PREDICTORS OF OUTCOME AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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"I would rather have questions that can't be answered

than answers that can't be questioned"

Richard Feynman

CONTENTS

1 ABSTRACT

An anterior cruciate ligament (ACL) injury is one of the most common injuries to the knee joint. It is also one of the most researched areas within sports medicine, orthopedics and physical therapy. The goal of this thesis was to evaluate patient-related, surgery-related and injury-related factors that affect the outcome after an ACL reconstruction.

This thesis comprises nine studies covering three themes: *developing a foundation for research, short-term predictors* and *long-term predictors*. The primary statistical methods used in this thesis were univariable and multivariable regression analyses with the various binary or continuous dependent outcomes.

The first theme consists of two studies; a cross-sectional analysis of a rehabilitation outcome register, Project ACL, and a systematic review of the Scandinavian knee ligament registers. Based on the results of the study presenting Project ACL, patients who returned to knee-strenuous sport were characterized as having superior patient-reported knee function and a superior psychological state compared with patients who had not returned to knee-strenuous sport. Moreover, this study also illustrated the differences in results related to various definitions of return to sport. Modifiable factors identified in the Scandinavian knee ligament registers that favor superior patient-reported outcome include not smoking, pre- and postoperative specialized rehabilitation, using a hamstring tendon autograft and less time between ACL injury and reconstruction. The non-modifiable factors found in the registers that favor a superior patient-reported outcome included male sex, younger age and not having sustained a concomitant intra-articular injury.

The second theme consists of five prospective studies based on the Swedish National Knee Ligament Register, Project ACL and a multicenter trial. This theme covered the short-term outcomes related to patient-reported knee function, achieving symmetrical knee function defined as a limb symmetry index of ≥ 90% in five tests of muscle function and return to sport. In terms of patient-related factors, male sex and younger age had a positive influence on returning to sport and patient-reported knee function in the short term, but not on recovering symmetrical knee function. In addition, a higher pre-injury level of physical activity was associated with returning to sport. In terms of surgery-related factors, the use of a hamstring tendon autograft had a positive effect on patient-reported knee function. Finally, patients who had sustained concomitant injuries appeared to run an increased risk of inferior outcome in patient-reported knee function and returning to sport after an ACL reconstruction.

The third theme consists of two studies; an exploratory analysis of two randomized trials and a long-term analysis of the Swedish National Knee Ligament Register. This theme covered the long-term outcomes related to patient-reported knee function and the development of osteoarthritis, i.e. Kellgren-Lawrence grade ≥ 2. In terms of patient-related factors, a minor effect on long-term knee function and osteoarthritis appears to be related to patient characteristics. A lower preoperative body mass index may, however, be an important attribute in understanding which patients report better long-term knee function. Surgery-related factors showed no clinically relevant effect on the long-term outcomes that were studied. The presence of concomitant injuries appears to have a negative influence on the long-term outcome, where cartilage lesions in particular are risk factors for inferior knee function.

2 SAMMANFATTNING PÅ SVENSKA

En främre korsbandsskada är en av de vanligaste allvarliga skadorna som kan drabba knäleden. Denna skada har stått i centrum för mycket forskning med över 19,000 publikationer inom idrottsmedicin, ortopedi och fysioterapi. Syftet med föreliggande avhandling är att studera faktorer som kan påverka utfallet hos patienter som genomgått en främre korsbandsrekonstruktion.

Föreliggande avhandling baseras på nio studier summerat i tre övergripande teman: *en grund för fortsatt forskning, kortsiktiga prediktorer* och *långsiktiga prediktorer*. De statistiska analyserna i avhandlingens delarbeten har i huvudsak utgjorts av univariabla och multivariabla regressionsanalyser, där både binära och kontinuerliga beroende utfallsmått har använts.

Avhandlingens första tema består av två studier; en tvärsnittsanalys baserat på data från ett rehabiliteringsregister, Projekt Korsband, och en systematisk översikt på de tre skandinaviska korsbandsregisterna. I studien baserad på Projekt Korsband karaktäriserades patienter som återgått till knäkrävande idrott av högre patient-rapporterad knäfunktion och bättre psykologisk status efter främre korsbandsrekonstruktion, jämfört med patienter som inte återgått. Studien illustrerade även hur resultat kan variera beroende på hur utfallet *återgång till idrott* definieras. Från den systematiska översikten på de skandinaviska korsbandsregisterna identifierades följande modifierbara faktorer ha positiv påverkan på patient-rapporterat utfall efter främre korsbandsrekonstruktion: att inte röka, specialiserad pre- och postoperativ rehabilitering, rekonstruktion med hamstringssenegraft och mindre tid mellan främre korsbandsskada och rekonstruktion. De icke-modifierbara faktorerna som identifierades innefattade manligt kön, yngre ålder vid rekonstruktion och avsaknad av associerad intra-artikulär knäskada.

Det andra temat består av fem prospektiva studier baserade på svenska korsbandsregistret, Projekt Korsband, och en multicenterstudie. I temat undersöks de kortsiktiga utfallsmåtten patient-rapportad knäfunktion, återhämtning av knäfunktion definierat som *limb symmetry index* ≥ 90 % i fem muskelfunktionstester, och återgång till idrott efter främre korsbandsrekonstruktion. Manligt kön och yngre ålder var de patient-relaterade faktorerna som identifierades ha positiv påverkan på återgång till idrott och kortsiktig patient-rapporterad knäfunktion. Dessutom hade patienter med en högre fysisk aktivitetsnivå innan skadan en högre sannolikhet att kunna återgå till idrott. Ingen patient-relaterad faktor var associerad med återhämtning av knäfunktion. En främre korsbandsrekonstruktion med hamstringssenegraft ökade sannolikheten att rapportera högre knäfunktion på kort sikt jämfört med patellasenegraft. Patienter med en associerad knäskada hade ökad risk för sämre knäfunktion och kunde inte återgå till idrott efter främre korsbandsrekonstruktion.

Avhandlingens tredje tema består av två studier; en explorativ analys av två randomiserade kontrollerade studier och en långtidsuppföljning av svenska korsbandsregistret. I temat undersöktes de långsiktiga utfallsmåtten patient-rapporterad knäfunktion och förekomsten av knäledsartros, definierat som en Kellgren-Lawrence grad ≥ 2. Ett högre preoperativt body mass index ökade sannolikheten för en sämre patientrapporterad knäfunktion tio år efter främre korsbandsrekonstruktion. Övriga patientrelaterade faktorer hade begränsad påverkan på långsiktig patient-rapporterad knäfunktion och utvecklingen av artros. Operationsrelaterade faktorer hade ingen klinisk påverkan på långtidsutfallen efter främre korsbandsrekonstruktion. Patienter med associerade knäskador, framförallt allvarlig broskskada, hade ökad risk för sämre långsiktig knäfunktion jämfört med patienter med isolerad främre korsbandsskada, som genomgått rekonstruktion.

3 LIST OF PAPERS

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

THEME 1 – CREATING A FOUNDATION FOR RESEARCH

I. **Return to knee-strenuous sport after anterior cruciate ligament reconstruction: a report from a rehabilitation outcome registry of patient characteristics**

   Hamrin Senorski E, Samuelsson K, Thomee C, Beischer S, Karlsson J, Thomee R

   Knee Surgery Sports Traumatology Arthroscopy, 2017 May;25(5):1364-1374

II. **Factors that affect patient-reported outcome after anterior cruciate ligament reconstruction – a systematic review of the Scandinavian knee ligament registers**

   Hamrin Senorski E, Svantesson E, Baldari A, Ayeni OR, Engebretsen L, Franceschi F, Karlsson J, Samuelsson K

   British Journal of Sports Medicine, Conditionally accepted

THEME 2 – SHORT-TERM PREDICTORS

III. **Preoperative knee laxity measurements predict the achievement of a patient-acceptable symptom state after ACL reconstruction: a prospective multicenter study**

   Hamrin Senorski E, Svantesson E, Sundemo D, Musahl V, Zaffagnini S, Kuroda R, Karlsson J, Samuelsson K

   Journal of ISAKOS, 2018, doi:10.1136/jisakos-2017-000186

IV. **Increased odds of patient-reported success at 2 years after anterior cruciate ligament reconstruction in patients without cartilage lesions: a cohort study from the Swedish National Knee Ligament Register**

   Hamrin Senorski E, Alentorn-Geli E, Musahl V, Fu F, Krupic F, Desai N, Westin O, Samuelsson K

   Knee Surgery Sports Traumatology Arthroscopy, 2017, doi:10.1007/s00167-017-4592-9

V. **Factors affecting the achievement of a patient acceptable symptom state one year after ACL reconstruction - A cohort study on 343 patients from two registries**

   Hamrin Senorski E, Svantesson E, Beischer S, Grassi A, Krupic F, Thomeé R, Samuelsson K

   Orthopaedic Journal of Sports Medicine, 2018, Accepted

VI. Concomitant injuries may not reduce the likelihood of achieving symmetrical muscle function one year after anterior cruciate ligament reconstruction – a prospective observational study based on 263 patients

Hamrin Senorski E, Svantesson E, Beischer S, Thomeé C, Grassi A, Krupic F, Thomeé R, Karlsson J, Samuelsson K

Knee Surgery Sports Traumatology Arthroscopy, 2018, doi:10.1007/s00167-018-4845-2

VII. Low one-year return to sport rate after anterior cruciate ligament reconstruction regardless of patient and surgical factors – A prospective cohort study on 272 patients

Hamrin Senorski E, Svantesson E, Beischer S, Thomeé C, Thomeé R, Karlsson J, Samuelsson K

American Journal of Sports Medicine, 2018, Accepted

THEME 3 – LONG-TERM PREDICTORS

VIII. Preoperative predictors of 16-year acceptable knee function and osteoarthritis after anterior cruciate ligament reconstruction – an analysis based on 147 patients from two randomised controlled trials

Hamrin Senorski E, Sundemo D, Svantesson E, Sernert N, Kartus J, Karlsson J, Samuelsson K

Manuscript

IX. Ten-year risk factors of the Knee injury and Osteoarthritis Outcome Score after anterior cruciate ligament reconstruction: a study of 874 patients from the Swedish National Knee Ligament Register

Hamrin Senorski E, Svantesson E, Spindler K, Alentorn-Geli E, Sundemo D, Westin O, Karlsson J, Samuelsson K

Manuscript

OTHER PAPERS BY THE AUTHOR NOT INCLUDED IN THE THESIS

X. No Differences in Subjective Knee Function between Surgical Techniques of Anterior Cruciate Ligament Reconstruction at Two Years Follow-Up - A Cohort Study from the Swedish National Knee Ligament Register

Hamrin Senorski E, Sundemo D, Murawski CD, Alentorn-Geli E, Musahl V, Fu F, Desai N, Stålman A, Samuelsson K

Knee Surgery Sports Traumatology Arthroscopy, 2017 Dec;25(12):3945-3954

XI. Double-bundle anterior cruciate ligament reconstruction is superior to single-bundle reconstruction in terms of revision frequency: a study of 22,460 patients from the Swedish National Knee Ligament Register

