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PO Box 117
221 00 Lund
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Anterior Cruciate Ligament injury, Patient Variables, Outcomes and Knee Osteoarthritis

Paul Neuman
Leg. Läkare

Akademisk avhandling
som med vederbörligt tillstånd från medicinska fakulteten vid Lunds Universitet för avläggande av doktorsexamen i medicinsk vetenskap kommer att offentligen försvaras i Aulan CRC, ingång 72,
Skånes Universitetssjukhus, Malmö
Torsdagen den 27 maj kl. 13.00

Fakultetsopponent

Professor Kurt Spindler
Professor and Vice-Chairman of the Department of Orthopaedics and Rehabilitation at Vanderbilt University Medical School, Nashville, Tennessee, USA

Huvudhandledare

Professor Leif Dahlberg
Enheten för led- och mjukvävnadsforskning
Institutionen för kliniska vetenskaper, Malmö
Skånes Universitetssjukhus, Malmö
Lunds universitet

Abstract

The ruptured anterior cruciate ligament (ACL) receives great attention in the scientific literature and among the scientific community, yet despite the variety of expert and non-expert opinions on the subject, there is still no consensus on the optional form of treatment. In recent years an increased incidence of this injury has been reported, especially in younger female athletes engaged in sports with a high level of knee pivoting movements and cutting. Unfortunately, the injury leads to immediate symptoms that severely affect the individual, making it difficult or in some cases impossible to carry on with high knee-demanding athletic activities. On top, according to the literature, an ACL injury is a well known high risk factor for the development of knee osteoarthritis (OA) some decades later, adding knee pain and further activity restrictions to the injury burden. Knee OA development after an ACL injury is multi-factorial and the mechanism and pattern of injury in every injured knee is quite unique and multifaceted, which is why all patient variables involved in the process must be further explored before better guidelines on ACL injury treatment can be issued.

I studied patients (n=100) with an acute complete and arthroscopically verified ACL injury over 15 years and evaluated the outcome after a primary non-surgical treatment algorithm based on early neuromuscular knee rehabilitation by a physical therapist specialized in knee injuries and initial activity restrictions to achieve long-lasting good knee function with an acceptable level of activity. In accordance with the treatment algorithm, a delayed ACL reconstruction was only performed in cases of remaining severe subjective knee joint instability with meniscal re-injuries or a meniscal injury suitable for meniscal repair. To the end of the 15-year follow-up, 22 out of 94 (23%) patients had been ACL reconstructed.

The main results are that ACL reconstructed and non-ACL reconstructed patients had less radiographic knee OA at the 15 year follow-up than is usually the case in historical retrospective series of ACL-injured patients, and still had an acceptable activity level with very small subjective symptoms. However, when OA was present, a concomitant meniscal injury treated by means of partial meniscectomy was the most important factor and a very strong risk factor for subsequent OA development.

The prevalence of patellofemoral OA was of the same magnitude as tibiofemoral OA. Patellofemoral OA occurred more frequently in ACL reconstructed (bone-patellar bone-tendon graft) knees, in knees with an extension or flexion deficit, in patients with a higher activity level and in meniscectomized knees.

According to clinical manual laxity testing with the Lachman and the pivot-shift test, knee laxity decreased during the 15 year follow-up, even in non-ACL reconstructed knees. However, knees that developed OA changes after 15 years had higher initial clinical manual laxity testing values at baseline to the 3-year follow-up after the ACL injury.

In order to estimate cartilage GAG content, as a proxy for cartilage integrity, another cohort of ACL-injured patients (n=29) were examined with delayed gadolinium-enhanced MRI of cartilage (dGEMRIC). Results indicated knee cartilage GAG changes, likely as an early sign of increased risk of OA development 2 years after an ACL injury. Patients who had sustained a meniscectomy, or had a BMI > 25 kg/m^2, two known risk factors for OA, had the most impaired cartilage quality.

In conclusion, I found that a concomitant meniscal injury treated with partial meniscectomy was the strongest risk factor for developing knee OA, shown by radiography 15 years after the ACL injury. dGEMRIC results 2 years after the ACL injury supports the contention that this method can detect a cartilage matrix change that may be indicative of increased risk of OA. The treatment algorithm used in studies I-III, with early neuromuscular rehabilitation by a physical therapist specialized in knee injuries seems to be beneficial regarding long-term outcomes after an ACL injury. The data presented in this thesis can help medical staff in decision-making when treating the ACL-injured patient.

Anterior Cruciate Ligament injury, Patient Variables, Outcomes and Knee Osteoarthritis

Paul Neuman
Leg. Läkare

Department of Orthopedics
Skåne University Hospital, Malmö
Department of Clinical Sciences, Malmö
Division of Joint and Soft Tissue Research
Lund University, Sweden

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Abbreviations

ACL	Anterior Cruciate Ligament
ACLR	Anterior Cruciate Ligament Reconstruction
ACR	American College of Rheumatology
ADL	Activity of Daily Living
AM	antero-medial
AOSSM	The American Orthopedic Society for Sports medicine
AP	antero-posterior
BMI	Body Mass Index
BML	Bone Marrow Lesion
BPBT	Bone-Patellar Bone-Tendon
BSP	Bone SialoProtein
CE-MRI	contrast enhanced MRI
COMP	Cartilage Oligomeric Matrix Protein
CTX-II	C-terminal crosslinking telopeptide of type II collagen
CKC	closed kinetic chain
dGEMRIC	delayed Gadolinium-Enhanced MRI of Cartilage
EEG	electroencephalography
EMG	electromyography
ESSKA	European Society of Sports Traumatology, Knee surgery and Arthroscopy
EULAR	European League Against Rheumatism
GAG	Glycosaminoglycan
IGF-1	Insulin Growth Factor 1
IKDC	International Knee Documentation Committee
Il-1	Interleukin-1
JSN	joint space narrowing
KANON	Knee, Anterior cruciate ligament, NON-surgical versus surgical treatment study
KAOS	Knee Arthroscopy Osteoarthritis Scale
KOOS	the Knee Injury and Osteoarthritis Outcome Score
LCL	lateral collateral ligament
MCL	medial collateral ligament
MRI	magnetic resonance imaging
MMP	matrix metalloproteinase
NACLR	non-ACLR
NKO	nationellt kompetenscentrum rörelseorganens sjukdomar
OA	osteoarthritis
OARSI	Osteoarthritis Research Society International
OF	osteophyte
OKC	open kinetic chain
PIIANP	serum N-propeptide of type IIA procollagen
PCL	posterior cruciate ligament

PET	Positron emission tomography
PF	patello-femoral
QOL	quality of life
RCT	randomized controlled trial
ROI	region of interest
ROM	range of motion
SF-36	Short form-36 item health survey
T1	T1 transverse relaxation time
T1Gd	T1 transverse relaxation time in the presence of Gadolinium
T2	T2 transverse relaxation time
TDPM	Threshold to Detection of Passive Motion
TF	tibio-femoral
TGF-β	Transforming Growth Factor- beta
TIMP	tissue inhibitors of metalloproteinase
TNF	tumor necrosis factor
WOAKS	Whole-organ Arthroscopic Knee Score
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

List of studies

This thesis is based on the following studies, which in the text have been referred to by their Roman numerals:

I. Neuman P, Englund M, Kostogiannis I, Friden T, Roos H, Dahlberg LE. Prevalence of tibiofemoral osteoarthritis 15 years after nonoperative treatment of anterior cruciate ligament injury: a prospective cohort study. *Am J Sports Med*. 2008 Sep;36(9):1717-25.

II. Neuman P, Kostogiannis I, Friden T, Roos H, Dahlberg LE, Englund M. Patellofemoral osteoarthritis 15 years after anterior cruciate ligament injury - a prospective cohort study. *Osteoarthritis Cartilage*. 2009 Mar;17(3):284-90. Epub 2008 Sep 3.

III. Neuman P, Kostogiannis I, Friden T, Roos H, Dahlberg LE, Englund M. Knee laxity after anterior cruciate ligament injury: a prospective study over 15 years. Re-submitted after revision to *Scandinavian Journal of Medicine and Science in Sports* May 2010.

IV. Neuman P, Tjörnstrand J, Svensson J, Ragnarsson C, Roos H, Englund M, Tiderius CJ, Dahlberg LE. Longitudinal assessment of knee cartilage quality after anterior cruciate ligament injury using dGEMRIC. Submitted to *Osteoarthritis Cartilage* May 2010.

Review of the literature

Introduction

Anterior cruciate ligament (ACL) injuries are common among athletes and occur primarily in individuals involved in sports with knee pivoting movements such as soccer, floorball, team handball, basketball and alpine skiing. ACL injuries are functionally disabling and their natural history is unclear. They predispose the knee to subsequent injuries and the early onset of OA (Beynnon et al., 2005).

According to the literature, ACL surgery is widespread, especially in patients engaged in high-level sports, while conservative treatment has been considered to have a satisfactory outcome in the general population (Casteleyn et al., 1996). The high number of ACL injuries is a growing problem with serious consequences for the patient and society. Approximately 3500 ACLRs are performed in Sweden annually. It is estimated that 175.000 ACLRs are performed with an estimated cost of $3 billion in the USA every year. (Gottlob et al., 1999) In addition, the personal, health and economic costs of subsequent osteoarthritis (OA) are even higher, with an estimated $8 billion for knee and hip replacements in the USA in 1997 (www.cdc.gov/arthritis). The prevalence of OA is expected to increase in the coming years since risk factors, such as obesity and participation in sports with a high risk of joint trauma, have become more prevalent. The yearly ACL injury incidence is estimated to be as high as 0.8 per 1000 inhabitants aged 10 to 64 years (Frobell et al., 2007), but the true number of ACL injuries might be even higher because all injured individuals do not suffer from major knee symptoms. The ACL injury rate in female athletes ranges from four to six times the rate in male athletes (Hewett et al., 2005). The reasons for a higher injury rate among women remains is still not fully understood but has been attributed to several factors such as; increased rate of valgus knee deformity, smaller notch width, hormonal factors, inferior neuromuscular control and different muscular activation and timing during dynamic activities (hop and landing). An acute ACL injury is seldom isolated (15%), and is usually associated with concomitant injuries to the menisci (60%), cartilage (20%) and collateral ligaments. The use of MRI has revealed traumatic bone marrow lesions (BML), especially in the lateral tibiofemoral compartment,

representing strong compressive forces at the time of the injury in almost every case (Johnson et al., 1998; Speer et al., 1992,; Spindler et al., 1993; Rosen et al., 1991; Frobell et al., 2009). The ACL is the primary passive restraint against forward movement of the tibia relative to the femur (Seitz et al., 1996). A rupture leads to changed knee joint kinematics with compromised stability, often resulting in recurrent injury (giving-way of the knee) and associated intra-articular pathology. Daniel proposed the "the ACL injury cascade" as a theoretical framework for explaining the events that may follow ACL injury (Daniel, 1993). In the short-term, an ACL injury is often associated with lifestyle changes and disability due to knee joint laxity, meniscal injuries and reduced quadriceps muscle strength. In the long-term, there is a high risk of meniscus injury and the development of knee OA. Historically, it has been estimated that OA develops in approximately 50% of patients with ACL tears 10-20 years after the injury, while they are still young or middle-aged adults (Lohmander et al., 2007) Obviously, it is difficult to measure knee OA after an ACL injury because different studies include heterogeneous populations in terms of activity level, combined knee injuries, treatment and rehabilitation explaining why the reported prevalence of knee OA ranges between 10-90%. (Öiestad et al., 2009) However, in the systematic review article on knee OA after anterior cruciate ligament injury by Öiestad et al., it was suggested that the prevalence rates of knee OA after ACL injury reported by previous reviews have been too high. If only the reports from the highest rated studies are used, individuals with isolated ACL injury and combined injuries had a prevalence of knee OA of 0-13% and 21-48% respectively.

The anterior cruciate ligament

The ACL is the primary passive restraint against anterior tibial translation and hyperextension of the knee. As a secondary stabiliser, it restrains the varus and valgus as well as internal and external stresses on the knee (Butler et al., 1980). It acts like a guide rope during knee extension from flexion (roll-and-glide mechanism of the knee). It averages 31-38 mm in length and 8-11 mm in width (Girgis et al., 1975) and is not a single cord but a collection of fascicles that fan out over a broad flattened area, with a wider and stronger tibial than femoral attachment (Furman et al., 1976). These fascicles can be divided in two groups, the anteromedial (AM) and posterolateral (PL) bundle. The AM bundle originates from the proximal/posterior aspect of the medial surface of the lateral femoral

condyle and is inserted into the anteromedial aspect of the tibial attachment, which is located in a fossa in front of and lateral to the anterior tibial spine, where a few fascicles may blend with the anterior horn of the lateral meniscus. The PL bundle is a bit shorter in length and originates even further below the AM bundle at the femoral attachment that is shaped like a segment of a circle so that the posterior convexity is parallel to the posterior articular margin of the lateral femoral condyle. The PL bundle inserts into the posterolateral aspect of the tibial attachment (Furman et al., 1976; Fuss et al., 1989). The AM bundle becomes tauter in flexion and the PL bundle becomes tauter in extension (Zantop et al., 2006). The anatomic ACL is anisometric, since the isometric point (constant ligament length throughout the range of motion) is found to lie anterior and superior to the femoral origin, towards the intercondylar roof (Odensten et al., 1985).

The cruciate ligaments are covered by a fold of the synovial membrane. The synovial layer is supplied by vessels from the middle geniculate artery and to a lesser extent by vessels from the lateral inferior geniculate artery. The nerve supply is from branches of the tibial nerve that penetrates the joint capsule posteriorly to run along the synovial covering. Mechanoreceptors are located in the ACL substance (Ruffini type and Pacinian corpuscles) and form the afferent limb of a reflex influencing quadriceps function (Butler et al., 1980). The ACL is inserted to the bone via a fibrocartilaginous enthesis. Ligament collagen fibres intermesh with a fibrocartilage region where progressive mineralisation occurs that eventually merges with the bone (Cooper et al., 1970). The ultimate tensile strength of this complex has been reported to range from 1725 to 2195 N (Noyes et al., 1984). The ACL is exposed to high forces during daily function, with a force of 823 N when descending a 19% decline (Kuster et al., 1994). The highest strain values measured in vivo occur with isometric contraction of the quadriceps with 15º of knee flexion (Beynnon et al., 1995). With increasing age, the tensile properties of the ACL decrease as a result of an increase in small over large collagen fibrils (Woo et al., 1991). Knee immobilisation in a cast for 8 weeks in primates decreases the load to failure by 39% of the ACL-bone ligament complex (Noyes et al., 1977).

Risk factors for ACL injury

Due to the fact that female athletes are 4-6 times more likely to sustain an ACL injury than their male counterparts when participating in the same sports, most studies evaluating risk factors focus on females (Hewett et al., 2005 and 2006). Approximately 70% of all ACL injuries are non-contact injuries (Griffin et al., 2000). Risk factors for an ACL non-contact injury can be divided into environmental, anatomic, hormonal and biomechanical.

Environmental

Environmental or extrinsic factors refer to how the friction between shoes and the playing surface has implications for the risk of sustaining an ACL injury. For female team handball players it was demonstrated that the risk of ACL injury is higher on artificial than wooden floors (Strand et al., 1990; Olsen et al., 2003). Moreover, in the National Football League the ACL injury rate for artificial grass surfaces is higher than for natural grass (Powell et al., 1992). It has also been found that artificial surfaces yield higher peak torque and rotational stiffness than natural grass surfaces. With the exception of the cleat pattern (Lambson et al., 1996), the construct of the shoe's upper is a shoe design factor that may influence a shoe's rotational stiffness and the risk of ACL injury (Villwock et al., 2009). Cold weather and rain are associated with lower knee and ankle injury risk in outdoor stadiums (both natural grass and artificial surfaces), probably because of reduced shoe-surface traction. (Orchard et al., 2003).

Anatomic

The dimensions of the intercondylar notch have been extensively studied in relation to ACL injuries. Due to the different methods employed to obtain data on notch width, results are difficult to interpret. It has been demonstrated that the notch width measurement of bilateral knees with ACL injury is smaller than that of unilateral knees with ACL injury, and notch widths of bilateral and unilateral knees with injury to the ACL are smaller than those of normal controls. This implies a strong association between notch width and ACL injury (Griffin et al., 2006). Another factor that might be relevant for the risk of sustaining an ACL injury or the extent of giving-way related knee symptoms after an injury is the posterior slope of the tibial plateau (Giffin et al., 2004; Griffin et al., 2006). MRI has revealed that subjects with ACL-deficient knees had a significantly greater slope of the lateral tibial plateau and a lower slope of the medial tibial

plateau than a control group, which hypothetically could make them especially vulnerable to knee-pivoting movements and giving-way of the knee (Stijak et al., 2008). A generally increased joint laxity has also been demonstrated as a risk factor for non-contact ACL injury in both female and male military cadets followed prospectively over 4 years (Uhorchak et al., 2003). Women also have greater tibiofemoral joint laxity, lower joint resistance to translation and rotation in addition to decreased muscular stiffness and higher genu recurvatum (Renström et al., 2008). Prospectively followed female soccer and basketball players with knee hyperextension and/or increased sagittal knee laxity had an increased risk of ACL injury (Myer et al., 2008). Moreover, it has also been found that females exhibit higher generalized joint laxity after the onset of puberty while males do not (Quatman et al., 2008).

Hormonal

Many studies have investigated whether hormonal factors contribute to the risk of ACL injury. Hormonal differences between men and women could to some extent explain the discrepancy in injury rates. The risk of an ACL injury seems to be higher in the preovulatory than the postovulatory phase of the menstrual cycle (Wojtys et al., 1998; Zazulak et al., 2006; Beynnon et al., 2006). Results from measurement of estrogen, progesterone and luteinizing hormone metabolites levels at the time of the anterior cruciate ligament tear have indicated that women had a significantly greater than expected percentage of anterior cruciate ligament injuries during midcycle (ovulatory phase) and a less than expected percentage during the luteal phase of the menstrual cycle (Wojtys et al., 2002). Moreover, sex hormone receptors have been demonstrated in the human ACL (Faryniarz et al., 2006). To date, it is clear that the sex hormones (oestrogen, testosterone and relaxin) have a significant role in the normal biology and physiology of collagen. While the specific causes/mechanisms of these sex differences are not well understood, hormonal involvement is implicated. The menstrual cycle with its monthly hormonal fluctuations is one of the most basic differences between men and women, which is why hormonal factors might also explain some of the divergence: Women have smaller ACLs (even after adjustment for body size), lower energy absorption and load at failure compared with men.

Biomechanical

ACL injuries often occur when landing from a jump, cutting or decelerating. A combination of anterior tibial translation and lower extremity valgus are probably important components of the injury mechanism in these athletes. By using 3-D video analysis it has been demonstrated that most non-contact ACL injuries occurred when the frontal knee valgus angle increased abruptly from 3 to 16° during 30-40 ms (Krosshaug et al., 2007). In terms of biomechanical gender differences, young women have higher knee abduction moment during impact on landing (Withrow et al., 2006; Hewett et al., 2005), lower knee flexion angles on landing (Malinzak et al., 2001; Hewett and Ford et al., 2005) and lower hamstrings/quadriceps-ratios (Myer et al., 2009). All these factors increase the risk of an eccentric quadriceps contraction with the knee near extension, thus adding a sudden forward displacement of the valgus-displaced tibiae and producing an ACL injury.

ACL historical review

The existence of the anterior cruciate ligament has been known since 3000 B.C. in ancient Egypt. Hippocrates (460-370 B.C.) was aware of the subluxation of the knee joint with ligament pathology. Claudius Galen (129-199 A.D.), a Greek physician in the Roman Empire, provided the first detailed description of the anterior cruciate ligament when depicting the supporting ligaments of the knee. In Germany, the Weber brothers (1836) noted an abnormally increased antero-posterior movement of the tibiae after transaction of the ACL. They also described the roll-and-glide mechanism of the knee, and explained the various tension patterns for different bundles of the ACL. Amadée Bonnet of Lyon, France, published the first cadaveric studies on the mechanism of knee ligament injuries in 1845. He recorded that the ACL most often ruptured at its femoral insertion with a cracking sound and a resulting hemarthrosis. He realized the risk of immobilization causing “absorption of the cartilage” and recommended mobilization as quickly as possible with the knee in an orthosis with 2 hinges. He was also the first to describe the subluxation phenomenon. Georgeos C. Noulis of Greece was the first to describe how to perform the Lachman test to detect an ACL injury and the antero-posterior drawer test with the knee in 70 degrees of flexion to determine the presence of a posterior cruciate ligament (PCL) injury. Paul Segond, a French surgeon and gynaecologist, outlined the symptoms and signs that accompany the rupture of cruciate ligaments.

He also described the so-called “Segond fracture”, a tiny pathognomonic fracture fragment above and behind Gerdy`s tubercle, sometimes visible on radiographs of knees with an ACL rupture

Historical review of ACL treatment

Non operative approach

Despite the fact that non-operative ACL treatment or no treatment at all were more common in the past, the natural history of ACL injuries remains unclear. The natural history of the ruptured ACL has been studied by several authors, but the results and conclusions vary extensively. ACL studies involve a complex interplay of many variables such as age; associated knee injuries; activity levels; rehabilitation; treatment; scoring systems etc. This makes it impossible to conduct a perfect ACL study where all questions can be answered. “The critical study still remains to be done”, as Ivar Palmer wrote in 1938. One of the first descriptions dates from 1850, when Stark described how he treated 2 cases of ACL tears with a cast and reported apparent recovery. Some present authors have described the course of non-operated ACL injuries as one of progressive and inevitable collapse of knee function and structure due to the development of sagital and rotatory knee instability, meniscal tears and post-traumatic OA (Gillquist et al., 1999; Louboutin et al., 2009; Satku et al., 1986; Walla et al., 1985; Bray et al.; 1989; Hawkin et al., 1986; Daniel et al., 1993) In most of these studies the non-operative treatment was not defined or was mixed. Even in the very few randomized ACL studies comparing ACLR and non-operative treatment, the latter was poorly defined (Sandberg et al., 1987; Andersson et al., 1991, 2001; Meunier et al., 2007). Other authors have reported more hopeful non-operative treatment results, including patients who were able to resume strenuous sports. All of the above studies stress the importance of an intensive rehabilitation programme for strengthening the quadriceps and hamstring musculature to enable the patient to regain functional stability (Giove et al., 1983, Buss et al., 1995; Casteleyn et al., 1996; Myklebust et al., 2003; Kostogiannis et al., 2007). In addition, the role of proprioception in adjusting the neuromuscular function in the management and rehabilitation of an ACL injury has been stressed both after ACLR (Risberg et al., 2001, 2009) and in non-operative treatment (Zätterström et al., 2000; Roberts et al., 1999; Fridén et al., 2001; Ageberg et al., 2008).

Surgical ACL treatment

Direct repair of ACL

In 1895 Mayo Robson from Leeds, England, performed the first known repair of the ACL and PCL in a miner. Robson sutured the cruciate ligaments to their normal femoral attachment sites with an excellent outcome after 6 years and described the operation in 1903. In Sweden, Ivar Palmer described ACL anatomy, biomechanics and surgical techniques but not results in his thesis *On the Injuries to the Ligaments of the Knee Joint* (Palmer, 1938). In his review of ACL injuries, he stated that ACL tears need to be diagnosed at an early stage and must be surgically repaired. He first developed a femoral drill guide and was also the first to separately repair both ACL bundles. For many years the orthopaedic society did not give his work the attention it deserved, until Girgis (1975) and Arnoczky (1982) once again described the anatomy of the AM and the PL bundles of the normal ACL. O´Donoghue was the first to report a follow-up of acute ACL ruptures in 25 patients treated by means of surgical repair within 2 weeks, where all 25 were functionally stable. In the case of chronic ACL injuries he suggested reconstruction (O´Donoghue, 1963). As far back as 1916, Jones declared that "stiching the ligaments is absolutely futile", which was confirmed 60 years later by Feagin and Curl when they presented a 5-year follow-up of West Point cadets who had ACL repairs using a figure of eight suture in the ACL that was passed through drill holes in the lateral femoral condyle. 94% had instability and 71% pain and stiffness (Feagin and Curl, 1976). In a randomized study in 1990, Engebretsen et al. demonstrated that primary ACL suturing is no more effective than non-operative treatment (Engebretsen et al., 1990).

Fascia lata graft

Numerous surgical techniques using *autologous grafts* instead of or as an adjuvant to primary suturing have been presented over the last 100 years. In 1913 Hesse reconstructed both ruptured cruciate ligaments with free grafts of fascia lata through tunnels in the femur. In 1917 Hey-Groves from Bristol, Great Britain, published his first case of ACLR with a tethered fascia lata graft. From Hey-Groves' detailed description of his technique it is clear that he was striving for an anatomic reconstruction. He drilled the femoral tunnel from inside-out as far back as possible on the lateral intercondylar notch similar to as today. He also described a technique for PCL reconstruction using semitendinosus and gracilis tendons.

