PREDICTORS OF COMPLICATIONS AFTER ANTERIOR CRUCIATE LIGAMENT INJURY

Daniel Andernord, MD

Department of Orthopaedics
Institute of Clinical Sciences
Sahlgrenska Academy at
University of Gothenburg
Gothenburg, Sweden

UNIVERSITY OF GOTHENBURG

Predictors of Complications after Anterior Cruciate Ligament Injury

ISBN 978-91-628-9297-5
http://hdl.handle.net/2077/38007

Printed by Ineko 2015
Design by Annika Samuelsson Enderlein, A Little Company AB
Illustrations by Pontus Andersson, Pontus Art Production
Front cover art: What can we predict from what we know? The ACL-injured individual in the crystal ball. Copyright © Daniel Andernord

Jag vill väga och pröva. Det är en av grunddrifterna i mitt väsen att icke tåla något halvmedvetet och halvklart, där det står i min makt att taga fram det och hålla det upp i ljuset och se efter vad det är.

Hjalmar Söderberg

General practice is the easiest job in the world to do badly, but the most difficult to do well.

Professor Sir Denis Pereira Gray

CONTENTS

ABSTRACT

BACKGROUND: An anterior cruciate ligament (ACL) tear is a serious knee injury that frequently affects young individuals active in soccer, alpine skiing, handball and basketball. Regardless of treatment, an ACL injury is associated with an increased risk of complications in the short and long term, such as meniscal and chondral injuries or a need to undergo surgery on the injured knee or the contralateral knee. In order to prevent these complications, the essential first step is to obtain knowledge of factors that make certain individuals susceptible to certain complications.

AIM: The aim of this thesis was to investigate patient- and health care-related factors and identify predictors of meniscal injury, chondral injury, revision surgery and contralateral ACL reconstruction.

METHODS: This thesis is based on six studies. Studies I-III are systematic reviews of randomized controlled trials and cohort studies. Studies IV-VI are registry-based cohort studies of patients in the Swedish National Knee Ligament Register.

RESULTS: Individuals with an ACL injury who underwent non-surgical treatment ran a more than 10 times higher risk of sustaining meniscal injuries and an at least 4 times higher risk of requiring meniscal surgery compared with individuals who underwent ACL reconstruction. Adolescents (individuals aged 13 to 19 years) who underwent ACL reconstruction ran a 2 to 3 times higher risk of revision surgery or contralateral ACL reconstruction. Adolescents who suffered an ACL injury while playing soccer ran a 3 times higher risk of revision surgery. Females who underwent ACL reconstruction with harvest of a contralateral hamstring tendon autograft ran a more than 3 times higher risk of future contralateral ACL reconstruction.

CONCLUSIONS: Non-surgical treatment, age 13 to 19 years, injury during soccer and contralateral hamstring tendon harvest were predictors of serious complications after ACL injury.

KEYWORDS: *Sports medicine, evidence-based medicine, knee, joint, menisci, cartilage, osteoarthritis, arthroscopy, physical therapy, rehabilitation, sex, adolescent, teenager, football*

SAMMANFATTNING PÅ SVENSKA

BAKGRUND: Främre korsbandsruptur är en allvarlig knäskada som ofta drabbar unga individer aktiva inom fotboll, alpin skidåkning, handboll och basket. Oavsett behandling så är en främre korsbandsskada förenad med en ökad risk för komplikationer på kort och lång sikt, så som menisk- och broskskador eller ett behov av att genomgå operation av det skadade knät eller det andra knät. För att kunna förebygga dessa komplikationer är det viktigt att först inhämta kunskap om faktorer som gör att vissa individer drabbas av särskilda komplikationer.

SYFTE: Syftet med avhandlingen var att undersöka patient- och sjukvårdsrelaterade faktorer och identifiera prediktorer för meniskskada, broskskada, revisionsoperation i det opererade knät eller främre korsbandsoperation i det andra knät.

METOD: Avhandlingen baseras på sex studier. Studierna I-III är systematiska litteraturstudier av randomiserade kontrollerade studier och kohortstudier. Studierna IV-VI är registerbaserade kohortstudier av patienter i det Svenska korsbandsregistret.

RESULTAT: Individer med en främre korsbandsskada som genomgick icke-operativ behandling löpte mer än 10 gånger högre risk att drabbas av meniskskador och åtminstone 4 gånger högre risk att behöva genomgå framtida meniskoperation jämfört med individer som genomgick främre korsbandsoperation. Ungdomar (individer i åldern 13 till 19 år) som genomgick en främre korsbandsoperation löpte 2 till 3 gånger högre risk att behöva genomgå revisionsoperation i det opererade knät eller främre korsbandsoperation i det andra knät. Ungdomar som ådrog sig en främre korsbandsskada när de spelade fotboll löpte 3 gånger högre risk att behöva genomgå revisionsoperation. Kvinnor som genomgick främre korsbandsoperation med böjsenegraft från det andra knät löpte mer än 3 gånger högre risk att behöva genomgå främre korsbandsoperation i det andra knät.

SLUTSATS: Icke-operativ behandling, ålder 13 till 19 år, skada i samband med fotbollsspel samt böjsenegraft från andra knät var prediktorer för allvarliga komplikationer efter en främre korsbandsskada.

LIST OF PAPERS

This thesis is based on six studies, referred to in the text by their Roman numerals.

I. Andersson D, Samuelsson K, Karlsson J

Treatment of anterior cruciate ligament injuries with special reference to surgical technique and rehabilitation: an assessment of randomized controlled trials

Arthroscopy. 2009;25(6):653-685

II. Samuelsson K, Andersson D, Karlsson J

Treatment of anterior cruciate ligament injuries with special reference to graft type and surgical technique: an assessment of randomized controlled trials

Arthroscopy. 2009;25(10):1139-1174

III. Andernord D, Karlsson J, Musahl V, Bhandari M, Fu FH, Samuelsson K

Timing of surgery of the anterior cruciate ligament

Arthroscopy. 2013;29(11):1863-1871

IV. Andernord D, Björnsson H, Petzold M, Eriksson BI, Forssblad M, Karlsson J, Samuelsson K

Surgical predictors of early revision surgery after anterior cruciate ligament reconstruction: results from the Swedish national knee ligament register on 13,102 patients

The American Journal of Sports Medicine. 2014;42(7):1574-1582

V. Andernord D, Desai N, Björnsson H, Ylander M, Karlsson J, Samuelsson K

Patient predictors of early revision surgery after anterior cruciate ligament reconstruction: a cohort study of 16,930 patients with 2-year follow-up

The American Journal of Sports Medicine. 2015;43(1):121-127

VI. Andernord D, Desai N, Björnsson H, Gillén S, Karlsson J, Samuelsson K

Predictors of contralateral anterior cruciate ligament reconstruction: a cohort study of 9061 patients with 5-year follow-up

The American Journal of Sports Medicine. 2015;43(2):295-302

ABBREVIATIONS

ACL	Anterior Cruciate Ligament
AMSTAR	Assessment of Multiple Systematic Reviews
BMI	Body Mass Index
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
DARE	Database of Abstracts of Reviews of Effects
EMBASE	Excerpta Medica Database
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
HT	Hamstring Tendon
HTA	Health Technology Assessment
ICRS	International Cartilage Repair Society
IKDC	International Knee Documentation Committee
LAD	Ligament Augmentation Device
MEDLINE	Medical Literature Analysis and Retrieval System Online

MeSH	Medical Subject Headings
NIHR	National Institute for Health Research
NNT	Number Needed to Treat
OARSI	Osteoarthritis Research Society International
OCEBM	Oxford Centre for Evidence-Based Medicine
OMERACT	Outcome Measures in Rheumatology
OR	Odds Ratio
PCL	Posterior Cruciate Ligament
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PT	Patellar Tendon
RCT	Randomized Controlled Trial
RR	Relative Risk
SBU	Swedish Council on Health Technology Assessment
ST	Semitendinosus
STG	Semitendinosus-Gracilis
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO	World Health Organization

DEFINITIONS

ACL reconstruction	Reconstruction of the native ACL using a graft
Allograft	Tissue from a donor of the same species as the recipient but not genetically identical
Autograft	Tissue from one point to another of the same individual's body
Bias	A systematic error
Case series	An uncontrolled observational study of outcomes in a group with a given exposure
Case-control study	A controlled retrospective observational study in which exposure in a group with a given outcome (cases) is compared with exposure in a group without the outcome (controls)
Cohort study	A controlled prospective observational study in which outcomes in a group with a given exposure are compared with outcomes in a similar group without the exposure
Completeness	The proportion of records in a register in relation to the total number of known records
Complication	A secondary condition aggravating an already existing one
Confidence interval	An estimated range of values from a sample which includes the unknown population parameter with a certain probability
Confounding factor	A factor that is associated with an exposure and has an impact on an outcome that is independent of the impact of the exposure
Contralateral	Belonging to or occurring on the opposite side of the body
Coverage	The proportion of units that report to a register in relation to the total number of eligible units
Graft failure	Insufficiency of the reconstructed ACL graft, which can be either patient-reported or objectively assessed
Incidence	The probability of the occurrence of new cases during a given period of time in a population at risk
Index	In epidemiology, the first known occurrence of its kind
Injury-to-surgery interval	The time interval from ACL injury to surgical treatment
Ipsilateral	Belonging to or occurring on the same side of the body
Levels of evidence	An hierarchical system which grades studies based on methodology
Long-term	A follow-up of at least 10 years

Mid-term	A follow-up of at least five years
Odds	The ratio of the probability of an event occurring in a group with a given exposure to the probability of the event not occurring in the same group
Odds ratio	The ratio of the odds in a group to the odds in another group
P value	The probability, under the null hypothesis, of obtaining a result equal to or more extreme than what was actually observed
Power	The probability of avoiding a Type II error for a true treatment effect of a given magnitude
Precision	The proportion of relevant records in relation to the total number of all records in a database
Predictor	A variable associated with an increased risk of an outcome
Prevalence	The proportion of cases at a given time in relation to the population at risk
Randomization	An unknown and unpredictable allocation sequence
Randomized controlled trial	A controlled prospective interventional study in which eligible participants are randomized to a group with a given intervention or a control group and then followed and compared over time
Recall	The proportion of relevant records in relation to the total number of relevant records in a database
Regression	A statistical model for the relationship between one or more explanatory variables and one or more dependent variables
Relative risk	The ratio of the probability of an event occurring in a group with a given exposure to a group without the exposure
Reliability	The extent to which an observation is free from random error and thus yields consistent results
Revision surgery	Replacement of a previous ACL reconstruction
Risk	The probability of the occurrence of new cases during a given period of time in the population initially at risk
Short-term	A follow-up of less than five years
Systematic review	A literature study in which an explicit and reproducible methodology is used to answer a specific question by analysis of evidence
Type I error	Incorrect rejection of a true null hypothesis
Type II error	Failure to reject a false null hypothesis
Validity	The extent to which an observation is free from systematic error and thus reflects the construct
Variable	An operationalized characteristic of a construct

"We don't know where we're going,
but we'll get nowhere if we've
forgotten where we've been."

Maria Taylor

One

INTRODUCTION

1.1 THE KNEE

The knee is the largest joint in the human body and is situated between the two largest bones, the femur (thigh bone) and the tibia (shin bone), as well as the largest sesamoid bone, the patella (knee cap). Basically, the knee has four functions: mobility during movement, stability during stance while also continuously communicating its whereabouts to our brain (proprioception). This thesis is a proof of concept of the fourth function: occupying the minds of researchers.

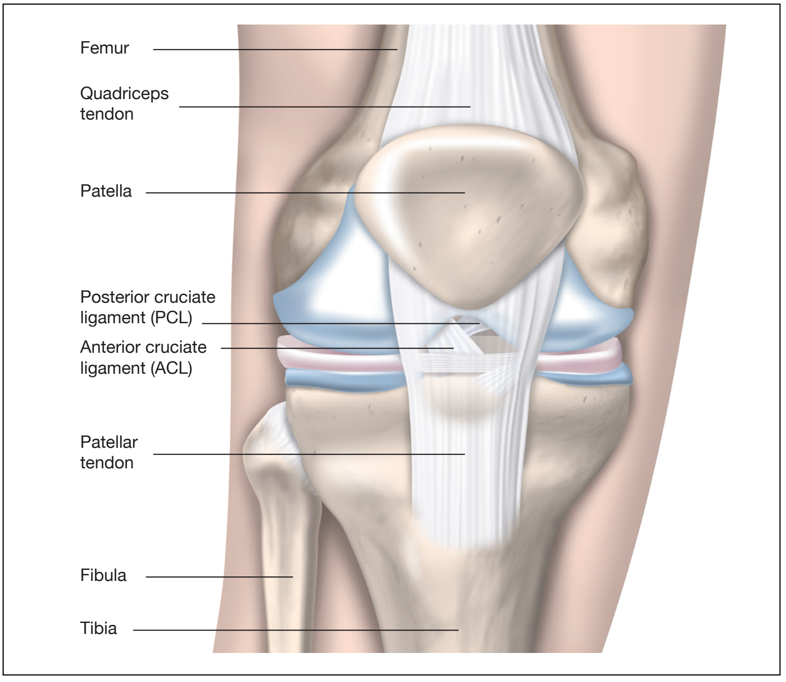

Figure 1. The knee (anterior view)
The anterior cruciate ligament (ACL) is situated in the center of the knee and connects the femur to the tibia. It stabilizes the knee by preventing forward displacement and limiting internal rotation of the tibia relative to the femur. Copyright © Daniel Andernord

1.1.1 The joint capsule

The knee is surrounded by a joint capsule, which is essential to knee stability. It consists of two layers. The external layer is a tough fibrous membrane composed mainly of collagen fibers. The internal layer is a thin synovial membrane composed of loose connective tissue. The free space inside the joint capsule is occupied by synovial fluid, which is a viscose, clear fluid primarily composed of hyaluronic acid secreted from fibroblasts in the synovial membrane and interstitial fluid filtered from blood plasma. The synovial fluid carries nutrients to the intra-articular structures with poor blood supply, primarily cartilage. The synovial fluid also contains macrophages that remove debris arising from everyday use.

1.1.2 The ligaments

The topographical design of the joint surfaces of the femur and tibia is incongruent and provides little in terms of knee stability. Instead, the stability is maintained by the surrounding soft tissue, particularly the accessory ligaments. Traditionally, there are four major ligaments which contribute to this stability: the anterior and posterior cruciate ligaments (which are located inside the joint capsule but outside the synovial cavity) and the medial and lateral collateral ligaments (which are located outside the joint capsule). The joint capsule is also strengthened by the quadriceps and patellar tendons and the oblique and arcuate popliteal ligaments.

The two major intracapsular accessory ligaments are known as the cruciate ligaments, because they cross one another like the letter X. They are named the anterior cruciate ligament (ACL) and the posterior cruciate ligament (PCL) based on their respective attachment in the anterior and posterior intercondylar area on the tibial plateau. The main function of the ACL is to act as the principal stabilizer of the knee by preventing the forward displacement of the tibia relative to the femur. The spiraling nature of the ligament fibers also helps resist the internal rotation of the tibia. The PCL prevents the posterior displacement of the tibia relative to the femur. It is the main stabilizer in the weight-bearing flexed knee (e.g. walking downhill).

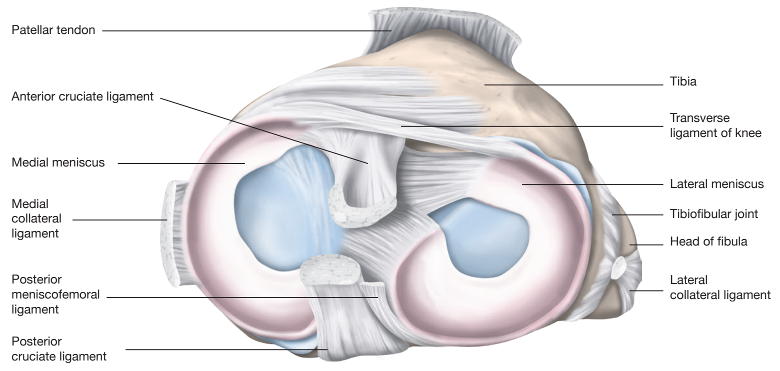

Figure 2. The tibial plateau (superior view)
The cruciate and collateral ligaments are essential to the stability of the knee. The menisci provide a contact area between the femur and the tibia and transmit the compressive loads in the knee. Copyright © Daniel Andernord

1.1.3 The menisci

The medial and lateral menisci are two semilunar discs of fibrocartilage that are located between the femoral condyles and the tibial plateau. They are composed predominantly of collagen but also contain fibroblasts and chondrocytes. The peripheral border of each meniscus is thick, while the inner free border is thin, creating a wedge-like shape in cross-section. The upper surface of each meniscus is, however, concave and articulates with the corresponding overlying femoral condyle.

The anterior and posterior horns of each meniscus are attached to the anterior and posterior intercondylar area of the tibial plateau respectively. The periphery and horns of the menisci are relatively well vascularized with branches from the genicular anastomosis. The inner free edges of the menisci are, however, avascular and depend on diffusion. The menisci are attached to the tibial rims via the coronary ligaments and to the anterior and posterior intercondylar area of the tibia. The menisci are also attached to one another via the anterior and posterior transverse ligaments of the knee.

The medial meniscus is semicircular and quite firmly attached to the deep fibers in the medial collateral ligament. The lateral meniscus is smaller and almost circular, with a uniform outline along its length. It moves more freely during knee movement compared with the medial meniscus. The lateral meniscus is not attached to the lateral collateral ligament, because the popliteal tendon separates the two along its course from the tibia to the lateral femoral epicondyle. The main function of the menisci is to provide a contact area between the femur and the tibia and transmit the compressive loads in the knee. The menisci also contain mechanoreceptors which contribute to knee proprioception.

1.1.4 The hyaline cartilage

The articular surfaces of the femur, patella and the tibial plateau are covered with hyaline cartilage, which, together with the synovial fluid, offers smooth, glistening and almost friction-free surfaces. Hyaline cartilage is composed of chondroblasts and chondrocytes which depend on diffusion of nutrients from the synovial fluid, as there are almost no blood vessels present except in the deepest calcified layers closest to the bone. The chondrocytes produce a very important complex mixture of hydrophilic molecules, the proteoglycans, which are responsible for the viscoelastic properties of the hyaline cartilage which is both compressible and elastic. These properties aid the menisci in transmitting the compressive forces to which the knee is subjected.

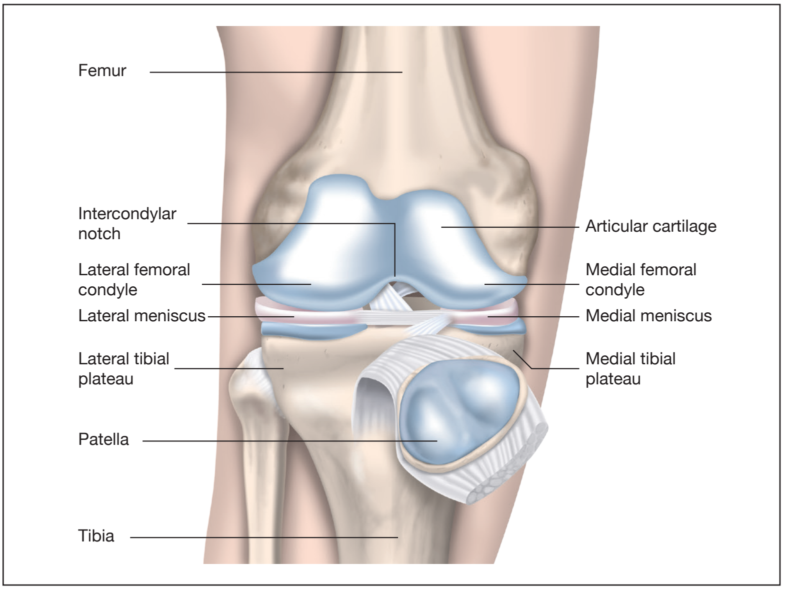

Figure 3. The hyaline cartilage
The hyaline cartilage (blue) covers all the articular surfaces in the knee and offers an almost friction-free surface. Copyright © Daniel Andernord

1.2 THE ANTERIOR CRUCIATE LIGAMENT

The ACL is situated in the very center of the knee and connects the femur to the tibia. It is approximately 30 to 40 mm long and 10 mm wide and consists mainly of collagen fibers.[65, 152] It is attached to the femur on the posterior part of the medial surface of the lateral condyle and then runs obliquely inside the knee (anteriorly, medially and inferiorly) down to its tibial attachment on the medial part of the anterior intercondylar area, immediately behind the anterior horn of the medial meniscus. There, its fibers fan out to form a triangular or oval footprint region, which is 3.5 times larger than the mid-substance cross-sectional area.[72] This enables the ligament to run freely under the roof of the intercondylar notch in full extension of the knee, which is crucial for normal knee function.