Svantesson E, Sundemo D, Hamrin Senorski E, Alentorn-Geli E, Musahl V, Fu FH, Desai N, Stålman A, Samuelsson K

Knee Surgery Sports Traumatology Arthroscopy, 2017 Dec;25(12):3884-3891

XII. Graft Diameter as a Predictor for Revision Anterior Cruciate Ligament Reconstruction and KOOS and EQ-5D Values: A Cohort Study From the Swedish National Knee Ligament Register Based on 2240 Patients

Snaebjornsson T, Hamrin Senorski E, Ayeni OR, Alentorn-Geli E, Krupic F, Norberg F, Karlsson J, Samuelsson K

American Journal of Sports Medicine, 2017 Jul;45(9):2092-2097

XIII. Adolescents and female patients are at increased risk for contralateral anterior cruciate ligament reconstruction: a cohort study from the Swedish National Knee Ligament Register based on 17,682 patients

Snaebjornsson T, Hamrin Senorski E, Sundemo D, Svantesson E, Westin O, Musahl V, Alentorn-Geli E, Samuelsson K

Knee Surgery Sports Traumatology Arthroscopy, 2017 Dec;25(12):3938-3944

XIV. Young athletes return too early to knee-strenuous sport, without acceptable knee function after anterior cruciate ligament reconstruction

Beischer S, Hamrin Senorski E, Thomee C, Samuelsson K, Thomee R

Knee Surgery Sports Traumatology Arthroscopy, 2017, doi:10.1007/s00167-017-4747-8

XV. Meniscal repair results in inferior short-term outcomes compared with meniscal resection: a cohort study of 6398 patients with primary anterior cruciate ligament reconstruction

Svantesson E, Cristiani R, Hamrin Senorski E, Forssblad M, Samuelsson K, Stålman A

Knee Surgery Sports Traumatology Arthroscopy, 2017, doi:10.1007/s00167-017-4793-2

XVI. **"I never made it to the pros…" Return to sport and becoming an elite athlete after pediatric and adolescent anterior cruciate ligament injury-Current evidence and future directions**

Hamrin Senorski E, Seil R, Svantesson E, Feller JA, Webster KE, Engebretsen L, Spindler K, Siebold R, Karlsson J, Samuelsson K

Knee Surgery Sports Traumatology Arthroscopy, 2017, doi:10.1007/s00167-017-4811-4

4 ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ADL	Activities of daily living
AARSC	Anatomic Anterior cruciate ligament Reconstruction Scoring Checklist
AUC	Area Under the Curve
CI	Confidence Interval
EBM	Evidence-Based Medicine
EUA	Examination under Anesthesia
EQ-5D	European Quality of Life Five Dimensions
HT	Hamstring Tendon autograft
ICC	Intraclass Correlation Coefficient
ICRS	International Cartilage Repair Society
IKDC-SKF	International Knee Documentation Committee Subjective Knee Form
KOOS	Knee injury and Osteoarthritis Outcome Score
K-SES	Knee Self-Efficacy Scale
LSI	Limb Symmetry Index
MCID	Minimal Clinical Important Difference
MDC	Minimal Detectable Change
MeSH	Medical Subject Heading
MIC	Minimal Important Change
MRI	Magnetic Resonance Imaging
NKLR	Norwegian Knee Ligament Register
OR	Odds Ratio
PAS	Physical Activity Scale
PASS	Patient Acceptable Symptom State

PCL	Posterior Cruciate Ligament
PIVOT	Prospective International Validation of Outcome Technology
PROMs	Patient-Reported Outcome Measurements
PT	Patellar Tendon autograft
QoL	Quality of Life
QPS	Quantitative Pivot Shift
QT	Quadriceps Tendon autograft
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
SD	Standard Deviation
SNKLR	Swedish National Knee Ligament Register
TP	Transportal
TT	Transtibial
WOMAC	Western Ontario and McMaster Universities Arthritis Index

5 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	Systematic error
Case series	Uncontrolled observational study of outcomes in a group with a given exposure
Case-control study	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	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	Secondary condition aggravating an already existing one
Confidence interval	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	The time interval from ACL injury to surgical treatment interval
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 that 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 study	Controlled prospective interventional study in which eligible controlled trial 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	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 reconstruction	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

06

INTRODUCTION

6.1 THE KNEE JOINT

The knee joint or *articulatio genus* is one of the largest and most complicated synovial joints in the human body (Figure 1). It has the complex function of providing both mobility and stability to the lower extremities.[220] The joint comprises the distal end of the femur and the proximal end of the tibia. In addition, the anterior part of the femur (*facies patellaris femoris*) articulates with the largest sesamoid bone of the human body, the patella, and together they form the patellofemoral joint.[225]

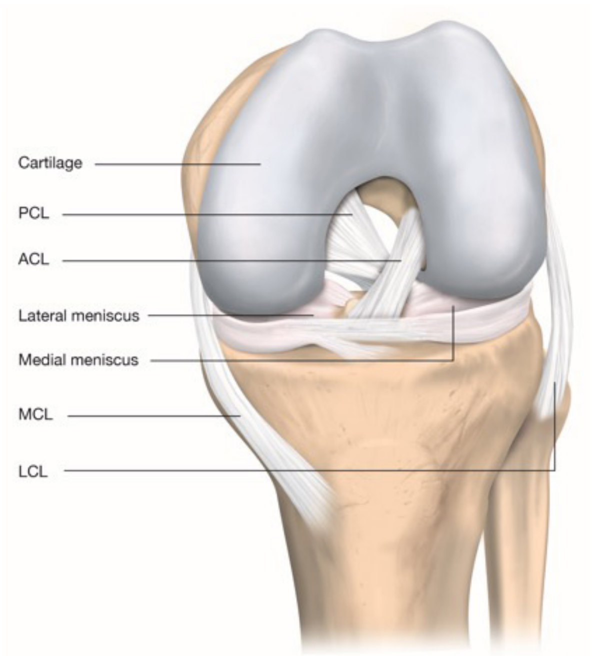

FIGURE 1

The gross anatomy of the knee joint.

6.1.1 ARTICULAR CARTILAGE

The articular surfaces of the knee joint, including the femur, the tibial plateau and the patella are covered by hyaline cartilage which, together with the synovial fluid, provides smooth, near friction-free surfaces for articulation.[50] Its principal function is also to facilitate the transmission of loads with a low frictional coefficient.[57 170] The hyaline articular cartilage consists primarily of water, but it also contains chondroblasts and chondrocytes. These cells depend on the diffusion of nutrients from the synovial fluid due to the near avascular presentation of cartilage in general, with the exception of the calcified layers closest to the bone.[57] To withstand the demanding biomechanical environment of the knee joint, the articular cartilage depends on the function of the chondrocyte cells to produce essential proteoglycans. The proteoglycans are responsible for the viscoelastic properties of the articular cartilage, compression and elasticity.[50] These properties of the cartilage make it easier for the meniscus to transmit the compressive forces to which the knee is subjected.[57] Evidently, due to the avascular presentation, articular cartilage has a limited capacity for intrinsic healing and repair. In cases where the low-friction hyaline cartilage has been disrupted but has started to heal, the injured cartilage is primarily replaced by fibrous cartilage with relatively higher friction, susceptible to new lesions. A healthy articular cartilage is therefore of paramount importance for the health of the knee joint.[51 57]

6.1.2. MENISCI

The two menisci, medial and lateral, are two C-shaped discs of fibrocartilage that are located between the tibial plateau and femoral condyles.[101] To facilitate the articulation of the knee joint, the upper surface of the menisci is concave, in contrast to the femoral condyle. The menisci are predominantly composed of collagen, but they also contain fibroblasts and chondrocyte cells.[57] In general, the menisci are wedge shaped in cross-section, with the peripheral border of each meniscus being thicker, while the inner parts are thinner.[101]

The menisci have several attachments to one another and the tibia through intra-articular ligaments.[101] The anterior and posterior horns of each meniscus are attached to the anterior and posterior intercondylar area of the tibial plateau respectively. Interestingly, the two menisci are well vascularized at the time of birth in humans.[101] However, as the menisci mature, the vascularization is reduced and limited to the peripheral third and the horns.[16] The inner area of the menisci is avascular and dependent on diffusion.[31] The neural supply, including mechanoreceptors of the menisci is also limited, but it is regarded as vital for the proprioceptive capacity of the knee joints.[57]

The main function of the menisci is to facilitate articulation and transmit the compressive loads in the knee between the femur and the tibia.[154] It is estimated that the menisci transmit 50-70% of the load placed on the knee away from the articular cartilage.[57 101] This naturally protects the articular cartilage from excessive pressures but requires intact menisci, including their attachments to the bones. The menisci also facilitate the nourishment of articular cartilage and lubricate the joint.[101] More importantly, recent literature has highlighted the function of the menisci in providing stability to the knee joint.[238 241] The medial meniscus is firmly attached to the deep fibers of the medial collateral ligament, which makes the medial meniscus particularly important for knee-joint stability in patients who have sustained an ACL injury.[57] The lateral meniscus has an almost circular shape and is smaller than 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 lateral meniscus can therefore move more freely during knee movement compared with the medial meniscus.[57] In terms of concomitant meniscal injury in a patient who sustains an ACL injury, these are represented in more than 40% of cases, the majority located in the medial meniscus.[35 43 57 183 191 260]

6.1.3. COLLATERAL LIGAMENTS

The collateral ligaments are two of four main stabilizing ligaments of the knee joint. The two extra-articular ligaments have been named after their location in the knee joint, medial and lateral, and act as the main restraints in these directions.

The medial collateral ligament is a strong, broad, ligamentous band, referred to as the largest structure situated on the medial side of the knee joint.[190] When the ligament is stressed, it aids control in transferring the joint through a normal range of movement, as well as contributing to the proprioceptive capacity of the knee joint.[56 189] The medial collateral ligament acts to prevent medial and anterior movement of the tibia as well as hyperextension.[125 190] The ligament is divided into two parts, the superficial (the tibiofemoral ligament) and the deep (the mid-third capsular ligament) ligaments.[56 189] The superficial part of the medial collateral ligament attaches to the medial epicondyle of the femur and blends into the semimembranosus tendon and the posteromedial crest of the tibia.[56 77] The deep aspect of the medial collateral ligament comprises the meniscofemoral ligament, attaching distally to the superficial medial collateral ligament, and the meniscotibial ligament, attaching to the femur.[77 125] Uniquely, both ligaments insert to the medial menisci.[56] The medial collateral ligament is one of the most commonly injured ligaments in the knee.[77 190]

The lateral collateral ligament is a cord-like extra-articular ligamentous band on the lateral side of the knee joint. The ligament originates from the lateral femoral epicondyle and attaches to the head of the fibula after joining the biceps femoris tendon,[89 333] thereby contributing to the formation of the posterolateral corner.[337] In comparison with the medial collateral ligament, the lateral collateral ligament does not attach to the meniscus, possibly explaining why this ligament is not as susceptible to injuries as its medial counterpart. In addition, these injuries often occur in contact situations where medially directed contact is more common. The main function of the lateral collateral ligament is to resist varus force and external tibial rotation.[333] An injury to the lateral collateral ligament is seldom isolated,[89] approximately approximately only 2% of cases.[73 147] Instead, the injury is most commonly referred to as a concomitant injury.

