.

Table 5. Summary of RCTs in cartilage surgery. C-ACI is an ACI technique using a porcine-derived collagen membrane as a cover, whereas p-ACI uses periosteum as a cover.

Article	Size of lesion in mean cm^2 (range)	Interventions	Favorable result	Radiographic OA
Bentley, 2003 [109]	4.7 (1.0-12.0)	ACI (both p- and c-) vs MP	19 months: ACI 10 years: ACI [110]	Did not report radiographic OA
Horas, 2003 [96]	3.9 and 3.6 (3.2-5.6)	p-ACI vs OCT	24 months: OCT	Did not include radiographs at 2-year follow-up
Schneider, 2003 [182]	5.4	ACI vs CaReS	CaReS yields improvement after 30 months. Retrospective matched-pair: no stat sign difference between CaReS and MF	Included radiographs and MRI but did not report results
Knutsen, 2004 [143]	5.1 (ACI) and 4.5 (MF)	p-ACI vs MF	24 months, 5 years: no stat sign difference macroscopically or histologically [40] At 15 years they found a stat insignificant favor of MF[183]	1/3 at 5 years follow up 57% (ACI) and 48% (MF) after 15 years
Visna, 2004 [151]	-	ACI vs abrasive techniques	12 months: ACI	-
Bartlett, 2005 [175]	6.0 and 6.1 (1.0-22)	c-ACI vs MACI	12 months: no stat sign difference	Did not include radiographs
Dozin, 2005 [140]	2.0 and 1.9	p-ACI vs MP	6 months: 1/3 improved after debridement, of the remaining a non-sign favorable result for MP was demonstrated after a mean 10 months	Did not include radiographs
Gudas, 2005 [106]	2.8 (1.0-4.0)	MP vs MF	37.1 months: OAT 10 years: OAT [39]	Defined as K&L $\geq$ 1: 25% (OAT) and 48% (MF) after 10 years

Gooding, 2006 [184]	4.54 (1-12)	p-ACI vs c-ACI	24 months: no stat sign difference	Did not include radiographs
Park, 2008 [185]	5.0	c-ACI vs MACI	24 months: non-sign favorable result for c-ACI	Did not include radiographs
Saris, 2008 [186]	2.6 and 2.4	CCI vs MF	12 months: CCI 5 years: no stat sign difference [108]	Did not include radiographs
Saris, 2014	4.8 (3.0-20)	MACI vs. MF	24 months: MACI	Did not report OA on x-ray, but included MRI
Basad, 2010 [147]	(4-10)	MACI vs MF	24 months: MACI	Did not report OA on x-ray, but included MRI
Zeifang, 2010 [155]	4.1	p-ACI vs c-ACI	24 months: no stat sign difference	Did not report OA on x-ray, but included MRI
Crawford, 2012 [160]	2.9 and 2.5	ACI (Neocart) vs MF	24 months: no stat sign difference	Did not include radiographs
Ulstein, 2013 [187]	2.6 (2.0-5.2) and 3.0 (2.0-6.0)	MF vs OAT/MP	10 years: no stat sign difference	Defined as K&L $\geq$ 2: 17% (OAT) and 45% (MF) after 10 years

Radiographic deterioration after cartilage repair range from 17% to 57% (table 5). We can see these results in the light of the results from a cohort of patients undergoing non-operative treatment and one cohort of meniscectomized patients. In the natural history study by Messner et al., radiographic signs of OA were evident in nearly 60% of the injured knees, whereas radiographic OA in the uninjured knee was evident in 35% of the knees.[41] These numbers are comparable to the highest results reported after cartilage surgery. Nevertheless, some studies exclude "failures" from follow-up in surgical trials, which may lead to biased results. The meniscectomized patients in the study by Rockborn et al. were all <23 years of age at baseline.[180] Nearly 50% of the involved knees showed radiographic changes, whereas only 5 of 43 had similar changes in the opposite knee. The JSN seemed to be higher in patients with cartilage defects when compared to patients undergoing partial meniscectomy with intact cartilage. However, these studies obtained anteroposterior radiographs and did not seem to use the Synaflex frame,

which ensures standardized radiographs. Messner et al. used the Ahlbäck classification which includes standing extension views rather than light flexion.[181]

Several RCTs have been performed, but no gold standard treatment has been established. The included subjects have an average age of approximately 33 years, whereas the average follow-up ranges from 1-5 years.[146;188;189] So far, 3 studies on long-term outcomes >10 years postoperatively have been published. From table 5 we can see that the results from more advanced cartilage surgery varied with overall good results in around 75% of patients. ACI was better than MP in the Bentley-study, whereas MP was better than MF in the Gudas-study and MP and MF had similar outcomes in the Ulstein-study. Knutsen et al. demonstrated satisfactory results in 77% without differences between ACI and MF after 5 years,[40] and a statistically insignificant difference in favor of MF after 15 years.[183] In general, small lesions have best results with OAT or MF, whereas intermediate and larger lesions seem to have best results from ACI.

Several factors must however be accounted for and the treatment should consequently be individualized. Subgroups of patients with superior results are documented, and some advocates for a more precise patient selection in order to achieve better outcomes.[190] As FCDs represent a wide spectrum of both lesions and patients, we do not expect one single treatment approach to fit all, there is a need for an individualized treatment or a detailed algorithm based upon identified prognostic factors. The current assumption is that some patients should be treated non-surgically and some should be treated surgically. Differences may be due to different healing response in different locations of the knee, but it implies an issue that is important to explore: Whether non-operative treatment is better for some lesions. The key is to identify who belongs to which treatment arm.

Challenges with knee cartilage research

Improved research methodology within orthopedic surgery in general and cartilage studies specifically is requested.[191] RCTs are the research method of choice when determining efficacy of an intervention. The results from these studies are important clinical tools when deciding treatment for patients. In order to maintain high quality, and thereby minimize the risk of bias, the studies must be carefully designed and thoroughly planned. Over the past decades, the focus of methodological quality has increased and we now have guidelines for designing and running RCTs.

Table 5. Summarizes methodological issues.

Main problems with evidence	*How to address*
Low methodology level Low quality	Follow CONSORT, or the checklist to evaluate a report of non-pharmacological trial (CLEAR NPT)[200]
Heterogeneous population	Assess all relevant prognostic factors
Low external validity	Wider inclusion criteria
Different outcomes	Standardized outcomes
Presents biased results	Study external validity and heterogeneity of patient population
Lack of histology and second-look evaluations due to invasiveness Still questionable accuracy between arthroscopy and MRI Many different techniques with no planned research field	Develop reliable biomarkers
Lack of non-surgical control group	Is included in an ongoing clinical study (the Norwegian Cartilage Project study)
Short-term follow-up Large loss to follow-up	More long-term follow-up studies are coming
Retrospective chart reviews	Learn clinicians what tools to use and what information that should be filed

An editorial stated that only 20% of procedures in orthopedics are supported by a low-risk-of-bias RCT.[192] Lim et al. found that 37% of the total volume of procedures performed over a period of 3 years was supported by evidence from at least one RCT.[191] The result from too few RCTs is that many orthopedic procedures are never tested in a controlled study. The amount of procedures supported by RCTs is generally higher for treatment in pharmacology and internal medicine,[193] and reflects that most of the factors that are being evaluated when assessing the quality of an RCT are factors that are easier to maintain with a non-surgical intervention. This is demonstrated by the generally lower methodological quality of cartilage repair studies, as in 3

studies from 2005, 2011 and 2013.[142;194;195] They concluded that the quality is poor when measured with Coleman Methodology Score (CMS), although it was a bit higher in the later studies (58 and 50.4 versus 43.5). Benthien et al.[195] found that studies including MF had a higher CMS than studies including other techniques.

A study performed by Worthen et al. found 9 major limitations and 7 common biases when reviewing RCTs in cartilage repair.[196] They suggested more rigorous research for the future in order to minimize common biases. Their suggestions included strict study designs and patient selection criteria, larger patient enrollment, more extended follow-up and standardized clinical treatment pathways. The checklist for maintaining high internal validity in an RCT contains several factors that are to be addressed in all clinical intervention trials.[197;198] Previous methodological issues in clinical studies within the orthopedic field are addressed in table 6 and summarized according to a systematic review of outcome after surgery for chronic Achilles tendinopathy.[199] Suggestions on how to meet the challenges are listed in the same table. The review presented an inverse and linear relationship between CMS and reported success rate.[199] It is a particular problem that studies with poor methodology report higher success rates and vice versa.

Surgical RCTs are challenged with blinding of patients, whereas double-blinding is impossible when a surgical intervention is involved. The placebo effect of surgery challenges results and there is a lack of standardization among different surgeons. Treatment is difficult to standardize, as surgery is largely dependent on human factors, as is the rehabilitation that often differs with type of injury, activity level of patients and treatment modality.[128] There are some additional challenges with the particular patient population with FCDs of the knee that lead to limitations for RCTs in cartilage surgery.

- An FCD may be considered a softer parameter than other orthopedic conditions, such as fractures or total ligament ruptures. A specific defect may seem focal to one orthopedic surgeon while diffuse or just degenerative by others. Nevertheless, FCDs within the knee joint seem to play a large part of the clinical picture when evident, and we need to standardize the evaluation of FCDs.
- As there is no gold standard, there are likely to be geographic variations in treatment, rehabilitation and outcome measures.

- The population of patients is heterogeneous, with different number, size, localization and pathogenesis (acute, chronic or OCD) of the defects. This challenges the external validity.
- The heterogeneous population also influences the inclusion rate when strict inclusion criteria exist. There is a risk of selection bias by removal either of the healthiest, or in the worst case, the sickest patients. If the latter happens, the treatment might be over-rated and thereby applied to a patient population that the particular treatment method was never really tested on.
- Several RCTs exist, however none with a non-operatively treated control group. A non-surgical treatment or sham surgery is difficult to compare with actual surgery in an RCT due to patient preference.[201] Also, some studies compare ACI with MF, which complicates the results as these two methods have different indications concerning the size of the defect. MF is indicated for smaller lesions. MF for larger lesions is thereby bound to have a lower outcome than ACI for the same specter of lesions, and vice versa.
- Long-time follow-up is challenging and many patients undergo several surgical procedures, which further complicates the results. Most clinical studies have short to mid-term follow-up, whereas much longer follow-up, meaning 15-20 years, is required for this patient group. We need long-term follow-ups in order to find prognostic factors for OA. Reliable biomarkers for early OA will secure the identification of detecting patients at increased risk of OA.
- There are no existing systematic data collection because of multiple and fragmented research environments.

External validity

The strict inclusion criteria decrease the number of patients eligible for inclusion. The recruitment process is also restricted by that some patients decline inclusion in research projects. However, more patients decline participation due to unwillingness of undergoing surgery than due to unwillingness of undergoing non-operative treatment.[201] Frobell et al. found that the *a priori sample size calculation* must be multiplied by at least 5.5 in order to estimate the number needed to screen (NNS).[202] This means that the patient pool must be much larger than expected from the sample size calculation. Other examples of low patient inclusion are described. [196] With low

external validity the applicability of the results is reduced and the actual effectiveness of treatment methods in the general patient population remains unknown, no matter how many RCTs are performed.

RCTs and prospective cohort studies

Salomon and McLeod reviewed the literature and determined that 39% of clinical research questions could have been answered by an RCT under given perfect clinical research settings, and that only 3% of research questions regarding surgery against a nonsurgical intervention could have been answered by an RCT.[201] RCTs are considered the gold standard in finding the effect of an intervention, although prospective cohort studies are considered better with research questions about prognosis (table 7).

Table 6 is adapted from a hierarchy table published by the National Health and Medical Research Council in Australia. It displays level of evidence based upon type of research question, here represented by questions on intervention and prognosis.

Level	*Intervention*	*Prognosis*
I	A systematic review of level II studies	A systematic review of level II studies
II	An RCT	A prospective cohort study
III-1	A pseudorandomized controlled trial	
III-2	A comparative study with concurrent controls - non-randomized experimental study, cohort study, case control study	Analysis of prognostic factors amongst persons in a single arm of an RCT
III-3	A comparative study without concurrent controls - historic controls	A retrospective cohort study
IV	Case-series	Case-series

The efficacy of an intervention is studied in an RCT, but its effectiveness can never be assessed in a controlled clinical study.[203] A register makes it possible to find the effectiveness of treatments. Prospective cohort studies with high quality might complement and complete research gaps. It is not possible to conclude on the best treatment through a register, but the hypothesis might be more focused and the design of RCTs may then be better. We are lacking

real-life clinical data as the current RCTs are performed under controlled conditions. The limitations of both RCTs and the limitations of retrospective analyses make it important to initiate more clinical effectiveness research. A register may be a useful supplement in this.

Criteria for a successful register

Certain factors for success are identified in the literature and from the experience from other orthopedic registers. These should be considered prior to establishing a register. Completeness and validity of the data are crucial for a register. If not, reliable analyses cannot be performed. A successful register:

- provides information
- motivates for change
- initiates change

Resistance to change is a well-known obstacle in an already busy clinical day. The motivation for change must be high among the participants, meaning both the orthopedic surgeons and the patients. The change must not be too difficult or time-consuming, as this will outbalance the motivational strength. The registration process must be as easy as possible and all persons involved must be informed thoroughly. There are already other orthopedic registers, although none yielding information on isolated FCDs. The implementation process should proceed slowly, not overwhelming an already busy clinic. These aspects, together with the challenges with research within this field, make it necessary to perform a pilot register. A pilot will explore benefits and challenges with a cartilage surgery register, and also clarify whether it is room for another orthopedic register in the clinic and how such a register should be established and organized.

Research gap

The main gaps in research addressed in this thesis are the epidemiologic data on cartilage surgery in Norway and the expected geographic variations and low generalizability of current RCTs. All are important arguments for a register. We also investigate the long-term effect of an FCD and the role of an upcoming biomarker of early OA for a further study of the natural history and "risk" of a non-operative approach. The prognostic factors for individualized treatment are explored in relation to this biomarker. All these gaps can be

further evaluated in a cartilage surgery register, and we discuss the results from a pilot study of a cartilage surgery register.

Aims of the study

The main goal is to contribute to an improvement in, and a quality control of, the treatment of patients with FCDs of the knee. The aim of this PhD-project is to explore whether a quality register in cartilage surgery of the knee should be established. Specific aims are:

1. Establish epidemiological data on cartilage surgery in Norway.
    a. What is the incidence of cartilage surgery in Norway?
    b. Are there geographical differences in incidence and treatment trends?
2. Find the external validity of RCTs in cartilage surgery
3. Explore the effect of an FCD in developing secondary early OA of the knee within 12 years after diagnosis.
    a. Is dGEMRIC a useful biomarker?
4. Explore logistic challenges and whether it is possible to establish a cartilage surgery register in Norway

Methods

Paper I: Cartilage defects are commonly encountered during knee arthroscopy, and in Norway all surgeries are registered in the National Patient Register (NPR). In this project we wanted to find the burden of the disease. Within this field it is challenging to identify non-operated patients. We aimed to find the incidence of patients with FCDs undergoing various forms of surgery. We looked into a large national electronic database which constitutes all data on activity from the specialist health service in Norway. To be paid for surgeries, all hospitals, public and private, are obliged to report their activity to this database. We could therefore identify patients with FCDs undergoing knee surgery based on specific diagnostic and procedural codes to estimate the size of a potential future cartilage surgery register. We also explored geographical differences and trends of cartilage surgery.

Paper II: The generalizability of RCTs has been addressed in other fields of medicine and pharmacology. Performing RCTs in the surgical field is challenging. Particularly patient inclusion, placebo from surgery,

standardization of treatment, and blinding of patients are challenging. We wanted to examine to what degree the results from RCTs in cartilage repair are applicable to a clinical setting. If the external validity is low, results from RCTs have limited relevance for most of these patients, and we must consider alternative ways of obtaining knowledge. We assessed the inclusion criteria from existing RCTs and looked at the potential inclusion rate from a non-biased group of patients with FCDs considered for surgery.

Paper III: The outcome of non-surgical treatment is not well described in the literature and the natural history of FCDs remains unresolved. Some clinical studies have found similar results in untreated patients as in patients treated with cartilage surgery. An early biomarker is important for the identification of patients at increased risk of knee OA after an FCD. We identified a cohort of patients with previously diagnosed FCDs, treated both non-surgically and surgically. These subjects were evaluated with dGEMRIC as a biomarker for early OA. We also included T2 mapping, K&L knee radiographs and PROMs.

Paper IV - Pilot register: Prior to conclude on benefits and challenges of a register, we wanted to run a pilot register. Two hospitals included patients with an FCD of the knee detected during knee surgery. The lesions were isolated or in combination with other injuries or diseases. The pilot aimed to describe the patient population and identify logistic challenges and to assess the compliance of a cartilage surgery register. The compliance was tested to ensure complete data of a potential future register.

Summary of results

Paper I

Cartilage surgery is common in Norway as we identified around 2,500 yearly incidences of cartilage surgery. The national age-adjusted incidence rate is 56 per 100,000 inhabitants. The incidences vary between regions and a large part of the procedures are performed in private institutions. Advanced cartilage surgery is uncommon with 400 yearly procedures in Norway.

Paper II

Only 6 of the 137 eligible patients matched all the inclusion criteria in the RCTs on cartilage surgery. This represents 4% of the patient population, which means that results from RCTs are not easily generalized to patients seen in

the clinic. After excluding the most restricting article, 20% would have been eligible for inclusion in the remaining RCTs.[40;109;140;162;175;184;186]

Paper III

Surprisingly few subjects developed degenerative changes in their knees measured with dGEMRIC. We detected no difference in cartilage quality between injured and non-injured knee 12 years after diagnosis. There was no detectable difference between subgroups of patients concerning baseline size, degree or meniscal resection or between surgical and non-operative treatment. Still, radiographic degenerative changes were present.

Pilot register

We ran 2 pilot studies. The first was carried out in 2010 whereas the second is currently ongoing. The compliance varies from 18% to 73%. The inclusion mainly relies on a few orthopedic surgeons. We have encountered some logistical challenges, but believe that it is possible to increase the compliance.

Methodological considerations

Study cohort and inclusion process

Paper I

We collected the data through the NPR and the patient pool is thereby all citizens in Norway. Inclusion criteria were set to all patients undergoing cartilage surgery of the knee during 2008-11.

Paper II

The common inclusion criteria of the identified RCTs were matched to a population of patients with FCDs of the knee. All patients referred to an orthopedic clinic within a specific year with suspected symptomatic FCDs were examined and evaluated by an experienced cartilage orthopedic surgeon. If they were candidates for surgery, they were also eligible for enrolment. The patients were referred from either a primary health service or secondary health service, such as orthopedic departments in other hospitals.

Paper III

We identified a cohort of patients with previously diagnosed FCDs, treated both non-surgically and surgically from 2 previous clinical studies. The first paper contains data on 993 patients undergoing knee arthroscopy due to knee pain in 1999.[2] Patients with an ICRS score grade 3-4 FCD, classified as not having knee OA and with age <50 years at baseline were reexamined after 6 years.[204] In the present 12-year follow-up we invited patients with full-thickness FCDs and age <50 years at baseline, no total knee ligament injury and more than 50% of their lateral and/or medial meniscus intact. A cohort of patients previously included in an RCT on cartilage repair[143] was also invited to participate in the study. In total, 42 patients were eligible for inclusion and 21 signed a written consent. 10 patients were treated with either MF or ACI at baseline, 11 patients had not undergone cartilage repair, neither at baseline nor later, whereas 3 patients from the latter group had debridement performed at baseline.

Pilot register

We aimed to include all isolated FCDs. If additional FCDs or degenerative changes were present in other compartments, we still included these patients. If they had reached a state of OA they were excluded as they had reached the end-stage disease. 2 hospitals recruited patients over a 6-8 months period in 2010 for the first pilot. During the second, and still ongoing, pilot we expanded

Inclusion criteria

- Diagnosed focal cartilage defect (ICRS grade 1-4) during arthroscopy or open surgery
- Operations/ reoperations in patients with a known FCD
- Age 12-67 years

Exclusion criteria

- Generalized knee OA
- Other systemic diseases with a known increased risk of knee OA, such as rheumatoid arthritis

Figure 5. The inclusion and exclusion criteria in pilot 2.

to 5 including hospitals. The patient pool is thereby restricted to the geographic

areas that these hospitals serve, although a few patients are referred from other geographic areas. The inclusion and exclusion criteria of pilot 2 are outlined in figure 5.

Through a register where the inclusion criteria is an FCD, we are able to register patients with isolated FCDs and exclude patients with knee OA. As opposed to the existing electronic registers that rely on registration from the International Classification of Diseases 10th edition (ICD-10) codes, the registration is then more robust against over-registration. Duplicates are easily noticed based on personal data and operation date. The data from a register is easily and quickly accessible. The database contains a much bigger pool of patients with increasing opportunities of detecting poor outcomes, correlations and prognostic factors that are not possible to find in strictly controlled studies.

The entire patient cohort must be registered to avoid selection bias. When analyzing the patients that did not match the RCT inclusion criteria in paper 2, we found that a few did not match due to age, localization of lesions or the occurrence of several lesions. Most patients did not fit due to the size of the lesions. In addition, 42 patients were excluded due to 2 non-matching factors, 21 due to 3 non-matching factors and 4 due to no matching factors. The eligibility rate to the various RCTs ranged from 7%-80%, and this variance seemed to be mainly influenced by size of the lesions. Three articles had a much higher eligibility rate[109;175;184] and one had a much lower rate.[96] Due to this, we include all lesions that are encountered as an FCD in the pilot cartilage surgery register with no restriction or exclusion due to size of the defect. Inclusion is dependent on the clinical decision done by the orthopedic surgeon. We believe that this is the best way of including all clinically relevant FCDs. Variations may still occur but by removing size as a limiting factor, clinically relevant inclusion is much more attainable. A broad and standardized data collection on all possible relevant factors is necessary for answering questions regarding prognostic factors as is exact descriptions of localization, depth and size of the FCDs.

Wide inclusion leads to an unbiased and general population of patients with FCDs eligible for surgery. It is important to include all levels of care, not only University Hospitals. Roughly, 45% of the included patients had experienced either previous cartilage repair or ACL reconstruction. If we see more "worst cases", there might exist a bias between the patient population seen at University hospitals and the population seen at local hospitals. This may have happened in the inclusion to paper II and led to a lower eligibility rate. The German Registry does not register patients treated with simple debridement, other palliating techniques or where a non-surgical approach is applied.[124;205]

In that sense, our design is a more complete register for all patients with FCDs within the knee treated in the specialist health service.

Other registers

The easiest way of collecting the data would have been through one of the already existing registers. There are several national registers holding clinical data from the health system in Norway. Successful orthopedic registers are established in several countries for joint replacement surgery (Norway-1987, Sweden-1975, Finland-1980, Denmark-1995, Australia-1998) and knee ligament surgery (Norway-2004, Sweden-2005 and Denmark-2005). Success means high quality of the register and that useful information is achieved with high compliance of registration. All Norwegian citizens have a personal identification number which is registered when they are treated in both private and public health care. The patients can therefore be followed if they migrate or are treated later at another hospital. The NPR contains general information on treatment and admittances in the specialist health service.

The Norwegian Knee Ligament Register (NKLR) also registers cartilage defects, but only when the patient undergoes an ACL-reconstruction. The Norwegian Prosthesis Register collects data on patients undergoing prosthesis surgery, meaning that patients are already at the hard end point of a cartilage surgery register. There are certain individual cartilage surgery registers initiated by the industry and by individual orthopedic surgeons.[131] Industrial registers tend to include more advanced cartilage surgery than what is common trends in general.[206] Data from one of the recently established registers, the German Cartilage Registry, is available.[124;205] There are currently no existing register for a systematic data collection of patients with isolated FCDs diagnosed during knee surgery in Norway.

Validation of databases

We used data from the NPR in paper I and we performed a pilot of a paper-based cartilage surgery register. The NPR was established to contribute to epidemiological research. Data from electronic databases are both under- and overestimated when compared to a gold standard.[207;208] The results from a validation study of arthroscopic codes for cartilage injuries of the knee from public hospitals in Denmark was published in 2014.[209] The study assessed the validity using surgical descriptions in the medical records as gold standard and found the positive and negative predictive value to be 88% and 99%,

respectively.[209] The same validation study for cartilage injuries and cartilage surgery has not been performed with our national database. We could have included a validation of the NPR for these diagnoses in paper I. However, the aim of this study was an evaluation of the extent of the problem. The Danish NPR is based on the same coding systems for registration of activity and we thereby have a reasonable estimate on the validity of a national electronic database that uses these coding systems.

We also used data from the NKLR to avoid double-registration of patients with FCDs in addition to undergoing ACL-reconstruction. The completeness of the NKLR was 97% 21 months after establishment.[210] The 2 year results were decreasing, with lower rates for smaller hospitals.[211] They are now introducing electronic registration, and hopefully this will lead to a rise in compliance.

