Treatment and outcome of anterior cruciate ligament injury: Truth or Consequences

Frobell, Richard

2007

Department of Orthopedics
Clinical Sciences Lund
Lund University

Treatment and outcome of anterior cruciate ligament injury: Truth or Consequences

Richard Frobell

Lund, December 14th, 2007

Contact address

Richard Frobell
Department of Orthopedics,
Clinical Sciences Lund
Lund University hospital
SE-221 85 Lund
Phone: +46-46-171572
Mobile phone: +46-708-507882
Fax: +46-46-176102
E-mail: richard.frobell@med.lu.se

Cover illustration by Lars Nilsson
Layout by Ortonova AB

ISSN 1652-8220
ISBN 978-91-85897-41-4
Lund University, Faculty of Medicine Doctoral Dissertation Series 2007: 163
Printed in Sweden
Mediatryck
2007

“Not everything that can be counted counts,
and not everything that counts can be counted.”

Albert Einstein

Contents

Prologue

The KANON study

This thesis is based on the planning, protocol design, patient recruitment and implementation of a randomized clinical trial (RCT), the KANON study. KANON is an abbreviation for Knee, Anterior cruciate ligament, NON-surgical versus surgical treatment. This RCT is a major ingredient of this thesis although the complete results from the trial are not yet available. The primary outcomes from the RCT will be presented when the 2-year follow up is completed, although some early results are included in this thesis (papers II, IV, and V). The history and design of the KANON study is thus presented as a prologue in this thesis.

Short history

Spring 2001, I was working as a physical therapist with the rehabilitation following ACL injury and assisted at surgical ACL reconstructions to learn more of the surgical method, anatomy, and possible causes of post-operative morbidity. In the initial phase of one of these operations it was found that the ruptured ACL had partially healed onto the posterior cruciate ligament (PCL). The knee was stable under anesthesia and a decision on wether the 'healed' ACL should be removed or not, was called upon. At the end of the day, the orthopedic surgeon, my co-advisor to be, dropped an outline of protocol for an RCT on my desk, asked me to review the protocol and inquired about my interest in performing such trial. Surprisingly, I found that there was no evidence in support of ACL reconstruction being superior to structured rehabilitation, and my interest and curiosity was awaked.

Only weeks later, I was introduced to my main advisor and more papers were dropped on my desk, among those a protocol for a previous drug trial, and ten months later the protocol for the KANON study was finalized. The first subject was included in the KANON study in February 2002 and the recruitment was not completed until four years later.

General aim of the KANON study

The main purpose of the KANON study is to compare the short-term (2 years) and long-term (5 years) effects of surgical and non-surgical treatment of acute ACL injury in a physically active population. Several hypotheses were presented in the protocol.

Visits and follow up

All subjects are followed with questionnaires at all visits (including self-reported knee function and activity level) and clinical assessment, including both self-reported instability in activity and instability at examination, is performed at each follow-up. Early structural changes are followed in a subsample (n=63) of the included subjects with frequent monitoring by magnetic resonance imaging (MRI) at all follow-up visits. All subjects are examined by MRI at baseline, 2 years and 5 years. Joint fluid (JF), serum and urine samples are collected at the same time as MRI assessment (Figure 1).

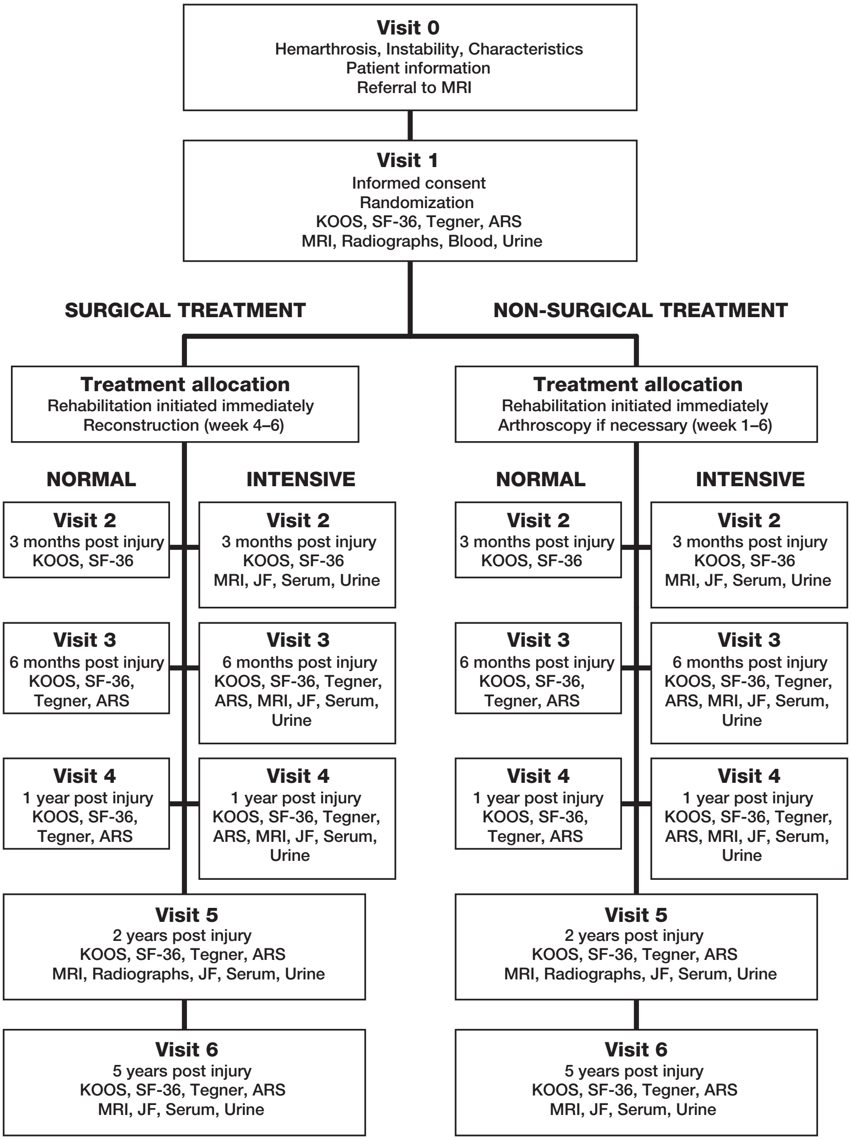


Figure 1. Flow chart over the logistics of follow up visits in the KANON study.

List of Papers

This dissertation is based on the following papers, referred to by their Roman numerals:

I **Frobell RB, Lohmander LS, Roos HP**
Acute rotational trauma to the knee – poor agreement between clinical assessment and MRI findings.
Scandinavian Journal of Medicine and Science in Sports 2007; 17(2): 109-114

II **Frobell RB, Lohmander LS, Roos EM**
The challenge of recruiting patients with anterior cruciate ligament injury of the knee into a randomized clinical trial comparing surgical and non-surgical treatment.
Contemporary Clinical Trials 2007; 28(3): 295-302

III **Frobell RB, Svensson E, Göttrick M, Roos EM**
Self-reported activity level and knee function in amateur soccer players – the influence of age, gender, history of knee injury and level of competition.
Submitted to *Knee Surgery, Sports Traumatology, and Arthroscopy*, October 2007

IV **Frobell RB, Roos HP, Roos EM, Hellio Le Graverand M-P, Buck R, Tamez-Pena J, Boegård T, Totterman S, Lohmander LS**
The acutely ACL injured knee assessed by MRI: Are large volume traumatic bone marrow lesions a sign of severe compression injury?
Revised version submitted to *Osteoarthritis & Cartilage*, October 2007

V **Frobell RB, Le Graverand M-P, Buck R, Roos EM, Roos HP, Tamez-Pena J, Totterman S, Lohmander LS**
The acutely ACL injured knee assessed by MRI: Changes in joint fluid, bone marrow lesions, and cartilage during the first year.
In manuscript

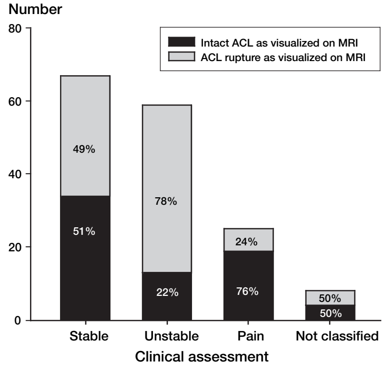
Thesis at a glance

I. What is the true population-based incidence of ACL rupture?

Subjects: 159 subjects with acute knee injury

Methods: Medical charts & sub-acute MRI

Conclusion: The annual incidence was 3 times higher than previously suggested, 81/100 000 individuals aged 10–64. The clinical assessment at the orthopedic ER was of limited value.



Paper I. The agreement between A-P laxity at clinical examination and ACL injury/uninjured ACL as visualized on MRI, N=159. The X-axis shows the result of clinically detected A-P laxity (Stable/Unstable), pain interfering with stability testing (Pain) and A-P laxity not assessed due to other reasons (Not classified).

II. Recruiting participants to a surgical RCT - How hard can it be?

Subjects: 560 subjects in Helsingborg with acute knee injury

Method: Medical charts, clinical assessment and MRI findings

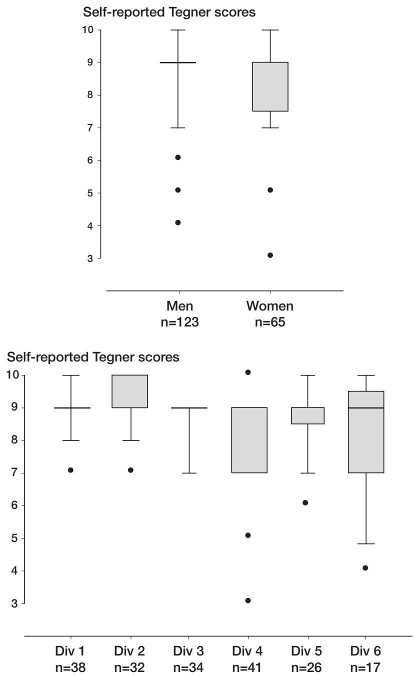
Conclusion: The protocol-based sample size needs to be multiplied by 5.5 to provide an estimate of the number of subjects that need to be screened for eligibility in a study comparable to the KANON study.

III. Can self-reported Tegner scores be used as a substitute for assessor-reported Tegner scores?

Subjects: 188 active competitive amateur soccer players, 65 women (all corresponding to an individual Tegner score of 9)

Method: Self-reported questionnaire

Conclusion: No. Older age, female sex and lower level of competition (division) was associated with worse self-reported Tegner scores and thus the validity of self-reported Tegner scores could be questioned.



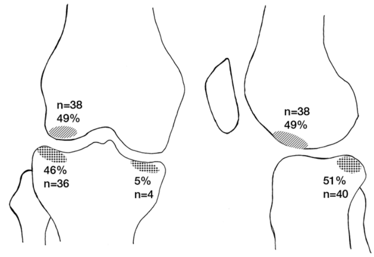
Paper III. Self-reported Tegner activity level by soccer division (lower) and sex (upper) (N=188). Box area represents 25th and 75th quartiles separated by a line representing the median value. Whiskers represent the 10th and 90th percentiles and circles represent subjects outside this interval.

IV. Acute ACL injury: is this all?

Subjects: 121 subjects, 32 women, with a not more than 5 weeks old ACL tear

Method: MRI

Conclusion: No, definitely not. Besides previously reported associated injuries, such as meniscal and collateral ligament injuries, 57% had a cortical depression fracture, and nearly all (98%) had bone marrow lesions.



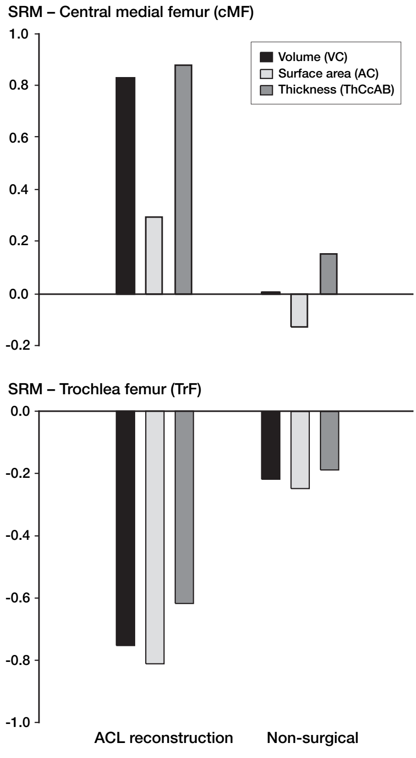
Paper IV. The distribution and frequency of cortical depression fractures presented in this study (n=78). Frontal view (left) and sagittal view (right).

V. Does an ACL reconstruction influence the 1st year development of joint fluid, bone marrow lesions and cartilage morphology?

Subjects: 58 subjects, 16 women, with a not more than 5 weeks old ACL tear

Method: Prospective MRI over the 1st year after ACL injury

Conclusion: Yes, joint fluid and BML volumes as well as morphometric change of knee cartilage were negatively affected by an ACL reconstruction.



Paper V. Standard Response Means (Mean change / $SD_{Mean\ change}$) of changes between 3 and 12 months of joint cartilage volume (VC, black bars), joint cartilage thickness (ThCcAB, dark grey bars) and joint cartilage area (AC, light grey bars) in the central medial femur (top) and trochlea femur (bottom) for knees treated with ACL reconstruction (n=34) and without ACL reconstruction (n=24).

Description of contributions

Paper I

Study design	Richard Frobell, Stefan Lohmander, Harald Roos, Ewa Roos
Data collection	Richard Frobell
Data analysis	Richard Frobell
Manuscript writing	Richard Frobell
Manuscript revision	Harald Roos, Stefan Lohmander
Journal correspondence	Richard Frobell

Paper II

Study design	Richard Frobell, Stefan Lohmander, Harald Roos, Ewa Roos
Data collection	Richard Frobell
Data analysis	Richard Frobell, Ewa Roos
Manuscript writing	Richard Frobell
Manuscript revision	Ewa Roos, Stefan Lohmander
Journal correspondence	Richard Frobell

Paper III

Study design	Richard Frobell, Ewa Roos
Data collection	Erik Svensson, Mattias Göttrick
Data analysis	Richard Frobell, Erik Svensson, Mattias Göttrick
Manuscript writing	Richard Frobell
Manuscript revision	Ewa Roos
Journal correspondence	Richard Frobell

Paper IV

Study design	Richard Frobell, Stefan Lohmander, Harald Roos, Ewa Roos
Data collection	Richard Frobell, Torsten Boegård
Data analysis	Richard Frobell, José Tamez-Pena, Robert Buck
Manuscript writing	Richard Frobell, José Tamez-Pena, Stefan Lohmander
Manuscript revision	Stefan Lohmander, Harald Roos, Ewa Roos, Marie-Pierre Le Graverand, Robert Buck, José Tamez-Pena, Saara Totterman, Torsten Boegård
Journal correspondence	Richard Frobell

Paper V

Study design	Richard Frobell, Stefan Lohmander, Harald Roos, Ewa Roos
Data collection	Richard Frobell
Data analysis	Richard Frobell, José Tamez-Pena, Robert Buck
Manuscript writing	Richard Frobell, José Tamez-Pena, Stefan Lohmander
Manuscript revision	Stefan Lohmander, Harald Roos, Ewa Roos, Marie-Pierre Le Graverand, Robert Buck, José Tamez-Pena, Saara Totterman

Abbreviations

AC	Cartilage surface area
ACL	Anterior cruciate ligament
A-P	Antero–posterior
ARS	Activity Rating Scale
BML	Bone marrow lesions
BTB	Bone–patella tendon–bone autograft
cLF	Central lateral femur
cMF	Central medial femur
CNS	Central nervous system
DETSE	Dual echo turbo spin echo
EBM	Evidence based medicine
ER	Emergency room
F	Femur
FOV	Field of view
FLASH	Fast low angle shot
GAG	Glycosaminoglycans
ICC	Intra-class correlation
ITT	Intention to treat
JF	Joint fluid
K	Knee
KOOS	Knee injury and Osteoarthritis Outcome Score
LCL	Lateral collateral ligament
LF	Lateral femur
LT	Lateral tibia
MCL	Medial collateral ligament
MF	Medial femur
MRI	Magnetic resonance imaging
MT	Medial tibia
OA	Osteoarthritis
P	Patella
PCL	Posterior cruciate ligament
pLF	Posterior lateral femur
pMF	Posterior medial femur
qMRI	Quantitative magnetic resonance imaging
QOL	Quality of life
RCT	Randomized controlled trial
ROI	Region of interest
ROM	Range of motion
SD	Standard deviation
SRM	Standard response mean (Mean change / $SD_{mean\ change}$)
STIR	Short tau inversionrecovery
T	Tibia
TE	Echo time
ThCcAB	Cartilage thickness
TR	Repetition time
TrF	Trochlea femur
VC	Cartilage volume

Populärvetenskaplig sammanfattning

Avhandlingens huvudsyfte var att undersöka årlig förekomst samt tidiga konsekvenser av akut främre korsbandsskada i knäleden. En klinisk studie med slumpvis fördelning mellan kirurgisk rekonstruktion och icke-kirurgisk behandling, KANON-studien, designades och användes för ändamålet.

På kort sikt orsakar en obehandlad främre korsbandsskada vikningsepisoder och instabilitet. Dessa symptom kan i hög grad lindras av strukturerad rehabilitering, med eller utan tillägg av kirurgi. På längre sikt drabbas varannan individ emellertid av artros (ledsvikt) oavsett kirurgisk eller icke-kirurgisk behandling.

Idag finns inga vetenskapliga resultat som stödjer att kirurgisk rekonstruktion av ett skadat främre korsband ger bättre resultat än andra behandlingsmetoder. Trots det rekommenderas vanligen kirurgi som behandling, särskilt för unga aktiva individer.

Främre korsbandsskadan är endast en del av problemet

Förutom tidigare kända skador på menisker och sidoledband visar vi att 60 % av dessa knän även drabbas av frakturer och att i stort sett alla har benmärgsskador, s.k. lesioner.

Genom att använda ny magnetkamera teknik (MR) visar vi även att benmärgslesionerna kvarstår i nästan 2/3 av knäna ett år efter skada. Dessutom finner vi en konstant förändring av ledbrosket i två olika regioner av knäleden ett år efter skada oavsett behandling.

Det förstörda främre korsbandet är således endast en del av ett större skadepanorama, vilket måhända delvis förklarar varför risken för knäartros är hög även efter behandling av det skadade ligamentet.

Förlängd läkning efter kirurgisk rekonstruktion?

Kirurgisk rekonstruktion, utförd inom 10 veckor efter skada, var en oberoende riskfaktor för fördröjd reduktion av såväl ledsvullnad som benmärgslesioner och lokala förändringar i ledbrosket ett år efter skada.

En möjlig slutsats är därför att individer med tidig rekonstruktion av främre korsbandet bör undvika idrott och fysiskt krävande aktiviteter under de första 12 månaderna efter skada.

Varannan främre korsbandsskada får fel diagnos i det akuta skedet

Den årliga förekomsten av främre korsbandsskador är nära tre gånger högre än tidigare känt, 81 per 100 000 individer i åldrarna 10–64 år. Ökningen beror sannolikt delvis på att varannan patient med främre korsbandsruptur, verifierad med MR-undersökning, inte upptäcktes vid den kliniska undersökningen på ortopedens akutmottagning.

Det akuta omhändertagandet av dessa patienter bör således förbättras genom ändrade rutiner.

Återgång i idrott återspeglar inte nödvändigtvis symptomfrihet

Fotbollsspelare som tidigare drabbats av knäskada rapporterar sämre knäfunktion än sina oskadade lagkamrater, trots att de spelar fotboll på samma nivå. Eventuellt betyder det att dessa individer är aktiva i spel trots symptomgivande knäleder vilket kan bidra till ökad risk för framtida knäartros.

Evidensbaserad behandling kräver stora resurser men är nödvändig

Randomiserade kontrollerade kliniska studier är de enda vedertagna vetenskapliga redskapen för att visa en behandlings effektivitet jämfört med placebobehandling eller annan etablerad behandling. Denna studiedesign är krävande och tidsödande, men är ett krav vid exempelvis introduktion av nya läkemedel. Däremot föreligger inget liknande krav för etablering eller introduktion av kirurgiska metoder. I den mån det är möjligt bör kanske även vissa knäkirurgiska behandlingar utvärderas på liknande sätt.

Denna avhandling visar att det är fullt möjligt att genomföra en klinisk studie med slumpmässig fördelning mellan kirurgisk och icke-kirurgisk behandling. Vi underlättar för liknande framtida studier genom att beskriva resultatet av rekryteringsprocessen. Forskare som vill genomföra en studie liknande KANON-studien bör räkna med att behöva undersöka minst fem patienter för att inkludera en i sin studie.

Sammanfattningsvis finns få *sanningar* om främre korsbandsskada. *Konsekvenserna* för den enskilda individen är emellertid ofta allvarliga. Såväl kortsiktiga som långsiktiga *konsekvenser* bör ingå vid utvärdering av dessa skador samtidigt som kvalitén på vetenskapliga rapporter rörande främre korsbandsskador behöver förbättras.