Autogenous hamstring graft
In 1934, Riccardo Galeazzi from Italy described a surgical technique for ACLR using the semitendinosus tendon, which was placed intra-articulary through drilled bone tunnels in the tibiae and femur using 3 skin incisions. Five years later, Macey also reported on ACLR with semitendinosus tendon through tibial and femoral holes into an anatomic position. In 1982, Mott published his surgical technique with double-bundle ACLR using a semitendinosus tendon through 2 tunnels in both femur and tibia via an arthrotomy. Peterson from Sweden presented his double-bundle ACLR technique and results in 1983.

Autogenous patellar tendon graft
In 1932, the German surgeon zur Verth reported on using a strip of the patellar tendon left distally attached with the proximal end of the graft attached to the PCL, for chronic ACL-deficient knees. In 1963, Jones from USA, described a surgical technique using the central strip of the patellar ligament with an attached bone block from the patella. Despite the fact that he presented astonishing results with an average follow-up of over 2 years and "all knees were completely stable", it is extremely doubtful that it really worked, as the graft was still attached to its tibial insertion and placed in an over-the-top position at the tibiae and was therefore too short to be located in an anatomic position on the femur. The German surgeon Bruckner described his method in 1966, where he took a medial strip of the patellar tendon, distally attached, and pulled it through a tibial tunnel. He used a blind inside-out tunnel on the femur for the first time. In 1976, Franke from Berlin, described his technique and the results of 130 ACLRs using the central third of the patellar tendon, with, for the first time, attached bone blocks on both sides (bone-patellar tendon-bone=BPBT) as a free graft (Franke, 1985).

Autogenous quadriceps tendon graft
Blauth first described the 2-strip substitution of the ACL with the quadriceps tendon in 1984.

Autogenous augmentation
Odensten et al. outlined a procedure and results 5 years after primary suture of fresh ACL ruptures augmented with a strip of fascia lata intra-articulary through drill holes in the tibiae and the lateral femoral condyle (Odensten et al., 1984). In a randomized study Andersson et al. revealed that ACL reconstructed subjects who had a primary ACL repair in combination with

augmentation resumed competitive sports significantly more often than subjects who had not undergone ACL surgery or only had a primary ACL repair (Andersson et al., 1991).

Extra-articular reconstructions
Several extra-articular procedures have been proposed but none of them have satisfactorily restored the stability of the knee and the results were poor with joint stiffness. In 1978, Losee proposed that a distally based strip of the iliotibial tract pulled through a drill hole in the lateral femoral condyle beneath the lateral collateral ligament and then sutured to Gerdy´s tubercle, could correct the anterolateral rotatory instability. However, at a consensual conference of the American Society of Sports Medicine in 1989 it was concluded that extra-articular procedures for ACL deficiency did not add to the benefit of intra-articular reconstructions of the ACL.

Allografts
During the 1980s a growing interest developed in the use of allografts for ACLR. There are several options available including; bone-patellar tendon-bone (BPBT), tibialis anterior, tibialis posterior, Achilles tendon, toe-flexor tendons and semitendinosus. Shino published results of ACLR by means of an allograft in 1986 (Shino, 1986). Further studies have shown that results of allografts are comparable to autografts, with no differences in functional outcome or knee laxity but perhaps a slightly higher number of failure rates (Foster et al., 2010). The main advantages are the absence of donor site morbidity and the ability to perform minimally invasive surgery. The greatest concern is the potential for disease transmission. Irradiation remains the least damaging method of sterilising the graft but graft strength is reduced by 20% after 3 Mrad Gamma irridation.

Artificial grafts
A great number of different prosthetic ACL replacements have been tried but all have failed. Silk sutures were proposed and used as prosthetic ligaments and in unstable knee joints by Fritz in 1903. In 1927, Ludloff used a broad strip of fascia lata wrapped around a thick silk suture. This construct was similar to the ligament augmentation device (LAD) proposed by Kennedy in 1980. The idea was to reduce the load on autografts and allografts in order to prevent early graft failure. In the 1970s and early 1980s several synthetic ligaments were introduced including the carbon fiber. In 1978, Jenkins began to use carbon fibers to reconstruct the ACL

and the intention was to stimulate ingrowth of fibroblastic tissue that would subsequently produce new collagen but the clinical results were poor.

Instruments and fixation devices
Arthroscopy is one of the most important advances in orthopedics and closely connected to the history of ACL surgery. Kenji Takagi was the first to view the inside of a knee via a cytoscope in 1918. Eugene Bircher became the first physician to perform a diagnostic arthroscopy of the knee on a live patient in 1921. Michael Burman viewed and described anatomy by means of arthroscopy during the 1930s. Masaki Watanabe, Japan, turned arthroscopy into a surgical instrument and performed his first arthroscopic surgery of the knee in 1962. The first arthroscopically assisted ACLR was performed in 1980 by Dave Dandy from Cambridge, England. Until 1970, fixation of the proximal graft end involved suturing to the periosteum of the femur. In 1970, Jones modified his original technique using the central third of the patellar tendon. The bone block was pushed into the femoral socketlike drill hole and fixed percutaneously with a cross-pin. The still popular interference screw fixation for BPBT graft was described by Lambert in 1983. The screw design was later improved with larger, specially designed screws. In 1994 Tom Rosenberg, Salt Lake City, USA, introduced the Endobutton fixation device for soft tissue grafts, which remains one of the most popular fixation devices in ACLR. Since then there has been tremendous industrial development in different fixation devices for hamstring and other soft tissue grafts.

Rehabilitation after surgery

The earliest rehabilitation programs included immobilization of the knee in a cast after ACL surgery, based on the principle of protecting the graft while healing occurred. Complications were muscle atrophy and arthrofibrosis (Sachs et al., 1989). It is interesting to note that in 1845 Bonnet realized the risks of immobilization and recommended mobilization as quickly as possible. As understanding of the biomechanics of the knee was re-born, prolonged cast immobilization was changed to limited immobilization in a range of motion brace. In 1917, Ernest Hey-Groves, Great Britain, used a knee-splint in full extension for 6 weeks after ACLR followed by a molded cast provided with lateral hinges at the knee. It was not until 1972 that Paessler demonstrated on cadaveric knees that the knee can be moved after ACL surgery without risk of graft failure. Paessler started to use a postoperative brace with hinges allowing a functional range of motion from 20 to 60 degrees after reconstruction of ACL. A decade

later the concept of early postoperative mobilization gradually replaced the use of cast immobilization for 6-12 weeks. It has since been concluded that postoperative knee bracing does not appear to have an effect on clinical outcome (McDevitt et al., 1975; Risberg et al., 1999). Shelbourne gave birth to the term "accelerated rehabilitation" (Shelbourne et al., 1990). He noted that, in patients operated with a BPBT graft, those who did not comply with his traditional rehabilitation and progressed as fast as they desired, returned to normal function without knee instability sooner than his compliant group. Consequently he developed the accelerated rehabilitation program with immediate weightbearing in accordance with the patient's tolerance. Rehabilitation consisted of a guided exercise and strengthening program, which was tailored to the individual patient's knee status during rehabilitation. The progression was based on absence of knee effusion, lack of pain and neuromuscular control (proprioception) rather than on a given time-table. Exercises involved the closed kinetic chain (CKC) of the knee joint with compressive axial loading by the body weight to maintain joint congruency. Closed kinetic exercises result in less shear forces across the joint than open kinetic chain (OKC) exercises (performed with the limb extremity free), and thus graft stresses are less and the joint can be loaded in a more functional way with greater loads. Shelbourne found that the accelerated program was effective in reducing common problems associated with ACLR using bone-patellar tendon-bone grafts such as extension deficit, anterior knee pain and loss of strength while maintaining stability. He presented his results from a series of 806 out of 1057 consecutive patients who had undergone an ACL reconstruction with an autologous BPBT graft 4 years earlier. The patients exhibited a full range of motion, excellent stability, good strength and in most cases a return of full function. (Shelbourne et al., 1997). However, the ideal rehabilitation of hamstring graft ACLR remains unclear.

Summary of historical review of ACL treatment

In summary, a vast number of approaches have been adopted over time for dealing with ACL knee injuries. Over the last 100 years, numerous different surgical techniques have been tried to stabilize the knee and relieve symptoms after an ACL injury. Currently, ACLR has evolved as the mainstay when surgical correction is planned. Today, graft options comprise autogenous hamstrings graft, autogenous BPBT graft, autogenous quadriceps graft or allograft.

Nowdays, there is still a great focus on different surgical techniques, with short-term performance and knee laxity measurement parameters. It was

not until the the mid-1980s that the outcome of OA in long-term follow-ups was presented. Characteristic of all these reports describing OA after non-operative ACL treatment is the inclusion bias of the study subjects. In the study by Noyes et al. (Noyes et al., 1983), only symptomatic patients were included retrospectively. McDaniel and Dameron (McDaniel et al., 1980, 1983) included subjects of whom most had had meniscectomies and all were operated on by means of arthrotomy. Since then, some authors have concluded that because the results presented after non-operative treatment are so inferior, the outcome would be better if the knee joint were stabilized operatively. However, so far there are no studies that prove that surgical treatment of ACL injury can minimise the future development of knee OA (Lohmander et al., 2007). On the basis of the studies in a recent systematic review by Öiestad et al. (Öiestad et al., 2009), one could conclude that meniscal injuries and meniscectomy are well documented risk factors for the development of knee OA after ACL injury. Additional possible risk factors such as ACLR, age, obesity, knee joint laxity, loss of knee motion, decreased muscle strength and inferior neuromuscular function need further documentation.

Osteoarthritis (OA)

OA is said to be the world's oldest known disease, with typical bony joint changes present in 50 to 70 million year old dinosaur skeletons (Wells, 1973). OA is a common finding in Egyptian Mummies (Braunstein et al., 1988). In ancient skeletons in England OA changes were more common in the shoulders and spine, while the knee joints were less frequently affected (Rogers et al., 1981), most likely reflecting differences in life style and less obesity.

Despite its widespread occurrence, clinicians did not start to recognise OA until the 18th century. Ever since Hippocrates (460-375 BC), all forms of chronic arthritis were regarded as manifestations of gout. Confusion with the nomenclature delayed recognition of the disease. William Heberden discriminated among chronic arthritis when he described the "digitorum nodi", in 1782. Virchow (1821-1902) named rheumatoid arthritis together with OA as arthritis deformans. Other synonyms that frequently occurred were malum coxae senilis for hip OA and osteoarthrosis that has been successively replaced by osteoarthritis (OA). John Kent Spender of Bath, England, first introduced the term osteo-arthritis (Spender, 1889). The introduction of radiography by Wilhelm Konrad Röntgen in 1895 led to the

recognition of two main forms of chronic arthritis: an atrophic form, which was often polyarticular and a hypertrophic form occurring in fewer joints. Atrophic and hypertrophic arthritis were then renamed as rheumatoid disease and OA, respectively. Hypertrophic arthritis refers to the extensive new synthesis of bone and capsular thickening seen in OA. Kellgren and Moore linked the Heberden nodule to OA and named it primary generalised OA in contrast to secondary OA of single traumatised joints. In the 1950s and 60s Kellgren and Lawrence's radiographic scoring system made it possible to provide the descriptive epidemiology of the disease. OARSI (Osteoarthritis Research Society International) produced a Radiographic Atlas for OA of the Hand, Hip, and Knee as a supplement to Osteoarthritis and Cartilage in 1995 (Altman et al., 1995).

Figure 1. Medial TF OA.

What is OA?

According to the World Health Organization, OA is among the top 10 conditions representing the global disease burden, (Lopez, 2006). In OA, the knee is one of the most frequently affected joints (Zhang, 2008). About 25% of adults aged over 55 years have significant knee pain and half of these have OA radiographic changes (Hill, 2003). OA is the most common arthropathy to affect the knee (Hernandez-Molina, 2008). Clinical features include knee pain, morning stiffness, impaired function, crepitus, restricted motion and bony enlargement (EULAR evidence based recommendations for the diagnosis of knee OA, 2009). For standardised research purposes, the classification criteria developed by the American College of Rheumatology (ACR) in 1986 are often used.

Traditionally, OA has been described as wear and tear of the articular hyaline cartilage. The first systematic histological reflection on the wearing away of joint cartilage was by A Ecker of Heidelberg in 1843. The term OA was in use in English speaking countries since the beginning of the 20th century, while the term degenerative joint disease came into use later on, largely due to the work of Walter Bauer and co-workers at Harvard University in 1942, from which two important conclusions were drawn: 1) OA has its origin in degeneration of the articular cartilage; and 2) the degeneration is an inherent senescence of the articular cartilage and not necessarily confined to that in the joints. More recently, there has been a shift in thinking of OA as a purely degenerative passive disorder, for which there is little hope of treatment, to the realisation that it is driven by an active disease process, which can be modulated by both biomechanical and biochemical (drugs) interventions. It has become clear that the disorder affects the whole joint, involving the synovium, capsule, ligaments and subchondral bone as well as the cartilage. It is characterised by an imbalance between biosynthesis and degradation of cartilage components so that the degradative process outpaces repair (Ishiguro et al., 1999; Dahlberg et al., 2000). In fact, much of the clinical, radiographic and histological signs of OA are due to attempted repair of the damaged joint. Early features of OA include glucosaminoglycan loss and destruction of the collagen network, which result in cartilage swelling (Maroudas, 1977; Heinegard, 1998). As the disease progresses, the tensile properties of the tissue decrease, with eventual cartilage macroscopic disruption with fibrillation and clefts. The histological progress of OA is catagorized according to the Mankin score (van der Sluijs, 1992).

OA and ACL

It has become clearer that OA affects the whole joint and recently MRI of knees with symptomatic OA has suggested a role for enthesopathy, since central bone marrow lesions (BMLs) frequently abut the ACL and are strongly related to ACL pathology (Hernández-Molina et al., 2008). Hill et al. claimed that ACL injury is underrecognized in middle-aged and elderly people with symptomatic knee OA, as MRI revealed that almost one quarter of them had a complete ACL rupture, of whom only half could recall a significant knee injury (Hill et al., 2005). Lee et al. investigated OA knees at the time of knee joint replacement and found deficient integrity of the ACL in 39% of the knees. The ACL deficient knees also had narrower intercondylar notch widths compared with knees with an intact ACL (Lee et al., 2005). Wada et al. demonstrated that the intercondylar notch width was smaller and that the sagittal depth of the femoral condyle was wider in knees with visible ACL pathology at the time of total knee arthroplasty (Wada et al., 1999). Thus, intercondylar notch narrowing as a result of the osteoarthritic process may lead to attrition and injury of the ACL, while the increased antero-posterior size of the femoral condyle may widen the contact area and increase stability.

Causes of OA, risk factors

When OA develops in knee joints with pre-existing disease, structural deformities or after injuries, it is termed secondary OA. The disease is classified as primary OA when there is no known causal disease or trauma to the joint. In a sense, all OA is secondary. In each individual case, the exact etiology of OA may be unknown. However, there are a number of risk factors for knee OA, as listed below:

Aging

Aging per se cannot be considered the cause of the disease, but with advancing age the time of exposure to all other risk factors is increased, and accordingly the risk of developing OA is greater. However, with age the hyaline cartilage does become more susceptible to failure as a result of biochemical changes in proteoglycans and collagen in the matrix (Elliot and Gardner, 1979; Mankin and Thrasher, 1975). The capacity of the chondrocytes to produce proteoglycans is diminished (Gray et al. 1988). The ratio of chondroitin 6-sulphate to chondroitin 4-sulphate rises progressively with age (Roughley and White, 1980). In contrast, in OA there is a higher content of chondroitin 4-sulphate to chondroitin 6-sulphate than in normal cartilage (Brandt, 1976). The joints in the elderly become

increasingly congruent with respect to their shape, which may interfere with cartilage nutrition as a result of altered load distribution (Freeman et al., 1975). The osteochondral ends of bone probably remodel (increased joint congruency) due to vascular invasion and endochondral ossification of the calcified cartilage (Lane et. al., 1977). Aging is also characterised by altered stereognostic control of opposing muscle groups due to muscle weakness and micro-incoordination of neuromuscular control, referred to as microklutziness (Radin et al., 1991).

Sex
Females are more prone to develop Heberden´s nodes. Women also have a higher prevalence of knee OA, and the sex difference increases exponentially over the age of 50, indicating that post-menopausal hormone deficiency plays a role (Felson et al., 1988). Under the age of 50, men have a higher prevalence of knee OA as a result of a greater incidence of traumatic knee injuries. OA of the spine and hip is more frequent in men.

Obesity
There is a strong association between obesity and knee OA, especially in females (Felson et al., 1988). Niu et al. (Niu et al., 2009) observed the relationship between obesity and the progression of knee OA, and found that progression increased in knees with neutral or valgus alignement, but not in knees with varus alignement.

Bone density
There is an inverse relationship between OA and osteoporosis, because increased bone density predisposes to OA whereas osteoporosis is protective, especially in the hip joint (Stewart et al., 1999). Since the hyaline articular cartilage is too thin to be an efficient shock absorber by itself, the joint is reliant on the subchondral cancellous bone also acting as a shock attenuator (Radin, 1976).

Genetic factors
Heredity has been examined in twin studies and been found to account for approximately 30 % of knee OA in women (Kirk, 2002). A large number of genetically transmitted disorders such as multiple epiphyseal dysplasia; congenital dislocation of the hip; Down´s syndrome; Ehlers-Danlos syndrome and Marfan's syndrome are recognized causes of OA.

Race
OA is widespread in all races (Solomon et al. 1975). However, there are differences in disease location and frequencies in various joints (Anderson and Felson, 1988). Hip OA is less frequent in the Chinese (Hoaglund et al., 1973), and Heberden´s nodes are less common in Africans (Solomon et al., 1975). Lateral gonartrosis is more than twice as common whereas medial OA is less prevalent in Chinese compared to Caucasian subjects (Felson et al., 2002).

Hormonal and metabolic factors
The evidence for a role of oestrogen in OA is conflicting, despite the fact that epidemiological studies constantly suggest a lower prevalence of OA in women taking oestrogen replacement therapy compared to those who do not, which may suggest a role for oestrogen in the disease (Felson and Nevitt, 1998). Elevated serum growth hormone concentrations have been reported in post-menopausal women (Dequeker et al., 1975) and in patients with OA (Dequeker et al., 1982), but their role in the pathogenesis remains to be determined. Excess growth hormone in acromegaly causes a thicker and more fragile hyaline cartilage and marginal bone thickening of the joints (Bagge et al., 1993).
Disturbance in insulin-like growth hormone levels has also been detected in OA patients compared to controls (Denko et al., 1994).

Mineral deposition
Both chondrocalcinosis (calcium pyrophosphate dehydrate deposition disease) and OA are common in the elderly. In some patients chondrocalcinosis precedes the development of OA, while in others OA appears first. Pyrophosphate is produced in large amounts by chondrocytes (Altman et al. 1973). A precipitation of calcium salts in cartilage occurs if the rate of production is increased and if there is a reduction in pyrophosphatase enzyme, as in both chondrocalcinosis and OA (Silcox and McCarty, 1974).

Trauma
Trauma to the knee joint frequently leads to OA. Major trauma that leaves the joint incongruent is a well known cause of OA. Several studies have indicated that knee distortion with injury to the ACL is associated with an increased risk of developing OA (McDaniel et al., 1983; Noyes et al., 1983; Kannus et al., 1987; Neyret et al., 1993; Roos et al., 1995; Gillquist et al., 1999; Myklebust et al., 2003). It is also apparent that an isolated meniscal

injury frequently leads to knee OA (Fairbank, 1948; Neyret et al., 1994; Roos et al., 1998; Cicuttini et al., 2002; Englund et al., 2003). Moreover, acute ACL injuries are accompanied by meniscal tears in more than 50% of cases with a slightly higher incidence of lateral compared to medial tears (Fithian et al., 2002). The prevalence of knee OA in retrospective follow-ups after ACL injury is additionally obscured by the fact that in chronic ACL injured patients who have sufficient symptoms to warrant arthroscopy, 80% have meniscal tears, where a medial tear is more common than a lateral (Fithian et al., 2002). Direct impact to the cartilage in accidents such as knee contusion against car dashboards has shown that cartilage matrix and chondrocytes are susceptible to damage by this mechanism (Chrisman et al., 1981). Repetitive trauma may lead to subchondral bone stiffening resulting in secondary injuries and damage to the hyaline cartilage (Radin, 1976). OA has also been reported in large numbers of patients with joint laxity and recurrent patella dislocation (Scott et al., 1979; Maenpaa et al., 1997).

Occupation

Knee OA has been found to occur more often in patients who have performed heavy work (Andersson and Felson, 1988; Lindberg and Montgomery, 1987; Vingard et al., 1991). Increased prevalence of knee OA was seen among former elite soccer players compared to controls, even in the absence of previous knee injuries (Roos and Lindberg, 1994). According to another study, the development of knee OA in former top-level athletes seemed to be explained by knee injuries in soccer players and by high body mass in weight lifters. Interestingly, long-distance runners had a significantly lower prevalence of knee OA than soccer players and weight lifters (Kujala et al., 1995). There appears to be an increased risk of lower limb OA in repetitive, high impact sports, and this is strongly linked to joint injury, while recreational running seems to be associated with little risk (Conaghan et al., 2002).

Diagnostic tools

Clinical assessment

ACL

Careful history taking and examination will in most cases allow a diagnosis of an ACL injury. In 40% of ACL injuries there is a history of a non-contact injury mechanism associated with a "pop" at the time of the injury. Commonly the injury mechanism is a valgus combined internal or external rotation or a hyperextension. The subject is often unable to continue activity and swelling with hemarthrosis of the knee develops within 2 hours (Noyes, 1980). Awareness and assessment of associated injuries is required, as an isolated ACL tear rarely occurs. During the physical examination the Lachman test and the pivot-shift test are useful in the evaluation of an ACL tear. The Lachman test, clinically introduced by Torg, is performed with the knee in 20º of flexion and the amount of anterior move of the tibiae under the femur is graded and the quality of the end-point noted (Torg, 1976). The pivot-shift test assesses the subluxation of the lateral tibial condyle on the distal femur and was clinically introduced by Mackintosh. It is performed with the knee held in extension and internal rotation with a valgus force applied, which causes the tibiae to be subluxed anteriorly if the ACL is injured. From this subluxed position the knee is then flexed and as it approaches 10-20º of flexion the tibiae suddenly reduces with a clunk (Galway et al., 1980). In a meta-analysis the pooled sensitivity and specificity of the Lachman test for an ACL tear was 85% and 94%, respectively. For the pivot-shift there was a high specificity of 98% but sensitivity was only 24% (Benjaminse, 2006).

OA

According to 17 OA experts from 12 European countries representing the European League Against Rheumatism (EULAR), a confident diagnosis of knee OA can be made on the basis of three clinical symptoms and three signs on examination (Zhang et al., 2009). Radiography is the current "gold" standard for monitoring structural tissue changes, although a diagnosis of knee OA can be made without imaging. The recommendations for knee OA diagnosis were developed using both research based evidence and expert consensus. The three clinical symptoms comprise: persistent knee pain, limited morning stiffness and reduced function and the three signs are: crepitus, restricted movement and bony enlargement. According to the report and assuming a 12.5% background prevalence of knee OA in

adults aged 45 years and older, the estimated probability of having radiographic knee OA increased in line with the number of positive features to 99% when all 6 symptoms and signs were present.

Radiography

In 1948, Fairbank presented a grading system that was originally designed to describe joint changes after meniscal lesions. His classification relates to flattening of the condyles, subchondral sclerosis and joint space narrowing and is of limited use today. Spector et al. found that the best predictors of knee pain caused by knee OA were the presence of osteophytes and the grade of OA according to Kellgren and Lawrence (Spector et al., 1993). Kellgren and Lawrence introduced a radiographic classification system in 1957 and an OA grading system for the knee by Kellgren in 1963. Ahlbäck, a radiologist at Lund University Hospital, proposed a grading system for OA in the knee from joint narrowing to severe bony changes in 1968. He also described the advantage of performing knee radiography during weight bearing (Ahlbäck et al., 1968). Felson et al. proposed that a knee should be considered as having radiographic OA if there are either grade 2-3 osteophytes or moderate to severe joint space narrowing (≥2 on a 0-3 scale; Kellgren-Lawrence scale used) (Felson et al., 1997).

Knee radiography has some limitations. It has been demonstrated that weight-bearing and the extent of knee flexion has a significant effect on the radiographic outcome (Wevers et al., 1982; Buckland et al., 1999; Vignon et al., 2003). Deep at al. observed up to 2 mm wider joint space at weight-bearing extension compared with a 30° flexion view in healthy subjects (Deep at al., 2003). Mazzuca et al. observed that the measured joint space narrowing on weight-bearing and extended-view anterior-posterior radiographs decreased in subjects with knee pain because they had difficulties extending their knees, which might influence results after resumption of analgetics in studies (Mazzuca et al., 2002). Today, weight-bearing radiography in the semiflexed position (20-30°) is commonly used, and has shown a reproducibility of 0.1-0.2 mm (Peterfy et al., 2003). Radiographic joint space narrowing of 3 mm or more should be present in order to diagnose OA based on comparison with cartilage defects in MR-images (Boegård et al., 1997). The most important limitation of radiography is its insensitivity in terms of detecting early articular cartilage loss in knee OA (Lysholm et al.; 1987; Brandt et al., 1991), which means that changes do not become visible until perhaps decades after the onset of the disease when the cartilage changes in the joint are beyond repair.