We collected data from the NPR on cartilage surgery using a combination of diagnostic and procedural codes derived from the NPR when performing paper I. Extracting data on this patient population is challenging as the registration to the NPR is based on ICD-10 and Nomesco Classification of Surgical Procedures (NCSP) codes that are too unspecific for identifying an FCD properly. The ICD-10 codes available for diagnosing FCDs do not reflect the complexity of these lesions. Although the ICD-10 contains both “acute FCD” (S83.3) and several codes for knee cartilage pathology, there are no codes for the common “non-acute FCD”, which might be subacute or chronic. The clinically important non-acute FCD is therefore difficult to identify. The ICD-10 system also does not allow for a proper identification of the specific factors of a defect, such as size, localization or depth. The different cartilage surgery techniques is neither clearly outlined nor organized within the NCSP coding system. The data on procedures is thereby also unspecific.

Many orthopedic surgeons tend to learn a few codes and then apply these when appropriate, leaving the activity somewhat unspecific at times. Our predefined codes matched with 92% of the reported diagnostic codes from members of the Norwegian Arthroscopic Association. However, the response rate was only 13%. The low response rate has limited effect on our final numbers since we have included most of the possible codes from the ICD-10 system. Many reported the use of M17 (knee OA) also for FCDs, and we included participants with M17-codes when these were coded together with procedures encountered as cartilage surgery. We excluded patients with knee OA by excluding participants without a concomitant procedural code. This may have led to both "false positive" included subjects and to an underestimation. We did not include the ICD-10 code M25.5 which codes for "pain in the knee joint", which may have led to an underestimation. These challenges co-exist

with the fact that some orthopedic surgeons might not code for FCDs at all if other intraarticular pathology is recognized. The existing data may be useful for the purpose of reports on knee cartilage injuries in total, but it is challenging to differentiate between injuries caused by trauma or degeneration.

We believe that *procedural* codes are reported in more detail than simply diagnostic codes as they are the basis for 60% of the government reimbursement to hospitals in Norway, and as such are reviewed several times by hospital controllers to ensure correct coding. However, all the uncertainties encountered about the diagnostic and procedural codes, make this an unreliable source for precise data on patients with FCDs. Additionally the NPR does not contain any form of outcomes or endpoints for this patient group. For paper I, we were mainly interested in the *burden* of cartilage surgery. We found that NPR was appropriate as a data source for estimating the burden of this particular disease on the specialist health service in Norway, using a combination of diagnostic and procedural codes. Overall, the Norwegian NPR is not suitable for obtaining precise data on patients with FCDs.

Pilot register

The patient records or surgical protocols are considered gold standard when it comes to valid data. However, large administrative databases allow for a more efficient data-collection, within its limitations, and may therefore be preferable when it comes to large amounts of data. It is still critical that the data are valid. High compliance is necessary to justify the establishment of a cartilage surgery register and is therefore main outcome of the pilot. Low compliance rate might lead to selection bias, and it is difficult to predict the direction of the bias. Maintaining high compliance and including all patients is therefore both a challenge and a necessity for any register.

As the compliance was low for the first pilot, the objective was to include even broader in the second pilot so that more patients were eligible and the inclusion of a patient occurred more frequently. We expected this to cause the registration process to be implemented in everyday clinical practice, leading to increased compliance. We calculated the compliance of the pilot register by going through the surgical protocols in each hospital. We identified all patients who matched the inclusion criteria based on the surgical descriptions from the operations during the inclusion period and matched those numbers with the records from the registration.

Outcomes

Several outcomes for the evaluation of patients FCDs may be considered whereas the most objective and standardized as of today is the development of knee OA, and TKR. Measures for current symptoms and function should be included, especially in short- and medium-term follow-up. Knee OA as an endpoint, both as a clinical and a radiological diagnosis, requires long-term follow-up and biomarkers for early OA may simplify the follow-up of patients where OA is a relevant outcome. These should be identified and developed. We included both objective and subjective outcomes (PROMs) in paper II, paper III and the pilot register (table 8).

Radiological outcomes

The assessment of the articular cartilage, both after non-surgically treated FCDs and after cartilage repair surgery, depends on high-resolution images. As changes in the cartilage structure occur without morphological changes, we also need techniques that assess the cartilage content. In the search of a biomarker of early OA, dGEMRIC seems promising. In paper III we performed a 12-year follow-up of patients with previously diagnosed FCDs on arthroscopy. We included dGEMRIC, T2 mapping of the injured knee and x-ray of both knees for the evaluation of knee OA according to K&L protocol. Protocols for dGEMRIC are established,[212;213] and the images were obtained correspondingly to standardized protocols. The dGEMRIC includes intravenous administration of gadolinium, which is bound to a chelate complex as gadopentetate dimeglumine (Gd-DTPA^{2-}), and a delayed image-acquisition. The delayed image-acquisition allows the contrast to penetrate the cartilage. Gd-DTPA^{2-} shortens T1 relaxation time in proportion to its concentration. T1 relaxation time measurements provides an inversely correlation to the contrast concentration whereas the contrast accumulates in an inverse relationship with [GAG].[84] The T1-values are transformed into the dGEMRIC index which again reflects the [GAG] throughout the cartilage.[212] A nearly linear relationship between dGEMRIC index and [GAG] in cartilage is seen.[86] A high dGEMRIC index means high [GAG] and good quality.

$$\text{dGEMRIC index} = [\text{Gd-DTPA}^{2-}] = (1/T1_{Gd} - 1/T1_{pre})/r1$$

$$r1 = 4.1\ s^{-1}\ mM^{-1}$$

Figure 6 outlines the calculation of the dGEMRIC index. Adapted from Hawezi et al[1]

The best distribution of the agent is achieved when the patient exercises prior to imaging.[212] The patients walked in stairs for 15 minutes immediately after contrast injection. Post-contrast images were taken 90 minutes after contrast

injection.[84;212;213] For the T1 imaging, a sagittal slice was oriented centrally on the MFC and the LFC. The T1 weighted images were transferred into color-coded T1 maps. The color blue represented areas absent of GAG, whereas red represents high levels of GAG. Originally, both pre- and post-contrast T1 were required to calculate delta R1 and depicting proteoglycan content. Previous studies looking at the difference between T1(Gd) and delta R1 found a high correlation between these in native cartilage.[214] The T1 of unenhanced native articular cartilage is also demonstrated to be constant, which implies that only post-contrast images are necessary.[212] However, the T1 after cartilage surgery changes[88] and only the delta R1 correlates with [GAG].[215] For imaging after cartilage repair, pre-contrast images is recommended in addition to post-contrast images, as the values for native cartilage are lower than values of repair cartilage.[215] The study cohort consists of both non-operated and operated patients, and we included both pre- and post-contrast images.

Outcome for paper II

We explored the generalizability of RCTs on the general population of patients with FCDs, meaning the external validity, in paper II. We measured the potential inclusion rate from an unselected cohort into RCTs on cartilage surgery. We performed a standardized literature search and identified 10 RCTs based on 8 different patient populations.[40;96;106;109;140;143;162;175;184;186] We failed to include Park 2008 (ACI vs MACI), Schneider 2003 (traditional ACI vs CaReS) and Visna 2004 (ACI vs abrasive techniques) in our article.[151;185;216] The article by Schneider et al. is however not available in the English language, but they have published an available case series on the same interventions in English.[182] A few more RCTs have since been published, two articles compare MACI with MF[147;217] and one article compares p-ACI vs c-ACI.[155] A systematic review with ACI as one of the interventions was published in 2011.[126]

All of the RCTs were evaluated according to the PRISMA-statement.[218] The common inclusion criteria from these studies served as a general description of the patient population that the results can be generalized to. These common inclusion criteria were matched to a population of patients with FCDs of the knee. The outcome was the eligibility rate for inclusion as a measure for external validity.

Patient reported outcomes

Validated outcome scores are essential for evaluating the progression of disease, after treatment and in long-term follow-up in clinical studies. The IKDC and KOOS are recommended for cartilage injuries as they have adequate reliability, validity and responsiveness in patients with pathology in the knee articular cartilage and after cartilage repair.[126;219] The subjective PROMs included in each study are outlined in table 8. The Lysholm Score[220] is commonly used to assess knee problems, it is validated,[221] it can be completed by the patients themselves,[222;223] and it quickly provides a good overview of knee symptoms presented in the outpatient clinic. The Lysholm Score, IKDC and KOOS maintain a close correlation in evaluating knees with cartilage defects.[224]

The KOOS score is validated for both cartilage injuries[225] and after cartilage repair,[226] and has acceptable test-retest reliability.[226;227] It consists of 42 items over 5 subscales; pain, symptoms, activity of daily living (ADL), sports and recreation and quality of Life (QoL). Each subscale is reported individually with a score ranging from 0–100, 100 being the best. Reference values for the general population exist.[228]

The Tegner activity score[229] is determined by the most demanding activity the patient is able to perform. The score ranges from 0–10, 0 being absent from work due to knee function and 10 being individuals competing on high-level in pivoting sports. The average Tegner score from normative data is 5.7.[230] Results from clinical trials are within the range of the normative data, however the patients included in clinical trials are often active at baseline.[145] There are other standardized outcome scores for assessing activity profile, for instance the Marx activity rating scale.[231] This scale emphasizes sports with increased knee joint impact, such as pivoting, and sports with frequent acceleration and deceleration. Patients with FCDs have a bimodal distribution of the activity level, and the Tegner thereby seemed more appropriate as it also includes subjects with very low activity.

Table 7. The included PROMs of paper II, paper II and the pilot register.

	Lysholm	Tegner	KOOS
Paper II	X		
Paper III	X	X	X
Pilot register		X	X

We included only the KOOS and Tegner in the pilot register in order to keep the data collection simple and short for patients. We chose KOOS over Lysholm because the NKLR include only KOOS, and we planned to include patients with combined injuries from the NKLR. Data can be pooled and all included patients are evaluated with the same subjective outcome measures.

Outcomes for the pilot register

Compliance of the database was discussed in the validation-section. The raw data must also be valid and reliable. Validity is defined as the ability to obtain all intended information that is clinically relevant for this group. The lesions are classified by location, size, depth and most likely pathogenesis. We also record any previous knee surgery and previous or additional injuries or surgery, if present. The validity of the cartilage form was assessed through an evaluation of all the different points of data collection throughout the form. This was done in collaboration with orthopedic surgeons from the participating hospitals. We developed the cartilage surgery form with the NKLR-form as a framework, but with focus on FCDs rather than ACL-injuries. We updated the form prior to the second pilot after a thorough discussion with the participating orthopedic surgeons. The goal was to obtain all relevant data, while maintaining a simple and minimally time-consuming form. The questions are arranged in a logic and chronological order to keep the scheme *flowing*, allowing for an easy and quick response.

The reliability of the cartilage form is an important issue, where a central aspect is the reliability of the specific data describing the lesions. The size is measured using a specific caliper and the localization is reported due to the anatomical location within the knee joint. An ongoing project is testing the reliability of the ICRS-grading (Kjennvold, unpublished). The PROMs and their reliability were discussed under the PROMs section. In addition to the soft end-points, end-stage OA (by arthroscopy, MRI or K&L-grading) will serve as a hard end-point. The hard endpoints for the NKLR and the National Prosthesis Registry are revision surgery and TKR. Many cartilage patients undergoes several surgical procedures, nearly 40% as detected in paper 2.[232] Revision surgery is therefore not a suitable hard endpoint for cartilage endpoint, and revision surgery will not lead to exclusion from the pilot register.

Design and methods – pilot register

The pilot register is designed as a prospective cohort. It is designed similar to the potential future cartilage surgery register. The patients will be followed at 5 and 10 years. We conducted two pilot studies throughout this project to make sure that the collection procedures are standardized and that the data is of high quality. The first pilot was carried out at two hospitals in the Southeast region of Norway. The logistics were kept simple and transparent so that one person could keep an overview of the paper-based data collection. Based on the results from pilot 1, we found it necessary to conduct another pilot to allow for adjustments of the form and the data collection. Pilot 2 is still running with planned inclusion until the end of 2017. Pilot 2 includes 3 hospitals in the western region and 2 hospitals in the Southeastern region. All 5 hospitals participate in a multicenter study, The Norwegian Cartilage Project. 2 hospitals started registration (OUS and Ahus) from 15 February 2015 whereas we expanded to 5 hospitals (Haukeland, Ålesund and Kristiansund) from March 2016. The registration period is elongated to minimum 2 years, and will provide more time for the cartilage surgery register to be established in each department.

By including a large amount of patients with wide, however still precise, inclusion criteria, and a standardized follow-up, the internal validity is prevailed. We then minimize systematic errors and selection biases and maintain a high quality trial design. We can account for the loss of randomization by controlling the prospective data collection, using objective outcome measures and stratified analyses. As long as there is a clinical equipoise regarding the treatment, this should be used as a tool for bringing the field forward.

Statistical considerations

Paper I

Numbers were extracted from a mandatory national electronic database where all activity in the specialist health service, including all public and most private hospitals, is reported. We defined cartilage surgery based on specific ICD-10 and NCSP codes. For the analyses, the patients were stratified based on year of surgery, geographical location, age and gender. Incidences are given per 100,000 person years. Age-adjusted incidences were also calculated based on population data from SSB. We used the chi square test to determine significance of distributions between the stratifications. The difference between years and geographical location was examined with RR and OR and 95%

confidence intervals (CI). Significance for all analyses was set to a p-value less than 0.05.

Paper II

We examined the proportion of patients seen in the clinic eligible for inclusion in RCTs. During the year of 2008, our clinic received 147 patients referred for cartilage surgery, whereas 10 were excluded. We thereby included more patients than each of the 8 RCTs, where Saris et al. included the most (n=118) and Horas et al. the least (n=40).[96;186] We therefore believe that we have included sufficient cartilage patients to answer our study hypothesis. A power analysis was performed to match the characteristics of included patients with the same characteristics from the RCTs. This resulted in a minimum of 101 included patients in this study. Continuously reported variables are presented as means with standard deviations and comparisons were tested by the Students unpaired t-test. Dichotomous variables are reported as frequency counts and percentages with comparisons performed by using the Fisher exact test. All tests were 2-sided with a significance level of $p < 0.05$.

Paper III

Both the single measurements from each regional of interest (ROI) and the average dGEMRIC index (values from several ROIs pooled together) from each condyle and for each knee were used for analyses. As the dGEMRIC measures had a normal distribution, we performed t-tests as initial analyses to explore any differences within, or between, the knees. Although the power was too low, we believed this was necessary to identify any potential large differences. We know from previous studies that these analyses have great variance, both between subjects and within the knee joint.[233;234] We considered a difference >100 ms to be clinically relevant.[235] As these measures are repeated, the variance is reduced. Using the contralateral knee as a control also decreases the number of patients needed. Significant age differences between subgroups for evaluation of potential bias were tested with the analysis of variance while sex differences were tested with Fisher exact test between the groups.

As we aimed at recruiting all eligible patients from a previous cohort, power analyses were not crucial for the inclusion process. Nevertheless, we examined the power with a one sided test with $1-\beta=0.80$, $\alpha=0.05$, mean value in population 410ms, and mean value in study group on 460ms and SD=80, the needed sample size was 20. The SD from the analyses in the paper varied from around 30 to over 200. The power calculations are based on an SD of 80.

The T2 mean values of each region were analyzed with the same tests as the dGEMRIC results. We used an independent t-test instead of a paired t-test when comparing injured condyle with corresponding condyle. Pearson correlation was used to test associations between injured and corresponding condyle. Possibly, a more adequate statistical method could have been to do repeated measures ANOVA of the means of median T2 values for each subregion. However, we demonstrated a near bell-shaped curve when all T2 values were pooled together indicating that a parametric test was appropriate. Although that shape disappeared for each of the 6 individual subregion. In the presence of statistically significant differences, these would have been further explored with non-parametric tests.

Paper IV

Power analysis were not applied as this is not an intervention study. Descriptive data are presented as means and standard deviations or as medians and interquartile ranges for continuous variables. Frequencies and percentages are used for summary of categorical variables. Linear or logistic regression analysis will be applied through univariable regression modelling for each outcome, to examine the time from symptoms to diagnosis and operation to identify to possible prognostic factors.

General discussion

Unstandardized treatment of FCDs in Norway

The Norwegian health care system is public and tax-funded which balances out possible geographic and socioeconomic differences. All patients should be provided the best level or care and it is therefore important to perform surgery on correct indications, with the appropriate techniques and with the correct rehabilitation programs. Until the best treatment for all patients is resolved there is a natural consequence that indications for surgery are made upon the preferences of the patient and the orthopedic surgeon, which may lead to unstandardized and variations in treatment.

Cartilage surgery is as common as ACL-reconstructions with 2,500 yearly procedures (paper I). Two studies on incidence rates were published prior to our study, both based on the same private-payer database in the United States.[138;206] They presented a large variation in their results with a yearly incidence ranging from 1.4 incidents per 100,000 inhabitants till 104

incidents/100,000. In 2014 Mor et al. found the incidence of arthroscopy-documented cartilage injuries within the knee in Denmark to be 40/100,000 person-years.[209] These numbers are in line with our findings. As suspected, we found varying incidence, both between different geographic areas and among the different age groups. We found a 30-fold difference in incidence between the counties with the lowest and highest incidence rate. There was also a high incidence for the oldest age group except from in the North region, which treated fewer older patients. This is in line with the clinical evidence that older patients benefit less from this type of surgery. For patients >65 years of age, the surgical technique was mainly debridement. Transplantation techniques seemed to be reserved for younger patients, which is in line with the literature were an upper age limit of 40 is suggested.[98]

There are private hospitals in Norway, in addition to the free public health care system mainly provided by public hospitals. Some private hospitals have reimbursement agreements for specific conditions, while some patients have private insurances or are paying out-of-pocket. There is a difference between private and public health care, as some ambulatory surgery centers in the USA have twice as high surgery rates as outpatient surgery in public hospitals. Public hospitals in Norway are paid per service, although the activity-related finances do not affect the individual surgeon`s income. The financial incentives for private and public hospitals might therefore differ. A Danish study[236] demonstrated an all over increase in meniscal procedures, although a larger increase in the private sector.

Several factors may explain these observed variations. The Danish study also found large regional differences in treatment of meniscal lesions.[236] These differences could not be explained by either different activity profile of the population or any regional differences in payment or financial incentives. It is unlikely that similar factors describe the variations seen in paper I. There is an increase in knee examinations with MRI in Norway. This may lead to more frequent surgical treatment due to increased diagnostic findings, also of asymptomatic conditions. We do not have numbers on MRI-documented cartilage injuries in Norway, but previous numbers from the Framingham study have demonstrated 60% cartilage injuries in the general population.[237]

Also, patient willingness for surgery is a factor for potential geographical differences and is previous shown to be higher in areas of high incidence for knee arthroplasty.[238] Some operations are performed without evidence from the literature. A survey among Canadian orthopedic surgeons illustrated that 41% reported no upper age limit for performing MF,[239] although studies have demonstrated a better outcome in patients younger than 30-40 years.[40;106;107]

The geographic variations cannot be explained by actual demographic differences among the population and are more likely to be described by local differences in guidelines, and even variations among orthopedic surgeons. The public health system allows patients to freely choose their treating hospital when elective surgery is performed. Also, local agreements where one hospital treats more of one particular disease or injury whereas another hospital handles other areas occur and may explain some of the differences. Due to anonymity of the patients, we were not able to obtain both home address and treating hospital, and were not able to see the patient flow between geographical locations from paper I. These differences can be further explored in a national register. If differences exist because there are large variations in indications for surgery, the variations should be monitored and studied.

RCTs in cartilage surgery

Paper II illustrates that only 4% of patients were eligible to inclusion in RCTs on cartilage repair. The results from RCTs are applicable to very few of the patients seen in the clinic, meaning that there is a bias between the population presented in the studies and the general patient population. The external validity of RCTs within cartilage surgery is low, although fluctuating. We identified strict inclusion criteria to be a great limitation for inclusion of patients and thereby the generalizability of the results.

McLeod et al. describe the problem with generalizing data and applying RCT results to all patients with a specific disease because of strict inclusion criteria and inherent differences in patients who volunteer for trials.[240] RCTs may help clarify whether there are differences among the various treatment modalities, given strict inclusion and exclusion criteria. The criteria are strict in order to reduce variability among treatment groups and to control for all factors beside the intervention methods. Different factors known to impact on the results must be equally distributed between treatment arms. This increases the internal validity and subsequently paradoxically leads to reduced external validity and generalizability of the results.[232] The applicability to the general patient population is thereby affected and the risk of selection bias occurs.

The insufficient methodological quality is an obstacle for the further evidence within this field, and perhaps with an emphasis on the low external validity. A study on the methodological quality, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[241] guidelines identified a statistically significant increase in quality, but the external validity remained low.[242] The most important goal of research is to develop and increase the

quality of diagnostics, treatment or follow-up of patients and external validation is the key for bringing information back to the patients. A low external validity is a major limitation in the application of results from RCTs to clinical practice.

To our knowledge, the eligibility rate has not been addressed in the orthopedic literature and the generalizability of orthopedic RCTs is therefore uncertain. Authors from other fields of medicine have identified eligibility rates of 33-75%.[244;245] Mitchell et al. examined patients prescribed with tyrosine kinase inhibitors for metastatic renal cell carcinoma in a real-life setting and compared them to patients included in RCTs.[246] They found that 39% of the patients who received the medication in the real-life setting would have been excluded from a clinical study. They concluded that inclusion criteria in clinical studies should be wider as the applicability rate was too low. Another solution may be to initiate larger phase IV-studies, meaning large prospective cohort studies in a real-life clinical setting, a cartilage surgery register. Both wider inclusions criteria in otherwise strict RCTs and more real-life settings or RCTs on clinical effectiveness, will lead to greater generalizability. However, such studies may lose control over the homogeneity across study groups resulting in lower internal validity, and still no more knowledge on prognostic factors or adverse events. Our findings support the addition of unbiased prospective cohort studies to address still unanswered clinical questions.

In some situations, the large challenges with RCTs may be of such a degree that they are unnecessary, or even inappropriate. Well-designed observational cohorts can then be a supplement or a substitute when the alternative is a low-quality RCT. The major drawback of an observational study is that the differences in treatment method depend on differences within the patient population. Grootendorst et al. describes some situations where RCTs are either unnecessary, inappropriate (hip fractures), not possible to perform (unethical) or inadequate.[243] RCTs are also inappropriate when the goal is the measurement of infrequent adverse outcomes and for adverse outcomes expected to occur long-term postoperatively, such as in cartilage surgery.

This does not mean that we do not need future RCTs. RCTs are still the most important method of depicting between different interventions, but there are definitely challenges in applying the results to “common” patients, since an RCT never will include exactly “common” patients. We must keep in mind also that more factors affect the outcome of treatment than the intervention itself and other research designs are therefore important supplements.

How does an FCD affect articular cartilage quality?

dGEMRIC

Paper III explored the long-term effect on knee articular cartilage quality after an FCD in both operated and non-operated patients, evaluated with dGEMRIC as the primary outcome. The dGEMRIC technique is a reliable variable for the content of GAG, and has good reproducibility for use in longitudinal studies including patients with early OA,[247] in healthy subjects,[66] in patients with superficial, deep and full-thickness defects[89] and also in patients with established OA.[248] The results varied from no visible cartilage degeneration to marked cartilage thinning. Although the number of patients was too small to conduct statistical analysis between subgroups, there was no indication of that the injured knee had lower dGEMRIC in comparison to the uninjured knee, nor was it any detectable difference between the injured and uninjured femoral condyle in the injured knee.

Table 8. The table demonstrates dGEMRIC values of different populations. The overall higher results laterally are believed to be due to cartilage thickness rather than GAG-content.

	dGEMRIC (ms)	
Cohort	*medially*	*laterally*
Early knee OA[254]	456-520	498-579
Healthy population and patients with knee OA[214]	455 (+/- 67) 683 (+/- 95) – 3T	
ACL-injured[233]	368 (+/- 48)	406 (+/- 44)
ACL-injury + partial meniscectomy[233]	296 (+/- 62)	380 (+/- 49)
Healthy population[233]	428 (+/-38)	445 (+/- 41)
Healthy volunteers[255]	418	488
After cartilage repair[251]	427 (+/- 159) – 3T	
Patients with painful knee[256]	479-541	
Reference population[251]	636 (+/- 181) – 3T	

There was a non-significant higher value of the injured condyle. These findings are in line with the results from Årøen et al. together with Souza et al., who did not find decreased quality of the cartilage immediately surrounding a focal defect. However, Tiderius et al. studied the contralateral *compartment* in the index knee, and not the corresponding compartment in the contralateral *knee*. The patients in the study by Årøen et al. had an average of 4 years duration of symptoms, whereas our study is a 12-year follow-up. The dGEMRIC for knees in different populations are displayed in table 9. Previous studies have found T1-values in healthy subject to be 426-570 ms, and these numbers are in line with the result from the current study.[212] There are few studies presenting dGEMRIC results in patients with FCDs,[249] and most studies are done in patients after cartilage repair,[251] meniscal resections,[82;233] ACL-injuries or in cohorts with known OA. Previous studies have demonstrated lower dGEMRIC index in patients with higher degrees of early OA (measured with Tönnis grading scale).[252] $T1_{Gd}$ values are lower with increasing age in lamb and sheep models, and may represent a reduction in GAG content with age.[253] T1 values are further higher with 3 T than with 1.5 T field strengths.[214] This must be taken into account when evaluating the results. We used 1.5 T field strength in the present study.