Introduction

A short historical review

It is not clear who published the first scientific report of a knee injury involving an ACL tear, but most likely the first description was made by Stark in the 1850s (Stark 1850). The first report of a surgical procedure to repair/reconstruct a ruptured ACL using the ilio-tibial band was described by Hey Groves in 1917 (Hey Groves 1917). However, few would dispute that the first comprehensive description of ACL tears and their surgical treatment was published in a thesis from 1938 by the Swedish professor and surgeon Ivar Palmer (Palmer 1938). In summary, his recommendations for the handling of ACL tears, based on his scientific work about 70 years ago, was:

1. ACL tears need to be diagnosed as early as possible.
2. The ruptured ACL needs to be surgically repaired.

These statements seem to have been unchanged through almost a century and would not be out of place in a talk given at a conference on orthopedic surgery today.

Surgical repair or reconstruction of the ACL has been the driving force in the development of treatment of ACL deficient knees ever since instability was found to be the major cause of disability in the active individual (Slocum et al. 1976). Surgical techniques, tunnel positioning and graft choice have been in the scientific focus over the years, but there is still no evidence in support of surgical treatment being superior to non-surgical treatment (Linko et al. 2005, Lohmander et al. 2007).

The anterior cruciate ligament

The knee joint is stabilized by static (i.e. ligaments) and dynamic (i.e. muscles) stabilizers (Levangie & Norkin 2001). The normal ACL is, along with the posterior cruciate ligament (PCL) and the medial and lateral collateral ligaments (MCL/LCL), a passive, static and viscoelastic stabilizer of the knee (Johansson et al. 1991). The ACL is attached to the femur and tibia, not as a single cord but as a collection of individual fascicles that fan out over a broad flattened area (Furman et al. 1976). In the normal human knee, the ACL is approximately 35 mm long and 8 mm thick, surrounded by a synovial layer and consisting of at least two separate bundles, the anteromedial (AM) and posterolateral (PL) bundle. The AM bundle is tauter in flexion and the PL bundle is tauter in extension. The proximal insertion is located on the posterior aspect of the medial surface of the lateral femoral condyle and the distal insertion is inferior to the tibial spine (Arnoczky 1983). At rest, the ACL is the primary restraint to anterior displacement of the tibia relative to the femur (Butler et al. 1980). In addition, the normal ACL also acts as a restraint to internal-external rotation, varus-valgus angulation and combinations thereof (Markolf et al. 1995, Kanamori et al. 2002). Furthermore, the ACL receives nerve fibers from the tibial nerve, suggested to provide the ACL with mechanoreceptors contributing to the dynamic stabilization of the knee joint over the central nervous system (CNS) (Solomonow & Krogsgaard 2001).

Due to its oblique pattern through the knee joint, a complete tear is unlikely to heal as the ruptured ends of the ligament are separated. However, spontaneous healing or healing onto the PCL has been reported (Kurosaka et al. 1998, Fujimoto et al. 2002, Boks et al. 2006), although the frequency of such healing potential is not known.

Incidence and prevalence of ACL injury

An ACL injury affects mainly young active individuals where the annual incidence of ACL injury in different sports was suggested to be 18/1000 players in soccer (Roos et al. 1995) and 1/1000 game hours in handball (Myklebust et al. 1998). Several studies also reported a higher rate of ACL injuries among female athletes compared with males (Arendt & Dick 1995, Arendt et al. 1999, Agel et al. 2005, Mihata et al. 2006). The incidence of ACL injury in the general population is however not well known. Only one report was found, suggesting an annual incidence of 30 ACL injuries per 100 000 inhabitants (Nielsen & Yde 1991). Extrapolated nationally, this implies that approximately 2700 ACL injuries would occur annually in Sweden, regardless of age, activity level etc. However, more than 3000 ACL reconstructions are performed in Sweden annually due to acute or chronic ACL insufficiency and thus an incidence of less than 3000 ACL injuries per year is likely to be an understatement.

The prevalence of ACL rupture is not known. However, a recent study using MRI for assessment found that 4.8% of ambulatory individuals aged 50–90 years, unselected for knee or other joint problems had an ACL tear (Englund et al. 2006). Thus, many subjects with ACL injury may be misdiagnosed, never receive medical attendance, have spontaneous (i.e. non-traumatic) ACL ruptures and/or suffer only from minor symptoms of their ACL injury.

The acutely ACL injured knee

An ACL rupture is usually the result of a specific trauma to the knee joint in young adults and adolescents where a history of recent trauma in combination with hemarthrosis is a good clinical indicator for ACL injury (Gillquist et al. 1977, DeHaven 1980, Noyes et al. 1980, Butler & Andrews 1988, Harilainen et al. 1988, Visuri et al. 1993, Sarimo et al. 2002). An increased antero-posterior (A-P) laxity at clinical assessment in the acute phase would further suggest malfunction of the ACL.

The injury mechanism for an ACL tear is complex and not well understood (Arendt & Dick 1995, Andersen et al. 2004, Arnason et al. 2004, Griffin et al. 2006). Hyperextension or combinations of valgus-external rotation or flexion-internal rotation were mechanisms suggested to produce an ACL tear (Jarvinen et al. 1994, Ettlinger et al. 1995, Palmer 2003). The complexity of such mechanisms implies a likelihood of additional anatomical injuries within the injured knee joint and consequently isolated ACL tears are rare. Collateral ligament injury and/or meniscal injury were found as concomitant injuries in 50–70% of ACL injured knees (DeHaven 1980, Butler & Andrews 1988, Sarimo et al. 2002) but possibly additional injuries could be detected using new and improved methods. The growing use of MRI has revealed traumatic bone marrow lesions (BML), also referred to as 'bone bruises', in the acute phase of ACL injury (Yu & Cook 1996, Hayes et al. 2000, Sanders et al. 2000, Palmer 2003). The relevance of such injuries is not yet fully known, although micro-fractures of cancellous bone, osteocyte necrosis, edema, bleeding in the fatty marrow and empty osteocyte lacunae were observed in the area of traumatic BML (Johnson et al. 1998, Rangger et al. 1998). It is thus possible that the knee cartilage, sub-chondral bone and bone marrow are affected by strong compressive forces at the time of ACL injury and case-reports of associated fracture-like findings support this possibility (Kaplan et al. 1992, Stevens & Dragoo 2006).

Animal and laboratory studies have shown cell death and chondrocyte senescence in cartilage affected by traumatic compression (Johnson et al. 1998, Lewis et al. 2003, Lahm et al. 2004, Martin et al. 2004, Milentijevic et al. 2005). Furthermore, chondrocyte necrosis was found to occur in the impacted cartilage, spreading in depth and width with increasing stress forces (Ewers et al. 2002, Borrelli et al. 2003, Milentijevic et al. 2005). Thus, it is likely that the knee cartilage is negatively affected by injuries involving compressive forces (Lohmander & Roos 1994, Lohmander et al. 2007).

Consequently, the ACL is possibly only one of many injured intra-articular structures of these knees and the rationale of classifying these knees as ACL injured knees could be questioned.

Treatment of ACL injuries

There is no treatment that fully restores an ACL injured knee and thus these knees will remain injured regardless of treatment. Individuals suffering from instability, pain or dysfunction are likely to seek medical care and offered the treatment option preferred at that specific medical institution. However, individuals with minor or no symptoms are not likely to seek medical care and will probably never receive any treatment. The frequency of asymptomatic ACL injuries is not known, although the high prevalence of ACL rupture found in older subjects unselected for knee complaints (Englund et al. 2006) suggest that this is not an uncommon phenomenon.

Surgical treatment is the most frequently reported treatment of ACL injury and the preferred treatment by most orthopedic surgeons. Arthroscopically assisted reconstruction of the ACL has been the method of choice since the 1990's, and the bone-patellar tendon-bone (BTB) autograft (Jones 1970) was initially the preferred graft for primary reconstruction of the ACL (Lipscomb et al. 1981). In recent years, however, a growing use of quadruple hamstring autografts (Semitendinosus / Gracilis tendon) (Aglietti et al. 1996) has been reported. No differences have been shown at two years after reconstruction in RCTs when comparing these methods (Eriksson et al. 2001a, O'Neill 2001, Laxdal et al. 2005, Biau et al. 2007). Recently, the double bundle technique (Hara et al. 2000, Takeuchi et al. 2002, Marcacci et al. 2003) was introduced as a more anatomically fit method for surgical reconstruction. However, there is no long term evidence (i.e. more than 2 years) in favor of this technique as compared to the single bundle technique mainly used today (Muneta et al. 2007), even though a better rotational stability compared with the single bundle technique was reported after 14 months (Jarvela 2007).

Non-surgical treatment following ACL injury is less frequently reported, especially in recent years, and unfortunately non-surgical treatment was poorly defined in studies comparing surgical and non-surgical treatment (Sandberg et al. 1987, Andersson et al. 1991, Zysk & Refior 2000, Meunier et al. 2007). Structured rehabilitation was however proven to be beneficial before and after surgical treatment (Shelbourne et al. 1991, Shelbourne & Patel 1995) and physiotherapist led programs consisting of specific muscle exercises, neuromuscular electrical stimulation and most likely also neuromuscular exercises have been shown to be effective in the rehabilitation after ACL reconstruction (Ageberg et al. 2001, Risberg et al. 2004). In the 1980's, several studies reported good outcome after non-surgical treatment where subjects treated with rehabilitation alone were shown to benefit at least equally to those treated surgically (McDaniel & Dameron 1980, Giove et al. 1983, Jokl et al. 1984). These findings were confirmed in two recent studies (Myklebust et al. 2003, Kostogiannis et al. 2007). Furthermore, physical therapy and rehabilitation of ACL deficient knees has improved significantly over the last 10–15 years, increasingly based on scientific evidence (Risberg et al. 2004).

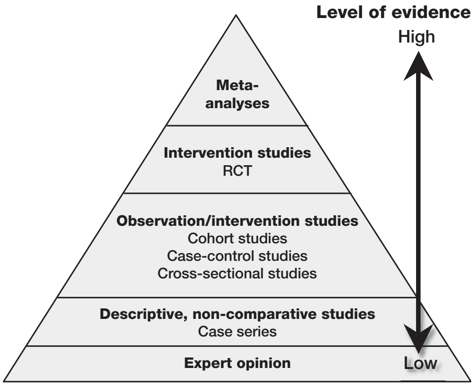


Figure 2. Different types of study designs and their level of evidence.

Study designs and Evidence Based Medicine (EBM)

There are numerous publications on the assessment of ACL injury. However, different study designs provide results of varying quality and results are not always generalizable to populations outside the study sample. There are three major clinical study designs: descriptive, observational, and interventional studies (Figure 2) (Audige et al. 2006). Descriptive and observational study designs have several known limitations affecting the possibility to draw generalized conclusions. Thus, such studies should mainly be used to generate hypotheses, enhance the quality of current treatments and to study effects of treatments already shown to be effective. Conclusions from such studies need to be carefully considered regarding study design, confounding factors and different types of bias. In order to prove one treatments' superiority over another, an RCT is recommended and considered the gold standard (Dunn et al. 2003, Audige et al. 2006).

Randomized Controlled Trials (RCT)

Designed properly, the randomized clinical trial (RCT) is a powerful tool to evaluate medical treatments (Begg et al. 1996, McLeod et al. 1996). RCTs evaluating surgical treatments are however challenging to design and conduct. In particular, the recruitment of patients has been described as difficult and time-consuming (Tognoni et al. 1991, McLeod et al. 1996, Ross et al. 1999). An RCT is superior to other study designs as randomization matches groups for unknown characteristics (confounders) as well as other prognostic variables. Selection bias is therefore reduced to a minimum (Dunn et al. 2003, Audige et al. 2006). Results and conclusions delivered in a report from an RCT are however not always reliable since RCTs can be performed and/or reported with large quality differences. Low quality reports from RCTs have been suggested to overestimate the effectiveness of interventions by some 30% when compared with high quality reports from RCTs assessing the same intervention (Schulz et al. 1995, Moher et al. 1998). A proposal for reporting results from RCTs, the CONSORT statement, was published in 1996 (Begg et al. 1996), revised in 2001 (Moher et al. 2001) and was shown to improve the quality of reports from treatment RCTs (Plint et al. 2006).

There are few available RCT reports in orthopedic surgery, especially from RCTs comparing surgical and non-surgical interventions. One reason for this is probably that such studies require substantial efforts in order to include a sufficient number of subjects. Traditionally it may have been considered unethical not to perform a surgical procedure earlier shown to be beneficial for subjects in descriptive and observational studies. Most surgical treatments in orthopedics were introduced prior to the development of RCTs and thus several frequently performed surgical interventions were never compared with non-surgical alternatives. A widely discussed recent study compared results after arthroscopic knee surgery and sham surgery in subjects with OA (Moseley et al. 2002). In this study, sham surgery was found to be as effective as arthroscopic lavage and debridement, although none of these treatments improved symptoms more than 10–20% compared to pre-surgery symptoms. Surgery obviously has a significant placebo effect. With regard to ACL injuries, the following was stated in a recently defended thesis: “due to the lack of good studies, comparing surgical and non-surgical treatment, it is currently almost impossible to advise the individual person with an ACL injury about whether or not non-surgical treatment can be safe” (Laxdal 2006). Surprisingly, one of the studies included in this thesis showed that 93% of the patients expected an excellent or good result from surgical reconstruction. However, at follow-up at 32 months almost 20% reported a poor or fair result, suggesting that treatment ‘safety’ was not very high in a surgically treated group. An RCT requires equipoise, meaning that treating surgeons as well as the patient admit that each treatment arm could be equally beneficial. A lack of equipoise could be an additional explanation of the low frequency of RCTs in orthopedics. RCTs comparing surgical and non-surgical treatment are however needed in orthopedic surgery, and in the treatment of ACL injury.

Sample size

An a priori sample size calculation is required in the planning of an RCT, but nevertheless rarely reported (Freedman & Bernstein 1999, Halpern et al. 2002). A too small sample size due to e.g. low recruitment leads to poor statistical power and compromises the ability to detect meaningful differences. The sample size calculation, when performed, provides an estimate of the number of patients needed to include in a trial in order to reject the null hypothesis with an a-priori defined power (commonly set to be 80%). An undersized RCT could produce false conclusions, mainly depending on the type II error where the null-hypothesis could not be rejected because there are too few subjects in each group. An undersized RCT may thus be of less value than an observational study. A report on the unethical conduct of underpowered trials was recently published, suggesting that investigators still fail to calculate appropriate statistical power prior to study start, or at least fail to provide such information in the published study report (Halpern et al. 2002). The calculated sample size does however not take into account loss to follow-up, eligible patients declining RCT participation, or the larger number of patients needed to screen to identify those eligible for the trial. A translation of theory (sample size calculation) into clinical prac-

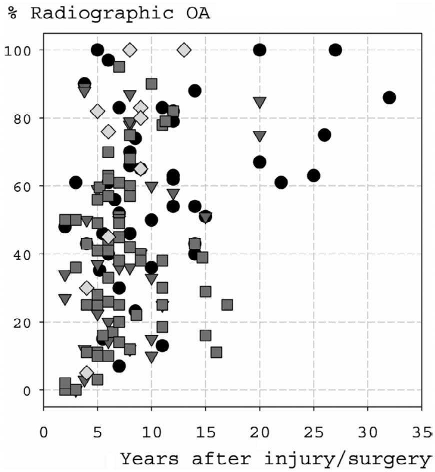


Figure 3. Scattergram of the proportion of individuals with radiographic osteoarthritis (OA) plotted against time after ACL injury or reconstructive surgery. Each data point represents a data set from 1 of 127 individual publications. The different radiographic assessment methods were translated into the Kellgren and Lawrence criteria, using as cutoff for the presence of radiographic OA any of the following: joint space narrowing grade ≥ 2, sum of osteophyte grades ≥ 2, or a combination of grade 1 joint space narrowing and a grade 1 osteophyte. Compare with Figure 1. (Lohmander & Roos 1994). Symbols: ● represents nonsurgical treatment; ▼ represents primary suture or enhancement; ■ represents reconstruction by autograft; ♦ represents reconstruction by synthetic graft or allograft.
Figure and figure legend from: Lohmander LS, Englund M, Dahl, LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am J Sports Med 2007; 35: 1756-69. With kind permission of the authors and publisher.

tice could thus help estimate the efforts needed to successfully complete a clinical trial with sufficient power. Parameters such as the Number Needed to Screen (NNS) and the Number Needed to Allocate (NNA), as determined from the clinical reality of an ongoing RCT comparing surgical and non-surgical treatment, could help in the planning of future studies. The use of such ratios could help an investigator to estimate the efforts needed to recruit subjects in order to reach a sufficient sample size for a future trial.

EBM of treatment after ACL injury

The MeSH-term 'anterior cruciate ligament' identified 5675 publications in PubMed in October, 2007 (http://www.ncbi.nlm.nih.gov/sites/entrez). However, according to a recent systematic review of RCTs comparing surgical and non-surgical treatment from the Cochrane Collaboration (Linko et al. 2005) (www.thecochranelibrary.com) there were only two reports from RCTs (Sandberg et al. 1987, Andersson et al. 1991). Both were found to be of poor methodological quality. The study from Andersson et al. (Andersson et al. 1991) received an overall methodological assessment score of 1 on a ten graded scale where 10 was the maximum score. Nevertheless, the authors concluded that: "patients with high functional demands should be treated by primary ACL repair and augmentation". The study by Sandberg et al. (Sandberg et al. 1987) received a score of 3 on the same scale. None of these studies showed differences between surgical and non-surgical treatment with regard to return to ordinary daily activities or sports activity, knee function or satisfaction with treatment. The authors of the systematic review concluded that there is no, and has never been, any evidence to determine whether surgery or non-surgery should be the treatment of choice for subjects with an ACL injured knee (Linko et al. 2005). In support of the Cochrane review, no long term differences of OA development were found between ACL injured knees treated with or without surgery in a recent analysis of the literature on OA development after ACL injury (Lohmander et al. 2007) (Figure 3).

Outcomes after ACL injury

Mechanical stability

As stated above, instability was early found to be the major limiting factor for activity after ACL injury and A-P laxity was a frequently used outcome of treatment of these injuries. Manual tests of A-P laxity, such as the Lachmann test or the anterior drawer test are still frequently reported (Sommerlath et al. 1991, Grontvedt et al. 1996, Eriksson et al. 2001a, Eriksson et al. 2001b, Laxdal et al. 2005, Laxdal et al. 2007). Instrumental tests, such as the KT 1000 or KT 2000 (Hirokawa et al. 1992, Huber et al. 1997) and the Stryker Knee Laxity Tester® (OSI Stryker, Kalamazoo, MI, USA) were suggested to be more objective measurements of knee laxity. However, as these tests are performed at rest only static stability of the relaxed knee is assessed and the association between static instability and knee stability in activity is not well documented.

Knee scoring systems

The Cincinnati knee scoring scale (Noyes et al. 1989) and the *Lysholm score* (Lysholm & Gillquist 1982) are historically the most frequently used outcomes of knee function after ACL injury. Both scores are assessor reported, an administration mode shown to introduce bias when applied in patients with ACL injury (Hoher et al. 1997, Roos 2001). The cut-off for good/excellent results according to the Lysholm score was revised from 77 to 84 points (best possible is 100) in 1985 (Tegner & Lysholm 1985) although previously both cut-offs were used. The Cincinnati knee ligament rating system includes physical examination and instrumented testing as well as a four-part evaluation format to assess symptoms and function where an overall grade is defined by the lowest score in any individual category. Static instability at clinical examination is likely to have a major impact on the final grading of this scale.

The International Knee Documentation Committee (IKDC) was formed by members of the American Orthopedic Society for Sports Medicine (AOSSM) and the European Society of Sports Traumatology, Knee surgery and Arthroscopy (ESSKA). IKDC developed a scoring system, specifically to be used in the assessment of ACL injured knees (Hefti et al. 1993), covering four problem categories: subjective (patient relevant) assessment; symptoms; Range of Motion (ROM); ligament examination (Irrgang et al. 1998). The worst grading within one category determines the category grade and the worst category grade classifies the final evaluation (IKDC-final). The presence of static instability upon clinical assessment would determine the final IKDC grading.

The Knee injury and Osteoarthritis Outcome Score (KOOS) (Roos et al. 1998a, Roos et al. 1998b) is a self-reported patient relevant outcome of knee function including the items of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy et al. 1988). The KOOS is validated for different orthopedic procedures such as ACL reconstruction, meniscectomy and knee OA (Roos et al. 1998a, Roos et al. 1998b, Roos et al. 1999). KOOS assesses the patients' perspectives of pain, symptoms, activities of daily living (ADL), sports & recreation, and knee related quality of life (QOL). One important difference between the KOOS and other scoring systems is that each separate dimension of knee function including knee related quality of life are presented individually. According to the user's guide a normalized score from 0 to 100, where 100 is the best possible result, is given separately for each subscale (www.koos.nu).