6.1.4. JOINT CAPSULE

The joint capsule surrounds the knee joint and provides additional stability.[135] It consists of two layers, an internal layer and an external layer. The internal layer of the joint capsule is described as a thin synovial membrane composed of connective tissue, while the external layer is composed of a fibrous membrane mainly consisting of collagen fibers.[78 135] The free space inside the knee joint is filled by synovial fluid, composed primarily of hyaluronic acid and interstitial fluid and produced by the joint capsule. The synovial fluid carries nutrients to the intra-articular structures with poor blood supply, such as the articular cartilage.[78]

The posterolateral corner is a specific area of the joint capsule, which consists of 28 individual structures that provide stability to the posterior and lateral aspects of the knee joint.[309] The most important structures that support this area are the lateral collateral ligament, the popliteus tendon and the popliteofibular ligament.[309] In addition, the common peroneal nerve is intimately related the posterolateral corner and fibula.

6.1.5. CRUCIATE LIGAMENTS

The two cruciate ligaments are extrasynovial, intra-articular ligaments in the tibiofemoral joint.[251] The cruciate ligaments are located to a large extent in the posterior area of the joint including the capsule, thereby providing stability without limiting range of motion in flexion and extension.[191] The ligaments work together to control the forward and backward motion (anteroposterior stability) and rotational stability of the knee.[195] The two cruciate ligaments run in torsion, crossing each other in an X-shaped pattern, which has given them their characteristic names. When the knee is in flexion, the cruciate ligaments are strongly crossed, while in extensions they run more parallel.[251]

The anterior cruciate ligament (ACL) runs from the tibia, area intercondylaris anterior, to the femur, the medial aspect of the lateral condyle.[320] This ligament extends upwards and fans out, dorsally and laterally, from the tibial plateau.[42 340] Although it is regarded as one ligament, the ligament fibers have been described as having different angles of insertion, described as creating two bundles, the anteromedial bundle and posterolateral bundle.[320 340] Together, they prevent the tibia from anterior translation and restrict the internal and external rotation of the tibia in relation to the femur.[42]

The posterior cruciate ligament (PCL) is comprised of a bundle of ligament fibers attaching to the back of the tibia, area intercondylaris posterior, to the femur and the lateral aspect of the medial femoral condyle.[373] The ligament thus runs medially, straight up in the knee joint and slightly forward. The PCL prevents the posterior translation of the tibia in relation to the femur, i.e. prevents the tibia displacing posteriorly.[373] The PCL is considered to be stronger than the ACL.[187]

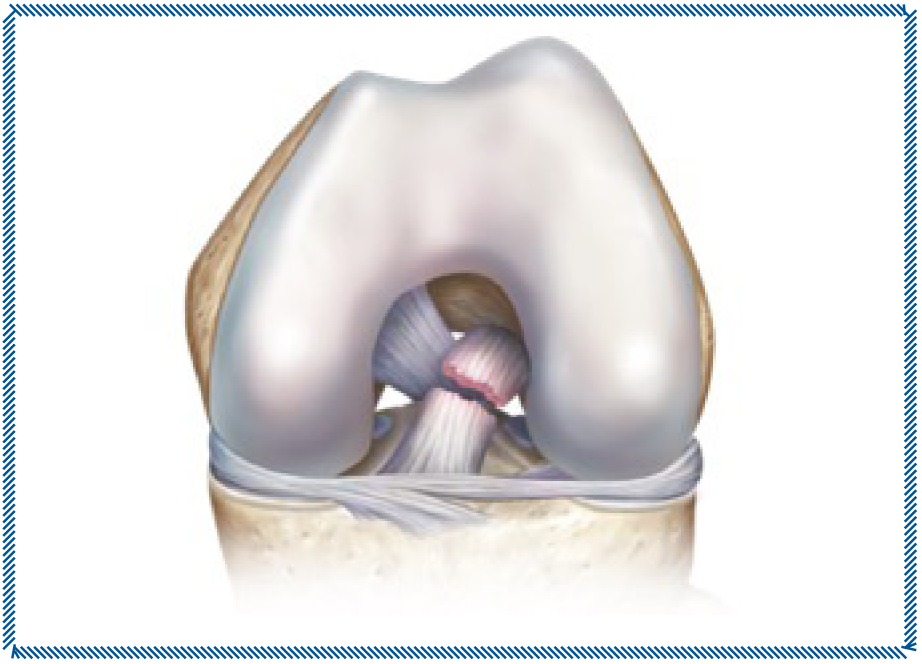

FIGURE 2
A tear in the ACL.

6.2. ANTERIOR CRUCIATE LIGAMENT INJURY

An ACL injury is characterized by the total rupture of the ligament located in the center of the knee joint (Figure 2).[42] In cases where the ACL does not totally rupture, this is referred to as a partial tear or an elongation. These groups of patients have seldom been the specific subject of research, since a partial tear is relatively uncommon and difficult to identify. In this thesis, the vast majority of patients have sustained a total ACL injury, isolated or in combination with other injuries referred to as concomitant injuries, and have undergone an ACL reconstruction as part of their treatment.

6.2.1. INCIDENCE

An injury to the ACL is regarded as common among athletes and patients participating in sport, where the incidence is suggested to be approximately 80 per 100,000 inhabitants in Sweden and worldwide.[212 231] The number of primary ACL injuries in 2016 was approximately 7,000 in the Swedish National Knee Ligament Register (SNKLR), based on the fact that it is suggested that 50% of the ACL injuries should undergo reconstructive treatment in Scandinavia.[121] The mean age for a primary ACL reconstruction in Sweden is 27 years and the number of reconstructions is fairly evenly matched between patient genders.[183] Interestingly, the age of revision ACL reconstruction in Sweden is 28 years for men and 23 years for women.

6.2.2. ETIOLOGY

The majority of ACL injuries are non-contact injuries, where as many as 80% of the injuries in handball and soccer occur in non-contact situations, such as landing or sidestep cutting.[245 265] The ACL injury mechanism is somewhat characteristic and understanding it may facilitate an early diagnosis. A previous study, which set out to determine the mechanism of injury, suggested that an ACL injury was caused by an impingement of the ACL against the lateral femoral condyle, induced by a combination of forced quadriceps contraction and tibial rotation.[265] More recently, a Norwegian research group used video analysis and computerized modeling of the knee to study the mechanism of non-contact ACL injuries.[176] Conclusively, the authors suggested that the injury occurs near knee extension, at approximately 20-30 degrees of knee flexion, together with a valgus force. This causes the compression of the lateral femoral condyle and the lateral tibial plateau. From the point of initial contact, the ACL ruptures after 40 milliseconds due to the lateral femoral condyle sliding posteriorly on the lateral tibial plateau, instead of anteriorly in a normal flexion movement (Figure 3). Compression forces in the knee joint at this moment were estimated to be 3.2 times body weight. The knee joint commonly continues to flex after injury, resulting in the lateral femoral notch impacting against the posterolateral tibial plateau, creating a forced internal rotation of the tibia and making the knee subject to concomitant injuries.

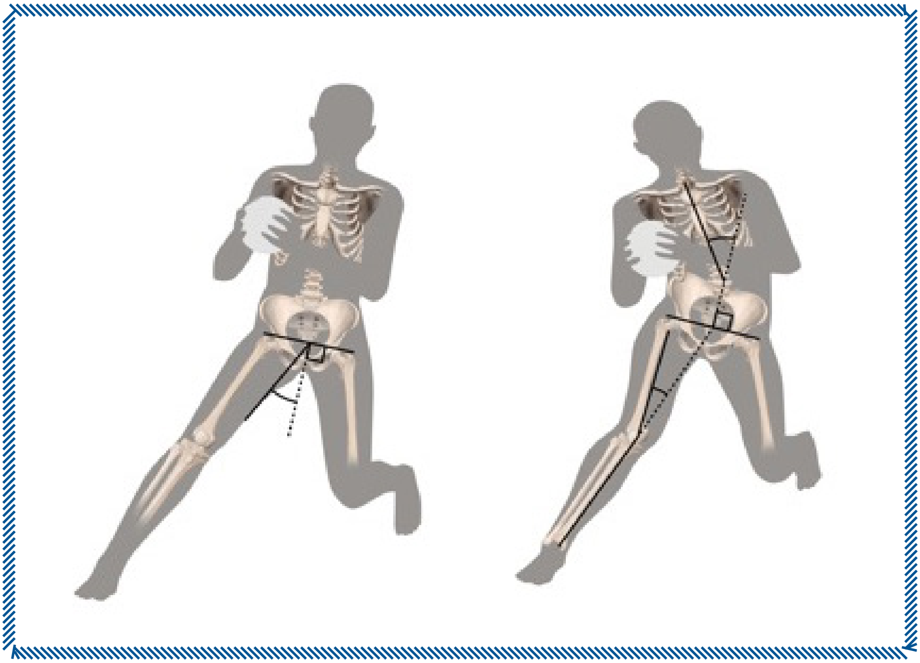

FIGURE 3
The mechanism of ACL injury from initial contact to 40 milliseconds later.

The ACL injury has been the subject of a great deal of previous research in order to identify extrinsic and intrinsic risk factors for sustaining the injury.[34 40 110 150 178 245-248 258 265 269 272 332 386-390] Interestingly, in the pursuit of evidence to reduce the number or ACL injuries in sports, the modification of intrinsic risk factors with primary prevention exercises and adequate neuromuscular training has proven effective.[245 364 365] The mechanism that gives these exercises the effect of reducing the number of severe knee injuries is yet to be identified. The current hypothesis is that it is an association of several factors, such as strength and muscle activation.[242 249 273 348] More importantly, consistency in performing the exercises is key in achieving the reduction of injuries, as exemplified by Myklebust et al.[248] in the top Norwegian handball leagues. There is also increasing evidence that non-modifiable intrinsic risk factors such as family history, general knee laxity and genu recurvatum (knee hyperextension) [232 342] and increased tibial slope[237 325 326] contribute to the occurrence of non-contact ACL injuries. In terms of the increased tibial slope, this has been associated with an anterior shift in the resting position of the tibia, relative to the femur, throughout the range of motion of the knee. This, in combination with axial loading, may cause an increase in anterior tibial translation, thereby increasing the risk of ACL injury.[237 325 326] Unfortunately, the prospective screening of individuals who run an increased risk of sustaining an injury is difficult and controversial.[165 184 331 386] There is a need for future research on secondary prevention in the light of the high risk of subsequent ACL injuries occurring, especially in younger patients.[145, 151, 22]

6.2.3. CONCOMITANT INJURIES

Depending on the energy of the trauma which leads to injury, the ACL rupture may be partial or complete. Interestingly, an isolated ACL rupture is uncommon, as only 30-40% of all ACL injuries are considered to be isolated. [183 349] Recent literature suggests that the numbers may actually be as low as 12%[266] and some even say that the isolated ACL injury does not exist. In most of the cases, several other anatomic structures of the knee may be injured, so-called concomitant injuries, affecting structures such as the PCL, the medial collateral ligament, the lateral collateral ligament, the menisci, or articular cartilage.