Arthroscopy

Arthroscopy makes it possible to directly visualise all cartilage surfaces in the knee joint and is more sensitive than radiography for detecting early articular cartilage loss (Lysholm et al., 1987; Brandt et al., 1991). Arthroscopy is also more sensitive than MRI for detecting early articular cartilage loss (Blackburn et al., 1994, 1996). In addition, tibiofemoral radiographic joint space narrowing can occur in the presence of a normal articular cartilage surface through calcification of the basal layers of cartilage with advancement of the cartilage tidemark (Brandt et al., 1991). However, of major concern is the lack of an exact arthroscopic cartilage grading system, which means that many different classification systems have been used. The intraobserver and interobserver coefficients for the Outerbridge classification system of chondral damage in the knee has been shown to be moderately accurate when used arthroscopically (Brismar et al., 2002; Cameron et al., 2003). In patients with primary medial compartment OA of the knee, a very high correlation between radiographic findings (especially with the Kellgren Lawrence score) and cartilage lesions by arthroscopy was found medially. However, the cartilage lesions of the lateral condyle correlated poorly with the radiographic changes (Wada et al., 1998). According to Wu et al., The American College of Rheumatology (ACR) clinical classification with or without radiographic change correlates well with articular cartilage damage (ACR/KAOS) in patients with knee OA (Wu et al., 2005). The Knee Arthroscopy Osteoarthritis Scale (KAOS) is a validated outcome instrument for knee OA based on arthroscopic findings. Another semi-quantitative score for whole-organ evaluation of the knee joint in OA based on results of arthroscopic evaluation is the Whole-organ Arthroscopic Knee Score (WOAKS), where both the cartilage and meniscus are evaluated. There is good correlation between the WOAKS and subjective symptoms as well as the radiological grade of OA, which may make it useful for clinical and epidemiological studies in the future (Spahn et al., 2008). However, according to Kiviranta et al. (Kiviranta et al., 2008), mechanical indentation and ultrasound indentation arthroscopic instruments correlate with cartilage degeneration based on the Osteoarthritis Research Society International (OARSI) OA-grading and have potential for diagnostics of early OA. A good correlation between arthroscopically assessed severity of OA and histopathological scoring systems has also been published (Acebes et al., 2009). The major disadvantage of arthroscopy is its invasiveness and that it primarily examines the articular cartilage surface and not the deeper cartilage layers or subchondral bone. Arthroscopy has a complication rate of 2.5% in

arthroscopic meniscal surgery, including nerve injuries, infections, vascular injuries and pulmonary embolism (Small et al., 1990)

Figure 2. Knee arthroscopy.

Molecular biomarkers

Cartilage is a composite tissue where type II collagen forms an organized network of triple-helix fibrils with high resistance to shear forces, in which aggregating proteoglycans termed aggrecan, are entrapped. It is a highly negatively charged molecule. Water constitutes 70-80% of the cartilage weight and is drawn into the tissue by osmotic pressure, creating a swelling pressure, which is counteracted by the collagen network. This allows the cartilage to resist deformation. The chondrocytes are sparsely distributed in the matrix and maintain the tissue integrity by a balanced synthesis and degradation of matrix molecules. The most abundant cartilage matrix molecules are type II collagen (50-60% of dry weight) and proteoglycans (15-30% of dry weight). There are also smaller matrix proteins such as cartilage oligomeric matrix protein (COMP), biglycan, decorin, fibromodulin and fibronectin (Heinegard et al., 1998). Their function is still to a large extent unknown. The chondrocytes maintain the dynamic equilibrium in the cartilage matrix in response to various stimuli. Defective matrix components are degraded and replaced with newly synthesized ones. The chondrocytes produce enzymes and enzyme inhibitors, such as cytokines and growth factors, to fulfil this task (Tchetina and Poole et al., 2006). Interleukin-1 (Il-1) and tumor necrosis factor (TNF) enhances matrix degradation and inhibit synthesis of matrix molecules while insulin-like growth factor (IGF-1) and transforming growth factor beta (TGF-β) increase the synthesis of cartilage matrix molecules (Malemud et al., 2010). The matrix metalloproteinases (MMPs) are a family of enzymes with

catabolic actions on connective tissues. The MMPs are strongly regulated at several different levels and can, for example, be inhibited by the tissue inhibitors of metalloproteinases (TIMPs).

Articular knee cartilage and synovial fluid analyses in patients at risk of developing OA have shown increased turnover and matrix changes in the articular cartilage (Dahlberg 1994; Tiderius et al., 2005). Molecular biomarkers are cartilage specific molecules, or their fragments, that can be analyzed in the synovial fluid, serum and urine (Garnero et al., 2000). Several biomarkers are relevant in OA, with characteristic profiles in the early and later stages of the disease (Lohmander et al., 1999). Thus, analyses of molecular biomarkers may be relevant for diagnosis and prediction of early joint disease. To date, COMP and type II collagen synthesis and degradation markers seem to be the best candidates for monitoring early joint disease leading to OA. Accordingly, serum concentrations of COMP and bone sialoprotein (BSP) increased significantly during longitudinal follow-up in subjects with chronic knee pain who developed radiographic knee OA, compared with subjects without radiographic knee OA, at follow-up after 3 years (Petersson et al., 1998). Furthermore, decreased type II collagen synthesis measured by serum N-propeptide of type IIA procollagen (PIIANP), and increased degradation measured by urinary excretion of the C-terminal crosslinking telopeptide of type II collagen (CTX-II), may predict the progression of joint damage over 1 year evaluated by radiography and arthroscopy in patients with knee OA (Garnero et al., 2002). In 2007, Cibere et al. suggested that the ratios of type II collagen degradation markers to collagen synthesis markers were better than individual biomarkers at differentiating OA stages in patients with knee pain (Cibere et al., 2009).

It has also been demonstrated that the CTX-II marker (increased cartilage collagen degradation) is released in the synovial fluid, with peak values within hours of an ACL injury, and values remained high at all time intervals monitored over 1 year (Lohmander et al., 2003). Many other potential molecular biomarkers exist. In the synovial fluid from patients with chronic ACL deficiency, elevated concentrations of chondrodestructive cytokines, such as interleukin-1-beta (IL-1β) and tumor necrosis factor alpha (TNF-α), have been detected. There was also a correlation between a higher concentration and more severe chondral damage at arthroscopy (Marks et al., 2005).

Magnetic resonance imaging

MRI provides high-resolution imaging of all joint structures of the knee, including cartilage, subchondral bone, menisci and ligaments. It is non-invasive and studies comparing MRI and arthroscopy have shown good diagnostic performance in detecting injuries to the menisci and cruciate ligaments (Rappeport et al., 1997). In a systematic review, the combined accuracy rate of MRI for evaluating the medial and lateral meniscus or ACL was 89%, when arthroscopy was considered the "gold standard" (Crawford et al., 2007). The accuracy rate for ACL (93%) was higher than for the lateral meniscus (89%) and the medial meniscus (86%). MRI has higher specificity (correctly identifies the absence of an internal dearangement of the knee) than sensitivity (accurately identifies an internal dearangement of the knee). MRI studies have higher false positive than false negative results (Heron et al., 1992). Clinical examination in combination with MRI provides the most accurate non-invasive investigation for pathological findings in the menisci and the ACL (Glashow et al., 1989). However, the routine clinical MRI examination techniques used at present are unable to replace arthroscopy for diagnosing *cartilage* injuries in the knee (Friemert et al., 2004). Arthroscopic evaluation is more valuable than MRI for grading OA and assessing the cartilage surface. Cartilage specific three-dimensional MRI-protocols have proven more sensitive for the diagnosis of cartilage defects (Peterfy et al., 1994). In addition, 3D-MRI or quantitative MRI (qMRI) has the ability to monitor changes in knee joint pathology longitudinally with changes of cartilage volume. Cartilage volume changes of the order of -5% per annum occur in OA in most knee compartments. Since the annual loss of cartilage exceeds the precision errors, qMRI has potential for evaluating epidemiological studies of OA progression (Eckstein et al., 2006). Risk factors for cartilage loss in knee OA longitudinally include a high BMI, meniscal pathology, malalignment, advanced radiographic OA, focal cartilage defects and bone marrow alterations (Eckstein et al., 2009). MRI is useful in detecting bone pathology in injured knees with acute knee effusions that are stable on manual ligament testing and present with normal findings on radiographs (Duncan et al., 1996). The growing use of MRI in cases of acute knee injury has revealed traumatic bone marrow lesions (BML), also called "bone bruises", which are due to the impact of the trauma (Rosen et al., 1991; Kaplan et al., 1992; Speer et al., 1992; Frobell et al., 2008). BMLs are very common in acute ACL knee injuries, with at least one knee compartment involved in 98%, and located in the lateral compartment in 97% of all cases (Frobell et al., 2008). A majority of

these knees also had a cortical depression fracture that correlated with larger BML volumes, which may be a risk factor for future OA development. Moreover, histology examination of cartilage/bone tissue adjacent to BMLs has revealed cell necrosis, edema, bleeding in the fatty marrow, loss of proteoglycans and altered distribution of COMP (Johnson et al., 1998; Fang et al., 2001). After an ACL injury, BML volumes gradually decrease over the first year (Frobell et al., 2009). There are many differential diagnoses of BMLs including: osteonecrosis, inflammation, tumor, transient idiopathic bone marrow edema and knee OA (Roemer et al., 2009). The presence of BMLs on MRI images in knees with OA, is strongly associated with OA progression and pain (Torres et al., 2006; Lo and Hunter et al., 2009). In subjects with knee OA or at increased risk of developing it who are followed longitudinally, it has been shown that progressing or new BMLs indicated a high risk of cartilage loss in the same subregion (Roemer and Guermazi et. al., 2009). Cross-sectionally, maximal BML and effusion scores are independently associated with weight-bearing knee pain (Lo and McAlindon et. al., 2009). BMLs are also associated with overlying meniscal derangement in symptomatic knee OA (Lo and Hunter et. al., 2009). Later radiographic signs of knee OA, such as subchondral cysts, were associated with enhanced BMLs in the vicinity of the cyst in 99% of cases (Crema et al., 2009). Prevalent and incident subchondral bone attrition in knee OA was associated with subchondral BMLs ipsilaterally (Roemer and Neogi et. al., 2009). Pain severity in knee OA with BMLs seems to require the presence of bone attrition (Torres et al., 2006). The underlying pathology is not well established. Histologically, these BMLs appear to be sclerotic with increased bone volume fraction and greater trabecular thickness with reduced mineral density. This may render the affected knee joint mechanically compromised and susceptible to attrition (Hunter et al., 2009). Occasionally, BMLs appear in healthy and pain-free subjects and may be implicated in the pathogenesis of OA. In such subjects, incident BMLs were associated with increased BMI and the development of pain during a 2 year follow-up. Incident BMLs developed in 14% of subjects over the study period, and among those in whom BMLs were present at baseline, 46% completely vanished (Davies-Tuck et al., 2009). It has also been demonstrated that BMLs in healthy and pain-free subjects were strongly associated with tibiofemoral cartilage defects (Baranyay et al., 2007).

Dynamic knee MRI has been introduced to study dynamic tibiofemoral translations in vivo in ACL deficient subjects during knee movement (Barrance et al., 2007).

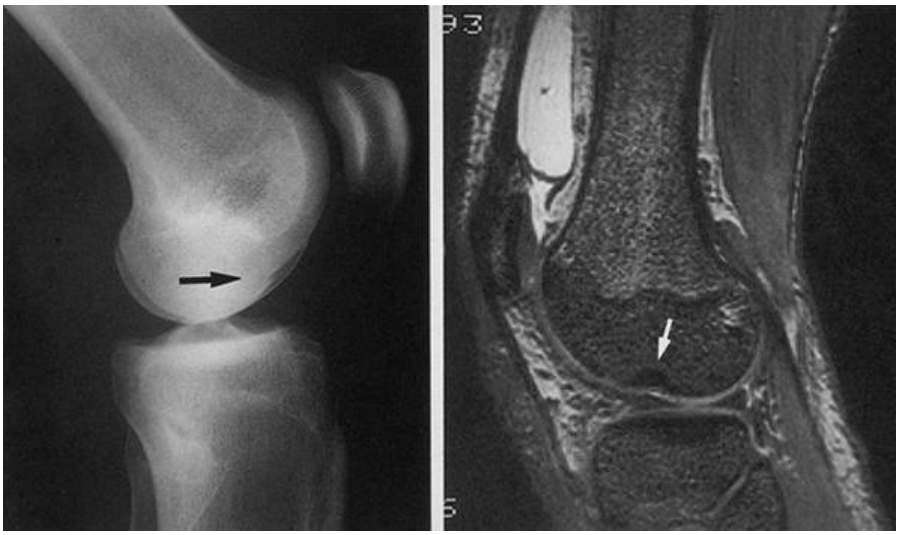


Figure 3. Osteochondral fracture in the lateral femoral condyle and BML at MRI after an ACL injury.

Bone scintigraphy

Bone scintigraphy has a predictive value for determining the outcome of knee OA. Scintigraphy predicts subsequent loss of joint space in patients with established knee OA (Dieppe et al., 1993). Although a study of the predictive value of bone scintigraphy with respect to joint space narrowing in patients with knee OA confirmed the predictive usefulness, similar predictive information can be obtained by standard radiographic techniques, with lower radiation and cost (Mazzuca et al., 2004). In a comparision between radiography, bone scintigraphy and MRI, there was good agreement between increased bone uptake and MRI-detected subchondral lesion, but the agreement between increased bone uptake and MRI-detected osteophytes or cartilage defects was generally poor (Boegård et al., 1998). An association between bone scintigraphy and synovial fluid biochemical markers of bone turnover (osteocalcin) has been found in patients with knee OA (Sharif et al., 1995). Disease progression in knee OA, as measured by bone scintigraphy, was also associated with an increase of serum cartilage oligomeric matrix protein (COMP) from baseline values during a 5 year follow-up (Sharif and Saxne et. al., 1995). In patients with chronic knee pain aged 37-54 years, early knee OA serum levels of COMP and bone sialoprotein (BSP) were higher in subjects with bone scan abnormalities (Petersson et al., 1998). The clinical value of (99m)Tc-methylene diphoshonate (MDP) bone single photon emission computed tomography (SPECT), in detecting early knee OA has been investigated, and it appears

to correlate well with clinical findings (Kim et al., 2008). SPECT has also been used to evaluate the long-term risk (10 years) of OA changes after bone-patellar tendon-bone reconstruction of the ACL. An increased risk of OA changes, evaluated with radiography and SPECT, was found in patients who had a concomitant partial meniscectomy (Hart et al., 2005). In another study of subjects who had undergone an ACL reconstruction, a positive pivot-shift test 2 years after surgery was associated with increased scintigraphic activity of the subchondral bone 5-9 years after surgery (Jonsson et al., 2004). Positron emission tomography (PET) found an increased uptake in knee OA, generally accumulated in the intercondylar notch, periosteophytic lesions and bone marrow (Nakamura et al., 2007).

New quantitative MRI techniques

The traditional MRI technique is limited in that only macroscopic cartilage defects are visible. Minor cartilage fissures and fibrillations are better visualized arthroscopically. Microscopic cartilage alterations and the first stages of OA development need a more specific investigation called the quantitative MRI technique, sometimes referred to as molecular imaging. The ability to detect early cartilage changes in OA prior to morphologic changes may allow us to carefully monitor the course and progression of OA, and to evaluate the benefit of different treatments in patients in the early stages of OA. These quantitative techniques assess hyaline cartilage specific macromolecules, such as collagen and GAG. Most techniques have only been validated in vitro at high field strengths, but some of them have proven applicable in the clinical setting:

T2 mapping is an MRI imaging technique that can estimate the hydration and collagen fiber integrity in articular cartilage (Watanabe and Wada, 2009). The spin-lattice relaxation time in the rotating frame ($T1_{rho}$) MRI has proven in vivo feasibility for quantifying early OA changes with GAG depletion (Akella et al., 2001; Regatte et al., 2004, 2006). Both in vivo $T1_{rho}$ and T2 relaxation times increase with the degree of knee OA cartilage change, and $T1_{rho}$ seems to be a more sensitive indicator of early cartilage changes in OA than T2 (Regatte et al., 2006; Li et al., 2007). It is possible that even earlier OA changes occur in the fibrocartilage of the menisci than in the hyaline joint cartilage. In support, meniscal $T1_{rho}$ and especially T2 values correlate with clinical findings of knee OA and can be used to differentiate between healthy subjects and patients with OA (Rauscher et al., 2008). In subjects with an ACL injury, a strong injury-related relationship has been demonstrated between $T1_{rho}$ values in the lateral meniscus and the lateral tibiae cartilage, with elevated values indicating

biochemical matrix changes compared with controls (Rauscher et al., 2008).

Delayed gadolinium enhanced MRI imaging of cartilage (dGEMRIC) is a contrast enhanced MRI (CE-MRI) technique that can evaluate the GAG concentrations in articular cartilage. dGEMRIC has been applied in both basic science and clinical studies. dGEMRIC was introduced by Bashir, Burstein and Gray in Boston (Bashir et al., 1996; Burstein et al., 2001). There is a very strong correlation between GAG content and the T1 in the presence of the contrast agent Gadolinium (T1Gd) (Bashir et al., 1996). The correlation between dGEMRIC in vitro and in vivo has been validated (Bashir et al., 1999; Mlynarik et al., 1999; Trattnig et al., 1999). Intra-observer variability in vivo was low (1.5-2.6%) when a large standardized ROI was used (in the medial vs. lateral femoral condyle) (Tiderius et al., 2004). In the same study the inter-observer variability was also low and ranged between 1.3-2.3% for 6 different investigators (Tiderius et al., 2004). The reproducibility of the dGEMRIC measurement in knees of asymptomatic volunteers was 5-7% for full-thickness ROIs (Multanen et al., 2008). A high dGEMRIC reproducibility of 4-7% has also been found in the hip (Bittersohl et al., 2009). The dGEMRIC method has made valuable contributions in clinical research on early cartilage matrix changes in OA. A cross-sectional dGEMRIC study indicated that human knee cartilage adapts to exercise by increasing the GAG content, with higher values in exercising than in non-exercising individuals (Tiderius et al., 2004). In subjects with ACL injuries there is an acute generalized biochemical change within the knee that leads to GAG loss from both the lateral and medial femoral cartilage, although the joint compression at injury is more often on the lateral side with a lateral bone bruise. Moreover, GAG release was related to cartilage GAG content rather than type or degeree of injury. In cartilage with a high GAG content (long T1Gd), more GAG is released into the synovial fluid (Tiderius et al., 2005). In knees at risk of OA, dGEMRIC values at baseline were predictive for radiographic knee OA six years later (Owman et al., 2008). A follow-up of middle-aged patients in whom a partial medial meniscectomy had been performed 1-6 years earlier, found a low medial dGEMRIC value that also correlated with a high BMI and low thigh muscle strength (Ericsson et al., 2009). Evaluation with dGEMRIC has demonstrated parallel degradative changes of knee cartilage and meniscus, indicating that early OA changes occur simultaneously in meniscus and cartilage (Krishnan et al., 2007). dGEMRIC seems to be a useful method for evaluating the patellar cartilage in patients with recurrent patellar dislocation, since these patients have

lower GAG concentrations, indicated by the dGEMRIC values, in comparison to controls (Watanabe et al., 2009).

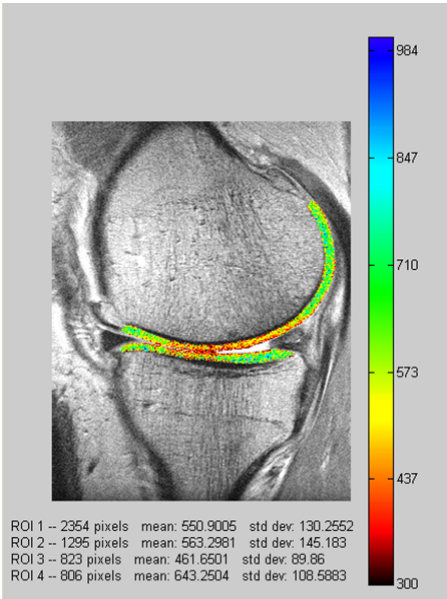


Figure 4. Picture of dGEMRIC results in the medial TF compartment in MRI-Mapper.

Outcomes after an ACL injury

There are many possible ways to evaluate the knee after an ACL injury. Various aspects of the injury require different evaluation methods. The International Classification of Functioning and health (ICF) is the WHO's framework for measuring health and disability at both individual and population levels. The ICF is a classification of health and health-related domains, classified from body, individual and societal perspectives by means of two lists: body functions and structure, and domains of activity and participation. Since an individual's functioning and disability occurs in a context, the ICF also includes a list of environmental factors. By shifting the focus from cause and structural damage to impact on health and disability, it places different conditions on an equal footing, thus allowing them to be compared. When evaluating knee function after an injury, it is important to acknowledge all these different aspects separately. For a complete evaluation of a knee-injured subject, assessment of impairment after, for example, an ACL injury could include MRI, arthroscopy and laxity testing. Activity and activity limitations are evaluated by means of an activity related knee score and functional performance tests. The subject's

ability or wish to participate is evaluated with an activity score. Quality of life is assessed with a generic score such as the SF-36 (Jenkinson et al., 1993) or EQ-5D (Ruchlin et al., 2008), which makes comparisons to other impairments or diseases possible.

Mechanical stability

The most widely used knee classification system describes the instability by the direction of the tibial displacement categorised as straight (non-rotatory) or rotatory (simple or combined) (Hughston et al., 1976). Straight instability can be medial, lateral, anterior and posterior and is assessed by stressing the knee. It is graded as: 0 -normal laxity; 1+ -translation of tibiae of less than 5mm; 2+ -translation of tibiae 5-10mm; 3+ -translation of tibiae >10mm. Rotatory instability can be anteromedial, anterolateral, posteromedial, posterolateral or a combination of these.

The ability to identify and quantify tibial displacement in relation to the femur has wide implications both for clinical practice and research. Historically, quantification of knee joint laxity was only possible by means of a physical examination performed by an experienced clinician. During the 1980s several mechanical devices to supplement physical examination were introduced. New devices continue to emerge as technological progress continues. According to a systematic review article, the KT-1000 knee arthrometer (KT-1000; MEDmetric Corp, San Diego) and the relatively new Rolimeter (Aircast Europa, Neubeuern, Germany) provide best results when testing anterior laxity at the knee (Pugh et al., 2008). When compared with roentgen stereophotogammetry (RSA), the KT-1000 arthrometer has been shown to measure lower antero-posterior translations than RSA in ACL deficient and ACL reconstructed subjects, probably because a lower anterior force was used in the KT-1000 arthrometer test (89N) than in the RSA test (150N) (Jonsson et al., 1993). Higher antero-posterior translations for the RSA test than the KT-1000 arthrometer test were also demonstrated in ACL reconstructed subjects when the same anterior force was used in testing (Fleming et al., 2002). The KT-1000 arthrometer has long been the mainstay among knee laxity testing devices. The accuracy of the KT-1000 in diagnosing ACL insufficiency shows sensitivities ranging from 89% to 92% and specificities of approximately 95% (Bach et al., 1990; Ganko et al., 2000). However, the reliability of the device has been questioned, as both favourable (Wroble et al., 1990) and unfavourable results have been reported (Sernert et al., 2001). The experience of the examiner seems to be crucial for ensuring reliable measurements (Ballantyne et al., 1995). Clinical manual laxity testing seems to be more effective diagnostically

than the KT-1000, which is why the use of the device in the clinical setting is questioned (Wiertsema et al., 2008). The most appropriate and perhaps only role for the KT-1000 may be in the research setting, where objective readings are required. The Rolimeter arthrometer measures the antero-posterior translation in mm in the course of an ordinary Lachman test. When testing for ACL insufficiency it has a sensitivity of 89% and a specificity of 95%. It has also been tested to be at least as reliable as the KT-1000 (Ganko et al., 2000).

The relationships between objective assessment of knee laxity and subjective assessment of symptoms and function after ACL injury or ACLR have not been clearly elucidated. In a prospective study of 202 ACL reconstructed subjects, subjective variables of symptoms at follow-up and subjective knee function were not associated with Lachman examination or KT-1000 arthrometer testing (Kocher et al., 2004). Other study groups have demonstrated the same results with no association between KT-1000 arthrometer laxity measurements and any functional outcomes measure (Eastlack, 1999). However, the pivot-shift test had significant associations with satisfaction, giving-way, difficulty cutting, difficulty twisting, activity limitation, sports participation and the Lysholm score (Kocher et al., 2004). Consequently, the pivot-shift test may be the best measure of laxity. In another study from the same group, patient satisfaction measured ordinally on a scale from 1 to 10 was associated with both KT-1000 and pivot-shift results, but subjective variables of symptoms and function had far more solid associations with patient satisfaction. The authors concluded that knee stiffness, giving-way, swelling and patellofemoral symptoms should be emphasized when assessing the outcome after ACLR from the patient perspective; (Kocher et al., 2002). In recent years there has been a growing interest in rotational laxity, which is common after an ACL injury and responsible for the symptom of giving-way that the patients experience. Consequently, there has also been a growing interest in double-bundle ACLR, which in some studies has been demonstrated to decrease antero-posterior (KT-1000) and rotational knee laxity better than single-bundle reconstructions (Muneta et al., 2007; Aglietti et al. 2009). So far (approximately 2 year follow-up), the patients' experience of symptoms and knee function has not yet been improved by double-bundle ACLR in comparision with single-bundle reconstructions. However, there has not been any simple, commercially available device to measure knee rotation. Recently a non-invasive device to measure knee rotation was presented. An easily detachable electromagnetic tracking system is used to record the motion of the tibia with respect to the femur while performing a pivot-shift

test (Tsai et al., 2008). As a result of the new interest in double-bundle ACLR, one could expect an increasing market for new rotational laxity devices. The Rotameter is another newly developed measurement device (Lorbach et al., 2009).