Activity level

The Tegner scale was published in 1985 as an assessor-reported outcome for evaluation of activity level in subjects suffering from anterior cruciate ligament (ACL) injury, and has been widely used also in evaluation of other knee injuries (Tegner & Lysholm 1985). The Tegner scale is increasingly used as self-reported by patients (Voloshin et al. 2003, Mithoefer et al. 2006, Herrlin et al. 2007, Kostogiannis et al. 2007) but several recent publications have not described the collection mode (Barrett et al. 2005, Marder et al. 2005, Gobbi & Francisco 2006, Karataglis et al. 2006, Asik et al. 2007, Laxdal et al. 2007, Thomee et al. 2007). We could, however, not find any study supporting the use of the Tegner scale as a self-reported outcome. Soccer is represented at three different levels of the Tegner scale: Tegner level 10 is equivalent to national level; Level 9 to competitive level; and level 7 to recreational level. Competitive soccer (level 9) is a wide concept including all divisions below the national league and individual interpretation of this level could vary. Self-reported Tegner scores could be influenced by level of competition (division) but we have not found any studies evaluating this possibility.

The Activity Rating Scale (ARS) was presented in 2001 as an alternative to the Tegner scale (Marx et al. 2001). This scale assesses the frequency of four specific activities: running; cutting; decelerating; pivoting, performed during the past year and was thus suggested to measure activity (what patients are doing) as an alternative of their health status (how patients are doing). Use of this scale in clinical trials has to our knowledge not yet been reported.

Magnetic resonance imaging – MRI

Magnetic resonance imaging (MRI) has made it possible to visualize the knee joint non-invasively. Arthroscopy is still considered to be gold standard and some authors have reported arthroscopy to be superior to MRI for diagnostic use in acute knee injuries (Lundberg et al. 1996, Smith 1996). Conversely, other studies suggested that MRI is as accurate as arthroscopy in detecting ligament and meniscal lesions in the knee joint (Munshi et al. 2000, Fritz 2003, Winters & Tregonning 2005). In addition, authors have advocated that an MRI often makes it possible for the orthopedic surgeon to avoid unnecessary surgical procedures (Rangger et al. 1996, Rappeport et al. 1996, Vincken et al. 2002). MRI performed in knees with uncertain diagnosis after injury was shown to improve patient satisfaction as well as patient management (Mackenzie et al. 1996, Muellner et al. 1999, Munshi et al. 2000, Frihagen et al. 2002). The use of MRI would most likely enhance diagnosis of acute knee injuries and could probably replace diagnostic arthroscopy in the acute phase of injury. In addition, MRI also provides the opportunity to non-invasively evaluate and re-evaluate the development of osseous, chondral, ligamentous and meniscal injuries of the injured knee over time.

In recent years, new and validated techniques of computer-assisted analysis of MR images have emerged. These methods were proven to be particularly powerful when quantitative metrics as continuous variables were derived from serial MR images, using image segmentation and analysis algorithms (Peterfy 2002, Burstein & Gray 2003, Eckstein & Glaser 2004, Gray et al. 2004). The use of this new technique offers new opportunities to quantify and regionalize traumatic bone marrow lesions (BML) and to monitor their development over time. In addition, joint fluid (JF) volumes and cartilage-related measures such as volume, thickness and surface area can be quantified non-invasively.

Consequences of acute ACL injury

Short term (i.e. within 1–2 years)

As stated above, mechanical instability was shown to be the major cause of disability the first years after injury and has been the subject of interest since the days of Ivar Palmer (Palmer 1938). Instability increases the risk of ‘give way’ episodes in activity, suggested to elevate the risk of secondary meniscal injury. A successful ACL reconstruction will restore or at least reduce instability in activity and possibly also reduce the frequency of secondary meniscal injuries in the long term (Meunier et al. 2007). Few would dispute the fact that an ACL reconstruction will stabilize the knee and instability is therefore the main indication for surgical treatment. Notwithstanding, some of the subjects treated with ACL reconstruction do not function well two years after treatment, indicating that reduced instability does not resolve all problems following this type of injury. Pain, swelling and locking are other factors suggested to be associated with the early phase of ACL injury (Tegner & Lysholm 1985), although the frequency of such manifestations is not well understood. It is possible that additional associated injuries were not previously detected or may have been disregarded in the assessment of acutely ACL injured knees.

Long term (more than 5 years)

The relation between good short term outcome and good long term outcome is unclear and the possibility of a good short term outcome (e.g. return to sports) as compromising a good long term outcome (e.g. osteoarthritis) must be considered. Every second ACL injured knee will develop radiographic signs of knee OA although the reported rate varies between 10 and 90% (Lohmander & Roos 1994, Gillquist & Messner 1999, Myklebust & Bahr 2005, Lohmander et al. 2007). The wide range of OA frequency is partly explained by the different methods used for grading radiographic OA. The lack of standardization of image acquisition and assessment are also likely reasons. In a recent review, 127 individual reports of follow-up after ACL injury published from the 1970s to 2007 were included (Lohmander et al. 2007). No evidence was found for a difference between surgically and non-surgically treated subjects, indicating a lack of difference between treatments in their ability to prevent development of OA (Figure 3). Further, knee related quality of life and knee symptoms according to KOOS deteriorated already 2 years after injury or reconstruction regardless of treatment (Lohmander et al. 2007). Maybe the urge for good short term outcome combined with an athlete's attempt to return to competition as early as possible creates intra-articular environments predisposing for OA, leading to negative long term outcomes (Dahlberg et al. 1994, Beynnon et al. 2005).

In summary, an ACL injury increases the risk of joint instability in the short term and OA in the long term. An ACL reconstruction can reduce mechanical instability but does not seem to reduce the risk of OA development associated with the injury. Possibly, ACL surgery reduces the risk of secondary meniscal lesions (Meunier et al. 2007), suggested to be a substantial risk factor for OA development (Lohmander et al. 2007, Meunier et al. 2007). However, this possibility needs to be confirmed by future studies.

Non-surgical treatment can reduce instability in activity although the influence of rehabilitation in static instability is not clear. However, non-surgical treatment will allow a possibility of spontaneous healing of the ACL (Kurosaka et al. 1998, Fujimoto et al. 2002, Boks et al. 2006). There are very few recent reports of the outcome after non-surgical treatment (Myklebust et al. 2003, Kostogiannis et al. 2007) and little evidence has been presented in support of a reduction in the frequency of long-term knee OA.

The traumatic event and the acute phase of ACL injury could partly explain the increased risk of OA development regardless of treatment (Lohmander & Roos 1994, Lohmander et al. 2007). A high quality RCT that monitors both short- and long-term outcomes may improve our understanding of this clinically relevant problem.

Objectives

General aims

The overall aim of the work presented in this thesis was to evaluate the incidence, outcome and early consequence (i.e. within the 1st year) of acute ACL injury of the knee by performing a treatment RCT comparing surgical and non-surgical treatment.

Specific aims

The specific aims of this thesis were:

- To determine the incidence of ACL injury in the general population.
- To describe the agreement between the initial clinical examination and an ACL tear as visualized on MRI.
- To provide methodological support for design and conduct of an RCT comparing surgical and non-surgical treatment by explaining and quantifying:
  - the Number of patients Needed to be Screened (NNS),
  - the Number of patients Needed to be Allocated (NNA),

  in order to include the required number of patients into an RCT on surgical versus non-surgical treatment of acute ACL injuries.
- To investigate if self-reported activity level or knee function was influenced by:
  - person characteristics (i.e. age, gender, BMI, and level of competition),
  - self-reported history of knee injury.
- To map fractures and meniscal injuries in the acutely ACL injured knee by MRI.
- To map the location and volume of traumatic bone marrow lesions (BML) in the acutely ACL injured knee using MRI.
- To, in the ACL injured knee, investigate the 1st year's morphometric development of:
  - joint fluid,
  - traumatic BML,
  - cartilage.
- To investigate risk factors for morphometric joint changes over the 1st year after ACL injury.

Subjects and Methods

Subjects presented in this thesis were either allocated through the recruitment process (paper I–II), as a control group (paper III) or as included subjects in the KANON study (paper IV and V). This RCT was approved by the ethics committee in Lund 2001 (LU535-01) and is registered in Current Controlled Trials (ISRCTN 84752559, http://www.controlled-trials.com).

Acutely ACL injured subjects – a challenge to identify

In the Swedish national health care system, the orthopedic emergency room (ER) at the local hospital or the local primary health care unit is the primary instance for medical assistance after acute knee injury. Routinely, severe knee injuries assessed at the primary health care unit are referred to the orthopedic ER at the local hospital for further handling. The orthopedic ER is mainly staffed with residents or interns and only in rare cases with experienced orthopedic surgeons.

The KANON study was designed to assess the treatment of acute ACL injuries and an early diagnosis was essential for the realization of the RCT. In addition, the aim was to identify all ACL injured knees during the recruitment phase as we would otherwise risk inclusion of only symptomatic ACL injuries. A rotational knee trauma combined with a rapid effusion is a good indicator for ACL tear even if no clinical instability is detected at physical examination (Gillquist et al. 1977, DeHaven 1980, Noyes et al. 1980, Butler & Andrews 1988). The department of orthopedics at Helsingborg Hospital in Sweden implemented a sub-acute routine MRI assessment of such traumatic knee injuries in 2000. Physically active individuals regardless of age, with an acute rotational trauma to the knee combined with a rapid knee effusion were referred to a sub-acute MRI examination via the orthopedic ER. This procedure replaced the traditional radiographic examination if no fracture was clinically suspected. All subjects handled this way in 2002 were included in paper I (Table 1).

The KANON study

The KANON study was performed at two separate orthopedic centers (Helsingborg hospital and Lund University hospital) where slightly different screening strategies were used in the recruitment of subjects.

In Helsingborg, the strategy described above was used to screen subjects eligible for inclusion in the RCT. The MRI referral was electronically forwarded to the department of radiology where a secretary was asked to announce all patients aged between 18–35 years to the study nurse. All patients reported this way entered the screening group (paper II), and their medical records were reviewed. Those meeting criteria for eligibility (Figure 4) were scheduled for a baseline/screening visit (visit 0).

Table 1. Patient characteristics for all subjects included in this thesis and study design

Paper	Subjects N (Men / Women)	Age mean (SD)	ACL injury n (% of N)	Type of study
I	159 (102 / 57)	27.8 (11.0)	89 (56%)	Retrospective case series
II	162 (125 / 37)	25.7 (4.9)	144 (89%)	Randomized controlled trial
III	188 (123 / 65)	21.6 (3.7)	16 (9%)	Cross sectional
IV	121 (89 / 32)	25.6 (4.9)	121 (100%)	Cross sectional
V	58 (42 / 16)	26.7 (4.7)	58 (100%)	Prospective cohort

General criteria for eligibility

1. Age 18–35 at entry.
2. An activity level of 5–9 on the Tegner activity rating scale prior to injury (Tegner et al. 1985).
3. A not more than 4 weeks old trauma to the knee.
4. An ACL insufficiency as determined by clinical examination (positive pivot shift and/or positive Lachmann test). The ACL injury can be either "isolated" or combined with a clinically assessed MCL injury grade I–II.
5. None of the following features isolated and/or in combination:
   a. Earlier major knee injury to the index knee (ACL or PCL injury, patella dislocation or fracture).
   b. Previous knee surgery (other than diagnostic arthroscopy) to index knee.
   c. Associated PCL injury or MCL/LCL injury grade III in index knee.
   d. Concomitant severe injury to contra- lateral knee at the time of assessment (i.e. ACL or PCL injury, patella dislocation or fracture).
   e. Injury to the lateral/posterolateral ligament complex with significantly increased laxity.
   f. Pregnancy.
   g. A history of deep vein thrombosis (DVT) or a disorder of the coagulative system.
   h. Claustrophobia.
   i. General systemic disease affecting physical function, any other condition or treatment interfering with the completion of the trial, including patients with metal devices or motion disorders.
   j. Systemic medication/abuse of steroids.

Figure 4. Criteria for eligibility in the KANON study.

In Lund, MRI availability was a severely limiting factor. All patients with a rotational knee trauma combined with a rapid effusion seen at the orthopedic ER were scheduled for a clinical follow-up visit at the orthopedic department within 1–2 weeks. I personally assessed all subjects scheduled for this visit and if general criteria for eligibility were met (Figure 4), the visit was extended into a baseline visit (Visit 0).

In total 642 subjects were screened for eligibility in the KANON study (Figure 5).

Baseline visit (visit 0)

Prior to clinical examination, a history of knee injury and/or knee surgery, medication, and presence of any general systemic disease relevant to the trial was collected. Age, gender, social status, education, working status, activity at injury and general activity level was collected using self administered questionnaires. At this first visit, all patients (n=255) were assessed clinically by me personally. Patient history was collected and hemarthrosis was aspirated by arthrocentesis, if not already performed at the ER. Laxity was assessed by the Lachmann test and, when possible in the acute phase, the Pivot shift test. Patients eligible for inclusion received information about the RCT.

Randomization and intervention allocation procedure

An MRI scan was performed at the randomization visit (visit 1). A total ACL rupture as visualized by MRI (Figure 6) verified the clinically detected A-P laxity and thereby confirmed the presence of an ACL tear. Randomization was done prior to the MRI scan for clinical logistic reasons and patients could thus be excluded post randomization but prior to the fulfillment of treatment allocation (Figure 5). Any surgical intervention was performed 4–6 weeks post randomization. In a few cases patients were excluded at the time of surgery due to findings consistent with exclusion criteria for eligible patients (Figure 7). All patients were allocated to a rehabilitation clinic engaged in the study.

Patient information

Patients fulfilling inclusion criteria all received the same written and verbal information, and the telephone number to the investigator (myself) for questions related to the RCT. A video tape with patient information (described below) was used throughout the study and was distributed to all patients fulfilling inclusion criteria. To ensure sufficient time for consideration, none of the patients were allowed to agree on participation at visit 0. However, two patients, both males, declined to receive patient information and thus refused to take part in the RCT already at the baseline visit. Neither one of them wanted to take the risk of undergoing any kind of surgery. Answers about willing/not willing to take part in the RCT were obtained by telephone by the RCT study nurse. None of the patients included in this RCT agreed to participate on the same day as the information was administrated; the average time between receiving information and calling the study nurse was 3 (1–13) days.

Video recorded patient information

Prior to study start a videotape, approximately 10 minutes long, was recorded. First, a randomly

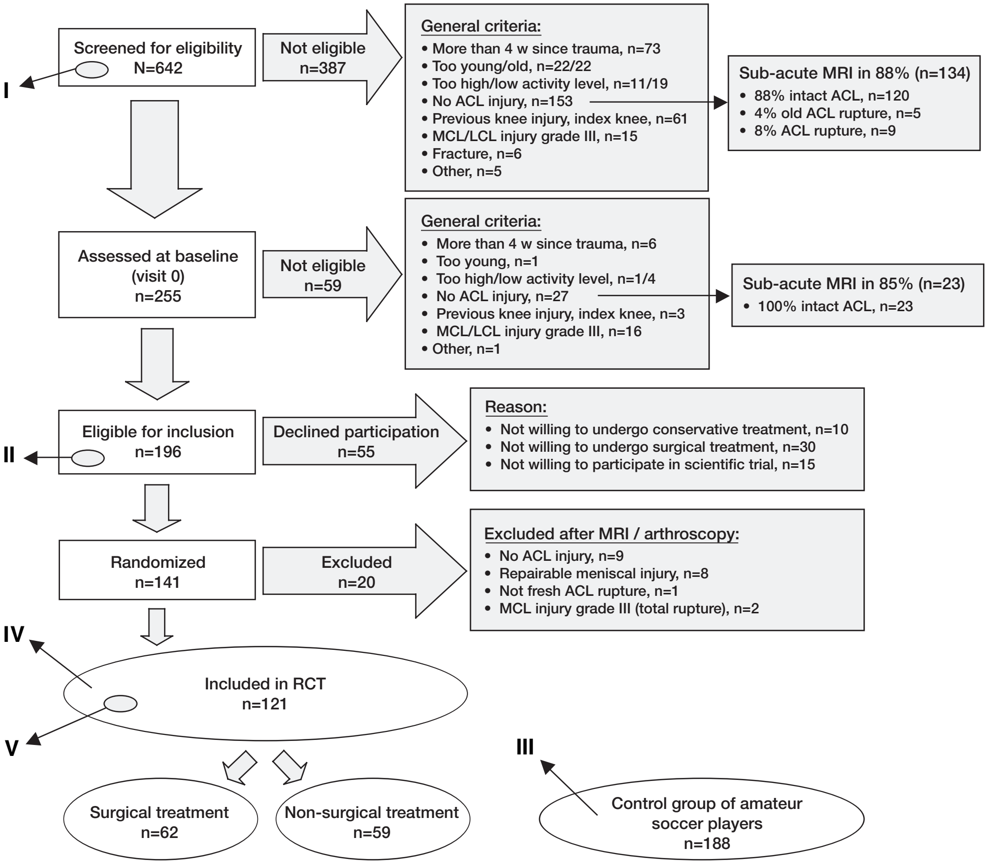


Figure 5. Flow chart over the recruitment process of the KANON study. Roman numerals indicate from what level of the recruitment phase the material for each paper was collected.

selected patient, not included into the RCT, with a fresh ACL tear was interviewed and video recorded throughout a clinical visit. The function and localization of the ACL was described to the patient using a knee model. Secondly, a sequence was recorded at the physical therapist's office where the rehabilitation procedure was summarized. Finally, the videotape ended with a panel of three experienced orthopedic surgeons discussing surgical and non-surgical treatment of ACL injuries. Throughout this panel discussion scientific evidence and clinical opinions for and against the two treatment options were presented. These surgeons subsequently operated on patients participating in the RCT.

Figure 6. A total ACL rupture as visualized on MRI (arrow).

Inclusion criteria for eligible patients

1. An ACL insufficiency as determined by clinical examination (positive pivot shift and/or positive Lachmann test) AND a complete ACL tear as visualized on MRI. The ACL injury can be either ”isolated” or combined with one or several of the following injuries visualized on MRI and/or arthroscopy:
   a. A meniscus tear that is either left untreated or treated with a partial resection.
   b. A small, stable meniscus tear treated with fixation, but fixation not interfering with the rehabilitation protocol.
   c. Cartilage changes verified on MRI but with arthroscopically determined intact surface.
2. A radiographic examination with normal joint status or combined with either one of the following findings:
   a. A small avulsed fragment located laterally, usually described as a Segond fracture.
   b. JSN grade 1 or osteophytes grade 1 as determined by the OARSI atlas (Altman et al. 1995).
3. Agreement to participate in the study and signed informed consent prior to inclusion.

Exclusion criteria for eligible patients

1. One of the following associated injuries to the index knee as visualized on MRI and/or arthroscopy:
   a. An unstable longitudinal meniscus tear that requires repair and where the following postoperative treatment (i.e. bracing and limited ROM) interferes with the rehabilitation protocol.
   b. Bi-compartmental extensive meniscus resections.
   c. A cartilage injury representing a full thickness loss down to bone.
   d. A total rupture of MCL/LCL as visualized on MRI.

Figure 7. Inclusion and exclusion criteria for patients eligible for inclusion in the KANON study.

Included subjects and loss to inclusion

The recruitment process of the KANON study ended in June 2006. In the first phase, 387 subjects were considered not eligible for inclusion in the RCT for various reasons (Figure 5). Of those, 153 were considered not to have an ACL injury after a thorough assessment of medical charts from the orthopedic ER. At the sub-acute MRI routine, 89% (136) of those had a sub-acute MRI exam of the injured knee revealing that this assumption was correct in 88% (120) of the cases and proven wrong only in 8% (9), respectively. The MRI protocol was not found for the remaining 7 knees. In the second phase, where a clinical examination was performed, 59 patients were considered not to be eligible for the study. Of those, 27 knees were not eligible due to lack of A-P laxity. Sub-acute MRI of 85% (23) of these injured knees confirmed an intact ACL in 100% (23) and the remaining four were not assessed by MRI. Thus, 196 patients met inclusion/exclusion criteria and were found eligible for inclusion in the RCT. Approximately every fourth eligible subject (55) declined participation where an unwillingness to undergo surgery was the most frequent reason (30) (Figure 5). Furthermore, clinical assessment was proven wrong in 6% (9/141) of the knees where MRI found an intact ACL in a knee assessed as clinically unstable. Consequently, 121 subjects were included in the KANON study (paper IV), 62 randomized to surgical treatment and 59 to non-surgical treatment (Figure 5). Paper II assessed all subjects screened, allocated and included in the KANON study at the time when 102 subjects were included (Table 1). Further, a sub group of 58 individuals, 34 surgically treated and 24 non-surgically treated, were followed intensively (Figure 1) with MRI during the first year after injury (paper V).