Question
How do concomitant injuries and injury-related factors affect patient-related outcomes after ACL reconstruction? Does the impact of injury-related factors shift between short-term and long-term follow-ups?

6.3. CLINICAL ASSESSMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES

The clinical assessment of a suspected ACL rupture is based on evaluating the increase in anteroposterior and rotational knee-joint laxity. The most common tests to evaluate knee-joint laxity are described below.

6.3.1 THE LACHMAN TEST

Under anesthesia, the Lachman test has been described with a diagnostic accuracy of acute ACL ruptures, < 2 weeks from injury, of 77.7% sensitivity and > 95% specificity.[212] The diagnostic accuracy of subacute or chronic ACL ruptures, > 2 weeks from injury, is 84.6% sensitivity and > 95% specificity.[212] It is important to note that, in this study,[212] all examinations were performed under anesthesia. The Lachman test is performed with the patient's knee in 30° of knee flexion and is assessed relative to the contralateral knee according to the IKDC guidelines.[143] The examiner places one hand behind the tibia and the other hand ventrally on the patient's distal femur (Figure 4). Anterior translation of the tibia, relative to the femur, with a soft end feel, indicates a positive test.[212] A side-to-side difference of more than about 2 mm of anterior translation suggests ACL involvement. Total anterior translation of 10 mm is considered to be an ACL injury.

KT-1000/ROLIMETER

The most common devices for quantifying the Lachman test, anteroposterior laxity, are the KT-1000 (Figure 5) and the rolimeter.[30 276 308] These devices allow for quantification in millimeters of the unidirectional force applied during this static laxity test.

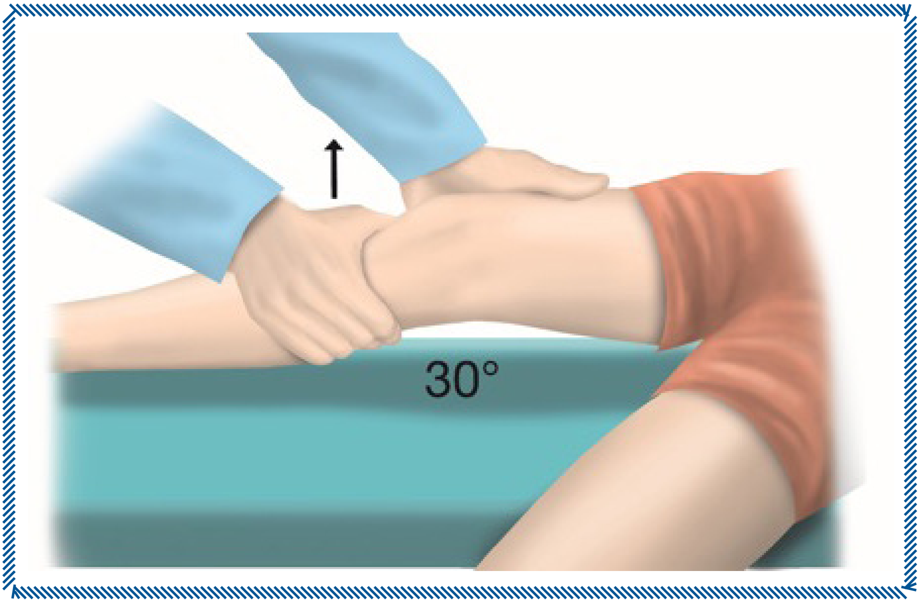

FIGURE 4
The Lachman test performed with the patient's knee in 30 degrees of flexion.

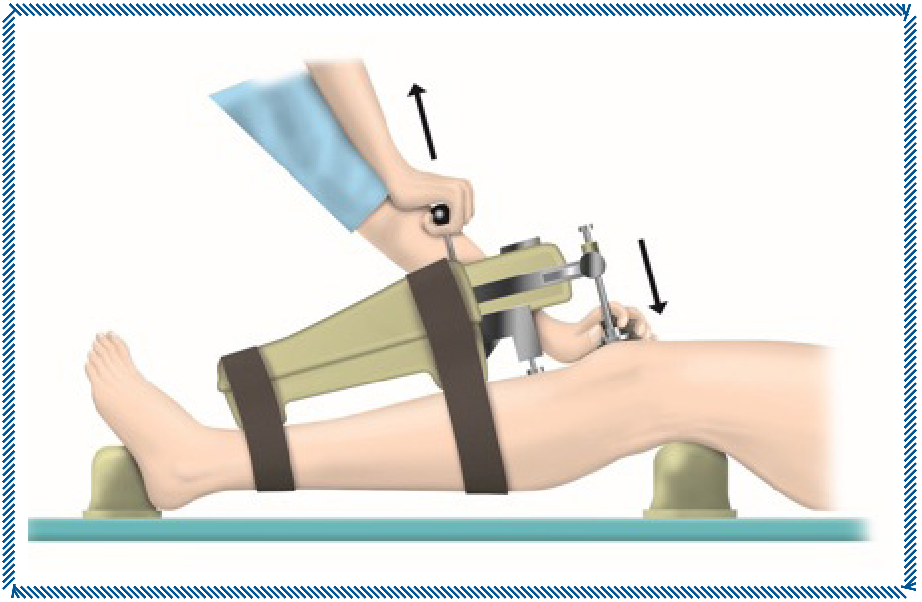

FIGURE 5
The KT-1000. A method to quantify anteroposterior laxity of the knee joint.

6.3.2. THE LELLI TEST

The Lelli test is a novel ACL clinical assessment test to identify ACL tears accurately. The examiner creates a fulcrum by placing one fist under the patient's calf while applying a force, downwards, towards the femur.[197] A positive test is seen when the patient's heel remains on the treatment table. The creator of the test reported a high sensitivity of 1.0,[197] suggesting that the test is more sensitive at identifying ACL ruptures than the Lachman, the anterior drawer and the pivot-shift tests.

6.3.3 THE ANTERIOR DRAWER TEST

The anterior drawer test has been reported with a sensitivity and specificity of 0.18-0.92 and 0.78-0.98 respectively.[41] The test has been reported to be better at identifying chronic ACL ruptures.[306] In the test, the patient lies supine, the hips should be flexed to 45 degrees, the knees should be flexed to 90 degrees and the feet should stay flat on the ground. The examiner grasps the proximal tibia, below the tibiofemoral joint line, and attempts to translate the tibia anteriorly relative to the femur.[168] To stabilize the patient's knee during the test, the examiner can sit on the patient's toes. The test is considered positive if there is side-to-side difference in anterior translation or if there is a lack of end feel.

6.3.4. THE PIVOT-SHIFT TEST

The pivot-shift test is a dynamic laxity test that simulates a physiologic multiaxial load to assess combined rotatory and translational knee laxity.[238] Because of this, the test is often referred to as the most specific test for the detection and quantification of ACL insufficiency and ruptures.[41] The test has a sensitivity of 0.18 to 0.48 and a specificity of 0.97 to 0.99 for identifying ACL ruptures.[238 306] The test is performed by the examiner grasping the heel of the patient's involved leg, with the examiner's other hand placed laterally on the proximal tibia just distal to the knee (Figure 6 and 7).[306] By applying a valgus stress and an internal rotation torque to the tibia while the knee is moved from an extended towards a flexed position, the sudden reduction in the anteriorly subluxated tibia at about 30 degrees of flexion can be felt as an episode of "giving way" by the patient, or a "clunk" in the examiner's hands.[108 186] This is regarded as a positive test. Although the test is the best indicator of a patient's subjective instability,[175] the validity of the test has been limited by the wide variability of execution techniques,[15 240 256] subjective grading [143] and large-scale intra- and inter-variability.[173 182]

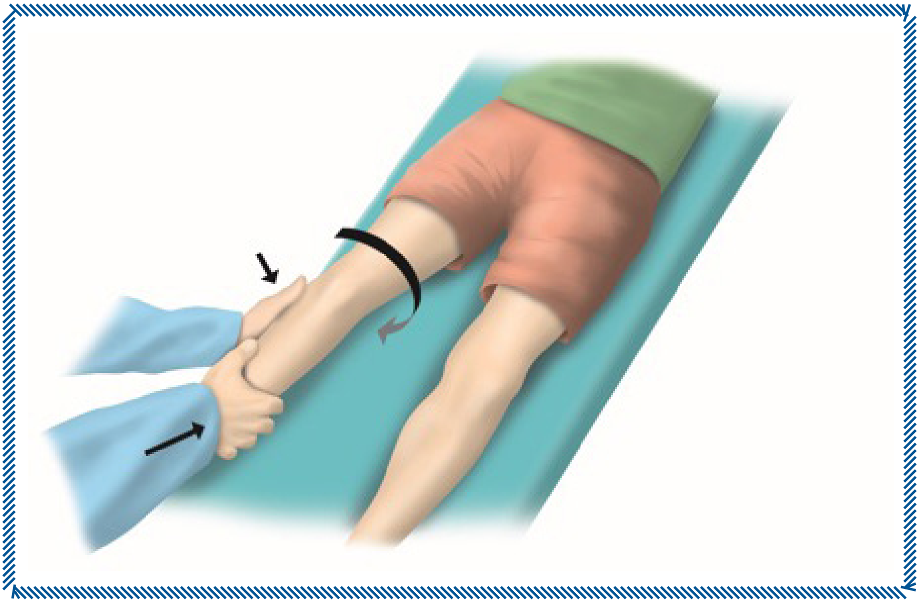

FIGURE 6
Starting position of the pivot-shift test where an internal rotation and valgus stress is applied.

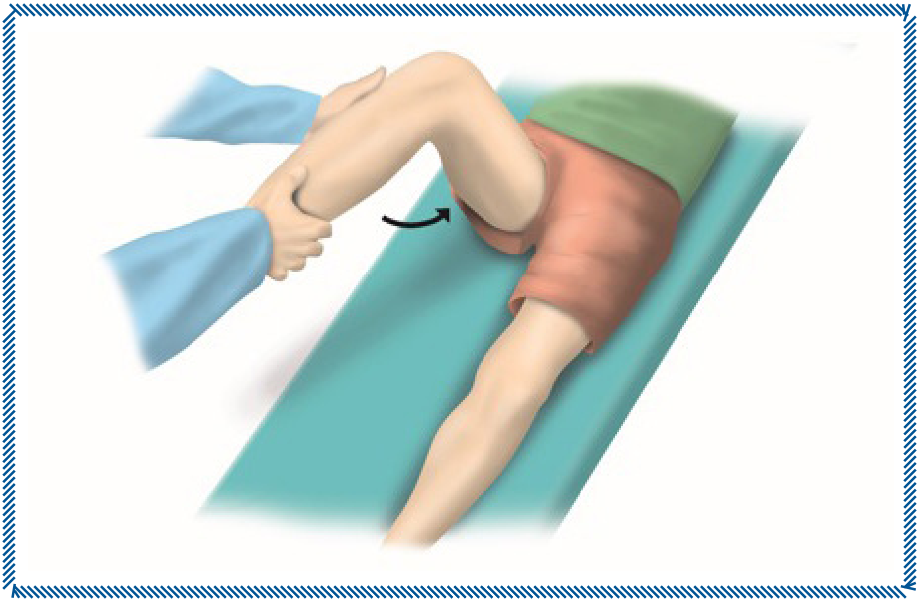

FIGURE 7
End position of the pivot-shift test.