Knee scoring systems

In the first reports on knee function after injury, subjects were simply divided into groups categorized as excellent, good or bad according to the physician. O`Donoghue (1955) was the first to present a numerical assessment of results after knee surgery. Marshall (1977) presented a standardized evaluation method after knee ligament injuries. A frequently used knee outcome instrument is the Cincinnati knee scoring scale (Barber-Westin et al., 1999). Although the Cincinnati Knee Score has been demonstrated to be an adequate tool for assessing knee function after ACLR (Risberg et al., 1999), it includes manual and instrumented stability testing to evaluate symptoms and function, making it difficult to separate different aspects of knee function after ACL injury. The most frequently used knee function score after ACL injury is the Lysholm score (Lysholm and Gillquist, 1982), which evaluates 8 separate aspects of the knee function. In the first scale from 1982, objective findings assessed by the investigator were included, but after modification (Tegner and Lysholm, 1985), only subjective findings remained. The Tegner activity scale (Tegner and Lysholm, 1985) was added to complement the Lysholm score, since patients with different activity levels are assumed to experience different grades of knee symptoms, with more symptoms when the activity level increases. Over the years, both the Tegner activity scale and the Lysholm score, used as a patient-administered score, have been extensively documented with validity, reliability and responsiveness testing and have been found to demonstrate acceptable psychometric parameters after an ACL injury (Briggs et al., 2006 and 2009). The Lysholm score and the Tegner scale are further presented in the section: Methods-Outcomes-*Lysholm knee score* and *Tegner activity scale*.

The International Knee Documentation Committee (IKDC) developed a scoring system for ACL injured knees in collaboration between The American Orthopedic Society for Sports medicine (AOSSM) and the European Society of Sports Traumatology, Knee surgery and Arthroscopy (ESSKA) (Hefti et al., 1993; Irrgang et al., 1998). The IKDC consists of different sections where patient subjective (patient-relevant) complaints are mixed with symptoms, clinical Range of Motion (ROM), manual and instrumented ligament testing and radiographic assessment and is further

presented in the section: Methods-Outcomes-*IKDC*. The IKDC, the Cincinnati knee scoring scale and the first version of the Lysholm score are assessor reported scores, which has been shown to be biased when applied in patients with an ACL injury (Hoher et al., 1997). The Knee Injury and Osteoarthritis Outcome Score (KOOS) (Roos et al., 1998) is a self-reported outcome of knee function including the items contained in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy et al., 1988) (a more extensive explanation of the KOOS is presented in the section: Methods-Outcomes-*KOOS*).
The ACL Quality of Life is a disease-specific, patient-reported outcomes measure of ACL injury (Mohtadi et al., 1998). The Marx activity level scale measures the activity level after injury and interventions and is used in conjunction with one of the outcomes measures mentioned above (Marx et al., 2001).

Neuromuscular function

The term neuromuscular function is a combination of all the consequences attributed to a disturbed somatosensory input affecting the central motor response programs after an ACL disruption. Proprioception, postural control, muscle strength, functional performance, movement and activation pattern, central mechanisms, motor control and learning are all affected after the injury and should be taken into account during rehabilitation after an ACL injury, ACLR, or in ACL injury prevention (Ageberg, 2002).

Functional performance tests

In the literature, different kinds of hop test are the most common method of evaluating performance-based outcome in subjets with ACL deficient or ACL reconstructed knees. It has been demonstrated that the one-legged hop for distance, the 6m-timed hop, as well as the 3-hop and cross-over hops for distance are reliable and valid performance-based outcome measures for patients undergoing rehabilitation following ACLR (Reid et al., 2007). In the literature, poor functional performance test results are frequently associated with decreased subjective function scores in subjets with ACL reconstructed knees (Goh et al., 1997). The Limb Symmetry Index (LSI) has been used to report differences between the injured and uninjured knee. A LSI of 85% (15% reduction) is regarded as a satisfactory outcome of one-leg hop tests for distance (Barber et al., 1990). However, it has been verified that the one-leg hop test performance is reduced in both the injured and the contralateral uninjured limb after an ACL injury, due to afferent nerve dysfunction with central adjustments of motor control (Gauffin et al.,

1990). The LSI could thus be unreliable, and ideally results should be compared with a control group. In a prospective study comparing the functional outcome in ACL injured subjects treated by ACLR or non-operative treatment, the latter group performed better in two out of four different hop-tests after one year. Both groups performed >90% in all four hop-tests in comparision with the uninjured leg (Moksnes et al., 2009). In a randomized controlled trial of training and surgical reconstruction versus training only (the Knee, Anterior cruciate ligament, NON-surgical versus surgical treatment (KANON) study), no differences between the two groups in hop performance or muscle strength were found at 2-5 years (Ageberg et al., 2008). However, there is certainly a need for a more sophisticated functional performance test or a battery of tests to comprehensively evaluate knee function after knee injuries. In a study, 50% of ACL deficient subjects performed normal one-legged hop tests despite suffering from persistent giving-way in sports, and those whose one-legged hop tests were abnormal were at serious risk of giving-way episodes and experienced limitations during sports activities (Barber et al., 1990).

Muscle strength and endurance

It is well known that the quadriceps femoris weakens soon after an acute anterior cruciate ligament injury. Activation deficits and atrophy occur and affect quadriceps strength (Williams et al., 2005). It has been proposed that loss of feedback from mechanoreceptors in ACL is the underlying mechanism behind weakness of quadriceps in patients with a deficient or reconstructed ACL. This conclusion is based on chronic suppression of the recruitment of high-threshold motor units during voluntary contraction because ACL injury leads to chronic reduction in Ia-feedback (neuronal) to muscles around the knee due to a lack of feedback from ACL to gamma motor neurons (Konishi et al., 2002). Compared to quadriceps strength, several studies have presented restoration of hamstrings muscle strength after ACL injury (Fridén et al., 1990; Keays et al., 2000; Wojtys et al., 2000). The quadriceps is critical for dynamic joint stability, and weakness of this muscle group is related to poor functional outcomes/stability in both patients with a deficient or reconstructed ACL (Keays et al., 2003; Moisala et al., 2007; Palmieri-Smith et al., 2008). It has recently been demonstrated that individuals with preoperative quadriceps strength deficits above 20% also had persistent significantly greater strength deficits two years after surgery. Preoperative quadriceps strength deficit in combination with a meniscus injury was identified as the two most significant predictors of knee function assessed by the Cincinnati Knee Score two years after ACLR

(Eitzen et al., 2009). For this reason, identifying strategies to minimize quadriceps weakness following ACL injury and reconstruction is of great clinical interest. Preoperative quadriceps muscle strength deficits have previously been assessed from isokinetic measurements to be between 7 and 17% (Keays et al., 2003; De Jong et al., 2007; Keays et al., 2007; Risberg et al., 1999). After ACLR with a BPBT-graft, the post-operative quadriceps muscle strength is even lower, but seems to improve over time. In a review article, the quadriceps deficits in comparison with the uninjured knee varied from 24 to 40.5%, 6 months post-operatively (Palmieri-Smith, 2008). Studies with a follow-up time of over five years after ACLR have shown that quadriceps asymmetry may persist, with quadriceps deficits of between 6 and 10%, generally with a slightly more pronounced quadriceps deficit in subjects operated on with a BPBT graft than with a four-stranded hamstrings graft (Keays et al., 2007; Moisala et al., 2007; Lautamies et al., 2008). Because decreased quadriceps strength is such a common finding with consequences for functional outcome both in rehabilitated non-operated ACL deficient and ACL reconstructed subjects, one could speculate whether it could be a predictor of future knee OA (Ageberg et al., 2008, A&R). However, few would disagree that decreased quadriceps strength is often associated with established knee OA (Pang et al., 2008). In knee OA, quadriceps neuromuscular dysfunction-weakness, impaired proprioceptive acuity and impaired protective reflexes are associated with pain and disability, which is usually assumed to be caused by joint damage. However, quadriceps dysfunction may play a role in the pathogenesis of knee OA. There is convincing evidence that in people with established OA, moderate exercise improves muscle neuromuscular dysfunction and reduces pain without exacerbating joint damage (Hurley et al., 2003). Accordingly, in another systematic review, clinical studies supported a muscle dysfunction hypothesis over a wear and tear hypothesis (Shrier et al., 2004). Reduced functional performance in the lower extremity (a test of one-leg rises) predicted the development of radiographic knee OA 5 years later among people aged 35-55 with chronic knee pain and normal radiographs at baseline (Thorstensson et al., 2004). In addition, a in vivo cartilage monitoring study in middle-aged patients who had undergone a medial meniscectomy 3-5 years previously and thus at risk of knee OA, indicates that adult human articular cartilage has a potential to adapt to loading change, as patients randomized to moderate supervised exercise improved in their knee cartilage GAG content as revealed by the CE-MRI (dGEMRIC) results (Roos and Dahlberg, 2005). Furthermore, the estimated cartilage quality was positively correlated to knee extensor and flexor

strength in relation to body weight and negatively correlated to BMI, suggesting that overweight is a factor that leads to cartilage deterioration, whereas strong and co-ordinated thigh muscles may have a protective effect on the cartilage integrity (Ericsson et al., 2009). Functional exercise training was well tolerated in the same group of patients (Ericsson et al., 2009) and improved functional performance and thigh muscle strength. The exercise program comprised postural stability training as well as functional strength and endurance exercises for leg and trunk muscles, supervised by a physical therapist and performed 3 times weekly for 4 months.

Proprioception and postural control

Joint stability cannot be attributed to the ligaments alone, but should be thought of as a synergistic function in which the shape of the joint surfaces, joint capsules, ligaments, muscles, tendons, and sensory receptors and their spinal and cortical neural projects and connections function in harmony. The ACL mechanoreceptors receive nerve fibers from the tibial nerve and provide the central nervous system (CNS) with postural information to achieve dynamic stabilization of the knee joint (Solomonow et al., 2001). In most studies, knee proprioception is evaluated by measuring the subject's threshold for detection of passive motion (TDPM) from 20º and 40º toward flexion and extension. The joint position sense (JPS), also widely used in the literature, measures active reproduction of a 30 degree passive angle change of the knee joint, or a visual reproduction of a 30 degree passive angle change (Roberts et al., 2000). The TDPM test seems to be superior to the JPS test in discerning differences between subjects (Roberts et al., 2000; Reider et al., 2003; Lee et al., 2009). Postural control is often evaluated by means of a dynamic single-limb stance balance test (Lee et al., 2009). Several studies have demonstrated that proprioception in patients with an ACL deficient knee is disturbed as well as decreased, with serious consequences for their neuromuscular coordination (Barrack et al., 1989). Moreover, decreased proprioception in subjects with an ACL injury is also commonly found in the uninjured leg by the TDPM test (Roberts et al., 2000) and the dynamic single-limb stance balance test (Herrington et al., 2009), which has clinical implications if inherent inferior proprioception makes these subjects more vulnerable to re-injury or a contra-lateral injury. Proprioception seems to be more relevant than the amount of mechanic instability in relation to subjective functional outcome after an ACL injury. In the literature, decreased proprioception has frequently been associated with reduced subjective function scores (Roberts et al., 1999; Fridén et al., 2001; Roberts et al., 2007). A correlation between proprioception and

functional performance tests has also been shown (Katayama et al., 2004). A decreased dynamic single-limb stance balance test result has also been associated with decreased functional outcome in subjects with ACL injuries and ACL reconstructions (Shiraishi et al., 1996; Ageberg et al., 2005; Lee et al., 2009). In non-operated subjects with a deficient ACL who have achieved a good functional and muscular knee performance after knee rehabilitation, proprioception still can detect decreased knee function even when subjects have achieved results in the normal range for hop-tests and thigh muscle strength (Fonseca et al., 2005; Ageberg et al., 2008). Interestingly, several studies have shown that after an anterior cruciate ligament (ACL) reconstruction, patients can attain improved proprioceptive function, even compared to subjects with ACL-deficient knees (Shiraishi et al., 1996; Reider et al., 2003; Ozenci et al., 2007; Anders et al., 2008). Other researchers have found the opposite, with a persistent decreased proprioception after an ACLR (Roberts et al., 2000; Fischer-Rasmussen et al., 2000). In recent years there has been increasing interest in ACL-sparing techniques when an ACLR is required. Theoretically, sparing the intact parts of the ACL may increase vascularization and proprioception, optimize the accuracy of the ACLR and result in better proprioception, stability and improved clinical outcome for the patient (Siebold and Fu, 2008). Improved proprioception may be expected if the ACL-hamstring reflex could be re-established. In research, an excitation in the hamstring muscles can be elicited by mechanical or electrical stimulation of the ACL. The ACL-hamstring reflex has been demonstrated in humans by electrodes invested in the ACL during arthroscopy to electrically stimulate its mechanoreceptors to elicit a muscular contraction (EMG) of the semitendinosus and biceps femoris muscles (Dyhre-Poulsen, 2000; Tsuda et al., 2001). Impulses from the sensory nerves in the ACL are also activated during motion of the knee, in particular overstretching and combined extension and rotation. During muscular activity, electrical stimulation of the ACL or PCL results in a inhibition of the ongoing activity, both during static isometric and isokinetic muscle work, and also during dynamic activity (gait). This inhibitory reflex subjectively resembled giving-way (Krogsgaard et al., 2002). Tsuda et al. have also demonstrated a re-established ACL-hamstring reflex after ACL-reconstruction (Tsuda et al., 2003), but according to an extended study of 45 subjects, the reflex was not re-established in 28 of them, although an evoked potential at stimulation could be detected in 22 (Iwasa et al., 2006). In 16 ACL reconstructed subjects where ACL remnants were spared, the TDPM values one year or more after surgery were better in the group in which more ACL remnants

were left intact, than in the other group that had less ACL remnants left at surgery (Lee et al., 2008). In ACL reconstructed subjects, the EEG was able to measure a change in joint position sense at the cortical level, which also seems to be a prerequisite for improved prioprioception and function (Baumeister et al., 2008).

Physiotherapy

Rehabilitation programs after ACL injury or ACLR aim at restoring or improving (maximising) the range of motion, muscle strength and functional outcome to the patients' desired activity level. Rehabilitation programs have been developed from theoretical models, research and clinical observations. The first programs were mainly focused on muscle atrophy and aimed at restoring muscle strength. Some 20 years ago, the sensory function of ligaments in relation to functional joint stabilisation was recognised as important in training (Johansson et al., 1991). Since then, neuromuscular training methods have gained increased acceptance in rehabilitation after an ACL injury (Fridén et al., 1991; Beard et al., 1994; Zätterström et al., 1998, 2000; Fitzgerald et al., 2000; Ageberg et al., 2002) and after an ACLR (Beard et al., 1998; Shelbourne et al., 1997). The neuromuscular training aims at improving the sensorimotor control and achieving compensatory functional knee stability. Knee joint excercises are performed in closed kinetic chain (CKC) training instead of in open kinetic chain (OKC) training (Palmitier et al., 1991). OKC training was preferred in previous muscle strengthening programs. The rationale behind CKC is that coexistent axial loading of the knee joint while performing exercises to improve mobility, strength and functional stability stimulates the antigravity postural functions of weightbearing muscles. CKC training also assists in obtaining congruency of joint surfaces during the exercise by muscular co-activation of the hamstring muscles (Shoemaker et al., 1985; Baratta et al., 1988), which has been demonstrated to unload the knee ligaments after an ACL injury or reconstruction (O´Connor et al., 1993). Several authors have demonstrated that the tibiofemoral antero-posterior translation (shear-force) is lower when performing CKC compared with OKC exercises in normal knees (Lutz et al., 1993; Wilk et al., 1996), in ACL deficient knees (Yack et al., 1993; Kvist et al., 2005) and in ACL reconstructed knees, five weeks after surgery (Tagesson et al., 2009). However, nowdays there is some evidence that the optimal ACL rehabilitation should include both CKC and OKC exercises to achieve the most favourable outcome. In a review of data it was concluded that both methods could be modified to minimize the strain on the ACL graft

postoperatively and avoid excessive patellofemoral joint stresses, especially for quadriceps muscle restoration (Fitzgerald et al., 1997). Moreover, in a recent randomized controlled trial between CKC and OKC exercises after an acute ACL injury in 42 subjects, greater quadriceps strength values were achieved in the OKC group, with equal static and dynamic translations and hamstring muscle strength (Tagesson et al., 2008). In a recent randomized clinical trial between neuromuscular (NE) and traditional muscle strength (SE) training after an ACLR, it was demonstrated that both groups had the same Cincinnati Knee Score, but the scores for global function (visual analogue scale, VAS) and pain during activity were better in the NE group, whereas the SE group achieved better hamstrings strength two years after surgery (Risberg et al., 2009). Patients with ACL deficiency may need OKC strengthening to regain good muscle torque, but after an ACLR exercises must be modified to avoid jeopardizing the initial graft healing.

ACL copers, compensators and non-copers

Despite the fact that much work has been done in trying to achieve some agreement in the treatment of ACL injuries, a great deal of controversy concerning different treatment strategies still persists. One problem is that the true natural history after an ACL injury remains unclear. In most cases ACL injuries are functionally disabling from early on and predispose the knee to subsequent injuries, as well as the early onset of symptomatic knee OA in many young or middle-aged adults, giving rise to another unsolved treatment challenge. We know from clinical practise and the literature that an ACL injury affects patients in different ways. Some are barely affected at all and can continue with the same activities as before the injury without any knee symptoms (copers), while others cannot perform activities of daily living because of giving-way and instability problems (non-copers). To enhance the success of any treatment strategies for ACL injuries it would be useful to know at an early stage to which group, coper vs. non-coper, the acute ACL injured patient belongs. As far back as 1983, Noyes et al. stated their famous “rule of thirds” for ACL injuries: “one-third of the patients with this injury will compensate adequately and be able to pursue recreational activities, one-third will be able to compensate but will have to give up significant activities, and one-third will do poorly and will probably require future reconstructive surgery.” Daniel et al. looked at factors present at the time of the injury that could determine which were predictive of late surgery in 292 patients after acute knee injury, followed for an average of 5.5 years (Daniel et al., 1994). They found that participation in high risk sports with knee cutting and pivoting knee movements (IKDC

grade I-II) and the average number of hours per year of pre-injury sports participation correlated with the failure of conservative treatment and an increased risk of ACLR. They also found that the manual maximum side-to-side difference using the KT-1000 ligament arthrometer (MedMetric Corporation, San Diego, USA) was predictive of the need for late ACLR or meniscus surgery. Based on their findings they presented a surgical injury risk factor (SURF) for making management decisions in patients presenting with an acute ACL injury (Daniel et al., 1994). In counseling patients about treatment after an ACL injury, the above treatment algorihtm was tested by Fithian et al. with evaluation of knee ligament arthrometry measurements and pre-injury sports activity to estimate the risk of injury over the next 5 to 10 years (Fithian et al., 2005). They concluded that the treatment algorithm used was effective in predicting the risk of late phase knee surgery. However, they faced another difficulty in counseling patients, since a substantial number did not chose the treatment (non-operative or operative) prescribed by the surgeon. Some patients engaged in high risk sports chose non-operative treatment, while others with a low activity level wanted an ACLR, thus disagreeing with the surgeon's advice. A systematic literature review to identify copers was conducted in 2006, but due to its poor methodical quality and few subjects contained in the four included articles, the results are not reliable (Herrington et al., 2006). The review could not find a single test that could satisfactory discriminate between ACL copers and non-copers. A combination of different tests measuring: knee symptoms (KOS-sport, Global Knee Function Rating, Lysholm score), muscle strength and functional performance tests (hop tests) evaluating different aspects of the injury, was proposed (Herrington et al., 2006). In ACL injured patients followed prospectively for 15 years and treated primarily without reconstruction, a high-grade pivot-shift test at 3 months was associated with an 11 times increased relative risk of reconstruction. Furthermore, a normal pivot-shift test at 3 months indicated a low risk of reconstruction and is characteristic of copers (Kostogiannis et al., 2008). Maybe the pivot-shift test or some of the new devices for measuring knee rotation non-invasively are better than evaluating plain antero-posterior laxity in differentiating between copers and non-copers.

In conclusion, some consensus exists in that the majority of patients with an injured ACL can walk normally and perform activities of daily life and straight plane activities such as cycling and jogging. Most patients will develop problems when trying to perform high risk activities with extensive cutting and pivoting knee movements at an elite level. The majority of authors also agree that certain occupations such as firefighting and law

enforcement require an ACL stabilized knee (nationellt kompetenscentrum rörelseorganens sjukdomar (NKO) www.nko.se; Spindler et al., 2008).

Prevention of ACL injuries

Today, the literature contains a great deal of evidence that it is possible to prevent ACL injuries by means of specific neuromuscular training with a combination of balance, coordination, strength, plyometric and agility exercises (Myklebust et al., 2003; Mandelbaum et al., 2005; Olsen et al., 2005; Gilchrist et al., 2008; Soligard et al., 2008). Because females are at higher risk of an ACL injury than males when engaged in high risk sports, most of these preventive studies include female soccer players. Moreover, it has been shown that female athletes with increased dynamic valgus and high abduction loads during a jump-landing task are at increased risk of anterior cruciate ligament injury. Such a method may be used to monitor neuromuscular control of the knee joint and may help develop simpler measures of neuromuscular control that can be used to direct female athletes to more effective, targeted interventions (Hewett et al., 2005; Myer et al., 2006).

Aims

General aims

The overall aim of this thesis was to study the incidence of post-traumatic knee OA, as well as relevant short and long-term variables and outcomes associated with the development of knee OA in prospectively followed patients with an ACL injury.

Specific aims

- To determine the prevalence of TF OA15 years after an ACL injury in a patient cohort treated by means of early neuromuscular knee rehabilitation (Study I).
- To assess the prevalence of associated meniscal injuries and meniscectomies and their impact on OA development 15 years after an ACL injury in a patient cohort treated by means of early neuromuscular knee rehabilitation (Study I)
- To evaluate patient-relevant knee function and symptoms in relation to OA and meniscal injuries 15 years after an ACL injury in a patient cohort treated by means of early neuromuscular knee rehabilitation (Study I-II).
- To examine the occurrence of PF OA in a prospectively followed ACL injured cohort primarily treated without ACLR but with early neuromuscular knee rehabilitation and activity modification (Study II).
- To investigate the association between: meniscal injuries; ACLR; activity level; knee symptoms; knee joint range of motion; functional performance and PF OA in a prospectively followed ACL injured cohort primarily treated without ACLR but with early neuromuscular knee rehabilitation and activity modification (Study II).
- To describe the history of knee laxity after an ACL injury over 15 years in a prospectively followed ACL injured cohort primarily treated without ACLR but with early neuromuscular knee rehabilitation and activity modification (Study III).

- To study the association between longitudinal change of knee laxity and associated meniscal injuries and knee OA in a prospectively followed ACL injured cohort primarily treated without ACLR but with early neuromuscular knee rehabilitation and activity modification (Study III).
- To evaluate the knee cartilage quality after an ACL injury by estimating the femoral cartilage GAG content cross-sectionally and longitudinally by CE-MRI (dGEMRIC) (Study IV).
- To examine the influence of a meniscectomy, BMI and an ACLR on cartilage matrix quality, estimated by CE-MRI (dGEMRIC) in an ACL injured cohort followed prospectively (Study IV).

Methods

This thesis includes four prospective longitudinal cohort studies of patients with ACL injuries.