T2 mapping

The mean T2-values of each ROI in the injured knee varied from 48-54 ms. There were large intraarticular variation, as previously reported from another study on healthy knees.[257] Some T2 values for the healthy population have been calculated and the mean vary from 40-54 ms.[257;258] Another study found the range in subjects without diagnostic evidence of cartilage degeneration and normal BMI to be 29.3 – 37.5 ms.[259] Patients at risk of OA have higher mean T2 in the medial femur than healthy controls (37.7 ms vs 36.9 ms).[260] Jungmann et al. demonstrated findings evident of early OA, measured with T2 values, in all compartments except the LFC of the knee 9 years after mega-OATS.[261] They found mean transplant-value of 40 +/-3 ms, whereas the mean global value was 42 +/-3 ms. The results from our study are thereby higher than what is reported for some patient populations, but also still in line with values described for healthy populations.

A study evaluating the correlations between T2 and histological grades of human cartilage found that T2 mapping and histology correlated (weakly), and that T2 in cartilage with histological grade 0 was lower (51.9 ms) than for grade 2 (59.6 ms).[262] Higher T2 values are associated with progression of cartilage degeneration, defined as increased depth, width or number of a

lesion.[263] The relationship between T2 and development of OA does not appear to be linear, so the technique is useful for depicting between normal and mild degeneration of the cartilage, although a distinction based on severity is not possible.[264] The T2 values should however be interpreted with caution as the reproducibility of T2 value measurements from center to center and time point to time point is still not established. The median T2 values are probably better to report than mean values due to the large variability and potential outliers. This points out the need for standardized treatment methods and also standardized ROIs within the knee.

Whether there is a correlation between T2 mapping and GAG content is controversial.[265] We found a medium to large correlation between T2 and dGEMRIC values only in the posterior ROI of the LFC and the central ROI of the MFC. However, when evaluating the scatter plots (figure 7), it is evident that this relationship is the result from a single outlier and there is really no correlation. For the anterior and central ROIs at LFC and anterior and posterior ROIs on the MFC, there was no evident correlation between scores. The present study concludes with no correlation between dGEMRIC and T2 values. This inconsistency might be due to magic angle effect, as demonstrated previously by Mosher et al.[266] The magic angle effect occurs with curved articular surfaces and is reduced by lesser bending of the knee joint and by maintaining a parallel axis of the cartilage surface with the main magnetic field.

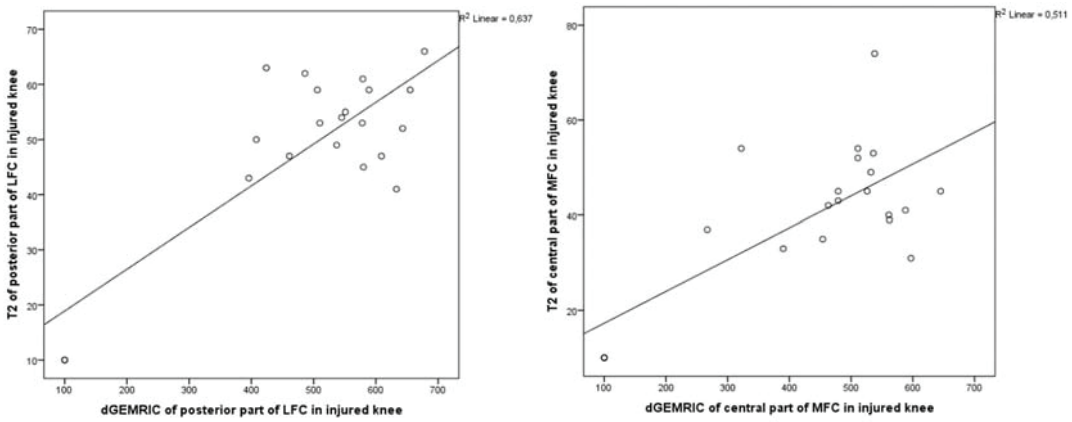

Figure 7. Scatter plots of T2 and dGEMRIC. There is no correlation as the relationship is a result from single outliers.

Is dGEMRIC reliable as a biomarker?

Although the dGEMRIC values were in line with previously described healthy subjects, both the T2 mapping and the plain radiographs demonstrated degenerative changes. For the radiographs there were degenerative changes in more than 80% of the injured knees. This is contradictory to other studies

that have found T1-weighted sequences to be more sensitive to the early degenerative changes within knee articular cartilage.[267] We did not find dGEMRIC to be a sensitive marker of early OA in this study as there was no difference between injured and non-injured knee 12 years after diagnosis. Altered gait mechanics following a traumatic FCD leading to a shift of the loading pattern within the joint may partially explain why the injured knees had similar results as the uninjured knees. Another possible explanation to the lacking difference between injured and non-injured knees is that similar degenerative changes are evident in the non-injured knees. A highly degenerated knee joint may yield unpredictable results. The wash-out kinetics of T1 vary between healthy and diseased cartilage.[85] This may have affected the knees differently in the present study, although the protocol was set up in accordance with previous recommendations.[212;213]

However, the overall results are not equivalent with degenerative changes when compared to previous values from healthy populations (table 9). Variations between equipment and centers occur. Still, some regions within the knees have unmeasurable values, which mean that the cartilage is too thin to be measured. It is possible that these areas represent the original defects and that the changes are strictly focal and thereby not assessed with our analyses, which are restricted to the predefined ROIs. The dGEMRIC is a sensitive tool for proteoglycan depletion, but it may depend on mechanically intact cartilage for precise measures.[268] Also, the radiographic diagnosis of OA is not associated with clinical symptoms,[269] and it is possible to have radiographic changes and still not qualify for the clinical diagnosis of knee OA.

The ROIs for evaluating the cartilage composition were placed in a standardized fashion. Previous studies on healthy subjects and patients with early OA have focused on the weight bearing areas (central ROI) of the cartilage which is most prone to early degenerative changes.[90;250] We found overall lower sores in the anterior ROIs. The central ROI on the MFC in the injured knee had the largest SD and the results are therefore uncertain. We concluded that little degeneration was detectable and that dGEMRIC did not act as a reliable measure for early OA in this population. We had no information on the localization of the defects in the sagittal plane in 13 patients, which challenges the interpretation of the results. Some areas had no detectable cartilage due to cartilage thinning. An exact knowledge on the baseline localization would have made it possible to see these areas in relation to the original defects.

A study evaluated cartilage quality with dGEMRIC quality 9-18 years after ACI.[270] Besides good cartilage quality, they also found evidence of

osteophytes and subchondral cysts. These findings are considered evidence of degenerative changes, and the occurrence of both good cartilage quality and degeneration may represent strictly local changes. Hingsammer et al. looked at dGEMRIC in hip dysplasia and found a globally decreased dGEMRIC index within the joint whereas tissue loss was a local finding.[252] Localized changes might explain why we did not demonstrate any difference in mean dGEMRIC, as the ROIs might have been placed outside the original defects. Still, we failed to identify any global decrease meaning that there was no decrease in overall knee joint health. Also, there is established a zonal variation, and a variation in contrast uptake, related to the depth of the articular cartilage.[255;256] The deeper layers tend to have a higher dGEMRIC index. This may relate to a higher content of GAG, but also to reduced uptake of contrast, since later studies have demonstrated this uptake to occur via the synovial joint fluid rather than the subchondral bone.[255]

The dGEMRIC as a biomarker must be further explored in both patients undergoing cartilage surgery and in patients treated non-operatively. There are no linear relationship between qMRI and arthroscopy when explored in 10 patients with suspected cartilage degeneration by Casula et al.[256] However, a mild correlation exists when ICRS grade 0 is removed. The focus should be to standardize the dGEMRIC protocols concerning characteristics of the baseline defect, as the study indicates that dGEMRIC can be reliable when applied to the exact location of the original defect. Furthermore, the dGEMRIC seems to vary both among individuals and within the knee joint. The intra- and interindividual variability makes it difficult to classify a specific value as normal or pathologic. The dGEMRIC might be a valuable tool for an indication of increased risk of OA and for longitudinal follow-up as decreased values mean loss of GAG. Longitudinal assessments should be performed to establish reference, or cut-off, values for early OA.

Prognostic factors

There are still many unclear aspects of prognostic factors. End-stage OA is a reliable outcome of knee joint health, but we also need biomarkers for early OA and a register may identify prognostic factors. We evaluated scatterplots on patient and defect characteristics against dGEMRIC results to find possible associations. The strongest association between baseline size and mean dGEMRIC based on injured or uninjured compartment was identified in defects on the LFC (figure 8).

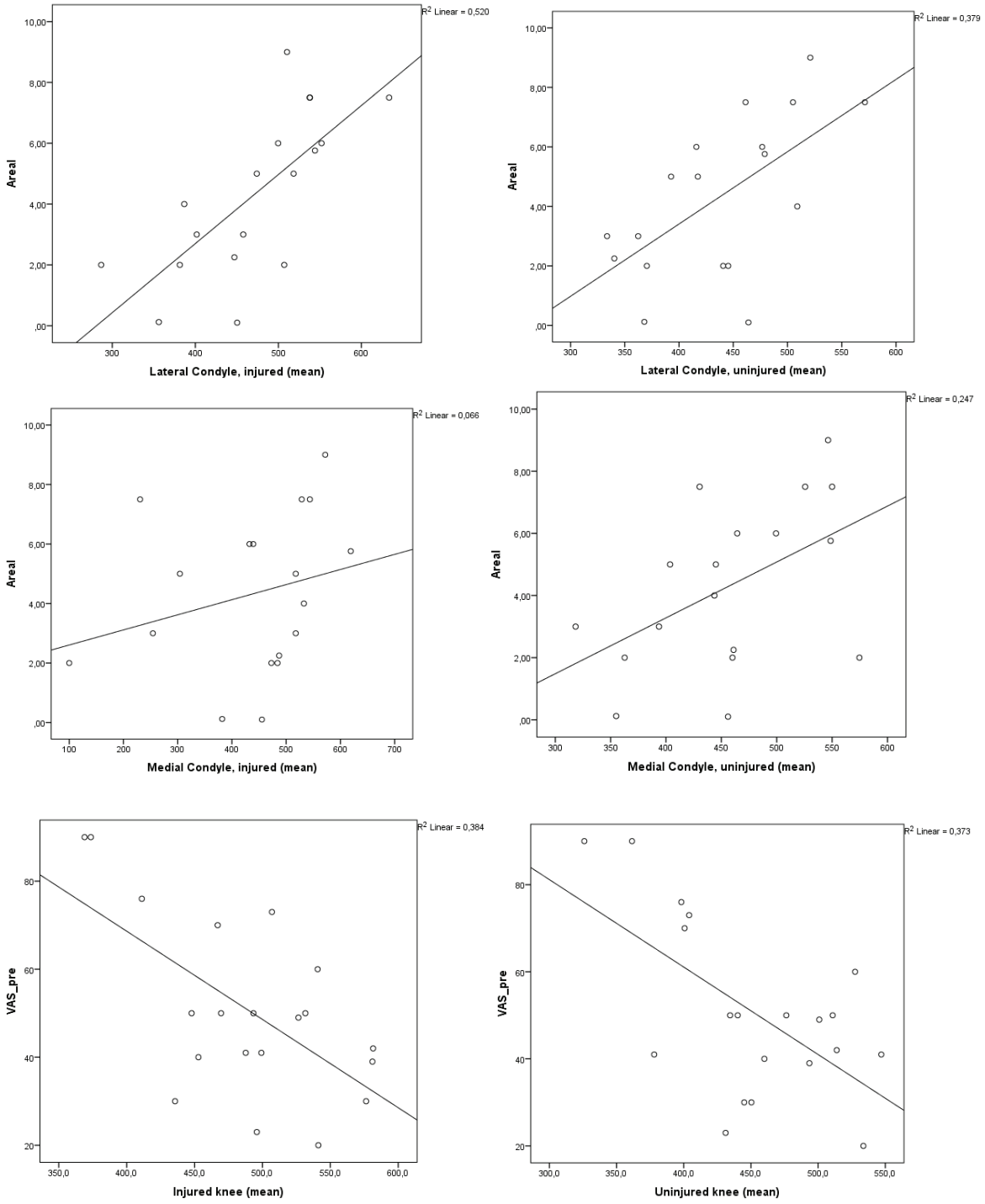

Figure 8. The figure illustrates scatter plots with regression lines regarding baseline size, and baseline VAS against mean dGEMRIC value of each injured and uninjured medial and lateral femoral condyle and injured and uninjured knee. The strongest association between baseline size and mean dGEMRIC based on injured or uninjured compartment was found in defects on the LFC, and only weak correlations for defects on the MFC. There was a weak correlation between VAS at baseline and the mean dGEMRIC value of both injured an uninjured knee.

We found a large and negative correlation (r=-0.673, p=0.033) between age at injury and dGEMRIC values for defects on the LFC. Low age at injury was associated with higher dGEMRIC at follow-up, and this is in line with previous

findings of better outcome for younger patients.[105] As the correlation exists in both knees, this may be considered a marker of the general joint health rather than symptoms from the focal defect. Another explanation is that high levels of pain leads to progressive degenerative changes bilaterally due to altered loading patterns.

A study looking at the relationship between the severity of hip dysplasia, found dGEMRIC index to correlate with the radiographic findings and pain.[271] The dGEMRIC index in symptomatic femoroacetabular impingement (FAI) is lower than in asymptomatic volunteers in a population of patients with grade 0 changes on conventional MRI.[272] We did not find any significant correlation between dGEMRIC and either K&L or PROMs in the present study.

10 patients underwent cartilage surgery at baseline. Cartilage surgery is demonstrated to affect the dGEMRIC index compared to native cartilage.[273] Pinker et al.[274] concluded that the [GAG] probably never reaches the level of normal healthy cartilage tissue after MACI. In the present study, there was a non-significant (p=0.152) difference between untreated/debrided defects and MF/ACI treated defects.

As dGEMRIC did not act as a reliable biomarker for early OA in the present study, further deductions on reliable prognostic factors are not possible and must be explored with other outcomes. It is therefore important to secure detailed descriptions of baseline factors in a cartilage surgery register as this is the best way of identifying clinically relevant prognostic factors.

Cartilage surgery register

Based on the current status on treatment of patients with FCDs of the knee and the challenges with high-quality research on this patient population, we wanted to explore a potential establishment of a cartilage surgery register. We explored the benefits of and challenges with a cartilage surgery register. Ultimately, we wanted to answer whether a cartilage surgery register should be established. The experiences from our pilot is that useful information is obtainable, although with challenges. Compliance and follow-up are the most obvious challenges. Care must be taken in the design and logistics of a register and a continuous effort to maintain high compliance is needed. This is not different from other registers. A cartilage surgery register seems important for the development of treatment indications, and how to identify patients who will benefit from surgical treatment.

Whether such a register is possible provide valuable data depends on 2 factors; that the data are valid and complete. The low compliance in pilot 1 seems to be a result from few participating hospitals and orthopedic surgeons and from a short registration period. We believe that this caused the registration to never truly be implemented into the daily clinical routine. We therefore decided to rerun the pilot before deciding the register's future, in order to identify challenges and assess whether complete data are attainable. The results from the second pilot is not included as it is still ongoing.

Paper I demonstrated large geographical variations in cartilage surgery. There are large variations in how these patients are treated, and there is a risk that individual surgeons opinions mean more than scientific evidence in some cases. For conditions where a surgical approach is necessary in order to regain function or prevent serious disease, it is easy to draw the conclusion that geographic variations follow variations in incidence of disease. For diseases or conditions where surgery has an unclear role, the variations may be caused by variations in diagnosis, or they can be attributed to physician and patient preferences.[275]

A challenge with patients undergoing cartilage surgery is that they often have had prior surgery.[34;109;137] Previous surgical procedures might impact on the current surgery and on prognosis.[135] This information is often difficult to attain as patients are admitted to different public hospitals and also visit private centers. The medical record system is separate for each hospital and the orthopedic surgeon must rely on the patient, who rarely has detailed information on the status and procedure. This probably also contributes to the large variations in treatment demonstrated in paper I.

Before these variations can be reduced, they must be identified, studied and acknowledged. We believe that both variations in diagnosis and preferences, the latter from both physician and patient, explain the reason for the observed variations. As there are no established gold standard treatment, such variations occur consequently.[276] The heterogeneous patient group might also contribute to the variations in treatment. These results are nevertheless important for planning and designing a national register. The numbers are appropriate for establishing a register, and the geographic variation reflects the need of more standardized conditions.

In paper II we found low external validity from RCTs on cartilage surgery. This means that many patients with FCDs are never studied in high-quality research. However, the most important reason for the lack of generalizability is the identified factors leading to ineligibility.[245] We identified *size* as the most

challenging factor, but also *age*, *localization* of defects and *number of* defects led to ineligibility. A cartilage surgery register will include and follow up all patients and will yield useful information on patients who are not included in RCTs. The heterogeneity seen in this patient group is a challenge for the generalizability of RCTs. Currently, care must be made when the orthopedic surgeon uses results from RCTs when deciding treatment for patients with FCDs as the results may not apply for the particular patient. This means that at least some trials should include a more unselected patient cohort. Observational studies with a prospective and standardized data collection and valid outcome measures may complement the results from RCTs.

Biomarkers of early OA are still lacking. Prognostic factors are also largely unresolved. A few factors for a good surgical result are identified. These factors are identified through RCTs, which is not designed for identifying prognostic factors as they are controlled for through the randomization of subjects. A cartilage surgery register, designed as a prospective cohort study, is therefore likely to contribute to new knowledge on prognostic factors.

The treatment of cartilage injuries is difficult, we have shown that large variations in treatment exists, and the generalizability is low. A cartilage surgery register has the potential to significantly impact clinical practice, such as the NKLR. Several clinical prognostic factors for outcome after ACL-reconstruction have been identified over the recent decades, where some have already led to alterations in treatment methods in Norway. Through the NKLR,[210] it was possible to discover an increased revision rate with hamstring tendon grafts compared to patellar tendon grafts (hazard ratio of 2.3).[277] Data from the NKLR have recently demonstrated a worsening in outcome if MF is performed in the same stage as the ACL-reconstruction.[278] The authors recommend avoiding doing both these surgical steps together, and rather reconstruct the ACL, rehabilitate and then evaluate cartilage surgery if sustained clinical symptoms. There is a large potential for increased quality in treating patients with FCDs of the knee with a specialized cartilage surgery register.

Compliance

In the first pilot, the compliance varied from 18% to 73% in pilot 1. Pilot 2 is ongoing in conjunction with a multicenter study in the same hospitals, which will cause more knowledge and activity around the pilot register. The inclusion criteria are less strict and the registration period is prolonged. This will hopefully results in that patients are included more frequently, and ensure

more complete data. High compliance is possible, but everyone involved must be motivated and the registration must be easy to conduct.

A paper published in 1992 looked at the completeness of an orthopedic database in England by comparing the database with Hospital Activity Data and found that overall completeness of the database increased after audit and feedback.[279] They suspected motivation to be the most effective factor in promoting correct use of the database. Frequent feedback to the participants is therefore an important factor for achieving high compliance as it acts as a motivational factor. Throughout pilot 2 we have given regular reminders to increase the compliance.

Strengths and weaknesses

Paper I

In paper I, data from the NPR was collected and incidences of cartilage surgery were calculated. The distinction between focal lesions, which are traumatic or degenerative, is difficult to make based on clinical examination. We encountered insufficient detail in the diagnostic and procedural codes used by the NPR. This is the largest study limitation and cannot be defeated by any methodological changes, but by information and education of orthopedic surgeons. This is a shortcoming of the ICD-10 system, which constitutes a challenge for cartilage pathology and affects the cartilage research field in general, including the current study. This can potentially be overcome by a revision of the current coding systems. The ICD-11 is already revised.

The strength of this study is that we have cross-sectional data from 4 years of a national cohort, as opposed to many similar studies where data are obtained from private insurance databases and involve only patients with a specific insurance plan. We based our data on specific surgical codes, which are more precise than the diagnostic codes. These codes are partly responsible for the yearly budget for each hospital and miscoding of surgical procedures leads to inconsistent funding.

Paper II

We searched for well designed RCTs and although we failed to include two studies, these would not have altered our result. There is a possibility that our included "general patient population" represent a biased population of the "worst cases" since some patients are referred from other hospitals to a

specialist hospital. The study revealed a substantial possibility of bias between the population presented in RCTs on cartilage surgery and those referred to a major orthopedic center.

Paper III

We found that dGEMRIC was not a reliable biomarker of early OA in paper III. The patients were diagnosed with an FCD 12 years prior and were expected to show early degenerative changes. The dGEMRIC technique is indicated for early OA, and our patient cohort may have had too advanced joint degeneration, which dGEMRIC was unable to identify.

The strength of this study is the inclusion of a group of patients with FCDs diagnosed with arthroscopy 12 years prior to dGEMRIC. A long-term follow up of non-operated patients has to our knowledge not been performed previously. We excluded patients with total ligament ruptures and unstable knees. However, the power of the study and potential false negative numbers may have influenced the results. We studied a small population where a few patients also had injuries in their uninjured knee. The ROIs in dGEMRIC and T2 mapping were drawn manually. The reader was an experienced radiologist with experience from reading MR images and also special training in drawing ROIs and analyzing dGEMRIC. The manual drawing is still a drawback as there is a large intraarticular variation. It is also previously demonstrated large variability in measures.[235] The intra- and interobserver variation is low[90] and previous studies have reported an intraclass correlation coefficient (ICC) for the measuring of dGEMRIC index to be 0.9.[252] The ICC of dGEMRIC readings was good in another study from this group.[249]

Pilot register

One of the strengths of a register is that it is an unbiased prospective cohort study. The patients are identifiable and may therefore be linked to other registers in the future. This means that the findings have a great potential external validity, as opposed to RCTs. However, as the inclusion relies on many different orthopedic surgeons and hospitals, the inclusion may vary. We have assessed operation descriptions in the medical records in order to check the compliance. A thorough analysis of inclusion bias was however not done. Certain challenges within surgical research are the difficulties of standardization and challenging patient enrolment, as described and demonstrated in paper II. Virtually all cartilage surgery occurs in an elective

setting, which allows thorough information and consideration on treatment options and prognosis. However, a register does not rely on strict randomization and patient, or surgeon, preferences do influence on the results.

A weakness of all registers is the internal validity, which will never be as high as a good quality RCT. But, it is possible to gain access to high quality data with a proper design, even in the absence of randomization and blinding. A register is the only method that measures the effectiveness of treatment in the general population. Internal validity is kept high with good control of all other variables.

As for all studies with inclusion based on surgical procedures, FCDs diagnosed with MRI and treated non-operatively are not included. As some patients and surgeons choose to “wait and see,” the time that elapses from when the symptoms actually appear until examination by an orthopedic surgeon will also vary greatly. This is a well-known diagnostic challenge for these defects as only around half of FCDs are encountered as acute.[2;8] ACL-ruptures based on MRI-findings are now included in the NKLR, and must also be considered for a potential future cartilage surgery register. A register contributes to a clinical validation of the defects as the surgeons are forced to consider the defect as a focal and localized defect or a change that is part of a degenerative status of the knee joint. The register thereby also contributes to education of younger surgeons as everyone involved in knee arthroscopy are involved in registration.

Conclusion

Cartilage surgery is common in Norway, on level with ACL-surgery. Surgical RCTs do not ensure high external validity. The dGEMRIC technique is not a good biomarker for long-term follow-up of patients with FCDs. Although the pilot register was unsuccessful, we nevertheless suggest that a nation-wide cartilage surgery register will benefit the quality of care and ultimately well-being of the patients.

The future

Objective of a future register

The aim of a future cartilage surgery register is to contribute to improved patient care, through continuous and systematic evaluation of the management of these patients in a real-life setting. Registers have the great opportunity of analyzing data on a significantly greater number of participants, when acceptable compliance is achieved.[280] Prognostic factors, failures and uncommon advents following any type of surgical technique or equipment can be identified. As for ACI it takes 2 years simply for the new tissue to mature.[282] And a cartilage surgery register will secure long-term follow-up data on this patient population. A register also addresses the factors identified by Worthen et al. to be important, specifically the larger patient enrolment and longer follow-up.[196]

A register will contribute to increased quality of the health care, as the adherence to clinical guidelines will be easier visible. The implementation of research results into the clinic will become easier to study. Potts et al. detected a decline in arthroscopic procedures for knee OA after publications had demonstrated their ineffectiveness.[281] The non-surgical treatment options are not fully explored, and never tested against a surgical intervention. With high methodological quality and standardized outcomes it is possible to compare different interventions in a cartilage surgery register.