KIRA

New innovative technology has been developed in order to quantify the pivot-shift test and thereby minimize the subjectivity of the assessor. An inertial sensor system, KiRA (Orthokey LLC, USA), is one example and works by recording tibial acceleration during the pivot-shift test (Figure 8).[384 385] The sensor, which includes a triaxial accelerometer and gyroscope, is positioned over Gerdy's tubercle and held in place by a hypoallergenic elastic strap. The validity of this device has been shown to be excellent in relation to the pivot-shift test.[205] This device was used in Study III.

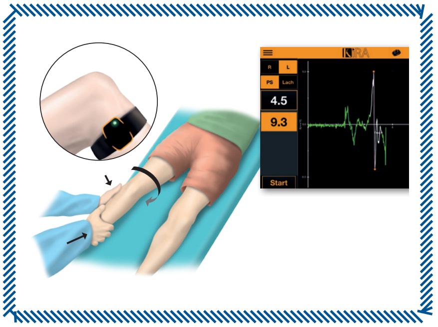

FIGURE 8

The KiRA for quantitatively assessing tibial acceleration during the pivot-shift test.

IPAD IMAGE ANALYSIS SYSTEM

Another method for quantifying the pivot-shift test is to measure lateral tibial translation using an image analysis system (Figure 9).[153] The device works by placing three markers on the patient's skin on the lateral aspect of the knee, each at the following specific landmarks; the lateral femoral epicondyle, Gerdy's tubercle and the fibular head (Figure 9). The position of the markers is tracked using commercial tablet (iPad, Apple Inc., Cupertino, CA) software to video-record the pivot-shift test. A software application on the tablet automatically calculates the tibial translation and also displays the results in a graph.[234] This device was used in Study III.

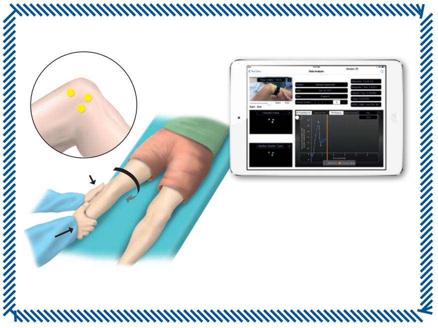

FIGURE 9

The iPad image analysis system for quantitatively assessing tibial translation during the pivot-shift test.

Question

How does preoperative knee laxity affect the patient-related outcome after an ACL reconstruction?

6.4. TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES

There are two primary approaches to the treatment of a patient who has sustained an ACL injury: rehabilitation with or without ACL reconstruction. The aim of both treatments is to reduce perceived instability and restore the function of the patient's knee. As a result, all patients will undergo a prolonged period of rehabilitation as treatment of their injury, independent of whether or not the patient has reconstructive surgery. The ACL reconstruction is used to restore laxity in patients who perceive instability, to prevent future dynamic instability in patients returning to pivoting sports, to protect the patient from subsequent intra-articular injuries and to reduce the future development of osteoarthritis. It is well known that ACL reconstruction reduces passive anteroposterior and rotational knee-joint laxity.[104] However, controversy still exists about whether an ACL reconstruction is superior compared with rehabilitation alone as treatment in terms of knee function, minimizing the number of subsequent intra-articular injuries, entailing a lower prevalence of osteoarthritis and facilitating the patients' return to higher levels of sport.

In the only known randomized controlled trial (RCT) on the subject,[104] 121 patients were allocated to either early ACL reconstruction or rehabilitation with delayed reconstruction if needed. At both the two- and five-year follow-up, the patients displayed no differences in terms of patient-reported knee function (in the Knee injury and Osteoarthritis Outcome Score (KOOS) including KOOS4), physical activity level, number of subsequent meniscus surgeries or the development of radiographic osteoarthritis.[105] The lack of differences between the three groups (early reconstruction, late reconstruction and rehabilitation alone) led the authors to conclude that rehabilitation alone should be regarded as primary treatment after ACL injury. However, half the group randomized to rehabilitation opted for delayed reconstruction and some of the outcomes of the analyses were underpowered, which partly limits the conclusions.

Similarly, a large multicenter cohort[129] reported no difference in the overall return-to-sport rate (68% and 68%) between patients treated with rehabilitation or rehabilitation with additional ACL reconstruction in a pair-matched cohort study based on 138 patients. In the patients treated with rehabilitation alone, there was, however, a lower return rate to level 1 sports among patients who, before their injury, participated in level 1 sports, compared with patients who participated in level 2 sports.[129] The same authors also reported that patients treated non-reconstructively had a more symmetrical hop performance and superior patient-reported outcome, despite the presence of increased anteroposterior knee-joint laxity. In a different publication,[128] patients treated with rehabilitation alone were significantly more likely to participate in level 2 and 3 sports during the first and second year after injury, compared with a patient who was treated with additional reconstructive surgery. The authors concluded that there were only a few differences between the treatment approaches and, in addition, both treatments show similar numbers of patients not having recovered two years down the line, with two out of three patients showing strength deficits and limitations in patient-reported knee function.[128]

Taken together, these studies suggest that patients treated with rehabilitation alone can attain results similar to those of patients treated with rehabilitation and an additional ACL reconstruction. However, there is not enough evidence to suggest that the treatment options are equally effective. The limitations of study design and lack of assessments to demonstrate which patients benefit most from the respective treatments leave questions that are still unanswered.

It is evident that the treatment course after ACL injury should be a shared decision between the patient, the physical therapist and the orthopedic surgeon. Worryingly, only a small number of the more than 19,000 studies published on the treatment approach for patients who have sustained an ACL injury have included a cross-professional approach, resulting in an essential knowledge gap in the literature.

Question

Based on preoperative characteristics, is it possible to identify who will do well and who will do less well after an ACL reconstruction?

6.4.1. SURGICAL TREATMENT

To date, the surgical reconstruction of ACL ruptures has been a treatment option for about 100 years.[164 290 304] This approach is far more common in countries relying on a privately funded health-care system.[161] The primary reasons for opting for a reconstruction of the ACL as part of treatment have included the promotion of dynamic stability of the knee joint, i.e. reducing excessive laxity,[38 283 290] a desire to return to sport with a minimal risk of perceiving persistent instability[38 290] and reducing the risk of developing osteoarthritis.[38 283 290] It is evident that not all patients will benefit from an ACL reconstruction and identifying the patients who are eligible for this treatment regimen is therefore of paramount importance. It has been reported that a number of patients do just as well, or better, with only rehabilitation as treatment.[105 128 357] At present, the choice of undergoing ACL reconstruction should be based on careful consideration of the patient's, the orthopedic surgeon's and, if possible, the physical therapist's judgment of the prognosis, after reflecting on individual factors, the patient's expectations and future level of activity.

GRAFT CHOICES

There are four primary graft choices for ACL reconstruction: the hamstring tendon (HT) autograft, the patella tendon (PT) autograft, the quadriceps tendon (QT) autograft and the allograft. Each graft will be presented briefly below. The ultimate strength and stiffness of the most commonly utilized ACL autografts are presented in Table 1.[255 372]

TABLE 1. Ultimate strength and stiffness of the native ACL and commonly utilized autografts.

Graft type	Ultimate strength (N)	Stiffness (KN/m)
Native ACL	2 160	292
Quadruple hamstring	4 590	861
Bone-patella tendon-bone	2 977	620
Quadriceps tendon	2 352	463

Hamstring tendon graft

The HT graft has increased in popularity in recent decades as a result of its low rate of postoperative morbidity and fewer donor-site complications compared with the PT graft.[382] Moreover, biomechanical studies support the use of the quadruple hamstring graft, as it is stronger than the PT graft, 4,590 N compared with 2,977 N, and stiffer, 861 N/mm compared with 620 N/mm.[255] Increasing evidence also suggests that the diameter of the HT graft is of major importance when it comes to understanding graft ruptures, where an increased diameter entails a decrease in the risk of rupture.[323 330] However, the concerns about using the HT graft include the fact that the graft employs soft tissue-to-bone fixation[160] and the negative effect on the hamstring muscles in terms of muscle strength in deep flexion and internal rotation,[177] caused by the tendon harvest. Soft tissue-to-bone healing takes longer compared with PT grafts, but this should not limit long-term outcome.[361] Nevertheless, the HT autograft is an appropriate graft for an ACL reconstruction (Figure 10). The graft also offers the opportunity of being eligible for both single- and double-bundle ACL reconstructions, over-the-top placement and augmentation with lateral extra-articular tenodesis.

FIGURE 10
A quadrupled semitendinosus tendon and gracilis tendon autograft prepared for ACL reconstruction.

Patellar tendon autograft
The PT graft has previously been referred to as the "gold standard" for ACL reconstruction (Figure 11).[54] The primary advantage of this autograft is its two bone plugs at both ends of the graft, which facilitate graft implementation and graft fixation. Because of this, the graft is often recommended in situations where an early return to sport is desired.[86] It has also been suggested that the PT graft may produce less residual knee-joint laxity than the HT graft.[36] In addition, the preoperative assessment of the PT graft is easy, as the thickness of the graft can be viewed with MRI and therefore creates a better foundation for decision-making before an ACL reconstruction. This is in contrast to the HT, where the length and diameter of the tendons are not known until after harvest, which puts the surgical skill of the orthopedic surgeon even more to the test. Based on the increased risk of harvest-related morbidity and the difficulty involved in using the PT graft,[382] it has lost ground in Sweden and is now second to the HT graft.[377]

FIGURE 11
A patellar tendon autograft prepared for ACL reconstruction.

Quadriceps tendon autograft

The QT as a graft option for ACL reconstruction has gained in popularity in recent years.[322] The QT has several advantages, including being easy to harvest with or without a patellar bone block (Figure 12), being possible to use for both single- and double-bundle reconstructions and having less harvest-related morbidity, anterior knee pain and numbness, compared with the PT graft.[111 322] Because of the potentially large cross-sectional area and biomechanical advantages of the QT graft,[255] it has been shown to be a satisfactory choice for revision reconstruction cases where an expanded bone tunnel may be necessary. Some concern should be shown in relation to the inferior tensile strength and lower collagen content of the graft.[134] Before harvest, the QT is approximately twice the size of the patellar tendon.[322] Moreover, the patient's knee extension strength, mainly quadriceps strength, is less impaired after a central-third QT harvest than after a PT graft harvest.[4] In addition, like the PT graft, the QT graft can be measured preoperatively using magnetic resonance imaging (MRI), which offers advantages to the orthopedic surgeon.[322]

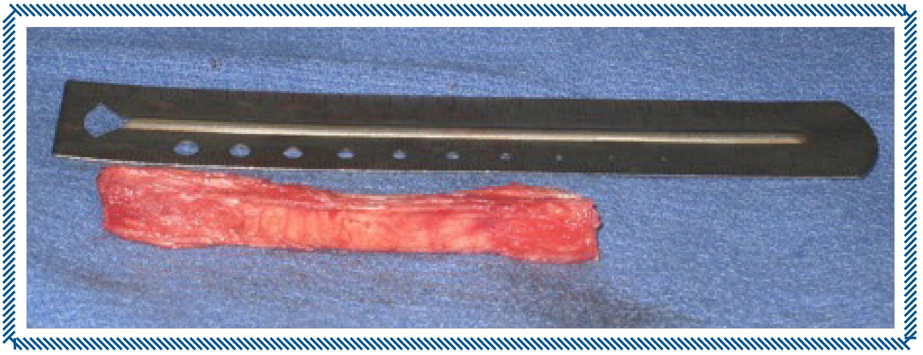

FIGURE 12

A quadriceps tendon autograft prepared for ACL reconstruction.