Control group similarity – necessary for adequate comparison

Reference data for the primary outcome in the KANON study (KOOS) was available for both population based controls (Paradowski et al. 2006) and ACL injured subjects (Thomee et al. 2007). However, 99% of the subjects included in the KANON study were injured in sports and were either competitive or recreational athletes. These subjects had a higher activity level than the normal population, possibly a better knee function and they could be more prone to disregard symptoms from their knee in order to be able to compete. In paper I, we found that more than 70% of all acute knee injuries were sustained during soccer play and in the KANON population approximately 60% were injured while playing soccer. For comparison we included a control group of competitive amateur soccer players (paper III). Here, the first senior team of 10 different soccer clubs (six male and four female) playing at different competitive levels (divisions) were selected, contacted and included in the study. All subjects were currently active players taking part in practice and competitive games regardless of history of knee injury. Questionnaires were distributed at a personal visit were 80% (188) of the invited participants attended (Table 1).

Population at risk (paper I)

In paper I the population based incidence of ACL injuries was investigated and population at risk needed to be defined. The study was performed at the orthopedic ER at Helsingborg hospital where individuals from the geographic recruitment area of Helsingborg hospital were expected to seek medical attendance. Further, ACL injuries are rarely found in subjects younger than ten or older than 65 years and population at risk should only include individuals within this age group. Through the National Population Registry, the Statistical Central Bureau (SCB) we located individuals between 10–65 years living within this geographic region. In 2002 the population at risk was 110 399 individuals.

Outcome and assessment tools

Knee scoring systems – paper III

Self-reported knee function was registered by the KOOS (Roos et al. 1998a, Roos et al. 1998b), also the primary outcome of the KANON study. This is a 42-item self-administered questionnaire with five separate sub-scales: pain, symptoms, activities of daily living (ADL), sport and recreation function (Sport/Rec), and knee-related quality of life (QOL). Standardized answer options are given in Likert boxes and each answer is scored from 0 to 4. Sub-scale scores are given separately (a guide for sub-scale calculation is available at www.koos.nu), ranging from 0 to 100 where 100 is the best possible result.

Activity level – papers II–V

Activity level was registered by the Tegner activity scale (Tegner & Lysholm 1985) and the Activity Rating Scale (ARS) (Marx et al. 2001). The Tegner scale is a numeric scale ranging from 1 to 10 where 1 is the least strenuous activity for the knee and 10 is the hardest. This scale was validated as an assessor reported outcome in 1985 for evaluation of activity level in subjects suffering from ACL injury and has been widely used in evaluation of knee injuries. Consistent with previous publications we used a self-reported Tegner scale (Voloshin et al. 2003, Mithoefer et al. 2006, Herrlin et al. 2007, Kostogiannis et al. 2007). Soccer is represented at three different levels of the Tegner scale: 10 –national level; 9 – competitive level; and 7 – recreational level. Competitive amateur soccer would be classified as level 9 on this scale by a trained assessor.

Knee laxity – paper I

In paper I, clinical findings of A-P laxity, assessed at the orthopedic ER by the Lachmann test (Torg et al. 1976) and/or the anterior drawer test, was collected retrospectively. In the KANON study, knee laxity was used to diagnose an acute ACL rupture and here all knees were assessed by the Lachmann test and/or the Pivot shift test. Knee laxity was not an outcome of any of the papers included in this thesis although it was used for inclusion of subjects in papers II, IV, and V.

Instrumental assessment of A-P laxity is performed at the two year follow up of the KANON study using a KT 1000 arthrometer (Huber et al. 1997) but is not an outcome used in any paper in this thesis.

Number Needed to Screen (NNS) and Number Needed to Allocate (NNA) – paper II

Number Needed to Screen (NNS) is a concept previously used and described in the literature although it was not used previously to describe a recruitment process of a clinical trial. The concept has been statistically described (Rembold 1998) and used in studies with radiographic assessment of different diseases, presented according to Number Needed to Treat (NNT) analysis terminology (Nelson et al. 2002). With the clear similarities between radiological and clinical screening, we suggest that the use of NNS is appropriate in describing the screening process of a clinical trial. The NNS presented in paper II was calculated by dividing the number of patients screened for eligibility with the number of patients included in the trial. Multiplied with the a priori determined sample size this product would give an estimate of how many patients one would need to screen in a trial with comparative design.

Further, we introduced the concept Number Needed to Allocate (NNA) in paper II. This concept is similar to NNS and has, to our knowledge, not been described previously. All patients eligible for inclusion were regarded as allocated to the RCT. The NNA was calculated by dividing the number of allocated patients with the number of included patients and thus provide an estimate of the number of eligible patients needed to include one patient in the RCT. When multiplied with an a priori sample size, this product would give an approximation of the total number of patients fulfilling inclusion criteria necessary to allocate in a clinical trial with similar design as the KANON study.

MRI

Imagers and sequences – paper I, IV, and V

In paper I, subjects were assessed by MRI according to normal clinical settings. Two different MRI machines were used. A 1.5 T imager (Gyroscan, Intera, Philips) was used with a circular polarized surface coil. The patients were examined with a T2-weighted turbo spin-echo sequence (tSEPdT2) and a T2-weighted turbo short tau inversion recovery sequence (tSTIRT2) in the coronal and in the sagittal views. The sagittal sequence was perpendicular to a line connecting the dorsal aspects of the femoral condyles and the coronal sequence was parallel to that line. The sequence parameters for the tSEPdT2 were: repetition time/echo time (TR/TE) 3335/15–100 ms with two signals averaged, echo train length 8, field of view (FOV) 170 × 170 mm, section thickness 3 mm with 0.6 mm intersection gap, matrix size 256 × 256 and acquisition time 4 min 52 s. The parameters for the tSTIRT2 were: TR/TE 2900/60 ms with two signals averaged, echo train length 4, inversion time (TI) 150 ms, FOV 170 × 170 mm, section thickness 3 mm, intersection gap 0.6 mm, matrix size 256 × 256 and acquisition time 4 min 30 s. A proton density- and T2-weighted turbo spin-echo sequence (tSE PdT2) was done sagittally, coronally and axially on a 1.0 T imager (Impact, Siemens) with a circular polarized surface coil. The sagittal sequence was perpendicular to a line connecting the dorsal aspects of the femoral condyles, and the coronal sequence was parallel to that line. The sequence parameters for the tSEPdT2 were: repetition time/echo time (TR/TE) 4200/15–105 ms with two signals averaged, echo train length 7, field of view (FOV) 160 × 160 mm, section thickness 3 mm with 0.2 mm intersection gap, matrix size 224 × 256 and acquisition time 4 min 34 s.

In papers II, IV, and V, subjects were included in the KANON study and thus all knees were assessed in the same scanner (1.5T, Gyroscan Intera, Philips) with a circular polarized surface coil. The MRI scans consisted of sagittal 3D Water excitation FLASH with TR/TE/flip angle of 20 ms/7.9 ms/25 degree, sagittal T2* weighted 3D GRE with TR/TE/flip angle of 20 ms/15 ms/50 degree. Both series were acquired with 15 cm FOV, 1.5 mm slice thickness, and 0.29 × 0.29 mm pixel size. In addition, sagittal and coronal Dual Echo Turbo Spin Echo (DETSE), both with TR/TE of 2900 ms/15 ms, 80 ms, 15 cm FOV, 3 mm slice thickness with 0.6 mm gap and 0.59 × 0.59 mm pixel size and sagittal and coronal STIR with TR/TE/TI of 2900 ms/15 ms/160 ms, 15 cm FOV, 3 mm slice thickness with 0.6 mm gap and 0.29 × 0.29 mm pixel size were acquired.

Clinical assessment of MR images

In papers I and II, MR images were consecutively assessed in the normal clinical setting by one of two well experienced musculoskeletal radiologists.

In paper II, baseline images in the KANON study (141) were initially assessed for the appearance of an ACL rupture in order to verify the clinically detected A-P laxity and thereby confirm a presence of an ACL tear. Further, meniscal injuries and associated ligamentous injury were assessed to verify inclusion/exclusion criteria of the RCT and to provide information useful in planning surgery.

In paper IV, a re-evaluation of all baseline scans was performed for all knees included in the KANON study (121). Here, one radiologist with 15 years experience of knee MRI, registered and classified meniscal injuries (Khanna et al. 2001) and fractures blinded from other radiological, clinical and surgical information. Meniscal injuries were classified where a meniscal tear was defined as increased signal extending to at least one articular surface of the meniscal body (grade 3–4 according to this classification) (Figure 8). Meniscal tears limited to either the medial or lateral meniscus were

Figure 8. A horizontal meniscal tear as visualized on MRI (arrow).

categorized as uni-compartmental meniscal tears and tears in both the medial and lateral menisci were categorized as bi-compartmental tears.

Fractures were categorized into: trabecular fracture; cortical depression fracture with or without cortical discontinuity; avulsion fracture. A trabecular fracture was defined as a line with low signal and parallel to the cortex, visualized on the DETSE sequences, and combined with a surrounding traumatic BML visualized on the STIR sequences indicating trabecular compression injury. A cortical depression fracture was defined as a trabecular fracture combined with depressed cortical bone, with or without cortical discontinuity (Figure 9). An avulsion fracture was defined as a disruption of cortical bone without signs of depression where the avulsed fragment was dislocated. The largest depth and width of the cortical depression and/or the largest diameter of the avulsed fragment was measured and registered. The appearance of cortical depression fractures in lateral femur (Figure 9) and lateral tibia (Figure 10) are presented, as well as an example of a knee classified as having no fracture (Figure 11).

In the data analyses, knees affected by at least one cortical depression fracture, regardless of size and cortical continuity, were classified as knees with cortical depression fractures and was considered as exposed to a strong compressive trauma.

Quantitative analysis of MR images (qMRI) – papers IV and V

Computer assisted quantitative analysis of MR images is a new non-invasive method used to quantify cartilage, joint fluid and BML. The method we have used here was performed by VirtualScopics Inc. (500 Linden Oaks, Rochester, NY 14625, USA) and was cross-validated to a method previously published (Graichen et al. 2004).

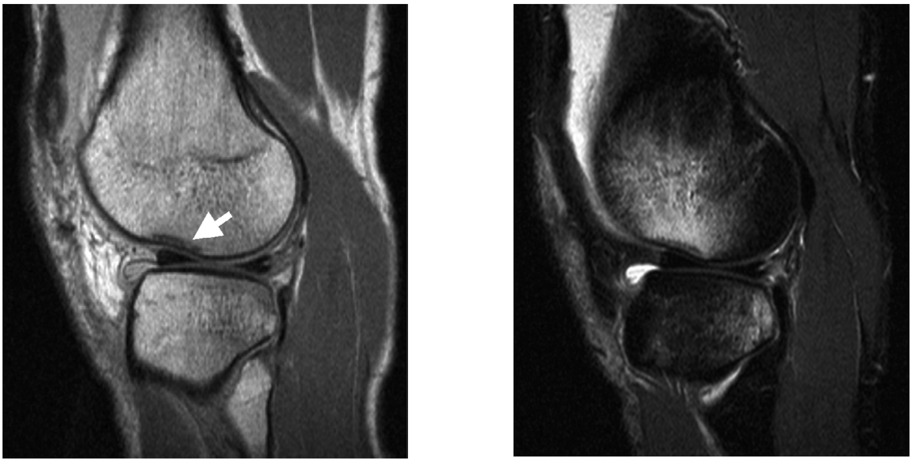


Figure 9. A cortical depression fracture, as visualized on MRI, located in the lateral femoral condyle in one of the knees assessed in this study (study id: KA1168). A line with low signal and parallel to a depressed cortex indicating trabecular fracture (arrow) as visualized on the proton density weighted image of the dual echo turbo spin echo (DETSE) sequence (left), surrounded by BML as visualized on one image of the short tau inversion recovery (STIR) sequence (right). On both images the depressed cortex without cortical discontinuity is visualized.

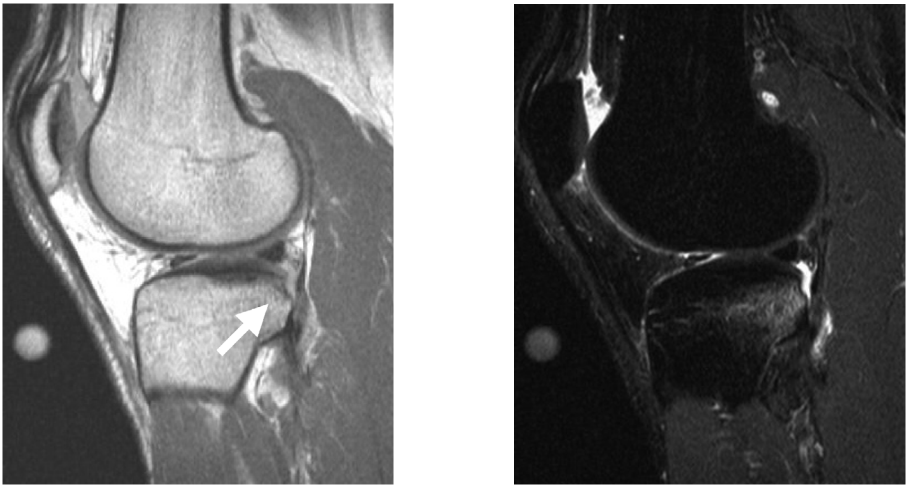


Figure 10. A cortical depression fracture, as visualized on MRI, located in the lateral tibial condyle in one of the knees assessed in this study (study id: KA1086). A line with low signal and parallel to a depressed cortex indicating trabecular fracture as well as a clear impression of the cortical bone (arrow) as visualized on the proton density weighted image of the dual echo turbo spin echo (DETSE) sequence (left) surrounded by BML as visualized on one image of the short tau inversion recovery (STIR) sequence (right). On both images the depressed cortex without cortical discontinuity is visualized.

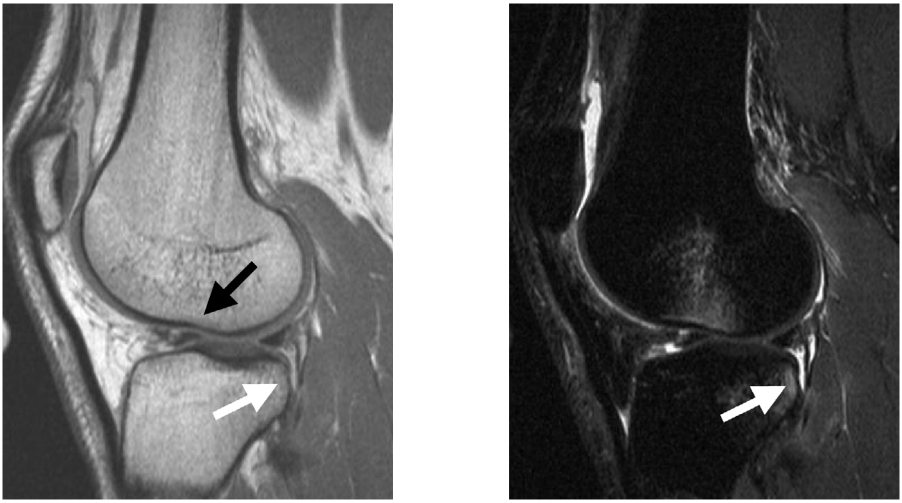


Figure 11. A knee classified as not having any fracture as visualized on MRI (study id: KA1096). A cortical depression of the lateral femoral condyle is noted on the proton density weighted image of the dual echo turbo spin echo (DETSE) sequence (left), surrounded by BML as visualized on one image of the short tau inversion recovery (STIR) sequence (right). However, there are no signs of trabecular fracture (black arrow). Posterior in the lateral tibial condyle, a straight cortical line without signs of depressions and/or trabecular fracture (white arrow) are noted on both the DETSE (left) and STIR (right) sequences although this area is surrounded by BML as visualized on the STIR sequence (right).

BML

Quantification of BML was done using a combination of image analysis techniques. First, the 3D sagittal MRI data sets were fused into a dual pulse sequence MRI dataset. Secondly, the dual sequence was automatically segmented by a proprietary computer algorithm separating all individual regions with unique signal and tissue boundaries condi-

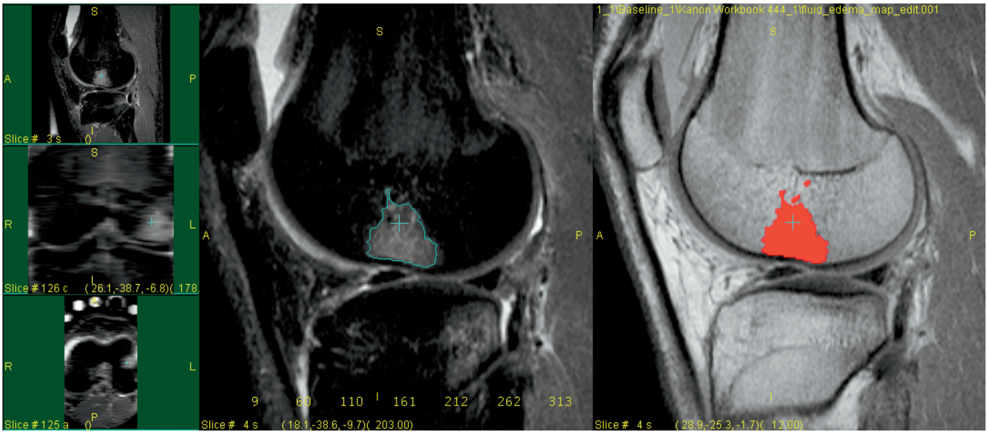


Figure 12. The appearance of bone marrow lesions (BML) as visualized on one image of the short tau inversion recovery (STIR) sequence (left) and the appearance of highlighted voxels of BML, derived from computer assisted algorithms using composite sequences, of that same slice (right).

tions (Tamez-Pena et al. 1999). The automated segmentation was inspected and edited by expert technicians who identified the regions belonging to the femur, tibia and patella. Once the bone structures were identified and labeled, an unsupervised cartilage extraction algorithm was used to extract cartilage tissue which was edited and inspected for accuracy (Tamez-Pena et al. 2004). Segmentation of BML used a similar approach as in a previous study (LeGraverand et al. 2005). Here, BML quantification was done by mapping the segmented bones and cartilage tissues into a three band composite data set composed of the two sagittal images from the dual echo and the inversion recovery MRI data set from the STIR acquisition. Furthermore, the dual echo data was used to compute the T2 values for each voxel in the image. Once the segmentation was mapped into the composite set, a computer algorithm identified all the voxels in the data set that had a large T2 value compared to bone marrow's T2, and all the voxels that had a hyper-intense STIR signal inside the bone tissue. Highlighted voxels were presented to an expert radiologist assigning the regional tissue labels to those voxels (Figure 12). Any highlighted voxels not assigned to a specific BML location were considered as false positive identifications. The expert radiologist also had the ability to correct false negatives by the use of a trace tool and match filter tool. The trace tool allowed the user to freely change the voxel by voxel classification from bone tissue to BML. The match filters tools was an algorithm based approach identifying bone voxel points sharing the same signal profile as the radiologist supplied sample. Once this last step was finished by the radiologist, the classifications of bone voxels into BML were entered into a computer algorithm and the volume of BML inside of each ROI was aggregated and reported. Longitudinally, BMLs were quantified as described above for each knee at each visit.

To assess reproducibility of the method, 28 scans were randomly selected for a re-analysis using the same procedure as described above. One image pair had a more than 2.5 times larger BML volume compared with the pair of second largest BML volume and was therefore removed from the analysis. Further, almost 50% of the pairs were found to have zero BML volumes at both assessments. These pairs were all removed from the analysis since it was possible that they could falsely affect the reproducibility in favor of our method. After these adjustments we found large correlations for all regions where the mean Intra Class Correlation (ICC) for all regions was 0.923.

Joint fluid

Joint fluid was computed using the estimated T2 values from the DETSE series. First, the T2 values were computed in each single voxel of the DETSE

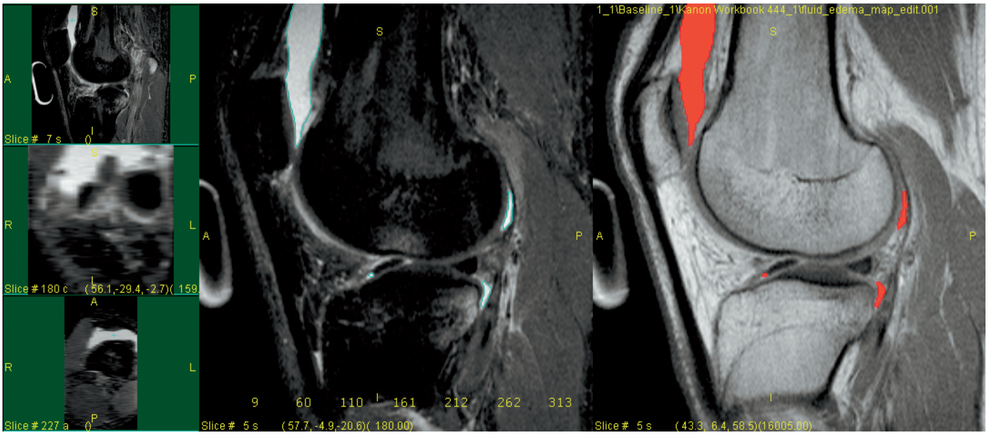


Figure 13. The appearance of joint fluid (JF) as visualized on one image of the short tau inversion recovery (STIR) sequence (left) and the appearance of highlighted voxels of JF, derived from computer assisted algorithms using composite sequences, of that same slice (right).