Morphologically, the ACL is a single ligament. However, during its course through the knee, the ACL is slightly twisted along its long axis, so that the collagen fibers arising most anteriorly from the tibia are attached most posteriorly to the femur and vice versa. As a result of this helical structure, the ACL is, in a functional sense, arranged into two distinguishable fiber bands or bundles, named after their respective insertion site on the tibia. The anteromedial bundle tightens during flexion of the knee and prevents the tibia from moving forward. The posterolateral bundle, which is much shorter than its anteromedial counterpart, tightens and stabilizes the knee during extension.

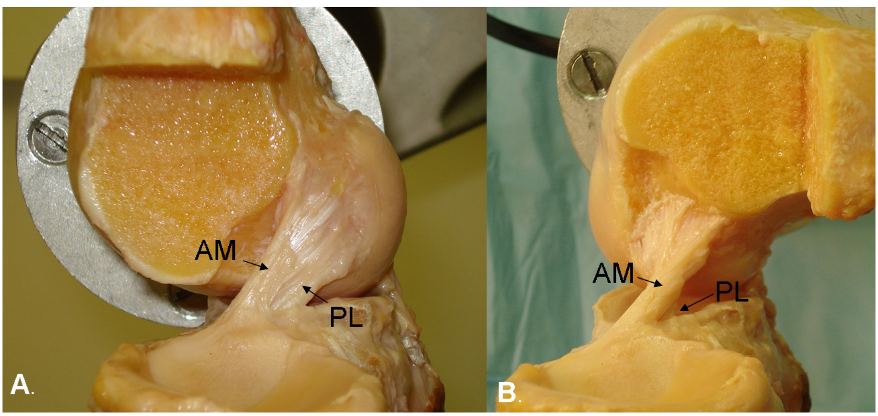

Figure 4. The double-bundle anatomy of the ACL (medial view)
The anteromedial (AM) and the posterolateral (PL) bundles of the ACL are oriented differently in A) extension and B) flexion of the knee. Copyright © University of Pittsburgh Medical Center

The ACL is, however, not only a mechanical stabilizer of the knee. It also contains receptors for both pain and proprioception and provides the brain's sensory cortex with afferent information via the genicular branches of the tibial, common peroneal and obturator nerves. The blood supply to the ACL is derived from the genicular branches (mainly the middle genicular branch) of the popliteal artery.

1.2.1 ACL injury

ACL injuries frequently affect individuals active in soccer, alpine skiing, handball and basketball.[53, 67, 107, 115] The annual incidence in the general population has been estimated to be 30 to 81 per 100,000.[53, 60, 145] In sports, incidence numbers are more commonly expressed as ACL injuries per 1,000 exposures, where one exposure can be defined as one practice, one match or one hour.[56, 163, 167]

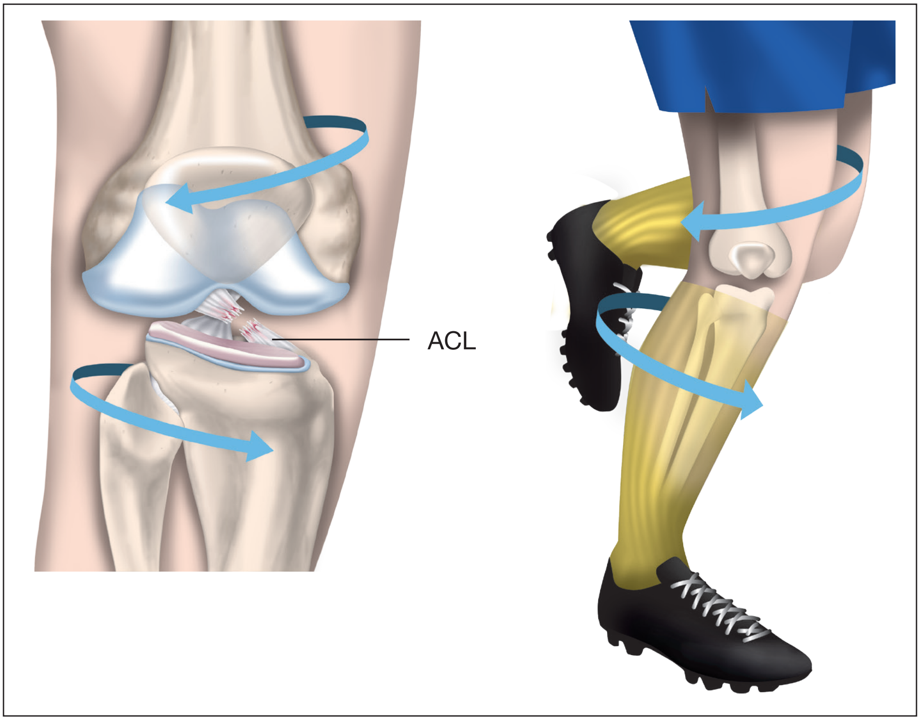

Figure 5. Injury mechanism
A sudden rotation of the knee where the femur and the tibia twist in opposite directions under full body weight is a frequent cause of ACL injury. Copyright © Daniel Andernord

The ACL in itself is prone to injury due to its location and surroundings. Literally situated "out on a limb", between the longest bones in the human body, the knee essentially becomes a fulcrum where small input forces from the thigh or the lower leg are amplified to greater forces which can exert considerable stress and strain on the ACL. The majority of all ruptures are a result of a non-contact mechanism, such as a sudden rotation, deceleration or landing on a knee near full extension. Acute symptoms are pain and swelling of the knee and further activity is generally not possible. Hemarthrosis is a common finding if acute arthrocentesis or arthroscopy is performed.[146] In general, female athletes run an approximately three times higher risk of primary ACL injury compared with male athletes.[16, 163] This is probably attributable to a wide array of factors of which anatomical, hormonal and neuromuscular aspects have been most frequently discussed.[77] Interestingly, this incidence disparity is not found among alpine skiers, where injury rates are equally distributed.[163]

1.2.2 Treatment of ACL injury

Non-surgical treatment

The management of an individual with an ACL injury aims to reduce pain and instability and restore the function of the knee. Structured rehabilitation is always essential, regardless of subsequent treatment. The first weeks focus on resolving the inflammatory process and restoring range of motion. During the following months, it is important to restore neuromuscular control by improving muscle strength, stability and proprioception. The last phase of rehabilitation concentrates on a return to the previous level of activity, while also minimizing the risk of re-injury and other complications. The length of each phase and the total duration of rehabilitation before the individual is ready to return to training or competition remains controversial, but a total of six to 12 months in total is common.[98, 200] In addition to structured rehabilitation, treatment options include both surgical reconstruction and non-surgical treatment, which always needs to be tailored to suit the individual. From a scientific point of view, it remains unclear whether stabilizing the knee surgically produces any benefit over non-surgical interventions.[109]

Non-surgical treatment is a common option for an individual with a sedentary lifestyle who is willing to accept occasional instability. Non-surgical treatment does not, however, imply that an active lifestyle or aspirations in sports are unattainable. Patients who choose non-surgical treatment can reach an activity level of recreational sports or competitive individual sports such as cycling, running and cross-country skiing.[96] It is also possible, at least in the short and mid-term, to reach a competitive level in team sports such as soccer and handball.[142, 172] Still, there is concern that a non-surgically treated patient will experience more recurrent episodes of giving-way that will traumatize intra-articular structures and cause progressive degeneration.[110]

Surgical treatment

In general, surgical reconstruction is recommended for an athletic individual with a high activity level and an obvious need for satisfactory knee function. In the general population of Scandinavia (Sweden, Norway and Denmark), the annual incidences of primary ACL reconstructions range from 32 to 38 per 100,000 inhabitants, which means that approximately 50% of the patients with an ACL injury choose to undergo reconstruction.[67] In contrast, the corresponding figure from the Multicenter Orthopaedic Outcomes Network (MOON) in the United States has been estimated to be 90%.[115]

Today, surgical treatment is normally performed using arthroscopic reconstruction of the ACL using a tendon autograft or allograft. Graft selections most commonly include a hamstring tendon (HT) autograft or a bone-patellar tendon-bone (PT) autograft.[185] In the whole of Scandinavia, HT autografts are the most frequent graft selections.[67] Surgical ACL reconstruction improves knee function for patients with disabling instability and recurrent episodes of giving-way and most patients are able to return to their pre-injury activity level in the short term,[140] but satisfactory results are also attainable in the long term.[162] Surgical treatment reduces the risk of re-injuries and the number needed to treat (NNT) to prevent one re-operation is approximately 5.[40] Surgery is, however, associated with a risk of complications, such as technical failure, nerve injury, infection, deep vein thrombosis and pulmonary embolism.[200]

1.2.3 Complications after ACL injury

Meniscal and chondral injuries

ACL injury is closely associated with meniscal and chondral injuries.[64, 66] Meniscal and chondral injuries arise as a result of the grinding actions of the femoral condyles on the tibial plateau during axial and rotational loading, which is aggravated by the increased anterior-posterior tibial laxity in the ACL-deficient knee. Intra-articular damage can occur at the time of acute injury, as well as progressively over time in the unstable knee with recurrent microtrauma[32, 49, 66, 139] and altered synovial fluid constituents.[123, 160] Meniscal and chondral injuries are registered in approximately 40% and 25% respectively of all patients at the time of ACL reconstruction in Scandinavia where the median injury-to-surgery interval varies between seven and 10 months.[67]

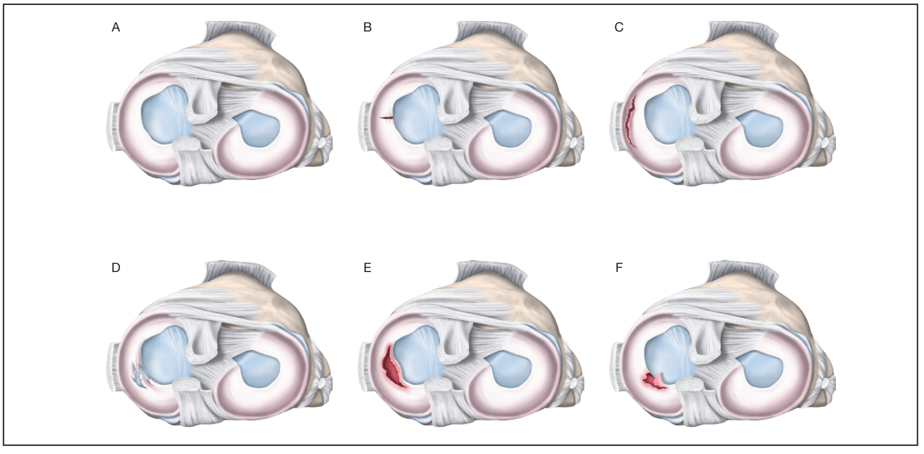

Figure 6. Meniscal injuries
A) Normal menisci. B) Radial tear. C) Longitudinal tear.
D) Degenerative tear. E) Bucket handle tear. F) Flap tear. Copyright © Daniel Andernord

Meniscal injury is associated with pain and functional impairment and is sometimes accompanied by a lack of full extension.[89] Longitudinal tears and flap tears in the posterior and middle-thirds are the most commonly encountered meniscal injuries.[204] Some of these injuries can be managed with structured rehabilitation and non-surgical treatment. The decision to proceed with surgical treatment is based on the patient's symptoms and functional impairment, as well as the type and size of the tear. The surgical treatment of meniscal injuries includes repair, partial or total meniscectomy and transplantation, which is followed by at least six months of rehabilitation.[23]

Concomitant chondral injuries are frequently located in the medial tibiofemoral compartment, especially on the medial femoral condyle.[80, 204] There are several classification systems for chondral injuries, including the widely used classifications by Outerbridge[156] and Noyes and Stabler.[147] Today, many studies use the International Cartilage Repair Society (ICRS) Hyaline Cartilage Lesion Classification System,[25] in which lesions are graded as ICRS 0 to 4, based on depth. Grades 1 and 2 (less than 50% of the cartilage thickness) account for approximately two thirds of the chondral injuries seen in conjunction with ACL injuries.[204] Focal injuries can be treated surgically by opening the subchondral space, which aims to imitate the vascular tissue inflammatory response including the release of mesenchymal cells. Other techniques include osteochondral allograft and autografts and autologous chondrocyte cultures.

Previous investigations have identified patient age,[204] return to a pivoting sport[142] and the injury-to-surgery interval[31, 32, 48, 66, 91, 204, 206] to be associated with meniscal injury, while patient age,[204] tear[114] or loss[139] of the meniscus, injury-to-surgery interval[66, 114, 204] and meniscectomy[171] have been shown to be associated with chondral injury. Although treatable to some extent, meniscal and chondral injuries are important to prevent,[203] since they are closely associated with worse patient-reported outcome,[177, 179, 190, 202] motion deficits,[89] longer rehabilitation,[133] development of osteoarthritis,[110, 127, 170] and because treatment strategies have not been shown to lower the risk of progressive joint degeneration.[36, 64, 132, 162]

Osteoarthritis of the knee

Osteoarthritis is a condition characterized by a generalized joint failure, where all the tissues of the joint are affected by deterioration. Symptoms include swelling, reduced range of motion and pain. Osteoarthritis of the knee is, in fact, the leading cause of knee-related pain and disability in older adults.[159, 231] More importantly, patients who have sustained an ACL injury run a considerable risk of developing post-traumatic osteoarthritis of the knee and show the first signs of radiographic joint space narrowing at the age of approximately 40 years,[170] which means that they are 15 to 20 years younger than patients with primary osteoarthritis.

Ten to 20 years after an ACL injury, the incidence of radiographic osteoarthritis has been estimated to be 70%,[64] although a more recent review suggests a lower rate of approximately 50%.[110] Contrasting estimations can be explained in part by the considerable difference in the risk of osteoarthritis between isolated and combined ACL injuries[234, 235] and the fact that there is no gold standard for the radiological assessment of knee osteoarthritis. Numerous classifications have been proposed, of which Fairbank,[47] Kellgren and Lawrence,[92] Ahlbäck,[1] IKDC[73] and the Osteoarthritis Research Society International (OARSI) atlas[4] have provided some of the more commonly used. In spite of this, a plain radiograph of the weight-bearing knee with measurements of joint space width is the common denominator among the available assessments tools and is in fact recommended by the OARSI-OMERACT initiative.[155]

Figure 7. Osteoarthritis of the knee after ACL injury
A 36-year old female basketball player who sustained an ACL injury and lateral meniscal and chondral injuries. Five years after ACL reconstruction, the radiograph showed moderate tibiofemoral osteoarthritis in the lateral compartment. Copyright © Jüri Kartus

There is another issue with regard to assessing osteoarthritis in studies, namely the lack of correlation between radiographic signs and clinical symptoms.[236] This issue was already the subject of discussion in the late 1960s.[205] So, is it possible to predict the patient's symptoms on the basis of the radiographic findings and vice versa? In all likelihood, the answer to this question is "No".[45, 142, 144, 162, 216] As long as this correlation is weak or moderate at best, it is probably best to regard radiographic signs and clinical symptoms as two distinctly different yet complementary outcome measures in the assessment of osteoarthritis.

In the ACL-deficient knee, the medial

meniscus takes on a very important role of restraining anterior-posterior laxity,[103, 193] which protects the hyaline cartilage from excessive shear forces.[139] Today, meniscal injury and meniscectomy are well-known predictors of knee osteoarthritis,[117] which was originally reported by Fairbank[47] almost 70 years ago. The treatment of ACL-injured patients aims, in part, to re-stabilize the knee and protect the menisci and hyaline cartilage from such secondary injuries. The best way to achieve this remains controversial.[109] Recent studies indicate that surgical treatment may be superior to non-surgical treatment with regard to preventing further injury to intra-articular structures.[40, 66] For reasons not yet entirely understood, ACL reconstruction does not appear to prevent the development of osteoarthritis of the knee.[110, 132, 216] For physicians working in the field of family medicine, the prevention and treatment of joint failure is as imperative as that of any other organ failure.

Graft injury

Re-injury of the reconstructed knee is a matter of great concern to both patients and health-care professionals. This frequently also applies to sports clubs, managers and fans.[84] For patients who, after a period of rehabilitation and careful consideration, choose to undergo the ACL reconstruction of their symptomatic knee, a re-injury might be emotionally devastating. For physicians and physical therapists, graft failure is sometimes regarded as the equivalent to treatment failure. Sporting activities at the time of injury are most common[107] and factors that have been associated with graft injury are patient age,[191] graft selection,[52] knee laxity[162] and a return to pivoting sports.[191]

The exact rate of graft injury is of course difficult to determine, because many individuals do not seek clinical consultation. Of those that actually do, many are not registered in any type of registry or study. There are, of course, numerous reasons for not consulting health care. Many individuals cope with occasional giving-way and instability, or are no longer active at the same level as they were at the time of their primary injury and might not be bothered by a subsequent graft rupture. Moreover, the proportion of individuals who sustain graft injuries is largely dependent on the length of follow-up after ACL reconstruction. Many studies report on "graft failure", which includes both subjective and objective outcome measures. Revision surgery is possibly a preferred outcome measure, because it is a firm end point and presumably represents a more accurate proportion of individuals with clinically relevant and disabling symptoms of graft insufficiency who wish to regain their previous level of activity.

The proportion of individuals who have sustained a graft injury has been estimated to be 2-4% at two years,[42, 46, 52, 102, 221] 4-6% at five years[182, 191] and 11% at seven years[184] and ten years[162] respectively. Graft failure is, however, most likely to occur during the first year following index reconstruction.[182] These failures probably occur owing to the relative weakness associated with the complex process of graft incorporation,[35, 124] which possibly takes up to three years, although the reconstructed graft has achieved sufficient capacity for most activities by one year after index reconstruction.[124, 154, 175, 182]

In contrast, the proportion of revision surgery in different studies is 2% at one year,[112] 3% at two years,[107] 10% at seven years[184] and 8% at ten years.[162] Revision surgery is most commonly performed during the first two years after index reconstruction.[209] Unfortunately, the outcome of revision surgery is less beneficial compared with index ACL reconstruction with regard to patient-reported outcome,[107, 183] laxity,[37] failure rate[183] and return to previous activity level.[107] For this reason, preventing this complication is an important objective.

Contralateral ACL injury

After ACL reconstruction, fear of a new injury includes not only the rupture of the newly implanted graft but also a tear to the intact ACL in the contralateral knee. Patient sex,[191] patient age,[162] previous ACL injury,[154] graft selection[162] and a return to moderate or strenuous activities[182] have been suggested as potential predictors of contralateral ACL injuries, which tend to occur during the first three years after index reconstruction.[162, 182, 191] Most of these injuries are sustained during participation in the same sporting activity as the index injury.[162, 182, 184, 191] Studies examining contralateral ACL injuries have reported a cumulative proportion of 3-4% at two years,[12, 34, 221] 5-6% at five years,[182, 191] 14% at seven years[169] and 16% at ten years.[162]

Like revision surgery, contralateral ACL reconstruction is an important outcome measure complementing the rate of injury, in view of the fact that it is a well-defined end point reflecting an individual with enough symptom severity to convince the patient, physiotherapist and surgeon to agree that reconstruction is the best hope of attaining improved knee function when structured rehabilitation has not achieved satisfactory results. However, little is actually known about the rate of contralateral ACL reconstruction, but it has been shown to be 3% at two years.[221] Injury to the intact ACL in the contralateral knee, like all other complications, is vital to prevent, because it too often signals the beginning of the end of a promising career.[5]

1.2.4 Prevention of ACL injury

Looking at ACL injury and its complications from another perspective, it seems only natural to ask a simple question: is it possible to prevent ACL injuries from occurring and re-occurring? The current literature shows that preventive strategies have focused on injuries among soccer and handball players.[141, 153, 167]

In a randomized controlled trial, Soligard et al.[197] implemented a 20-minute injury prevention programme among adolescent female soccer players with special emphasis on compliance. The study failed to demonstrate a significant reduction in knee injuries between the intervention and the control group (3.1% vs. 5.6%, RR=0.6 [95% CI, 0.4-1.1], p=0.079). In addition, Gilchrist et al.[63] studied female soccer players in a randomized controlled trial and designed a warm-up routine focusing on optimizing strength and neuromuscular coordination performed three times a week during the regular season. In overall terms, this did not result in significantly fewer ACL injuries. Nonetheless, the intervention significantly reduced the number of primary ACL injuries in practice sessions compared with matches. It also significantly reduced non-contact ACL injuries among participants with a history of previous ACL injury.