Allografts

An allograft refers to a tissue from a donor of the same species as the recipient but not genetically identical (Figure 13).[277] The theoretical advantage of using allografts, compared with autografts, is the non-existent harvest-related morbidity, reducing the impairment of knee extension and knee flexion strength.[233] On the other hand, allografts have a clear disadvantage in terms of healing and graft implementation,[159] making them less appropriate for the primary selection of ACL reconstruction. Allografts are also related to an increased risk of graft failure, disease transmission, entail a higher cost, have low availability and inferior tensile properties compared with autografts.[47 217 233] Nevertheless, if time is given, allografts have been reported to revascularize, with results comparable to those of autografts in some studies.[26 253] The referred indications in the literature for using allografts are in athletes who do not want any harvest-site symptoms or strength deficits and in patients undergoing revision ACL reconstruction or multiple ligament reconstructions.[47 217 233]

Question

Does the choice of autograft affect patient-related outcomes after an ACL reconstruction? Does the impact of surgery-related factors shift between short-term and long-term follow-ups?

FIGURE 13
A doubled tibialis anterior allograft prepared for ACL reconstruction.

SURGICAL TECHNIQUES

The overall aim of an ACL reconstruction is to restore knee-joint laxity by reducing the excessive joint laxity caused by the rupture of the ligament. During the last few decades, there has been a transition in the surgical techniques used by surgeons striving for an anatomic replacement of the ruptured ACL. Examples of these techniques include the anatomic single- and double-bundle ACL reconstructions, which are more technically difficult to perform and entail a longer learning curve. These techniques opt for an individualized approach in reconstructive surgery, emphasizing the ACL's original anatomic placement as a blueprint for the graft placements to re-create normal physiologic graft tensions.[167 380] Several studies have confirmed near to normal knee-joint kinematics when the bone tunnels are drilled in and cover as much as possible of the native ACL footprint.[203 310 379-381] The anatomic techniques of ACL reconstruction have also proven superior in aiding excessive rotational knee-joint laxity as compared with the older, transtibial techniques.[248] To aid surgeons in performing a more anatomic ACL reconstruction and evaluating the technique that is used, the Anatomic ACL Reconstruction Scoring Checklist (AARSC) has been developed. This checklist allows for the identification of essential items of anatomic reconstruction and has been associated with a reduction in revision ACL reconstruction.[248] The AARSC has been tested for validity and reliability and consists of 17 items covering surgical technique and one item relating to the documentation of bone tunnel placement. The checklist enables the calculation of an "anatomic score" with a total of 19 points and can summarize the use of different surgical techniques (Table 2).[70] The AARSC was used in Study IV.

Question

Do surgery-related factors such as surgical technique and graft fixations affect short- and long-term patient-reported knee function after an ACL reconstruction?

TABLE 2. Summary of the Anatomic ACL Reconstruction Scoring Checklist.[a]								
	Use of an acc. medial portal	Visualization of the femoral ACL insertion site	Visualization of the tibial ACL insertion site	Lateral intercon-dylar ridge identified	Bifurcate ridge identified	Placing the femoral tunnel(s) in the femoral ACL insertion site	Placing the tibial tunnel(s) in the tibial ACL insertion site	Transportal drilling of the femoral ACL tunnel(s)
Group								
TP reference	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
TP anatomic						Yes	Yes	Yes
TT anatomic						Yes	Yes	No
TT partial-anatomic						No	Yes	No
TT non-anatomic						No	No	No
All landmarks		Yes	Yes	Yes	Yes			
No landmarks		No	No	No	No			
TP drilling								Yes
TT drilling								No

Acc; accessory, TP; transportal TT; transtibial
[a] Empty spaces are not assigned a mandatory answer requirement. Surgeons can thus answer 'Yes' or 'No' to these items.

6.4.2. REHABILITATION

Rehabilitation after ACL reconstruction requires a prolonged period of time for treatment.[3 180 356 369 378] In this thesis, rehabilitation will be described briefly as consisting of three phases, which should preferably be criteria based rather than time based, without risking the biological healing process of affected structures.[243 346] The goals for progression to the next phase of rehabilitation and the choice of interventions during each phase should be based on the International Classification of Functioning, Disability and Health,[96 360] similar to the recommended recurrent evaluation of muscle function.

The current state of the art for rehabilitation after ACL reconstruction recommends a period of nine to 12 months before a full return to sport.[132 346] This recommendation may, however, be revised in the coming years, adding time in order to set realistic expectations and optimize outcome. There is a lack of studies evaluating whether supervised rehabilitation offers an additional benefit compared with home-based rehabilitation, or even no rehabilitation at all.[63 356] It is suggested that a minimally supervised rehabilitation program can produce satisfactory results in specific groups of patients that are highly motivated and live far away from a physical therapy clinic.[63 356] However, based on clinical experience, supervised physical therapy treatment should be advised and is also supported by recent literature, where patients undergo rehabilitation at a specialized clinic.[130]

The role of concomitant injuries may require some necessary modification of rehabilitation to protect the integrity of the knee joint.[3 148] Continued understanding of the role of the articular cartilage and the menisci is needed. Since these injuries are seldom accounted for in the guidelines for treatment after ACL reconstruction, it is likely that rehabilitation will undergo large-scale revisions and modifications in the years to come.[3 148 243 369]

Rehabilitation for patients undergoing an ACL reconstruction starts directly after the injury and, hopefully, ends with the patient returning to unrestricted sports participation. The principles of rehabilitation include the continuous use of objective measurements during rehabilitation in order to aid in decision-making relating to progression and a return to activities.[19]

The preoperative goals for a patient who has sustained an ACL injury include achieving full knee extension range of motion, absent or minimal effusion and no knee extension lag during a straight leg raise.[356 357 375] In addition, improving knee extension strength with the goal that the patient will show less than a 20% difference between legs has been associated with an improvement in two-year patient-reported outcome.[80]

EARLY PHASE

Immediate full weight-bearing is permitted directly after ACL reconstruction, provided that the patient is able to withstand the load and walk symmetrically without symptoms of pain or effusion.[357 369 375] In cases where the patient has a continued limp, crutches are recommended. Immediate weight-bearing will not impose a higher risk of a future increase in laxity or induce pain if recommendations are followed.[357] Cryotherapy may be used during the first week post-surgery to reduce pain.[115 311] As early as possible, the patient is recommended to start isometric quadriceps exercises.[3 315] These exercises are important in order to reactivate the quadriceps muscles. Isometric exercises should, however, be performed at an intensity that does not cause persistent pain. If considered appropriate, electrostimulation may be used for the first two months after ACL reconstruction, in combination with rehabilitation exercises.[155 356 357 376] Some studies suggest that there is an additional strength gain during the first two months when these modalities are combined.[155 356 357 376]

In terms of non-body-weight-bearing and body-weight-bearing strength training, also referred to as open kinetic chain and closed kinetic chain respectively, they should both be considered for use as soon as they are tolerated by the patient.[336] These exercises often begin from four weeks after ACL reconstruction, as long as the exercises do not increase pain or joint effusion.[3 357] Some concern has been raised about the risk of graft slippage in HT grafts when non-weight-bearing strength training is started too early.[146 357 376] The opposite suggestion is only to allow non-weight-bearing exercises in a restricted range of motion, 90-45 degrees of flexion, and wait until graft interference healing is completed, approximately twelve weeks after reconstruction. After this, unrestricted strength training is allowed. This statement is, however, based on studies with limited cohort sizes and simple statistics and should therefore not be regarded as strict guidelines.[99 106 146]

Suggested landmarks of the early phase of rehabilitation, up to three months after ACL reconstruction, include recovering near full range of motion (within 10 degrees of that of the non-injured knee), a straight leg raise without any lag in knee extension, walking without crutches and without limping, cycling without difficulties, symmetrical stair gait and an limb symmetry index (LSI) in knee extension strength greater than 70%.[55 243 346 356 357 375 378]

LATE PHASES

In the later phases of rehabilitation after ACL reconstruction, so-called neuromuscular training should be added to the primary intervention of strength training.[3 356 357] This has been suggested as an appropriate treatment to optimize outcome in order to reduce strength impairment, recover knee-joint biomechanics and improve patient-reported outcome.[148 180 243 346] In addition, these treatment strategies may have an important effect on the secondary prevention of subsequent ACL injury.[243 248 250 357]

During all phases of rehabilitation, it is also beneficial to pay attention to psychological factors, including knee self-efficacy, locus of control and fear of re-injury, which can strongly influence the outcome of the rehabilitation process.[20 67 141 344]

The suggested landmarks of this rehabilitation phase include recovering symmetrical knee extension and flexion strength, i.e. LSI > 90%, improving hop performance with the goal of achieving symmetrical function, i.e. LSI > 90%, and recovering normal gait, running and jumping patterns.[3 33 243 356 357] It is also necessary to ensure that the patient does not have persistent problems with increasing pain due to joint effusion or other reasons.

RETURN TO SPORT

The last stage of rehabilitation after ACL reconstruction, depending on the patient's ultimate goal, is sometimes referred to as the return-to-sport phase.[19 346] In many ways, this phase is the most difficult one for both the patient and the physical therapist, since it balances on the edge of what is regarded as health care. Specific treatment in this phase consist of sports-specific exercises relevant to the patient, plyometric, agility exercises, advanced jumping tasks, sprinting and other advanced neuromuscular training challenging motor control.[3 33 180 208 356 357] The physical therapist may have to opt for changes in rehabilitation as needed to promote progression that emphasizes single-leg activities and explosive types of exercise. The focus includes improving performance, promoting secondary injury prevention and maintaining strength training.[19 346] Recent state-of-the-art rehabilitation also stresses that return to sport is a rehabilitation phase that starts from the day of injury, which is an important expectation to promote to the patient.[19]

The suggested landmarks of this phase include maintaining strength and symmetrical function, i.e. LSI > 90% across strength and hop tests, reporting sufficient patient-reported outcome including psychological readiness, i.e. > 85% of max score, and, ultimately, returning to sport.[3 148 208 346 357]

6.4.3 EVALUATION

Rehabilitation after ACL reconstruction has become increasingly criteria based in comparison with the previous emphasis on time from reconstruction.[55 148 357] As a result, the rehabilitation after ACL reconstruction has become more individualized, in a fashion similar to the actual ACL reconstruction. This has highlighted the importance of evaluating muscle function and patient-reported outcome continuously throughout the rehabilitation period.[208 346] This allows for a patient-specific selection of exercises and load management, with the goal of optimizing outcome.