Patients

Studies I-III

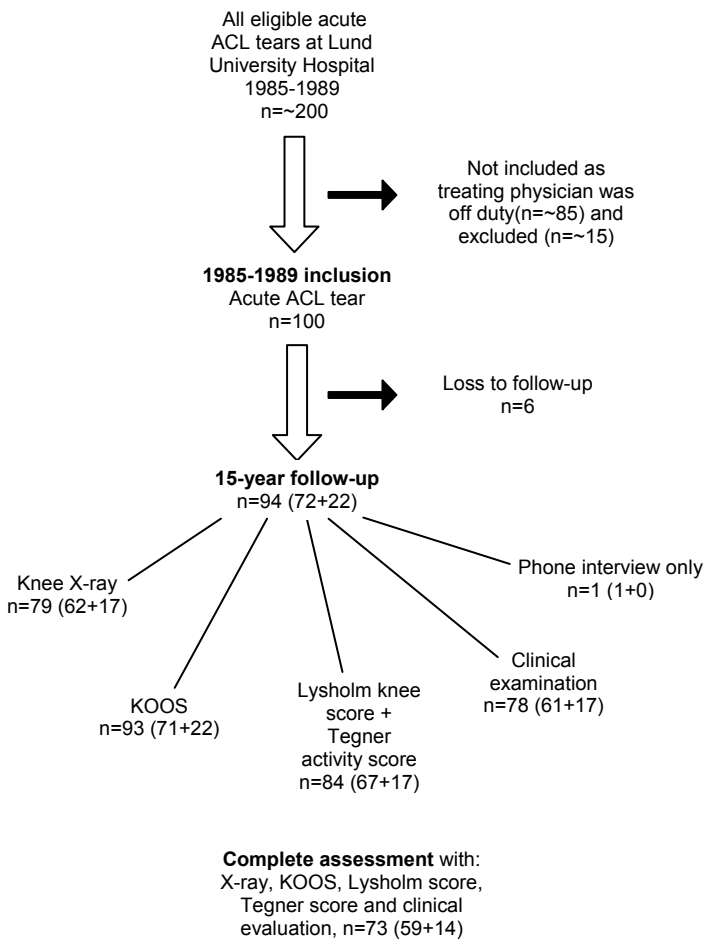
Between February 1985 and April 1989 one hundred (42 women and 58 men) patients with acute ACL injuries were prospectively recruited from the Department of Orthopedics at Lund University Hospital. Mean age at injury was 26 (15-43) years. In general, the patients´activity level was high with a mean Tegner score of 7 (3-9) at baseline. Patient management followed a specific treatment algorithm (Table 1).

Table 1. Treatment Algorithm.

1. Patients in whom an ACL injury could be ruled out, such as patellar dislocations and knee contusions, were treated according to diagnosis.
2. Patients with an ACL injury where excluded in cases of: previous significant injury to the lower extremities, radiographic skeletal lesions, age < 15 or > 45 years, psycho-social disorders, Tegner activity level 10 and unwilling to decrease their activity level (n=5) or an explicit wish for primary ligament reconstruction (n=3)
3. All other patients with a complete tear of the ACL irrespective of associated injuries and activity level were included in the study. A non-operative treatment was advocated and patients in doubt were actively encouraged and persuaded.
4. Knees were tested for laxity, arthroscopic evaluation was performed within 10 days of the injury and concomitant injuries were treated appropriately
5. All included patients were informed about the consequences of an ACL injury and discouraged from continuing contact sports, especially soccer, basketball and team handball.
6. All patients underwent immediate knee rehabilitation by a physiotherapist specialized in knee injuries, details of which have been provided before (Zätterström, 1998). The progression of training level and activity was guided by the patient's neuromuscular function.
7. Late reconstructions were performed in patients with unacceptable knee function, frequent give-way, unacceptable low activity level, or a re-injury resulting in a symptomatic reparable meniscal lesion. Reconstructions were regarded failures in terms of the main aim of the study i.e. an acceptable knee function after non-operative treatment, but the patients in question remained in the study population with respect of the second aim i.e. to prevent degenerative derangement of the joint.

Patients with an acute knee sprain combined with hemarthrosis and/or suspected instability on manual testing, were consecutively recruited within 5 days from the emergency unit to the same orthopedic surgeon (T.F.) who specialized in knee injuries. No referrals occurred when T.F. was off duty. The flow of patients is presented in Figure 1.

Figure 1. Flowchart detailing inclusion and loss to follow-up. KOOS=Knee injury and Osteoarthritis Outcome Score. For further explanation of the Lysholm knee score, Tegner activity scale and clinical examination, see Methods. Number of subjects and the relation between (ACL reconstructed + non-ACL reconstructed) are shown in brackets.



One hundred patients were consecutively included, all of whom had normal knee radiographs at injury. In all included patients the diagnosis of a complete ACL injury was verified by arthroscopy within 10 days of the injury. During arthroscopy, associated meniscal, cartilage and collateral ligament injuries were noted and characterized (Table 2).

Table 2. Descriptions of activity causing knee injury and knee structure(s) injured at baseline, i.e. reinjuries not included (figures represent actual numbers).

Characteristic	Men (n = 58)	Women (n = 42)	Total (n = 100)
Activity			
Soccer	29	6	35
Downhill skiing	9	21	30
Team handball	6	9	15
Other activities	14	6	20
*Injured knee structure(s)**			
ACL (no other associated injury)	9	5	14
+ MCL	12	10	22
+ medial meniscal tear	4	4	8
+ lateral meniscal tear	11	5	16
+ medial and lateral meniscal tear	3	2	5
+ MCL + medial meniscal tear	4	3	7
+ MCL + lateral meniscal tear	6	5	11
+ MCL + medial and lateral meniscal tear	5	2	7
+ tibiofemoral (TF) chondral tear	0	1	1
+ TF chondral tear + MCL	0	3	3
+ TF chondral tear + lateral meniscal tear	2	0	2
+ TF chondral tear + MCL + lateral meniscal tear	2	2	4

ACL = anterior cruciate ligament, MCL = medial collateral ligament (grade1-3 not specified). TF = tibiofemoral. * Figures for meniscal tears include both minor tears left in situ and major tears that were partially resected during baseline arthroscopy.

None of the associated medial collateral injuries were treated surgically, but patients whose knees had medial opening instability wore a hinged knee brace for the first 6-8 weeks after the injury. No cartilage injuries were judged to require specific surgical intervention. 60 patients had accompanying meniscal injuries, of whom 25 underwent a partial meniscectomy. Only seriously injured and unstable meniscal lesions were

resected and in 35 of the patients the meniscal lesion was left in situ. Meniscal repair was not a standard procedure in Lund at the time of inclusion, which explains why no meniscal injuries were sutured at inclusion. Both short- and long-term follow-ups were planned for this cohort of patients. Follow-ups were performed at 6 weeks, 3 months, 1 year, 3 years, and 15 years after the ACL injury. Non-operative ACL treatment was advocated and patients in doubt were actively encouraged and persuaded. Immediately after arthroscopy, patients were randomized to neuromuscular training, either supervised by a physical therapist specialized in training patients with knee injuries, or self-monitored training. The aim of both training methods was to regain joint mobility and improve neuromuscular function in order to obtain compensatory functional stability. All aspects of defective neuromuscular function after an ACL injury such as decreased strength and functional performance, alterations in movement and muscle activation patterns, proprioceptive deficiences and impaired postural control, were taken into account during the rehabilitation. The training was based on the closed kinetic chains principle, focusing on postural function of weight-bearing muscles whilst paying attention to and avoiding knee swelling or new giving-way episodes. At the 6 week follow-up 49% of the patients in the self-monitoring training group were referred to the supervised training group because of restricted joint mobility or considerable muscle atrophy. As a result, the majority of the patients underwent neuromuscular supervised training, comprising two 1 hour sessions weekly for 5 to 8 months. Patients were allowed to increase their activity level as long as their compensatory functional stability gradually improved. The first aim of the original study was to achieve acceptable knee function after non-ACL reconstructive treatment. In cases of > 1 significant re-injury, unacceptable knee function from the patient´s perspective with frequent giving-way or a symptomatic repairable meniscal injury, a late ACLR was performed using a medial miniarthrotomy incision and an isometrically placed BPBT graft. Reconstructions were regarded failures in terms of the main aim of the study i.e. acceptable knee function after non-operative treatment, but the patients remained in the study population with respect to the second aim i.e. to prevent degenerative derangement of the joint. The local institutional review board approved the study and written informed consent was obtained from all participants.

Study IV

Between February 2000 and June 2005, 29 patients (10 of who were women) with an acute ACL rupture verified by means of MRI in a previously uninjured knee were recruited from the Department of Orthopedics, Skåne University Hospital, Malmö. Their mean age was 27 (14-40) years and in general, their activity level was high. With respect to injury mechanism, 19 of the 29 patients were injured during high knee-demanding activities with knee pivoting moments such as soccer, floor-ball, European handball or basketball. Five were injured while alpine skiing and another five in the course of other activities. Only two out of the 29 patients did not exercise and had a sedentary lifestyle. None of them had any radiographic signs of knee OA at baseline. They were included prospectively at irregular intervals depending on the compliance of the emergency unit physicians. Repeat CE-MRI (dGEMRIC) examinations were planned for this cohort, shortly after the injury (average 3 weeks) and after approximately 2 years. In all other respects these patients were treated according to the standard treatment algorithm used at the Department of Orthopedics, Malmö. Patients with suspected instability after a knee sprain were re-examined by an experienced orthopedic surgeon 1-2 weeks after injury. All patients were referred to a physical therapist for knee rehabilitation training before a definite decision on surgical stabilization was made due to subjective instability problems or high knee-demands. The local institutional review board approved the study and written informed consent was obtained from all participants. dGEMRIC results from the ACL injured patients were compared with 24 healthy volunteers (14 men) who have been reported and used previously (Tiderius et al., 2005). The reference group had a mean age of 25 years and similar BMI (22.5±2.3 kg/m^2), as well as similar exercise habits (mean activity level 3), as the ACL injured group.

Table 3 presents the number of women and men with and without ACL reconstructions available at the last follow-up in studies studies I-IV.

Table 3. Outcome in respect of ACLR or NACLR in studies I-IV.

Group	Study	
	I-III	IV
NACLR women	32	3
NACLR men	40	12
ACLR women	8	7
ACLR men	14	7

Outcomes

A summary of outcomes used in studies I-IV is presented in Table 4.

Table 4. Overview of outcome measures

Outcome	Study I	Study II	Study III	Study IV
Knee Laxity examination			X	
Range of motion		X	X	
One-leg hop test for distance		X		
Lysholm knee score	X	X	X	X
Tegner activity scale	X	X	X	
KOOS	X	X		
IKDC	X	X	X	
Knee Radiography	X	X	X	
CE-MRI (dGEMRIC)				X
BMI	X		X	X

Knee laxity examination (Study III)

Manual knee laxity was evaluated with the Lachman test and the pivot-shift phenomenon. The Lachman test was graded according to the International Knee Documentation Committee (IKDC) Knee Ligament Evaluation Form (Andersson et al., 2006) and performed with the subject in the supine position and the knee at 15° to 25° of flexion. The anterior displacement of the tibiae in relation to the femur was estimated in comparision with the contralateral (non-injured) knee, with Lachman grade 0 as < 3 mm, grade 1 as 3-5 mm, grade 2 as 6-10 mm and grade 3 as > 10 mm. The pivot-shift phenomenon was elicited with the Flexion-Rotation Drawer (FRD) test (Larson et al., 1983; Andersson et al., 2000) performed with the subject in the supine position. A coupled axial compression and valgus stress with

simultaneous internal rotation was applied to the muscular relaxed and extended knee-joint and when the knee-joint was brought into flexion, the relocation of the subluxed lateral femoral condyle against the tibial plateau was estimated. The pivot-shift test was graded as 0 (negative), 1 (glide), 2(clunk), 3(gross), in comparison with the uninjured side. However**,** as no specific measurement in millimetres of the laxity or displacement between the femur and the tibiae is performed these tests are examiner-biased and not fully objective. Nevertheless, good correlation between the Lachman test and more objective measurements of the anterior displacement between tibiae and femur with the KT-1000 arthrometer has been demonstrated (Sernert et al., 2002).
Instrumented knee testing was performed with the KT-1000 arthrometer (MEDmetric Corp San Diego, California) in accordance with the manufacturer`s manual. This device measures the anterior and posterior displacement of the tibiae in millimetres by pulling or pushing the tibiae in relation to the femur, with the subject in the supine position and the knee at 15° to 25° of flexion. It has been found to yield reproducible and valid results (Daniel et al., 1985; Pugh et al., 2008). Data on manual laxity and KT-1000 were produced in 78 (83%) of the 94 patients followed-up after 15-years (Figure 1).

Range of motion (Studies II-III)

Range of motion of the index and contralateral knee was measured with a goniometer. Extension and flexion deficits were determined as the loss of extension or flexion in the ACL injured index knee in comparison to the passively maximally extended or flexed posture of the contralateral uninjured limb.

One-leg hop test for distance (Study II)

The one-leg hop test for distance with the arms free was recorded. The test has previously been described in detail (Ageberg et al., 2007). Each patient was asked to perform the single-legged hop for distance as far as possible, with taking off and landing on the same foot. The test was performed three times with each leg, alternating the right and left leg. A trial single-legged hop preceded the measurements. Three trials for each leg were recorded and averaged.

Lysholm knee score (Studies I-IV)

The patient administered Lysholm score (Lysholm et al., 1982) was used to document subjective knee symptoms. In the Lysholm score the highest obtainable score is 100. If the patient has impaired knee function with locking, instability, pain, swelling, limp, walking aid, decreased ability to climb stairs and squat, the score is less than 100. A score of 95 to 100 points is considered an excellent result; 84 to 94, good; 65 to 83, fair; and less than 65 points, poor. This score has been extensively documented with validity, reliability and responsiveness testing (Johnson et al., 2001; Briggs et al., 2006, 2009). It was originally designed for assessment by a physician, but can be used as a patient-administered evaluation (Hoher et al., 1997; Briggs et al., 2006, 2009).

Tegner activity scale (Studies I-III)

The Tegner score (range 0-10) was used to assess the individual's physical activity level (Tegner and Lysholm, 1985). The Tegner activity scale was added to complement the Lysholm score, as patients with differing activity levels are expected to experience different grades of knee symptoms, with more symptoms when the activity level increases. Over the years, both the Tegner activity scale and the Lysholm score were used preferentially as patient-administered scores. Grade 10 represents high demanding knee-activities such as professional soccer or American football and 0 represents sick-leave or disability pension. Grade 4 represents non-competitive activities such as jogging, cycling and cross-country skiing.

KOOS (Studies I-II)

The Knee Injury and Osteoarthritis Outcome Score (KOOS) (Roos et al., 1998) is a self-reported outcome of knee function including the items contained in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy et al., 1988) (see also; Review of the literature-Outcomes after ACL injury-*Knee scoring systems*). The KOOS score has been extensively employed during recent years, especially in Scandinavia, and is currently used in the Swedish ACL-register (www.aclregister.nu). KOOS consists of five subscales that assess the patients' perception of pain, symptoms, activities of daily living (ADL), sports and recreation, and knee related quality of life (QOL). In KOOS, the complete WOMAC dimension of function is included in the dimensions of ADL and sports and recreation.

While the WOMAC score focuses on long-term consequences of knee OA, the KOOS score was developed to be used both in the acute phase after knee injuries and at long-term follow-up. It was developed with the awareness that traumatic meniscus, cartilage and ligament injuries often lead to OA, and an instrument was needed that could evaluate different aspects of symptoms longitudinally, that are relevant both in the short and long-term after the injury. According to the user's guide, a score from 0 to 100, where 100 is the best possible result, is calculated separately for each of the five different subscales. One important difference of the KOOS and other scoring systems is that a total score of all five subscales is not calculated. The five different subscales are unequally relevant in different patient populations and at different follow-up periods. The ADL subscale, for example, is only relevant in older patients, while the sports and recreation subscale is relevant for both young and older patients. The KOOS has shown good validity, reliability and responsiveness (Roos et al., 1998; Paradowski at al., 2006; Roos et al., 2003).

IKDC (Studies I-III)

The International Knee Documentation Committee (IKDC) developed a scoring system for ACL knee injuries in collaboration between The American Orthopedic Society for Sports medicine (AOSSM) and the European Society of Sports Traumatology, Knee surgery and Arthroscopy (ESSKA) (Hefti et al., 1993; Irrgang et al., 1998). The IKDC consists of different parts in which patient subjective (patient-relevant) complaints are combined with symptoms, clinical Range of Motion (ROM), manual and instrumented ligament testing and radiographic assessment, where the worst category grade determines the final evaluation (IKDC-final). In IKDC, the activity level is assessed in five different categories according to the extent of knee cutting and pivoting knee movements. In studies I-II, the IKDC data were collected at the 15 year follow-up. The IKDC Knee Forms 2000 version was used, including the Demographic Form, the Current health Assessment Form, the Subjective Knee Evaluation Form and the Knee Examination Form. This instrument has been proven valid and reliable (Irgang et al., 2001, 2002). In studies I-II data from the Subjective Knee Evaluation were presented and data from the Knee Examination Form were employed in study III. We did not use the final evaluation (IKDC-final) score, since it contains both subjective and objective data.

Knee Radiography

Standing anteroposterior radiographs were obtained in a standardized knee position with both knees in 20° of flexion and weight bearing using a General Electric Prestige 2 on a tilt table (film-focus distance 1.5 m). A fluoroscopically positioned x-ray beam was used to optimize medial tibial plateau alignment. The radiographs were all independently read within a period of 2 days by 2 observers (P.N. and M.E.) blinded to clinical details. However, reconstructed ACLs could easily be detected by the graft fixation device. The presence of joint space narrowing (JSN) and osteophytes were graded on frontal images on a 4-point scale (range 0-3, 0 = no evidence of JSN or bony change) according to the Osteoarthritis Research Society International atlas (Altman et al., 1995). The inter-rater reliability (kappa statistic) was $\kappa = 0.78$ for JSN and $\kappa = 0.52$ for osteophytes. No discrepancy of more than 1 grade was observed. All discrepancies were reread and consensus was reached.

Radiographic tibiofemoral (TF) OA was considered present if any of the following criteria were fulfilled in any of the 2 TF compartments: JSN of grade 2 or higher, sum of the 2 marginal osteophyte scores from the same compartment ≥ 2, or grade 1 JSN in combination with grade 1 osteophyte in the same compartment. This cutoff approximates grade 2 knee OA based on the Kellgren and Lawrence (K/L) scale (Kellgren and Lawrence, 1957). The presence of medial or lateral marginal osteophytes and medial or lateral joint space narrowing (JSN) in the PF joint were graded on the patella axial images on a 4-point scale (range 0-3, 0 = no evidence of JSN or bony change) according to the Osteoarthritis Research Society International atlas (Altman et al., 1995). Radiographic PF OA was considered present if any of the following criteria were fulfilled: JSN of grade 2 or higher in either the medial or lateral compartment, sum of marginal osteophyte grades ≥2, or grade 1 JSN in combination with a grade 1 marginal osteophyte.

CE-MRI (dGEMRIC) (Study IV)

Patients were investigated with CE-MRI (dGEMRIC) approximately 3 weeks (range 3-47 days) and 2 years (range 7-60 months) after the injury using a standard 1.5 T MRI-system with a dedicated knee coil (Magnetom Vision; Siemens Medical Solutions, Erlangen, Germany) (Burstein et al., 2001; Tiderius et al., 2005; Roos and Dahlberg, 2005; Ericsson et al., 2009). Initially, a diagnostic series was performed to verify the ACL rupture and concomitant cartilage and meniscus injuries. Gd-DTPA^{2-} (Magnevist®, Schering Ag, Berlin, Germany) was injected at 0.3 mmol/kg body weight. To optimize the distribution of Gd-DTPA^{2-} into the cartilage,

the patients exercised by walking up and down stairs for approximately ten minutes, starting five minutes after the injection. Post-contrast imaging with subsequent T1-relaxation time calculation of the cartilage (T1Gd) was performed two hours after the injection. Central parts of the weight-bearing lateral and medial femoral cartilage were identified and quantitative relaxation time calculations made in a three mm thick sagittal slice on each condyle, using sets of six turbo inversion recovery (IR) images with different inversion times (TR=2000 ms, TE=15 ms, FoV 120 x 120 mm^2, matrix=256 x 256, TI= 50, 100, 200, 400, 800 and 1600 ms). In the lateral and medial slices, a full thickness region of interest (ROI) was drawn within the cartilage between the center of the tibial plateau and the rear insertion of the meniscus using the MRI-Mapper developed at the Beth Israel Deaconess Medical Center (Boston, USA). All ROI drawings were blinded to per-operative findings and surgical treatment (Tiderius et al., 2004). T1Gd was calculated by using the mean signal intensity from each ROI as input to a three-parameter fit (Kingsley et al., 1998).

Ethics

The local institutional review board (the Medical Ethics Committee at Lund University) approved the study and written informed consent was obtained from all participants.

Statistical analysis

Statistical analysis of all studies in this thesis was made using the Statistical Package for the Social Sciences for Windows (SPSS, version 14.0 and 17.0). *P*-values for binary data in contingency tables were calculated with Fisher's exact test and *P*-values for continuous data by the Mann-Whitney test or t-test as appropriate. In study III, the effects of evaluated baseline risk factors including knee laxity, using the presence or absence of an inferior outcome with re-injuries and additional surgery as the dependent variable, were analyzed by means of logistic regression. The multivariate odds ratio (OR) estimates with 95% confidence intervals (95% CIs) were based on the models with all variables entered. All tests were 2-paired and $P \leq 0.05$ was considered statistically significant. An overview of the statistical methods used is presented in Table 5.

Table 5. Statistical methods employed in studies I-IV.

Statistical method	Study I	Study II	Study III	Study IV
One sample t-test	X	X	X	X
Paired samples t-rest				X
Independent samples t-test	X	X	X	X
Mann Whitney test	X	X	X	
Pearson`s correlation			X	X
Spearman`s correlation			X	
Kappa statistic	X			
Fischer`s exact test	X	X	X	
Logistic regression analysis			X	

Aspects of methodological errors

Subjects

Several studies have revealed a high, but variable, prevalence of knee OA in ACL-injured patients 15 years and more after the injury, suggesting these patients suitable in a model to study post-traumatic OA.

The data presented in studies I-III are based on a well described cohort of 100 consecutive subjects with a complete rupture of the ACL and planned, regular follow-ups. The follow-up rate after 15 years was high (94%).

The treatment algorithm prescribed no ACLR as the first treatment strategy. Our exclusion criteria may have biased our results in terms of finding a lower OA prevalence, as sports participation at professional level may be a characteristic of high risk patients and a handful of patients with the highest Tegner activity score of 10 were excluded (studies I-III). However, we consider it unlikely that this fully explains the low prevalence of OA observed.

Our patient groups were quite homogenous as all patients had a clinically verified ACL injury (verified arthroscopically (studies I-III) or by MRI (study IV)). The patients from the Departments of Orthopedics, Lund (studies I-III) respectively Malmö (study IV), are representative of the general population of patients with ACL injuries and included a wide range of ACL-injured patients, i.e. not only soccer players for instance, who may constitute a particularily high risk category with regard to knee OA due to the high knee load and frequent knee injuries. Since the injured ACL has a very broad and individual spectrum of concomitant injuries to the cartilage and menisci, the patients included were heterogenous in this aspect. However, the careful monitoring of the condition of the knee and of meniscal injuries are unique factors in the presented studies (I-IV).
The KOOS control subjects were of the same age and from the same geographic area as the patients (studies I-II).

One limitation of studies I-II is that they were not powered to identify risk factors for OA development in multivariate analyses. Absence of statistically significant differences may be due to a type II error, thus interpretation of negative findings should be undertaken with caution.

Outcome methods

We wanted to assess knee symptoms, knee function and objective measures of developing knee OA after an ACL injury. We used gold standard radiographic procedures (studies I-III) to diagnose knee OA. The presence of joint space narrowing (JSN) and osteophytes were graded according to the Osteoarthritis Research Society International atlas (Altman et al., 1995). The radiographs were all independently read within a period of 2 days by 2 observers. The inter-rater reliability (kappa statistic) was $\kappa = 0.78$ for JSN and $\kappa = 0.52$ for osteophytes, which is considered moderately good. Due to geographical and practical reasons 79% of the 100 patients were radiographed at the 15 year follow-up, which could be a limitation, especially in the analysis of different sub-groups.

In general we used validated, reliable and patient-relevant outcome measures, i.e. self-administered questionnaires (studies I-IV) as well as the Tegner activity scale (studies I-III), which is commonly employed for athletes. It is not easy to assess physical activity and self-reported activity tends to be over-estimated, especially by men.

In study III we wanted to examine knee laxity. We had to use established methods such as the Lachman test, the pivot-shift test and the KT-1000 arthrometer, despite the fact that they can be criticized for being subjective due to questionable reliability. However, the KT-1000 arthrometer has long been the mainstay among knee laxity testing devices. Its accuracy in diagnosing ACL insufficiency shows sensitivities ranging from 89% to 92% and specificities of approximately 95% (Bach et al., 1990; Ganko et al., 2000). Nevertheless, the reliability of the device has been questioned and found both good (Wroble et al., 1990) and poor (Sernert et al., 2001). The experience of the examiner seems to be crucial for obtaining reliable measurements (Ballantyne et al., 1995). Clinical manual laxity testing appears to be more diagnostically effective than the KT-1000, which makes use of the device in the clinical setting questionable (Wiertsema et al., 2008). The most appropriate and perhaps only role of the KT-1000 may be in the research setting, where objective readings are required.

The relationship between knee laxity and functional knee stability is, of course, more important but difficult to assess, and no consensus has been achieved.

In study IV we wanted to measure the molecular status of the knee cartilage at an early stage and 2 years after ACL injury. The CE-MRI (dGEMRIC) has been found to estimate cartilage GAG content and demonstrates good correlation with known biochemical and biomechanical properties of the

cartilage (Bashir et al., 1999; Gray et al., 2008). In this respects it may be argued that the study sample is relatively low. However, previous studies showing that activity level, quadriceps strength and BMI, but not gender and age, affect T1Gd, suggest that only a limited number of patients are needed to detect statistically significant and clinically relevant differences using dGEMRIC. This is mainly due to a low variability in T1Gd values in examined cohorts. Furthermore, it is not feasible to include patients enabling multivariable modeling in dGEMRIC studies due to costs, shortage of MRI capacity and difficulties to schedule patients. Unfortunately, we had to exclude more patients than expected because of motion artifacts in the MR images. However, MRI signals are objective measures suggesting that excluded patients are at random.