In contrast, two meta-analyses have reported positive results, with a decrease in the rate of ACL injuries, after implementing a neuromuscular and proprioceptive training program. Hewett et al.[76] performed a meta-analysis of interventions of this kind among female athletes active in soccer, handball, basketball and volleyball and found an overall reduction in ACL injuries in favor of prevention programs (OR=0.4 [95% CI, 0.3-0.6]). Another meta-analysis by Prodromos et al.[163] also reported a reduction of 0.24 ACL tears per 1,000 exposures among both male and female soccer players. So, to some extent, it seems possible to prevent ACL injuries from occurring and re-occurring.

1.3 REVIEW OF THE LITERATURE

1.3.1 Health Technology Assessment

Health Technology Assessment (HTA) refers to a systematic and multidisciplinary evaluation of health-care interventions developed to solve a health problem. These continuous, structured assessments of evidence are crucial in order to enhance the rational use of health interventions and determine whether and when these interventions should be integrated into health-care systems, as the efficient use of resources is the most crucial factor in the sustainability of health-care systems.[219]

Consequently, the World Health Organization (WHO) has approved a resolution which urges all member states to consider establishing national monitoring systems for health interventions, such as national quality registries, and national health technology assessment organizations.[220] In this respect, Sweden is at the forefront, as it was the first country in the world to initiate a national quality registry in 1975, the Swedish Knee Arthroplasty Register, as well as an HTA organization in 1989, the Swedish Council on Health Technology Assessment (SBU).[86]

With the aim of identifying similar previous, ongoing or planned projects investigating complications after ACL injury and identifying possible knowledge gaps and literature conflicts, a search for relevant HTA reports was carried out by consulting SBU as well as the two largest HTA organizations in the world, the Cochrane Collaboration and the National Institute for Health Research.

Swedish Council on Health Technology Assessment

A search of this HTA database did not yield any records of reports pertaining to ACL injuries.

The Cochrane Collaboration

The Cochrane Database of Systematic Reviews (CDSR) is available in the Cochrane Library provided by the Cochrane Collaboration. A search of the CDSR produced four relevant systematic reviews issued by the editorial group, the Cochrane Bone, Joint and Muscle Trauma Group. The systematic review by Linko et al.[109] of the surgical versus the non-surgical treatment of ACL ruptures was based on two randomized trials of poor quality conducted in the early 1980s. The remaining systematic reviews relating to meniscal injuries[81] and rehabilitation[212, 214] had all been withdrawn because they were regarded as substantially out of date.

National Institute for Health Research

The Database of Abstracts of Reviews of Effects (DARE) is produced by the Centre for Reviews and Dissemination and provided by the National Institute for Health Research (NIHR) in the United Kingdom. The DARE contains systematic reviews that evaluate the effects of health-care interventions and the delivery and organization of health services. The DARE is an important complement to the CDSR, because it includes systematic reviews that are not issued by the Cochrane Collaboration.

A search of the DARE produced six relevant systematic reviews. Four of them focused on graft selection in ACL reconstruction[17, 51, 75, 228] and two on aspects of rehabilitation after ACL reconstruction.[194, 222] The literature searches in four of these systematic reviews,[51, 75, 222, 228] although pertinent to the aim and research question, were regarded as out of date. There were no assessments of meniscal and chondral injuries, revision surgery or contralateral ACL reconstruction.

1.4 RATIONALE FOR THIS THESIS

Complications are by nature troublesome. One way to help our patients to overcome this fate is to prevent the complications from occurring in the first place. Prevention is possibly the best intervention there is, for both primary ACL injuries and subsequent complications. Strategies should focus on factors that make certain individuals susceptible to certain complications.

In order to implement both effective and efficient prevention interventions, the essential first step is to obtain knowledge of factors associated with the risk of complications after ACL injury. Currently, no HTA reports on predictors of complications after ACL injury are available. After a thorough review of the literature and recognizing the significant contribution of systematic reviews and registry-based cohort studies to new evidence, it was decided that there was a need for updated systematic reviews that could act as a platform upon which further studies could be based. Furthermore, a need for cohort studies based on large patient samples from the Swedish National Knee Ligament Register focusing on predictors of complications after ACL injury was identified.

"Nothing contributes so much to tranquillize the mind as a steady purpose, a point on which the soul may fix its intellectual eye."

Mary Shelley

Two

AIM

The aim of this thesis was to investigate patient- and health care-related factors and identify possible predictors of meniscal or chondral injuries, as well as the need for revision surgery and contralateral ACL reconstruction.

2.1 STUDY I

The aim of Study I was to investigate whether non-surgical or surgical treatment, the timing of surgical treatment, graft tension, ligament augmentation, graft fixation, a post-operative knee brace, the timing of post-operative rehabilitation, home-based or supervised rehabilitation and open kinetic chain or closed kinetic chain exercises were associated with meniscal and chondral injuries, revision surgery and contralateral ACL reconstruction.

2.2 STUDY II

The aim of Study II was to investigate whether graft selection, harvest site and single-bundle or double-bundle reconstruction were associated with meniscal and chondral injuries, revision surgery and contralateral ACL reconstruction.

2.3 STUDY III

The aim of Study III was to investigate whether the timing of surgical treatment was associated with meniscal and chondral injuries.

2.4 STUDY IV

The aim of Study IV was to investigate whether graft selection, graft width, single-bundle or double-bundle reconstruction, graft fixation, the timing of surgical treatment or meniscal and chondral injuries were associated with revision surgery.

2.5 STUDY V

The aim of Study V was to investigate whether patient sex, age, height, weight, body mass index, use of tobacco and activity at the time of injury were associated with revision surgery.

2.6 STUDY VI

The aim of Study VI was to investigate whether patient sex, age, activity at the time of injury, the timing of surgical treatment, graft selection, harvest site or meniscal and chondral injuries were associated with contralateral ACL reconstruction.

"It is common sense to take a method and try it. If it fails, admit it frankly and try another. But above all, try something."

Franklin D. Roosevelt

Three

METHODS

3.1 DATA SOURCES

3.1.1 PubMed

PubMed is a free search engine developed and maintained by the National Center for Biotechnology Information, which is a division of the United States National Library of Medicine at the National Institute of Health. First initiated in 1966, it was not until 1997 that it was made freely available on the internet. Currently, it comprises more than 24 million citations and abstracts relating to biomedical literature indexed in the Medical Literature Analysis and Retrieval System Online (MEDLINE) database, life science journals and online books, which primarily provide information on biomedicine and health. New citations are assigned a PubMed ID (PMID) and become available in PubMed within 48 hours after the publishers of journals have submitted citation and abstract data electronically. All citations in MEDLINE, which is the central component of PubMed, are indexed with the Medical Subject Headings (MeSH) thesaurus. However, the indexing process is performed manually and takes up to a few months after submission. This is why PubMed also contains in-process citations which provide records for articles before they are indexed and then added to MEDLINE.[28]

3.1.2 Excerpta Medica Database

The Excerpta Medica Database (EMBASE) is provided by the European publisher Elsevier and requires a subscription for access. The EMBASE covers the biomedical literature, with an in-depth focus on pharmacology, and it is indexed with Elsevier's thesaurus, Emtree, but allows for search queries with MeSH terms as well. Currently, the database contains more than 28 million records from approximately 8,400 journals. It covers all of MEDLINE but does not contain PubMed's other contents.

3.1.3 Cochrane Central Register of Controlled Trials

The Cochrane Central Register of Controlled Trials (CENTRAL) is a bibliographic database comprising randomized and non-randomized controlled trials retrieved from pertinent bibliographic databases through the extensive handsearching of relevant journals or conference proceedings, reference lists of articles and consulted trialists and experts, all of which have been identified by the Cochrane Collaboration's respective editorial groups during their work on systematic reviews. The CENTRAL is therefore a very important complement to searches in electronic bibliographic databases.

3.1.4 The Swedish National Knee Ligament Register

The Swedish National Knee Ligament Register[211] is a national quality registry which gathers information on patients with ACL injuries and associated knee surgery. It was initiated on 1 January 2005, with the primary aim of monitoring the development of treatment of individuals with ACL injuries, in addition to continuous reporting to healthcare providers. Patient data and surgical treatment data are registered online at baseline. Follow-ups are administered exclusively by obtaining patient-reported outcome measures one, two, five and 10 years after ACL reconstruction. There are no clinical follow-ups. Events of associated knee surgery, such as revision surgery or contralateral ACL reconstruction, are, however, registered continuously with the same completeness as index events. Participation in the Swedish National Knee Ligament Register is voluntary for patients and surgeons, owing to the fact that there is no legislation making participation or data input mandatory.

The coverage (proportion of participating units in relation to all eligible units) and completeness (proportion of target population in the registry) are 92.9%[43] and 89.4%[208] respectively. Every patient is identified by his/her unique Swedish Personal Identity Number.[111] Currently, the Swedish National Knee Ligament Register is one of three Scandinavian ACL registries which, according to Engebretsen and Forssblad,[44] serve three basic purposes: the improvement of treatment outcomes via feedback to health care, the detection of procedures and devices that result in early failure and the identification of factors associated with good and poor outcomes.

3.2 STUDY DESIGN

3.2.1 Systematic review

A systematic review is a structured literature review addressing a specific question that is to be answered by analysis of evidence. A systematic review is distinguished from a *literature review* or *overview* by an objective literature search, study selection based on predetermined inclusion and exclusion criteria, standardized data extraction, a quality appraisal of included studies and, finally, a synthesis of data from the included studies. In a systematic review, it is essential that all studies, regardless of positive, negative or inconclusive results, are eligible for inclusion.

The Cochrane Collaboration is a renowned producer and publisher of high-quality systematic reviews in most fields of medicine. The Cochrane Handbook for Systematic Reviews of Interventions[78] or the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[134] provide thorough guidelines for the reporting of data in a systematic review. The Assessment of Multiple Systematic Reviews (AMSTAR)[189] is a useful tool when it comes to assessing the quality of the systematic review in itself. According to the Swedish SBU, the oldest health technology assessment organization in the world, a systematic literature search in the three databases, PubMed, EMBASE and the Cochrane Library, is sufficient for research questions pertaining to biomedical research.[187] Due to the fact that a systematic review accumulates studies, aggregates and analyzes all data and produces new results and conclusions, it is always more than the sum of its parts.

Meta-analysis vs. data-synthesis

In principle, there are two ways of analyzing data in a systematic review: the *meta-analysis* and the *data-synthesis* or *best-synthesis* approach. The decision to perform either one is based on the heterogeneity of the included studies. A meta-analysis with statistical analysis of aggregated data is often preferable, but it is only attainable when certain criteria are met, e.g. homogeneity of participants, interventions, comparisons, outcomes and settings. As a result, a meta-analysis obtains a quantitative estimate of the overall effect of a variable on a defined outcome.

In contrast, the data-synthesis approach is used when an area of research contains studies with a wide variety of study methods that are not suitable for traditional statistical modeling. As a result, the data-synthesis method produces a qualitative estimate of the effect of a variable on a defined outcome. It is very important to report these results in order to implement harmonizing improvements in a field of research. Consequently, the meta-analysis and data-synthesis approaches are two distinctly different, yet complementary and equally important ways of conducting a systematic review.

Precision and efficacy vs. recall and effectiveness

Another important aspect of a systematic review is the scope of the literature search. The optimal search strategy would naturally identify all relevant studies and nothing but relevant studies. In reality, this never happens. In principle, the focus of a literature search can be broad or narrow, and this is often a matter of resources.

The result of a literature search can be described using the following terms: precision and efficacy vs. recall and effectiveness. Precision refers to the proportion of *relevant* records in relation to the total number of *all* records. In contrast, recall refers to the proportion of *relevant* records in relation to the total number of *relevant* records. A broad literature search takes account of the fact that studies may have varying index terms, inadequate indexing or a complete lack of indexing. The aim of a broad literature search is high recall, i.e. finding as many as possible of all the studies that answer the research question. A broad search does not guarantee high recall, but it most certainly improves the chances.

A narrow literature search yields fewer records, which is time saving, and will hopefully produce many relevant records, i.e. high precision. On the other hand, the narrow search will probably fail to generate a considerable part of the relevant literature. In general, a narrow literature search is not sufficient for the purpose of a *systematic review* but may be adequate for a *literature review*. In conclusion, a broad literature search improves recall and effectiveness, whereas a narrow literature search will hopefully improve precision and efficacy.

3.2.2 Cohort study

A cohort study is a controlled prospective observational study (investigators do not intervene or manipulate the sample, exposure or setting), where outcomes in a group with a given exposure (e.g. environmental factors or an intervention) are compared with outcomes in a similar group without the exposure. Data are gathered at baseline, after which the two groups are followed forward in time until a follow-up assessment is carried out and the outcomes are compared. As such, a cohort study leads from exposure to outcome and allows for estimations of incidence, risk and number needed to treat.

It is essential to distinguish a cohort study from a *non-randomized controlled trial,* a *case-control study* and a *case series,* which are fundamentally different in terms of methodology, temporality, statistical analysis, causality and level of evidence. Cohort studies can be subject to selection bias, which occurs when there are differences between the study groups in the distribution of known or unknown factors in ways that can affect the outcomes. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement[215] provides guidelines for reporting observational studies.

Registry-based cohort study

A cohort study based on registry data is a special cohort study design. Sweden is well known for its high-quality national quality registries.[41, 43] Registries generally contain large patient samples with a representative cross-section of a real-world patient population compared with randomized controlled trials (RCTs), which increases statistical inference and generalizability (high external validity), but might reduce the confidence of the estimate (low internal validity). Even though the study per se starts after data collection, it is neither considered retrospective nor subject to recall bias, owing to the fact that the data are registered prospectively.

The registry-based design helps to reduce possible detection bias, because patients and assessors, although aware of a given exposure, are not aware of future study objectives and outcome measures. Furthermore, the completeness of the registry helps to manage possible attrition bias, where a high level of completeness reduces attrition bias. Due to these properties, registry-based cohort studies are very useful in determining the rate of adverse events which can be detected long before any interventional study would have detected them.[44]

3.3 ASSESSMENT OF RISK OF BIAS

Bias refers to a *systematic error* in an observation which increases the risk that a study will overestimate or underestimate the true effect of an exposure.[78] As such, bias may arise from any factor other than the exposure of interest that systematically distorts the magnitude of an estimate from the true effect. In this way, bias limits the accuracy or validity of the estimate. Bias does not, however, limit the precision or reliability of the estimate, since the precision is the extent to which the estimate is free from *random error*. The precision is represented by the confidence interval. A wide confidence interval reflects imprecision but not inaccuracy. Moreover, a particular source of bias may vary in both direction and magnitude, e.g. a reduction in internal validity but an increase in external validity, or lead to underestimation in one study but overestimation in another study. The results of a study might even be unbiased, despite methodological flaws.

In a systematic review, it is important always to assess the potential risk of bias, because this can help to explain variations in the results of the included studies. However, homogeneous results between studies do not automatically imply unbiased methodology, since all the studies may in fact be flawed. The conclusion in a systematic review must therefore be carefully assessed with regard to the methodological quality of the included studies from which the conclusion is drawn.

In general, there are five categories of bias: selection bias, performance bias, detection bias, attrition bias and reporting bias (Table 1). There are, however, other kinds of bias that do not fit into these categories.

Table 1. Categories of bias[78]

Category	Definition	Examples of determinants
Selection bias	Systematic differences in baseline characteristics between study groups	Sequence generation Allocation concealment
Performance bias	Systematic differences in interventions or other exposures between study groups	Blinding of participants Blinding of personnel Number of care givers Experience of care givers Rescue therapies Spillover of participants Crossover of participants Study protocol does not reflect clinical practice
Detection bias	Systematic differences in outcome assessments between study groups	Blinding of assessors Blinding of statisticians Diagnostic activity
Attrition bias	Systematic differences in withdrawals between study groups	Incomplete outcome data Loss to follow-up Exclusion of participants
Reporting bias	Systematic differences in reported and unreported findings between study groups	Selective outcome reporting

3.4 ASSESSMENT OF LEVEL AND QUALITY OF EVIDENCE

The levels and quality of evidence applied in this thesis are the classification systems presented by the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence Working Group[151] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group[207] respectively. These two classification systems categorize the evidence based on careful considerations of study design, risk of bias (accuracy), precision of the estimate (reliability), consistency of the results across studies, directness of the inference and effect size, but they serve different purposes. The OCEBM levels of evidence are used to grade a single study, whereas GRADE is used to grade each outcome. As a result, within a single study (OCEBM I-V), the quality of each outcome may differ (GRADE A-D). Brief summaries of the categories in each classification are presented in Tables 2 and 3.

Table 2. OCEBM Levels of Evidence[151]	
Ia Ib	Systematic review of RCTs (with level of evidence I) Individual RCT
IIa IIb	Systematic review of RCTs (level of evidence II) or cohort studies Individual RCT (level of evidence II) or cohort study
IIIa IIIb	Systematic review of case-control studies Individual case-control study
IV	Case series or poor-quality cohort studies and case-control studies
V	Expert opinion without explicit critical appraisal

Table 3. GRADE Quality of Evidence[207]	
A	Further research is very unlikely to change our confidence in the estimate of effect
B	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
C	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
D	Any estimate of effect is very uncertain

3.5 STUDY I

Study design

Systematic review of RCTs (OCEBM IIa)

Study protocol

The CONSORT statement[135] guided the quality appraisal and reporting of data.

Patients and methods

The electronic literature search was carried out using PubMed in April 2007, with an updated search in March 2009. English-language, randomized controlled trials (OCEBM Ib and IIb) published between 1 January 1995 and 20 March 2009 were eligible for inclusion. Records were screened by reading the title and abstract and study selection was based on predetermined inclusion and exclusion criteria. The investigated variables were surgical or non-surgical treatment, timing of surgical treatment, graft fixation, graft tension, ligament augmentation, post-operative knee brace, timing of rehabilitation, home-based or supervised rehabilitation and open kinetic chain or closed kinetic chain exercises. For exclusion criteria, see Study I.[9] A standardized data extraction sheet was used for the purpose of data extraction. The quality appraisal was based on the CONSORT statement. Levels of evidence were based on the Oxford 2009 Levels of Evidence.[150] Data analysis was performed using the data-synthesis approach.

Search string

"anterior cruciate ligament"[Major topic] AND ("1995/01/01"[PDAT]: "2009/03/20"[PDAT]) AND English[lang] AND Randomized Controlled Trial[ptyp]

Outcome measures

The outcome measures were meniscal and chondral injuries and surgery, osteoarthritis, revision surgery and contralateral ACL reconstruction.

3.6 STUDY II

Study design

Systematic review of RCTs (OCEBM IIa)

Study protocol

The CONSORT statement[135] guided the quality appraisal and reporting of data.

Patients and methods

The electronic literature search was carried out using PubMed in April 2007, with an updated search in March 2009. A broad literature search was performed to improve search recall. Only English-language, randomized controlled trials (OCEBM Ib and IIb) published between 1 January 1995 and 20 March 2009 were eligible for inclusion. Records were screened by reading the title and abstract and study selection was based on predetermined inclusion and exclusion criteria. The investigated variables were graft selection, harvest site and single-bundle or double-bundle reconstruction. For exclusion criteria, see Study II.[186] A standardized data extraction sheet was used for the purpose of data extraction. The quality appraisal was based on the CONSORT statement. Levels of evidence were based on the Oxford 2009 Levels of Evidence.[150] Data analysis was performed using the data-synthesis approach.