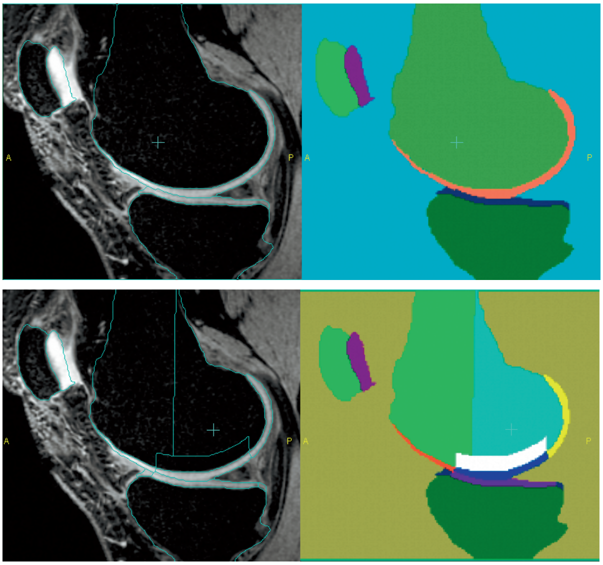
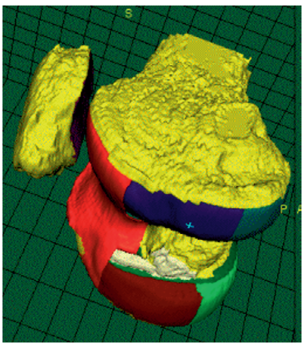



Figure 14. Segmentation using a computer assisted approach extracting the bone of femur, tibia and patella as well as the cartilage tissue associated with these regions (top). Automatic separation of cartilage into regions of interest using a feature-based atlas (bottom).

series by solving the set of linear equations given by the two separate echoes, the mono exponential model and the signal formation. Secondly, a computer algorithm highlighted each voxel with a T2 value similar to the computed T2 values within the FOV (Figure 13). Thirdly, an expert user inspected the highlighted voxels and assigned the appropriate identification only to voxels truly representing joint fluid. This procedure was performed separately for each knee and each time point.

Cartilage

Metric analysis of cartilage was performed following proprietary analysis techniques, in part described previously. Baseline scans were segmented using a computer assisted approach extracting the bone of femur, tibia and patella as well as the cartilage tissue associated with these regions (Kubilay Pakin et al. 2002, Tamez-Pena et al. 2004). Further, a feature-based atlas of the knee was used to automatically separate cartilage into regions of interest (Figure 14) (Tamez-Pena et al. 2005). This segmentation was reproduced in the follow-up scans using a computer algorithm. Thus, all the segmented components from the baseline segmentation were automatically tracked into the follow-up scans using a piece-wise mesh based approach (Tamez-Pena et al. 1998). The tracking algorithm reproduced cartilage segmentation as well as cartilage region definitions which then were controlled by an expert user to ensure accurate definition of all cartilage boundaries. The expert user control was replaced by a paired trimming algorithm used to remove the edges of the cartilage tissue and thus the need for further manual control was eliminated (Tamez-Pena et al. 2006).

Bias and presentation of change in cartilage morphometry – paper V

In paper V, we analyzed change in cartilage metrics as changes occurring from 3 months as an alternative to change from actual baseline. There were several reasons for this procedure. As described above, longitudinal segmentation of cartilage was done using a forward tracking method. The methodology is new, few publications on it have been presented so far. We have identified at least three different types of potential bias: Method bias (b_M), Internal bias (b_I) and Artifact bias (b_A). First, b_M was defined as the difference between expected (long term average) change when using the tracking algorithm and when using independent segmentations as algorithm. A value of b_M could not be estimated as the data collected was found insufficient. However, in a small sample analysis (4 knees), tracked segmentation was suggested to overestimate thickness and volume parameters compared with independent segmentation although with variations across regions. However, a more thorough analysis of b_M is needed to confirm the validity of these findings. Secondly, b_I was defined as the bias from differences between Forward and Backward tracking methodology. Thus, b_I could be reduced by random Forward / Backward tracking although such procedure was not performed in this study. Thirdly, b_A was defined as the bias introduced by altered MR signals due to metal artifacts from implants and thus only likely to occur in knees treated with an ACL reconstruction. These artifacts would equally affect all the tracked time points but could also influence results when comparing the independently segmented baseline scan (prior to surgery) to the tracked follow-up scans.

By replacing the values of the actual baseline scan with values from the 3 months scan we believe that b_I and b_A were reduced to a minimum as all analyses in this study were done only on tracked images, surgery was already performed and consequently any artifacts from implants were present at the time of the 3 month scan. However, b_M could not be corrected for. Still, the dilemma from this source of bias is always present in studies like ours and results presented here are comparable to any other study with regard to this issue. Mean changes at 12 months after an ACL injury are presented in absolute metrics although the metric change is presented from the period of 3–12 months after ACL injury.

Regions of interest (ROI)

Regions of the knee were reported in conformity with a proposal for nomenclature in MRI studies of knee OA (Eckstein et al. 2006) (Figure 15). BML volumes were provided as described above for: lateral tibia (LT), medial tibia (MT), lateral femur, medial femur, lateral trochlea femur, medial trochlea femur, patellar crista, patella lateral facet, patella medial facet. We aggregated BML volumes for the lateral femur and the lateral trochlea femur into the lateral femoral condyle (LF), the medial femur and medial trochlea femur into the medial femoral condyle (MF) and patella crista, lateral and medial facet into patella (P). Furthermore, BML volumes for LF and MF were summarized into femur (F) and BML volumes for LT and MT into tibia (T). BML volumes of the total knee (K) were summarized by adding BML volumes of T, F and P. Additionally, LF and LT were summarized to form the lateral compartment and MF and MT to form the medial compartment.

Joint fluid was not regionalized and thus acquired and presented as JF volume within the entire knee joint. Cartilage volume (VC), cartilage thickness (ThCcAB) and cartilage surface area (AC) were acquired as described above for: Femur (F), central lateral/medial femur (cLF/cMF), posterior lateral/medial femur (pLF/pMF), trochlea femur (TrF), lateral tibia (LT), medial tibia (MT), patella (P). Volume and surface area was summarized for medial femur (MF) by adding parameters for cMF

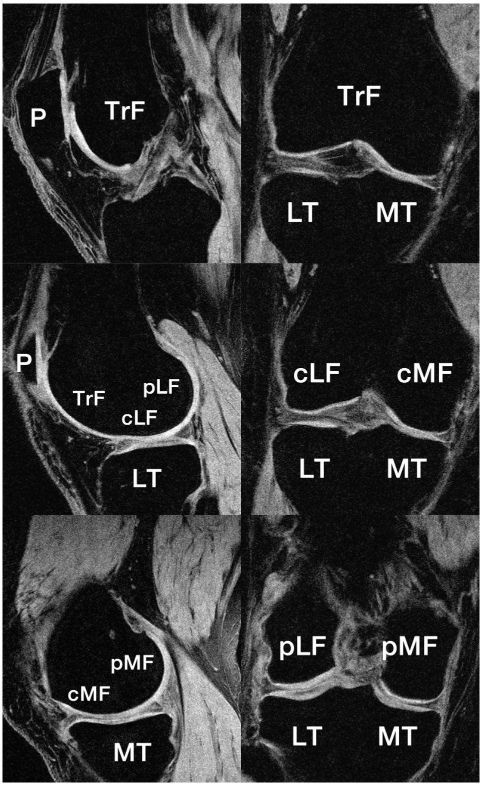


Figure 15. Anatomical labels of knee joint cartilage plates. Sagittal images (left row) and coronal images (right row). Figure and figure legend from: Eckstein F, Ateshian G, Burgkart R, Burstein D, Cicuttini F, Dardzinski B, et al. Proposal for a nomenclature for magnetic resonance imaging based measures of articular cartilage in osteoarthritis. Osteoarthritis Cartilage 2006; 14(10): 974-83. With kind permission of the authors and publisher.

and pMF, lateral femur by adding cLF and pLF, lateral compartment by adding LF and LT and medial compartment by adding MF and MT. Thickness was however not averaged and thus only acquired parameters from analyzed regions were presented.

Statistical methods

Statistical analysis of all papers in this thesis were made using SPSS (version 14.0 and 15.0, SPSS).

Descriptive statistics

Means and standard deviations (SD) were calculated for all continuous variables except for the Tegner scale, a nominal scale, where median (range) was reported. In paper III, the KOOS was calculated according to the principles in the user's manual (available at www.koos.nu) and given as mean (SD). In paper IV, BML volumes were not normally distributed for any region and thus data were presented as median (25^{th}, 75^{th} percentile). In paper V, descriptive statistics of time between injury, MRI scans and surgery were given as median (25^{th}, 75^{th} percentiles) as was JF volumes since this variable was not normally distributed. BML volumes were given as mean (SD) for all time points and morphometric parameters of cartilage (i.e. VC, ThCcAB, AC) were given as mean (SD). Morphometric change of cartilage was given as mean change (SD), percent (mean, SD) and Standard Response Mean (SRM). SRM was defined as the mean change divided by the standard deviation of that change.

Between group differences and correlations (univariate)

In paper I, the agreement between MRI findings and clinical instability was calculated as the Kappa value of correlation (κ) (Altman 1991). In paper II, group comparisons of age were made using one-way ANOVA and group comparisons of activity level were made by the Kruskal–Wallis test. All other comparisons on group level were made using the Chi square test. In paper III, comparisons of KOOS data between those reporting a history of minor and severe knee injury were made using the t-test. In paper IV, between-group analysis was made using the Mann-Whitney U-test except for age where comparisons were made using one-way ANOVA. The Spearman coefficient of correlation (r_S) was used for analysis of correlation between variables. In paper V, factors tested for association with BML volume were analyzed using the Pearson correlation coefficient and the t-test, respectively.

Independent associations (multivariate models)

In paper III–V, General Linear models were used to determine independent associations. In paper IV, BML volume for separate regions of the knee joint was set as the dependent variable. Residual plots were visually analyzed to control the accuracy of assumptions of each model. Self-reported Tegner scores were related to the classification of activity at injury ($p<0.001$) and only the classification of activity at injury (i.e. contact vs. non-contact sports) was used in the analyses. In paper V, factors tested for association with morphometric change were: age, sex, pre-injury activity level (Tegner score), ACL reconstruction (yes/no), complementary arthroscopy (yes/no), cortical depression fracture (yes/no), JF volumes after 12 months (mm^3) and persistent BML after 12 months (yes/no). JF volumes were logarithm transformed and analyzed for all above factors with adjustment for baseline volumes. Change in cartilage morphometry was correlated to baseline values for some regions and all factors were analyzed with adjustment for baseline values. All factors and regions with an influence at a significance level of less than 5% were presented, although a significance level of 1% was defined as a significant relation to morphometric change.

Results and Discussion

This part of the thesis summarizes the results of and discussions in each included paper. Details are found in each separate paper (I–V).

ACL injuries are common and often misdiagnosed in the acute phase (paper I)

Acute swelling after knee trauma – a good indicator of severe knee injury

A hemarthrosis was verified by aspiration in 52% (83/159) of subjects with acute intra-articular swelling after rotational trauma to the knee. MRI revealed an average of 1.6 acute traumatic anatomic lesions per investigated knee where 89 knees (56%) had a total or partial ACL injury and 25 (16%) had sustained a patellar dislocation. Approximately 80% of subjects with knee trauma followed by effusion assessed at the orthopedic ER had knee injuries in need of further medical attendance, confirming findings from previous studies (DeHaven 1980, Noyes et al. 1980, Butler & Andrews 1988, Sarimo et al. 2002). A history of injury combined with effusion within 24 hours is a good indicator of severe knee injury. These subjects should be further assessed by MRI or, alternatively, a well experienced clinician regardless of clinical findings in the acute phase.

Poor agreement between knee laxity assessed at orthopedic ER and injuries found on MRI

The physician at the emergency unit assessed A-P laxity in 79 (90%) of the ACL injured knees found in this study, with an agreement between clinical and MRI findings in 50% of these knees (κ=0.281). In addition, the kappa value for correlation between clinically detected valgus instability and MCL grade II–III as visualized on MRI was poor (κ=0.351) and only 3/25 (12%) patellar dislocations visualized on MRI were adequately diagnosed at clinical assessment. These findings contradicts previous studies showing that MRI could not provide any valuable information on the status of the ACL compared with clinical assessment (Rose & Gold 1996, Adalberth et al. 1997, Kocabey et al. 2004). However, these studies differ in various important aspects from the present study as the clinical examination was performed by an experienced orthopedic surgeon in the quiet phase, five weeks after the knee trauma. Possibly, a selection of knees occurred already at the ER where only those knees with the most obvious laxity were scheduled for a second assessment. ACL injured knees assessed by the experienced orthopedic surgeon in the quiet phase are likely those suffering from severe symptoms and with great instability. Consequently, selection bias could be expected in reports from trials not reporting subjects lost to inclusion.

At least three-fold higher incidence of ACL injury

In a previous study, the population based annual incidence of ACL injury was suggested to be 30 per 100 000 individuals (Nielsen & Yde 1991). Here, ACL injuries were classified according to clinical assessment and A-P laxity at the ER and population at risk included all individuals from the geographic region regardless of age. As described above, only one of two ACL injured knees were detected at clinical assessment in our own study. Further, ACL injuries were rarely seen in subjects younger than 10 or older than 65, and population at risk should be estimated accordingly. We estimate the annual incidence of ACL injury to be 81 per 100 000 individuals aged 10–64 years, which is almost three times higher than the incidence presented in 1991. This incidence is however most likely also an underestimation since ACL injuries predominantly occur among active individuals and some of the injured subjects may not have sought medical attendance or could have been attended to by other clinics.

An RCT of surgical versus non-surgical treatment is a true challenge (paper II)

Number of subjects you need to screen and allocate

Number Needed to Screen (NNS) found in this study was 5.5 patients with acute knee injury to include one patient into the treatment RCT. However, NNS is greatly affected by screening filter design and hence NNS could vary considerably between different trial designs. Number Needed to Allocate (NNA) was 1.6 patients fulfilling criteria for eligibility to include one patient into the RCT. We could not find any study presenting results from the recruitment process of an RCT on surgical treatment and/or using the concept of NNA. However, hypothetical trials were reported from which the NNA could be extrapolated. A hypothetical RCT on arthroscopic surgery in OA knees (Creel et al. 2005) found that 39 out of 88 patients were “definitely not willing” to participate in this RCT, which would yield an NNA of 1.8. Yet, an additional 30 patients in this study were “unsure or probably willing” to participate, bringing the NNA up to 4.6. In another hypothetical RCT on hormone therapy (Wragg et al. 2000) including only women, 28 of 50 patients were “not willing” to participate in RCT providing a calculated NNA of 2.3. Halpern and co-workers conducted a hypothetical RCT on antihypertensive drug therapy vs. placebo on 126 patients where approximately 47% (n= 59) were willing to participate in the trial (Halpern et al. 2003). The calculated NNA for this study would be 2.1. The NNA of 1.6 from this reality RCT could be considered low, possibly depending on the efforts put into the design of this RCT.

Athletes accept and self-employed decline participation

The two most common reasons for declining participation in our RCT were ‘not willing to risk surgical treatment’ (23/41) and ‘not willing to risk non-surgical treatment’ (8/41). Demographic factors, such as age, race, gender and level of education were shown to relate to patient’s willingness to participate in clinical trials (Tognoni et al. 1991, Lovato et al. 1997, Ross et al. 1999, Grant et al. 2000, Patel et al. 2004). However, we failed to confirm these findings. We assessed acute ACL injured subjects in the age range 18-35 years and it is possible that this age range was too narrow to detect influence of age. Still, we found that those self employed were more likely to decline participation and subjects injured in sports were more prone to accept participation in the RCT. Possibly, the self-employed do not prioritize the time needed to undergo the prolonged intense rehabilitation following surgical treatment or maybe they are irreplaceable in their small businesses. Sportsmen/women with ACL injuries are more likely to have a stronger preference for surgical treatment since the attitude in sports medicine is pro-surgery and this could partly explain the differences seen in this study.

Return to pre-injury activity: Does it reflect relief of symptoms? (paper III)

Self-reported Tegner scores need adjustment for age, gender and level of competition

The Tegner activity rating scale was developed and validated as an assessor-reported outcome (Tegner & Lysholm 1985), although an increasing use of self-reported Tegner scores was found. We show that older age, female gender and lowered level of competition, adjusted for each other, were associated with worse self-reported Tegner levels. Since self-report of the Tegner activity rating scale seems to be associated with altered measurement properties, the results of this study suggest that comparison of cross-sectional studies where different administration modes have been employed cannot be performed without adjustments. This is important as the Tegner activity rating scale is frequently used to describe study populations. However, the Tegner scale is also used to assess treatment effect after knee injury. In our study, longitudinal information was not obtained although, most likely, adjustments are needed also in longitudinal studies when comparing treatment effects to allow for different administration modes between studies. Another implication for longitudinal studies is the importance of keeping the same administration mode at all time points. One common scenario, a baseline clinical visit followed by mailed questionnaires, may yield a worse treatment outcome than if all assessments were performed by an assessor.

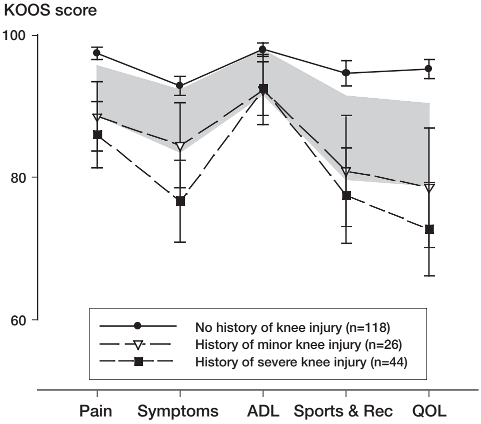


Figure 16. Mean KOOS scores (95% CI) of the subscales pain, symptoms, activities of daily living (ADL), Sports and Recreation (Sports & Rec) and knee related quality of life (QOL). Symbols: ● represent subjects reporting no history of knee injury; ▽ represent subjects reporting a history of minor knee injury; ■ represent subjects reporting a history of severe knee injury. Shadowed area (grey) represents 95% CI of the mean of a previously published population based reference group (age 18–34) (Paradowski et al. 2006), with kind permission from the authors.

Those with a history of knee injury have worse knee function than those without

In paper III, we found that currently active amateur soccer players with a history of knee injury had worse knee function according to KOOS than those without a history of knee injury, but also worse knee function than an age-matched population based group of individuals (Figure 16). The ability to participate in amateur soccer after knee injury may not automatically reflect symptom relief. On the other hand, poor knee function may not necessarily reflect inability to participate in amateur soccer. Thus, it could be emphasized that return to amateur soccer play, a commonly used outcome in sports medicine, does not necessarily reflect treatment success with regard to knee function or knee symptoms. The assessment of treatment effect after knee injury remains a challenge and we suggest the use of separate outcomes to assess activity level and self-reported knee function in studies on treatment effects after knee injury.

The ACL rupture is only a part of the problem (paper IV)

Almost 2/3 of ACL injured knees are fractured

Eighty six associated fractures were found in 73 acutely ACL injured knees and 92 meniscal tears were found in 68 knees, respectively, suggesting that an intra-articular fracture was as common as a meniscal tear in the acutely ACL injured knee. Sixty nine (57%) of all knees suffered from at least one cortical depression fracture, regardless of location and cortical discontinuity, and were grouped for further analyses. Reports on fractures in the acutely ACL injured knee are rare, most likely because they do not show at arthroscopic evaluation or radiographs and rarely influence treatment. Case-reports have presented a deep lateral notch sign, similar to a cortical depression fracture described here (Kaplan et al. 1992, Stevens & Dragoo 2006), although this is to our knowledge the first report on the frequency of such fractures in ACL injured knees. Including these fractures in the panorama of associated anatomical injuries of the ACL injured knee, only some 20% of the knees had an isolated ACL tear, suggesting that the ACL injured knee actually is a traumatized knee with an associated ACL rupture. This could in part explain why an ACL reconstruction fails in reducing OA development.

BML volume and location

To our knowledge, this is the first report on traumatic BML using a quantitative MRI method. The occurrence of BMLs in traumatized knees is well described, and suggested to represent a footprint of the injury mechanism (Yu & Cook 1996, Hayes et al. 2000, Sanders et al. 2000, Palmer 2003). In our study, all but two knees (98%) had at least one BML as detected by the qMRI method. Tibia was affected in 117 (97%) knees, femur in 109 (90%) and patella in 14 (12%) knees. All but 4 knees (97%) had BMLs within the lateral compartment (i.e. femur and tibia laterally). The median BML volume of the total knee was 19.8 cm^3, where 75% of the volume (14.8 cm^3) was located within the lateral compartment.