A register will be helpful for planning health services and health economy. We will be able to see both where patients are treated and the results. A register will provide information on the costs of treatment. The outcomes of the pilot register may serve as both health outcomes and as an outcome for effectiveness of treatment. In that way, the register may serve both clinicians and health care leaders. It is also an increasing demand to report quality parameters for politicians and administrators to measure and compare results from different health services and regions. How quality is defined and measured is medically important, and the quality of treatment must be our priority. Data from a cartilage surgery register may be used directly when informing the patients in the outpatient clinic. The register will serve as an important supplement in the research field; to bridge the gap between basic research and RCTs in this field. By following large cohorts prospectively with standardized data collection and outcome measures in a uniform fashion, we will be able to rule out some of the methodological drawbacks in this field. Furthermore, it is ethically important that the accessibility to a register exists in order to tailor the best treatment available for each patient.

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Appendix

PILOTSTUDIE BRUSKREGISTER
Senter for Idrettsskadeforskning,
Norges Idrettshøgskole
Sognsveien 220
Postboks 4014 Ullevål
0806 OSLO

F.nr. (11 sifre) .....
Navn.....
Sykehus.....
(Skriv tydelig ev. pasient klistrelapp – **spesifiser sykehus.**)

FOKALE BRUSKSKADER I KNE

ALL KNEKIRURGI på pasienter med fokale bruskskader eller som tidligere har skadet/operert brusk i kneet.

(Bilateral operasjon = 2 skjema)
AKTUELL OPERASJONSDATO (dd.mm.åå) |__|__|__|__|__|__|

AKTUELT KNE (ett kryss) ☐ Høyre ☐ Venstre

AKTUELL OPERASJON (ev. flere kryss)
- ☐ Diagnostisk skopi
- ☐ Meniskoperasjon
- ☐ Fjerning av implantat
- ☐ Osteosyntese
- ☐ Osteotomi
- ☐ Operasjon pga infeksjon
- ☐ Bruskkirurgi
- ☐ Biopsi, øvrig
- ☐ Synovektomi
- ☐ Bentransplantasjon
- ☐ Protese
- ☐ Annet .....

DAGKIRURGISK OPERASJON ☐ Ja ☐ Nei

TIDLIGERE OPERASJON I AKTUELLE KNE (ev. flere kryss)
☐ ACL ☐ MCL ☐ PLC ☐ Medial menisk
☐ PCL ☐ LCL ☐ Brusk ☐ Lateral menisk
☐ Ingen ☐ Annet, spesifiser ....

ER DET VED TIDL. OPR. påvist fokal bruskskade i kne?:
☐ Ja ☐ Nei ☐ Vet ikke

HVIS TIDL PÅVIST: mnd/år påvist 1. gang (mm.åå): |__|__| |__|__|

HVIS TIDL PÅVIST: aktuell status for tidl påvist(e) bruskskade(r). (For koder – se i høyre kolonne. Bruk evt flere koder i hver rubrikk):

	Areal (cm^2)	ICRS gr* (1-4)	Tidligere beh*** (1-18)	Aktuell beh av tidl påviste skader*** (1-18)	Degenerative forandringer, ICRS*
Patella M					
Patella L					
Trochlea fem					
Med fem cond					
Med tib plat					
Lat fem cond					
Lat. tib plat					

ER DET NYOPPDAGEDE FOKALE BRUSKSKADER VED AKT. OPR:
☐ Ja ☐ Nei ☐ Vet ikke om ny el. tidl. påvist

HVIS JA; ER NYOPPDAGET SKADE TRAUMEUTLØST:
☐ Ja ☐ Nei ☐ Vet ikke

HVIS TRAUME; TRAUMEDATO: (mm.åå) |__|__| |__|__|

HVIS TRAUME: AKTIVITET VED TRAUMETIDSPKT.:
- ☐ Fotball
- ☐ Snowboard
- ☐ Arbeid
- ☐ Trafikk
- ☐ Annet .....
- ☐ Alpint
- ☐ Håndball
- ☐ Mosjon/friluftsliv
- ☐ Ikke spurt
- ☐ Ukjent

HVIS IKKE TRAUME, symptomvarighet (i mnd) .....

ANDRE SKADER PÅVIST VED AKT. OPR. (inkl. de som ikke behandles)
☐ Menisk ☐ PLC ☐ Annet ....

HVILKE ICD-10 kode(r) ble brukt: ....

STATUS FOR NYOPPDAGET fokal bruskskade(r), og evt eksisterende degenerative forandringer (For koder – se under tabell og bruk evt flere koder):

	Areal (cm^2)	ICRS gr* (1-4)	Etiologi** (1-5)	Behandling *** (1-18)	Degenerative forandringer, ICRS*
Patella M					
Patella L					
Trochlea fem					
Med fem cond					
Med tib plat					
Lat fem cond					
Lat tib plat					

KODER:
***ICRS Grade:** 1 Nearly normal: Superficial lesions, soft indentation and/or superficial fissures and cracks; 2 Abnormal: Lesions extending down to <50% of cartilage depth; 3 Severely abnormal: Cartilage defects extending down >50% of cartilage depth as well as down to calcified layer; 4 Severely abnormal: Osteochondral injuries, lesions extending just through the subchondral boneplate or deeper defects down into trabecular bone.
****Sannsynlige årsaker:** 1 Traume; 2 CM: chondromalacia patellae; 3 OCD: osteochondritis dissecans; 4 Ukjent; 5 Annet: Spesifiser årsak i aktuelle rubrikk
*****Behandlingskoder**: 1 Ingen behandling; 2 Debridement; 3 Stabilisert bruskskaden; 4 Mikrofraktur; 5 Mosaikkplastikk; 6 Biopsi til dyrking; 7 Celletransplantasjon; 8 Celletransplantasjon med matrix; 9 Periosttransplantasjon; 10 Fiksering OCD; 11 Fjernet ost.mat OCD; 12 Annet: Spesifiser behandling i aktuelle rubrikk; **Ved bruk av BRUSKIMPLANTAT;** 13 MACI; 14 Chondrogide; 15 Cartipatch; 16 HYAF; 17 TrueFit; 18 Annet implantat: .....

AKTUELL BEHANDLING AV MENISK:

	Reseksjon	Sutur	Syntetisk fiksasjon*	Menisk-transpl.	Trepanering	Syling
Medial	☐	☐	☐	☐	☐	☐
Lateral	☐	☐	☐	☐	☐	☐

Hvis meniskreseksjon; angi andel gjenværende menisk i %
☐ Mediale: ..... ☐ Laterale: .....

PEROPERATIVE ORTOPEDISKE KOMPLIKASJONER
☐ Nei ☐ Ja, hvilke(n).....

OPERASJONSTID (hud til hud) .....min.

SYSTEMISK ANTIBIOTIKAPROFYLAKSE
☐ Nei ☐ Ja, hvilken.....

NSAIDs: ☐ Nei ☐ Ja, hvilken type .....

Kommentar.....
.....
.....
.....
.....

Lege: .....
Legen som har fylt ut skjemaet (navnet registreres ikke i databasen).

Errata

Paper I-IV

I

BMJ Open

Incidence of knee cartilage surgery in Norway, 2008–2011

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To cite: Engen CN, Årøen A, Engebretsen L. Incidence of knee cartilage surgery in Norway, 2008–2011. *BMJ Open* 2015;**5**:e008423. doi:10.1136/bmjopen-2015-008423

▸ Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2015-008423).

Received 7 April 2015
Revised 31 July 2015
Accepted 25 September 2015

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ABSTRACT

Objective: A systematic and long-term data collection on the treatment of focal cartilage defects (FCDs) of the knee is needed. This can be achieved through the foundation of a National Knee Cartilage Defect Registry. The aim of this study was to establish the nationwide burden of knee cartilage surgery, defined as knee surgery in patients with an FCD. We also aimed to identify any geographical differences in incidence rates, patient demographics or trends within this type of surgery.

Setting: A population-based study with retrospective identification of patients undergoing knee cartilage surgery in Norway through a mandatory public health database from 2008 to 2011.

Participants: We identified all patients undergoing cartilage surgery, or other knee surgery in patients with an FCD. All eligible surgeries were assessed for inclusion on the basis of certain types of ICD-10 and NOMESKO Classification of Surgical Procedures codes.

Primary and secondary outcome measures: The variables were diagnostic and surgical codes, geographic location of the performing hospital, age and sex of the patients. Yearly incidence and incidence rates were calculated. Age-adjusted incidences for risk ratios and ORs between geographical areas were also calculated.

Results: A total of 10 830 cases of knee cartilage surgery were identified, with slight but significant decreases from 2008 to 2011 ($p<0.0003$). The national incidence rate was 56/100 000 inhabitants and varied between regions, counties and hospitals. More than 50% of the procedures were palliative and nearly 400 yearly procedures were reparative or restorative.

Conclusions: Knee cartilage surgery is common in Norway, counting 2500 annual cases with an age-adjusted incidence rate of 68.8/100 000 inhabitants. There are significant geographical variations in incidence and trends of surgery and in trends between public and private hospitals. We suggest that a national surveillance system would be beneficial for the future evaluation of the treatment of these patients.

Strengths and limitations of this study

- This cohort study presents the national burden of knee cartilage surgery in Norway.
- The geographical differences and differences in trends are reliable as the data collection is mandatory for all hospitals.
- ICD codes were used for inclusion and this represents a limitation, as there are no specific codes for 'non-acute focal cartilage defect', which leads to unspecific diagnosis. This limitation is partly corrected for by adding NOMESKO Classification of Surgical Procedures surgical codes to the inclusion criteria.
- Compliance and validity are limitations for the data quality in most registry studies. The register included in the present study has previously been shown to both overestimate and underestimate clinical conditions; however, studies that are more recent have demonstrated high validity.

INTRODUCTION

Knee cartilage injury is a well-known condition after the introduction of knee arthroscopy and MRI. Cartilage injury might consist of a single or several focal lesions or it might constitute generalised degenerative changes within the knee. Focal lesions are classified as traumatic or degenerative and some exist without causing symptoms. They are believed to lead to a chronic osteoarthritic stage with pain and reduced function, which however has been demonstrated only in animal models.[1 2] Arthroscopic studies have shown that focal cartilage defects (FCDs) within the knee occur in 19–67% of patients with painful knees.[3–6] A systematic review found a prevalence of 36% in athletes examined by arthroscopy, MRI or both, whereas 14% were asymptomatic.[7] Another study conducted MRI of the tibiofemoral joint in persons aged 50 years or more from the general population (mean age of 62.3 years).[8] They found cartilage abnormalities in 69%. We suspect FCDs to be common also in the general population including participants under the age of 50 years.

Several years of research on cartilage surgery have still not led to a clear gold standard treatment of FCDs within the knee. The results from randomised controlled trials (RCTs) are variable,[9–16] the patient population is heterogeneous[17] and a group

of non-operated controls has still not been included in an RCT, making it difficult to decide the role of rehabilitation alone. Also, the quality of clinical studies on cartilage research is low.[18 19] The most commonly performed procedures on patients with knee cartilage injuries are palliating procedures, such as chondroplasty (CP) and debridement, which have demonstrated symptomatic relief in uncontrolled cohort studies but failed to do so in RCTs.[20 21] Unfortunately, in this area of orthopaedic surgery, the practice of evidence-based medicine is lacking and the procedures are still used for patients with degenerative changes within their knees.

Results from other orthopaedic registries have led to improved treatment quality and we are currently looking into the potential benefits and challenges of establishing a National Knee Cartilage Defects Registry. Before establishing such a registry, several conditions must be explored. This study intends to present the burden of surgery for the disease.

Two studies from the USA have calculated incidence rates from an insurance database.[22 23] Montgomery *et al* showed incidence rates ranging from 1.27 to 1.57/10 000, while McCormick *et al* presented incidence rates ranging from 63 to 104/10 000. These numbers would represent 635–52 000 yearly procedures when applied to the number of inhabitants in Norway, which is a very wide interval. In 2014, a study on trends of cartilage injuries documented by arthroscopy in Denmark was published.[24] It excluded patients with osteoarthritis (OA) and found an incidence of 40/100 000 person-years for the years 1996–2011.

The aim of this study was to establish the nationwide burden of surgery on knees with knee cartilage defects in Norway. This will play an important role in the evaluation of the possible establishment of a National Knee Cartilage Defects Register in Norway. We calculated the national and regional incidences and aimed at detecting any geographical variations. The latter is of major interest for health development research, the medical industry as well as healthcare providers. Our hypothesis was that cartilage surgery is uncommon and performed mainly in hospitals around the larger cities and that only University hospitals perform advanced cartilage surgery.

PATIENTS AND METHODS

Data source

The study is descriptive with population-based data from the years 2008 to 2011 in Norway. It is a retrospective cohort study through the continuous data collection done by the Norwegian Patient Registry (NPR). The NPR is run by the Norwegian Directorate of Health and contains data on the activity in specialist health services. Norway has approximately 5 million inhabitants. The country consists of 4 health regions and 19 administrative counties. The South East region is most populous, followed by the West, Mid and North regions. Norway has a national public healthcare system aiming at equal health services to all inhabitants regardless of their income or private insurances. Also, a growing number of private hospitals and surgical centres offer mainly elective orthopaedic surgery to patients with private insurance, reimbursed by public funding through government contracts or paying out of pocket (previously 10–15% of specific elective surgeries, however, influenced by substantial geographical variation[25]).

The NPR contains reports on the International Statistical Classification of Diseases and Related Health Problems (ICD) code and the NOMESKO Classification of Surgical Procedures (NCSP) code along with other reported factors. It is obligatory for all public hospitals, and for private hospitals with a contract with the public healthcare system, to report their activity to NPR. The arrangements thereby also involve all major private hospitals. The present patient pool consists of all Norwegian patients.

We aimed at detecting cases undergoing surgery for knee cartilage defects. Distinguishing between traumatic and degenerative lesions is often difficult clinically and the development from an FCD to OA might be seen as a continuum. In addition, the ICD-10 coding system is unspecific and further challenges this distinction. Cases were identified from the NPR through predefined surgical procedure codes (all NCSP codes constituting surgery on the knee and/or calf) and ICD-10 codes (table 1) and retrieved as eligible for inclusion if any combination of surgical and diagnostic codes, according to table 1, was present. ICD-10 codes for concomitant injuries are not included. The list (table 1) was chosen after a consensus meeting between head orthopaedic surgeons of the largest hospital in our region. We also contacted experienced orthopaedic surgeons from other hospitals by mail in order to ensure that all possible codes were included. We included diagnosis M17 after these interchanges as several stated that they use M17 also for FCDs. Patients coded with M17 may have degenerative changes, although some have actual focal lesions. Therefore, we made an upper age limit of 67 years for inclusion and presented descriptive analyses with a distinction between those under and above 50 years of age.

Our data were anonymous and considered as statistical data rather than information on health from individual participants. We received the data set within an SPSS file and recognised all cases that underwent knee cartilage surgery during the 4 years 2008–2011. Cases *more* likely to constitute OA were excluded; therefore, patients aged 67 years or more, patients undergoing prosthesis surgery and patients with M17 in combination with non-cartilage procedures (only meniscal resection for instance) or high tibial osteotomy were excluded. Cases with M17 and procedures classified as cartilage surgery were included. The final number after exclusion was 10 830 in the 4-year period (figure 1).

Variables and data

The variables were ICD code, NCSP code, age, gender and length of the hospital stay. Additionally, we

Table 1 An overview of surgical procedures on the knee and calf, defined as cartilage surgery, from NCSP[26] and the predefined ICD-10-codes

NCSP code	Explanation	Corresponding surgical procedure and/or abbreviation	ICD-10-code	Disease/injury
NGA11	Endoscopic exploration		M17	OA of the knee
NGA12	Open exploration		M22.4	Chondromalacia patellae
NGF21	Endoscopic fixation of corpus liberum, either traumatic or OCD	fCL	M23.4	Loose body within the knee
NGF22	Open fixation of corpus liberum, either traumatic or OCD	fCL	M23.8	Other internal derangements of the knee
NGF31	Endoscopic resection of articular cartilage	CP/debridement	M23.9	Internal derangement of the knee, unspecified
NGF32	Open resection of articular cartilage	CP/debridement	M24	Other specific joint derangements
NGF91	Other endoscopic procedure on synovia or articular cartilage	MP and OAT	M93.2	OCD
NGF92	Other open procedure on synovia or articular cartilage	MP and OAT	M94.8	Other specific pathology in cartilage
NGH41	Endoscopic removal of corpus liberum	rCL	M94.9	Unspecific pathology in cartilage
NGH42	Open removal of corpus liberum	rCL	S83.3	Acute tear of articular cartilage of the knee
NGK29	Drilling of bone in the knee or calf	MF		
NGK59 +69	High tibial osteotomy	HTO		
NGN	Transplantation of cartilage, bone, muscle, etc	ACI		

The two explorative procedures (NGA11 and NGA 12) are included due to the group of patients with specific cartilage diagnosis, but without specific knee cartilage surgery.
ACI, autologous chondrocyte implantation; CP, chondroplasty; fCL, fixation of corpus liberum; ICD, International Classification of Diseases; MF, microfracture; MP, mosaicplasty; NCSP; NOMESKO Classification of Surgical Procedures; OA, Osteoarthritis; OAT, osteochondral allograft transplantation; OCD, osteochondritis dissecans; rCL, removal of corpus liberum.

requested data on the health region, county and institution and received geographical variables only for the years 2008–2009.

Statistics

We defined NCSP codes as cartilage surgery, meniscal surgery or other types of surgery. The different types of cartilage surgery were defined as palliative, repairing or restorative. All cases were divided into subgroups on the basis of these definitions. We chose the term palliative as these procedures are meant to decrease pain for the patients, although its efficacy is not proven for all indications. CP or debridement was defined as palliative surgery, cartilage repair included microfracture (MF) and cell-based repair with either autologous chondrocyte implantation (ACI) or stem cells and restorative techniques included techniques aiming at restoring the articular cartilage without cartilage repair tissue produced on-site as well as mosaicplasty (MP) and allograft transplantation (which is currently not in use in Norway).

The data were analysed with IBM SPSS Statistics (V.22.0). We assessed the distribution of the data with age as the dependent value and concluded with a non-normality distribution. The categorical variables on events of cartilage surgery were assumed to fulfil the criteria of a Poisson distribution. Cases were stratified by age, sex, health region, county and year of surgery. Incidences of cartilage surgery were given per 100 000 inhabitants and were adjusted to age group, region or county by calculation based on population data from Statistics Norway, which is an academically independent organisation administered under the Ministry of Finance in Norway. The data were assembled from their web pages. We compared the incidences for each of the 4 years to each other using rate ratios (RRs) and tested for significance using Wald tests. We used the Cochran-Armitage trend test for comparing trends in the current study with the existing literature.

Demographics were considered by descriptive statistics. Differences in categorical variables were calculated with ORs and tested with Pearson χ^2 tests with geographical localisation as the dependent variable. We explored age differences between subgroups with box plots and performed a Kruskal-Wallis test to test the statistical difference. A Bonferroni correction adjusted the new α level to 0.0125 with four independent analyses (CP vs MF, MF vs ACI, CP vs ACI, MF vs MP) before Mann-Whitney U tests were performed. We were not able to address potential confounders such as actual differences in the

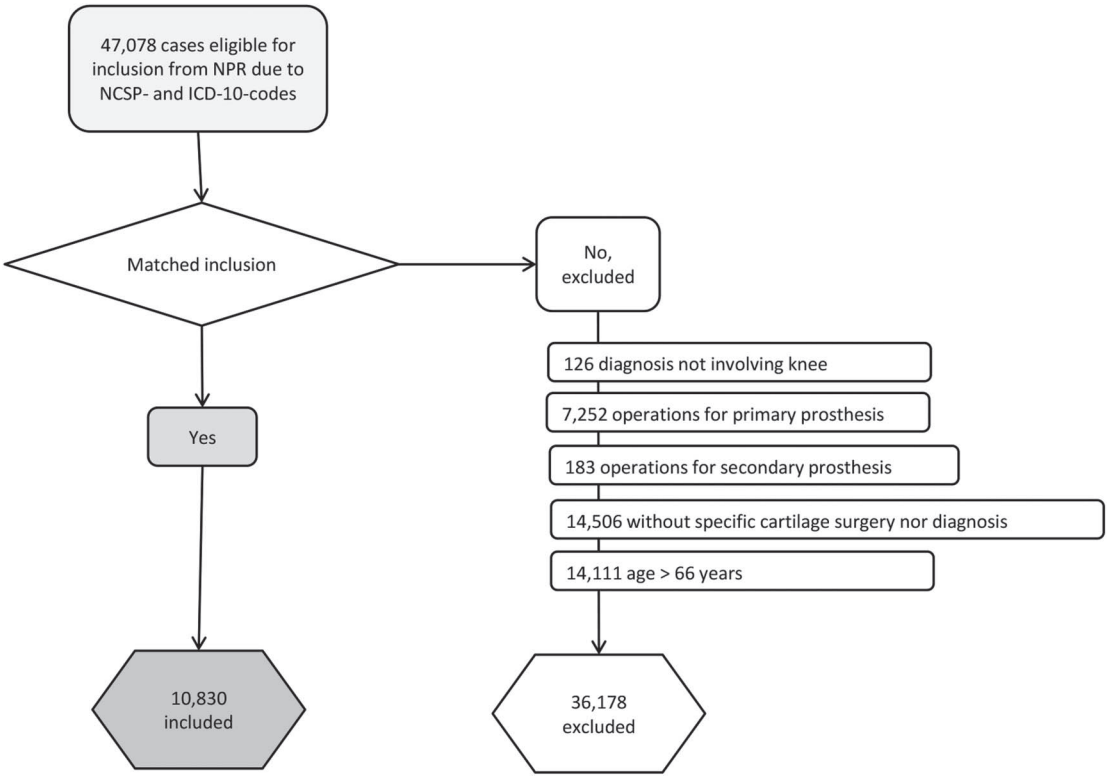

Figure 1 Flow chart of patients eligible for inclusion (ICD-10, International Classification of Diseases Tenth Revision; NCSP, NOMESKO Classification of Surgical Procedures; NPR, Norwegian Patient Registry).

prevalence of knee cartilage defects, or differences in the willingness to seek medical assistance for painful knees or the willingness to undergo surgery.

Ethics

We received anonymous data from the NPR, which acts under approvals of the Norwegian Directorate of Health. The study was evaluated by the Regional Committees for Medical and Health Research Ethics (REC) (ref: 2010/777) and approval is not necessary as the data are anonymous. We consulted the Norwegian Data Protection Authority and the study is not obliged for notification due to the collection of anonymous data. The data are to be considered as statistical data rather than information on health in individual participants.

RESULTS

A total of 10 830 cases matched our inclusion criteria for cartilage surgery for the years 2008–2011 and a flow chart is presented in figure 1. There were 2897 cases in 2008, 3114 in 2009, 2732 in 2010 and 2087 in 2011. A total of 21 143 procedures (see online supplementary appendix 1) were reported throughout the 4 years, which results in a mean of 1.96 procedures per included case. The most common cartilage surgery was resection of the articular cartilage (NGF3y) followed by fenestration or forage or bone/MF (NGK29). The most common non-cartilage surgery was meniscal surgery followed by synovectomy. The mean age for all years was 45.0 (SD 13.7), whereas the mean age for 2008 was 45.6 (SD 13.7) and for 2011 was 43.1 (SD 14.2), which was significantly lower than for the other years (p value <0.001). The male ratio varied from 55.2% to 58.7%.

Incidences

The incidence rate of having experienced cartilage surgery in Norway throughout 2008–2011 is 56/100 000 inhabitants and age-adjusted incidence rate is 68/100 000 inhabitants between 4 and 66 years of age. Table 2 displays the age-adjusted incidence rates for the different years and age groups. The incidence rate from 2008 was set as the reference when calculating RR between included years. The only significant RR was for 2011, which was 0.69 (95% CI 0.65 to 0.73, p value <0.0003).

The incidences of cartilage surgery in public hospitals in the four different health regions display great diversity as cartilage surgery is twice as common within the Northern region as opposed to the South East region (figure 2). However, when all the procedures performed privately are included, the regional differences change and the Western region becomes the region with the highest incidence (figure 3). The incidence in the Western region (161/100 000 inhabitants) is four times higher than that in the South East region, which has the lowest incidence (37/100 000 inhabitants). The incidences throughout the 19 different counties also display

Table 2 The distribution of number of cases about year and age group and the age-adjusted yearly incidence rates (with 95% CI in parenthesis) for all three age groups

Year	Total, 4–66 years			0–20 years			20–50 years			50–66 years		
	Cases	Inhabitants	Incidence	Cases	Inhabitants	Incidence	Cases	Inhabitants	Incidence	Cases	Inhabitants	Incidence
2008	2897	3 888 191	74.5	225	1 281 185	17.6	1347	1 881 409	71.6	1325	960 849	137.9
2009	3114	3 943 356	79.0	225	1 293 171	17.4	1532	1 905 524	80.4	1357	983 943	137.9
2010	2732	3 988 476	68.5	191	1 303 549	14.7	1319	1 926 981	68.5	1222	1 002 526	121.9
2011	2087	4 035 623	51.7	198	131 169	15.1	1109	1 954 251	56.8	780	1 017 321	76.7

When analysing the rates for each year within the age groups, we found a significant decrease from 2008 to 2011 for the two oldest age groups; no significant change was evident for the patients between 0 and 20 years.

large variations (figure 2). The incidences range from 7.3 to 278.1/100 000 inhabitants.