Search string

"anterior cruciate ligament"[Major topic] AND ("1995/01/01"[PDAT]: "2009/03/20"[PDAT]) AND English[lang] AND Randomized Controlled Trial[ptyp]

Outcome measures

The outcome measures were meniscal and chondral injuries and surgery, osteoarthritis, revision surgery and contralateral ACL reconstruction.

3.7 STUDY III

Study design

Systematic review of RCTs, cohort studies and prognostic studies (OCEBM IIa)

Study protocol

The PRISMA statement[134] and the Cochrane Handbook for Systematic

Reviews of Interventions[78] guided the reporting of data and quality appraisal.

Patients and methods

The electronic literature search was carried out using PubMed, EMBASE and CENTRAL in October 2011. A broad literature search was performed to improve search recall and effectiveness. All English-language articles (OCEBM Ib and IIb) published between 1 January 1995 and 31 August 2011 were eligible for inclusion. To assess data on the timing of surgical treatment, all records were screened by reading the title, abstract, methods and results. Study selection was based on predetermined inclusion and exclusion criteria. The investigated variable was the time interval between ACL injury and ACL surgery (the injury-to-surgery interval). Original study data were obtained from respective journals where available. For exclusion criteria, see Study III.[8] A standardized data extraction sheet was used for the purpose of data extraction according to the PRISMA checklist. The level of evidence was based on the Oxford 2011 Levels of Evidence.[151] Data analysis was performed using the data-synthesis approach.

Search string

("Anterior Cruciate Ligament"[Mesh] OR "anterior cruciate ligament"[tiab] OR ACL[tiab]) AND ("Surgical Procedures, Operative"[Mesh] OR surgical[tiab] OR surgery[tiab] OR reconstruction[tiab] OR reconstructive[tiab] OR reconstructed[tiab]) AND (English[lang] AND ("1995"[PDAT] : "3000"[PDAT]))

Outcome measures

The outcome measures were meniscal and chondral injuries and surgery as well as osteoarthritis of the knee.

3.8 STUDY IV

Study design

Registry-based cohort study (OCEBM IIb)

Study protocol

The STROBE statement[215] guided the reporting of data.

Patients and methods

Patient data were extracted from the Swedish National Knee Ligament Register. Patients registered for index (primary ipsilateral) ACL reconstruction between 1 January 2005 and 31 December 2009 and registered for revision surgery between 1 January 2005 and 31 December 2011 were assessed for eligibility. Only patients who underwent index ACL reconstruction with an HT autograft or a PT autograft were included. Follow-up started on the date of index ACL reconstruction and ended with revision surgery, after 24 months of follow-up or on 31 December 2011, whichever occurred first. The investigated variables were the timing of surgical treatment, graft selection, graft width, single-bundle or double-bundle techniques, graft fixation, and meniscal or chondral injuries.

Outcome measure

The study end point was the two-year risk of revision surgery.

3.9 STUDY V

Study design

Registry-based cohort study (OCEBM IIb)

Study protocol

The STROBE statement[215] guided the reporting of data.

Patients and methods

Patient data were extracted from the Swedish National Knee Ligament Register. Patients registered for index (primary ipsilateral) ACL reconstruction between 1 January 2005 and 31 December 2011 and registered for revision surgery between 1 January 2005 and 31 December 2013 were assessed for eligibility. Only patients aged 13 to 59 years who underwent index ACL reconstruction with an HT autograft or a PT autograft were included. Patients with concomitant fractures and ligament injuries were excluded. Follow-up started on the date of the index ACL reconstruction and ended with revision surgery, after 24 months of follow-up or on 31 December 2013, whichever occurred first. The investigated variables were activity at the time of injury, patient sex, patient age, body height, body weight, body mass index (BMI) and the use of tobacco. Males and females were expected to differ significantly in terms of demographics and anthropometric data and were therefore analyzed separately.

Outcome measure

The study end point was the two-year risk of revision surgery.

3.10 STUDY VI

Study design

Registry-based cohort study (OCEBM IIb)

Study protocol

The STROBE statement[215] guided the reporting of data.

Patients and methods

Patient data were extracted from the Swedish National Knee Ligament Register. Patients registered for index (primary ipsilateral) ACL reconstruction between 1 January 2005 and 31 December 2008 and registered for contralateral ACL reconstruction between 1 January 2005 and 31 December 2013 were assessed for eligibility. Patients aged 13 to 59 years who underwent index ACL reconstruction with an HT autograft or a PT autograft were included. Patients with concomitant fractures and ligament injuries were excluded. Follow-up started on the date of the index ACL reconstruction. Follow-up ended with contralateral ACL reconstruction, after five years of follow-up or on 31 December 2013, whichever occurred first. The investigated variables were patient sex, patient age, activity at the time of injury, the timing of surgical treatment, graft selection, graft harvest site and meniscal and chondral injuries. Soccer, basketball, floorball, handball, volleyball and racket sports were grouped and analyzed as "cutting/pivoting" activities. Sex-specific results were of special interest and male and female participants were expected to differ significantly in terms of demographics and anthropometric data and were therefore analyzed as separate samples.

Outcome measure

The study end point was the five-year risk of contralateral ACL reconstruction.

3.11 STATISTICS

Tables and diagrams were generated using Microsoft Excel® (Microsoft Corp, Redmond, Washington, USA). Statistical analysis was performed using SPSS® Statistics (IBM, Armonk, New York, USA) and Stata® (StataCorp LP, College Station, Texas, USA). Data were characterized according to the level of measurement.[201] Ratio scale data were stratified into ordinal scale data when comparing risk estimates in order to obtain clinically appropriate groups. Arithmetic means of normally distributed continuous data were compared with the independent-samples t-test. The Mann-Whitney U test was used for comparisons of independent non-parametric continuous data. Two-tailed p values for categorical data were calculated using Fisher's exact test and the two-tailed chi-square test with Yates' correction for continuity. The relative risk (RR), its standard error and 95% confidence interval (CI) were calculated according to Altman.[3] Survival functions were analyzed with the Kaplan-Meier estimator. In studies IV-VI, adjusted risk estimates were calculated using a stratified relative risk regression model for binary dependent variables and presented with 95% CIs. Confidence intervals for proportions were calculated with the Agresti-Coull method for the interval estimation of binomial proportions. Where null values caused computational problems in the relative risk or its confidence interval, 0.5 was added to all cells according to Pagano.[157] Statistical significance was defined as a 95% CI for relative risks not including 1.0, as well as $p<0.05$ for comparisons of means and proportions.

3.12 ETHICS

Studies I-III are systematic reviews for which ethical review board consent is not applicable or necessary, as they are based on data from studies for which ethical approval has already been granted. Studies IV-VI were approved by the Regional Ethical Review Board in Stockholm, Sweden. Personal identity numbers were replaced by unidentifiable serial numbers before delivery to investigators in order to ensure the integrity of the participants.

“Everything we hear is an opinion, not a fact. Everything we see is a perspective, not the truth.”

Marcus Aurelius

Four

RESULTS

4.1 MENISCAL INJURY AND SURGERY

Studies I and III identified three controlled clinical trials that compared the non-surgical and surgical treatment of patients with ACL injuries. Frobell et al.[54] reported results from the only RCT (OCEBM Ib). There were no significant differences in meniscal injury or meniscal surgery between the groups at baseline and, if the total number of menisci with surgery at baseline, as well as during follow-up, were combined, the difference was not statistically significant (42% [50/118] vs. 32% [40/124], RR=1.3 [95% CI, 0.9-1.8], p=0.106). However, during the two-year follow-up, the participants randomized to non-surgical treatment reported significantly more signs and symptoms of serious meniscal injury (22% [13/59] vs. 2% [1/62], RR=13.7 [95% CI, 1.8-101.2], p=0.011) and a significantly larger proportion underwent meniscal surgery (32% [19/59] vs. 8% [5/62], RR=4.0 [95% CI, 1.6-10.0], p=0.003) compared with the participants randomized to ACL reconstruction within 10 weeks. In addition, the number of menisci in the index knee that required surgery during follow-up was five times higher among participants randomized to non-surgical treatment (25% [29/118] vs. 5% [6/124], RR=5.1 [95% CI, 2.2-11.8], p<0.001).

Two non-randomized controlled trials (OCEBM IIb) reported similar findings. Fithian et al.[48] reported that participants allocated to non-surgical treatment were more likely to undergo meniscal surgery (20% [29/146] vs. 2% [1/63], RR=12.5 [95% CI, 1.7-89.9], p=0.012), which was also reported by Meunier et al.[132] (35% [18/52] vs. 12% [5/42], RR=2.9 [95% CI, 1.2-7.2], p=0.021) [I, III].

Patients who underwent surgical treatment with different injury-to-surgery intervals were also assessed. Studies I and III identified six controlled trials (OCEBM Ib and IIb) that investigated the timing of surgery as a primary objective, while also analyzing meniscal injury or meniscal surgery. There was a wide variety in the respective classification of early and delayed reconstruction (within two days to five months vs. beyond three weeks to 24 months) and the results with regard to meniscal outcomes were contrasting.

The RCT by Bottoni et al.[21] (OCEBM Ib) reported significantly more meniscal injuries among patients with early ACL reconstruction (94% [32/34] vs. 69% [24/35], RR=1.4 [95% CI, 1.1-1.7], p=0.010). In contrast, the cohort study by Åhlén and Lidén[233] (OCEBM IIb) showed that there was no difference in the number of meniscal injuries, but the need for partial meniscectomy was significantly higher among patients with delayed ACL reconstruction (42% [13/31] vs. 10% [3/30], RR=4.2 [95% CI, 1.3-13.3], p=0.015), whereas three RCTs[122, 129, 165] and one cohort study[83] found no such associations [I, III].

Graft selection between an HT or a PT autograft[12, 13, 46, 70, 106, 149] or the choice between single-bundle or double-bundle reconstruction[87, 88, 137, 225, 226] were not reported to be associated with the risk of meniscal injury or meniscal surgery. Also, graft fixation did not influence meniscal outcomes.[71, 101, 126] Finally, the use of a post-operative brace after surgical treatment with ACL reconstruction did not reduce the risk of meniscal injury or meniscal surgery.[18, 24, 143, 168] None of these studies had performed a sample size calculation with regard to meniscal injury or meniscal surgery [I-III].

4.2 CHONDRAL INJURY AND SURGERY

Patients who underwent surgical treatment but at different time intervals after injury were assessed with regard to chondral injury or chondral surgery. Studies I and III identified four controlled trials (OCEBM Ib and IIb) that investigated the timing of surgery as a primary objective, while also analyzing chondral outcomes. There were three RCTs by Bottoni et al.,[21] Marcacci et al.[122] and Raviraj et al.[165] and one cohort study by Åhlén and Lidén,[233] which consistently found no associations between the timing of ACL reconstruction and chondral injury or chondral surgery. No study had performed a sample size calculation with regard to this outcome. In the study by Raviraj et al.,[165] the authors had performed a sample size calculation for the primary outcome measure, post-operative range of motion [I, III].

Graft selection between an HT or a PT autograft in ACL reconstruction was not found to be associated with the risk of chondral surgery in the RCT by Harilainen et al.[70] (OCEBM IIb) (13% [5/39] vs. 5% [2/40], RR=2.6 [95% CI, 0.5-12.4], p=0.243) [II].

4.3 REVISION SURGERY

Adolescents (participants aged 13 to 19 years) ran a significantly higher two-year risk of revision surgery compared with all other age groups (males: 3.5% vs. 1.3%, RR=2.7 [95% CI, 1.9-3.7], p<0.001 and females: 2.9% vs. 1.3%, RR=2.3 [95% CI, 1.6-3.2], p<0.001) [V]. ACL injury during soccer was also associated with a significantly increased two-year risk of revision surgery compared with all other activities (males: 2.2% vs. 1.4%, RR=1.6 [95% CI, 1.1-2.2], p=0.009 and females: 2.4% vs. 1.7%, RR=1.4 [95% CI, 1.0-2.0], p=0.045) Individuals with a combination of these two factors (adolescents who sustained an ACL injury while playing soccer) ran a further increased risk of revision surgery (males: 4.3% vs. 1.5%, RR=2.9 [95% CI, 1.8-4.6], p<0.001 and females: 4.6% vs. 1.8%, RR=2.6 [95% CI, 1.7-4.0], p<0.001) [V].

For patients who underwent surgical treatment with ACL reconstruction, the timing of surgery,[83, 129] graft selection between an HT autograft or a PT autograft[12, 13, 42, 46, 70, 85, 102, 118, 149, 181, 188, 229] or the choice between single-bundle or double-bundle reconstruction[87, 88] were not found to be associated with the risk of revision surgery. These studies comprised RCTs and non-randomized controlled trials (OCEBM Ib and IIb), but none presented a sample size calculation or adequate power with regard to revision surgery [I-IV].

Moreover, ACL reconstruction with an ST autograft and metal interference screw fixation on the tibia was associated with a significantly lower two-year risk of revision surgery compared with all other graft fixations (1.0% vs. 3.1%, RR=0.3 [95% CI, 0.1-0.9], p=0.031) [IV]. However, two RCTs by Harilainen et al.[71] (OCEBM Ib) and Rose et al.[173] (OCEBM IIb) did not find any differences in the revision surgery rates with regard to the choice of graft fixation between cross-pins or interference screws. Finally, the use of a ligament augmentation device[69] or a post-operative knee brace[18] did not reduce the two-year risk of revision surgery [I].

4.4 CONTRALATERAL ACL RECONSTRUCTION

Patients aged 13 to 19 years ran a significantly higher five-year risk of contralateral ACL reconstruction compared with all other age groups (males: 5.2% vs. 2.2%, RR=2.4 [95% CI, 1.7-3.4], p<0.001 and females: 4.6% vs. 1.6%, RR=2.9 [95% CI, 1.9-4.5], p<0.001) [VI].

Graft selection between an HT autograft or a PT autograft was not associated with the five-year risk of contralateral ACL reconstruction [VI], which was supported by two RCTs[70, 181] (OCEBM IIb) with five-year follow-ups [II].

Among females who underwent ACL reconstruction, harvesting an HT autograft from the contralateral knee significantly increased the five-year risk of contralateral ACL reconstruction compared with an ipsilateral graft harvest (9.4% vs. 2.8%, RR = 3.4 [95% CI, 1.4-7.9], p=0.006). There were no significant associations among females who received a PT autograft or among males [VI].

"The aim of discussion should not be victory, but progress."

Joseph Joubert

Five

DISCUSSION

This doctoral thesis is based on six studies, three systematic reviews [I-III][8, 9, 186] and three registry-based cohort studies [IV-VI][5-7] that investigated predictors of complications after ACL injury. Important findings were that adolescence, injury during soccer, non-surgical treatment and contralateral hamstring tendon harvest at reconstruction were associated with increased risks of complications. Patient-related factors, such as sex, height, weight, BMI and tobacco use, as well as health care-related factors, such as the timing of surgical treatment, graft selection, single-bundle or double-bundle reconstruction, ligament augmentation, graft fixation or the use of a post-operative knee brace, were not found to be associated with complications.

5.1 MENISCAL INJURY AND SURGERY

The non-surgical treatment of patients with ACL injuries was associated with a significantly increased risk of meniscal injury, as well as a need for meniscal surgery. The RCT by Frobell et al.[54] with a short-term follow-up of two years had the highest methodological quality, including a random and concealed allocation procedure, adequate power for its primary outcome measure and minimal loss of participants (OCEBM Ib). The participants, aged 18 to 35 years, had a high pre-injury activity level of median 9 on the Tegner Activity Scale. There were no differences in meniscal injury or meniscal surgery between the groups at baseline. During follow-up, however, patients randomized to non-surgical treatment (structured rehabilitation with the option of subsequent ACL reconstruction) reported signs and symptoms of serious meniscal injury almost 14 times more frequently and required four to five times more surgical meniscal procedures compared with the patients who were randomized to surgical treatment (structured rehabilitation and ACL reconstruction within 10 weeks). In the recently published five-year follow-up, Frobell et al.[55] reported that the participants randomized to non-surgical treatment continued to undergo significantly more repetitive surgery on their index knee menisci.

These results were supported by two non-randomized controlled trials (OCEBM IIb) by Fithian et al.[48] and Meunier et al.[132] in which non-surgical treatment was also associated with a significantly increased risk of subsequent meniscal surgery. However, a high risk of both selection and performance bias might limit the accuracy of the estimates. In addition, these findings are contradicted by a cohort study with a two-year follow-up by Grindem et al.[68] (OCEBM IIb) and a case-control study with a 10-year follow-up by Meuffels et al.[131] (OCEBM IIIb) that did not find any significant differences in meniscal injury or surgery between surgically and non-surgically treated patients. However, in the study by Meuffels et al.,[131] the risk of meniscectomies was noticeable and did in fact reach borderline significance in favor of surgical treatment (40% [10/25] vs. 12% [3/25], RR=3.3 [95% CI, 1.0-10.7], p=0.043).

Although there was a risk of bias in the study by Frobell et al.[54] (no blinding of participants, personnel or assessors, as well as the between-groups spill-over of participants), it is still, to our knowledge, the only RCT that has investigated the non-surgical vs. surgical treatment of ACL injuries. Two recent meta-analyses have compared the minimum 10-year outcomes of the non-surgical and surgical treatment of ACL-injured individuals. Chalmers et al.[29] reported that non-surgically treated patients required twice as much meniscal surgery compared with patients that underwent ACL reconstruction (29% vs. 14%, p=0.002). Smith et al.[196] also found that participants who underwent surgical treatment had a lower probability of partial meniscectomy compared with non-surgically treated participants (OR=0.2 [95% CI, 0.1-0.5]).

It is well acknowledged that individuals with an ACL injury run a greater risk of developing osteoarthritis compared with their non-injured counterparts; additional meniscal injury or meniscectomy are also recognized as further increasing this risk.[14, 90, 110, 117, 127, 144, 216, 234, 235] If ACL reconstruction actually does reduce the risk of subsequent meniscal injury, it would also, by implication, be expected to reduce the risk of osteoarthritis in the long term as well. This has not yet been established.[234] Two meta-analyses have shown that, after 10 years, radiographic signs of osteoarthritis were similar among surgically and non-surgically treated patients respectively (35% vs. 33%, p=0.768)[29] and (OR=1.6 [95% CI, 1.0-2.4], p=0.05)[196], although this has been challenged in the meta-analysis by Ajuied et al.,[2] who reported an increased risk of developing radiographic osteoarthritis after 10 years of non-surgical treatment of ACL injury (RR=5.0 [95% CI, 2.5-10.2], p<0.001).

The timing of surgical treatment was not clearly associated with the risk of meniscal injury or surgery after ACL injury. If an individual with an ACL injury comes to the decision to undergo surgical treatment, the rationale of early surgery is to minimize the risk of further meniscal and chondral injuries, as well as an expected earlier return to sporting or occupational activities. In contrast, delayed surgery allows for adequate decision-making, as well as optimal mental and physical preparation, as not every patient requires surgery.

The studies which investigated the injury-to-surgery interval, displayed marked heterogeneity with regard to participants, interventions, comparisons, outcome measures and study design [I, III]. This diversity made comparison and inference complex. The RCT by Bottoni et al.[21] found more meniscal injuries among patients who underwent early (within three weeks) as compared to delayed reconstruction (beyond six weeks). There is, however, concern about performance and detection bias that limits the generalizability of this study. First, the patients randomized to early surgical treatment were scheduled for surgery at the earliest possible date without any exceptions for swelling, limited range of motion or pain, which cannot be considered customary. Second, although the total number of meniscal injuries was higher in the early group, most of these tears were small lateral posterior horn tears that required minimal debridement. Moreover, in the early group, twice as many medial meniscal tears were reparable compared with the tears in the delayed group.

The three other RCTs[122, 129, 165] that did not find any differences between early and delayed surgery comprised small samples and did not present a sample size calculation or adequate power for differences in meniscal outcomes. In 2010, Smith et al.[195] published a meta-analysis of early versus delayed surgery (within three weeks vs. after six weeks post-injury) and found no increased risk of meniscal injury with delayed surgery (RR=0.92 [95% CI, 0.7-1.2], p=0.53). Their search strategy identified 254 records (of which six papers were included) compared with 7,154 records in Study III (of which 22 papers were included), which provides an example of precision vs. recall.