37 of the 40 patients were re-examined with MRI. 7 had to be excluded because of motion artifacts in the MR images, defined as having >10% of the pixels within the ROI outside a T1 interval of 0-1300 ms. One patient had to be excluded because his opposite knee was examined by mistake at follow-up. However, the 8 excluded patients did not differ regarding patient characteristics.

There are biological and technical variations in repeated CE-MRI (dGEMRIC) measurements. In the femoral condyle cartilage, the measured 2-D T1Gd root-mean-square value of the coefficients of variation (CV_{RMS}) has been estimated to 5-8% in a cohort consisting of 9 non ACL reconstructed patients 20 years after injury, with 2 weeks between MR investigations (Siversson et al., 2010). In another study by Multanen et.al. in asymptomatic volunteers with a an average interval of 5 days between the scans, the CV_{RMS} for full-thickness ROIs was 5-7%, which is considered good (Multanen et al., 2008). Another study has shown that the mean T1Gd inter-individual variability in ROI drawing was 1-2% for six different investigators and the intra-observer T1Gd variability coefficient of variation (C.V.%) was 1-2% medially and 2-3% laterally (Tiderius et al., 2004).

The central weight-bearing cartilage of the medial and lateral femoral condyles was examined with CE-MRI (dGEMRIC). This volume was chosen because early degenerative cartilage changes are most common at this site (Boegard et al., 1997). Most likely more information could have been obtained if total knee cartilage volume, including tibiae, had been measured. Future studies may therefore consider using a 3-D protocol (McKenzie et al., 2006).

Intervention

In studies I-III and study IV our original intention was not to compare different treatment regimens.

In studies I-III the intention was to obtain functional knee stability in all subjects by means of neuromuscular rehabilitation and activity modification in order to cope with the injury. The secondary treatment strategy was to avoid further meniscal injuries and OA joint changes in study participants who did not succeed in obtaining functional knee stability, which explains why 22 subjects were subsequently reconstructed because of significant reinjuries and refusal to accept any decrease in activity level.

In study IV all patients were treated according to the standard treatment algorithm used at the Department of Orthopedics, Skåne University Hospital, Malmö. Patients with a knee distortion with or without hemarthrosis, and with instability suspected by the emergency room physician, were all scheduled for repeated clinical assessment after 1-2 weeks by an experienced orthopaedic surgeon specialized in knee surgery. All patients were referred to a physical therapist for knee rehabilitation training before a definite decision on surgical stabilization was made due to persistent subjective instability problems or high knee-demands.

Thus, there was no random allocation to surgery or non-surgical rehabilitation. Hence the patients in this thesis who underwent ACL reconstruction represent a group of non-copers and those who regained functional knee stability a group of copers.

Randomized controlled trials using validated patient-relevant outcome measures comparing surgical techniques, rehabilitation protocols and optional non-surgical treatments are scarce and difficult to design but nevertheless necessary. However, an ethical problem is the need to randomize patients to an operation they may not require or be interested in, or vice versa, not being randomized to a necessary operation.

Results

Knee cartilage quality after an ACL injury with or without meniscal injury (Study IV)

In the same study cohort it had previously been shown that 3 weeks (baseline) after the ACL injury there was a decreased cartilage T1Gd consistent with GAG loss, in both the lateral and medial femoral weight-bearing cartilage, possibly due to a generalized environmental disturbance within the knee (Tiderius et al., 2005). Additionally, T1Gd was shorter in the medial than the lateral femoral cartilage, suggesting lower GAG content, both at the first (P=0.006) and the second (P=0.006) MRI. T1Gd of the medial femoral cartilage at follow-up (357 ms) was 17% lower than in previously examined comparable healthy volunteers (428 ms), (Tiderius et al., 2005). Results from this longitudinal follow-up study indicate that the cartilage GAG content was partially regained in the lateral but not in the medial compartment. T1Gd (mean±SD) for all subjects in the medial compartment did not differ between baseline and the 2 year follow-up, 357±50 and 363±61 ms, respectively (P=0.57). In the lateral compartment, T1Gd increased between the two examinations, from 374±48 to 396±48 ms (P=0.04), indicating that GAG had been partially regained at the follow-up.

The healthy reference group had longer T1Gd (mean±SD) values than the ACL-injured patients at follow-up, medially: 428±38 vs. 363±61 ms (P<0.0001) and laterally: 445±41 vs. 396±48 ms (P=0.0002).

Cartilage quality and meniscal injury

Longitudinal analysis (change in T1Gd between first and second MRI) showed that patients operated on with a medial partial meniscectomy (n=6) tended to decrease their T1Gd by (mean±SD) 30±53 ms in the *medial* femoral cartilage, whereas patients without medial meniscectomy (n=23) tended to increase their T1Gd by 16±56 ms (P=0.09, Independent samples t-test between the two groups). Similarily, having a *lateral* partial meniscectomy (n=8) tended to decrease T1Gd in the lateral femoral cartilage by in average 12±42 ms, whereas the absence of meniscectomy (n=21) resulted in increased T1Gd by in average 35±55 ms (P=0.04, Independent samples t-test between the two groups).

Cross-sectional T1Gd analysis at the second MRI showed that patients who underwent a partial meniscectomy had a shorter T1Gd in the ipsilateral knee compartment than patients without ipsilateral meniscectomy (mean±SD), 296±62 vs. 380±49 ms medially (P=0.002), and 368±48 vs. 406±44 ms laterally (P=0.05).

Cartilage quality and patient characteristics

In normal-weight patients (BMI <25), T1Gd increased between baseline and follow-up (Figure 2). However, in over-weight patients (BMI >25), T1Gd *decreased* between the two MRI investigations, P=0.01 (Figure 2). Subgroup-analysis revealed a trend towards more GAG loss (decrease in T1Gd) in over-weight patients with a meniscectomy compared to normal-weight patients with a meniscectomy (Figure 2). Furthermore, in the medial femoral cartilage we found a negative correlation between BMI at baseline and T1Gd at follow-up, r=-0.43 (P=0.02), but there was no such correlation in the lateral femoral cartilage, r=0.09 (P=0.6). T1Gd (ms, mean±SD) in the medial femoral condyle was lower at baseline in patients with a lower activity level than in patients with a high activity level, 321±48 and 366±47 respectively (P=0.05). T1Gd did not differ between patients with an ACL reconstruction vs. no ACL reconstruction, at baseline or the follow-up examination. No significant relationship was found between T1Gd and age and sex.

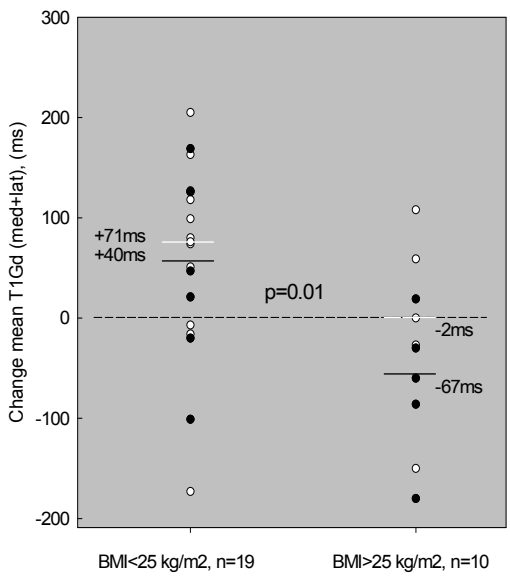


Figure 2. Change in T1Gd (ms) between the first and second MRI (mean of medial and lateral femoral cartilage) in patients with an ACL injury related to BMI and concomitant partial meniscus surgery with ● or without a meniscectomy ○). The change in T1Gd (mean±SD) was +61±95 ms in patients with a low BMI (range 19-24.9 kg/m^2) compared to -35±89 ms in patients with a high BMI (range 25-31 kg/m^2), P=0.01. Subgroup-analysis in meniscectomized knees showed a change in T1Gd (mean±SD) of +40±98 ms in patients with a low BMI (range 19-24.9 kg/m^2) compared to -67±74 ms in patients with a high BMI (range 25-31 kg/m^2), P=0.07.

Radiographic TF OA after an ACL injury with or without meniscal injuries (Study I)

Radiographic TF OA was present in 13 of 79 (16%) patients (9 men) at follow-up 15 years after the ACL injury (Figure 3). Seven patients had medial, 3 had lateral, and the remaining 3 had OA in both compartments. The mean age of patients with and without TF OA was 45 and 41 years, respectively (P=0.09). There were no significant differences in BMI or Tegner activity scale at the 15 year follow-up between patients with or without TF OA. All 13 patients with TF OA were meniscectomized due to a major meniscal tear either at index (n=5) or follow-up (n=8). In contrast, none of the remaining radiographed patients with no known or only a minor meniscal tear developed TF OA (n=44) (P<0.0001). The TF OA was found in the same compartment as the meniscal tear.

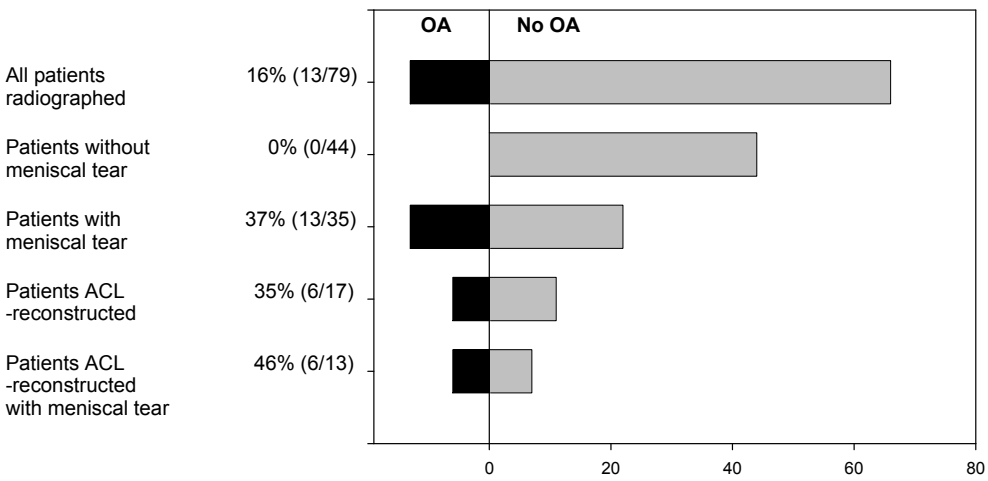


Figure 3. The prevalence of TF OA after an ACL injury in different study sub-groups. The cutoff value for defining radiographic TF OA approximated Kellgren/Lawrence grade 2. A major meniscal tear was defined by a full thickness tear in the substance or a peripheral tear, which required excision or suturing. Only cases with cumulative major meniscal tears are represented in the figure.

Radiographic PF OA and ACLR after an ACL injury (Study II)

15 years after the ACL injury we found PF OA in 12/75 knees (16%), (whereof 7 had coexistent TF OA). Mean age of subjects with and without PF OA was 45 and 41 years, respectively (P=0.19). In subjects who had been meniscectomized during follow-up, 10 of 33 had PF OA compared with 2 of 42 subjects not meniscectomized (P=0.004), (Figure 4). 15 years after the ACL injury 22 out of 94 patients (23%) had had their ACL reconstructed. In the ACL reconstructed group, PF OA was present in 7 out of 15 knees (15 out of 22 ACL reconstructed patients available and consented to radiography). The corresponding figure for non-reconstructed knees was 5 out of 60 (P=0.002), (Figure 4).

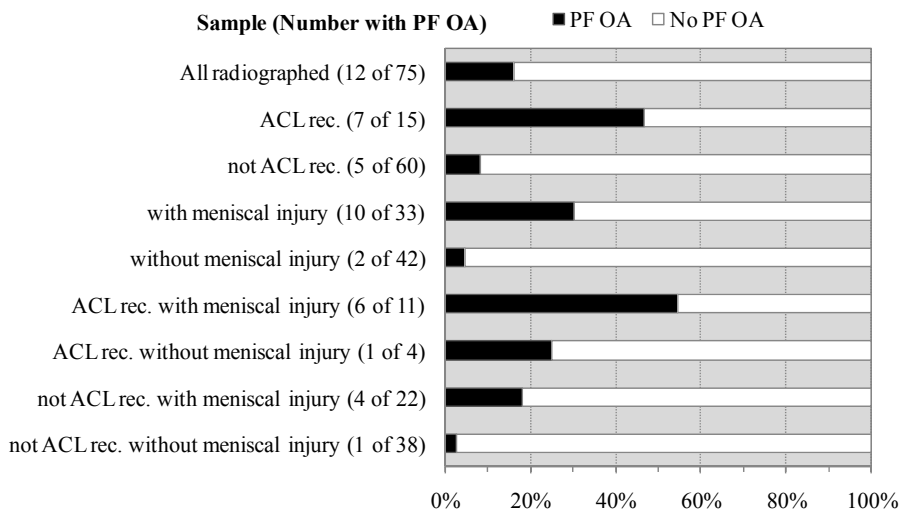


Figure 4. The fraction of subjects with PF OA after an anterior cruciate ligament (ACL) injury in different study sub-groups.

Self-reported knee symptoms after an ACL injury (Studies I-II)

Male gender, subjects ≥ 26 years old at injury with intact menisci, non-reconstructed knees without radiographic TF or PF OA at the 15-year follow-up achieved the best KOOS scores (Table 6), (Figures 5, 6).

Table 6. The Mean (SD) KOOS results related to different patient carachteristics and clinical outcome 15 years after an ACL injury. ACLR = ACL reconstructed. TF = tibiofemoral. PF = patellofemoral.

		KOOS subscales mean (SD) at 15-year f.u.					
		Pain	Symptoms	ADL	Sports/ Rec.	QOL	P-value Mann-Whitney test
All subjects	(n=93)	90 (13)	88 (16)	94 (10)	76 (25)	74 (24)	
Sex	Women (n=38)	89 (14) [1]	87 (14) [2]	93 (12) [3]	72 (27) [4]	70 (27) [5]	0.24 [1] 0.47 [2] 0.16 [3] 0.29 [4] 0.27 [5]
	Men (n=55)	91 (13) [1]	88 (17) [2]	96 (9) [3]	79 (24) [4]	77 (22) [5]	
Age at injury	<26y. (n=58)	88 (14) [1]	85 (17) [2]	93 (12) [3]	73 (26) [4]	68 (25) [5]	0.010 [1] 0.087 [2] 0.075 [3] 0.14 [4] 0.0001 [5]
	≥26y. (n=35)	94 (12) [1]	92 (11) [2]	97 (7) [3]	81 (23) [4]	84 (19) [5]	
Major meniscal injury from baseline to f.u.	Yes (n=43)	88 (14) [1]	84 (17) [2]	93 (12) [3]	70 (27) [4]	71 (25) [5]	0.033 [1] 0.040 [2] 0.076 [3] 0.045 [4] 0.20 [5]
	No (n=50)	92 (12) [1]	91 (13) [2]	96 (9) [3]	81 (22) [4]	76 (23) [5]	
ACLR	Yes (n=22)	87 (13) [1]	84 (17) [2]	95 (10) [3]	69 (25) [4]	69 (23) [5]	0.031 [1] 0.29 [2] 0.10 [3] 0.14 [4] 0.11 [5]
	No (n=71)	91 (13) [1]	88 (15) [2]	92 (12) [3]	78 (25) [4]	75 (24) [5]	
TF OA	Yes (n=13)	83 (18) [1]	79 (21) [2]	86 (17) [3]	65 (30) [4]	64 (30) [5]	0.11 [1] 0.088 [2] 0.11 [3] 0.20 [4] 0.15 [5]
	No (n=66)	91 (13) [1]	89 (14) [2]	96 (9) [3]	77 (25) [4]	76 (23) [5]	
PF OA	Yes (n=12)	85 (19) [1]	80 (20) [2]	90 (16) [3]	65 (33) [4]	74 (27) [5]	0.34 [1] 0.23 [2] 0.40 [3] 0.38 [4] 0.82 [5]
	No (n=63)	90 (13) [1]	88 (15) [2]	95 (10) [3]	76 (25) [4]	74 (24) [5]	

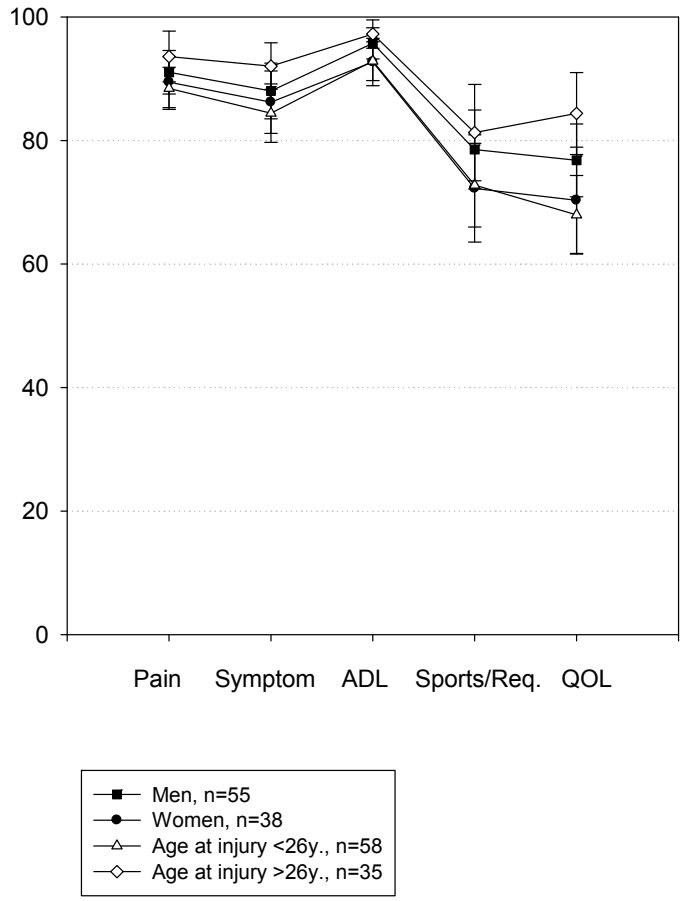


Figure 5. The Knee injury and Osteoarthritis Outcome Score (KOOS) mean score profile for sub-groups of the anterior cruciate ligament (ACL) injury study sample at the 15 year follow-up (Studies I-II), see legends. There was a difference in the subscales Pain (P=0.010) and QOL (P<0.0001) between patients aged <26 years at injury -Δ- (n=58) ≥26 years at injury -◊- (n=35).

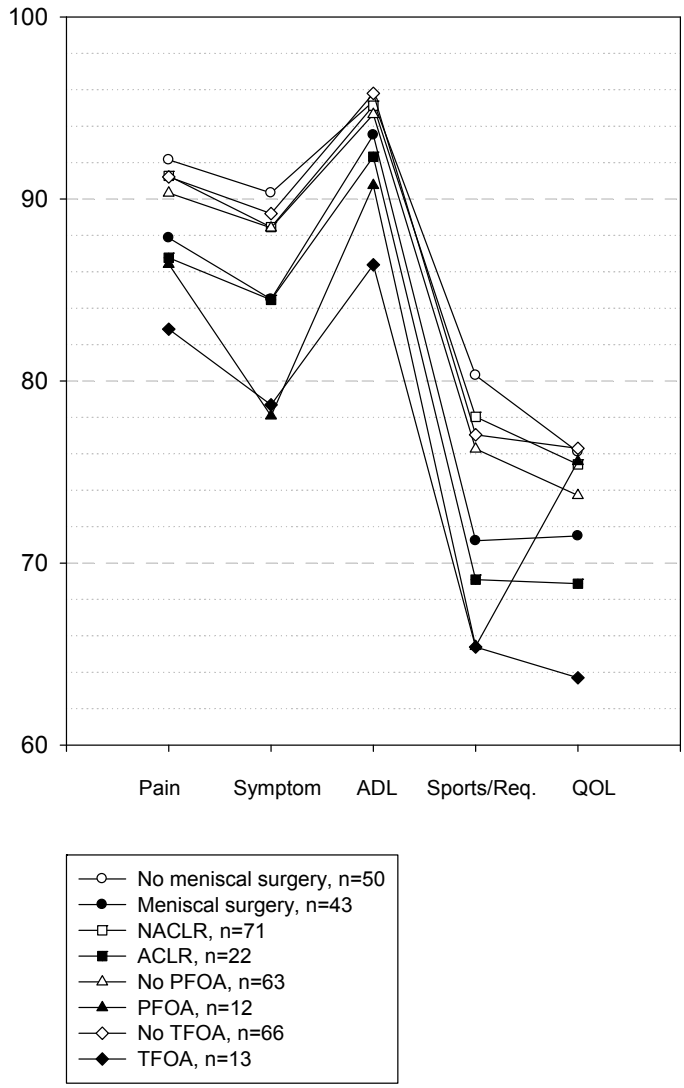


Figure 6. The mean score profile of Knee injury and Osteoarthritis Outcome Score (KOOS) for sub-groups of the anterior cruciate ligament (ACL) injury study sample at the 15 year follow-up (Studies I-II), see legends. NACLR = non-ACL reconstructed. ACLR = ACL reconstructed. PF = patellofemoral. TF = tibiofemoral. There was a difference in the subscales Pain (P=0.033), Symptoms (P=0.040) and Sport/Rec. (P=0.045) between patients with -●- (n=43) or without –○- (n=50) meniscal surgery and in the subscale Pain between those who had -■- (n=22) or did not have -□- (n=71) an ACLR (P=0.031).

Physical activity level after an ACL injury (Studies I-III)

The median (range) Tegner activity score in all patients decreased from 7 (3-9) at index injury to 4 (0-7) at the 15 year follow-up (n=84). There were no significant differences in the Tegner activity score at the 15 year follow-up between patients with or without TF OA. In patients with or without PF OA the Tegner activity score decreased to 5 (4-7) and 4 (0-7), respectively (P=0.003). At injury, 92 of the 100 patients regularly participated in activities such as soccer, handball, tennis and skiing (the two highest levels of activity in the IKDC Subjective Knee Evaluation Form, level 1 and 2) compared with 44 of 79 (56%) patients at follow-up, P<0.0001. In subjects *still* participating in the two highest activity levels at follow-up (despite the recommended activity level restriction in the treatment algorithm) 9 out of 37 had PF OA compared with 2 out of 30 in cases where the activity level was lower at follow-up (P=0.09). Subjects with PF OA maintained a higher activity level from injury to follow-up, but did not differ significantly from those without PF OA regarding patient-relevant symptoms and knee function.
The median Tegner activity score at index injury was 7 in both ACL reconstructed and non-reconstructed patients. At the 15 year follow-up, reconstructed patients tended to have a higher Tegner activity score of 4.5 compared with 3.7 for those without a reconstruction (P=0.09).

When the multivariate effects of each investigated risk factor related to an inferior long-term outcome with secondary knee surgery and/or OA were analyzed using logistic regression, the Tegner activity score at baseline was non-significant. Thus, patient activity level at the time of the ACL injury was not of major relevance for the long-term outcome.

Knee laxity after an ACL injury (Study III)

During the first 3 years knee joint laxity, as determined by the Lachman test, remained relatively unchanged with an average grade of approximately 2 in knees that were later reconstructed and an average grade of about 1.5 in those which were not (Figure 7). The Lachman test grade was lower at the 15 year follow-up than at baseline both in ACL reconstructed and non-ACL reconstructed knees, $P<0.0001$ for both, although knees that were reconstructed were generally more stable than non-reconstructed knees, $P=0.007$ (Figure 7).

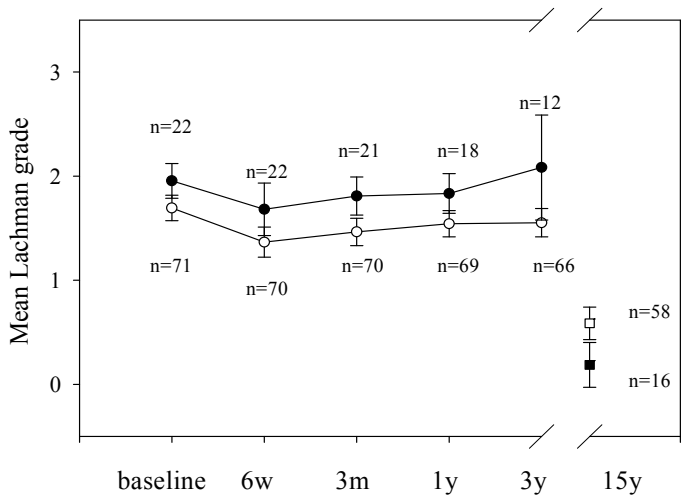


Figure 7. Mean Lachman test results during the first 3 years of subjects who subsequently underwent an ACL reconstruction during follow-up (●) and individuals who did not have an ACL reconstruction during the 15 year follow-up (○). 15-year results for ACL reconstructed (■) and non-ACL reconstructed subjects (□). Error bars show 95% confidence intervals. ACLRs were performed in three patients between the 3 month and 1 year follow-up, in six patients between the 1 and 3 year follow-up and in 13 patients between the 3 and 15 year follow-up.