Trends

The trends for type of surgery varied between both regions and between private and public hospitals (table 3). Whereas private hospitals had nearly 90% debridement, this represented only approximately half of the procedures in public hospitals. Advanced cartilage surgery (repair or restorative techniques) accounted for almost 400 procedures per year. The middle health region had the lowest proportion of advanced cartilage surgery (13.4%) in 2009. In comparison, the northern region performed 42.6% of such procedures in 2009. The corresponding numbers for 2008 were 11.7% and 49.6%. The OR of having advanced cartilage surgery performed in the northern region compared to the other regions was 7.44 (6.11–9.06). Nationwide, the MP/OAT was the most frequent of the repair or restorative procedures for all years, ranging from 57.6% to 62.8%, whereas 4.2%–6.6% were cell transplantation techniques.

A substantial part of all included cases of cartilage surgery was performed in private institutions, whereas they performed 19.8% of the repair or restorative procedures (table 3). The OR of being treated with these methods over palliative procedures in private rather than public institutions was 0.18 (0.08–0.43). A Pearson χ^2 confirmed a highly significant association between the regions and between private and public hospitals. Most patients were treated in an outpatient setting and this accounted especially for private institutions. University hospitals performed 44.5% of cases with advanced cartilage surgery, whereas they performed 57.5% of all transplantation techniques, 56.8% of MP procedures and only 13.6% of MF procedures.

Age

The ages between the seven different subgroups were statistically significantly different ($p<0.001$); whereas the CP group (median 51.0) was significantly older than both the MF (median 39.0) and ACI groups (median 29.0), the MF group was older than the ACI group and not statistically significant different from the MP group (median 42.0). The age distribution of advanced cartilage surgery showed that the majority of procedures are performed on patients aged 20–50 years. Transplantation procedures were seldom performed in the oldest age group (50–67 years of age), whereas the youngest group (<20 years of age) was more commonly treated with MF followed by transplantation. ORs demonstrated that MP/OAT and ACI were more common for patients under 50 years of age, whereas MF and MP/OAT were more common for patients under the age of 20 years.

DISCUSSION

A total of 10 830 cases were included and represent the nationwide load of knee cartilage surgery in Norway

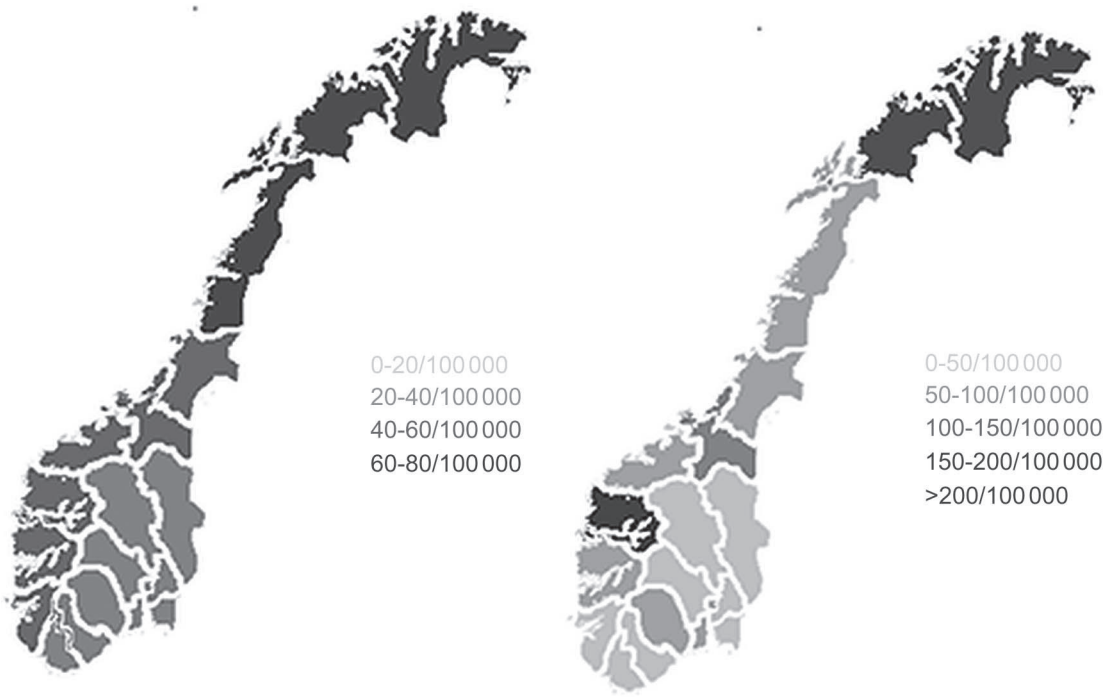

Figure 2 The incidence rates in the four different health regions in Norway (top) and the incidence rates throughout Norway`s 19 counties (bottom) in 2009. Numbers are based on the localisation of the hospital and not the patient's home address. Activity from private hospitals is excluded for these figures as they mostly perform palliative surgeries in middle-aged patients and thereby account more for degenerative surgery than cartilage surgery. The incidence rates are age-adjusted to the population included in this study, which ranged from 4 to 66 years of age. All surgeries performed in private institutions are excluded from this material, which included 1475 surgeries in 2009. (The map of Norway was downloaded from Wikipedia Commons and edited).

throughout 2008–2011. There are 2500 cartilage surgeries yearly and 400 of these are advanced cartilage surgery. The total incidence of all cartilage surgery over these four years is 56/100 000. These numbers are within the range of incidences for knee ligament surgery in Norway, which is considered a common surgery. Granan *et al*[27] found an incidence of ACL surgery of 34/100 000 inhabitants, although there were 85/100 000 in the age group 16–39 years of age in Norway in their baseline study of the Scandinavian Knee Ligament Registries.

Although common, the yearly incidence varies greatly among age groups, health regions, counties and between public and private hospitals. Cartilage surgery is not in use mainly around the largest cities or regional hospitals and University clinics, in contrast to our

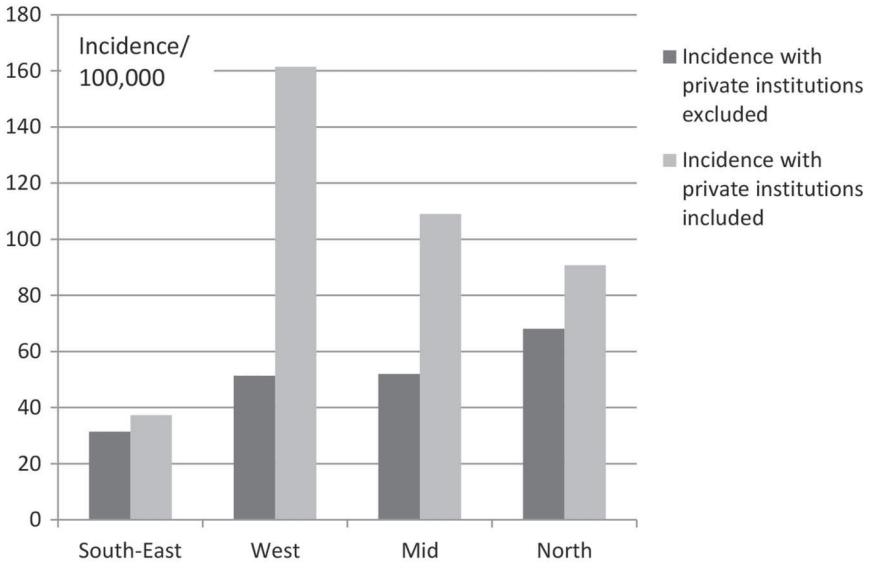

Figure 3 The differences in incidences when excluding and including numbers from private institutions for the year 2009.

Table 3 The distribution for all the public cases, among the different subgroups within the regions and for the private institutions from 2008 to 2009

	CP	MF	MP/OAT	rCL/fCL	ACI	HTO	Other/no	Total
Public	1763 (50.9)	184 (5.3)	387 (11.1)	525 (15.2)	71 (2.0)	329 (9.5)	205 (5.9)	3464
South East	222 (57.7)	45 (11.7)	14 (3.6)	22 (5.7)	2 (0.5)	65 (16.9)	15 (3.9)	385
West	484 (54.6)	93 (10.5)	30 (3.4)	112 (12.6)	4 (0.5)	99 (11.2)	64 (7.2)	886
Mid	373 (59.6)	23 (3.7)	40 (6.4)	104 (16.6)	15 (2.4)	33 (5.3)	38 (6.1)	626
North	186 (37.6)	19 (3.8)	183 (37.0)	44 (8.9)	25 (5.1)	16 (3.2)	21 (4.3)	496
Private	2338 (89.3)	70 (2.7)	87 (3.3)	82 (3.1)	1 (0.0)	0 (0)	40 (1.5)	2618

ACI, autologous chondrocyte implantation; CP, chondroplasty; fCL, fixation of corpus liberum; HTO, high tibial osteotomy; MF, microfracture; MP, mosaicplasty; OAT, osteochondral allograft transplantation; rCL, removal of corpus liberum.

hypothesis. Private institutions accounted for 43% of all cases, whereas only 40% of the public cases were performed in the South East region. These findings imply that if a cartilage registry is developed, an important consideration is whether to include hospitals from several health regions in addition to private hospitals. Furthermore, the data demonstrate a significant reduced frequency of advanced cartilage surgery for patients treated at private institutions ($p<0.001$). It is not possible to outline whether this is a case of reduced accessibility, but it is likely that procedures leading to more overnight stays are less available at these institutions.

Similar differences between public and private hospitals are seen in other Scandinavian countries for menisical surgery,[28] and these differences might also be due to financial incentives. Codes for palliative procedures were mainly in use for middle-aged patients in combination with M17. It has been previously demonstrated in studies that debridement is no better than sham surgery[20] or rehabilitative training with a Physiotherapist,[21] whereas the latter also failed to show the efficacy of surgery in patients with mechanical symptoms. These studies changed the trends in surgery on patients with OA as the rates of arthroscopy declined in the following years, at least in the USA.[29] It is possible that a larger part of these procedures is now performed on patients with actual FCDs, although these procedures are also still used in patients with knee OA. On the basis of the recent literature, this type of surgery should be abandoned.

Few studies have explored incidences of cartilage surgery, whereas one study presents national numbers on cartilage injuries diagnosed with arthroscopy.[24] Two studies presented remarkably different numbers based on data from the PearlDiver database in the USA. Montgomery *et al*[23] report an incidence rate of 1.27–1.57/10 000 (2004–2009) patients and McCormick *et al*[22] report an incidence rate of 90/10 000 (2004–2011). McCormick seems to calculate incidences on the basis of all individual patients within the database, whereas Montgomery calculates incidences on the basis of all patient records, which may explain the different results. Our incidence rates are within the same range as those reported by Montgomery *et al* when compared to the number presented in the articles. However, when we recalculated new incidence rates on the basis of the numbers provided by the two articles and applied the same approach as used in this study, we found quite different incidence rates from both articles. Consequently, the incidence rates from this study then appear in the vicinity of McCormick *et al* (table 4). Both studies focused on cartilage surgery only, and excluded patients with simply the diagnosis of an FCD or patients undergoing osteotomy in the absence of knee OA. These two subgroups accounted for <10% in this study and were excluded when comparing incidence rates for the years 2008–2011 (table 4). The same table displays the numbers from the Danish study, which are in close range with the numbers from this study.

Trends

We found that 56 hospitals performed cartilage surgery, whereas 15 hospitals operated <10 cases throughout 2009. Katz *et al*[30] found that patients operated in low-volume hospitals by low-volume surgeons had worse functional outcomes 2 years after total knee replacement. When performing procedures that have failed to prove efficacy, the volume of the operating surgeons means less. However, this is a field with many patients and presumably low evidence-based adherence. Cartilage surgery is a complex treatment where several options exists, indicating that the availability of several techniques as well as an optimised rehabilitation programme is needed. In order to form a standardised treatment for as many patients as possible, each hospital or surgeon probably needs to see a certain, but not yet defined, number of patients yearly to maintain adequate quality of care. A discussion on whether to make specific cartilage centres must be made.

This study cannot explain the reasons for the geographical differences, but possible factors might be differences between the orthopaedic surgeons' personal preferences and experience more than differences in the patient populations. A study aiming to describe the practice of MF among Canadian orthopaedic surgeons found widespread variation concerning indication for surgery.[31] A patient's willingness to undergo surgery is also an important consideration and is higher in areas with an already high incidence of surgery.[32]

Table 4 The incidence rates from two American studies on trends and incidences from a private database for health insurance, together with the national incidences from the Danish and the current studies

Year	Montgomery *et al* (reported)	McCormick *et al* (reported)	Mor *et al*, (numbers are reported for all years together)	Present study*
2008	154.1 (1.54)	9.1 (91)	4.0	6.8
2009	152.7 (1.53)	9.3 (92)		7.2
2010	–	10.4 (104)		6.2
2011	–	9.3 (93)		4.6

Incidence rates are given per 10 000 patients/inhabitants and are calculated from the numbers of procedures and patients that are given by the two articles. The reported numbers are presented in parentheses.
*These numbers are calculated after exclusion of the patient group without cartilage surgery and the patient group where osteotomy was performed alone or in addition to cartilage surgery and thereby represent the same patient population as in the two published studies.

Knee cartilage surgery consists of several different techniques and although attempts on recommendations have been made, there is no gold standard treatment.[9–16 33] MF is traditionally chosen for smaller defects, whereas OAT and ACI are chosen for larger defects.[34] More specific recommendations do not exist, and we know little of the decision-making for surgical technique other than the size of the lesion and the patient's age. We do not have data on the size or location of the lesions in this study. CP is the most common procedure in our material and is performed for both FCDs and in knees with developing degenerative changes. The study by Montgomery *et al*[23] found that MF and CP are the preferred procedures in 98% of cases with cartilage surgery. These procedures constituted 71.1% of all procedures in our material. The study by Mor *et al*[24] found repair procedures (MF, osteochondral transplantation or chondrocyte transplantation) to be performed in 16.7% of the cases. The trends from the articles of Montgomery *et al*[23] were significantly different from the trends of our material when compared with a χ^2 test (p value<0.001). The difference was still significant after excluding the groups which had no cartilage surgery or osteotomies. Also, the trends in procedures from the study by Mor *et al* were different from the trends of this study with a lower proportion of palliative procedures, also after excluding the cases with no cartilage surgery or osteotomies.

Limitations

The ICD-10 codes available for diagnosing FCDs do not reflect the complexity of the clinical situation of these lesions. The distinction between focal lesions that are traumatic or degenerative is often difficult clinically, and location, size and depth matter greatly. The ICD-10 does not account for these conditions, and a distinction based on these codes is impossible. Although the ICD-10 contains both 'acute FCD' (S83.3) and several codes for knee cartilage pathology, there are no codes for the common 'non-acute FCD', which might be subacute or chronic. Our predefined codes matched with 92.3% of the reported diagnostic codes from the Norwegian Arthroscopic Association. However, the response rate was only 13.2%. The low response rate has limited effect on our final numbers since we have included most of the possible codes from the ICD system, but these challenges coexist with the fact that some orthopaedic surgeons might not code for FCDs at all if other intra-articular pathology is recognised. This is probably the largest limitation and cannot be defeated by any methodological changes, but by the information and education of orthopaedic surgeons. This is therefore a challenge concerning cartilage pathology and the ICD system and is as such a problem for the entire research field and not only for this study.

Among 11 566 ICD-10 codes, there are 789 coded as S83.3. The frequency of M17 codes increases with age; however, several orthopaedic surgeons have stated that they use M17 also for focal lesions. The inclusion of patients with an M17 diagnosis might lead to an overestimation of surgery for cartilage injury. However, an exclusion of these would definitely lead to an underestimation. This study reports a lower portion of palliative procedures than the Danish study[24] (where they excluded all patients with OA), which might imply that most of those included in this study are actual knee cartilage defects and not OA.[24] We did not include the ICD-10 code for 'painful joint' (M25.5) which might have underestimated the results.

The patient records or surgical protocols are considered the gold standard. However, large administrative databases allow the process of data collection to be efficient, detailed and precise, within its limitations. The Norwegian healthcare system is public and tax funded, which balances out possible geographic or socioeconomic differences. Studies have demonstrated that numbers extracted from electronic databases are being both overestimated and underestimated. Lofthus *et al*[35] found that the Norwegian NPR overestimated hospitalisation for hip fractures by 29%, although the number of those having surgery for hip fractures was underestimated. Readmissions due to the same hip fracture were registered as a new hospitalisation for a new hip fracture by the NPR, which inflated the number. In our material, 297 cases (4.9%) were duplicates and only 73 procedures (0.67%) were classified as reoperations. We believe that *procedure* codes are reported in more detail as they are the basis of 60% of the government

reimbursement in Norway and, as such, are reviewed several times by hospital controllers to ensure correct coding. For this study, we were interested in the burden of cartilage surgery and a combination of diagnostic and procedure codes seemed most appropriate.

The validity for the Norwegian NPR database was later assessed in a national study on hip fractures and the accuracy was found to be 98.2% (CI 96.5% to 99.9%) when diagnostic codes were combined with procedure codes.[36] In that same study, the authors suggested possible coding errors from fractures that were treated conservatively or from patients that were admitted to hospital with such a fracture, but died before the operation. This does not apply to this study, as the diagnosis is set during the operation. The study by Mor *et al*[24] assessed the validity against surgical descriptions in the medical records as the gold standard and found the positive and negative predictive values to be 88% and 99%, respectively. As for all studies with inclusion based on surgical procedures, FCDs diagnosed with MRI and treated conservatively are not included. An underestimation or overestimation might exist; however, the main goal of this study was to estimate the nationwide burden of cartilage surgery with the numbers available in NPR.

Future clinical implications

Cartilage surgery concerns a large and severely troubled patient group with no gold standard treatment. No nationwide surveillance currently exists to study the efficacy or effectiveness of treatment for this patient group. Development of a cartilage registry emphasising cartilage treatment being palliative, reparative or regenerative, in addition to non-surgical procedures, will be essential for clinical progression in this field.

Our numbers indicate that CP or debridement is still performed in degenerative knees.

CONCLUSION

In Norway, there are 2500 annual procedures classified as cartilage surgery, resulting in an age-adjusted incidence rate of 68.8/100.000 inhabitants. There are large variations between the different regions and between public and private hospitals.

This illustrates the need for a larger surveillance database for evaluation of results and calculation of costs in order to secure high quality treatment for all knee cartilage patients.

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Acknowledgements The authors would like to thank Ingar Holme, PhD for his advice concerning relevant statistics.

Contributors LE and AÅ conceived the study, whereas all the authors planned the method. CNE was responsible for data collection and analyses, whereas all the authors participated in the interpretation. CNE drafted the manuscript, whereas AÅ and LE revised it. All the authors approved the final version.

Funding The study was supported through grants from the Oslo Sports Trauma Research Centre (OSTRC), where the corresponding author is employed. The South-Eastern Norway Regional Health Authority, the Royal Norwegian Ministry of Education and Research, the Norwegian Olympic Committee & the Confederation of Sport and Norsk Tipping finance the centre. The Faculty of Medicine, University of Oslo (UiO) also supported the work as CNE previously was a student at the Medical Student Research Programme at UiO and thereby received financial support from the Research Council of Norway.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Incidence of knee cartilage surgery in Norway, 2008–2011

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BMJ Open 2015 5:
doi: 10.1136/bmjopen-2015-008423

II

Knee Cartilage Defect Patients Enrolled in Randomized Controlled Trials Are Not Representative of Patients in Orthopedic Practice

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Cartilage published online 30 July 2010
DOI: 10.1177/1947603510373917

Cartilage OnlineFirst, published on July 30, 2010 as doi:10.1177/1947603510373917

Original Article

Cartilage
XX(X) 1–8

DOI: 10.1177/1947603510373917
http://cart.sagepub.com
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Knee Cartilage Defect Patients Enrolled in Randomized Controlled Trials Are Not Representative of Patients in Orthopedic Practice

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Abstract

Objective: Knee cartilage defects represent a socioeconomic burden and may cause lifelong disability. Studies have shown that cartilage defects are detected in approximately 60% of knee arthroscopies. In clinical trials, the majority of these patients are excluded. This study investigates whether patients included in randomized controlled trials (RCTs) represent a selected group compared to general cartilage patients. *Design:* Published randomized clinical trials on cartilage repair studies were identified (May 2009) and analyzed to define common inclusion criteria that in turn were applied to all patients submitted to our cartilage repair center during 2008. Patient-administered Lysholm knee score was used to evaluate functional level at referral. In addition, previous surgery and size and localization of cartilage defects were recorded. *Results:* Common inclusion criteria in the referred patients and patients included in the published RCTs were single femoral condyle lesion, age range 18 to 40 years, and size of lesion range 3.2 to 4.0 cm^2. Six of 137 referred patients matched all the 7 RCTs. Previous cartilage repair and multiple lesions were associated with decreased Lysholm score ($P < 0.002$). Lysholm score was independent of age, gender, and time of symptoms from the defect. *Conclusion:* The heterogeneity of the referred cartilage patients and the variation in inclusion criteria in the RCTs may question whether RCTs actually represent the general cartilage patients. The present study suggests that results from published RCTs may not be representative of the gross cartilage population.

Keywords

cartilage defect, Lysholm, RCT, cartilage repair

Introduction

Patients with articular cartilage injuries experience decreased mobility and pain, although their symptoms differ based on affected joint. These injuries affect a large number of patients. Studies have shown cartilage injuries in 66% of the patients undergoing an arthroscopy for knee pain.[1,2] In evidence-based medicine, randomized controlled trials (RCTs) are perceived as the gold standard for evaluating treatment options. Still, only 3% to 6% of published articles in orthopedics are RCTs.[3] Several studies with the aim to measure the outcome of cartilage repair have been performed during the past decade. Numerous articles have described good or excellent results, but the methodological quality has been questioned, as evident in an analysis of cartilage repair studies from 2005.[4]

An issue that has been less discussed in the orthopedic literature is the heterogeneity in etiology and the anatomical locations of cartilage lesions. Patients with lesions in only one anatomical location resulting from one specific injury may not represent general cartilage patients. The size of the defects and the age of the patients may also result in exclusion of patients in controlled studies. These limitations, which are necessary to achieve a high internal validity due to the study design of RCTs, may naturally interfere with the external validity and clinical applicability of them.

The present study was designed to evaluate the difference between patients included in published RCTs and the total number of patients referred to a major cartilage clinic. The study's main questions were the following: how well can the RCT inclusion criteria be applied to our general cartilage group, and are results from RCTs applicable when advising

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a general cartilage injured population? This offers an additional and important clinical perspective on the ability of extrapolation of RCT results on cartilage repair surgery.

Methods and Materials

Inclusion Criteria in Published RCTs

To find inclusion criteria for patients enrolled in RCTs on standard cartilage surgery, we searched PubMed and Embase, using words such as *cartilage*, *surgery*, *repair*, *outcome*, and *randomized*. Procedures included were microfracture (MF), mosaicplasty (MP), autologus chondrocyte implantation (ACI), characterized chondrocyte implantation (CCI), and periosteal grafting (APT). Outcome measures were the Lysholm score, Knee Injury and Osteoarthritis Outcome Score (KOOS), and Cincinnati scores. The search was performed May and September 2009; only studies published in the English language were included.

All of the RCTs were evaluated according to the PRISMA statement,[5] but not all of the criteria were applicable for the current study.

Patient Material

All patients referred to our clinic with knee symptoms suspected to be caused by focal cartilage defects were eligible for enrollment. The patients were enrolled from either a primary health service or secondary health service (orthopedic departments in other hospitals).

Patients were evaluated by an experienced cartilage orthopedic surgeon and with a patient-administered Lysholm knee score form. In the few cases of incomplete information, the primary author contacted the patients by telephone or letter and asked them to complete the form.

Our cartilage clinic has standardized the use of the Lysholm score in assessing cartilage knee problems in this patient group during their clinic visits. The Lysholm score was selected because it has been commonly used to assess knee problems, it is validated,[6] it can be filled out by the patients themselves,[7] and it quickly provides a good overview of knee symptoms presented in the outpatient clinic. Additional recent work from our clinic has demonstrated that the Lysholm score, International Knee Documentation Committee (IKDC), and KOOS maintain a close correlation in evaluating knees with cartilage defects.[8]

All patients referred to the orthopedic clinic with symptoms from their knees suspected to be caused by focal cartilage defects were examined with magnetic resonance imaging (MRI) and/or knee arthroscopy. In most cases, both arthroscopy and MRI were performed.

Demographic data, such as anatomical location and size of patients' lesions, are reported. Arthroscopy was the gold standard in reporting size of the lesions, but in the cases where arthroscopy had not been performed, we used MRI scans. These were evaluated by an experienced radiologist not participating in this study.

Statistics

Dichotomous data are presented as numbers and percentages and continuous data as means with standard deviations (SD). The study's main questions were the following: how well can the RCT inclusion criteria be applied to our general cartilage group, and are results from RCTs applicable when advising a general cartilage injured population? This was evaluated by simply matching the referred patients with the common inclusion criteria and for the inclusion criteria from each of the 8 RCTs.