Assessed by radiologists, some 80% of acutely ACL injured knees have been reported to show BMLs, mainly located in the lateral compartment

(Vellet et al. 1991, Graf et al. 1993). Our results are in agreement with these publications although we show that 98% of the knees had BML within the knee joint and 97% had BML in the lateral compartment. It is likely that our method is more sensitive than those used earlier. We found large variations of BML volume, both between subjects and between locations, suggesting differences in trauma mechanisms. However, we found no relationship between BML volume and activity at injury suggesting that activity at injury does not reflect the injury mechanism.

Large BML volumes are hallmarks of strong compressive forces

Knees with a cortical depression fracture had larger BML volumes in all regions except for the medial femoral condyle, after adjustment for age, sex, activity at injury, and time between injury and MRI scan. Microfractures of cancellous bone, subchondral lesions, edema and bleeding in the fatty marrow were observed in the area of traumatic BML (Rangger et al. 1998). An animal study confirmed the presence of substantial hemorrhage and edema in the marrow spaces but found no evidence of trabecular fracture or fibrosis (Ryu et al. 2000). Our findings support the presence of trabecular and cortical fractures in areas of large BML volumes as visualized on MRI. We suggest that large BML volumes could be an indicator of strong compressive forces to the articular surface and the subchondral bone.

ACL reconstruction or not – it makes a difference (paper V)

Morphometric changes of joint fluid, BML and cartilage during the first year after ACL injury regardless of treatment

Median joint fluid (JF) volume at baseline was 19500 (25^{th}, 75^{th} percentiles 9100, 31200) mm^3 and 4000 (2400, 6900) mm^3 after one year. There was a gradual decrease over the assessment period, and median JF volume had decreased to 7092 (3103, 13521) mm^3 already after 3 months (Figure 17). We have not found any previous report assessing the short term development of knee effusion after ACL injury. JF volumes were high at baseline even if all knees were aspirated for hemarthrosis in the acute phase of injury. Early aspiration of JF does not prevent effusion within the first 4 weeks of injury. A normalization of JF volumes, although within a wide range, was found already after three months where median volumes were comparable to JF volumes of healthy controls (data not shown). A slower reduction of median JF volumes continued until 12 months after injury indicating that some knees followed a different pattern or increased in JF volumes over the assessment period.

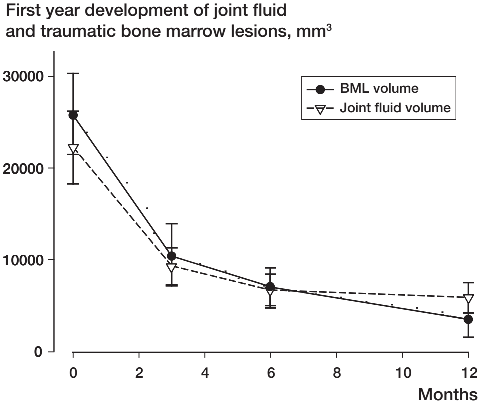


Figure 17. Mean (95% CI) joint fluid volume (un-filled triangles – dashed lines) and BML volume (filled circles – solid lines) development over the first year for all 58 subjects regardless of treatment.

There are several reports of varying quality assessing the development of traumatic BML after knee injury (Costa-Paz et al. 2001, Bretlau et al. 2002, Roemer & Bohndorf 2002, Davies et al. 2004), only one of them prospective (Boks et al. 2007). In our study, all knees were affected by traumatic BML at baseline, where the total mean BML volume of the knee joint was 25923 (SD 16784) mm^3. A gradual decrease of BML volume, similar to the development of JF volumes, was found over the assessment period and mean BML volume after one year was reduced to 3550 (SD 7596) mm^3 (Figure 17). A complete resolution of traumatic BML was found in 22 (38%) knees one year post injury which is in contrast to the only prospective study of traumatic BML development available, where BMLs were found to persist in 28% of the knees after one year and where a median healing time of 42 weeks was suggested (Boks et al. 2007). The majority of knees in our study followed a decreasing pathway although 17 (29%) of the knees showed increased BML volumes at one or more follow-up visits, indicating heterogeneity within the sample.

MRI derived morphologic biomarker values of cartilage, as measured in this study, were reduced in the majority of sub-regions of ACL injured knees one year after ACL injury. SRMs (Mean change / $SD_{Mean\ change}$) were however generally small and for most regions no consistent change was found. A consistent reduction of cartilage measures was found in trochlea femur (TrF) where SRMs of all morphometric parameters were -0.588<SRM>-0.440. This is in contrast to a study on subjects with symptomatic knees and radiographic evidence of osteophytes selected for a high risk of progressive knee OA where almost no change was found in this region (SRM=–0.006) (Hunter et al. 2007). Further, a consistent increase in cartilage morphometry values was found in the central medial femur (cMF) where SRMs for VC and ThCcAB were 0.477<SRM>0.567. This region was found to be the area of greatest consistent change of VC in the study by Hunter et al, although the direction of change was reversed (SRM=–0.394 versus SRM=0.477) (Hunter et al. 2007). The increase in volume of this region in our study was largely explained by an increase in cartilage thickness (SRM=0.567), suggesting a possible swelling of the cartilage of this specific region. Hypertrophy of cartilage was reported from animal studies after transection of the ACL and was suggested to precede the stage of cartilage breakdown (Brandt et al. 1991). The significance of cartilage swelling for future OA development remains to be determined.

ACL reconstruction is a risk factor for morphometric change over the first year

After three months, knees treated with an ACL reconstruction had more than threefold larger JF volumes than knees not reconstructed, after six months the difference was more than twofold. No differences were however found after one year and no other factor was related to JF volumes at any time during the first 12 months after an ACL injury. In addition, knees treated with an ACL reconstruction had a mean of 4693 (434–8952, 95% CI) mm^3 larger BML volumes after six months, compared with knees treated without reconstruction.

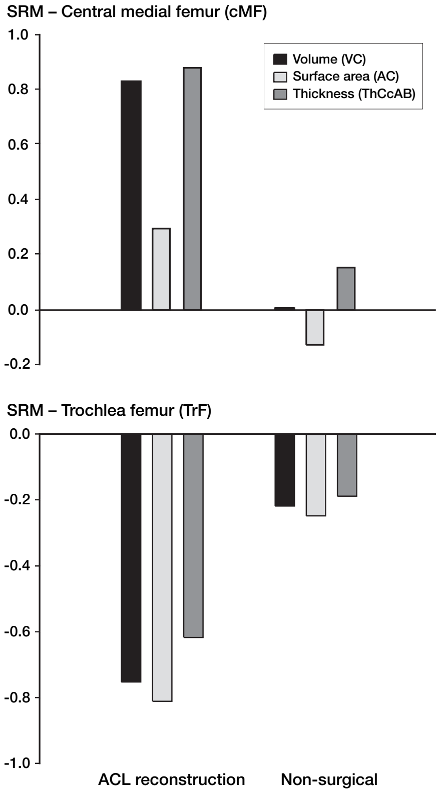


Figure 18. SRMs (Mean change / SD_M) of change between 3 and 12 months in cartilage volume VC (black bars), cartilage thickness ThCcAB (dark grey bars) and cartilage surface area AC (light grey bars) in the central medial femur (top) and trochlea femur (bottom) for knees treated with ACL reconstruction (n=34) and without ACL reconstruction (n=24).

Factors associated with change in cartilage morphometry were only analyzed in TrF and cMF as these regions were the only regions of consistent change. Here, ACL reconstruction was a risk factor for a decrease of cartilage surface area (AC) in TrF as well as an increase of cartilage volume (VC) and cartilage thickness (ThCcAB) in cMF at 12 months, after adjustment for the 3 month values. No other factors were related to cartilage change at 12 months after an ACL injury. An un-adjusted graphic comparison of SRMs for the 3–12 month period of subjects treated with/without ACL reconstruction is shown in Figure 18.

Notch areas were not included in the segmentation of cartilage and any intra-operative cartilage resections would not affect the results of cartilage morphometric change as we compared 12 months values to 3 months values when surgery was already performed. Possibly, an ACL reconstruction performed as early as ten weeks after injury could introduce a traumatic insult similar to the traumatic episode of the injury. Hemarthrosis alone was shown to activate inflammatory pathways of the joint and was suggested as a possible risk factor for knee OA development (Tajima et al. 2005, Borsiczky et al. 2006). Possibly, intra-operative hemorrhage and/or intra-articular introduction of bone (from tunnel drilling) will amplify the normal molecular response of injury recovery and thus in part explain our findings.

BML, effusion and change in cartilage morphometry were all parameters negatively affected by reconstructive surgery during the first year after injury. These parameters could be indicators of structural restitution within the knee joint and a prolonged period of restitution in surgically treated knees could be suggested from our results.

General discussion

ACL injury

The results of this thesis show that an ACL injury is common in the population with an annual incidence of at least 81 per 100000 individuals aged 10-64 years. In addition, it was suggested that every second ACL injury could be misdiagnosed in the acute phase. Therefore, previous studies on treatment efficacy could have a selection bias, especially if an analysis of 'loss to inclusion' was not presented. The use of MRI, or improved clinical handling, in the acute phase of knee injury will enhance recognition of an ACL tear and probably double the frequency of this diagnosis.

Treatment of ACL injury

In the short term, an ACL injury will create knee instability and an ACL reconstruction will reduce or sometimes prevent this instability (Eriksson et al. 2001a, Laxdal et al. 2005, Biau et al. 2007). Reconstructive surgery may improve short-term knee function for those suffering from severe instability in activity and/or repeated give-way episodes, especially if extensive rehabilitation was insufficiently effective. Studies assessing ACL injured knees treated with extensive rehabilitation alone are few, although promising results with regard to return to pre-injury activity level was recently presented (Myklebust et al. 2003, Kostogiannis et al. 2007). High quality RCTs comparing surgical and non-surgical treatment to guide the clinical decisions are lacking (Linko et al. 2005, Lohmander et al. 2007).

In the long term, an ACL injury is a major risk factor for OA development and no currently available treatment has been shown to reduce this increased risk (Lohmander et al. 2007). A recent publication suggests that meniscal injury was a major risk factor for OA development 15 years after ACL injury regardless of treatment (Meunier et al. 2007). However, it is not clear if it is the associated meniscal injury at baseline, the development of a secondary meniscal injury, the meniscectomy, or if all of these constitute risk factors for knee OA development. An ACL reconstruction would most likely reduce the frequency of secondary meniscal tears and could theoretically protect against OA development although no such benefit has yet been presented (Lohmander et al. 2007). The pathogenic mechanisms leading to OA following traumatic ACL rupture are complex (Figure 19). The results presented in this thesis could possibly support the hypothesis of an association between associated injuries from the traumatic phase of ACL injury

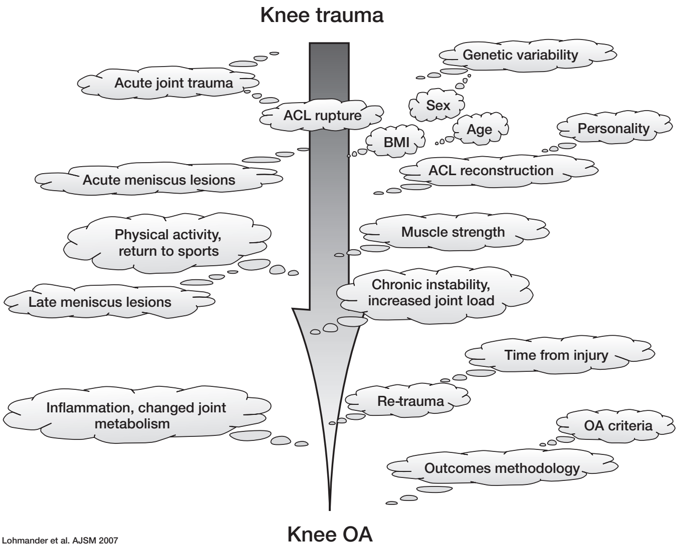


Figure 19. Variables that influence the outcome of an injury to the ACL or meniscus, and the subsequent risk of OA. BMI, body mass index; OA, osteoarthritis. Figure and figure legend from: Lohmander LS, Englund M, Dahl, LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: Osteoarthritis. Am J Sports Med 2007; 35: 1756-69. With kind permission of the authors and publisher.

and the risk of later OA development (Lohmander & Roos 1994, Lohmander et al. 2007).

Reduction or even prevention of instability in the short term does not necessarily prevent knee OA development and both short and long term consequences need to be recognized in future studies of treatment efficacy of ACL injury.

Evidence based treatment of ACL injury

Introduction of a new drug is surrounded by rigorous regulations where superiority over placebo needs to be presented in at least one placebo-controlled RCT, and more often several large RCTs, prior to approval. In addition, adverse events are thoroughly monitored and analyzed in such trials and in most cases adverse events are found to be of greater importance than the actual benefit from the drug in question. In comparison, regulations of knee surgery procedures are almost non-existent and adverse events following surgical treatment in orthopedics are too often not systematically presented. RCTs are time consuming and expensive although we have, in conformity with others (Moseley et al. 2002), shown that RCTs comparing surgical and non-surgical treatment are possible to perform. Rigorous preparations as well as investigator and patient equipoise are however needed.

Numbers Needed to Treat (NNT) and Numbers Needed to Harm (NNH), are two outcomes commonly used in RCTs but we have not found any study reporting these outcomes after treatment of ACL injured knees. NNT indicates how many patients would require treatment to reduce the expected number of cases of a defined endpoint by one. NNH indicates how many patients need to be exposed to a risk factor to cause harm in one patient that would not otherwise have been harmed. To use these measures correctly, a control group is needed and 'harm' as well as 'success' need to be defined using valid and reliable outcome measures and definitions of adverse events. In the assessment of ACL injuries, short term and long term outcomes do not necessarily correlate and a definition of treatment success should thus include both. If only short term outcomes are assessed, this should be clearly stated. Adverse events to be reported include but are not limited to 'give-way' episodes producing additional intra-articular injuries, post surgical complications such as arthrofibrosis, infections and graft harvesting site morbidity. Improved quality of future reports in line with EBM principles, and consensus is needed in defining treatment success as well as treatment failure applicable to all subjects and regardless of treatment.

Outcomes after ACL injury, what is the gold standard?

As described in this thesis, instability following ACL injury was reported to be the main restraint in ACL injured subjects and has been the most frequently used outcome in the assessment of treatment efficacy of ACL injury. The IKDC-2000 was presented in 1993 (Hefti et al. 1993) and was recommended for all trials assessing the consequences after ACL injury. However, this scale classifies all subjects not treated with ACL reconstructions or with spontaneously healed ACL as 'abnormal' or 'severely abnormal' based on the increased static A-P laxity found by the examiner. Consequently, results from trials including non-surgically treated subjects assessed by the IKDC-2000 should be interpreted with caution. The Lysholm knee score (Lysholm & Gillquist 1982) is historically the most frequently used outcome and includes instability in activity, most likely of greater value than instability at rest. However, an individual suffering from frequent instability in activity, limping and walking with crutches could be classified as a good/excellent result (85 points) according to this scale. In addition, both outcomes include several aspects of consequences after ACL injury although these aspects are summarized into one final score and the separate dimensions of valuable information are therefore lost.

Patient relevant outcomes, such as the KOOS and WOMAC, assess the individual's own opinion of his/her knee and are considered as gold standard in drug trials. When used as intended, i.e. self-administered, these outcomes are not affected by assessor bias. In this thesis, we found that KOOS was not associated with age, gender or BMI in young amateur soccer players, confirming previous reports on the validity of this outcome. KOOS was not related to self-reported activity level, verifying this outcome's independence from activity level, and thus self-reported knee function should be accompanied by a separate outcome assessing level of activity. In addition, self-reported knee function according to

KOOS has a poor correlation to objective measures of knee function (i.e. physical tests) and these two entities cannot be assumed to measure similar concepts (Roos et al. 2007).

Activity level and knee function after ACL injury are multi-dimensional issues where each aspect is likely to be individually important. Furthermore, patient relevant outcomes assess the individuals own opinion of his/her knee which is in contrast to other outcomes, such as radiography, stability, ROM etc, only sensitive to separate aspects of the disease. Possibly, self-reported and objective (physical performance) knee function as well as knee related QOL, activity level and adverse events could be used to form a model of responder criteria for future use when defining treatment success and failure in clinical trials of ACL injured knees.

Structural outcomes of ACL injury

Arthroscopy is considered gold standard for assessment of knee injuries. However, an increasing use of MRI was reported, shown to be a valid and non-invasive alternative to arthroscopy in detecting ligament injuries as well as meniscal lesions. Both methods share the limitation of examiner bias as the arthroscopic results are only presented to the orthopedic surgeon and the MR images are only presented to the radiologist. Published results from both methods are therefore strongly dependent on the experience and specific interest of the examiner, although MRI has the advantage of a possibility of repeated evaluations by one or several investigators. Arthroscopy is a dynamic method where the clinical relevance as well as the mechanical influence of injury could be evaluated. However, arthroscopy is limited by the difficulty in visualizing the entire joint without using additional portals and only the superficial structures of the joint can be accurately assessed. MRI on the other hand, provides a possibility of assessing intra-articular as well as extra-articular structures.

Using MRI for assessment we show that the isolated ACL tear is an infrequent phenomenon. In addition to meniscal tears and collateral ligament injuries we found that most of the acutely ACL injured knees have associated cortical depression fractures associated with large BML volumes. Knees with ACL injury suffer from a complex set of anatomical lesions and these injuries should therefore not be referred to simply as ACL injured knees.

In studies assessing longitudinal structural change, MRI is favorable due to its non-invasive nature. However, specific sequences need to be used in these routines as sequences commonly used in the clinical setting are likely to have a low sensitivity in detecting changes in cartilage morphology. In this thesis we have used a new, state-of-the-art methodology to quantify intra-articular morphometric parameters, both cross-sectionally and longitudinally. This method has shown great promise in detecting early cartilage change suggested to be associated with OA development. However, one limitation of this method is the assessment of cartilage quality (i.e. collagen network, proteoglycan content, etc.). Delayed Gadolinium enhanced MRI (dGEMRIC) and T2-mapping are two separate methods shown to be of value in the assessment of cartilage structural quality. Possibly, a combined use of these different techniques of MRI could further enhance the understanding of OA development after joint injury.

We show that BMLs persist in 60% of the ACL injured knees one year after injury. We also found a consistent reduction of cartilage morphometry in trochlea femur and possible cartilage swelling in central medial femur one year after ACL injury. These results are most likely the first suggesting early structural change in ACL injured knees. An ACL reconstruction performed within 10 weeks after injury increased volumes of joint fluid and BML at 6 months as compared to knees treated without ACL reconstruction. Further, cartilage reduction in trochlea femur and cartilage swelling in central medial femur after one year was strongly associated with ACL reconstruction. Possibly, all of these changes reflect structural restoration after injury which could be prolonged by the additional traumatic insult introduced by surgery. Return to strenuous activities during this period of structural recovery could increase the risk of both short and long term consequences. Further monitoring of these changes as well as an establishment of their clinical relevance is however needed.

In summary, the truths of treatment and outcome after ACL injury are few, while the consequences are likely to be severe, both in the short and long term and regardless of treatment. The overall quality of publications assessing treatment and outcome after ACL injury is poor and few strong conclusions can be made. On the one hand, some subjects probably need to be treated surgically in order to return to pre-injury activity although the timing of return to strenuous activity could be of great importance. On the other hand, some subjects should probably not be treated by surgery due to increased risk of post surgical complications and some subjects are definitely able to return to their pre-injury activity level after rehabilitation alone. Improved quality of scientific publications, considerations of both short and long term consequences for the individual and a correct use of outcomes applicable to the assessment of both surgical and non-surgical treatment will enhance our understanding of the truths and consequences of anterior cruciate ligament injury.

Future perspectives

The KANON study continues and short term results from the RCT will be presented in terms of Intention To Treat (ITT) analysis in 2009. Adverse events are thoroughly monitored and will be analyzed with self-reported knee function and activity level in order to present the short term consequences of surgical and/or non-surgical treatment after ACL injury. Using highly specialized computer assisted techniques of MRI we expect to find early features of knee OA at the 5 year follow up, together with risk factors and long term consequences.

Radiographs are gold standard in the assessment of knee OA and we have included radiographs at various follow up visits throughout the KANON study. In addition, we have collected knee alignment measures at the two year follow up. MRI derived cartilage morphometry could be correlated to gold standard radiographic signs of OA, such as osteophytes and Joint Space Narrowing (JSN). In addition, MR images from all visits will be re-evaluated with regard to fractures and meniscal injuries and the long term development of these structures will be analyzed.

Joint fluid, serum and urine were collected from subjects in the KANON study. Concentrations of disease specific molecular biomarkers will be analyzed for association with self-reported knee function, radiographic findings and MRI at various time points after ACL injury.

A common clinical problem today is to identify ACL injured subjects responding well to surgical or non-surgical treatment. However, a possibility to identify subjects at high risk of poor outcome after treatment is of even greater importance. Both short term and long term outcomes of the KANON study will be used to identify responders and non-responders for surgical and non-surgical treatment.