During the first 3 years, knee joint laxity as determined by the pivot-shift test changed from an average grade of approximately 1.5 to 2 in knees that were later reconstructed and from an average grade of about 1.5 to 1 in those which were not (Figure 8). The pivot-shift test grade was also lower at the 15 year follow-up than at baseline both in reconstructed and non-reconstructed knees, $P<0.0001$ for both, and knees that were reconstructed had on average lower grades of pivot-shift than non-reconstructed knees, $P<0.001$ (Figure 8).

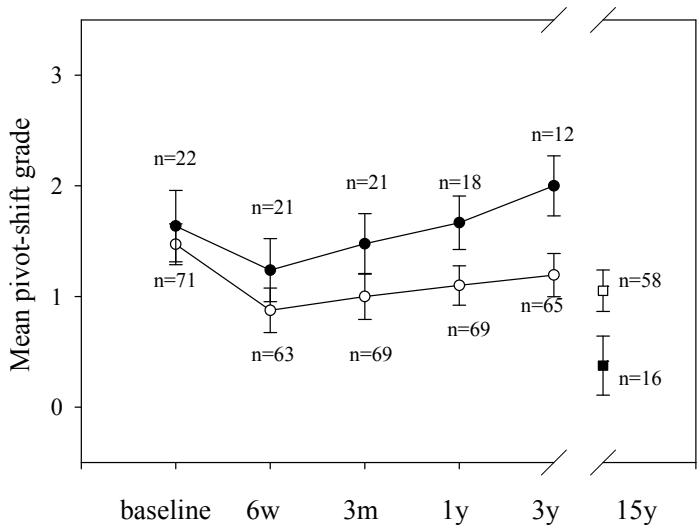


Figure 8. Mean Pivot-shift test results during the first 3 years of subjects who subsequently underwent an ACL reconstruction during follow-up (●) and individuals who did not have an ACL reconstruction during the 15 year follow-up (○). 15 year results for ACL reconstructed (■) and non-ACL reconstructed subjects (□). Error bars show 95% confidence intervals. ACLRs were performed in three patients between the 3 month and 1 year follow-up, in six patients between the 1 and 3 year follow-up and in 13 patients between the 3 and 15 year follow-up.

On manual maximum testing, non-ACL reconstructed subjects (n=58) had a mean (SD) difference between the injured and non-injured knee of 2.4 (2.7) mm compared with 1.8 (4.2) mm in ACL reconstructed subjects (n=16), P=0.46. There was a correlation between the KT-1000 arthrometer manual maximum difference testing values and the Lachman test. Spearman`s correlation coefficient 0.40, P=0.0001. There was also a correlation between the KT-1000 arthrometer (MM) values and the pivot-shift test grade. Spearman`s correlation coefficient 0.36, P=0.001.

Range of motion after an ACL injury (Studies II-III)

Knees with PF OA had a greater extension and flexion deficit than knees without PF OA. The mean (SD) degree of *extension* deficit was 4.8 (4.1) in knees with PF OA and 0.8 (3.6) in knees without PF OA (P=0.002). In subjects with PF OA 6 out of 11 had an extension deficit of 6-11 degrees compared with 5 out of 55 subjects without PF OA (P=0.002). The mean (SD) degree of *flexion* deficit was 9.6 (7.0) in knees with PF OA and 1.5 (4.6) in knees without PF OA (P<0.0001). Furthermore, knees with greater extension or flexion deficiencies at follow-up tend to have lower arthrometer test values. When comparing mean KT-1000 arthrometer values between knees with extension deficits of <3° and 6-11°, the P-value was 0.08. When comparing mean KT-1000 arthrometer values between knees with flexion deficits of <3° and 3-11°, the P-value was 0.06.

Additional results

Additional results not published in Studies I-IV.

Radiographic OA, osteophytosis and knee laxity at the 15 year follow-up (Studies I-III)

The prevalence of TF OA (16%) and/or PF OA (16%) was 24% for the whole study cohort 15 years after ACL injury. There was no subject with radiographs who had more than a grade 1 JSN and isolated grade 2 osteophyte in the TF or PF-joint. All radiographed subjects had JSN grade 0 in the PF-joint. In radiographed knees there was a 50% and 75% prevalence of an osteophyte (grade 1-2) in either the TF and/or PF-joint in non-reconstructed and reconstructed ACLs respectively. The cumulative sum osteophyte score (range 0-8) for each radiographed knee including the medial and lateral TF and PF joint-lines was calculated. According to the KT-1000 arthrometer, there seems to be a trend between the amount of knee osteophytosis and decreased sagittal knee stability 15 years after an ACL injury.

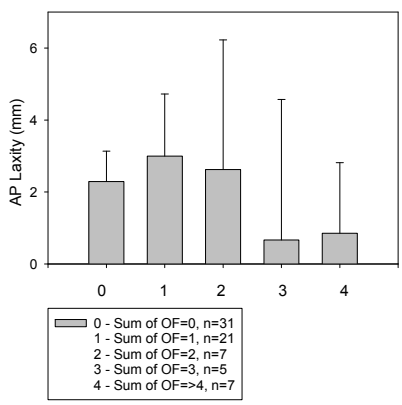


Figure 9. KT-1000 arthrometer manual max (MM) antero-posterior (AP) difference in knees with an osteophyte score ≤2 (n=59) or >2 (n=12) was mean (SD) 2.6(3.1) mm and 0.9(2.9) mm respectively, *P*=0.09

When all 3 knee compartments where analyzed in both NACLR and ACLR patients, the KT-1000 arthrometer appeared to indicate a trend towards lower sagittal knee stability 15 years after the ACL injury in ACLRs that had developed at least a grade 2 osteophyte (Table 7).

Table 7. Mean(SD) manual max KT-1000 arthrometer values of sagittal knee laxity after an ACL injury in NACLR versus ACLR patients according to radiographic OF grade in the medial and lateral TF and PF joint-lines at 15 year follow-up.

	Radiography	Nr	Mean(SD) mm	P-value
NACLR	**Med OF grade < 2**	**55**	**2.5(2.7)**	**0.31**
	Med OF grade ≥ 2	**2**	**0.50(0.70)**	
	Lat OF grade < 2	**56**	**2.4(2.7)**	**0.60**
	Lat OF grade ≥ 2	**1**	**1.0**	
	PF OF grade < 2	**50**	**2.4(2.8)**	**0.35**
	PF OF grade ≥ 2	**5**	**3.6(2.3)**	
ACLR	**Med OF grade < 2**	**11**	**2.3(4.8)**	**0.61**
	Med OF grade ≥ 2	**3**	**0.67(4.0)**	
	Lat OF grade < 2	**11**	**2.4(4.8)**	**0.43**
	Lat OF grade ≥ 2	**3**	**0.0(3.0)**	
	PF OF grade < 2	**7**	**4.3(5.0)**	**0.05**
	PF OF grade ≥ 2	**6**	**-0.67(2.8)**	

Med = medial. Lat = lateral. OF grade according to the OARSI atlas.

The association between knee laxity, meniscal tears and radiographic OA (Studies I-III)

A high grade Lachman or pivot-shift test in the initial period (baseline to 3 years) was associated with a higher frequency of secondary meniscal injuries, ACLR, and OA after 15 years. This relationship was stronger if only men were included in the analysis (Table 8).

Table 8. Outcome (number and percentage) of secondary meniscal surgery, i.e., partial meniscectomy or meniscal suture, ACLR, PF OA and TF OA 15 years after ACL injury in relation to the Lachman test and pivot-shift (low = grade 0-1 and high = grade 2-3), at 3 year follow-up.

		Secondary meniscal surgery	ACL reconstructed	PF OA	TF OA
Lachman (all), n=83	Low	4/35 (11%)	3/35 (9%)	2/32 (6%)	3/34 (9%)
	High	11/43 (26%)	9/43 (21%)	9/35 (26%)	10/36 (28%)
	P-value	0.15	0.21	0.05	0.06
Lachman (men), n=49	Low	1/20 (5%)	0/20 (0%)	1/19 (5%)	1/19 (5%)
	High	8/26 (31%)	7/26 (27%)	7/23 (30%)	8/24 (33%)
	P-value	0.06	0.01	0.05	0.06
Pivot-shift (all), n=82	Low	5/44 (11%)	1/44 (2%)	2/39 (5%)	5/41 (12%)
	High	10/33 (30%)	11/33 (33%)	9/27 (33%)	8/28 (29%)
	P-value	0.05	0.0002	0.005	0.12
Pivot-shift (men), n=48	Low	2/29 (7%)	0/29 (0%)	1/26 (4%)	2/27 (7%)
	High	7/16 (44%)	7/16 (44%)	7/15 (47%)	7/15 (47%)
	P-value	0.006	0.0003	0.002	0.006

The correlation between anteroposterior knee laxity, as measured with the KT-1000 arthrometer, and BMI (Study III)

There was a correlation between BMI in subjects at baseline and at the 15 year follow-up, Pearson correlation coefficient 0.76, *P*=0.0001. Obese subjects (BMI ≥30 kg/m^2, n=14) at the 15 year follow-up had a lower value in the KT-1000 manual maximum difference between the injured and non-injured knee than subjects with normal BMI (<25 kg/m^2, n=32), mean (SD) 0.6 (2.0) mm vs. 3.2(3.3) mm, *P*=0.009. Subjects with higher BMI had less sagittal laxity than subjects with lower BMI. Pearson correlation coefficient, r=-0.33 and *P*=0.004 (Figure 10). At the 15-year follow-up, the mean (SD) BMI of ACL reconstructed and non-reconstructed subjects did not differ, 27 (4) vs. 26 (4) kg/m^2, *P*=0.3.

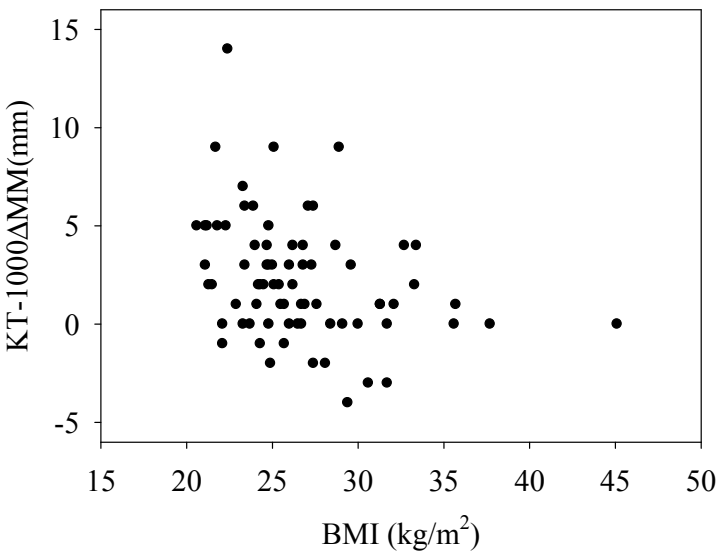


Figure 10. The correlation between anteroposterior knee laxity, as measured with the KT-1000 arthrometer, and body mass index (BMI) 15 years after an unilateral ACL injury (n=74). The KT-1000 results are presented as the difference in sagittal laxity in mm between the injured and non-injured knee.

The history of meniscal injuries over 15 years after an ACL injury (Study I)

Sub-groups of study subjects and flow-chart according to the extent and incidence of meniscal lesions at index, at follow-up and prevalence of TF OA. Only subjects who sustained a major meniscal lesion developed TF OA (Figure 11).

Index injury, (n = 100)		**15 year follow-up (n = 94)**	**Prevalence of TF OA after 15 years (13/79)**
No meniscal lesion, n=40	12	No meniscal lesion, n=26	0% (0/24)
Major meniscal lesion, n=25 *	9	Major meniscal lesion, n=46 * (including 2 lost to f.u.)	37% (13/35)
Minor meniscal lesion, n=35 *		Minor meniscal lesion, n=24 *	0% (0/20)

Figure 11. * A meniscus tear was defined as *minor* if considered to heal by itself (partial or shorter full thickness but stable tears in the red-red zone) or *major* if there was a full thickness tear in the substance or a peripheral tear which required excision. Meniscus repair was not a standard procedure in Lund *at the time of inclusion* in this study. Meniscal suturing was performed in 6 knees, of which 4 eventually underwent a partial meniscectomy during follow-up. All these 6 knees are recorded in the group with a major meniscal lesion.

In study I we found that 60 out of 100 patients had a coexisting meniscal tear at baseline. Among these 60 subjects, 35 had a minor meniscal tear that was left in situ and 25 had a partial meniscectomy performed. The risk of a secondary meniscectomy for all 100 patients over 15 years was 31% with no difference between patients having no meniscal tear, a minor tear left in situ, or a meniscectomy at baseline arthroscopy. The cumulative number of meniscectomies at the 15 year follow-up was 48%. Patients in our study sample who had reconstructive ACL surgery performed had sustained more cumulative major meniscal injuries (18/22) compared with patients who managed to cope with their ACL injury without reconstruction (26/72). We found an association between a higher Lachman grade from the baseline

injury to the 3 year follow-up and the prevalence of secondary meniscal surgery during the 15 year follow-up (Figure 12).

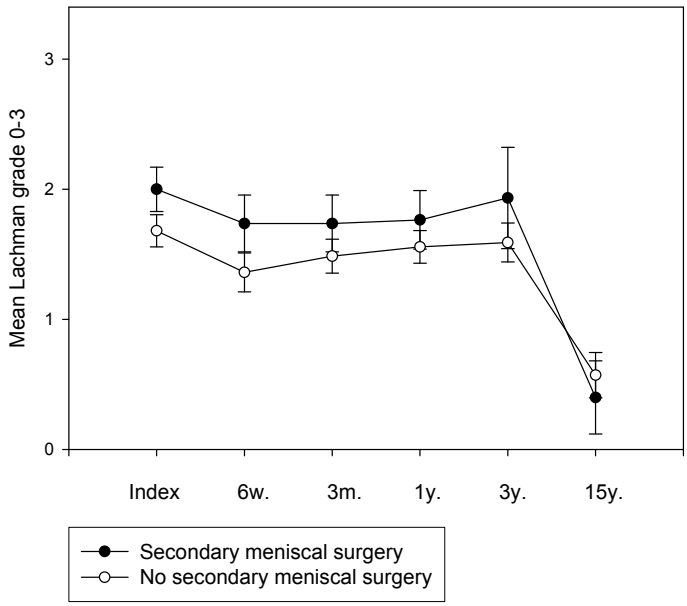


Figure 12. P-values at Index (baseline) of the 3 year follow-up; *P*=0.011, *P*=0.012, *P*=0.062, *P*=0.12 and *P*=0.055 respectively (n=87 to 93).

The association between functional tests, muscular thigh strength and KOOS (Study II)

The KOOS score revealed a correlation between the one-leg jump test, muscular thigh strength and knee symptoms 15 years after an ACL injury. Non-ACL reconstructed (n=59) and ACL reconstructed (n=16) subjects who, according to the KOOS score, were judged as asymptomatic, jumped longer and had stronger quadriceps and hamstring muscles. A ratio of the index to the normal knee was calculated (Table 3). In subjects considered symptomatic according to KOOS, the ratio of the index to the normal knee in the one-leg hop test was significantly worse than in subjects considered asymptomatic according to KOOS (P=0.002) (Table 3). At the 15 year follow-up we found significantly lower isometric strength of hamstrings and significantly lower isokinetic strength of quadriceps and hamstrings, when a ratio of the index to the normal knee was calculated for subjects considered symptomatic according to KOOS (Table 9).

Table 9. Values for the one-legged hop test, Peak torque isometric and isokinetic knee extension and flexion, Total Work isokinetic knee extension and flexion, Mean difference and 95% CI in subjects with or without knee symptoms based on the KOOS questionnaire in NACLR (n=59) and ACLR (n=16) subjects 15 years after the ACL injury.

	KOOS not symptomatic			KOOS symptomatic					
	Uninjured Leg Mean (SD)	Injured Leg Mean (SD)	Ratio Index Leg/ Uninjured Leg Mean(SD)	Uninjured Leg Mean (SD)	Injured Leg Mean (SD)	Ratio Index Leg/ Uninjured Leg Mean (SD)	KOOS not symptomatic vs KOOS symptomatic Ratio Index/ Uninjured Leg Mean Difference	KOOS not symptomatic vs KOOS symptomatic Ratio Index/ Uninjured Leg 95% CI	P
Single-legged hop test (cm)	157.6(34.4) N=51	151.9(33.3) N=51	0.97(0.082) N=48	147.0(30.4) N=24	130.9(34.0) N=24	0.88(0.13) N=23	0.082	0.03-0.13	0.002
Peak torque isometric extension (Nm)	248.0(57.8) N=50	240.1(58.2) N=50	0.98(0.14) N=50	244.5(75.3) N=24	230.9(80.3) N=25	0.93(0.16) N=24	0.044	-0.028-0.12	0.23
Peak torque isometric flexion (Nm)	112.0(31.8) N=50	116.0(27.3) N=50	1,06(0.16) N=50	117.1(34.7) N=24	111.9(36.5) N=25	0.94(0.12) N=24	0.12	0.047-0.19	0.002
Peak torque isokinetic extension (Nm)	170.9(43.0) N=46	163.0(43.6) N=45	0.97(0.15) N=45	179.8(62.1) N=23	162.0(65.5) N=24	0.88(0.16) N=23	0.095	0.017-0.17	0.018
Peak torque isokinetic flexion (Nm)	76.8(23.4) N=46	78.0(22.0) N=45	1.04(0.12) N=45	78.3(28.2) N=23	76.2(31.2) N=24	0.94(0.17) N=23	0.099	0.027-0.17	0.008
Total work isokinetic extension (J)	4488(1034) N=46	4437(1088) N=45	0.99(0.14) N=45	4581(1284) N=23	4220(1263) N=24	0.91(0.12) N=23	0.084	0.018-0.15	0.014
Total work isokinetic flexion (J)	2114(650) N=46	2146(628) N=45	1.03(0.18) N=45	2092(667) N=23	1952(726) N=24	0.91(0.18) N=23	0.12	0.03-0.21	0.009

General discussion

Cartilage quality and OA development after an ACL injury

In study I we found a strong association between partial meniscectomy and radiographic OA 15 years after the injury. Three weeks after the injury a decreased T1Gd was shown in the ACL injury cohort from study IV (Tiderius et al., 2005). In study IV, we focused on the influence of meniscectomy on cartilage matrix quality in the chronic phase after the ACL injury and demonstrated that a meniscal lesion, necessitating partial meniscectomy, increases the risk of having a shorter T1Gd in the ipsilateral compartment. Accepting a shorter T1Gd to be indicative of increased OA risk, our findings agree well with the suggestion by Englund et al. that a meniscal lesion is an early event in OA (Englund et al., 2003). In addition, Krishnan et al. have demonstrated parallel degradative processes in cartilage and meniscus in the knee with CE-MRI (dGEMRIC) (Krishnan et al., 2007). Furthermore, results from study IV suggested a trend for negative correlation between BMI and T1Gd in agreement with previous studies (Tiderius et al., 2006; Ericsson et al., 2009). Results also indicate that a meniscus lesion warranting a meniscectomy is more harmful in subjects with a higher BMI (>25 kg/m^2), suggested by the decrease in T1Gd between baseline and follow-up (Figure 2).

In this regard it is important to acknowledge that several studies have shown good agreement between cartilage GAG content and T1Gd (Bashir et al., 1999; Watanabe et al., 2009; Juras et al., 2009) and that a short T1Gd is a feature of early-stage knee and hip OA (Williams et al., 2005: Cunningham et al., 2006: Nojiri et al., 2006: Lammentausta et al., 2007: Owman et al., 2008). Several factors may be involved in OA mechanisms in the injured ACL joint. First, an ACL deficient knee will have an altered gait due to instability. In addition, a joint lacking meniscus function has a higher pressure per unit of cartilage area during gait. Furthermore, a cartilage matrix with insufficient GAG content is probably more susceptible to fatigue and progressive destruction of the collagen fibril network. The cumulative effect of these factors may result in increased mechanical

shearing of the collagen network with subsequent fibrillations and overt OA changes.

In study IV, there was no difference in T1Gd between ACL reconstructed and non-ACL reconstructed patients. However, it cannot be ruled out that the CE-MRI (dGEMRIC) results in reconstructed knees would have been worse without reconstruction, given that it was the most unstable and severely injured knees that were reconstructed. The similar CE-MRI (dGEMRIC) results in reconstructed and non-reconstructed knees may support the idea that an ACLR can prevent or at least postpone OA cartilage changes in selected subjects. Randomized controlled trials, using CE-MRI (dGEMRIC) or another quantitative MRI method, are needed to determine the advantage of an ACLR with respect to cartilage quality and OA development. So far, several radiographic studies have shown that ACLR does not decrease the risk of post-traumatic OA development (Lohmander et al., 2007: Myklebust et al., 2003: Cohen et al., 2007: Salmon et al., 2006: van der Hart et al., 2008).
Results from study IV also indicate that the cartilage GAG content was partly regained in the lateral but not in the medial compartment. Indeed, the T1Gd of the medial femoral cartilage at follow-up (357 ms) was 17% shorter than in the previously examined healthy volunteers (428 ms) from 2005 (Tiderius et al., 2005). Our findings support the fact that in general, knee OA most often affects the medial compartment.
Furthermore, patients who had a medial meniscectomy between the investigations tended to have shorter T1Gd in the medial femoral cartilage at their first MRI. A speculative suggestion is that subjects with lower cartilage quality (measured as a short T1Gd) are more prone to both meniscal tears (inferior meniscal tissue) and subsequent knee OA than subjects with higher knee cartilage quality.

In summary, results from study IV suggest that CE-MRI (dGEMRIC) is able to identify subjects who are at increased risk of OA by detecting and monitoring qualitative cartilage changes as exemplified by the shorter T1Gd in ACL-injured patients, especially in those meniscectomized and in those with a higher BMI. Further follow-up of this ACL injury cohort are needed to confirm the eventual relationship between short T1Gd and radiographic OA development.

OA after an ACL injury

We found a substantially lower prevalence of radiographic knee OA (TF OA and/or PF OA) than previously shown (Lohmander et al. 2007). Allthough risk factors for post-traumatic OA are multi-factorial, we found that the primary risk factor for developing OA after an ACL injury was the performance of a meniscectomy. No subject without meniscectomy developed TF OA (Study I) and only 2 subjects without meniscectomy developed PF OA (Study II). Studies I-II confirm that in a knee with an ACL injury a meniscectomy is a potent risk factor for OA (Cohen et al., 2007; Meunier et al., 2007; Neyret et al., 1993; Roos et al., 1995; Segawa et al., 2001; Shelbourne et al., 2000). The neuromuscular rehabilitation in combination with the strong recommendation to modify sports activity and avoid contact sports, as well as the careful monitoring of the knee for signs of meniscal injuries are unique factors in studies I-III. We had rates of acute meniscal tears corresponding to other studies (Daniel et al., 1994; Indelicato et al., 1985; Meunier et al., 2007); Noyes et al., 1980; Palmer, 1938). However, the cumulative number of meniscectomies during follow-up seems to be lower in the present study, 48% (46/96), compared with the 80% previously reported (Fithian et al., 2002; Indelicato et al., 1985). Additionally, 35 of the 60 patients had an acute meniscal tear that was left *in situ,* i.e., they did *not* undergo meniscectomy. These two factors may be a substantial contributing cause to the lower incidence of OA. Preservation of the meniscus seems to be beneficial, irrespective of whether or not an ACLR was performed, corroborating earlier results.

There are several possible explanations of PF OA development in the ACL injured knee. Activation of cytokine and protease cascades primarily in the TF joint may act locally on all joint surfaces and compartments, or even systematically (Sandy et al., 2003). Combined PF and TF OA are common after meniscectomy in the absence of ACL injury (Englund et al., 2005). An interaction between local joint factors and a genetic predisposition to OA is likely (Englund et al., 2004). Early clinical signs of degenerative disease after an ACL injury and ACLR are PF pain, quadriceps weakness and extension loss. In study II, we found that ACLR, knee joint extension/flexion deficit, meniscal injury and high activity level seemed to be associated with PF OA. Similarly in study I, ACLR, meniscal injury and knee joint extension/flexion deficit were associated with TF OA. However, higher activity level was only associated with PF OA and not TF OA in these subjects.

Nevertheless, despite radiographic OA (albeit mild) and impaired range of motion, the self-reported outcome and activity level remained relatively good. This observation highlights the importance of even longer follow-ups to assess when OA will lead to more severe symptoms. This is in accordance with studies on knee OA showing a relatively weak correlation between radiographic findings and subjective knee symptoms and function (Creamer et al., 2000; Hannan et al., 2000).