To evaluate whether patients who had undergone previous cartilage surgery differed from those without previous surgery, we performed a *t* test to see if there was a statistically significant difference between these two groups.

The relationship between the Lysholm score and the total number of overall knee surgeries was also calculated. In total, comparisons between 4 parameters (no surgery, 1 surgery, 2 surgeries, and 3 or more surgeries) were performed, and Bonferroni correction with a P value of 0.01 was applied.

A multiple regression analysis was performed to evaluate the correlation between the Lysholm score and factors such as age, gender, time of symptoms, and size of lesions. The correlation between Lysholm score and localization of defects was explored with a one-way analysis of variance (ANOVA) because localization of defects cannot be analyzed with a multiple regression analysis due to its nonscale nature.

Ethics

The study was approved by the regional ethical committee.

Results

Inclusion of RCTs

We found 10 RCTs based on 8 different patient materials.[9-18] The inclusion criteria in these articles are summarized in **Table 1**. Number of patients and treatment allocation in the RCTs are presented in **Table 2**.

Patient Characteristics

During 2008, our clinic received 147 referred patients, whereas 10 were excluded from this study; this number of referral of patients is in line with our previously reported numbers regarding the incidence of these lesions in our patient population.[1] This present study included more patients

Table 1. Assessment of the Inclusion Criteria of the 8 Articles and Common Inclusion Criteria

	Number	Size, cm^2	Age	Localization	% Eligibility
Knutsen *et al.*[9,10]	Single lesion	2-10	18-45	Femoral condyle	31
Saris *et al.*[14]	Single lesion	1-5	18-50	Femoral condyle	37
Gudas *et al.*[12,13]	Single lesion	1-4	<40	Weight-bearing femoral condyle	30
Bentley *et al.*[11]	Symptomatic lesion	1-12	16-49	Whole knee joint	74
Bartlett *et al.*[17]	Lesion	>1	15-50	Whole knee joint	77
Gooding *et al.*[16]	Symptomatic lesion	1-12	15-52	Whole knee joint	80
Dozin *et al.*[15]	Focal defect	>1	16-40	Weight-bearing condyle	45
Horas *et al.*[18]	Single lesion	(3.2-5.6 as descriptive)	18-45	Weight-bearing femoral condyle	7
Common	Single, symptomatic lesion	3.2-4	18-40	Weight-bearing femoral condyle	4

Eligibility is due to the matching patients from our included patients.

Table 2. The 8 Included RCTs, the 2 Compared Cartilage Repair Procedures for Each Study, and Number of Included Patients

RCT	Procedure 1	Procedure 2	Number of Included Patients
Knutsen *et al.*[9,10]	ACI	MF	80
Saris *et al.*[14]	CCI	MF	118
Gudas *et al.*[12,13]	MOAT	MF	60
Bentley *et al.*[11]	ACI	MP	100
Bartlett *et al.*[17]	ACI	Matrix-induced ACI	91
Gooding *et al.*[16]	ACI (periosteum)	ACI (collagen type I/III)	68
Dozin *et al.*[15]	ACI	MP	47
Horas *et al.*[18]	ACI	OCT	40

RCT, randomized controlled trial; ACI, autologus chondrocyte implantation; MF, microfracture; CCI, characterized chondrocyte implantation; MOAT, mosaic osteochondral autologus transplantation; MP, mosaicplasty; OCT, osteochondral cylinder transplantation.

than each of the 8 RCTs,[9-18] whereas Saris *et al.*[14] included the most, $n = 118$, and Horas *et al.*[18] included 40 patients. We therefore believe that we have included enough cartilage patients to answer our study hypothesis.

We also performed a power analysis on behalf of the statistical analysis. We wanted to simply match the characteristics of included patients with the same characteristics from the 8 RCTs. This resulted in a minimum of 101 included patients in this study. **Figure 1** illustrates the inclusion of the patients in this present study.

In total, 46 women and 91 men were included, with their ages ranging from 13 to 58 (median 37). Nine patients had bilateral lesions, 34 had been experiencing symptoms for less than 10 months, and 75 had not been through either cartilage repair or anterior cruciate ligament (ACL) reconstruction previously, whereas 13 had not been through any intervention at the time of inclusion. In this material, 65 patients had symptoms that could be related to one specific incident, and the defects were thereby classified as acute.

We performed an independent-samples *t* test on those who matched the common inclusion criteria (after excluding the article of Horas *et al.*[18]) and those that did not match. This yielded a nonsignificant *P* value (0.9).

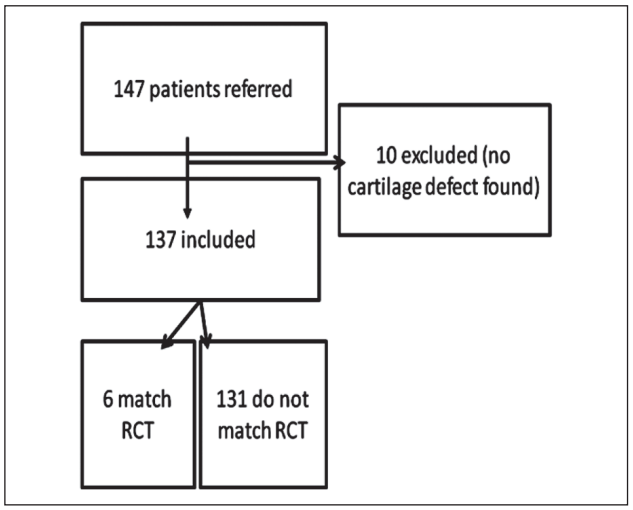

Figure 1. Flowchart of the inclusion of the patients in the study. RCT, randomized controlled trial.

The total number of patients not receiving any surgical treatment at the end of this study was 7. We obtained information on cartilage lesion size, International Cartilage

Table 3. Group Statistics: *t* Test Comparing Mean Lysholm Score between Previous Cartilage Surgery and No Previous Cartilage Surgery

	Additional Surgery	*n*	Mean	Standard Deviation	Standard Error Mean
Lysholm	No	74	60.86	17.010	1.977
	Yes	48	53.38	13.570	1.959

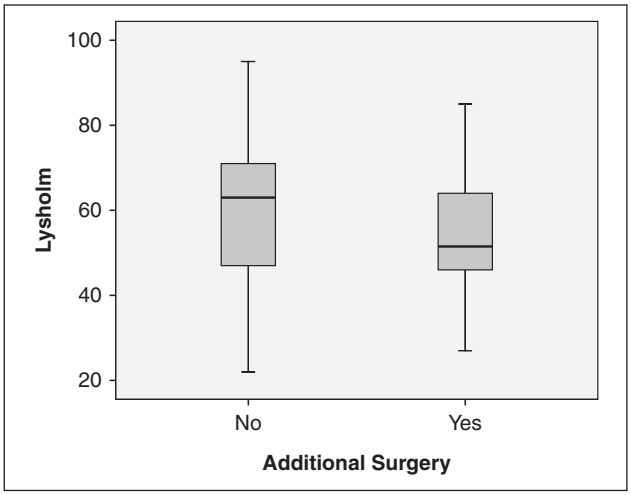

Figure 2. Confidence intervals on Lysholm score with respect to previous surgery.

Table 4. Group Statistics: *t* Test Comparing Mean Lysholm Score between Patients with 1 Lesion and Patients with Several Lesions

	Number	*n*	Mean	Standard Deviation	Standard Error Mean
Lysholm	≥2	25	49.44	12.842	2.568
	<2	93	60.60	16.300	1.690

Repair Society (ICRS) grade, and localization from MRI on these.

Analyses of the mean values of the Lysholm score based on the medical history of previous cartilage surgery patients did reveal a statistical difference. The difference between patients with previous cartilage surgery and patients with no previous cartilage surgery was evident, with $P < 0.008$ (**Table 3**). **Figure 2** illustrates confidence intervals on the Lysholm score with regard to previous cartilage surgery. As evident in **Table 4**, more than 1 lesion was significantly associated with a lower Lysholm score. A *t* test comparing the Lysholm score between those with 1 lesion and those with 2 or more yielded $P < 0.002$.

A comparison of Lysholm scores demonstrated that there was no correlation with age, gender, or time of symptoms in our patient data, which were analyzed using a multiple regression analysis. Regarding the localization of the defect, the *P* value was 0.001; however, as this is not a continuous variable, we performed further analysis with one-way ANOVA, with Lysholm as the dependent variable and anatomical localization as the independent variable. There was no significant correlation.

Demographic data in our referred patients (**Table 5**) showed that the medial femoral condyle was the most common location with large mean size (3.12 cm^2) of the cartilage defect and low mean Lysholm score (60). Cartilage defects located on the patellae were few and associated with a low mean Lysholm score (40). However, as illustrated in **Table 6**, there was no clear relation between the size of the lesion and the registered Lysholm score. Coinjuries were common, with meniscus injury as the most common one, as illustrated in **Table 7**.

Applicability of RCTs

We included 8 randomized studies that each use specific criteria when including participants. We assessed the inclusion criteria from these articles, as shown in **Table 1**. Only 6 of the 137 patients matched all the inclusion criteria in the RCTs on cartilage surgery. When analyzing the remaining patients, we found that 2 did not fit the RCT inclusion criteria due to age, 3 due to anatomical localization of lesions, 2 due to the occurrence of several lesions, and 55 due to the size of their lesions. In addition, 42 patients were excluded due to 2 nonmatching factors, 21 due to 3 nonmatching factors, and 4 due to nonmatch in all 4 factors. Two patients had missing data. **Figure 3** provides more detailed information on why the patients did not the match the RCT inclusion criteria.

We also matched the patients with the common inclusion criteria after excluding the article by Horas *et al*.,[18] and we then found that 27 patients (20.3%) would have been eligible for inclusion in all of the remaining RCTs.

When we matched our patients with each of the studies, 42 could have been included in Knutsen *et al*.,[9,10] 51 in Saris *et al*.,[14] 41 in Gudas *et al*.,[12,13] 101 in Bentley *et al*.,[11] 9 in Horas *et al*.,[18] 61 in Dozin *et al*.,[15] 106 in Bartlett *et al*.,[17] and 109 in Gooding *et al*.[16]

Discussion

This study suggests that the potential of extrapolating results from RCTs to the general cartilage patient population is limited. Commonly, our scientific evidence used for clinical decisions concerning cartilage repair is based on the 8 RCTs referenced in the current study. However, as evidenced by the current study, there is considerable variation in the number of patients to whom it can be applied.

Table 5. Lysholm Score Due to Different Size of the Lesions

Anatomical Location	Size, Mean ± SD (*n*), cm^2	Range, cm^2	Lysholm Score, Mean ± SD (*n*)	Range
Patella	6.2 ± 3.5 (5)	3.2-10.0	40.4 ± 9.5 (5)	27-49
Tibiae plateau	1.5 ± 1.0 (5)	0.5-3.0	66.2 ± 12.6 (6)	51-85
Both femoral condyles	4.5 ± 3.0 (6)	1.6-10.0	52.8 ± 11.3 (5)	39-65
Trochlea	2.1 ± 1.5 (19)	0.1-6.8	58.6 ± 11.4 (16)	36-73
Medial femoral condyle	3.1 ± 3.1 (65)	0.2-16.0	59.6 ± 17.8 (62)	27-95
Lateral femoral condyle	2.4 ± 2.1 (20)	0.5-10.0	60.2 ± 14.0 (19)	41-85
Kissing lesion	3.2 ± 3.5 (9)	0.3-10.0	48.5 ± 15.1 (8)	22-65

Table 6. Lysholm Score and Size of Lesions Due to Anatomical Localization

Cartilage Lesion	Lysholm	Range	Standard Deviation
0-1 cm^2 ($n = 27$)	62.3	30-95	17.3
1-2 cm^2 ($n = 33$)	56.0	22-88	17.1
2-3 cm^2 ($n = 20$)	57.7	27-85	13.2
3-4 cm^2 ($n = 16$)	55.8	27-87	14.1
4-5 cm^2 ($n = 4$)	45.5	30-60	13.5
>5 cm^2 ($n = 15$)	61.1	34-94	19.0

Table 7. Additional Injuries in Included Patients

Coinjury	Number
Meniscus	34
Anterior cruciate ligament	22
Patella luxation	3
Other	25
None	49

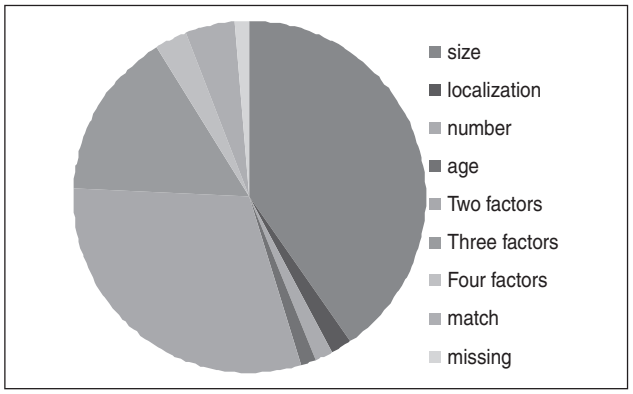

Figure 3. Reasons for ineligibility due to size, localization, age, and number of lesions. Fifty-five patients did not match only due to size of lesion. The figure also accounts the 6 matching patients.

RCTs

The eligibility rate of patients from our center to the various RCTs ranged from 7% to over 80%. The reason for a relatively high patient eligibility rate in 3 of the articles[11,16,17] seems to be the fact that a wide range of defect sizes and all anatomical locations in the knee were accepted. On the other hand, Horas *et al*.[18] had very strict inclusion criteria concerning size of lesion, and this accounts for the main disparity between the referred patients in this study and our referred patients.

As mentioned, the greatest variable resulting in bias is the inclusion criterion regarding size. Other variables in our data set that have led to exclusion are age, localization, and number of lesions. Although there is lack of knowledge concerning the importance of each parameter for the prognosis, there is evidence that anatomical localizations do affect the result, with lateral femoral condyle as the most favorable one and patellae as the most challenging one.[19] Lesions on the femoral condyles also show more improvement when treated with ACI than lesions on the patellae and trochlea.[20]

Patient Characteristics

One of the main findings of this study is that only 4.4% of patients referred to our cartilage clinic in 2008 would have been eligible for inclusion in all of the available RCTs on cartilage surgery. The study's hypothesis, that patients included in RCTs on cartilage repair represent a selected group, has been verified. Even though only 6 patients satisfied all the inclusion criteria of the RCTs, a larger number of them would have been eligible for one or more of the RCTs. The large variation in eligibility is of major concern for the current literature in the field.

The results from this current study did not demonstrate a statistical difference in Lysholm score, reflecting knee symptoms, between those eligible for inclusion and those not eligible for inclusion. This suggests that the patients included in RCTs are not more disabled than the remaining knee cartilage defect patients.

Cartilage defects on the patellae, although few, were associated with a lower Lysholm score than the defects on the medial femoral condyle.

Applicability

The large variation in eligibility illustrates the variability between the RCT results and the population of cartilage defect patients. Exclusion of the article from Horas *et al*.[18] and a new eligibility test expanded the range of sizes and thereby the number of patients eligible, but still only 20.3% of our patients' material matched the inclusion criteria of the remaining 7 RCTs.[9,11,13-17] To our knowledge, the number of referred patients who should match the inclusion criteria presented by an RCT before the results in the RCT are applicable to the general patient seen in the clinic has not been addressed in the orthopedic literature. Authors from other fields of medicine have focused on this discrepancy. In a study regarding patient enrollment in large RCTs of secondary prevention after transient ischemic attack (TIA) or stroke, it was found that the patients seen in private practice were not representative of the patients in the published RCTs, as 33% to 75% were not eligible for participation.[21] They concluded therefore that the inclusion criteria, which resulted in only partial applicability, were too strict. In a review by the US National Institute of Health of 41 US institutions on the same matter, an average exclusion rate of 73% was reported.[22] The conclusion in these studies was that this was not acceptable, yet in our current study, the exclusion rate is within the same range or even higher.

Clinical Value

In this study of the unselected enrollment of patients with symptomatic focal cartilage lesions in the knee, we found that 95.6% were ineligible for participation if all the published RCT inclusion criteria were to be used. When looking at one article after another, we found an enrollment percentage ranging from 6.6% to 79.6%, which in the best case excludes 1 out of 5 patients. This large variance also shows little consistency regarding inclusion criteria between different studies. In terms of advising our patients, the study of Gooding *et al*.[16] is the one with the highest applicability.

One way to elucidate the problem of inconsistency between RCTs and patients seen in the clinic would be for the journals to demand that all RCTs present a flowchart so that the exclusion rate of the full patient selection process is visible.[23] The main goal of an RCT is to compare two treatment options or modalities and not necessarily generalize to the entire population of patients with a certain diagnosis. Nevertheless, for the RCTs to be clinically helpful, there is a need to analyze if there is discrepancy between the group of patients seen in the clinic and the inclusion criteria of the RCTs you are leaning on when advising patients. RCTs are stated to be the gold standard of study designs due to low chance of bias when randomization, concealment of treatment allocation, and blinding have been performed. Even though the study design does not lead to bias, because the tests themselves are not biased, the reports still might present bias to the readers. Narrow inclusion criteria are necessary to minimize interindividual differences with regard to the study analysis. Thereby, there might exist a bias toward the population of patients seen in the clinic because this often is a much more heterogeneous group.

In our study, we have found that there is a bias between the population presented in the studies and the population of cartilage patients in the clinic. This is mainly due to the strict and varying inclusion criteria in the referenced RCTs.

There are both advantages and disadvantages related to RCTs in the orthopedic field. In their article, McLeod *et al*.[24] describe the problem with generalizing data and applying RCT results to all patients with the current disease because of strict inclusion criteria and inherent differences in patients who volunteer for trials. Randomized controlled trials may help clarify whether there are differences among the various treatment modalities, but there are definitely challenges in applying the results to "common" patients because an RCT never will include exactly "common" patients.

We have searched for good, randomized controlled studies in order to define the injuries of the group of patients who account for the population of cartilage patients presented in the "best" studies. Our study aimed to question whether current methods may be extrapolated to everyone with cartilage injuries.

Our study reveals a substantial possibility of bias between the population presented in RCTs on cartilage surgery and those referred to a major orthopedic center. This study illustrates that the inclusion criteria in RCTs do not necessarily match the majority of patients. More general agreement among clinicians on inclusion criteria may result in more representative studies. Another solution is to use data from a cartilage registry when informing the patients, as was recently done for ACL surgery patients.[25]

A registry on cartilage repair of the knee would give an extended understanding of the long-term outcome of cartilage defects. The treatment modalities in this consent will then be chosen based on clinical impression, so a distinction between the different techniques will of course be impossible. But we believe there is a clinical value in founding such a registry.

Cartilage defect patients represent a mixed group in terms of age, size of defect, anatomical location of defect, coinjuries, and previous surgery, as illustrated in the current study. A reader of an RCT that does not present a flowchart of the patient selection runs the risk of misjudging the results when interpreting the study. Additionally, the variations found in inclusion criteria in the published RCTs represent a concern related to whether the studies actually include the same patient groups. This is also a problem in other fields of medicine, as mentioned earlier and stated by the two articles regarding the applicability of RCTs to the general patient population.[21,22]

Conclusion

The results of the present study establish that RCTs on cartilage repair are not representative of the general cartilage patient population. New clinical trials conducted in line with the CONSORT rules[23] and with inclusion criteria constructed to include a larger proportion of the general cartilage patients are necessary to provide more definitive guidance for cartilage defect patients concerning treatment.

Funding and Acknowledgments

The authors would like to thank Ingar Holme, PhD, for his advice concerning relevant statistics.

The work was supported by the Faculty of Medicine, University of Oslo (UiO). Cathrine N. Engen is a student at the Medical Student Research Program at UiO and is supported by the Research Council of Norway. The study was supported by grants from the Oslo Sports Trauma Research Centre (OSTRC). The center is financed by the South-Eastern Norway Regional Health Authority, the Royal Norwegian Ministry of Education and Research, the Norwegian Olympic Committee, and the Confederation of Sport and Norsk Tipping.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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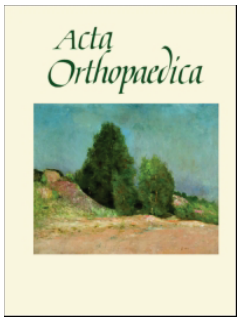

Acta Orthopaedica

ISSN: 1745-3674 (Print) 1745-3682 (Online) Journal homepage: http://www.tandfonline.com/loi/iort20

No degeneration found in focal cartilage defects evaluated with dGEMRIC at 12-year follow-up

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To cite this article: Cathrine Nørstad Engen, Sverre Løken, Asbjørn Årøen, Charles Ho & Lars Engebretsen (2016): No degeneration found in focal cartilage defects evaluated with dGEMRIC at 12-year follow-up, Acta Orthopaedica, DOI: 10.1080/17453674.2016.1255484

To link to this article: http://dx.doi.org/10.1080/17453674.2016.1255484

OPEN ACCESS

Acta Orthopaedica 2016; 87 (x): x–x

No degeneration found in focal cartilage defects evaluated with dGEMRIC at 12-year follow-up

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Submitted 2016-04-21. Accepted 2016-09-11.

Background and purpose — The natural history of focal cartilage defects (FCDs) is still unresolved, as is the long-term cartilage quality after cartilage surgery. It has been suggested that delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) is a biomarker of early OA. We aimed to quantitatively evaluate the articular cartilage in knees with FCDs, 12 years after arthroscopic diagnosis.

Patients and methods — We included 21 patients from a cohort of patients with knee pain who underwent arthroscopy in 1999. Patients with a full-thickness cartilage defect, stable knees, and at least 50% of both their menisci intact at baseline were eligible. 10 patients had cartilage repair performed at baseline (microfracture or autologous chondrocyte implantation), whereas 11 patients had either no additional surgery or simple debridement performed. Mean follow-up time was 12 (10–13) years. The morphology and biochemical features were evaluated with dGEMRIC and T2 mapping. Standing radiographs for Kellgren and Lawrence (K&L) classification of osteoarthritis (OA) were obtained. Knee function was assessed with VAS, Tegner, Lysholm, and KOOS.

Results — The dGEMRIC showed varying results but, overall, no increased degeneration of the injured knees. Degenerative changes (K&L above 0) were, however, evident in 13 of the 21 knees.

Interpretation — The natural history of untreated FCDs shows large dGEMRIC variations, as does the knee articular cartilage of surgically treated patients. In this study, radiographic OA changes did not correlate with cartilage quality, as assessed with dGEMRIC.

The best treatment for focal acute or chronic cartilage defects (FCDs) is not yet resolved. A non-invasive technique of visualizing defects, and of evaluating the status following treatment of such defects, would be of value. The sensitivity of conventional MRI in detecting FCDs varies from 18% to 100% (Spiers et al. 1993, Yoshioka et al. 2004), whereas the specificity is more than 90% (Friemert et al. 2004, Bredella et al. 1999). The sensitivity and accuracy of MRI increased throughout the late 1990s, and after 2000 with the development of newer modalities and more powerful field strengths, but small superficial changes and small defects are still generally invisible using MRI. The idea of detecting each of the components of the cartilage led to the development of several quantitative techniques. One of these techniques is based on the loss of glycosaminoglycans (GAGs) seen in early osteoarthritis (OA), and is called delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC). It detects degenerative changes earlier than standard modalities. The technique seems promising for assessment of the natural progression of the disease, for timing of therapeutic intervention, and in defining the functional status of the tissue after repair.

FCDs induce OA in animal models (Lefkoe et al. 1993). We know from animal studies that small defects might heal spontaneously, but when the diameter approaches 6 mm that tendency disappears. The natural development of isolated cartilage defects in humans remains unknown. There is general agreement that full-thickness defects larger than 2 cm^2 in an otherwise stable and healthy knee can be treated surgically with cartilage repair. However, we are not aware of any original research to support this assumption.

Debridement is a common and effective technique for smaller cartilage lesions in the knee, as a first-line treatment

DOI 10.1080/17453674.2016.1255484

(Hubbard 1996). Cartilage repair leads to clinical improvement after 2 years followed by a further stable clinical situation or a slight deterioration 5 to 10 years after autologous chondrocyte implantation (ACI) (Niemeyer et al. 2014). 3 long-term follow-up randomized controlled trials (RCTs) on cartilage surgery have been published. Radiological OA after cartilage surgery occur in 17% (10 years) to 57% (14–15 years) of patients treated with osteochondral autologous transplantation (OAT) (Ulstein et al. 2014, Knutsen et al. 2016).

The efficacy of cartilage repair surgery has never been tested against non-operative treatment in an RCT. Some cohort studies have demonstrated a potential benefit of non-operative treatment. Wondrasch et al. (2013) included a preoperative training program in an RCT for surgical treatment of an FCD. Following "prehabilitation", two-thirds of the patients had improved functional scores, so that surgery was cancelled or delayed for at least 2 years.