The quandary is that the classification of early and delayed surgery by Smith et al.[195] is arbitrary, since there is no consensus in the literature on what is to be considered as early or delayed surgery. In fact, within three weeks or beyond six weeks are still intervals located at the very early end of the wide injury-to-surgery spectrum, which is an important fact that is clearly elucidated in Study III. This illustrates the important complementary effects of systematic reviews employing meta-analysis and data-synthesis in order to fully investigate an objective.

To summarize, the literature provided limited evidence from which to draw any conclusions with regard to the association between the timing of surgical treatment and the risk of meniscal injury or surgery. Nonetheless, other investigators have found a relationship between delayed surgical treatment and the development of meniscal injuries. Based on a large patient sample from the Norwegian National Knee Ligament Registry, Granan et al.[66] found small yet significantly increased odds of meniscal tears for each month that elapsed since ACL injury. In addition, several case series have reported significantly more meniscal tears among patients who have undergone ACL reconstruction beyond six months[10, 206] as well as 12 months,[31, 50, 93] and the menisci were also significantly less likely to be salvageable.[50]

Six studies[12, 13, 46, 70, 106, 149] assessed meniscal injury or surgery based on graft selection. None of these studies had meniscal outcomes as a primary objective and none presented adequate power to show a relevant difference with regard to this outcome. In all but one study, outcomes were clinically similar. In the RCT by Barenius et al.,[13] which was also the study with the highest quality, the PT group had a larger proportion of meniscal surgery after index reconstruction compared with the ST group (12% [9/78] vs. 7% [5/75], RR=1.7 [95% CI, 0.6-4.9], p=0.304) [II, III]. In a systematic review by Herrington et al.,[75] there was no difference with respect to meniscal complications between the HT and the PT group. In 2011, the Cochrane Collaboration published a systematic review[136] of graft selection for ACL reconstruction in adults and noted that complications were inconsistently reported and that no conclusions could be drawn based on graft selection. Consequently, when the identified studies are taken into account, a type II error cannot be ruled out. As a result, a conclusion with regard to any association between graft selection and meniscal complications is uncertain.

The rationale of the double-bundle ACL reconstruction is allegedly a more anatomical approach with less rotational laxity, which would in theory reduce the risk of subsequent injury to menisci and hyaline cartilage. However, none of the identified studies[87, 88, 137, 225, 226] of single-bundle vs. double-bundle reconstruction reported any difference with regard to meniscal complications between these two techniques [II]. No study presented adequate statistical power to be able to rule out a type II error. Interestingly, a more recently published systematic review by the Cochrane Collaboration[213] found significantly fewer patients with new meniscal injuries in the double-bundle than the single-bundle group (4% [9/240] vs. 7% [24/358], RR=0.5 [95% CI, 0.2-0.9]) and this remained statistically significant after the exclusion of quasi-randomized trials. The authors concluded that double-bundle reconstruction may have some superior results when it comes to protection from recurrent injury. It is important to note, however, that the systematic review by the Cochrane Collaboration included PT reconstructions in the single-bundle group.

Study I identified three studies that investigated associations between graft fixation and meniscal complications. Harilainen et al.[71] investigated pins vs. metal interference screws, while Laxdal et al.[101] and McGuire et al.[126] investigated bioabsorbable vs. metal interference screws. There were no statistically significant or clinically relevant differences between patient groups based on graft fixation. Two recent systematic reviews by Shen et al.[192] and Colvin et al.[33] have also assessed graft fixation in ACL reconstruction, but they did not report on meniscal complications.

The rationale of a post-operative knee brace after ACL reconstruction is to protect the intra-articular structures by enhancing neuromuscular control and restraining extremes of range of motion. In theory, less meniscal and chondral damage would be expected. Study I identified four RCTs[18, 24, 143, 168] that investigated the effect of bracing on meniscal complications after ACL reconstruction. The outcomes between patients treated with and without a brace were clinically similar. However, the patient samples were small and none of the studies had performed a sample size calculation of a relevant difference with regard to meniscal complications. Similar results were reported by Wright and Fetzer[222] who, in their systematic review of bracing after ACL reconstruction, found no evidence that subsequent injuries were prevented by using a brace.

5.2 CHONDRAL INJURY AND SURGERY

The timing of surgical treatment, specifically delayed ACL reconstruction, was not found to be associated with an increased risk of chondral injury. Three RCTs[21, 122, 165] and one cohort study[233] investigated this but did not find any association [I, III]. However, as none of the studies presented adequate power, a type II error cannot be ruled out. Interestingly, several other studies, including registry-based cohort studies[30, 66] and case series,[50, 59, 93, 139, 148, 204] have noted that delayed surgical treatment significantly increased the likelihood of chondral complications after ACL injury. On the other hand, Kluczynski et al.[95] found increased odds of early surgery among patients with chondral injuries. Moreover, Røtterud et al.[178] have reported that an injury-to-surgery interval of more than 12 months, as well as male sex, male handball players, increasing age and previous surgery, were associated with full-thickness chondral injuries (ICRS 3-4).

Only one study investigated the effect of graft selection on chondral complications. Harilainen et al.[70] found no significant difference between patients who received HT autografts and PT autografts, although there were twice as many chondral operations in the HT group [II]. The study was, however, powered to detect differences in the Lysholm knee score and not chondral complications. Although there are numerous systematic reviews of graft selection in ACL reconstruction, it is difficult to put these findings in context, because reports on chondral injury and surgery are rare.[17, 51, 52, 75, 136, 200]

5.3 REVISION SURGERY

Adolescence (patient age 13 to 19 years) was associated with a more than two times greater risk of revision surgery compared with older age [V]. No other studies that analyzed the association between patient age and revision surgery were identified [I, II]. It remains unknown whether this finding represents a significant difference in ipsilateral graft injuries or revision surgery exclusively. Moreover, it is important to consider that the follow-up time was only two years. Younger patients might have a higher pre-injury activity level,[191] in addition to an eager early return to strenuous activities, and would therefore choose to undergo revision surgery at an earlier stage compared with their older counterparts. In fact, Desai et al.[38] showed that increasing patient age was associated with significantly longer injury-to-surgery intervals. It is therefore not known whether the rate of revision surgery is similar among older individuals, only that this occurs beyond two years. Data on activity level were not available in the Swedish National Knee Ligament Register at the time of the study, thus not allowing for adjustment in the analysis. Whether there are other important biological factors associated with young age per se, is not known. Nevertheless, the results are validated by several previous and subsequent studies that have consistently reported a higher rate of graft failure and revision surgery among young patients.[58, 61, 99, 108, 116, 120, 121, 161, 217, 218]

Sustaining an ACL injury while playing soccer was associated with a small yet significantly increased risk of revision surgery compared with all other activities [V]. No other studies that analyzed the association between activity at the time of injury and revision surgery were identified [I, II]. In all, effect sizes were clearly small and, among females, the risk was of borderline significance. However, individuals with a combination of the two risk factors (adolescence and playing soccer) ran an almost three times higher risk of revision surgery. Interestingly, in a recent and much larger cohort study by Gifstad et al.,[61] based on data from all three Scandinavian ACL registries, activity at the time of ACL injury was no longer associated with the five-year risk of revision surgery, even if soccer, handball and alpine activities were grouped and analyzed together as pivoting activities. The study based on all Scandinavian registries and Study V are comparable in terms of patients and methods, as well as statistical analyses; as a result, the larger data set in the paper by Gifstad et al.[61] is believed to provide more accurate inferences and generalizability.

The timing of surgical treatment was not found to be associated with the risk of revision surgery [IV], which was supported by one RCT[129] and one cohort study[83] [I, III]. There are, however, important limitations to consider. The results in Study IV were not adjusted for pre-injury activity level, which is important, as activity level and injury-to-surgery interval might display inverse proportionality (i.e. a high pre-injury activity level is associated with earlier ACL reconstruction, should the patient choose to undergo surgical treatment). Without an adjustment of this kind, higher revision rates after early reconstruction could potentially be misinterpreted as being attributable solely to the injury-to-surgery interval. Furthermore, patients undergoing early reconstruction might undergo potential revision surgery at an early stage as well, which would be detected during study follow-up and possibly bias results towards lower revision rates after delayed reconstruction. Finally, the decision to delay reconstruction might be based on low functional demands, adaptation to an injured knee or fear or sustaining other injuries, which in turn reduces the risk of exposing the knee to strenuous activities and subsequent graft failure. However, the pre-injury activity level was not available in the Swedish National Knee Ligament Register at the time of the study. The studies identified in Studies I and III found only minimal differences in revision surgery between groups but did not present a sample size calculation or adequate power to identify relevant differences.

For many years, graft selection in primary ACL reconstruction has been an area of intense discussion and research, although the HT and the PT autografts are currently without question the most common choices in both research and clinical practice.[185] In Study IV, based on data from 13,000 patients, graft selection between an HT autograft and a PT autograft was not found to be associated with the risk of revision surgery, which was in accordance with the results of twelve RCTs[12, 13, 42, 46, 70, 85, 102, 118, 149, 181, 188, 229] identified in Studies II and III.

These results are supported by several mid-term[62, 74] and long-term studies[104, 162, 180] as well as systematic reviews.[17, 51, 75, 166, 200] In fact, the Cochrane Collaboration[136] has systematically reviewed outcomes of ACL reconstruction with regard to graft selection between HT and PT autografts. The difference in re-ruptures between the two groups was small and not statistically significant (PT 2.6% vs. HT 3.3%, RR=0.78 [95% CI, 0.41-1.50]. Even when the analyses were stratified into quasi-randomized studies and randomized studies, the results remained insignificant. The rates of revision surgery were, however, inconsistently reported across studies to enable a meaningful comparison between PT and HT reconstructions. These findings were substantiated in a more recent meta-analysis by Li et al.[105] (HT 5.0% vs. PT 3.8%, RR=1.37 [95% CI, 0.67-2.81]).

However, contrary to consistent findings in recent years, there is now emerging evidence from large registry-based cohort studies from Scandinavia[61, 161, 164] and the United States (Kaiser Permanente Anterior Cruciate Ligament Reconstruction Registry)[119, 121] that the risk of revision surgery is, in fact, significantly higher for patients who have received an HT autograft reconstruction. The study by Gifstad et al.,[61] based on more than 45,000 patients from Norway, Sweden and Denmark, showed that the five-year risk of revision was significantly lower in the PT group compared with the HT group (2.8% vs. 4.2 %, adjusted HR=0.63 [95% CI, 0.53-0.74]). Based on 10,000 patients registered in the Kaiser Permanente ACL Reconstruction Registry, Maletis et al.[121] showed that the HT autograft carried an increased risk of revision surgery compared with the PT autograft (2.4% vs. 1.9%, HR=1.53 [95% CI, 1.16-2.02]). Nevertheless, it is important to note that these numbers indicate successful ACL reconstructions with an overall low five-year risk (less than 5%) of revision surgery in both Scandinavia and the USA.

To summarize, it appears that most systematic reviews only find relevant differences with regard to graft-specific harvest-site symptoms and instrumented laxity. The recent findings from the national and regional registries are very interesting and suggest that it takes patient samples of considerable sizes, as suggested by Salmon et al.,[182] in order to detect statistical significance regarding graft failure and revision surgery. In spite of this, there appear to be small or no differences in clinical relevance that justify discontinuing the use of one graft type in favor of the other. Instead, small advantages or disadvantages, e.g. harvest-site symptoms and strength deficits, associated with certain graft types might be of great importance when it comes to tailoring surgical treatment for every unique ACL-injured individual.

It has been suggested that the double-bundle ACL reconstruction more closely mimics the anatomy and function of the native ACL compared with the commonly used single-bundle technique in order better to withstand both anterior translation and rotation of the tibia. In theory, this construct accomplishes increased stability and presumably also a reduced risk of subsequent graft failure and a need for revision surgery. Although ACL reconstruction with the double-bundle technique produced better short-term stability, it was not found to be associated with a lower risk of graft failure[87, 88] or revision surgery [II, IV].

In a systematic review, Meredick et al.[130] concluded that the double-bundle reconstruction does not provide any clinically relevant advantages with regard to knee joint stability. In 2012, the Cochrane Collaboration[213] showed that double-bundle reconstruction was associated with a small yet significantly larger proportion of patients with normal or nearly normal rotational knee stability tested by the pivot-shift test (98% vs. 92%, RR=1.06 [95% CI, 1.02-1.09]), although it was not associated with a reduction in graft failure compared with single-bundle reconstruction (0.5% vs. 2.2%, RR=0.45 [95% CI, 0.07-2.90]). In addition, three more recent systematic reviews[19, 224, 232] have reported less anterior and rotational knee laxity, but not graft failure, in favor of double-bundle reconstruction. These findings support the view that the double-bundle technique must contribute to a clinically relevant reduction in complications, e.g. revision surgery, before it can be regarded as the new standard for modern ACL reconstruction. This is because it potentially adds to operating time, surgical complexity and cost[27] and because cost-effective interventions are crucial for the sustainability of modern health care.[219, 220]

Successful ACL reconstruction is highly dependent on techniques that keep the new ligament in a satisfactory position, without being affected by mechanical loading during rehabilitation. Satisfactory fixation should hold the graft firmly in place for at least three to six months following reconstruction to allow for the optimal healing of the bone-tendon interface.[158] Graft fixation with a metal interference screw was found to be associated with a significantly reduced risk of revision surgery. However, the difference was small and only attributable to the subgroup of patients who received ST autograft fixation on the tibia. Moreover, it was not possible to obtain support for this finding, as there were only two RCTs[71, 173] that assessed metal interference screws in comparison with cross-pin fixation [I]. In fact, different fixation techniques have not been shown to produce clinically relevant differences.[33, 125, 192, 199] In view of these findings, it was not possible to conclude that metal interference screw fixation is superior to other fixation techniques in preventing revision surgery.

The idea of supporting the healing graft during incorporation after ACL reconstruction is appealing. In 1980, Kennedy et al.[94] proposed the use of a ligament augmentation device (LAD) which would, in theory, protect the graft from excessive elongation and rupture during rehabilitation. It is therefore surprising that only one study[69] was identified, in which the protective properties of ligament augmentation was assessed, although graft failure was not the primary outcome. After two years of follow-up, Grøntvedt et al.[69] found that the device made no difference to the results but did not present adequate power to detect a relevant difference in graft failure or revision surgery between the study group with and without ligament augmentation [I]. After eight years, there was still no difference with regard to failure rate[39] and the LAD was withdrawn from the market in 2000.[138]

Like ligament augmentation, the use of a post-operative knee brace is also thought to protect the healing graft by the mechanical restraint and improvement of neuromuscular control. Only one RCT[18] (OCEBM Ib) was identified that assessed the protective properties of a knee brace or a neoprene sleeve on subsequent revision surgery [I]. The two-year rate of graft failure and revision surgery was equal in both study groups, although the primary outcome was a patient-reported outcome measure with a corresponding sample size calculation. The conclusion that a post-operative knee brace after ACL reconstruction does not protect the knee from complications, such as meniscal injury or surgery, chondral injury or surgery, or revision surgery, is in agreement with three other systematic reviews.[97, 222, 223]

5.4 CONTRALATERAL ACL RECONSTRUCTION

Patient sex was not associated with the risk of contralateral ACL reconstruction, which is consistent with the population-based study with a five-year follow-up by Wasserstein et al.[217] This finding is also supported by three long-term studies with 15-year follow-ups[22, 82, 104] and a meta-analysis,[176] all of which report no difference in contralateral graft survival based on patient sex.

Adolescence (patient age 13 to 19 years) was associated with a more than two times higher five-year risk of contralateral ACL reconstruction compared with older age. This finding is consistent with previous studies. The population-based study by Wasserstein et al.[217] reported that patient age of 15 to 19 years was associated with a doubled five-year risk of contralateral ACL reconstruction (HR=2.1 [95% CI, 1.6-2.7], p<0.0001). In addition, a cohort study by Leys et al.[104] and two case series by Bourke et al.[22] and Hui et al.[82] all showed that contralateral graft injury was at least twice as common among adolescents compared with older participants during their 15-year follow-ups. Finally, a recent case-control study by Webster et al.[218] also found that patients who had undergone contralateral ACL reconstruction had more than three times higher odds of being younger than 20 years of age at the time of index reconstruction. It is not known whether age per se is a risk factor or a proxy measure for unknown factors, e.g. activity level. Data on activity level were not available in the Swedish National Knee Ligament Register at the time of Study VI. However, other studies have shown a relationship between younger age and higher activity level.[11, 26, 191, 218]

In contrast to the risk of revision surgery, activity was not associated with the risk of contralateral reconstruction. To our knowledge, this is the first study to investigate this association. On the other hand, Salmon et al.[182] and Webster et al.[218] found significantly more contralateral injuries among individuals who returned to cutting or pivoting activities compared with those who did not.

Graft selection between an HT autograft and a PT autograft at index ACL reconstruction was not associated with the risk of contralateral ACL reconstruction. Two long-term studies with 15-year follow-ups have assessed the association between graft selection and contralateral injury and presented contrasting results. Bourke et al.[22] reported that contralateral graft survival was similar between the HT and the PT group throughout the follow-up (HR=1.5 [95% CI, 1.0-2.2], p=0.061), whereas Leys et al.[104] noted that, although contralateral graft survival was comparable during the first five years after index reconstruction, the PT group had sustained twice as many contralateral graft injuries at final follow-up (26% vs. 12%, OR=2.6 [95% CI, 1.1-5.9], p=0.022). The basis for this difference is unclear. Patient selection was not randomized, but similar surgical techniques and rehabilitation protocols were used and more than 80% follow-up was achieved in both studies.

Among females, harvesting an HT autograft from the contralateral knee was associated with a more than three times higher five-year risk of contralateral ACL reconstruction compared with harvest from the ipsilateral knee that was subject to reconstruction. No such associations were found among female participants with PT autograft reconstructions or among male participants. Study II identified one RCT[227] that investigated harvest-site morbidity, but this study did not analyze the need for subsequent surgery. To our knowledge, only McRae et al.[128] have reported results of an RCT of ipsilateral versus contralateral hamstring harvest. After two years of follow-up, there were no differences between the two groups with regard to patient-reported outcome, strength or pain. Only one participant, in the contralateral group, suffered a contralateral ACL injury. As a result thereof, an analysis of a possible association with harvest site was not meaningful.

Study VI is a landmark study of the association between graft harvest site and the risk of contralateral ACL reconstruction. This association might be attributable to a combination of different factors. It is well known that the hamstrings perform an important agonist function with regard to the ACL in restraining the forward translation of the tibia relative to the femur. Harvesting the hamstring tendons during ACL reconstruction is also known to cause significant hamstring muscle strength deficits, which have been shown to persist for up to five years after ACL reconstruction.[100] Moreover, female athletes have been reported to possess more lax hamstrings[20] and higher mean anterior tibial translation compared with males at comparable forces,[174] which may lead to the delay or absence of hamstring muscle activation,[15, 198, 230] which in part might explain the three times higher risk of sustaining a primary ACL injury[163] compared with their male counterparts. The native ACL in females is, by implication, more likely to depend on the unrestricted performance of the hamstrings rather than the quadriceps,[77] compared with the male ACL. As a result, harvesting the contralateral hamstring tendons might theoretically increase the risk of contralateral ACL injury and subsequent reconstruction.

This finding is intriguing. However, the potential implications for clinical practice are still unknown and should be treated with caution owing to the fact that this is the first study to show this association. Further research is likely to have an important impact in this area.

5.5 LIMITATIONS AND STRENGTHS

It is important to consider both the limitations and the strengths of this thesis. Work on the first two studies began in April 2007. During this period, a great deal of research has been undertaken and many papers have been published. Moreover, knowledge based on data from the Scandinavian ACL registries has started to attract widespread attention. This thesis is based on systematic reviews and registry-based cohort studies. It does not include interventional studies. In a registry-based cohort study, it is not possible to prove causality, primarily due to the risk of selection and performance bias. In order to establish contributory causes, it is necessary to perform a controlled interventional study with adequate random allocation of known and unknown confounding factors, i.e. an RCT or a meta-analysis of these studies with significant homogeneity across all studies with regard to participants, interventions, comparisons, outcomes and settings.