For the evaluation of patients who have undergone ACL reconstruction, an extensive battery of tests, including muscle function tests and patient-reported outcome, is recommended to determine the patient's current state and subsequently guide the return to sport. However, there are no current tests or battery of tests that have been assessed for construct or predictive validity for return to sport. Because of this, there are no cut-off points for strength and hop tests to determine what is a satisfactory outcome.[19 208 346] Nevertheless, a battery of tests should include at least one strength test and one hop test.[33

346] Some type of measurement of quality of movement may be advised, but these tests are still difficult to quantify.[356 357] The current state of the art suggests that an LSI of > 90% across a battery of tests could be advised as a minimal cut-off point, since this has been associated with a remarkable decrease in subsequent ACL injuries.[132 184] Achieving a 90% symmetrical function across several tests is, however, difficult for this population. This has been exemplified by Thomeé et al.[347] who reported that, two years after ACL reconstruction, only 23% of patients passed when using these criteria.

Question

How do patient-related, surgery-related and injury-related factors influence rehabilitation-specific outcome such as the recovery of muscle function and return to sport?

MUSCLE FUNCTION

Numerous batteries of tests have been used over the last few decades. Importantly, a battery of tests needs to cover several levels of the International Classification of Functioning, Disability and Health. The results of these tests are usually reported using the LSI,[254] where the results from the injured limb are divided by the results for the non-injured limb and multiplied by 100, producing a final result expressed as a percentage. The battery of tests used in this thesis and presented below consisted of two reliable, valid isokinetic tests for muscular strength, to reflect quadriceps and hamstring muscular strength in knee extension and knee flexion.[252] The battery of tests also consisted of three reliable, valid tests for hop performance.[133]

Isokinetic strength of knee extension and knee flexion

Isokinetic dynamometry provides an objective measurement of muscle strength and it is used in sport, research and clinical settings. One criticism of isokinetic dynamometry is that it lacks functional relevance to sporting and training situations. However, it is regarded as the "gold standard" for measuring muscle strength and its convenience, reproducibility and reliability support its use as an appropriate method of assessment after ACL injury and reconstruction.[353] The test procedure used in this thesis consisted of three repetitions of concentric knee extension and flexion at an angular velocity of 90°/sec, at a set range of motion of 0-90°, using gravity correction and measuring peak torque in a Biodex System 4 (Figure 14).

FIGURE 14
The isokinetic test of knee extension and knee flexion in the Biodex.

Unilateral vertical jump

From a starting position standing on one leg, the patient is asked to jump as high as possible with his/her hands placed on his/her back (Figure 15). In this thesis, the Muscle Lab (Ergotest Technology, Oslo, Norway) was used. Vertical jump height is calculated by recording flight time. A unilateral vertical jump has an interclass correlation coefficient (ICC) between 0.74 and 0.98.[142]

Unilateral hop for distance

From a starting position standing on one leg, the patient is asked to jump as far as possible with his/her hands placed on his/her back (Figure 16). The unilateral hop for distance is considered to have good sensitivity to changes in knee function and an ICC = 0.94-0.95[133] for patients after an ACL injury.

Unilateral side hop

The test starts with the patient standing on one leg with his/her hands placed on his/her back. During the test, the patient is asked to jump as many times as possible over the two parallel lines, 40 cm apart, on one leg for 30 seconds (Figure 17).[29 347] The side-hop test has an ICC = 0.87-0.95.[133]

PATIENT-REPORTED OUTCOME MEASUREMENTS

Optimizing short- and long-term outcomes after an ACL injury remains a challenge for both physicians and physical therapists. The aim of patient-reported outcome measurements (PROMs) is to highlight the patient's perspective of treatment outcome and they represent the cornerstone when evaluating the success of intervention.[216 328] In the case of ACL reconstruction, there are several outcome measurements and they are frequently reported in the literature.[121 288] Increasing interest has recently been paid to PROMs, especially in terms of evaluating psychological state and readiness for sports participation, and their place in aiding the assessment of a patient. The patient-reported outcomes used in this thesis are described below.

FIGURE 15 *The unilateral vertical jump.*

FIGURE 16 *The unilateral hop for distance.*

FIGURE 17 *The unilateral side-hop test.*

Knee injury and Osteoarthritis Outcome Score

The KOOS is a valid, reliable and responsive disease-specific, self-administered questionnaire for patients with a knee injury and knee osteoarthritis (Figure 18). It comprises 42 questions in five subscales: pain (9 items), other symptoms (7 items), activities in daily living (ADL)(17 items), function in sport and recreation (5 items) and knee-related quality of life (QoL) (4 items). Additionally, the KOOS4 can be calculated and is an average score of four KOOS subscales, in which function throughout daily living is excluded to avoid any ceiling effect due to the fact that relatively young and active patients rarely have difficulty with function in daily living, such as taking off socks or picking up an object.[104] Each subscale is scored from 0 (worst) to 100 (best). The KOOS has high test-retest reliability for patients with knee injuries. The ICC has been described as 0.85-0.93 for the subscale of pain, 0.83-0.95 for the subscale of symptoms, 0.75-0.91 for the subscale of function in daily activities, 0.61-0.89 for the subscale of function in sport and recreation and 0.83-0.95 for the subscale of knee-related QoL.[10] The minimal detectable change (MDC) for patients with a knee injury is 6-6.1 points for the subscale of pain, 5-8.5 points for the subscale of symptoms, 7-8 points for the subscale of function in daily activities, 5.8-12 points for the subscale of function in sports and recreation and 7-7.2 points for the subscale of knee-related QoL.[59] The minimal important change (MIC) of the KOOS is considered to be 8-10 points for all subscales.[174]

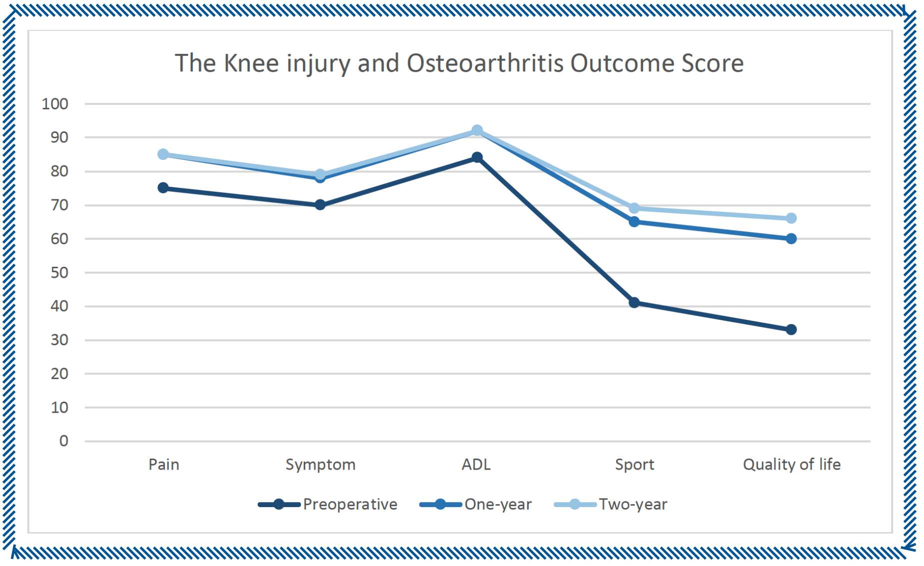

FIGURE 18

Schematic figure of the suggested presentation of results from the Knee injury and Osteoarthritis Outcome Score.

The International Knee Documentation Committee

The International Knee Documentation Committee Subjective Knee Form (IKDC-SKF) has recently been frequently implemented to evaluate patients' perception of outcome relative to knee function after an ACL reconstruction.[158 163 358] Together with the KOOS, the IKDC-SKF is one of the most used PROMs in terms of evaluating patients after an ACL injury and reconstruction. The form comprises 18 knee-specific items related to function, symptoms and sports activity. Each item is scored from 0 to 100 and a higher score indicates the absence of symptoms and higher levels of function and sports activities. The IKDC-SKF has an ICC = 0.87 to 0.98.[158] The form has been validated and the responsiveness in terms of minimal clinically important difference of the IKDC-SKF has been established at 3.2 to 16.7 points.[14 157 158]

Tegner activity scale

The Tegner activity scale is used for grading the level of work and sporting activities.[341] The Tegner activity scale was modified in 2000, but that version has not yet been published. The modified version will be used in this thesis with the permission of the original authors. A score of 1 on the Tegner represents the least knee-strenuous activity and a score of 10 represents the most knee-strenuous activities, such as rugby or international soccer.[343] The Tegner activity grading scale has been shown to have acceptable test-retest reliability at group level, with an ICC = 0.82 (95% confidence interval, 0.66-0.89).[48] Content validity is regarded as acceptable in terms of ceiling and floor effects with isolated ACL injuries and ACL injuries with associated injuries. The MDC for the Tegner activity scale is 1, the standard deviation (SD) of the mean 0.4-0.64.[48]

Physical Activity Scale

A modified version of the Physical Activity Scale (PAS) was used in this thesis. The instrument evaluates patients' intensity and frequency of physical activity on a weekly basis.[344] The PAS was developed using a previously validated and reliable self-rating scale with the aim of assessing physical activity in older people.[126]

European Quality of Life-Five Dimensions

The European Quality of Life-Five Dimensions (EQ-5D) is a standardized instrument for use as a measurement of health outcome. The EQ-5D is regarded as a validated, reliable self-assessment questionnaire to assess health status.[49 355] For patients with osteoarthritis of the knee joint, the EQ-5D has an acceptable level of ICC = 0.70 and the EQ-VAS has ICC = 0.74.[102] The content validity of the EQ-5D is considered good for patients with osteoarthritis and chronic pain.[102 257] However, there are discussions about a possible ceiling effect for patients who have sustained an ACL injury.

Knee Self-Efficacy Scale

This instrument allows patients to report on their self-efficacy, i.e. how certain they are about being able to perform different tasks at present, despite knee pain and/or discomfort, and also how certain they feel about their future capabilities. The Knee Self-Efficacy Scale (K-SES) has been shown to have good test-retest reliability of r = 0.73 and ICC = 0.75. Face, conceptual and content validity for patients after ACL injury is considered good in correlation to the KOOS, the Multidimensional Health Locus of Control, Coping Strategies Questionaire and the SF-36th. The MCD of the K-SES is regarded as one step on the 11-point Likert scale.[343]

Patient-acceptable symptom state

An additional outcome that will be used in this thesis is the patient-acceptable symptom state (PASS).[235] The PASS can be calculated for any PROMs and consists of a global dichotomized simple question about the patients' satisfaction with their state of symptoms with regard to treatment. The PASS is defined as: *the highest level of symptom beyond which patients consider themselves well.*[235] The reason for using the PASS is to aid in the interpretation of clinical or research outcomes by providing a reference value at which the majority of a population feels well.