ACLR

In study I, we found a higher OA prevalence in ACL reconstructed patients than in non-surgically treated patients, which is in agreement with previous studies (Daniel et al., 1994; Fithian et al., 2005). However, neither our study nor studies by others were designed to compare surgery versus no surgery. Patients in our study sample committed to reconstructive surgery had sustained more cumulative major meniscal injuries (18/22) compared with patients who managed to cope with their ACL injury without reconstruction (26/72). Importantly, all the mentioned factors found to be associated with PF OA in study II are inter-related, since it was prescribed in the treatment algorithm that late ACLR would only to be performed if the neuromuscular rehabilitation together with a lowered activity level was not sufficient to prevent further injuries (meniscal injury in particular). Subjects with ACL reconstructions could be expected to have had a wish to maintain a high activity level and thereby were at higher risk of sustaining meniscal injuries leading to ACLR (all according to the treatment algorithm). According to the Lysholm score, ACLR patients also had decreased knee function preoperatively, compared with patients who were not reconstructed. Furthermore, the increased *ability* to return to sports with pivoting movements and joint compression after a meniscal injury and ACLR may be disadvantageous with regard to the risk of developing knee OA (Roos et al., 1994). On the other hand, some individuals who are unable to participate in sports because of a knee injury, may be more affected in terms of their quality of life than by OA changes at radiography. We have previously demonstrated that subjects who sustained their ACL injury in contact sports scored significantly worse at follow up in the KOOS quality of life subscale (Kostogiannis et al., 2007).(Kostogiannis et al. 2007)

All reconstructions were performed with an ipsilateral BPBT- graft without accelerated post-operative knee rehabilitation, which is a known risk factor

for post-operative patellofemoral symptoms (Shelbourne et al., 1990; Shelbourne et al., 1997). This may be an important risk factor for the observed extension deficit and PF OA in study II (Roe et al., 2005; Shino et al., 1993; Keays et al., 2007 and 2010). Using the same operating technique as in the present study, Muellner et al. have shown that the patella migrates slightly medially and inferior one year after the operation, probably because of shrinkage and scar formations that change the patellofemoral alignement (Breitfuss et al., 1996; Muellner et al., 1998, 1999; Jarvela et al., 2001). Altered loading patterns act on the PF joint after an experimental ACL excision (*decreased* pressure and contact area), which is normalized after an experimental ACLR (Hsieh et al., 2002). However, even if the sagital instability is restored after an ACLR, there is much evidence that excessive tibial rotation still persists during activities that are more demanding than walking (Stergiou et al., 2007). Today, a more horizontally placed graft or a double-bundle ACLR has been suggested to limit the excessive tibial rotation and thus theoretically slow down the development of OA, which still remains to be proven. One might also hypothesize that the PF joint is under constant increased pressure if an extension deficit is present. Altered loading patterns may also act on the PF joint at a later stage, due to malalignment caused by more advanced unicompartmental TF OA, as a result of meniscal injury (Elahi et al., 2000). Subsequent PF OA development and anterior knee pain might thus be the outcome of PF imbalance after both ACL injury and ACLR (Hunter et al., 2007; Kalichman et al., 2007). It has also been shown that female subjects at increased risk of an ACL injury exhibit decreased neuromuscular control and increased valgus knee joint loading (Hewett et al., 2005), which theoretically would make the PF joint more vulnerable to malalignement, PF injuries and subsequent OA. Moreover, the development of OA changes in the knee joint has not been alleviated by the advent of endoscopic techniques (Salmon et.al, 2006).

ACL injury and knee laxity

In study III we found that patients treated without ACLR, in accordance with the treatment algorithm, were considerably more stable at long-term follow-up (15 years) than during the first 3 years after injury. This finding may be explained by some healing capacity or scarring of the torn ACL between baseline and the 6-week follow-up, i.e. if the patient is properly rehabilitated without the risk of immediate "giving way" episodes at the beginning of the healing process. Accordingly, some spontaneous healing of the torn ACL has been demonstrated by Fujimoto et al. ((Fujimoto et al. 2002)) and Crain et al. ((Crain et al. 2005)). In the later phases after an injury is reasonable to assume that the joint is exposed to passive stabilizing compensatory mechanisms such as ligament and soft-tissue contraction and possibly osteophyte formation.

Using the same cohort as in study III, it was shown that the pivot-shift test at 3 months is a good predictor of the future need of an ACLR (Kostogiannis et al. 2008). We also found that a low grade Lachman test 3 months after an ACL injury seems to correlate with a more successful outcome without secondary knee surgery or knee OA 15 years later. Jonsson et al. revealed that a positive pivot-shift test after ACLR predicts later OA in knees followed for 5-9 years after surgery, which is partly in accordance with our findings (Jonsson et al. 2004). However, despite having an inferior outcome in our study, the self-reported outcome of these subjects remained relatively good. Moreover, at the 15-year follow-up, subjects with an inferior outcome seemed to maintain a higher activity level than subjects with a more successful outcome, which is why even longer follow-ups are necessary to determine when knee OA will more severely affect the activity level and self-reported outcome.

In conclusion, we found that subjects with an acute ACL injury treated without reconstruction, but with neuromuscular rehabilitation, can in general expect a low grade knee laxity according to the Lachman test, pivot-shift test and the KT-1000 arthrometer. Furthermore, patients with higher anterior sagittal knee laxity 3 months after the injury had a worse long-term outcome in terms of meniscal injuries and knee OA development. However, their risk of developing OA, even 15 years after the injury, seems to be low.

Since an ACL injury is often complex with a great number of different concomitant injuries and every patient has individual preferences, expectations, mental status and training abilities, the treatment of every ACL injury must also be highly individualized. Both surgical

reconstruction and non-operative treatment with rehabilitation by a physical therapist can be argued for. Study III contributes to a better understanding of the longitudinal development of knee laxity in patients with an ACL injury and its relevance for additional secondary knee injuries, surgery or development of OA, and may partly help orthopedic surgeons in decision making about whether or not to surgically reconstruct the ACL. We conclude that in patients with an ACL injury who are willing to moderate their activity level, initial treatment without ACLR should be considered especially in those with lower grades of knee laxity.

Symptoms and functional limitations after an ACL injury

In studies I-II, the outcome with respect to patient satisfaction is in line with the low prevalence of OA. However, patients with intact menisci, non-reconstructed knees and knees without TF and/or PF OA achieved the best KOOS scores. Our study sample of non-ACL reconstructed and ACL reconstructed patients had very similar KOOS scores compared to a random population based postal survey of inhabitants in southern Sweden, n=158, age 35-54 years, 51% women (Paradowski et al., 2006), (Figure 13).

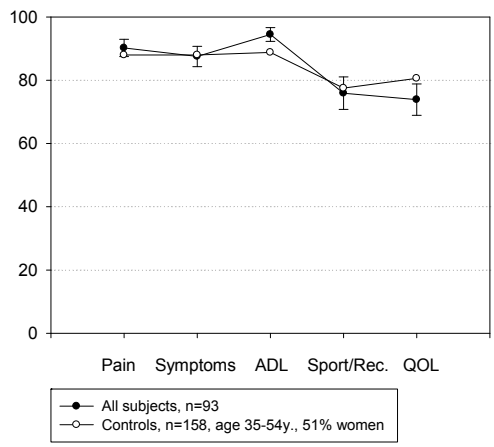


Figure 13. The Knee injury and Osteoarthritis Outcome Score (KOOS) mean score profile for the anterior cruciate ligament (ACL) injury study sample -●- (n = 93) and a random population-based reference group of individuals, 35-54 years -○- (n = 158, 51% women), (Paradowski et al., 2006). The ACL injury sample had a significantly higher ADL score but lower QOL score compared to the reference group, *P*=0.0074 and *P*=0.032 respectively.

We also found that 15 years after an ACL injury, women experienced more knee symptoms than men in all KOOS subscales, although without statistical significance. This finding is *not* in agreement with the population-based study (Paradowski et al., 2006) in which women aged 35-54 years scored higher on the KOOS than men of the same age. Moreover, we found that younger (<26y.) ACL injured subjects had lower scores in all KOOS subscales 15 years later, than subjects ≥ 26 years old at the time of injury. In particular, the QOL subscale differed, $P<0.0001$. This finding has implications when different patient cohorts are compared using the KOOS score, since both sex and age seem to correlate with the subjective outcome. Although the age factor may be the most important, it is perhaps not the only explaination as to why all KOOS subscale scores of patients in the Swedish ACL register 1 year after an ACLR are lower than in our study cohort (studies I-III) 15 years after injury (Figure 14).

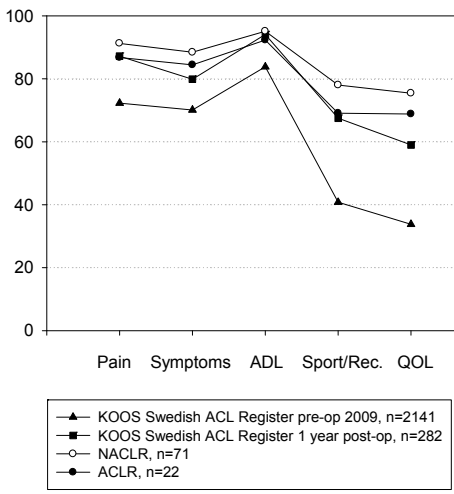


Figure 14. The KOOS mean score profile for ACL reconstructed patients in the Swedish ACL Register pre-op -▲- , ACL reconstructed in the Swedish ACL Register 1 year post-op -■- , ACL reconstructed (ACLR) in study I-III -●- and non-ACL reconstructed (NACLR) in study I-III -○-.

At the 15 year follow-up most patients in studies I-II rated their knee function as normal or nearly normal and the average patient administered Lysholm Knee Score was 85, which is considered a good result (Kostogiannis et al., 2007). This relationship between patient satisfaction and the low OA prevalence in the present study emphasizes restrictiveness to reconstructing ACL injured patients at an early stage, or at least those who accept the need to moderate their activity level. The average decrease in the Tegner activity score from 7 to 4 may be caused by several factors, all of which are unrelated to the ACL injury. Likely reasons are: 1) an active choice due to the information and recommendations provided, 2) a consequence of knee symptoms and/or reduced knee function, and 3) a natural decrease in activity level due to aging. It is noteworthy that the median activity level in the study sample is almost comparable to the Tegner score of 5 found in a Swedish reference group with a mean age of 43 years without any knee symptoms or injuries (Andersson-Molina et al., 2002). In a more recent study (Briggs et al. 2009), the Lysholm and Tegner scores were analysed in 488 subjects (mean age 41 years, 50% women) in the community who considered their knee function as normal and those reporting a history of injury or surgery was excluded. The average Lysholm score was 94 and not correlated to sex or age. The average Tegner score was 6 in men and 5.4 in women. The Tegner activity level was inversely correlated with age in accordance with our conclusion 3) above (Briggs et al., 2009).

BMI, ACL injury and development of knee osteophytes

Patients in the cohort in studies I-III had a mean increase in body mass of 10 kg 15 years after their ACL injury. Their mean (SD) Body mass index (BMI) kg/m^2 changed from 23 (3) to 26 (4). There was also a correlation between BMI in subjects at baseline and at the 15 year follow-up, P=0.0001 (additional results). Since a high BMI is a known risk factor for incident knee OA (Felson et al., 1988) and progression of knee OA in neutral or valgus aligned knees (Niu et al., 2009), this definitely has implications for the ACL injury population, who are already at increased risk of developing knee OA.

We found that obese subjects (BMI ≥30 kg/m2) had significantly lower values in the KT-1000 manual maximum difference between the injured and non-injured knee than subjects with normal BMI (<25 kg/m2), P=0.009

(additional results) at the 15 year follow-up. The Lachman and Pivot-shift tests showed similar results. Likely reasons for the difference in sagital knee laxity between obese subjects and subjects with a normal BMI could be: 1) some unknown systematic measurement error with the arthrometer device in more heavy-weight legs, 2) a greater mechanical stimuli to the injured knee in obese subjects to compensate for the laxity with stabilizing mechanisms such as ligament and soft-tissue contraction and osteophyte formation, and 3) A genetic predisposing association between higher BMI, OA and less sagital knee laxity. Bearing in mind that mechanical instability is an accepted cause of osteophyte formation clinically (Jacobsen, 1977; Kannus et al., 1989) and experimentally (Marshall et al., 1971; Telhag and Lindberg, 1972; Moskowitz et al., 1987), the latter two statements 2-3) could be favoured. Interestingly, it is known from previous studies on knee OA that greater OA severity is associated with less sagittal knee laxity, despite the presence of ACL pathology in advanced stages of OA (Brage et al., 1994; Wada et al., 1996). There is also some evidence that supports the view that knees which develop primary OA are initially more lax before progressive OA changes can be seen on radiographs (Brage et al., 1994; Wada et al., 1996; Sharma et al., 1999). Dayal et al. found a correlation between a decrease in sagittal laxity in knees with OA followed longitudinally and a higher osteophyte grade at follow-up (Dayal et al., 2005). Most of the decrease in sagittal laxity in that study occurred between knees with a Kellgren and Lawrence (K/L) score of 0-1 and knees with a K/L score of 2, well comparable to our study where all subjects had a K/L score of between 0 and 2. Moreover, in the study by Dayal et al., knees in which sagittal laxity decreased had less medial joint space loss than did knees without a decrease in sagittal laxity, which could indicate that joint space loss occurs when there is an absence of osteophyte compensation. In later stages of knee OA with loss of meniscal and cartilage integrity and volume, sagittal laxity could probably be increased. Different aspects of OA pathology may have opposing effects, e.g., cartilage and bone loss is likely to lead to increased laxity and osteophyte growth to decreased laxity (Sharma et al., 1999). From these and our results I speculate that decreased knee joint laxity after an ACL injury could be part of an increased growth of osteophytes. This is further supported by a study on radiographic OA knee joint differences between ACL injury and subjects with non-traumatic primary knee OA, which revealed that tibiofemoral osteophytes were more frequent in ACL-injured subjects (Swärd et al., 2009). This biological response with increased cartilage turnover and growth of osteophytes might

be further “fueled” = increased after repeated “giving-way” or changed knee joint biomechanics by subsequent cartilage and meniscal injuries.

Clinical relevance of the main findings

In optimizing the clinical and radiographic outcome after an ACL injury, prevention of additional meniscal lesions (and probably other knee injuries too, especially injuries to the cartilage and the subchondral bone plate) after subsequent giving-way episodes must receive great attention. Avoiding further giving-way episodes of the knee includes early patient education and activity modifications/restrictions as well as early neuromuscular knee training. Neuromuscular training aimed at achieving a better knee movement pattern and lowering the risk of subsequent acute or over-use knee injuries is probably the key to better knee function with less knee OA, or at least delaying the onset of OA. However, we have not evaluated or monitored the subject`s neuromuscular skills in this thesis. We have merely presented a lower prevalence of knee OA than in historical series of ACL injured subjects, with an acceptable activity level and a fairly low level of subjective knee symptoms in a cohort where all subjects received neuromuscular training as described above. We conclude that in ACL injured patients willing to moderate their activity level during early neuromuscular rehabilitation, initial treatment without ACLR should be considered, especially in patients with lower grades of knee laxity, as long as the integrity of the menisci is not jeopardized.

Final considerations and future research

Quantification of the quality of the cartilage, meniscus and ligaments of the knee

Techniques to quantitatively measure the quality of the joint cartilage and the meniscus, such as the CE-MRI (dGEMRIC) method, should be used longitudinally in future research. In addition or in combination, biomarkers for cartilage and meniscus injury should also be evaluated longitudinally. In the future, it may be possible to discriminate between a *low* or *high* grade injury to a knee with *inferior* or *superior* quality of the cartilage and the meniscus. If MRI proves capable of confirming the relationship between a low cartilage quality and eventual radiographic OA development in long-

term longitudinal follow-ups, it should also be assessed whether the CE-MRI (dGEMRIC) method, or a similar quantitative method, is better correlated to patient subjective knee symptoms than conventional radiography. Then, an early more precise prognosis regarding the eventual risk of knee symptoms and OA development might be made, which could help clinicians in decision making after an acute ACL injury and in the evaluation of new treatments.

Early neuromuscular rehabilitation by a physical therapist specialized in knee injuries

Today, there is a great deal of evidence from the literature that it is possible to prevent ACL injuries with specific neuromuscular training (Myklebust et al., 2003; Mandelbaum et al., 2005; Olsen et al., 2005; Gilchrist e al.; 2008; Soligard et al. 2008). The first step to reduce the burden of knee OA after an ACL injury should obviously be to implement these preventive programs among young athletes, which is quite a demanding task. We recommend that future studies should conduct measurements of neuromuscular ability. Both the risk of injury related to neuromuscular performance and the quality of the knee is, of course, crucial for determining the chances of injury on any given occasion. In analogy with osteoporosis, if you have good balance and never fall, you will almost never sustain a fracture even if you have osteoporosis according to a DEXA measurement. In addition, training can also improve the cartilage quality.

Register for all ACL injuries

It would be of enormous importance for future longitudinal studies if all acute ACL injured patients were included in a register, and not only those who are operated on (Swedish ACL-register, www.aclregister.nu).

Conclusions

- In acute ACL-injured patients estimated GAG content by dGEMRIC is partially regained in the lateral, but not in the medial femoral cartilage over 2 years.
- ACL injured patients who underwent a concomitant meniscectomy or had a higher BMI (>25 kg/m$^{2)}$ had shorter T1Gd at the 2 year follow-up, which may indicate that CE-MRI (dGEMRIC) is able to identify subjects who are at increased risk of OA by detecting and monitoring qualitative knee cartilage changes.
- A concomitant meniscectomy in ACL injured patients was a very strong risk factor for the development of TF OA 15 years after the injury.
- ACLR, a higher activity level, a concomitant meniscectomy and a knee flexion or extension deficit were risk factors for the development of PF OA 15 years after the ACL injury.
- In the clinical course of an ACL injury treated with early neuromuscular rehabilitation without ACLR, longitudinal knee laxity decreased and was of low level 15 years after the injury.
- Patients with higher degrees of knee laxity during the first 3 years after ACL injury had an increased risk of additional meniscal injuries, ACLR and the development of knee OA 15 years after injury.
- Although a number of ACL injured patients underwent a meniscectomy or ACLR or developed knee OA 15 years later, in general, their subjective outcomes and their activity level remained close to the average.

Summary

The aim of this thesis was to study the development of knee OA and its consequences after a previous ACL injury in ordinary subjects, representative of most individuals with an ACL injury in the general public. This thesis is based on four studies, comprising 2 patient cohorts in which all subjects had sustained an ACL injury, with or without concomitant associated cartilage, meniscus or collateral ligament injuries. Different outcomes after the knee injury were assessed prospectively at regular planned intervals.

The main results are that ACL reconstructed and especially non ACL reconstructed patients, who were all treated with neuromuscular knee rehabilitation after the injury but without primary reconstructive surgery, had less radiographic knee OA at the 15 year follow-up than usually presented in historical retrospective series of non-ACL reconstructed patients (Studies I-II). However, a concomitant meniscal injury treated with partial meniscectomy was the most important factor for subsequent OA development (Study I).

The prevalence of patellofemoral knee (PF OA) was of the same magnitude as for tibiofemoral knee (TF OA) (Study II). However, PF OA occurred more frequently in ACL-reconstructions (BPBT-graft), in knees with an extension or flexion deficit, in patients with a higher activity level and in meniscectomized knees.

According to clinical manual laxity testing with the Lachman and the pivot-shift test, knee laxity decreased during the 15 year follow-up, also in non ACL-reconstructed knees. However, knees that developed OA changes after 15 years had higher initial clinical manual laxity testing values at baseline to the 3 year follow-up after the ACL injury (Study III).

Longitudinal investigation with the CE-MRI (dGEMRIC) method indicated early knee cartilage GAG changes, most likely a sign of OA development after ACL injury. Patients who had undergone a meniscectomy, or had a BMI > 25 kg/m^2 compared with < 25 kg/ m^2, two known risk factors for OA development, had lower cartilage quality according to the CE-MRI (dGEMRIC) index 2 years after the injury (Study IV).

In conclusion, we found that a concomitant meniscal injury treated with partial meniscectomy was the strongest risk factor for developing knee OA shown by radiography at the 15 year follow-up. dGEMRIC results 2 years after the ACL injury supports the contention that this method can detect a

cartilage matrix change that may be indicative of increased risk of OA. The treatment algorithm used in studies I-III, with early neuromuscular rehabilitation by a physical therapist specialized in knee injuries, seems to be beneficial as subjects had a lower incidence of knee OA than usually presented in historical series of ACL injured subjects, irrespective of ACL reconstruction, and still had an acceptable activity level and very little subjective knee symptoms.

Sammanfattning

Avhandlingen består av fyra delarbeten. Alla arbeten behandlar olika aspekter av en korsbandsskada och specifikt faktorer som ökar risken för artros.
Knäartros är synnerligen vanligt förekommande och ger funktionsnedsättning och smärtor. Slutstadiet behandlas ofta med konstgjord knäled. En stor grupp som drabbas är de som råkat ut för en främre korsbandsskada. Emellertid är naturalförloppet av en korsbandsskada dåligt beskrivet, liksom är kunskapen om hur följdskador respektive rehabilitering spelar in avseende artrosrisk. Rekonstruktion av korsbandet görs ofta, men det vetenskapliga underlaget för denna procedur är begränsad.
För att kunna förbättra livskvaliteten hos den korsbandsskadade patienten och för att utnyttja sjukvårdsresurser rätt behöver riskfaktorer för artros liksom operationsbehov kartläggas. På senare tid har allt mer fokus riktats mot meniskektomi, som ofta görs i samband med titthålsoperation för att kartlägga det korsbandsskadade knäet, som en påtaglig riskfaktor för artros.
I avhandlingen ingår två kohorter med korsbandsskadade patienter som följs longitudinellt. Delarbeten 1-3 undersöker artrosförekomst i femuro-tibialleden (I), i femuro-patellarleden (II) samt hur instabiliteten förändras med tiden i det icke opererade korsbandsskadade knäet (III). Denna Lunda-kohort insamlades av bl.a. Thomas Fridén.
Delarbete IV undersöker med kontrastförstärkt magnetkamerateknologi hur broskkvalitéten förändras inom två år efter korsbandsskada samt hur framförallt en meniskskada påverkar broskkvalitén. Denna Malmö-kohort insamlades av bl.a. Carl Johan Tiderius, Skånes universitetssjukhus och första redovisningen av kohorten ingick i Tiderius avhandling.

Delarbete I.

100 konsekutiva patienter med korsbandsskada följdes i 15 år. Alla behandlades primärt utan stabiliserande operation men med aktivitetsmodifiering och neuromuskulär rehabilitering. 79 patienter genomförde röntgenundersökning och 93 svarade på enkät. Endast 13 patienter (16%), av vilka alla var meniskektomerade, utvecklade artros i femuro-tibialleden. Ingen av de icke meniskektomerade utvecklade artros. 63 patienter (68%)

var asymptomatiska. Endast 22 patienter (23%) hade blivit korsbands-opererade.
Studien visar på betydligt färre fall av post-traumatisk artros än tidigare studier samt att meniskektomi starkt försämrar prognosen.

Delarbete II.

På samma kohort som ovan visar röntgenundersökning att artros i femuro-patellarleden förelåg i 12 av 75 knän (16%). Det var fler med artros bland de 22 som hade blivit korsbandsopererade. Meniskskada var vanligare hos dem med femuro-patellarledsartros liksom hade de med artros oftare fortfarande högre aktivitetsnivå.
Även denna studie visar på låg artrosförekomst, speciellt hos dem som inte var korsbandsopererade.

Delarbete III.

I samma kohort som ovan undersöks betydelsen av knäinstabiliteten efter korsbandsskada. Tveklöst har det främre korsbandet en stabiliserande funktion i knäet och avsikten med korsbandsopereration efter skada är att stabilisera knäet. Emellertid är det mindre väl utrett hur knäinstabiliteten förändras över tiden samt hur den påverkar utfallet både på kort och lång sikt avseende aktivitetsnivå och artrosutveckling.
Patienterna undersöktes med olika stbilitetstester efter skada samt efter 6 veckor, 3 månader, 1 år, 3 år, och 15 år efter skadan. Efter 15 år uppvisade de icke korsbandsopererade endast en liten grad av instabilitet. Knän som var mer instabila vid 3 månader hade större risk att drabbas av meniskskada och artrosutveckling.

Delarbete IV.

Ur en kohort av 40 akut korsbandsskadade patienter har 29 genomgått 2 kontrastförstärkta magnetkameraundersökningar (MR) av knäet. Genom att låta ett negativt laddat paramagnetsiskt kontrast medel diffundera in i brosket kan broskets innehåll av negativt laddade molekyler skattas eftersom mängden kontrastmedel i brosket kommer att vara inverst relaterad till broskets negativa laddning. Den negativa laddningen i brosket suger in vatten och spänner ut brosket vilket ger bättre biomekaniska egenskaper. MR-signalen blir således relaterad till broskkvalitén.
En främre korsbandsskada, och då särskilt i kombination med en meniskektomi, var förenad med sämre broskkvalitet. En korsbandsoperation medförde varken sämre eller bättre broskkvalitet. Då vi från delarbete I vet att meniskektomi ger artros, tror vi att den kvalitetsmässiga försämringen med minskad laddningstäthet i brosket är relaterad till en förhöjd risk att utveckla artros.

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