A systematic literature search is essential to a systematic review. The fact that the electronic literature searches in Studies I and II were only carried out in PubMed and not EMBASE and CENTRAL as well, compared with Study III, is therefore a limitation. Moreover, depending on the search strategy, an electronic literature search might not be sufficient to detect every record relevant to the objective. Sometimes, a hand search of pertinent journals reveals papers that have not been indexed in the database.

In registry-based cohort studies with large patient samples, it is possible to obtain statistically significant differences that might not be of clinical relevance. Consequently, it is important always to consider the statistics and effect size in detail before implementing any advancement in clinical practice. Studies IV, V and VI were based on data from the Swedish National Knee Ligament Register and not all the Scandinavian ACL registries in Norway, Sweden and Denmark.

In the Swedish National Knee Ligament Register, data on activity level, injury mechanism, graft failure and non-surgical treatment were not available at the time of data collection in Studies IV, V and VI. It was therefore not possible to adjust for the possible confounding properties of activity level. Moreover, the rate of graft failure was not possible to determine, because these events are not identified by the registry. Furthermore, activity at the time of ACL injury is only assumed to correspond to the primary pre-injury activity and, hopefully, also the primary post-injury activity, which are not necessarily the same. In Study VI, it would have been interesting to include a control group comprising ACL-injured individuals who underwent non-surgical treatment but subsequently sustained a contralateral ACL injury.

The length of follow-up in Studies IV, V and VI was two and five years respectively, which can be regarded as short and mid-term. However, in a registry-based cohort study, the length of follow-up has to be carefully balanced with respect to the patient sample, as patients enter the registry continuously and not all at the same time. In fact, 70-90% of the included RCTs had short-term follow-ups [I, II]. A longer follow-up is not always better. Instead, the follow-up has to be considered with the outcome measures in mind. In Studies IV and V, the aim was to investigate factors that predispose individuals to the need for early revision surgery and not revision surgery overall.

The main strength of this thesis is clearly the comprehensive scope and high recall in the investigation of four important complications after ACL injury. In addition, the fact that the results were supported by those reported elsewhere suggests high external validity. Studies I, II and III used extensive electronic literature searches and included 131 RCTs and cohort studies respectively. The included papers were also carefully assessed with regard to quality.

The registry-based cohort studies, IV, V and VI, comprised data from a large sample of ACL-injured individuals with well-defined end points instead of indistinct outcome measures such as graft failure and contralateral ACL injury, which are subject to a wide variety of interpretations. Another important strength is the quality of the data source; the Swedish National Knee Ligament Register has excellent coverage (93%) and completeness (89%).

Finally, all the studies in this thesis displayed high levels of evidence (OCEBM IIa and IIb) and the conclusions were classified according to GRADE[207] to enable the reader to determine the quality of the evidence behind each conclusion.

"Long experience has taught me this about matters requiring thought: the less people know and understand, the more they attempt to argue, while on the other hand to know and understand renders men cautious in passing judgment upon anything new."

Galileo Galilei

Six

CONCLUSIONS

6.1 MENISCAL INJURY AND SURGERY

- Non-surgical treatment of ACL injury was a predictor of meniscal injury and a need for meniscal surgery (GRADE B)
- The timing of surgical treatment, graft selection, single-bundle or double-bundle reconstruction, graft fixation and the use of a post-operative knee brace were not predictors of meniscal injury or a need for meniscal surgery (GRADE D)

6.2 CHONDRAL INJURY AND SURGERY

- The timing of surgical treatment and graft selection were not predictors of chondral injury or a need for chondral surgery (GRADE D)

6.3 REVISION SURGERY

- Age 13 to 19 years and ACL injury while playing soccer were predictors of a need for revision surgery (GRADE C)
- Patient sex, height, weight, BMI, use of tobacco, the timing of surgical treatment, graft selection, graft size, single-bundle or double-bundle reconstruction, graft fixation, meniscal and chondral injuries were not predictors of a need for revision surgery (GRADE C)
- A ligament augmentation device or a post-operative knee brace did not reduce the risk of revision surgery (GRADE D)

6.4 CONTRALATERAL ACL RECONSTRUCTION

- Age 13 to 19 years was a predictor of a need for contralateral ACL reconstruction (GRADE C)
- In females, contralateral hamstring tendon harvest was a predictor of a need for contralateral ACL reconstruction (GRADE C)
- Patient sex, activity at the time of injury, graft selection, meniscal and chondral injuries were not predictors of a need for contralateral ACL reconstruction (GRADE C)

“The scientific man does not aim at an immediate result. His work is like that of the planter – for the future. His duty is to lay the foundation for those who are to come, and point the way.”

Nikola Tesla

Seven

FUTURE PERSPECTIVES

There is much to be gained from consensus. Research would benefit greatly from consensus on a strict selection of valid, reliable and responsive outcome measures that reflect both objective and subjective constructs. In addition, these outcome measures have to be relevant with regard to clinical practice and, in the end, our patients. Encouraging work has fortunately already begun.[113]

There is a need for agreement on what is to be regarded as a clinically relevant effect size for each outcome. This would hopefully promote the use of sample size calculations. Moreover, the consistent reporting of results is required. Risk estimates and confidence intervals are indispensable complements to p values in order to facilitate future data analyses in systematic reviews. However, the seductive simplicity of statistics is a complement to, but can never replace, common sense.[79] Just as it is not possible to draw a general conclusion from a single event, inference from a sample only applies to other similar samples and not to the unique individual. The responsibility for accomplishing all of this lies not only with study investigators but with ethical review boards and journal reviewers and editors as well.

Today, the potential value of registry data is unquestionable. Nonetheless, the results are never better than the quality of the data source. Continuous improvements are important in order to maintain credibility and high-quality research. In the Swedish National Knee Ligament Register, work has begun with the inclusion of all ACL-injured individuals regardless of treatment, the removal of variables with poor reliability and increasing patient response rates.[210] There is, however, concern about missing or inaccurately reported data, which might be reduced by a coordinating controller. Suggestions regarding possible improvements also include using data on main pre- and post-injury activity, including the level of activity, injury mechanism, turf material and menstrual cycle.

Finally, it is important to continue to investigate the potentially protective properties of the hamstrings in females in addition to the implications of surgical vs. non-surgical treatment of individuals with ACL injury.

I wish to express my sincere gratitude towards the following persons. Without them, this doctoral thesis would not have become what it is today or perhaps not even seen the light of day.

Eight

ACKNOWLEDGEMENTS

Jón Karlsson, professor and my supervisor, for believing in my potential many years ago when I was only a medical student. Your enthusiasm, diplomacy and problem-solving nature are unparalleled.

Bengt Eriksson, professor and my co-supervisor, for your positive attitude and continuous encouragement. Your laughter and rapid west coast-rhetoric are really uplifting.

Kristian Samuelsson, my mentor and friend, for unsurpassed teamwork and friendship. You are the most resourceful friend I've ever had.

Jürgen Staub-Lambrecht, head of Vårdcentralen Gripen in Karlstad, for believing in me and supporting this project at a time when no one else did.

Kersti Theander, head of the Primary Care Research Unit, County Council of Värmland, for financial support.

Anders Hallberg, head of the Centre for Clinical Research, County Council of Värmland, for financial support.

Jüri Kartus, professor and member of the Swedish ACL Registry steering committee, for your incisive comments on the registry studies and constructive criticism of this thesis.

Magnus Forssblad, registrar of the Swedish ACL Registry and co-author, for your help with providing and interpreting the register data.

My co-authors and research colleagues, Neel Desai, Haukur Björnsson, Freddie H. Fu, Volker Musahl, Mohit Bhandari, Max Petzold, Mattias Ylander and **Sofia Gillén,** for your insightful comments, methodological considerations, statistical analyses and clinical perspectives that were necessary to complete every study.

Martina Åhlén, research colleague and friend, for constructive criticism of this thesis and help with the cover photo.

Emma-Johanna Samuelsson, radiologist and friend, for assessing the radiographs and for teaching me about musculoskeletal imaging.

Annika Samuelsson Enderlein, graphic designer and friend, for your accommodating assistance in the design and layout of this thesis.

My family, for your unconditional love, patience and invaluable support that helped me through the many trials, ventures and adventures of doctoral studies and research. I love you.

"This, which I now publish must necessarily be imperfect. No doubt errors will have crept in, though I hope I have always been cautious in trusting to good authorities."

Charles Darwin

Nine

REFERENCES

1. Ahlbäck S. Osteoarthrosis of the knee. A radiographic investigation. *Acta Radiol Diagn.* 1968;Suppl 277:7-72.

2. Ajuied A, Wong F, Smith C, Norris M, Earnshaw P, Back D, Davies A. Anterior cruciate ligament injury and radiologic progression of knee osteoarthritis: a systematic review and meta-analysis. *Am J Sports Med.* 2014;42(9):2242-2252.

3. Altman DG. *Practical Statistics for Medical Research*. London: Chapman Hall; 1991.

4. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage*. 2007;15 Suppl A:A1-56.

5. Andernord D, Björnsson H, Petzold M, Eriksson BI, Forssblad M, Karlsson J, Samuelsson K. Surgical Predictors of Early Revision Surgery After Anterior Cruciate Ligament Reconstruction: Results From the Swedish National Knee Ligament Register on 13,102 Patients. *Am J Sports Med*. 2014;42(7):1574-1582.

6. Andernord D, Desai N, Björnsson H, Gillén S, Karlsson J, Samuelsson K. Predictors of Contralateral Anterior Cruciate Ligament Reconstruction: A Cohort Study of 9061 Patients With 5-Year Follow-up. *Am J Sports Med*. 2015;43(2):295-302.

7. Andernord D, Desai N, Björnsson H, Ylander M, Karlsson J, Samuelsson K. Patient Predictors of Early Revision Surgery After Anterior Cruciate Ligament Reconstruction: A Cohort Study of 16,930 Patients With 2-Year Follow-up. *Am J Sports Med*. 2015;43(1):121-127.

8. Andernord D, Karlsson J, Musahl V, Bhandari M, Fu FH, Samuelsson K. Timing of surgery of the anterior cruciate ligament. *Arthroscopy*. 2013;29(11):1863-1871.

9. Andersson D, Samuelsson K, Karlsson J. Treatment of anterior cruciate ligament injuries with special reference to surgical technique and rehabilitation: an assessment of randomized controlled trials. *Arthroscopy.* 2009;25(6):653-685.

10. Anstey DE, Heyworth BE, Price MD, Gill TJ. Effect of timing of ACL reconstruction in surgery and development of meniscal and chondral lesions. *Phys Sportsmed*. 2012;40(1):36-40.

11. Ardern CL, Taylor NF, Feller JA, Webster KE. Return-to-sport outcomes at 2 to 7 years after anterior cruciate ligament reconstruction surgery. *Am J Sports Med*.

2012;40(1):41-48.

12. Aune AK, Holm I, Risberg MA, Jensen HK, Steen H. Four-strand hamstring tendon autograft compared with patellar tendon-bone autograft for anterior cruciate ligament reconstruction.A randomized study with two-year follow-up. *Am J Sports Med.* 2001;29(6):722-728.

13. Barenius B, Nordlander M, Ponzer S, Tidermark J, Eriksson K. Quality of life and clinical outcome after anterior cruciate ligament reconstruction using patellar tendon graft or quadrupled semitendinosus graft: an 8-year follow-up of a randomized controlled trial. *Am J Sports Med*. 2010;38(8):1533-1541.

14. Barenius B, Ponzer S, Shalabi A, Bujak R, Norlén L, Eriksson K. Increased Risk of Osteoarthritis After Anterior Cruciate Ligament Reconstruction: A 14-Year Follow-up Study of a Randomized Controlled Trial. *Am J Sports Med*. 2014;42(5):1049-1057.

15. Bencke J, Zebis MK. The influence of gender on neuromuscular pre-activity during side-cutting. *J Electromyogr Kinesiol.* 2011;21(2):371-375.

16. Beynnon BD, Johnson RJ, Abate JA, Fleming BC, Nichols CE. Treatment of anterior cruciate ligament injuries, part I. *Am J Sports Med*. 2005;33(10):1579-1602.

17. Biau DJ, Tournoux C, Katsahian S, Schranz PJ, Nizard RS. Bone-patellar tendon-bone autografts versus hamstring autografts for reconstruction of anterior cruciate ligament: meta-analysis. *BMJ*. 2006;332(7548):995-1001.

18. Birmingham TB, Bryant DM, Giffin JR, Litchfield RB, Kramer JF, Donner A, Fowler PJ. A randomized controlled trial comparing the effectiveness of functional knee brace and neoprene sleeve use after anterior cruciate ligament reconstruction. *Am J Sports Med.* 2008;36(4):648-655.

19. Björnsson H, Desai N, Musahl V, Alentorn-Geli E, Bhandari M, Fu F, Samuelsson K. Is double-bundle anterior cruciate ligament reconstruction superior to single-bundle? A comprehensive systematic review. *Knee Surg Sports Traumatol Arthrosc*. 2013:DOI: 10.1007/s00167-00013-02666-x.

20. Boden BP, Dean GS, Feagin JA, Jr., Garrett WE, Jr. Mechanisms of anterior cruciate ligament injury. *Orthopedics*. 2000;23(6):573-578.

21. Bottoni CR, Liddell TR, Trainor TJ, Freccero DM, Lindell KK. Postoperative range of motion following anterior cruciate ligament reconstruction using autograft hamstrings: a prospective, randomized clinical trial of early versus delayed reconstructions. *Am J Sports Med*. 2008;36(4):656-662.

22. Bourke HE, Salmon LJ, Waller A, Patterson V, Pinczewski LA. Survival of the anterior cruciate ligament graft and the contralateral ACL at a minimum of 15 years.

Am J Sports Med. 2012;40(9):1985-1992.

23. Bowen TR, Feldmann DD, Miller MD. Return to play following surgical treatment of meniscal and chondral injuries to the knee. *Clin Sports Med*. 2004;23(3):381-393.

24. Brandsson S, Faxén E, Kartus J, Eriksson BI, Karlsson J. Is a knee brace advantageous after anterior cruciate ligament surgery? A prospective, randomised study with a two-year follow-up. *Scand J Med Sci Sports.* 2001;11(2):110-114.

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

26. Brophy RH, Schmitz L, Wright RW, Dunn WR, Parker RD, Andrish JT, McCarty EC, Spindler KP. Return to play and future ACL injury risk after ACL reconstruction in soccer athletes from the Multicenter Orthopaedic Outcomes Network (MOON) group. *Am J Sports Med.* 2012;40(11):2517-2522.

27. Brophy RH, Wright RW, Matava MJ. Cost analysis of converting from single-bundle to double-bundle anterior cruciate ligament reconstruction. *Am J Sports Med*. 2009;37(4):683-687.

28. Canese K, Weis S. PubMed: The Bibliographic Database. *in: The NCBI Handbook [Internet].* 2 ed. http://www.ncbi.nlm.nih.gov/books/NBK153385/?report=reader: National Center for Biotechnology Information (US), Bethesda (MD); 2002 [Updated 2013 Mar 20]:1-17.

29. Chalmers PN, Mall NA, Moric M, Sherman SL, Paletta GP, Cole BJ, Bach BR, Jr. Does ACL reconstruction alter natural history?: A systematic literature review of long-term outcomes. *J Bone Joint Surg Am*. 2014;96(4):292-300.

30. Chhadia AM, Inacio MC, Maletis GB, Csintalan RP, Davis BR, Funahashi TT. Are meniscus and cartilage injuries related to time to anterior cruciate ligament reconstruction? *Am J Sports Med*. 2011;39(9):1894-1899.

31. Church S, Keating JF. Reconstruction of the anterior cruciate ligament: timing of surgery and the incidence of meniscal tears and degenerative change. *J Bone Joint Surg Br.* 2005;87(12):1639-1642.

32. Cipolla M, Scala A, Gianni E, Puddu G. Different patterns of meniscal tears in acute anterior cruciate ligament (ACL) ruptures and in chronic ACL-deficient knees. Classification, staging and timing of treatment. *Knee Surg Sports Traumatol Arthrosc.* 1995;3(3):130-134.

33. Colvin A, Sharma C, Parides M, Glashow J. What is the best femoral fixation of hamstring autografts in anterior cruciate ligament reconstruction?: a meta-analysis. *Clin Orthop Relat Res*. 2011;469(4):1075-1081.

34. Corry IS, Webb JM, Clingeleffer AJ, Pinczewski LA. Arthroscopic reconstruction of the anterior cruciate ligament. A comparison of patellar tendon autograft and four-strand hamstring tendon autograft. *Am J Sports Med.* 1999;27(4):444-454.

35. Corsetti JR, Jackson DW. Failure of anterior cruciate ligament reconstruction: the biologic basis. *Clin Orthop Relat Res.* 1996;325(4):42-49.

36. Daniel DM, Stone ML, Dobson BE, Fithian DC, Rossman DJ, Kaufman KR. Fate of the ACL-injured patient. A prospective outcome study. *Am J Sports Med*. 1994;22(5):632-644.

37. Denti M, Lo Vetere D, Bait C, Schonhuber H, Melegati G, Volpi P. Revision anterior cruciate ligament reconstruction: causes of failure, surgical technique, and clinical results. *Am J Sports Med.* 2008;36(10):1896-1902.

38. Desai N, Björnsson H, Samuelsson K, Karlsson J, Forssblad M. Outcomes after ACL reconstruction with focus on older patients: results from The Swedish National Anterior Cruciate Ligament Register. *Knee Surg Sports Traumatol Arthrosc*. 2014;22(2):379-386.

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

40. Dunn WR, Lyman S, Lincoln AE, Amoroso PJ, Wickiewicz T, Marx RG. The effect of anterior cruciate ligament reconstruction on the risk of knee reinjury. *Am J Sports Med*. 2004;32(8):1906-1914.

41. Editorial. National disease registries for advancing health care. *The Lancet*. 2011;378(9809):2050.

42. Ejerhed L, Kartus J, Sernert N, Köhler K, Karlsson J. Patellar tendon or semitendinosus tendon autografts for anterior cruciate ligament reconstruction? A prospective randomized study with a two-year follow-up. *Am J Sports Med.* 2003;31(1):19-25.

43. Emilsson L, Lindahl B, Koster M, Lambe M, Ludvigsson JF. Review of 103 Swedish healthcare quality registries. *J Intern Med.* 2015;277(1):94-136.

44. Engebretsen L, Forssblad M. Why knee ligament registries are important. *Knee Surg Sports Traumatol Arthrosc.* 2009;17(2):115-116.

45. Englund M, Lohmander LS. Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy. *Arthritis Rheum.* 2004;50(9):2811-2819.

46. Eriksson K, Anderberg P, Hamberg P, Löfgren AC, Bredenberg M, Westman I, Wredmark T. A comparison of quadruple semitendinosus and patellar tendon grafts in reconstruction of the anterior cruciate ligament. *J Bone Joint Surg Br.* 2001;83-B(3):348-354.

47. Fairbank TJ. Knee joint changes after meniscectomy. *J Bone Joint Surg Br.* 1948;30-B(4):664-670.

48. Fithian DC, Paxton EW, Stone ML, Luetzow WF, Csintalan RP, Phelan D, Daniel DM. Prospective trial of a treatment algorithm for the management of the anterior cruciate ligament-injured knee. *Am J Sports Med*. 2005;33(3):335-346.

49. Fithian DC, Paxton LW, Goltz DH. Fate of the anterior cruciate ligament-injured knee. *Orthop Clin North Am*. 2002;33(4):621-636.

50. Fok AW, Yau WP. Delay in ACL reconstruction is associated with more severe and painful meniscal and chondral injuries. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(4):928-933.

51. Forster MC, Forster IW. Patellar tendon or four-strand hamstring? A systematic review of autografts for anterior cruciate ligament reconstruction. *Knee*. 2005;12(3):225-230.

52. Freedman KB, D'Amato MJ, Nedeff DD, Kaz A, Bach BR, Jr. Arthroscopic anterior cruciate ligament reconstruction: a metaanalysis comparing patellar tendon and hamstring tendon autografts. *Am J Sports Med.* 2003;31(1):2-11.