Clinical implications

Firstly, ACL injuries are common and frequently misdiagnosed at the orthopedic ER in the acute phase. In order to find the majority of these injuries, a sub-acute MRI routine could be implemented or possibly all knees with a history of rotational trauma and rapid effusion should be scheduled for a second assessment by an experienced clinician regardless of clinical findings in the acute phase.

Secondly, the ACL tear is only part of the problem. Apart from previously known associated injuries, such as meniscal tears and collateral ligament injuries, our results suggest that the ACL injured knee joint surfaces suffer from substantial compressive trauma, indicated by cortical depression fractures and bone marrow lesions (BML). An ACL reconstruction may only solve part of the problem, which in part may explain why surgical stabilization has failed in reducing the risk of knee OA development.

Thirdly, resolution of BML and the normalization of joint fluid volumes were slower in knees treated with ACL reconstruction compared with knees treated without surgery. We also found that an ACL reconstruction was a risk factor for increased cartilage loss in the trochlea femur and cartilage swelling in the central medial femur one year after injury. It is possible that these findings indicate an extended period of restitution and that an ACL reconstruction performed within 10 weeks from the trauma delays this process. Based on our findings, it may be recommended that subjects treated with an early ACL reconstruction should not return to strenuous activities involving the knee within the first year after injury.

Acknowledgements

The KANON study is a large project performed over many years and several individuals have contributed to the performance of this clinical trial. I wish I had the opportunity to name all of you since this work would never have been accomplished without your assistance. I greatly appreciate all efforts put into the completion of the KANON study and therefore express my sincere THANK YOU! to everyone involved. Still, I wish to express my deep and sincere gratitude to:

Stefan Lohmander, my main advisor, tutor, and friend, for your industrious struggle in teaching me as much as possible from your never ending knowledge and experience of orthopedic research, osteoarthritis and in writing fruitful applications. Thank you also for, at a very early stage, pointing out the fact that science is a demanding mistress, now my wife knows! In short – thank you for everything!

Harald Roos, my advisor, mentor and friend, who introduced me to this project and to my main advisor. Thank you for sharing your knowledge and experience, for believing in my ability of producing good science but also for believing in my clinical skills and for giving me all your support in the field of orthopedics. Without your support nothing of this would ever have happened.

Ewa Roos, my advisor, mentor and friend, for sharing your knowledge and experience, for your valuable support in the work of science as well as in my doctoral studies and for providing a fruitful environment for me (and others) as a PhD student. Thank you also for letting me use 'Sjötorpet', where I am currently writing this section of the thesis. Finally, you also succeeded in teaching me some research methodology!

Kerstin Åkesson, my dear friend, for your never ending encouragement and sympathy. Without your skills and efforts the KANON study would not have been what it is today. Thank you for taking care of me and for looking after me. I forget many things but I'll never forget you.

Marie-Pierre LeGraverand, Robert Buck, Patricia Redifer at Pfizer Global Research, my co-authors, for your support in the achievement of the KANON study. Thank you Robert, for all your efforts in making complicated statistical analyses understandable even for me.

Torsten Boegård, my co-author and friend, for sharing your enormous interest and knowledge in knee radiology. Our fruitful discussions have increased my understanding of knee injuries, both as a clinician and researcher.

José Tamez-Pena & Saara Totterman, my co-authors, for your efforts in describing the complicated methodology behind the quantification of MRI derived biomarkers.

Jan-Åke Nilsson, for your valuable assistance in the world of statistics and for always answering your phone, even when my name is shown on the display.

Viveca Wiklund, for always acting supportingly and for our philosophic discussions in general. Thank you also for your linguistic advise in each paper but also in this thesis.

Ola Olsson and all other orthopedic surgeons at Helsingborg Hospital and Lund University hospital for your open-hearted view of accepting and appreciating knowledge and comments from a non-physician. Thank you for all interesting discussions regarding orthopedics in general and knee injuries in particular.

All physiotherapists involved in the KANON study, for your kind co-operation and genuine interest in the rehabilitation of ACL injured knees.

All the staff from the orthopedic department in Helsingborg & Lund, department of radiology in Helsingborg and department of clinical chemistry in Helsingborg who has successfully contributed to the collection and handling of subjects and samples from the KANON study.

The doctoral student group and the osteoarthritis research group in Lund, for our long lasting, enjoyable and fruitful discussions.

All subjects in the KANON study, you are all amazing and admirable in many ways! In addition, you are of course the main contributors to all of the knowledge that will arise from the KANON study.

Science, my demanding mistress, for our daily struggles. Thank you for increasing my knowledge just to find that I understood less than the day before, for providing answers to my questions just to give me more to wonder about, and for introducing me to fellow researchers all over the world just to find that you prevented me from having the time to meet with them.

The generous funders of my research, Thelma Zoegas fund, Stig & Ragna Gorthon research foundation, Region Skåne, Centrum för idrottsforskning and Pfizer Global Research.

And above all:

my beloved wife Veronica for all your support, encouragement, understanding and love. Thank you for just being there and for sharing me with my mistress! I realize that it is now pay-back time!

my wonderful children Samuel and Rebecca for entering and being a part of my life and for reminding me of what really matters.

my parents, Sonja and Sixten, for never loosing faith in my abilities, although I know there were periods of serious doubt. Thank you for your never ending support, encouragement, understanding and love.

References

Adalberth T, Roos H, Lauren M, Akeson P, Sloth M, Jonsson K, et al. Magnetic resonance imaging, scintigraphy, and arthroscopic evaluation of traumatic hemarthrosis of the knee. Am J Sports Med. 1997 Mar-Apr; 25(2): 231-7.

Ageberg E, Zatterstrom R, Moritz U, Friden T. Influence of supervised and nonsupervised training on postural control after an acute anterior cruciate ligament rupture: a three-year longitudinal prospective study. J Orthop Sports Phys Ther. 2001 Nov; 31(11): 632-44.

Agel J, Arendt EA, Bershadsky B. Anterior cruciate ligament injury in national collegiate athletic association basketball and soccer: a 13-year review. Am J Sports Med. 2005 Apr; 33(4): 524-30.

Aglietti P, Buzzi R, Menchetti PM, Giron F. Arthroscopically assisted semitendinosus and gracilis tendon graft in reconstruction for acute anterior cruciate ligament injuries in athletes. Am J Sports Med. 1996 Nov-Dec; 24(6): 726-31.

Altman DG. Practical Statistics for Medical Research London: Chapman & Hall 1991.

Andersen TE, Tenga A, Engebretsen L, Bahr R. Video analysis of injuries and incidents in Norwegian professional football. Br J Sports Med. 2004 Oct; 38(5): 626-31.

Andersson C, Odensten M, Gillquist J. Knee function after surgical or nonsurgical treatment of acute rupture of the anterior cruciate ligament: a randomized study with a long-term follow-up period. Clin Orthop Relat Res. 1991 Mar(264): 255-63.

Arendt E, Dick R. Knee injury patterns among men and women in collegiate basketball and soccer. NCAA data and review of literature. Am J Sports Med. 1995 Nov-Dec; 23(6): 694-701.

Arendt EA, Agel J, Dick R. Anterior Cruciate Ligament Injury Patterns Among Collegiate Men and Women. J Athl Train. 1999 Apr; 34(2): 86-92.

Arnason A, Tenga A, Engebretsen L, Bahr R. A prospective video-based analysis of injury situations in elite male football: football incident analysis. Am J Sports Med. 2004 Sep; 32(6): 1459-65.

Arnoczky SP. Anatomy of the anterior cruciate ligament. Clin Orthop Relat Res. 1983 Jan-Feb(172): 19-25.

Asik M, Sen C, Tuncay I, Erdil M, Avci C, Taser OF. The mid- to long-term results of the anterior cruciate ligament reconstruction with hamstring tendons using Transfix technique. Knee Surg Sports Traumatol Arthrosc. 2007 Aug; 15(8): 965-72.

Audige L, Hanson B, Kopjar B. Issues in the planning and conduct of non-randomised studies. Injury. 2006 Apr; 37(4): 340-8.

Barrett G, Stokes D, White M. Anterior cruciate ligament reconstruction in patients older than 40 years: allograft versus autograft patellar tendon. Am J Sports Med. 2005 Oct; 33(10): 1505-12.

Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. Jama. 1996 Aug 28; 276(8): 637-9.

Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988 Dec; 15(12): 1833-40.

Beynnon BD, Uh BS, Johnson RJ, Abate JA, Nichols CE, Fleming BC, et al. Rehabilitation after anterior cruciate ligament reconstruction: a prospective, randomized, double-blind comparison of programs administered over 2 different time intervals. Am J Sports Med. 2005 Mar; 33(3): 347-59.

Biau DJ, Tournoux C, Katsahian S, Schranz P, Nizard R. ACL reconstruction: a meta-analysis of functional scores. Clin Orthop Relat Res. 2007 May; 458: 180-7.

Boks SS, Vroegindeweij D, Koes BW, Bernsen RM, Hunink MG, Bierma-Zeinstra SM. MRI follow-up of posttraumatic bone bruises of the knee in general practice. AJR Am J Roentgenol. 2007 Sep; 189(3): 556-62.

Boks SS, Vroegindeweij D, Koes BW, Hunink MG, Bierma-Zeinstra SM. Follow-up of posttraumatic ligamentous and meniscal knee lesions detected at MR imaging: systematic review. Radiology. 2006 Mar; 238(3): 863-71.

Borrelli J, Jr., Tinsley K, Ricci WM, Burns M, Karl IE, Hotchkiss R. Induction of chondrocyte apoptosis following impact load. J Orthop Trauma. 2003 Oct; 17(9): 635-41.

Borsiczky B, Fodor B, Racz B, Gasz B, Jeges S, Jancso G, et al. Rapid leukocyte activation following intraarticular bleeding. J Orthop Res. 2006 Apr; 24(4): 684-9.

Brandt KD, Braunstein EM, Visco DM, O'Connor B, Heck D, Albrecht M. Anterior (cranial) cruciate ligament transection in the dog: a bona fide model of osteoarthritis, not merely of cartilage injury and repair. J Rheumatol. 1991 Mar; 18(3): 436-46.

Bretlau T, Tuxoe J, Larsen L, Jorgensen U, Thomsen HS, Lausten GS. Bone bruise in the acutely injured knee. Knee Surg Sports Traumatol Arthrosc. 2002 Mar; 10(2): 96-101.

Burstein D, Gray M. New MRI techniques for imaging cartilage. J Bone Joint Surg Am. 2003; 85-A Suppl 2: 70-7.

Butler DL, Noyes FR, Grood ES. Ligamentous restraints to anterior-posterior drawer in the human knee. A biomechanical study. J Bone Joint Surg Am. 1980 Mar; 62(2): 259-70.

Butler JC, Andrews JR. The role of arthroscopic surgery in the evaluation of acute traumatic hemarthrosis of the knee. Clin Orthop. 1988 Mar(228): 150-2.

Costa-Paz M, Muscolo DL, Ayerza M, Makino A, Aponte-Tinao L. Magnetic resonance imaging follow-up study of bone bruises associated with anterior cruciate ligament ruptures. Arthroscopy. 2001 May; 17(5): 445-9.

Creel AH, Losina E, Mandl LA, Marx RJ, Mahomed NN, Martin SD, et al. An assessment of willingness to participate in a randomized trial of arthroscopic knee surgery in patients with osteoarthritis. Contemp Clin Trials. 2005 Apr; 26(2): 169-78.

Dahlberg L, Friden T, Roos H, Lark MW, Lohmander LS. A longitudinal study of cartilage matrix metabolism in patients with cruciate ligament rupture--synovial fluid concentrations of aggrecan fragments, stromelysin-1 and tissue inhibitor of metalloproteinase-1. Br J Rheumatol. 1994 Dec; 33(12): 1107-11.

Davies NH, Niall D, King LJ, Lavelle J, Healy JC. Magnetic resonance imaging of bone bruising in the acutely injured knee--short-term outcome. Clin Radiol. 2004 May; 59(5): 439-45.

DeHaven KE. Diagnosis of acute knee injuries with hemarthrosis. Am J Sports Med. 1980 Jan-Feb; 8(1): 9-14.

Dunn WR, Lyman S, Marx R. Research methodology. Arthroscopy. 2003 Oct; 19(8): 870-3.

Eckstein F, Ateshian G, Burgkart R, Burstein D, Cicuttini F, Dardzinski B, et al. Proposal for a nomenclature for magnetic resonance imaging based measures of articular cartilage in osteoarthritis. Osteoarthritis Cartilage. 2006 Oct; 14(10): 974-83.

Eckstein F, Glaser C. Measuring cartilage morphology with quantitative magnetic resonance imaging. Semin Musculoskelet Radiol. 2004 Dec; 8(4): 329-53.

Englund M, Hunter DJ, Gale D. Prevalence of anterior cruciate ligament tear and its association with knee osteoarthritis and giving-way among older adults in the community. Osteoarthritis Cartilage. 2006; 14(suppl 2): 121.

Eriksson K, Anderberg P, Hamberg P, Lofgren AC, Bredenberg M, Westman I, et al. A comparison of quadruple semitendinosus and patellar tendon grafts in reconstruction of the anterior cruciate ligament. J Bone Joint Surg Br. 2001a Apr; 83(3): 348-54.

Eriksson K, Anderberg P, Hamberg P, Olerud P, Wredmark T. There are differences in early morbidity after ACL reconstruction when comparing patellar tendon and semitendinosus tendon graft. A prospective randomized study of 107 patients. Scand J Med Sci Sports. 2001b Jun; 11(3): 170-7.

Ettlinger CF, Johnson RJ, Shealy JE. A method to help reduce the risk of serious knee sprains incurred in alpine skiing. Am J Sports Med. 1995 Sep-Oct; 23(5): 531-7.

Ewers BJ, Jayaraman VM, Banglmaier RF, Haut RC. Rate of blunt impact loading affects changes in retropatellar cartilage and underlying bone in the rabbit patella. J Biomech. 2002 Jun; 35(6): 747-55.

Freedman KB, Bernstein J. Sample size and statistical power in clinical orthopaedic research. J Bone Joint Surg Am. 1999 Oct; 81(10): 1454-60.

Frihagen F, Kvakestad R, Melhuus K, Engebretsen L. The use of MRI scan of knee injuries in an emergency department. Scand J Med Sci Sports. 2002 Jun; 12(3): 150-3.

Fritz RC. MR imaging of meniscal and cruciate ligament injuries. Magn Reson Imaging Clin N Am. 2003 May; 11(2): 283-93.

Fujimoto E, Sumen Y, Ochi M, Ikuta Y. Spontaneous healing of acute anterior cruciate ligament (ACL) injuries - conservative treatment using an extension block soft brace without anterior stabilization. Archives of Orthopaedic and Trauma Surgery. 2002; 122(4): 212-6.

Furman W, Marshall JL, Girgis FG. The anterior cruciate ligament. A functional analysis based on postmortem studies. J Bone Joint Surg Am. 1976 Mar; 58(2): 179-85.

Gillquist J, Hagberg G, Oretorp N. Arthroscopy in acute injuries of the knee joint. Acta Orthop Scand. 1977; 48(2): 190-6.

Gillquist J, Messner K. Anterior cruciate ligament reconstruction and the long-term incidence of gonarthrosis. Sports Med. 1999 Mar; 27(3): 143-56.

Giove TP, Miller SJ, 3rd, Kent BE, Sanford TL, Garrick JG. Non-operative treatment of the torn anterior cruciate ligament. J Bone Joint Surg Am. 1983 Feb; 65(2): 184-92.

Gobbi A, Francisco R. Factors affecting return to sports after anterior cruciate ligament reconstruction with patellar tendon and hamstring graft: a prospective clinical investigation. Knee Surg Sports Traumatol Arthrosc. 2006 Oct; 14(10): 1021-8.

Graf BK, Cook DA, De Smet AA, Keene JS. “Bone bruises” on magnetic resonance imaging evaluation of anterior cruciate ligament injuries. Am J Sports Med. 1993 Mar-Apr; 21(2): 220-3.

Graichen H, von Eisenhart-Rothe R, Vogl T, Englmeier KH, Eckstein F. Quantitative assessment of cartilage status in osteoarthritis by quantitative magnetic resonance imaging: technical validation for use in analysis of cartilage volume and further morphologic parameters. Arthritis Rheum. 2004 Mar; 50(3): 811-6.

Grant CH, 3rd, Cissna KN, Rosenfeld LB. Patients’ perceptions of physicians communication and outcomes of the accrual to trial process. Health Commun. 2000; 12(1): 23-39.

Gray ML, Eckstein F, Peterfy C, Dahlberg L, Kim YJ, Sorensen AG. Toward imaging biomarkers for osteoarthritis. Clin Orthop Relat Res. 2004 Oct(427 Suppl): S175-81.

Griffin LY, Albohm MJ, Arendt EA, Bahr R, Beynnon BD, Demaio M, et al. Understanding and preventing noncontact anterior cruciate ligament injuries: a review of the Hunt Valley II meeting, January 2005. Am J Sports Med. 2006 Sep; 34(9): 1512-32.

Grontvedt T, Engebretsen L, Benum P, Fasting O, Molster A, Strand T. A prospective, randomized study of three operations for acute rupture of the anterior cruciate ligament. Five-year follow-up of one hundred and thirty-one patients. J Bone Joint Surg Am. 1996 Feb; 78(2): 159-68.

Halpern SD, Karlawish JH, Berlin JA. The continuing unethical conduct of underpowered clinical trials. Jama. 2002 Jul 17; 288(3): 358-62.

Halpern SD, Karlawish JH, Casarett D, Berlin JA, Townsend RR, Asch DA. Hypertensive patients’ willingness to participate in placebo-controlled trials: implications for recruitment efficiency. Am Heart J. 2003 Dec; 146(6): 985-92.

Hara K, Kubo T, Suginoshita T, Shimizu C, Hirasawa Y. Reconstruction of the anterior cruciate ligament using a double bundle. Arthroscopy. 2000 Nov; 16(8): 860-4.

Harilainen A, Myllynen P, Antila H, Seitsalo S. The significance of arthroscopy and examination under anaesthesia in the diagnosis of fresh injury haemarthrosis of the knee joint. Injury. 1988 Jan; 19(1): 21-4.

Hayes CW, Brigido MK, Jamadar DA, Propeck T. Mechanism-based pattern approach to classification of complex injuries of the knee depicted at MR imaging. Radiographics. 2000 Oct; 20 Spec No: S121-34.

Hefti F, Muller W, Jakob RP, Staubli HU. Evaluation of knee ligament injuries with the IKDC form. Knee Surg Sports Traumatol Arthrosc. 1993; 1(3-4): 226-34.

Herrlin S, Hallander M, Wange P, Weidenhielm L, Werner S. Arthroscopic or conservative treatment of degenerative medial meniscal tears: a prospective randomised trial. Knee Surg Sports Traumatol Arthrosc. 2007 Apr; 15(4): 393-401.

Hey Groves E. Operation for repair of crucial ligaments. Lancet. 1917; 2: 674-5.

Hirokawa S, Solomonow M, Lu Y, Lou ZP, D'Ambrosia R. Anterior-posterior and rotational displacement of the tibia elicited by quadriceps contraction. Am J Sports Med. 1992 May-Jun; 20(3): 299-306.

Hoher J, Bach T, Munster A, Bouillon B, Tiling T. Does the mode of data collection change results in a subjective knee score? Self-administration versus interview. Am J Sports Med. 1997 Sep-Oct; 25(5): 642-7.

Huber FE, Irrgang JJ, Harner C, Lephart S. Intratester and intertester reliability of the KT-1000 arthrometer in the assessment of posterior laxity of the knee. Am J Sports Med. 1997 Jul-Aug; 25(4): 479-85.

Hunter DJ, Niu J, Zhang Y, Totterman S, Tamez-Pena J, Dabrowski C, et al. Change in cartilage morphometry: a sample of the progression cohort of the Osteoarthritis Initiative. Arthritis Rheum. 2007; Submitted June 2007.

Irrgang JJ, Snyder-Mackler L, Wainner RS, Fu FH, Harner CD. Development of a patient-reported measure of function of the knee. J Bone Joint Surg Am. 1998 Aug; 80(8): 1132-45.

Jarvela T. Double-bundle versus single-bundle anterior cruciate ligament reconstruction: a prospective, randomize clinical study. Knee Surg Sports Traumatol Arthrosc. 2007 May; 15(5): 500-7.

Jarvinen M, Natri A, Laurila S, Kannus P. Mechanisms of anterior cruciate ligament ruptures in skiing. Knee Surg Sports Traumatol Arthrosc. 1994; 2(4): 224-8.

Johansson H, Sjolander P, Sojka P. Receptors in the knee joint ligaments and their role in the biomechanics of the joint. Crit Rev Biomed Eng. 1991; 18(5): 341-68.

Johnson DL, Urban WP, Jr., Caborn DN, Vanarthos WJ, Carlson CS. Articular cartilage changes seen with magnetic resonance imaging-detected bone bruises associated with acute anterior cruciate ligament rupture. Am J Sports Med. 1998 May-Jun; 26(3): 409-14.