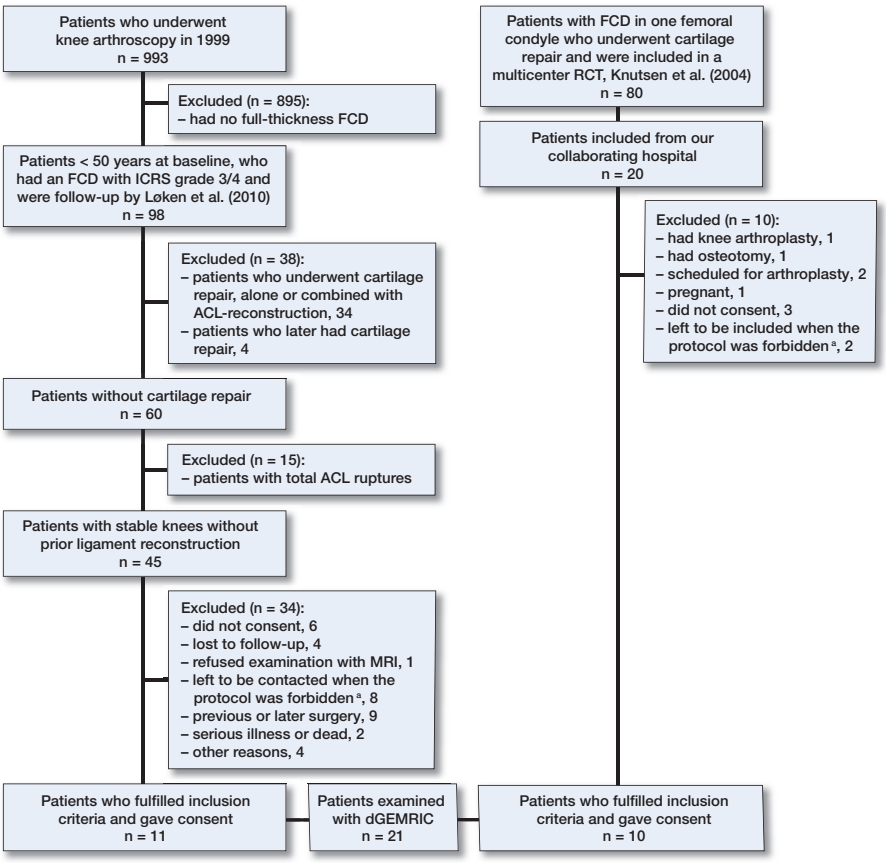


Figure 1. The flow of patients. *As a double dose of Magnevist was given, the protocol was allowed only for a limited amount of time at our hospital. We were therefore unable to examine all of the subjects included. We excluded them, as dGEMRIC was the main outcome.

The purpose of this study was to evaluate the biochemical status of knee articular cartilage 12 years after the diagnosis of full-thickness FCDs. We hypothesized that these patients would have a low dGEMRIC index, indicating degenerative changes. Our null hypothesis was that the cartilage quality is normal for more than 10 years after a diagnosed FCD. We included T2 mapping and assessed radiographs of both knees and information on patient-related outcome measures (PROMs).

Patients and methods

Data on 993 patients undergoing knee arthroscopy during a 6-month period in 1999 were collected from 3 hospitals (Aroen et al. 2004). All these knee arthroscopies were performed because of knee pain. Patients with an International Cartilage Repair Society (ICRS) classification grade 3–4 focal cartilage lesion, classified as not having OA and less than 50 years of age at baseline, were re-examined after 6 years (Loken et al. 2010). Of these, 98 patients fulfilled the inclusion criteria and 84 were included. In the present 12-year follow-up, we invited patients with full-thickness cartilage lesions who were less than 50 years of age at baseline, who had no total knee ligament injury, and who had more than 50% of their lateral and/or medial meniscus intact (Figure 1). A cohort of patients previously included in an RCT on cartilage repair (Knutsen et al. 2004) was also invited to participate in the study. 42 patients from these 2 original studies were eligible for inclusion, and 21 agreed to participate and signed a written consent document. 10 patients were treated with either microfracture (MF) or ACI at baseline. 11 patients had not undergone cartilage repair, either at baseline nor later. 3 patients from the latter group had debridement performed at baseline. Median time from baseline to follow-up was 12 (11–12) years.

MRI protocol

The dGEMRIC was performed as a T1 mapping based on 3-dimensional gradient-echo (3D-GRE) sequence with different flip angle combinations compared to standard IR sequence at 1.5T. We used a Siemens Avanto MRI machine (Siemens

Healthcare GmbH, Erlangen, Germany) with similar methods to those used by Årøen et al. (2016). Protocols have been established by Burstein et al. (2001) and Tiderius et al. (2001). Our local protocol at Oslo University Hospital was modified based on the post-contrast imaging protocol of Burstein et al. (2001). The patients exercised on stairs for 15 min after contrast injection, then rested in 75 min, after which the post-contrast images were taken. The patients were in supine position until completion. The dGEMRIC value was read as T1(Gd). A T2 mapping for the index knee was also performed. The measurements were taken at 6 regions of interest (ROIs)—anteriorly, centrally, and posteriorly on the medial and lateral femoral condyles. An experienced MRI radiologist (HB), who was blinded regarding all other information related to the patients, evaluated the images. The dGEMRIC index could not be calculated for 8 regions in the injured knee in 5 patients and for 1 region in the uninjured knee in 1 patient, due to marked cartilage thinning.

Kellgren and Lawrence grading

The standing radiographs were obtained with bilateral weight bearing in a posteroanterior direction using a SynaFlexer 64 frame (Synarc Inc., Newark, CA) to standardize knee position in 20° flexion and 5° external rotation of the feet. The images were evaluated (LE) according to the Kellgren and Lawrence (K&L) protocol for assessment of knee OA .

Statistics

The ROI values of the index condyle in injured knees were compared to the values of the corresponding ROIs in knees that had the baseline defect located on the opposite and presumably normal condyle. Both the single measurements from each ROI and the average dGEMRIC index (values from several ROIs pooled together) were used for analyses. The data file was arranged to contain the mean value of the injured condyle and compartment, that of the uninjured condyle in the injured knee, that of the corresponding compartment (to the injured compartment) in the uninjured knee, the mean value of the medial and lateral condyles in both the injured knee and the uninjured knee, and the mean of the entire injured and uninjured knee.

The primary outcome was dGEMRIC. The uninjured knee was used as control. Analyses were done using IBM Statistics SPSS 22. As we aimed to recruit all the eligible patients from a previous cohort, power analyses were not crucial for the inclusion process. We still examined the power, and with a 1-sided test with $1 - \beta = 0.80$, $\alpha = 0.05$, mean value in population 410 ms, mean value in study group 460 ms, and SD = 80, the sample size needed would be 20.

The dGEMRIC measurements were normally distributed. We initially performed t-tests. The result from a Wilcoxon signed rank test did not differ from the parametric test. The same tests were used for the T2 mapping, except for independent t-test instead of paired t-test when comparing the injured condyle with its corresponding condyle. Pearson correlation was used to test associations between the injured condyle and the corresponding condyle. A Wilcoxon (Mann Whitney U) test was done for comparison of subgroups based on whether there had been cartilage surgery at baseline, meniscal resection of more than one-third or less, or defects larger than 2 and 4 cm^2. Associations between baseline factors (patient and defect demographics) and primary or secondary outcomes were assessed with scatter plots. For cases with a possible line plot, correlation was tested with Spearman tests. There were too few patients included to compare subgroups with patient-related outcome measures (PROMs) as outcome, but the descriptive results from the 12-year follow-up are reported, expressed as median with interquartile range (IQR) to account for possible bias from outliers.

Ethics

The study was approved by the regional ethics committee (reference numbers S-09234a 2009/5791 and 2011/1141).

Results

Study group

Pertinent baseline data were similar between patients with defects left untreated or treated with debridement and patients treated with cartilage repair (Table 1). The long-term results from PROMs were as follows: Lysholm 69 (52–81), Tegner 4 (3–5), VAS 30 (10–50), KOOS sports 45 (30–66), and KOOS quality of life 56 (38–71).

dGEMRIC and T2

The mean dGEMRIC index in injured knees was statistically significantly higher than in uninjured knees (Table 2). There was a statistically insignificant lower value for the injured compartment relative to the corresponding compartment of the uninjured knee. For 8 knees, we knew the exact location of the original defect in the sagittal plane, and we found a trend of a lower value for the injured area than for the matching area of the uninjured knee. Analyses regarding the location of defects medially or laterally revealed no statistically significant differences in the injured knee, for either medial or lateral localization. There was a strong correlation (r = 0.68) between the scores of the injured medial femoral condyle (MFC) and the uninjured MFC for all medial ROIs when an FCD was present medially (Figure 2). No correlation was found laterally. We also explored the relationship between medial and lateral defects based on the localization in the sagittal plane (Table 3). The mean dGEMRIC of all ROIs is given in the same table.

There were no statistically significant differences in dGEMRIC between groups based on cartilage surgery or degree of meniscal resection. Age at operation did not appear to influence the later dGEMRIC values in either the injured knee or

Table 1. Baseline data

Variable	No treatment or debridement of the defect	Cartilage repair
Age at injury, median	30 (13–44)	28 (10–40)
Age at operation, median	32 (14–44)	33 (24–42)
Male sex, n/total	7/11	5/10
BMI	25 (19–40) [a]	27 (19–37)
Defect class, III:IV, n	8:3	7:3
Size of defects < 2 : > 2 cm^2, n	6:5	2:8
mean size	3.2	4.8
Patients previously operated, n	3 previous arthroscopy, 3 previous PMR	3 previous arthroscopy, 1 drilling, 1 Herbert screw, 1 debridement, 1 previous patella dislocation, and 1 intra-articular fracture
Patients with meniscal resection, n none : 1/3 : >1/3	4:4:3	8:2:0
Cartilage repair	None	6 with ACI, 4 with MF
VAS, mean (SD)	46 (27)	51 (18)

PMR: partial meniscal resection.
ACI: Autologous chondrocyte implantation; MF: Microfracture.
[a] A BMI of 19 in a 13-year-old boy is normal according to WHO growth reference values.

Table 2. Mean dGEMRIC values based on localization within the index knee, compartment/condyle, and even in the sagittal plane (the latter only in 8 patients)

Location	dGEMRIC value, mean (SD) Injured	Uninjured	p-value[a]
Knee	490 (61)	453 (60)	0.002
Injured compartment and corresponding compartment of uninjured knee	425 (133)	449 (67)	0.3
Injured area in sagittal plane and corresponding area in uninjured knee	282 (197)	394 (136)	0.09
Medial condyle	447 (127)	458 (69)	0.6
Lateral condyle	476 (84)	442 (65)	0.07

[a] Paired t-test

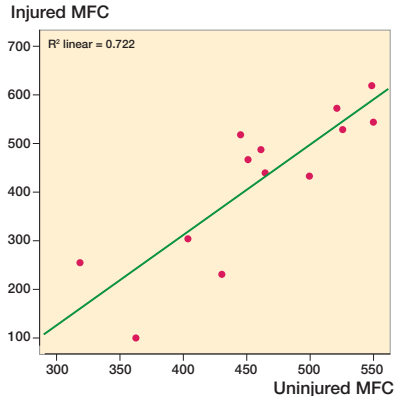


Figure 2. The association between dGEMRIC values on the injured and uninjured medial femoral condyles (MFCs).

condyle. There were no statistically significant differences in T2 values between injured and non-injured ROIs (Table 4).

Discussion

The principal finding in this study was that there were no more degenerative changes in the injured knees than in the uninjured knees, as evaluated by dGEMRIC.

dGEMRIC and T2

There have been some long-term studies on clinical outcome in humans. A study following young and athletic patients after arthroscopic diagnosis of an isolated FCD found that 92% of patients had returned to pre-injury activity levels by 12–15 years (Messner and Maletius 1996). Another study performed T1-weighted fat-saturated MRI at baseline and after 2 years and found that one-third of the knees deteriorated whereas 37% improved in cartilage defect score (Ding et al. 2006). Widuchowski et al. (2009) found outcomes comparable to those following cartilage repair in patients with isolated untreated severe cartilage lesions (size 2–4 cm^2) in the knee after 15 years. Furthermore, 39% had OA and there was no difference when injured and uninjured knees were compared.

Table 3. Mean dGEMRIC index in all 6 ROIs of both the injured and the uninjured knee. The delta (dGEMRICuninjured knee – dGEMRICinjured knee) is also given, which was tested by t-test against the value zero

Knee	Condyle	Sagittal position	dGEMRIC value		p-value
Mean dGEMRIC (SD) range					
Injured knee					
	MFC	A	438 (135)	100–607	
		C	408 (191)	100–597	
		P	432 (177)	100–690	
	LFC	A	402 (162)	302–544	
		C	495 (88)	297–614	
		P	370 (226)	337–641	
Uninjured knee					
	MFC	A	402 (82)	100–551	
		C	468 (104)	364–623	
		P	508 (87)	100–655	
	LFC	A	391 (74)	324–513	
		C	437 (31)	413–492	
		P	499 (114)	314–597	
Delta [a] (95% CI)					
	MFC	A	–36 (–89 to 16)		0.2
		C	60 (–17 to 137)		0.1
		P	76 (–4 to 156)		0.06
	LFC	A	–47 (–246 to 151)		0.5
		C	-93 (–214 to 28)		0.09
		P	63 (–453 to 579)		0.7

MFC: medial femoral condyle; LFC: lateral femoral condyle;
A: anterior; C: central; P: posterior.
[a] ($dGEMRIC_{uninjured\ knee} - dGEMRIC_{injured\ knee}$)

Table 4. The mean T2 values for the injured knee. The lower part of the table illustrates the results from the t-test as explained in text

Condyle	Sagittal position	T2 value		p-value
Mean T2 (SD) range				
MFC	A	51 (10)	28–65	
	C	45 (10)	31–74	
	P	52 (16)	34–79	
LFC	A	48 (11)	35–82	
	C	48 (9)	29–61	
	P	54 (7)	41–66	
Mean delta [a] T2 (95% CI)				
MFC	A	4 (–5 to 14)		0.3
	C	–3 (–12 to 6)		0.5
	P	4 (–10 to 19)		0.5
LFC	A	–4 (–21 to 13)		0.6
	C	–1 (–11 to 10)		0.9
	P	3 (–6 to 12)		0.5

[a] ($T2_{uninjured\ knee} - T2_{injured\ knee}$)

Previous studies with dGEMRIC have found T1 values in healthy subjects to be 440–570 ms (Burstein et al. 2001) and 480–560 ms (Tiderius et al. 2001). Lower values and later joint space narrowing (JSN) have been found in meniscectomized patients (Owman et al. 2014). Results from previously explored populations are given in Table 5 (see Supplementary data). 9 patients in our study group underwent meniscal resection at baseline, and there were no statistically significantly lower dGEMRIC in those patients.

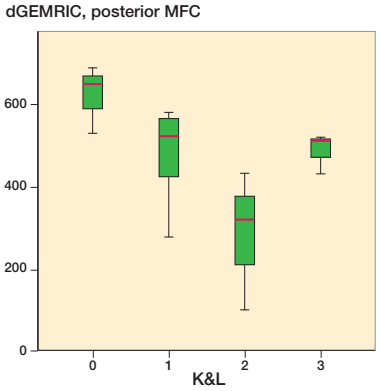


Figure 3. Box plot with dGEMRIC values for the posterior aspect of the MFC in the injured knee and K&L grade in the injured knee. The horizontal line within the box represents the median, whereas the distance between the top and bottom of the box is the interquartile range, between the 25th percentile and the 75th percentile. The whiskers show the smallest and largest values of the sample.

The numbers in our study are within this lower range of reference values from healthy populations, and indicate that no degenerative changes were evident in our study group. The lack of differences between the injured knee and the uninjured knee support this. However, the degenerative changes present with the K&L grading suggest the opposite: that degeneration had occurred within the injured knees. We found established radiological OA in 6 injured knees and in 4 uninjured knees, and degenerative changes (K&L 1) in 7 injured and 2 uninjured knees. To our surprise, it was not possible to demonstrate this clearly with dGEMRIC in this population, and there was no overall correlation between dGEMRIC and K&L grading. There were, however, some indications of a relationship between these 2 variables based on box plots (Figure 3). Especially in the posterior part of the medial condyle, decreased values of dGEMRIC were associated with increased K&L grade. A possible explanation might be that severe OA produces a biochemical environment where dGEMRIC is no longer sensitive.

The dGEMRIC index gives a numeric value on a scale from around 300–700 ms. A difference of > 100 has been considered to be clinically/radiographically significant (Cunningham et al. 2006). Unmeasurable T1 results were assigned the value of 100 ms for the purposes of statistical analysis. This number is lower than what have been previously demonstrated from studies with dGEMRIC. If these absent values were defined as "missing", it would lead to major bias—since most areas with thin cartilage are in the areas of the original defects.

The use of the uninjured knee as a control is controversial. An experimental study of the patellofemoral joint in rabbits

evaluated the degeneration of cartilage 12 months after blunt impacts (Newberry et al. 1998). The cartilage in the index knee was significantly thinner and the subchondral plate thicker than in controls, but changes were also seen in the unimpacted side. The low values in uninjured knees may be the result of a general degenerative joint disease, changed body habitus, or loading pattern of the joints. An alternative would be to compare absolute values to a reference standard. However, standardized reference values do not yet exist.

We are not aware of any published studies that have evaluated knees after isolated FCDs not undergoing cartilage repair. However, Årøen et al. (2016) studied cartilage defects in knees with dGEMRIC after initial arthroscopy, and before cartilage surgery. The patients had an average duration of symptoms of 4 years, and 8 of 26 had previously had cartilage repair. The authors found no substantial degeneration of the impacted condyle compared to the opposite knee, which is in line with the results of our study. We also found an almost statistically significant difference for the posterior ROI when the defect was located on the MFC.

When all T2 values were pooled together, the histogram had a near bell-shaped curve. The mean value was 50 ms (SD 10, range 28–82). The overall T2 values were higher than the reference values from Joseph et al. (2015). They seem, however, to overlap with the results of an asymptomatic cohort study (Joseph et al. 2011). We performed a simple t-test with 40 as the test value (Table 6, see Suplementary data). All locations, except from the anterior LFC, had statistically significantly higher values. No T2 results were obtained from the uninjured knee. We therefore compared the injured condyle with the corresponding condyle in patients with defects located on the opposite condyle, and found no significant differences. The T2 values in our study appear to be associated with OA.

The T2 values must, however, be interpreted with caution. Reproducibility of T2 value measurements between centers and time points has still not been established. The values may be influenced by different factors such as MRI scanners (within and across manufacturers), coils (Chang et al. 2012), diverse magnetic field strength, and by joint or cartilage loading status at the time of T2 measurement. Like Wei et al. (2015), we found no correlation between dGEMRIC and T2 values. This inconsistency might be due to magic angle effect, as demonstrated previously by Mosher et al. (2001).

Outliers

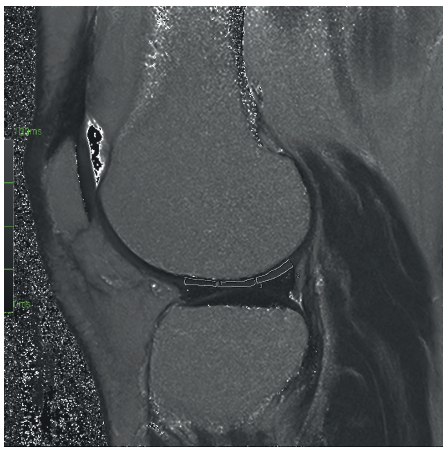
3 patients had clinically relevant lower dGEMRIC scores in their contralateral knee. This does not correspond to previous findings where low dGEMRIC in knees was associated with an increased risk of OA. We have assessed these patients individually. 1 of them had an earlier meniscal resection, while the other 2 had no known injury to the contralateral knee. When we removed these 3 patients from the analyses, there were still no group differences when comparing injured and uninjured knees.

Strengths and weaknesses

The long-term follow-up of the patients is a strength with MRI examination performed at an average of 12 years from baseline. An obvious weakness was the small number of patients. Previous studies have shown a low variability in T1(Gd) and the number of patients needed to detect statistically and clinically significant differences may be as low as 15–20 subjects (Neuman et al. 2011). These analyses have great variance, both between subjects and within the knee joint (Neuman et al. 2011). Repeated measures reduce the variance and are helpful, but are expensive. Using the contralateral knee as a control also reduces the number of patients required. Our radiological protocol takes 3 hours per patient. This, in addition to the financial costs, makes studies on larger patient groups difficult to perform.

Another weakness was the heterogeneity of the patients, and that they were recruited from 2 different clinical studies. We did not have all the clinical scores at all time points. However, the main purpose of the study was the extended MRI investigations, with clinical scores serving as supplementary information. The 2 sub-cohorts of patients were of almost equal size, with 11 subjects in the group with untreated or debrided defects and 10 in the group with defects treated with cartilage repair. We did not find any significant differences in age, sex distribution, or depth of the lesion between unoperated/debrided and operated patients. Symptoms may have differed between patients, although there was no statistically significant difference in VAS at baseline ($p = 0.5$). The median baseline size for the unoperated/debrided group was 3.5 cm^2, and it was 5.0 cm^2 for the operated group. There were more lesions with size over 2 cm^2 in the operated group, and similar numbers of lesions with size over 4 cm^2. There is a common distinction at 2 cm^2, as a cutoff for surgical treatment. The difference concerning size might still be of clinical significance, as some clinical guidelines operate with a cutoff of 4 cm^2.

A potential source of bias in this study was the manual drawing of the ROIs. Automated drawing is possible, but previous studies have shown low intra- and interobserver reliability when large and standardized ROIs are used (Tiderius et al. 2004). The ROIs were drawn manually in a standardized fashion, where the anterior ROI stretched from the end of the anterior horn of the menisci to the anterior border of the tibia plateau. The central ROI included the posterior part of the area between the anterior and posterior menisci, whereas the posterior ROI spanned from the end of the posterior horn of the menisci to the posterior border of the tibial plateau (Figure 4). Previous studies have found an intraclass correlation coefficient (ICC) for measurement of dGEMRIC index with manually drawn ROIs of 0.9 (Hingsammer et al. 2013). The ICC of the dGEMRIC readings from another study by the same research group was 0.882 (Aroen et al. 2016). The substantial degree of degenerative changes, as well as previous meniscal injuries, within this patient cohort may have challenged the placement of the anterior border of the anterior ROI and the posterior border of the



posterior ROI, due to possible meniscal extrusions. This was accounted for during the drawing, when evident.

We did not perform volume estimations and can therefore not evaluate our findings in relation to cartilage thickness. However, the ROIs were standardized with height ranging from 0.7 mm to 1.6 mm in the central ROI and length ranging from 8 mm to 16 mm. In the cases with severely thin cartilage, the T1(Gd) was not measured. We did not perform analyses regarding correlation between T1(Gd) and T2 on the one hand and height of the ROIs on the other. This is a source of error, because it has been shown that thin cartilage will have a lower T1(Gd) due to facilitated diffusion of the contrast medium (Hawezi et al. 2011).

It has been shown that differences in BMI will affect T1(Gd) due to different distribution volumes in lean and obese patients (Tiderius et al. 2006). In the present study, there was a large variation in BMI at baseline, but even so 16 had BMI values near the range classified as normal weight. We therefore chose not to use the correction factor suggested by Tiderius et al. There were 2 obese patients in our study, with a BMI of 37 and 40 at baseline. The T1(Gd) was within the normal range (except for low T1(Gd) in both medial posterior ROIs of 1 patient), and there were no differences between injured and uninjured knees.

In summary, we found no increase in degenerative changes 12 years after the diagnosis of an FCD, as measured with dGEMRIC. The natural history of untreated/debrided FCDs and of FCDs treated with MF or ACI shows large variations. The dGEMRIC values for defects on the MFC in the posterior sagittal plane tend to be lower than in the uninjured knee. Consequently, these FCDs can more easily be followed with dGEMRIC. However, in this study, radiographic OA changes did not correlate with cartilage quality, as assessed with dGEMRIC.

Supplementary data

Tables 5 and 6 are available online at: http://dx.doi.org/10.1080/17453674.2016.1255484.

LE and AÅ conceived the study and all the authors planned the method. CNE collected data and performed the analyses, whereas all authors and especially CH interpreted the dGEMRIC and T2 results. CNE and SL drafted the manuscript, and AÅ, CH, and LE revised it.

We thank Ingar Holme for his advice concerning relevant statistics. We also thank Helga Brøgger for performing the calculations of dGEMRIC and T2.

No competing interests declared.

The study was supported by grants from the Oslo Sports Trauma Research Center (OSTRC), where the first author is employed, and from Sophies Minde AS. The OSTRC is financed by the South-Eastern Norway Regional Health Authority, the Royal Norwegian Ministry of Education and Research, the Norwegian Olympic Committee, the Confederation of Sport, and Norsk Tipping. The work was also supported by the Faculty of Medicine, University of Oslo (UiO). Cathrine N. Engen previously attended the Medical Student Research Program and thereby received financial support from the Research Council of Norway.