53. Frobell RB, Lohmander LS, Roos HP. Acute rotational trauma to the knee: poor agreement between clinical assessment and magnetic resonance imaging findings. *Scand J Med Sci Sports.* 2007;17(2):109-114.

54. Frobell RB, Roos EM, Roos HP, Ranstam J, Lohmander LS. A randomized trial of treatment for acute anterior cruciate ligament tears. *N Engl J Med*. 2010;363(4):331-342.

55. Frobell RB, Roos HP, Roos EM, Roemer FW, Ranstam J, Lohmander LS. Treatment for acute anterior cruciate ligament tear: five year outcome of randomised trial. *BMJ*. 2013;346:f232.

56. Fuller CW, Ekstrand J, Junge A, Andersen TE, Bahr R, Dvorak J, Hagglund M, McCrory P, Meeuwisse WH. Consensus statement on injury definitions and data collection procedures in studies of football (soccer) injuries. *Clin J Sport Med.* 2006;16(2):97-106.

57. Fältstrom A, Hägglund M, Kvist J. Patient-reported knee function, quality of life, and activity level after bilateral anterior cruciate ligament injuries. *Am J Sports Med.* 2013;41(12):2805-2813.

58. Fältstrom A, Hägglund M, Magnusson H, Forssblad M, Kvist J. Predictors for additional anterior cruciate ligament reconstruction: data from the Swedish national ACL register. *Knee Surg Sports Traumatol Arthrosc.* 2014:DOI: 10.1007/s00167-00014-03406-00166.

59. Ghodadra N, Mall NA, Karas V, Grumet RC, Kirk S, McNickle AG, Garrido CP, Cole BJ, Bach BR, Jr. Articular and meniscal pathology associated with primary anterior cruciate ligament reconstruction. *J Knee Surg.* 2013;26(3):185-193.

60. Gianotti SM, Marshall SW, Hume PA, Bunt L. Incidence of anterior cruciate ligament injury and other knee ligament injuries: a national population-based study. *J Sci Med Sport*. 2009;12(6):622-627.

61. Gifstad T, Foss OA, Engebretsen L, Lind M, Forssblad M, Albrektsen G, Drogset JO. Lower Risk of Revision With Patellar Tendon Autografts Compared With Hamstring Autografts: A Registry Study Based on 45,998 Primary ACL Reconstructions in Scandinavia. *Am J Sports Med.* 2014;42(10):2319-2328.

62. Gifstad T, Sole A, Strand T, Uppheim G, Grontvedt T, Drogset JO. Long-term follow-up of patellar tendon grafts or hamstring tendon grafts in endoscopic ACL reconstructions. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(3):576-583.

63. Gilchrist J, Mandelbaum BR, Melancon H, Ryan GW, Silvers HJ, Griffin LY, Watanabe DS, Dick RW, Dvorak J. A randomized controlled trial to prevent noncontact anterior cruciate ligament injury in female collegiate soccer players. *Am J Sports Med*. 2008;36(8):1476-1483.

64. Gillquist J, Messner K. Anterior cruciate ligament reconstruction and the long-term incidence of gonarthrosis. *Sports Med.* 1999;27(3):143-156.

65. Girgis FG, Marshall JL, Monajem A. The cruciate ligaments of the knee joint. Anatomical, functional and experimental analysis. *Clin Orthop Relat Res*. 1975;106(1):216-231.

66. Granan LP, Bahr R, Lie SA, Engebretsen L. Timing of anterior cruciate ligament reconstructive surgery and risk of cartilage lesions and meniscal tears: a cohort study based on the Norwegian National Knee Ligament Registry. *Am J Sports Med*. 2009;37(5):955-961.

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

68. Grindem H, Eitzen I, Engebretsen L, Snyder-Mackler L, Risberg MA. Nonsurgical or Surgical Treatment of ACL Injuries: Knee Function, Sports Participation, and Knee Reinjury: The Delaware-Oslo ACL Cohort Study. *J Bone Joint Surg Am*. 2014;96(15):1233-1241.

69. Grontvedt T, Engebretsen L, Bredland T. Arthroscopic reconstruction of the anterior cruciate ligament using bone-patellar tendon-bone grafts with and without augmentation. A prospective randomised study. *J Bone Joint Surg Br.* 1996;78(5):817-822.

70. Harilainen A, Linko E, Sandelin J. Randomized prospective study of ACL reconstruction with interference screw fixation in patellar tendon autografts versus femoral metal plate suspension and tibial post fixation in hamstring tendon autografts: 5-year clinical and radiological follow-up results. *Knee Surg Sports Traumatol Arthrosc.* 2006;14(6):517-528.

71. Harilainen A, Sandelin J, Jansson KA. Cross-pin femoral fixation versus metal interference screw fixation in anterior cruciate ligament reconstruction with hamstring tendons: results of a controlled prospective randomized study with 2-year follow-up. *Arthroscopy.* 2005;21(1):25-33.

72. Harner CD, Baek GH, Vogrin TM, Carlin GJ, Kashiwaguchi S, Woo SL. Quantitative analysis of human cruciate ligament insertions. *Arthroscopy.* 1999;15(7):741-749.

73. 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):226-234.

74. Heijne A, Hagströmer M, Werner S. A two- and five-year follow-up of clinical outcome after ACL reconstruction using BPTB or hamstring tendon grafts: a prospective intervention outcome study. *Knee Surg Sports Traumatol Arthrosc.* 2013:DOI: 10.1007/s00167-00013-02727-00161.

75. Herrington L, Wrapson C, Matthews M, Matthews H. Anterior cruciate ligament reconstruction, hamstring versus bone-patella tendon-bone grafts: a systematic literature review of outcome from surgery. *Knee.* 2005;12(1):41-50.

76. Hewett TE, Ford KR, Myer GD. Anterior cruciate ligament injuries in female athletes: Part 2, a meta-analysis of neuromuscular interventions aimed at injury prevention. *Am J Sports Med.* 2006;34(3):490-498.

77. Hewett TE, Myer GD, Ford KR. Anterior cruciate ligament injuries in female athletes: Part 1, mechanisms and risk factors. *Am J Sports Med.* 2006;34(2):299-311.

78. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]:* The Cochrane Collaboration; 2011.

79. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med.* 1965;58(5):295-300.

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

81. Howell JR, Handoll HH. Surgical treatment for meniscal injuries of the knee in adults. *Cochrane Database Syst Rev.* 2009(1):CD001353.

82. Hui C, Salmon LJ, Kok A, Maeno S, Linklater J, Pinczewski LA. Fifteen-year outcome of endoscopic anterior cruciate ligament reconstruction with patellar tendon autograft for “isolated” anterior cruciate ligament tear. *Am J Sports Med.* 2011;39(1):89-98.

83. Hunter RE, Mastrangelo J, Freeman JR, Purnell ML, Jones RH. The impact of surgical timing on postoperative motion and stability following anterior cruciate ligament reconstruction. *Arthroscopy*. 1996;12(6):667-674.

84. Hägglund M, Waldén M, Magnusson H, Kristenson K, Bengtsson H, Ekstrand J. Injuries affect team performance negatively in professional football: an 11-year follow-up of the UEFA Champions League injury study. *Br J Sports Med*. 2013;47(12):738-742.

85. Jansson KA, Linko E, Sandelin J, Harilainen A. A prospective randomized study of patellar versus hamstring tendon autografts for anterior cruciate ligament reconstruction. *Am J Sports Med.* 2003;31(1):12-18.

86. Jonsson E. History of health technology assessment in Sweden. *Int J Technol Assess Health Care*. 2009;25(Suppl S1):42-52.

87. Järvelä T. Double-bundle versus single-bundle anterior cruciate ligament reconstruction: a prospective, randomize clinical study. *Knee Surg Sports Traumatol Arthrosc*. 2007;15(5):500-507.

88. Järvelä T, Moisala AS, Sihvonen R, Järvelä S, Kannus P, Järvinen M. Double-bundle anterior cruciate ligament reconstruction using hamstring autografts and bioabsorbable interference screw fixation: prospective, randomized, clinical study with 2-year results. *Am J Sports Med*. 2008;36(2):290-297.

89. Kartus J, Magnusson L, Stener S, Brandsson S, Eriksson BI, Karlsson J. Complications following arthroscopic anterior cruciate ligament reconstruction. A 2-5-year follow-up of 604 patients with special emphasis on anterior knee pain. *Knee Surg Sports Traumatol Arthrosc*. 1999;7(1):2-8.

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

91. Keene GC, Bickerstaff D, Rae PJ, Paterson RS. The natural history of meniscal tears in anterior cruciate ligament insufficiency. *Am J Sports Med*. 1993;21(5):672-679.

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

93. Kennedy J, Jackson MP, O’Kelly P, Moran R. Timing of reconstruction of the anterior cruciate ligament in athletes and the incidence of secondary pathology within the knee. *J Bone Joint Surg Br.* 2010;92(3):362-366.

94. Kennedy JC, Roth JH, Mendenhall HV, Sanford JB. Presidential address. Intraarticular replacement in the anterior cruciate ligament-deficient knee. *Am J Sports Med.* 1980;8(1):1-8.

95. Kluczynski MA, Marzo JM, Bisson LJ. Factors associated with meniscal tears and chondral lesions in patients undergoing anterior cruciate ligament reconstruction: a prospective study. *Am J Sports Med.* 2013;41(12):2759-2765.

96. Kostogiannis I, Ageberg E, Neuman P, Dahlberg L, Fridén 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;35(7):1135-1143.

97. Kruse LM, Gray B, Wright RW. Rehabilitation after anterior cruciate ligament reconstruction: a systematic review. *J Bone Joint Surg Am*. 2012;94(19):1737-1748.

98. Kvist J. Rehabilitation following anterior cruciate ligament injury: current recommendations for sports participation. *Sports Med*. 2004;34(4):269-280.

99. Kvist J, Kartus J, Karlsson J, Forssblad M. Results From the Swedish National Anterior Cruciate Ligament Register. *Arthroscopy*. 2014;30(7):803-810.

100. Lautamies R, Harilainen A, Kettunen J, Sandelin J, Kujala UM. Isokinetic quadriceps and hamstring muscle strength and knee function 5 years after anterior cruciate ligament reconstruction: comparison between bone-patellar tendon-bone and hamstring tendon autografts. *Knee Surg Sports Traumatol Arthrosc.* 2008;16(11):1009-1016.

101. Laxdal G, Kartus J, Eriksson BI, Faxén E, Sernert N, Karlsson J. Biodegradable and metallic interference screws in anterior cruciate ligament reconstruction surgery using hamstring tendon grafts: prospective randomized study of radiographic results and clinical outcome. *Am J Sports Med*. 2006;34(10):1574-1580.

102. 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;21(1):34-42.

103. Levy IM, Torzilli PA, Warren RF. The effect of medial meniscectomy on anterior-posterior motion of the knee. *J Bone Joint Surg Am*. 1982;64(6):883-888.

104. Leys T, Salmon L, Waller A, Linklater J, Pinczewski L. Clinical results and risk factors for reinjury 15 years after anterior cruciate ligament reconstruction: a prospective study of hamstring and patellar tendon grafts. *Am J Sports Med*. 2012;40(3):595-605.

105. Li S, Chen Y, Lin Z, Cui W, Zhao J, Su W. A systematic review of randomized controlled clinical trials comparing hamstring autografts versus bone-patellar tendon-bone autografts for the reconstruction of the anterior cruciate ligament. *Arch Orthop Trauma Surg.* 2012;132(9):1287-1297.

106. Lidén M, Ejerhed L, Sernert N, Laxdal G, Kartus J. Patellar tendon or semitendinosus tendon autografts for anterior cruciate ligament reconstruction: a prospective, randomized study with a 7-Year follow-up. *Am J Sports Med.* 2007;35(5):740-748.

107. Lind M, Menhert F, Pedersen AB. The first results from the Danish ACL reconstruction registry: epidemiologic and 2 year follow-up results from 5,818 knee ligament reconstructions. *Knee Surg Sports Traumatol Arthrosc.* 2009;17(2):117-124.

108. Lind M, Menhert F, Pedersen AB. Incidence and outcome after revision anterior cruciate ligament reconstruction: results from the Danish registry for knee ligament reconstructions. *Am J Sports Med.* 2012;40(7):1551-1557.

109. 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.

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

111. Lunde AS, Lundeborg S, Lettenstrom GS, Thygesen L, Huebner J. The person-number systems of Sweden, Norway, Denmark, and Israel. *Vital Health Stat.* 1980;Series 2(84):1-59.

112. Lyman S, Koulouvaris P, Sherman S, Do H, Mandl LA, Marx RG. Epidemiology of anterior cruciate ligament reconstruction: trends, readmissions, and subsequent knee surgery. *J Bone Joint Surg Am.* 2009;91(10):2321-2328.

113. Lynch AD, Logerstedt DS, Grindem H, Eitzen I, Hicks GE, Axe MJ, Engebretsen L, Risberg MA, Snyder-Mackler L. Consensus criteria for defining 'successful outcome' after ACL injury and reconstruction: a Delaware-Oslo ACL cohort investigation. *Br J Sports Med.* 2013:DOI: 10.1136/bjsports-2013-092299.

114. Maffulli N, Binfield PM, King JB. Articular cartilage lesions in the symptomatic anterior cruciate ligament-deficient knee. *Arthroscopy.* 2003;19(7):685-690.

115. Magnussen RA, Granan LP, Dunn WR, Amendola A, Andrish JT, Brophy R, Carey JL, Flanigan D, Huston LJ, Jones M, Kaeding CC, McCarty EC, Marx RG, Matava MJ, Parker RD, Vidal A, Wolcott M, Wolf BR, Wright RW, Spindler KP, Engebretsen L. Cross-cultural comparison of patients undergoing ACL reconstruction in the United States and Norway. *Knee Surg Sports Traumatol*

Arthrosc. 2010;18(1):98-105.

116. Magnussen RA, Lawrence JT, West RL, Toth AP, Taylor DC, Garrett WE. Graft size and patient age are predictors of early revision after anterior cruciate ligament reconstruction with hamstring autograft. *Arthroscopy*. 2012;28(4):526-531.

117. Magnussen RA, Mansour AA, Carey JL, Spindler KP. Meniscus status at anterior cruciate ligament reconstruction associated with radiographic signs of osteoarthritis at 5- to 10-year follow-up: a systematic review. *J Knee Surg*. 2009;22(4):347-357.

118. Maletis GB, Cameron SL, Tengan JJ, Burchette RJ. A prospective randomized study of anterior cruciate ligament reconstruction: a comparison of patellar tendon and quadruple-strand semitendinosus/gracilis tendons fixed with bioabsorbable interference screws. *Am J Sports Med*. 2007;35(3):384-394.

119. Maletis GB, Inacio MC, Desmond JL, Funahashi TT. Reconstruction of the anterior cruciate ligament: association of graft choice with increased risk of early revision. *Bone Joint J*. 2013;95-B(5):623-628.

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

121. Maletis GB, Inacio MC, Funahashi TT. Risk Factors Associated With Revision and Contralateral Anterior Cruciate Ligament Reconstructions in the Kaiser Permanente ACLR Registry. *Am J Sports Med*. 2014:DOI: 10.1177/0363546514561745.

122. Marcacci M, Zaffagnini S, Iacono F, Neri MP, Petitto A. Early versus late reconstruction for anterior cruciate ligament rupture. Results after five years of followup. *Am J Sports Med*. 1995;23(6):690-693.

123. Marks PH, Donaldson ML. Inflammatory cytokine profiles associated with chondral damage in the anterior cruciate ligament-deficient knee. *Arthroscopy*. 2005;21(11):1342-1347.

124. Marumo K, Saito M, Yamagishi T, Fujii K. The "ligamentization" process in human anterior cruciate ligament reconstruction with autogenous patellar and hamstring tendons: a biochemical study. *Am J Sports Med*. 2005;33(8):1166-1173.

125. Mascarenhas R, Saltzman BM, Sayegh ET, Verma NN, Cole BJ, Bush-Joseph C, Bach BR, Jr. Bioabsorbable Versus Metallic Interference Screws in Anterior Cruciate Ligament Reconstruction: A Systematic Review of Overlapping Meta-analyses. *Arthroscopy*. 2014:DOI: 10.1016/j.arthro.2014.1011.1011.

126. McGuire DA, Barber FA, Elrod BF, Paulos LE. Bioabsorbable interference screws for graft fixation in anterior cruciate ligament reconstruction. *Arthroscopy.* 1999;15(5):463-473.

127. McNicholas MJ, Rowley DI, McGurty D, Adalberth T, Abdon P, Lindstrand A, Lohmander LS. Total meniscectomy in adolescence. A thirty-year follow-up. *J Bone Joint Surg Br.* 2000;82(2):217-221.

128. McRae S, Leiter J, McCormack R, Old J, MacDonald P. Ipsilateral versus contralateral hamstring grafts in anterior cruciate ligament reconstruction: a prospective randomized trial. *Am J Sports Med.* 2013;41(11):2492-2499.

129. Meighan AA, Keating JF, Will E. Outcome after reconstruction of the anterior cruciate ligament in athletic patients. A comparison of early versus delayed surgery. *J Bone Joint Surg Br.* 2003;85(4):521-524.

130. Meredick RB, Vance KJ, Appleby D, Lubowitz JH. Outcome of single-bundle versus double-bundle reconstruction of the anterior cruciate ligament: a meta-analysis. *Am J Sports Med.* 2008;36(7):1414-1421.

131. Meuffels DE, Favejee MM, Vissers MM, Heijboer MP, Reijman M, Verhaar JA. Ten year follow-up study comparing conservative versus operative treatment of anterior cruciate ligament ruptures. A matched-pair analysis of high level athletes. *Br J Sports Med.* 2009;43(5):347-351.

132. 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;17(3):230-237.

133. Mithoefer K, Hambly K, Della Villa S, Silvers H, Mandelbaum BR. Return to sports participation after articular cartilage repair in the knee: scientific evidence. *Am J Sports Med.* 2009;37(Suppl 1):167-176.

134. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012.

135. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet.* 2001;357(9263):1191-1194.

136. Mohtadi NG, Chan DS, Dainty KN, Whelan DB. Patellar tendon versus hamstring tendon autograft for anterior cruciate ligament rupture in adults. *Cochrane Database Syst Rev.* 2011(9):CD005960.

137. Muneta T, Koga H, Mochizuki T, Ju YJ, Hara K, Nimura A, Yagishita K, Sekiya I. A prospective randomized study of 4-strand semitendinosus tendon anterior cruciate ligament reconstruction comparing single-bundle and double-bundle techniques. *Arthroscopy*. 2007;23(6):618-628.

138. Muren O, Dahlstedt L, Dalén N. Reconstruction of acute anterior cruciate ligament injuries: a prospective, randomised study of 40 patients with 7-year follow-up. No advantage of synthetic augmentation compared to a traditional patellar tendon graft. *Arch Orthop Trauma Surg.* 2003;123(4):144-147.

139. Murrell GA, Maddali S, Horovitz L, Oakley SP, Warren RF. The effects of time course after anterior cruciate ligament injury in correlation with meniscal and cartilage loss. *Am J Sports Med.* 2001;29(1):9-14.

140. Myklebust G, Bahr R. Return to play guidelines after anterior cruciate ligament surgery. *Br J Sports Med.* 2005;39(3):127-131.

141. Myklebust G, Engebretsen L, Braekken IH, Skjolberg A, Olsen OE, Bahr R. Prevention of anterior cruciate ligament injuries in female team handball players: a prospective intervention study over three seasons. *Clin J Sport Med*. 2003;13(2):71-78.

142. 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;31(6):981-989.

143. Möller E, Forssblad M, Hansson L, Wange P, Weidenhielm L. Bracing versus nonbracing in rehabilitation after anterior cruciate ligament reconstruction: a randomized prospective study with 2-year follow-up. *Knee Surg Sports Traumatol Arthrosc.* 2001;9(2):102-108.

144. Neuman P, Englund M, Kostogiannis I, Friden T, Roos H, Dahlberg LE. Prevalence of tibiofemoral osteoarthritis 15 years after nonoperative treatment of anterior cruciate ligament injury: a prospective cohort study. *Am J Sports Med.* 2008;36(9):1717-1725.