Jokl P, Kaplan N, Stovell P, Keggi K. Non-operative treatment of severe injuries to the medial and anterior cruciate ligaments of the knee. J Bone Joint Surg Am. 1984 Jun; 66(5): 741-4.

Jones KG. Reconstruction of the anterior cruciate ligament using the central one-third of the patellar ligament. J Bone Joint Surg Am. 1970 Jun; 52(4): 838-9.

Kanamori A, Zeminski J, Rudy TW, Li G, Fu FH, Woo SL. The effect of axial tibial torque on the function of the anterior cruciate ligament: a biomechanical study of a simulated pivot shift test. Arthroscopy. 2002 Apr; 18(4): 394-8.

Kaplan PA, Walker CW, Kilcoyne RF, Brown DE, Tusek D, Dussault RG. Occult fracture patterns of the knee associated with anterior cruciate ligament tears: assessment with MR imaging. Radiology. 1992 Jun; 183(3): 835-8.

Karataglis D, Bisbinas I, Green MA, Learmonth DJ. Functional outcome following reconstruction in chronic multiple ligament deficient knees. Knee Surg Sports Traumatol Arthrosc. 2006 Sep; 14(9): 843-7.

Khanna AJ, Cosgarea AJ, Mont MA, Andres BM, Domb BG, Evans PJ, et al. Magnetic resonance imaging of the knee. Current techniques and spectrum of disease. J Bone Joint Surg Am. 2001; 83-A Suppl 2 Pt 2: 128-41.

Kocabey Y, Tetik O, Isbell WM, Atay OA, Johnson DL. The value of clinical examination versus magnetic resonance imaging in the diagnosis of meniscal tears and anterior cruciate ligament rupture. Arthroscopy. 2004 Sep; 20(7): 696-700.

Kostogiannis I, Ageberg E, Neuman P, Dahlberg L, Friden T, Roos H. Activity Level and Subjective Knee Function 15 Years After Anterior Cruciate Ligament Injury: A Prospective, Longitudinal Study of Nonreconstructed Patients. Am J Sports Med. 2007 Jul; 25(7): 1135-43.

Kubilay Pakin S, Tamez-Pena J, Totterman S, Parker KJ. Segmentation, surface extraction and thickness computation of articular cartilage. Proceedings of SPIE - The International Society for Optical Engineering Medical Imaging' 2002. 2002; 4684: 155-66.

Kurosaka M, Yoshiya S, Mizuno T, Mizuno K. Spontaneous healing of a tear of the anterior cruciate ligament. A report of two cases. J Bone Joint Surg Am. 1998 Aug; 80(8): 1200-3.

Lahm A, Uhl M, Erggelet C, Haberstroh J, Mrosek E. Articular cartilage degeneration after acute subchondral bone damage: an experimental study in dogs with histopathological grading. Acta Orthop Scand. 2004 Dec; 75(6): 762-7.

Laxdal G. The influence of graft choice and fixation materials on the outcome after arthroscopic anterior cruciate ligament reconstruction. Gothenburg: Gothenburg University; 2006.

Laxdal G, Kartus J, Hansson L, Heidvall M, Ejerhed L, Karlsson J. A prospective randomized comparison of bone-patellar tendon-bone and hamstring grafts for anterior cruciate ligament reconstruction. Arthroscopy. 2005 Jan; 21(1): 34-42.

Laxdal G, Sernert N, Ejerhed L, Karlsson J, Kartus JT. A prospective comparison of bone-patellar tendon-bone and hamstring tendon grafts for anterior cruciate ligament reconstruction in male patients. Knee Surg Sports Traumatol Arthrosc. 2007 Feb; 15(2): 115-25.

LeGraverand M-P, Pickering E, Redifer P, Tamez-Pena J. The Prevalence Of Bone Marrow Edema In Sibling Pairs With Familial Osteoarthritis At Multiple Sites. Arthritis Rheum. 2005; 52- 91 Suppl S(9): 69-70.

Levangie PK, Norkin CC. Joint structure and function. A comprehensive analysis. 3rd ed. Philadelphia, F.A.: Davis Company 2001.

Lewis JL, Deloria LB, Oyen-Tiesma M, Thompson RC, Jr., Ericson M, Oegema TR, Jr. Cell death after cartilage impact occurs around matrix cracks. J Orthop Res. 2003 Sep; 21(5): 881-7.

Linko E, Harilainen A, Malmivaara A, Seitsalo S. Surgical versus conservative interventions for anterior cruciate ligament ruptures in adults. Cochrane Database Syst Rev. 2005(2): CD001356.

Lipscomb AB, Johnston RK, Snyder RB. The technique of cruciate ligament reconstruction. Am J Sports Med. 1981 Mar-Apr; 9(2): 77-81.

Lohmander LS, Englund PM, Dahl LD, Roos EM. The Long-Term Consequence of ACL and Meniscus Injuries: Osteoarthritis. Am J Sports Med. 2007 Oct; 35(10): 1756-69.

Lohmander LS, Roos H. Knee ligament injury, surgery and osteoarthrosis. Truth or consequences? Acta Orthop Scand. 1994 Dec; 65(6): 605-9.

Lovato LC, Hill K, Hertert S, Hunninghake DB, Probstfield JL. Recruitment for controlled clinical trials: literature summary and annotated bibliography. Control Clin Trials. 1997 Aug; 18(4): 328-52.

Lundberg M, Odensten M, Thuomas KA, Messner K. The diagnostic validity of magnetic resonance imaging in acute knee injuries with hemarthrosis. A single-blinded evaluation in 69 patients using high-field MRI before arthroscopy. Int J Sports Med. 1996 Apr; 17(3): 218-22.

Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med. 1982 May-Jun; 10(3): 150-4.

Mackenzie R, Dixon AK, Keene GS, Hollingworth W, Lomas DJ, Villar RN. Magnetic resonance imaging of the knee: assessment of effectiveness. Clin Radiol. 1996 Apr; 51(4): 245-50.

Marcacci M, Molgora AP, Zaffagnini S, Vascellari A, Iacono F, Presti ML. Anatomic double-bundle anterior cruciate ligament reconstruction with hamstrings. Arthroscopy. 2003 May-Jun; 19(5): 540-6.

Marder RA, Hopkins G, Jr., Timmerman LA. Arthroscopic microfracture of chondral defects of the knee: a comparison of two postoperative treatments. Arthroscopy. 2005 Feb; 21(2): 152-8.

Markolf KL, Burchfield DM, Shapiro MM, Shepard MF, Finerman GA, Slauterbeck JL. Combined knee loading states that generate high anterior cruciate ligament forces. J Orthop Res. 1995 Nov; 13(6): 930-5.

Martin JA, Brown T, Heiner A, Buckwalter JA. Post-traumatic osteoarthritis: the role of accelerated chondrocyte senescence. Biorheology. 2004; 41(3-4): 479-91.

Marx RG, Stump TJ, Jones EC, Wickiewicz TL, Warren RF. Development and evaluation of an activity rating scale for disorders of the knee. Am J Sports Med. 2001 Mar-Apr; 29(2): 213-8.

McDaniel WJ, Jr., Dameron TB, Jr. Untreated ruptures of the anterior cruciate ligament. A follow-up study. J Bone Joint Surg Am. 1980 Jul; 62(5): 696-705.

McLeod RS, Wright JG, Solomon MJ, Hu X, Walters BC, Lossing A. Randomized controlled trials in surgery: Issues and problems. Surgery. 1996 May; 119(5): 483-6.

Meunier A, Odensten M, Good L. Long-term results after primary repair or non-surgical treatment of anterior cruciate ligament rupture: a randomized study with a 15-year follow-up. Scand J Med Sci Sports. 2007 Jun; 17(3): 230-7.

Mihata LC, Beutler AI, Boden BP. Comparing the incidence of anterior cruciate ligament injury in collegiate lacrosse, soccer, and basketball players: implications for anterior cruciate ligament mechanism and prevention. Am J Sports Med. 2006 Jun; 34(6): 899-904.

Milentijevic D, Rubel IF, Liew AS, Helfet DL, Torzilli PA. An in vivo rabbit model for cartilage trauma: a preliminary study of the influence of impact stress magnitude on chondrocyte death and matrix damage. J Orthop Trauma. 2005 Aug; 19(7): 466-73.

Mithoefer K, Williams RJ, 3rd, Warren RF, Wickiewicz TL, Marx RG. High-impact athletics after knee articular cartilage repair: a prospective evaluation of the microfracture technique. Am J Sports Med. 2006 Sep; 34(9): 1413-8.

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet. 1998 Aug 22; 352(9128): 609-13.

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001 Apr 14; 357(9263): 1191-4.

Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2002 Jul 11; 347(2): 81-8.

Muellner T, Nikolic A, Kubiena H, Kainberger F, Mittlboeck M, Vecsei V. The role of magnetic resonance imaging in routine decision making for meniscal surgery. Knee Surg Sports Traumatol Arthrosc. 1999; 7(5): 278-83.

Muneta T, Koga H, Mochizuki T, Ju YJ, Hara K, Nimura A, et al. A prospective randomized study of 4-strand semitendinosus tendon anterior cruciate ligament reconstruction comparing single-bundle and double-bundle techniques. Arthroscopy. 2007 Jun; 23(6): 618-28.

Munshi M, Davidson M, MacDonald PB, Froese W, Sutherland K. The efficacy of magnetic resonance imaging in acute knee injuries. Clin J Sport Med. 2000 Jan; 10(1): 34-9.

Myklebust G, Bahr R. Return to play guidelines after anterior cruciate ligament surgery. Br J Sports Med. 2005 Mar; 39(3): 127-31.

Myklebust G, Holm I, Maehlum S, Engebretsen L, Bahr R. Clinical, functional, and radiologic outcome in team handball players 6 to 11 years after anterior cruciate ligament injury: a follow-up study. Am J Sports Med. 2003 Nov-Dec; 31(6): 981-9.

Myklebust G, Maehlum S, Holm I, Bahr R. A prospective cohort study of anterior cruciate ligament injuries in elite Norwegian team handball. Scand J Med Sci Sports. 1998 Jun; 8(3): 149-53.

Nelson HD, Helfand M, Woolf SH, Allan JD. Screening for postmenopausal osteoporosis: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002 Sep 17; 137(6): 529-41.

Nielsen AB, Yde J. Epidemiology of acute knee injuries: a prospective hospital investigation. J Trauma. 1991 Dec; 31(12): 1644-8.

Noyes FR, Barber SD, Mooar LA. A rationale for assessing sports activity levels and limitations in knee disorders. Clin Orthop Relat Res. 1989 Sep(246): 238-49.

Noyes FR, Bassett RW, Grood ES, Butler DL. Arthroscopy in acute traumatic hemarthrosis of the knee. Incidence of anterior cruciate tears and other injuries. J Bone Joint Surg Am. 1980 Jul; 62(5): 687-95, 757.

O'Neill DB. Arthroscopically assisted reconstruction of the anterior cruciate ligament. A follow-up report. J Bone Joint Surg Am. 2001 Sep; 83-A(9): 1329-32.

Palmer I. On the injuries to the ligaments of the knee joint. A clinical study. Acta Chir Scand. 1938; LXXXI: Supplement 53.

Palmer WE. Magnetic resonance imaging of knee trauma: biomechanical approach. Top Magn Reson Imaging. 2003 Apr; 14(2): 161-78.

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

Patel A, Wilke HJ, 2nd, Mingay D, Ellis JE. Patient attitudes toward granting consent to participate in perioperative randomized clinical trials. J Clin Anesth. 2004 Sep; 16(6): 426-34.

Peterfy CG. Imaging of the disease process. Curr Opin Rheumatol. 2002 Sep; 14(5): 590-6.

Plint AC, Moher D, Morrison A, Schulz K, Altman DG, Hill C, et al. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. Med J Aust. 2006 Sep 4; 185(5): 263-7.

Rangger C, Kathrein A, Freund MC, Klestil T, Kreczy A. Bone bruise of the knee: histology and cryosections in 5 cases. Acta Orthop Scand. 1998 Jun; 69(3): 291-4.

Rangger C, Klestil T, Kathrein A, Inderster A, Hamid L. Influence of magnetic resonance imaging on indications for arthroscopy of the knee. Clin Orthop. 1996 Sep(330): 133-42.

Rappeport ED, Mehta S, Wieslander SB, Lausten GS, Thomsen HS. MR imaging before arthroscopy in knee joint disorders? Acta Radiol. 1996 Sep; 37(5): 602-9.

Rembold CM. Number needed to screen: development of a statistic for disease screening. Bmj. 1998 Aug 1; 317(7154): 307-12.

Risberg MA, Lewek M, Snyder-Mackler L. A systematic review of evidence for anterior cruciate ligament rehabilitation: how much and what type? Physical Therapy in sport. 2004; 5: 125-45.

Roemer FW, Bohndorf K. Long-term osseous sequelae after acute trauma of the knee joint evaluated by MRI. Skeletal Radiol. 2002 Nov; 31(11): 615-23.

Roos EM. Outcome after anterior cruciate ligament reconstruction--a comparison of patients' and surgeons' assessments. Scand J Med Sci Sports. 2001 Oct; 11(5): 287-91.

Roos EM, Bremander AB, Englund M, Lohmander LS. Change in self-reported outcomes and objective physical function over 7 years in middle-aged subjects with or at high risk of knee OA. Ann Rheum Dis. 2007 Aug 17.

Roos EM, Roos HP, Ekdahl C, Lohmander LS. Knee injury and Osteoarthritis Outcome Score (KOOS)--validation of a Swedish version. Scand J Med Sci Sports. 1998a Dec; 8(6): 439-48.

Roos EM, Roos HP, Lohmander LS. WOMAC Osteoarthritis Index--additional dimensions for use in subjects with post-traumatic osteoarthritis of the knee. Western Ontario and MacMaster Universities. Osteoarthritis Cartilage. 1999 Mar; 7(2): 216-21.

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

Roos H, Ornell M, Gardsell P, Lohmander LS, Lindstrand A. Soccer after anterior cruciate ligament injury--an incompatible combination? A national survey of incidence and risk factors and a 7-year follow-up of 310 players. Acta Orthop Scand. 1995 Apr; 66(2): 107-12.

Rose NE, Gold SM. A comparison of accuracy between clinical examination and magnetic resonance imaging in the diagnosis of meniscal and anterior cruciate ligament tears. Arthroscopy. 1996 Aug; 12(4): 398-405.

Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol. 1999 Dec; 52(12): 1143-56.

Ryu KN, Jin W, Ko YT, Yoon Y, Oh JH, Park YK, et al. Bone bruises: MR characteristics and histological correlation in the young pig. Clin Imaging. 2000 Nov-Dec; 24(6): 371-80.

Sandberg R, Balkfors B, Nilsson B, Westlin N. Operative versus non-operative treatment of recent injuries to the ligaments of the knee. A prospective randomized study. J Bone Joint Surg Am. 1987 Oct; 69(8): 1120-6.

Sanders TG, Medynski MA, Feller JF, Lawhorn KW. Bone contusion patterns of the knee at MR imaging: footprint of the mechanism of injury. Radiographics. 2000 Oct; 20 Spec No: S135-51.

Sarimo J, Rantanen J, Heikkila J, Helttula I, Hiltunen A, Orava S. Acute traumatic hemarthrosis of the knee. Is routine arthroscopic examination necessary? A study of 320 consecutive patients. Scand J Surg. 2002; 91(4): 361-4.

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. Jama. 1995 Feb 1; 273(5): 408-12.

Shelbourne KD, Patel DV. Timing of surgery in anterior cruciate ligament-injured knees. Knee Surg Sports Traumatol Arthrosc. 1995; 3(3): 148-56.

Shelbourne KD, Wilckens JH, Mollabashy A, DeCarlo M. Arthrofibrosis in acute anterior cruciate ligament reconstruction. The effect of timing of reconstruction and rehabilitation. Am J Sports Med. 1991 Jul-Aug; 19(4): 332-6.

Slocum DB, James SL, Larson RL, Singer KM. Clinical test for anterolateral rotary instability of the knee. Clin Orthop Relat Res. 1976 Jul-Aug(118): 63-9.

Smith HJ. MR imaging before arthroscopy in knee joint disorders? Acta Radiol. 1996 Sep; 37(5): 601.

Solomonow M, Krogsgaard M. Sensorimotor control of knee stability. A review. Scand J Med Sci Sports. 2001 Apr; 11(2): 64-80.

Sommerlath K, Lysholm J, Gillquist J. The long-term course after treatment of acute anterior cruciate ligament ruptures. A 9 to 16 year followup. Am J Sports Med. 1991 Mar-Apr; 19(2): 156-62.

Stark J. Two cases of ruptured cruciate ligaments of the knee joint. Edinburgh Med Surg. 1850; 74: 267-71.

Stevens KJ, Dragoo JL. Anterior cruciate ligament tears and associated injuries. Top Magn Reson Imaging. 2006 Oct; 17(5): 347-62.

Tajima T, Yoshida E, Yamashita A, Ohmura S, Tomitaka Y, Sugiki M, et al. Hemoglobin stimulates the expression of matrix metalloproteinases, MMP-2 and MMP-9 by synovial cells: a possible cause of joint damage after intra-articular hemorrhage. J Orthop Res. 2005 Jul; 23(4): 891-8.

Takeuchi R, Saito T, Mituhashi S, Suzuki E, Yamada I, Koshino T. Double-bundle anatomic anterior cruciate ligament reconstruction using bone-hamstring-bone composite graft. Arthroscopy. 2002 May-Jun; 18(5): 550-5.

Tamez-Pena J, Barbu-McInnis B, Lerner AL, Totterman S. Unsupervised definition of the Tibia-Femoral joint regions of the human knee and its applications to cartilage analysis. SPIE: Medical Imaging. 2006; February.

Tamez-Pena J, Barbu-McInnis B, Totterman S. Knee Cartilage Extraction and Bone-Cartilage Interface Analysis from 3D MRI Data Sets. SPIE: Medical Imaging: Image Processing. 2004; 5370: 1774-84.

Tamez-Pena J, Parker KJ, Totterman S. The integration of automatic segmentation and motion tracking for 4D reconstruction and visualization of musculosceletal structures. IEEE workshop on Biomedical Image Analyzes. 1998: 154-63.

Tamez-Pena J, Parker KJ, Totterman S. Unsupervised statistical segmentation of multispectral volumetric MR images. Proceedings of SPIE - The International Society for Optical Engineering Medical Imaging' 99: Image Processing. 1999; 3661: 300-11.

Tamez-Pena JG, Barbu-McInnis B, Lerner AL, Totterman S. Virtual performance assessment of 3D quatification systems. SPIE: Medical Imaging: Image Processing. 2005; February.

Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. Clin Orthop. 1985 Sep(198): 43-9.

Thomee P, Wahrborg P, Borjesson M, Thomee R, Eriksson BI, Karlsson J. Self-efficacy, symptoms and physical activity in patients with an anterior cruciate ligament injury: a prospective study. Scand J Med Sci Sports. 2007 Jun; 17(3): 238-45.

Tognoni G, Alli C, Avanzini F, Bettelli G, Colombo F, Corso R, et al. Randomised clinical trials in general practice: lessons from a failure. Bmj. 1991 Oct 19; 303(6808): 969-71.

Torg JS, Conrad W, Kalen V. Clinical diagnosis of anterior cruciate ligament instability in the athlete. Am J Sports Med. 1976 Mar-Apr; 4(2): 84-93.

Vellet AD, Marks PH, Fowler PJ, Munro TG. Occult post-traumatic osteochondral lesions of the knee: prevalence, classification, and short-term sequelae evaluated with MR imaging. Radiology. 1991 Jan; 178(1): 271-6.

Vincken PW, ter Braak BP, van Erkell AR, de Rooy TP, Mallens WM, Post W, et al. Effectiveness of MR imaging in selection of patients for arthroscopy of the knee. Radiology. 2002 Jun; 223(3): 739-46.

Winters K, Tregonning R. Reliability of magnetic resonance imaging of the traumatic knee as determined by arthroscopy. N Z Med J. 2005 Feb 11; 118(1209): U1301.

Visuri T, Koskenvuo M, Dahlstrom S. Hemarthrosis of the clinically stable knee due to sports and military training in young recruits: an arthroscopic analysis. Mil Med. 1993 Jun; 158(6): 378-81.

Voloshin I, Schmitz MA, Adams MJ, DeHaven KE. Results of repeat meniscal repair. Am J Sports Med. 2003 Nov-Dec; 31(6): 874-80.

Wragg JA, Robinson EJ, Lilford RJ. Information presentation and decisions to enter clinical trials: a hypothetical trial of hormone replacement therapy. Soc Sci Med. 2000 Aug; 51(3): 453-62.

Yu JS, Cook PA. Magnetic resonance imaging (MRI) of the knee: a pattern approach for evaluating bone marrow edema. Crit Rev Diagn Imaging. 1996 Sep; 37(4): 261-303.

Zysk SP, Refior HJ. Operative or conservative treatment of the acutely torn anterior cruciate ligament in middle-aged patients. A follow-up study of 133 patients between the ages of 40 and 59 years. Arch Orthop Trauma Surg. 2000; 120(1-2): 59-64.