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IV

Development of a pilot cartilage surgery register

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Key words: Cartilage surgery, articular cartilage, cartilage repair, knee, register

Abstract

Background: Norway has no prospective surveillance system monitoring outcome of knee cartilage surgery. In 2004 the Norwegian Registry of Knee Ligament (NKLR) was successfully established, and has yielded useful information on the treatment of patients with knee ligaments and on patients with combined knee injuries. Patients with focal cartilage defects (FCDs) in their knees have reduced function and the treatment is difficult. There are geographical variations in treatment and the generalizability from RCTs is low. These patients would benefit from a standardized long-time follow-up through a cartilage surgery register.

Purpose: Run a pilot of a knee cartilage surgery register. Describe the development and report baseline challenges.

Methods and material: The study was designed as a prospective cohort study in the form of a register. Patients with full-thickness FCDs in the knee with International Cartilage Repair Society (ICRS) grade 3-4 on arthroscopy were included. The pilot included two hospitals; Oslo University Hospital (OUS), Ullevål and Akershus University Hospital (Ahus).

Results: We registered 58 patients with isolated FCDs, whereas 16 additional patients with full-thickness FCDs were registered through the NKLR. The patient cohort of patients with isolated FCDs consists of 65% men and had a mean age of 29.8 years. The data are incomplete and the compliance varies from 18-73%. The distribution of mean KOOS scores were similar to previous patient cohorts with FCDs, with low scores for the KOOS Sport/Rec and QoL subscales.

Conclusion: The level of compliance demonstrates a large difference between the two participating hospitals. The compliance for the isolated FCDs were low in both locations, although it reached an acceptable level in one hospital when the patients with combined injuries from the NKLR were included. The form filled by the surgeons postoperatively demonstrated many missing values and will be revised prior the establishment of a nation-wide register.

Background

Patients with Focal cartilage defects (FCDs) are young,[1-3] they have increased risk of knee OA[4] and the treatment is challenging. Which surgical technique, if any, should be offered? Is surgery always better than non-surgical treatment? The lack of evidence within parts of this field suggests that many patients are treated based on surgeons preferences rather than evidence-based medicine.

Randomized controlled trials (RCTs) are a natural part of an evolving clinical research field, but the field of FCDs seems to be demanding as the patient population is heterogeneous and there are many different surgical techniques. Also, cartilage surgery has still not been compared to non-surgical treatment. The results from RCTs are somewhat inconsistent [5-14] and the RCTs demonstrate low methodological quality.[15] The external validity is also low,[16] and the results from RCTs are thereby not easily applied to a clinical setting.

Orthopedic registers have been successful in Norway and Scandinavia, with high quality and acceptable compliance.[17] The completeness of the NKLR was 97% 21 months after establishment.[18] Compliance is an important part of valid data, and clinical results from the NKLR have already led to changes in treatment.[19,20]

A cartilage surgery register, or rather a prospective cohort study, on a non-biased patient population, will be beneficial for the treatment of these patients. A register will follow trends in surgical treatment and allow feedback on the results to participating hospitals. The quality of treatment will increase through the reporting system. Surgical procedures and devices that result in an unacceptable outcome at an early stage may also be identified. This research design is further valuable for finding prognostic factors, whereas an RCT will not be able to determine the influence of several important potential prognostic factors, such as overweight, age, previous surgery, localization of the defect. Orthopedic registers [21,22] increase the quality of the treatment in certain patient populations, and we want to explore the potential benefits and challenges for a knee cartilage surgery register. Patients with FCDs of the knee have subtle clinical symptoms, the treatment

options are many and varied and the patient population is heterogeneous, even compared to other orthopedic patient populations. It is therefore necessary to perform a pilot prior to the establishment of a nation-wide cartilage surgery register. In order to explore challenges related to inclusion and logistics and to calculate an expected compliance.

Figure 1

Figure 1 illustrates the inclusion and exclusion criteria.

Inclusion criteria

- Diagnosed focal cartilage defect (ICRS grade 3-4) during arthroscopy or open surgery
- Operations/ reoperations in patients with a known FCD
- Age <67 years

Exclusion criteria

- Generalized knee OA
- Other systemic diseases with a known increased risk of knee OA, such as rheumatoid arthritis

Design and study cohort

The project was designed as a prospective cohort study with follow-up at 5 and 10 years. The inclusion and exclusion criteria are outlined in figure 1. We aimed to include all isolated FCDs. If additional FCDs or degenerative changes were present in other compartments, we still included these patients. If they had reached a state of generalized knee OA they were excluded as they had reached the end-stage disease. Participation was voluntarily and a written consent was signed before surgery. Two hospitals recruited patients over a 6-8 months period in 2010. The patient pool is thereby restricted to the geographic areas that these hospitals serve, which is approximately 1 million. Although, a few patients were referred from other geographic areas of Norway. We also

included patients with FCDs in combination with a surgical reconstruction of the anterior cruciate ligament (ACL).

Data collection

We recorded patient demographics, injury variables, findings during operation and surgical techniques, additional injuries at the time of operation and PROMs. Non-operative treatment was also registered when FCDs were diagnosed during knee arthroscopy but without further surgical intervention. Oslo University Hospital (OUS) registered patients from 08.02.10 – 08.10.10, and Akershus University Hospital (Ahus) registered from 01.10.10 – 01.03.11. The data from the NKLR was collected by requesting data on patients treated at the participating hospitals within the data collection period with registered full-thickness FCDs. We received the data as both copies of the NKLR-form, completed by the orthopedic surgeon postoperatively, and in a data file on a CD. We did not get KOOS data on these patients.

The pilot was paper-based and the cartilage surgery form (appendix) was constructed with the design of the NKLR-form as a model, but with focus on FCDs. The form is on one page with chronologic questions regarding the FCDs. The variables were chosen after discussions with experienced orthopedic surgeons from the participating hospitals in order to include all important aspects. The form was completed immediately after surgery. Most patients completed the KOOS and the Tegner Activity Scale and questions regarding smoking/tobacco status, BMI, use of NSAIDs and sick-leave (appendix) on their clinical evaluation before knee arthroscopy. However, some patients were included *during* knee arthroscopy due to a newly diagnosed FCD. These patients completed the forms postoperatively based on their experience with the knee prior to operation.

The KOOS score is validated for both cartilage injuries[23] and after cartilage repair,[24] and has acceptable test-retest reliability.[24] It consists of 42 items over five subscales; pain, symptoms, activity of daily living (ADL), sports and recreation and quality of Life (QoL). Each subscale is reported

individually with a score ranging from 0–100, 100 being the best. Reference values for the general population exist.[25] The Tegner activity score[26] is determined by the most demanding activity the patient is able to perform. The score ranges from 0–10, 0 being absent from work due to knee function and 10 being individuals competing on high-level in pivoting sports. The average Tegner score from normative data is 5.7.[27]

One person was responsible for collecting the forms at each hospital. The forms were then checked and plotted into an SPSS-file by the first author of this paper. Incomplete registration files was returned with a request of fulfilling the form. If this was not done after reminders, the form was registered as “missing”.

End points

The main outcome was the compliance of the registration, which first and foremost reflects the involvement of the orthopedic surgeons. We included both objective and subjective clinical end points. Total knee replacement (TKR) is an obvious hard endpoint, and another is the diagnoses of severe OA (by arthroscopy, MRI or K&L-grading). The hard endpoints for the NKLR and the National Prosthesis Registry are revision surgery and TKR. Arøen et al. found that 28 % of the patients had previous arthroscopic procedures performed to their knees.[3] Revision surgery is not a suitable hard endpoint for cartilage endpoint, since many of them already have had previous surgery to the knee when scheduled for surgery. Revision surgery therefore did not lead to exclusion from the register. The study end points are knee OA and KOOS QoL.

Validity and reliability

High compliance is necessary to justify the establishment of a cartilage surgery register and was therefore the main outcome of the pilot. Low compliance rate might lead to selection bias, and it is

difficult to predict the direction of the bias; patients might be non-compliant either because they are satisfied with the treatment and feel that they do not need any extra follow-up, or because they are dissatisfied and have sought help elsewhere. Maintaining high compliance and including all patients with FCDs is therefore both a challenge and a critical necessity for any register. We calculated the compliance of the pilot register by going through the operation protocol/local databases in each hospital, which we used as a gold standard. We identified all patients who matched the inclusion criteria based on the surgical description from the operation during the inclusion period and then matched those numbers with the records from the registration. The same was carried out for the data included through the NKLR.

The reliability of the cartilage surgery form is an important issue, where a central aspect is the data describing the lesions. The size was calculated by the surgeon using a specific caliper, and the localization was reported corresponding to six predefined areas of the knee joint. Concerning the depth of the lesion, there is an ongoing project with aim of testing the reliability of the ICRS-grading of FCDs (Kjennvold, unpublished). The ICRS score is validated for use after cartilage repair.[28]

Statistics

We did not do power analysis as this is not an intervention study. We expected to include approximately 150 patients in two hospitals over a six-month period. We finally included 74 patients over an eight-month period.

Descriptive data included the cartilage surgery form (appendix) and PROMs. Descriptive data is presented as means and standard deviations or as medians and interquartile ranges for continuous variables. Frequencies and percentages will be used for summary of categorical variables.

Wel also examined the dataset for associations and correlations among baseline factors and PROMs with scatter plots and correlation analyses. Roos and Lohmander suggested ten points as a clinical

relevant change in score.[29] For the follow-up, we will compute survival plots with KOOS QoL of less than 44 as an end-point. A KOOS QoL less than 44 points has been suggested and tested as a tool for "clinically failure" in patients undergoing ACL reconstruction.[30] This may not be appropriate as a measure for the same clinical outcome in patients with FCD, and must be further explored.

Results

Descriptive results

We performed descriptive analyses on the patients with isolated FCDs (table 1). The patient cohort with combined injuries is previously discussed in articles based on data from the NKLR.[31] 70% of patients with isolated FCDs had a single lesion, whereas 16% had three or more. Regarding localization of the "clinical significant" defects, 55% were on the MFC, 16% on the LFC, 10% on trochlea, 19% on patella, and none on the MTP and LTP. Nearly 14% had a known FCD in the contralateral knee. Only one patient were reported to have none previous surgeries, although information on this was missing in 56%. 3.9% operative complications were reported. Nearly 50% of patients received antithrombotic prophylaxis whereas 35% received NSAIDs postoperatively.

Diagnostic arthroscopies accounted for 22% of the procedures, 55% were primary cartilage surgery, 10% were revision surgery, 2 % were other surgeries and 10% were missing classification. 38% of patients had an additional surgical procedure performed. 90% did not report on tobacco, regular use of NSAIDs or sick-leave.

There were no gender differences regarding age, size or depth of lesion or number of lesions. We did not find any correlation between age, lesion or ICRS grade. A weak correlation ($r^2 = 0.02$) between age and number of defects (p .003) seems to exist. size of the

Table 1 demonstrates descriptive data of the patient population with isolated FCDs.

Variable	Result
Sex	65.5% men
Age in mean (range)	29.8 (10-55)
Size in mean cm^2 (range)	2.49 (0.04-7.02)
Number of defects in mean (range)	1.57 (1-6)
Normal contralateral knee	81%
Pathogenesis	38% acute injuries, 50% degenerative and 12% unknown
ICRS grade	
3	68%
4	23%
Missing	9%

Compliance

We included 58 patients with isolated FCDs from the two hospitals, whereas additionally 16 were included through the NKLR. Table 2 illustrates the registration of patients with isolated FCDs. At OUS the compliance of isolated FCDs was 60%, whereas it was 73% when we included patients with FCDs in combination with ACL-reconstruction. The corresponding numbers for Ahus was 18% and 22%.

Table 2 illustrates the monthly registration of patients throughout 2010. The column at the right side demonstrates the total number of patients included in the pilot with total number of patients with isolated full-thickness FCDs detected in the operation protocols in parenthesis. OUS=Oslo University Hospital and, Ahus=Akershus University Hospital.

	Jan	**Feb**	**Mar**	**Apr**	**May**	**June**	**July**	**Aug**	**Sept**	**Oct**	**Nov**	**Dec**	**No date**	**Total (by protocol)**
OUS	-	4	9	13	3	9	2	2	7	4	-	1	1	55 (105)
AhUS	-	-	-	-	-	-	-	-	-	2	1	-		3 (17)
Total		4	9	13	3	9	2	2	7	6	1	1	1	58

Cartilage surgery form

Some of the variables of the form demonstrated many missing values (table 3).

Table 3 outlines some of the variables from the cartilage surgery form with a high level of missing values.

Variable	Missing
Previous surgery	50%
Chronic lesion	6.5%
Date of diagnose	42%
Current injury	36%
Current procedure	10%
Table describing lesion	0-9%
Other procedures	56%

Patient-reported outcome measures

The mean Tegner score was 4.5 (SD 3.2). The KOOS values are demonstrated in table 4. We detected gender differences in the symptoms score (p .003 and 95% CI -26.5-(-6.0)) and the sport activity score (p .018 and 95% CI -35.8-(-3.5)) of the KOOS (figure 2). Age correlated with Tegner score (p .002), and Tegner correlated with both the sport activity score (p .027) and the QoL score (p .019) of the KOOS.

Table 4 illustrates the results from the KOOS subscales for the patients with isolated FCDs.

KOOS value in mean (SD)	
Pain	62.9 (19.7)
Symptoms	62.4 (19.0)
Activity of daily living	73.5 (19.0)
Sports and recreation	37.6 (28.1)
Knee-related quality of life	36.3 (22.6)

Figure 2

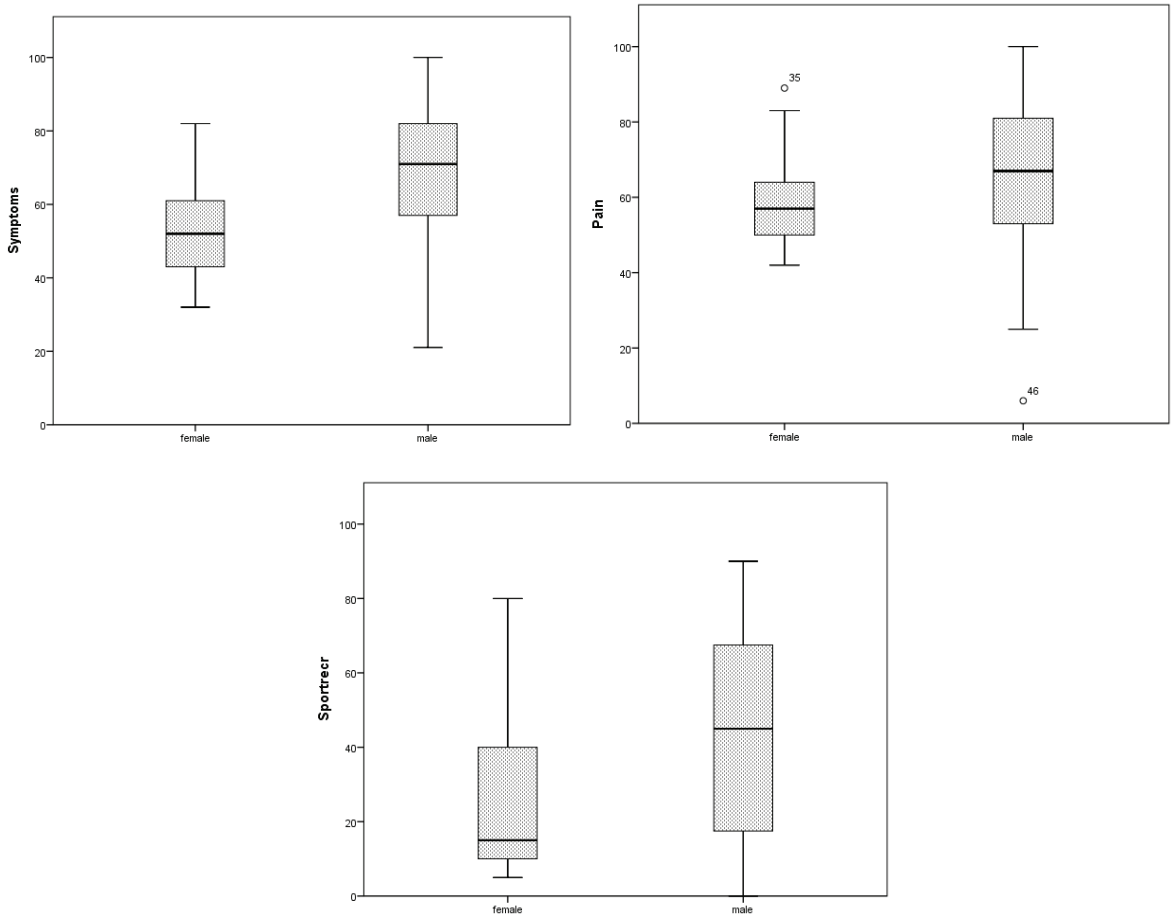

Figure 2 demonstrates box plots of the results from three subscales of the KOOS with gender as a discriminating variable. The box represents the interquartile range, meaning between the 25th and 75th percentile, while the whiskers represents the range of the data excluding extremes and outliers. The line within the box represents the median. Outliers are marked individually.

Discussion

This paper describes a pilot for a nation-wide cartilage surgery register. The results show a low compliance and weaknesses in the cartilage surgery form. Worthen et al. have suggested ways of ensuring larger patient enrolment and longer follow-up.[15] Other larger cartilage surgery registers have been initiated after this pilot. It might be that the similar problems will be noted also in these registers, though little information exists on this currently.

Patient population and clinical results

The data describes a patient population with isolated FCDs where 65% were men and with a mean age of 29.8 years. This is similar to what is found in clinical studies on cartilage surgery.[32,33] The medial femoral condyle was the most common localization of the FCD, which is also in line with existing clinical studies.[34] There was a weak correlation between age and number of FCDs, which we suspect to be a result from increased degenerative lesions with age. The gender distribution of the patients included from the NKLR was similar with 66% men and the mean age was 34.7 years. The size of the lesions are not registered with continuous numbers in the NKLR, but in categories as larger or smaller than 2 cm^2, and 83.3% were larger than 2 cm^2. It is therefore likely that they are comparable to the patients with isolated FCDs, but this is not definite. The localization of the defects included from the NKLR was different as only 33.3% were located on the MFC and 22% were located on the tibial plateau. Nearly 30% had defects on "large parts of the joint", and this might represent more degenerative changes than what is evident from the patients with isolated FCDs.

Compliance

The compliance was variable. One of the hospitals had 73% compliance for the combination of both patient cohorts. The second hospital registered few patients, but they also had a low total incidence of full-thickness FCDs evident from their surgical protocols over the inclusion period.

The NKLR has a reporting system where hospitals are provided with continuous feedback from the register in an effort to achieve high compliance. The completeness of the NKLR was 97% 21 months after establishment.[18] The 2 year results was decreasing, with lower rates for smaller hospitals.[35] Still, the compliance is nearly 100% at some hospitals, whereas it is 10-20% in others.[36] The reason is not clear, although low motivation among orthopedic surgeons is a possible explanation. They are now shifting towards electronic registration, and hopefully this will lead to a rise in compliance. The Danish Knee Ligament Reconstruction-registry had a compliance of 60% in 2005 and 86% in 2011.[37]

The compliance for both the joint prosthesis registry and for the femoral neck fracture registry is high. Generally, high-volume hospitals perform better and the same trend is expected for the registration of patients with FCDs. The yearly report of the NKLR (2010) found 60% patient compliance for the KOOS at the 2 year follow-up, which means that effort must be made also to raise the patient-response-rate.

Cartilage surgery form

We identified several variables with 50% missing values. This may have been due to an unclear way of presenting the variables or a difficult order of the variables. The cartilage surgery form was re-evaluated after the experiences from this pilot study and the new edition is currently being tested in a second pilot.

Cartilage surgery register

The current pilot was run in 2010. There are certain individual cartilage surgery registers initiated by the industry and by individual orthopedic surgeons internationally.[38] Genzyme Tissue Repair initiated an international registry in order to assess the effectiveness of ACI. Industrial registers tend to include more advanced cartilage surgery than what is common trends in general.[39] Data from a more recently established register, the German Cartilage Registry, is now available.[40,41] The ICRS has also recently initiated a cartilage surgery register. Both of the latter registers are established outside of Norway, which restricts our contribution due to restrictions in export of clinical person-identifiable data. Also, none of the existing cartilage surgery registers includes patients undergoing non-operative treatment and less invasive cartilage surgery, such as debridement. There are reasons to believe that patients from the existing registers differ from the general patient population with FCDs of the knee.

Through a register where the inclusion criteria is an FCD, we are able to register only FCDs and exclude patients with knee OA. As opposed to the existing electronic registers that rely on registration from ICD-10 codes, the registration is then more robust against over-registration. Duplicates are easily noticed based on personal data and operation date. The data from a register is easily and quickly accessible. The database contains a much bigger pool of patients with increasing opportunities of detecting poor outcomes, correlations and prognostic factors that are not possible to find in strictly controlled studies.

As a cartilage surgery register will include patients with different levels of cartilage surgery, it is possible to find prognostic factors for all levels of treatment. A register will secure long-term follow-up data on this patient population. It is necessary to ensure that these patients are followed for a longer period, as they are still young and have several potential years with both work and recreation/sports. As for ACI it takes 2 years simply for the new tissue to mature.[42] The register will identify failures earlier than what is possible today.

The efficacy of an intervention or a product is studied in an RCT, but its effectiveness can never be assessed in a controlled clinical study.[43] A register makes it possible to find the effectiveness of specified knee cartilage surgery compared to no surgery (or simple debriding techniques). The patients treated non-operatively will not act as true controls as the indication for surgery is probably biased. Although comparisons can be made, if there is good control of prognostic factors and possible confounders. Prospective cohort studies with high quality may complement research gaps. The limitations of both RCTs and the limitations of retrospective analyses make it important to establish a register. However, it is important to include all patients and all level of treatment to avoid selection bias. Registers can also be used in RCTs as described in the field of clinical effectiveness research. Given such an application, a cartilage surgery register will be particular helpful in questions that otherwise only can be answered through costly and challenging RCTs.

Strength and weaknesses

A weakness of all registries is the internal validity, which will never be as high as a high-quality RCT. However, it is possible to obtain high quality data with a proper design, even in the absence of randomization and blinding. A register is the only method that measures the effectiveness of treatment in the general population. Internal validity is kept high with good control of all other variables.

The challenges concerning suboptimal IT-solutions is another weakness of most quality registries. Data must often be manually written a second time and then transferred to the register. However, electronic solutions are now required for quality registers in Norway. Solutions where the data collection with relevant and predefined data are automatically extracted from the electronic journal system are being developed.

The register is publicly funded. This is important to prevent bias due to commercial interests. It is a strong association between private industrial funding and lower level of evidence where the level of evidence is higher in non-industrial studies.[44] Another challenge is that research becomes more dependent on funding from the industry. In a review by Harris et al.,[45] 26% of the studies reported a financial conflict of interest while 40% failed to report the existence of this. The risk of bias decreases with a non-industrial register.

Future organization

Successful orthopedic registries have been established in several countries for joint replacement surgery (such as Norway, 1987, Sweden, 1975, Finland, 1980, Denmark, 1995, Australia, 1998) and knee ligament surgery (Norway, 2004, Sweden, 2005 and Denmark, 2005). An important issue to discuss is which and how many hospitals to include in the register. Whether the register should be national and include all hospitals, or only hospitals performing advanced cartilage surgery must be addressed. Another solution is to include the largest hospitals within each of the four health regions

in Norway or to develop a Scandinavian register. The NKLR cooperates with the Swedish and Danish registries. A cooperation with the NKLR will also be discussed for a potential future cartilage surgery register in Norway.

Conclusion

We have demonstrated that it is possible to achieve a similar compliance for a cartilage surgery register in one of our participating hospitals, as demonstrated in other successful orthopedic registers. Although, it requires both surgeons participation and an awareness of logistical challenges. We are currently running a second pilot in 5 hospitals in Norway, with the new cartilage form and with a longer registration period, taking into account the lessons learned from this pilot.

Ethics

Inclusion was voluntarily, and the surgeon was not registered. The regional ethics committee for medical research in Norway approved the pilot (ref: 2010/3352).

Competing interests

The authors declare that they have no competing interests.

Funding

The study was supported through grants from the Oslo Sports Trauma Research Centre (OSTRC), where the corresponding author is employed. The South-Eastern Norway Regional Health Authority, the Royal Norwegian Ministry of Education and Research, the Norwegian Olympic Committee & the Confederation of Sport and Norsk Tipping, finances the centre. The Faculty of Medicine, University of Oslo (UiO), also supported the work as Cathrine N. Engen previously was a student at the Medical Student Research Program at UiO and thereby received financial support by the Research Council of Norway. The research project did not receive any specific grant from any funding agency.

Availability of data and materials

The dataset used during the current study is available from the corresponding author on reasonable request.

Authors' contribution

CNE collected, plotted and analysed the data and drafted the manuscript. AÅ and LE conceived the study idea, interpreted the data and revised the manuscript.

Acknowledgements

The authors would like to thank professor Mats Brittberg for his input and advice concerning cartilage repair and design of a register.

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