145. Nielsen AB, Yde J. Epidemiology of acute knee injuries: a prospective hospital investigation. *J Trauma.* 1991;31(12):1644-1648.

146. 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;62(5):687-695.

147. Noyes FR, Stabler CL. A system for grading articular cartilage lesions at arthroscopy. *Am J Sports Med.* 1989;17(4):505-513.

148. O'Connor DP, Laughlin MS, Woods GW. Factors related to additional knee injuries after anterior cruciate ligament injury. *Arthroscopy*. 2005;21(4):431-438.

149. O'Neill DB. Arthroscopically assisted reconstruction of the anterior cruciate ligament. A prospective randomized analysis of three techniques. *J Bone Joint Surg Am*. 1996;78(6):803-813.

150. OCEBM Levels of Evidence Working Group. The Oxford 2009 Levels of Evidence. *Oxford Centre for Evidence-Based Medicine.* Available at: http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/.

151. OCEBM Levels of Evidence Working Group. The Oxford 2011 Levels of Evidence. *Oxford Centre for Evidence-Based Medicine.* Available at: http://www.cebm.net/ocebm-levels-of-evidence/.

152. Odensten M, Gillquist J. Functional anatomy of the anterior cruciate ligament and a rationale for reconstruction. *J Bone Joint Surg Am.* 1985;67(2):257-262.

153. Olsen OE, Myklebust G, Engebretsen L, Holme I, Bahr R. Exercises to prevent lower limb injuries in youth sports: cluster randomised controlled trial. *BMJ.* 2005;330(7489):449.

154. Orchard J, Seward H, McGivern J, Hood S. Intrinsic and extrinsic risk factors for anterior cruciate ligament injury in Australian footballers. *Am J Sports Med.* 2001;29(2):196-200.

155. Ornetti P, Brandt K, Hellio-Le Graverand MP, Hochberg M, Hunter DJ, Kloppenburg M, Lane N, Maillefert JF, Mazzuca SA, Spector T, Utard-Wlerick G, Vignon E, Dougados M. OARSI-OMERACT definition of relevant radiological progression in hip/knee osteoarthritis. *Osteoarthritis Cartilage.* 2009;17(7):856-863.

156. Outerbridge RE. The etiology of chondromalacia patellae. *J Bone Joint Surg Br.* 1961;43-B(4):752-757.

157. Pagano M, Gauvreau K. *Principles of biostatistics*. 2nd ed. Pacific Grove: Duxbury; 2000.

158. Pauzenberger L, Syré S, Schurz M. “Ligamentization” in hamstring tendon grafts after anterior cruciate ligament reconstruction: a systematic review of the literature and a glimpse into the future. *Arthroscopy*. 2013;29(10):1712-1721.

159. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis.* 2001;60(2):91-97.

160. Pelletier JP, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. *Arthritis Rheum*. 2001;44(6):1237-1247.

161. Persson A, Fjeldsgaard K, Gjertsen JE, Kjellsen AB, Engebretsen L, Hole RM, Fevang JM. Increased risk of revision with hamstring tendon grafts compared with patellar tendon grafts after anterior cruciate ligament reconstruction: a study of 12,643 patients from the Norwegian Cruciate Ligament Registry, 2004-2012. *Am J Sports Med.* 2014;42(2):285-291.

162. Pinczewski LA, Lyman J, Salmon LJ, Russell VJ, Roe J, Linklater J. A 10-year comparison of anterior cruciate ligament reconstructions with hamstring tendon and patellar tendon autograft: a controlled, prospective trial. *Am J Sports Med.* 2007;35(4):564-574.

163. Prodromos CC, Han Y, Rogowski J, Joyce B, Shi K. A meta-analysis of the incidence of anterior cruciate ligament tears as a function of gender, sport, and a knee injury-reduction regimen. *Arthroscopy*. 2007;23(12):1320-1325.

164. Rahr-Wagner L, Thillemann TM, Pedersen AB, Lind M. Comparison of hamstring tendon and patellar tendon grafts in anterior cruciate ligament reconstruction in a nationwide population-based cohort study: results from the danish registry of knee ligament reconstruction. *Am J Sports Med*. 2014;42(2):278-284.

165. Raviraj A, Anand A, Kodikal G, Chandrashekar M, Pai S. A comparison of early and delayed arthroscopically-assisted reconstruction of the anterior cruciate ligament using hamstring autograft. *J Bone Joint Surg Br.* 2010;92(4):521-526.

166. Reinhardt KR, Hetsroni I, Marx RG. Graft selection for anterior cruciate ligament reconstruction: a level I systematic review comparing failure rates and functional outcomes. *Orthop Clin North Am.* 2010;41(2):249-262.

167. Renstrom P, Ljungqvist A, Arendt E, Beynnon B, Fukubayashi T, Garrett W, Georgoulis T, Hewett TE, Johnson R, Krosshaug T, Mandelbaum B, Micheli L, Myklebust G, Roos E, Roos H, Schamasch P, Shultz S, Werner S, Wojtys E, Engebretsen L. Non-contact ACL injuries in female athletes: an International Olympic Committee current concepts statement. *Br J Sports Med.* 2008;42(6):394-412.

168. Risberg MA, Holm I, Steen H, Eriksson J, Ekeland A. The effect of knee bracing after anterior cruciate ligament reconstruction. A prospective, randomized study with two years' follow-up. *Am J Sports Med.* 1999;27(1):76-83.

169. Roe J, Pinczewski LA, Russell VJ, Salmon LJ, Kawamata T, Chew M. A 7-year follow-up of patellar tendon and hamstring tendon grafts for arthroscopic anterior cruciate ligament reconstruction: differences and similarities. *Am J Sports Med*. 2005;33(9):1337-1345.

170. Roos H, Adalberth T, Dahlberg L, Lohmander LS. Osteoarthritis of the knee after injury to the anterior cruciate ligament or meniscus: the influence of time and age. *Osteoarthritis Cartilage.* 1995;3(4):261-267.

171. Roos H, Lauren M, Adalberth T, Roos EM, Jonsson K, Lohmander LS. Knee osteoarthritis after meniscectomy: prevalence of radiographic changes after twenty-one years, compared with matched controls. *Arthritis Rheum.* 1998;41(4):687-693.

172. 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;66(2):107-112.

173. Rose T, Hepp P, Venus J, Stockmar C, Josten C, Lill H. Prospective randomized clinical comparison of femoral transfixation versus bioscrew fixation in hamstring tendon ACL reconstruction--a preliminary report. *Knee Surg Sports Traumatol Arthrosc.* 2006;14(8):730-738.

174. Rosene JM, Fogarty TD. Anterior tibial translation in collegiate athletes with normal anterior cruciate ligament integrity. *J Athl Train.* 1999;34(2):93-98.

175. Rougraff B, Shelbourne KD, Gerth PK, Warner J. Arthroscopic and histologic analysis of human patellar tendon autografts used for anterior cruciate ligament reconstruction. *Am J Sports Med.* 1993;21(2):277-284.

176. Ryan J, Magnussen RA, Cox CL, Hurbanek JG, Flanigan DC, Kaeding CC. ACL Reconstruction: Do Outcomes Differ by Sex?: A Systematic Review. *J Bone Joint Surg Am.* 2014;96(6):507-512.

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

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

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

180. Sajovic M, Strahovnik A, Dernovsek MZ, Skaza K. Quality of Life and Clinical Outcome Comparison of Semitendinosus and Gracilis Tendon Versus Patellar Tendon Autografts for Anterior Cruciate Ligament Reconstruction: An 11-Year Follow-up of a Randomized Controlled Trial. *Am J Sports Med.* 2011;39(10):2161-2169.

181. Sajovic M, Vengust V, Komadina R, Tavcar R, Skaza K. A prospective, randomized comparison of semitendinosus and gracilis tendon versus patellar tendon autografts for anterior cruciate ligament reconstruction: five-year follow-up. *Am J Sports Med.* 2006;34(12):1933-1940.

182. Salmon L, Russell V, Musgrove T, Pinczewski L, Refshauge K. Incidence and risk factors for graft rupture and contralateral rupture after anterior cruciate ligament reconstruction. *Arthroscopy*. 2005;21(8):948-957.

183. Salmon LJ, Pinczewski LA, Russell VJ, Refshauge K. Revision anterior cruciate ligament reconstruction with hamstring tendon autograft: 5- to 9-year follow-up. *Am J Sports Med.* 2006;34(10):1604-1614.

184. Salmon LJ, Refshauge KM, Russell VJ, Roe JP, Linklater J, Pinczewski LA. Gender differences in outcome after anterior cruciate ligament reconstruction with hamstring tendon autograft. *Am J Sports Med.* 2006;34(4):621-629.

185. Samuelsson K, Andersson D, Ahldén M, Fu FH, Musahl V, Karlsson J. Trends in surgeon preferences on anterior cruciate ligament reconstructive techniques. *Clin Sports Med.* 2013;32(1):111-126.

186. Samuelsson K, Andersson D, Karlsson J. Treatment of anterior cruciate ligament injuries with special reference to graft type and surgical technique: an assessment of randomized controlled trials. *Arthroscopy*. 2009;25(10):1139-1174.

187. SBU. *Utvärdering av metoder i hälso- och sjukvården: En handbok.* 2 ed. Stockholm: Statens beredning för medicinsk utvärdering (SBU); 2014.

188. Shaieb MD, Kan DM, Chang SK, Marumoto JM, Richardson AB. A prospective randomized comparison of patellar tendon versus semitendinosus and gracilis tendon autografts for anterior cruciate ligament reconstruction. *Am J Sports Med.* 2002;30(2):214-220.

189. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* 2007;7:10.

190. Shelbourne KD, Gray T. Results of anterior cruciate ligament reconstruction based on meniscus and articular cartilage status at the time of surgery. Five- to fifteen-year evaluations. *Am J Sports Med.* 2000;28(4):446-452.

191. Shelbourne KD, Gray T, Haro M. Incidence of subsequent injury to either knee within 5 years after anterior cruciate ligament reconstruction with patellar tendon autograft. *Am J Sports Med*. 2009;37(2):246-251.

192. Shen C, Jiang SD, Jiang LS, Dai LY. Bioabsorbable versus metallic interference screw fixation in anterior cruciate ligament reconstruction: a meta-analysis of randomized controlled trials. *Arthroscopy*. 2010;26(5):705-713.

193. Shoemaker SC, Markolf KL. The role of the meniscus in the anterior-posterior stability of the loaded anterior cruciate-deficient knee. Effects of partial versus total excision. *J Bone Joint Surg Am.* 1986;68(1):71-79.

194. Smith TO, Davies L. The efficacy of continuous passive motion after anterior cruciate ligament reconstruction: a systematic review. *Phys Ther Sports.* 2007;8(3):141-152.

195. Smith TO, Davies L, Hing CB. Early versus delayed surgery for anterior cruciate ligament reconstruction: a systematic review and meta-analysis. *Knee Surg Sports Traumatol Arthrosc.* 2010;18(3):304-311.

196. Smith TO, Postle K, Penny F, McNamara I, Mann CJ. Is reconstruction the best management strategy for anterior cruciate ligament rupture? A systematic review and meta-analysis comparing anterior cruciate ligament reconstruction versus non-operative treatment. *Knee.* 2014;21(2):462-470.

197. Soligard T, Myklebust G, Steffen K, Holme I, Silvers H, Bizzini M, Junge A, Dvorak J, Bahr R, Andersen TE. Comprehensive warm-up programme to prevent injuries in young female footballers: cluster randomised controlled trial. *BMJ.* 2008;337:a2469.

198. Solomonow M, Baratta R, Zhou BH, Shoji H, Bose W, Beck C, D'Ambrosia R. The synergistic action of the anterior cruciate ligament and thigh muscles in maintaining joint stability. *Am J Sports Med.* 1987;15(3):207-213.

199. Speziali A, Delcogliano M, Tei M, Placella G, Bartoli M, Menghi A, Cerulli G. Fixation techniques for the anterior cruciate ligament reconstruction: early follow-up. A systematic review of level I and II therapeutic studies. *Musculoskelet Surg.* 2014;98(3):179-187.

200. Spindler KP, Kuhn JE, Freedman KB, Matthews CE, Dittus RS, Harrell FE, Jr. Anterior cruciate ligament reconstruction autograft choice: bone-tendon-bone versus hamstring: does it really matter? A systematic review. *Am J Sports Med.* 2004;32(8):1986-1995.

201. Stevens SS. On the theory of scales of measurement. *Science.* 1946;103(2684):677-680.

202. Swirtun LR, Renstrom P. Factors affecting outcome after anterior cruciate ligament injury: a prospective study with a six-year follow-up. *Scand J Med Sci Sports.* 2008;18(3):318-324.

203. Takeda H, Nakagawa T, Nakamura K, Engebretsen L. Prevention and management of knee osteoarthritis and knee cartilage injury in sports. *Br J Sports Med.* 2011;45(4):304-309.

204. Tandogan RN, Taser O, Kayaalp A, Taskiran E, Pinar H, Alparslan B, Alturfan A. Analysis of meniscal and chondral lesions accompanying anterior cruciate ligament tears: relationship with age, time from injury, and level of sport. *Knee Surg Sports Traumatol Arthrosc.* 2004;12(4):262-270.

205. Tapper EM, Hoover NW. Late results after meniscectomy. *J Bone Joint Surg Am.*

1969;51(3):517-526.

206. Tayton E, Verma R, Higgins B, Gosal H. A correlation of time with meniscal tears in anterior cruciate ligament deficiency: stratifying the risk of surgical delay. *Knee Surg Sports Traumatol Arthrosc.* 2009;17(1):30-34.

207. The Grading of Recommendations Assessment Development and Evaluation (GRADE) Working Group. GRADE. Available at: http://www.gradeworking-group.org/index.htm.

208. The National Board of Health and Welfare. National Quality Register Reporting. Available at: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19285/2013-12-12.pdf. Accessed July 3, 2014.

209. The Swedish National Knee Ligament Register. *Svenska korsbandsregistret: Årsrapport 2008*. http://www.artroclinic.se/info/rapport2008.pdf 2009.

210. The Swedish National Knee Ligament Register. *Swedish ACL Register: Annual Report 2013.* http://www.artroclinic.se/info/rapport2013en.pdf 2014.

211. The Swedish National Knee Ligament Register. The Swedish National Knee Ligament Register. Available at: http://www.artroclinic.se/scripts/cgiip.exe/WService=skreg/xb_index?land=US.

212. Thomson L, Handoll HHG, Cunningham AA, Shaw PC. Physiotherapist-led programmes and interventions for rehabilitation of anterior cruciate ligament, medial collateral ligament and meniscal injuries of the knee in adults. *Cochrane Database Syst Rev.* 2002(2):CD001354.

213. Tiamklang T, Sumanont S, Foocharoen T, Laopaiboon M. Double-bundle versus single-bundle reconstruction for anterior cruciate ligament rupture in adults. *Cochrane Database Syst Rev.* 2012(11):CD008413.

214. Trees AH, Howe TE, Dixon J, White L. Exercise for treating isolated anterior cruciate ligament injuries in adults. *Cochrane Database Syst Rev.* 2005(4):CD005316.

215. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology*. 2007;18(6):805-835.

216. von Porat A, Roos EM, Roos H. High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: a study of radiographic and patient relevant outcomes. *Ann Rheum Dis.* 2004;63(3):269-273.

217. Wasserstein D, Khoshbin A, Dwyer T, Chahal J, Gandhi R, Mahomed N, Ogilvie-Harris D. Risk factors for recurrent anterior cruciate ligament reconstruction:

a population study in Ontario, Canada, with 5-year follow-up. *Am J Sports Med*. 2013;41(9):2099-2107.

218. Webster KE, Feller JA, Leigh WB, Richmond AK. Younger patients are at increased risk for graft rupture and contralateral injury after anterior cruciate ligament reconstruction. *Am J Sports Med*. 2014;42(3):641-647.

219. World Health Organization. *Health system financing: the path to universal coverage*. http://www.who.int/whr/2010/en/ 2010.

220. World Health Organization. *Health intervention and technology assessment in support of universal health coverage*. http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R23-en.pdf May 24, 2014 2014.

221. Wright RW, Dunn WR, Amendola A, Andrish JT, Bergfeld J, Kaeding CC, Marx RG, McCarty EC, Parker RD, Wolcott M, Wolf BR, Spindler KP. Risk of tearing the intact anterior cruciate ligament in the contralateral knee and rupturing the anterior cruciate ligament graft during the first 2 years after anterior cruciate ligament reconstruction: a prospective MOON cohort study. *Am J Sports Med*. 2007;35(7):1131-1134.

222. Wright RW, Fetzer GB. Bracing after ACL reconstruction: a systematic review. *Clin Orthop Relat Res.* 2007;455:162-168.

223. Wright RW, Preston E, Fleming BC, Amendola A, Andrish JT, Bergfeld JA, Dunn WR, Kaeding C, Kuhn JE, Marx RG, McCarty EC, Parker RC, Spindler KP, Wolcott M, Wolf BR, Williams GN. A systematic review of anterior cruciate ligament reconstruction rehabilitation: part I: continuous passive motion, early weight bearing, postoperative bracing, and home-based rehabilitation. *J Knee Surg.* 2008;21(3):217-224.

224. Xu M, Gao S, Zeng C, Han R, Sun J, Li H, Xiong Y, Lei G. Outcomes of anterior cruciate ligament reconstruction using single-bundle versus double-bundle technique: meta-analysis of 19 randomized controlled trials. *Arthroscopy*. 2013;29(2):357-365.

225. Yagi M, Kuroda R, Nagamune K, Yoshiya S, Kurosaka M. Double-bundle ACL reconstruction can improve rotational stability. *Clin Orthop Relat Res.* 2007;454:100-107.

226. Yasuda K, Kondo E, Ichiyama H, Tanabe Y, Tohyama H. Clinical evaluation of anatomic double-bundle anterior cruciate ligament reconstruction procedure using hamstring tendon grafts: comparisons among 3 different procedures. *Arthroscopy*. 2006;22(3):240-251.

227. Yasuda K, Tsujino J, Ohkoshi Y, Tanabe Y, Kaneda K. Graft site morbidity with autogenous semitendinosus and gracilis tendons. *Am J Sports Med.* 1995;23(6):706-714.

228. Yunes M, Richmond JC, Engels EA, Pinczewski LA. Patellar versus hamstring tendons in anterior cruciate ligament reconstruction: A meta-analysis. *Arthroscopy*. 2001;17(3):248-257.

229. Zaffagnini S, Marcacci M, Lo Presti M, Giordano G, Iacono F, Neri MP. Prospective and randomized evaluation of ACL reconstruction with three techniques: a clinical and radiographic evaluation at 5 years follow-up. *Knee Surg Sports Traumatol Arthrosc*. 2006;14(11):1060-1069.

230. Zebis MK, Andersen LL, Bencke J, Kjaer M, Aagaard P. Identification of athletes at future risk of anterior cruciate ligament ruptures by neuromuscular screening. *Am J Sports Med*. 2009;37(10):1967-1973.

231. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage.* 2007;15(9):981-1000.

232. Zhu Y, Tang RK, Zhao P, Zhu SS, Li YG, Li JB. Double-bundle reconstruction results in superior clinical outcome than single-bundle reconstruction. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(5):1085-1096.

233. Åhlén M, Lidén M. A comparison of the clinical outcome after anterior cruciate ligament reconstruction using a hamstring tendon autograft with special emphasis on the timing of the reconstruction. *Knee Surg Sports Traumatol Arthrosc.* 2011;19(3):488-494.

234. Øiestad BE, Engebretsen L, Storheim K, Risberg MA. Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. *Am J Sports Med.* 2009;37(7):1434-1443.

235. Øiestad BE, Holm I, Aune AK, Gunderson R, Myklebust G, Engebretsen L, Fosdahl MA, Risberg MA. Knee Function and Prevalence of Knee Osteoarthritis After Anterior Cruciate Ligament Reconstruction: A Prospective Study With 10 to 15 Years of Follow-up. *Am J Sports Med.* 2010;38(11):2201-2210.

236. Øiestad BE, Holm I, Engebretsen L, Risberg MA. The association between radiographic knee osteoarthritis and knee symptoms, function and quality of life 10-15 years after anterior cruciate ligament reconstruction. *Br J Sports Med.* 2011;45(7):583-588.