In this thesis, the PASS in the KOOS and IKDC-SKF was used in several of the included studies. The achievement of a PASS in the

KOOS and the IKDC-SKF was assessed by the threshold values suggested by Muller et al.[235] These values were established by asking patients who had undergone ACL reconstruction: "Taking account of all the activity you have during your daily life, your level of pain and also your activity limitations and participation restrictions, do you consider the current state of your knee satisfactory?".[211 351] The corresponding PASS for the subscales of the KOOS are as follows: pain ≥ 88.9, symptoms ≥ 57.1, ADL = 100, sport and recreation ≥ 75.0 and QoL ≥ 62.5. The corresponding value for the IKDC-SKF is 75.9.

Question

Can using a PASS in patient-reported knee function identify factors that will enable a better understanding of which patients will do well or less well after ACL reconstruction?

6.5. OUTCOMES AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

6.5.1. SHORT-TERM RESULTS

In general, a short-term follow-up refers to an evaluation less than five years after an event. In the case of this thesis, the event referred to is an ACL reconstruction. Most short-term results reported in this thesis are related to one and two years after ACL reconstruction.

GRAFT FAILURE

A graft failure refers to the insufficiency of the reconstructed ACL graft, with the ultimate negative outcome of a graft rupture. However, a graft failure is difficult to define in cases when a graft rupture is not present. Previous studies have used a broad spectrum of different definitions, including patient-reported instability, increased pain, loss of range of motion, persistent postoperative laxity, episodes of giving way and a reduction in the physical activity level.[65 162] It is difficult to determine the exact rate of ACL graft rupture, because patients may not seek clinical consultation or consider participating in studies.

Re-injuries are most common shortly after the ACL reconstruction, before graft ligamentization and sometimes referred to as "biological failure".[212] This complex area lacks precision in its definition and is usually based on excluding other potential reasons for failure. In spite of this, this pathological state is not completely understood. The "diagnosis" biological failure includes factors such as inappropriate collagen remodeling and ligamentization, the impairment of revascularization because of over-tensioning of the graft, the lack of cellular repopulation and proliferation caused by hypoxia and limited growth factor production. In addition, reasons for short-term graft failure include patient-related factors such as smoking and diabetes, and stress shielding with the appropriate postoperative load, as well as failures of surgical technique.[58 212] An aggressive physical therapy program during the early rehabilitation period has sometimes also been suggested as a potential cause of suboptimal graft incorporation. However, recent literature highlights the fact that most re-injuries occur shortly after the patients' return to sport, suggesting that the criteria for returning to sport may need to be revised. On this topic, two studies have shown that the achievement of symmetrical knee function has a major impact on reducing graft ruptures after ACL reconstruction.[132 184]

On the other hand, so-called technical failures are commonly implied as the reason for graft rupture in patients who go on to a revision ACL reconstruction, sometimes reported in as many as 77% of cases.[112 303] Reasons for technical failure include non-anatomic femoral tunnel placement, leaving residual laxity, untreated concomitant injuries, inappropriate graft tensioning, graft impingement, insufficient graft size, graft fixation failure and incorrect graft selection.[212]

The proportion of individuals who will sustain a graft rupture has been estimated to be 2-4% at two years[81 88 103 307] and 4-6% at five years.[299] In terms of revision ACL reconstruction, the estimated proportions are approximately 2% at one year[207] and 3% at two years.[200]

There is also an evident risk of contralateral ACL rupture in patients who have sustained an ACL injury. These injuries typically occur during the first three years[274 299 303 317] when the patients are participating in sport.[274 299 317] An increased risk of sustaining a contralateral ACL injury has been reported in females,[317] younger patients,[274 303]in relation to several multiple previous ACL injuries,[267] graft selection[274] and a return to moderate or strenuous sport.[299] Studies examining contralateral ACL injuries have reported a cumulative proportion of 3-4% at two years[303 374] and 5-6% at five years.[299 317]

KNEE FUNCTION

Patient-reported knee function is a common outcome assessed after both ACL injury and reconstruction.[208] Numerous different outcome measurements are available, including the commonly used KOOS[288] and the IKDC-SKF.[157] Patients with an ACL injury, reconstructed or not, generally report impaired knee function in comparison with a knee-healthy counterpart.[35 183 201 210 294] A proportion of patients, approximately 20%, will, however, report knee function comparable to that of their knee-healthy controls.[35 156] This raises the question of the factors that are associated with the successful recovery of patient-reported knee function. If identified, this could result in important considerations in the treatment selection for these patients. On the other hand, the presence of a concomitant injury, such as a meniscal injury or chondral lesion, has been identified on several occasions as a factor impairing knee function in the short term.[36 85 183 188 294] There is room for improvement of treatment and setting adequate expectations for these patients, since a proportion of patients with a concomitant injury appear only to perceive minor limitations, or none at all, despite the additional injury to the knee joint.

RECOVERY OF MUSCLE FUNCTION

Recovering muscle function is regarded as one of the cornerstones of rehabilitation after ACL injury and reconstruction. The recovery of function across a battery of tests covering the different levels of the International Classification of Functioning, Disability and Health[96 360] has important implications for minimizing short-term graft failure and potential impairment due to the development of osteoarthritis.[284] Recovering a symmetrical function, strength and hop performance can, however, be challenging and take a prolonged period of time. The strength recommendations are based on between-leg comparisons, usually reported as an LSI, and are a good reference for clinicians to guide postoperative treatment. Unfortunately, no normative data are available on the absolute strength requirements for sports.[346] Reduced quadriceps and hamstring strength can persist one to two years after an ACL reconstruction in a general population,[114 181 305] where less than 10% of patients are able to achieve a symmetrical performance, an LSI of > 90%, across a battery of strength and hop tests one year after surgery.[347]

RETURN TO SPORT

In many cases, a return to sport is the ultimate goal for a patient who has sustained an ACL injury. The criteria for a return to sports have been a topic of increasing interest during the last decade, but they have previously been poorly studied and described. The most commonly used criteria described in the scientific literature are the time that has elapsed from ACL reconstruction (as an estimate of healing), range of motion in the knee joint, functional tests, balance testing and isokinetic knee extension and knee flexion strength as a measurement of quadriceps and hamstring muscle strength.[32] It is recommended that the injured leg should regain 90%-100% of the strength of the non-injured side before returning to sport-specific training and pivoting contact participation in sport.[3 132 139 346] Achieving an LSI of > 90% in several tests of muscle function should be regarded as a minimal criterion before a return to sport, due to the association with a large reduction in secondary injuries among patients who achieve these criteria.[132 184] It has been shown that athletes who fail to meet the discharge criteria before returning to professional sport run a four times greater risk of sustaining an ACL graft rupture compared with those who meet all criteria.[184]

Although the majority of patients will be able to resume participation in some type of physical activity, a successful return to sport after an ACL reconstruction can never be guaranteed. A recent systematic review, using different levels of return to sport as the outcome (Figure 19), showed that only two-thirds of patients managed to return to their previous sport, which is lower than expected.[22 25] In general, however, return-to-sport rates are higher in elite level athletes, as reflected by an overall 83% return-to-sport rate[185] and as high as 97% in elite level soccer players.[354] In cases where a patient has undergone a revision ACL reconstruction, approximately 53% return to their preinjury sport.[122] Overall, this suggests that there is room for improvement in the treatment after ACL injury.

Patients who have sustained an ACL injury may potentially benefit from a continued specific strength program, secondary prevention, even more than one year after reconstruction, but no data have been reported on its efficacy. Patient-reported psychological state should also be a part of the return-to-sport evaluation after ACL injury, but this has not attracted much attention in the literature. However, a recent study reported psychological deficits in high-level athletes.[20] For instance, patient perception of knee function among ACL-injured athletes is strongly affected by the injury history, with clinically relevant lower KOOS on the subscales of pain, function, sport and quality of life.[244] It has been suggested that the general score of at least 85% in a patient-reported outcome should be used as a guideline for return to sport.[208]

In patients returning to sport under the age of 20, roughly one in three to four athletes experiences a recurrent rupture of the reconstructed ACL in the index knee or the contralateral knee. This number is remarkably high, considering that the corresponding number in elite athletes is 5.2%.[185] The reasons for this are not clear and they are currently being studied. It is important to consider the increased risk of sustaining an additional ACL injury among younger patients, since the proportion of pediatric and adolescent patients who return to high-risk sports has been reported to be between 69% and 92%.[219 230 317 362] These results show that a return to sport in young athletes, under the age of 20, needs to be considered with great care. In addition, fear of a new injury is one of the primary reasons for never returning to or quitting sport in young patients after an ACL injury.[363]

FIGURE 19

The return-to-sport continuum modified from Ardern et al.[19]

6.5.2. LONG-TERM RESULTS

In general, a long-term follow-up refers to an evaluation more than ten years after an event. In the case of this thesis, the event referred to is an ACL reconstruction.

GRAFT FAILURE

Re-injury of the reconstructed knee, or an injury to the contralateral knee, is a matter of great concern. Long-term graft failures are mostly described as being caused by some sort of trauma, particularly sports related. The cumulative proportions of patients sustaining a graft rupture or a contralateral injury is higher compared with the short-term risk. At seven and ten years after an ACL reconstruction, the failure rate is approximately 11%.[299 303 317] In terms of contralateral ACL injury, the numbers are 14% at seven years[286] and 16% at ten years.[274] It is extremely important to note in this area that younger patients, especially adolescents, run a remarkably higher risk of subsequent ACL injury, where as many as one in three to four may end up with this unfortunate outcome.[362 368]

KNEE FUNCTION

Patient-reported knee function is commonly reported at long-term follow-ups after an ACL reconstruction.[36 43 151 298] It is known that patients who have sustained a serious knee injury will generally report inferior knee function compared with an uninjured individual.[35] However, considering the common decline in patient-reported knee function as an individual gets older, it is difficult to determine the impact of the injury itself.[14] In a similar fashion, patients who have undergone an isolated ACL reconstruction will report superior short-term knee function compared with a patient who has undergone ACL reconstruction with signs of concomitant knee injury.[188 294] These differences appear to decrease over time, where, for instance, at mid-term follow-up, five to seven years after reconstruction, no differences have been reported between patients with and without concomitant injuries.[352] The reasons why differences diminish or disappear have not yet been established, but they may be related to adjustments in the participation level in physical activity or acceptance of the current state. Partly because of this, there is no publication defining better or acceptable long-term knee function. The risk of developing osteoarthritis after a serious knee injury adds further to this difficult topic.[260 285]

OSTEOARTHRITIS

Osteoarthritis is a condition regarded as general joint failure, where all the tissues in the joint are affected by traumatic or degenerative deterioration. In fact, osteoarthritis of the knee is the leading cause of knee-related pain and disability in older adults,[44 127 391] despite the undetermined correlation between joint changes and perceived symptoms.[8 261] The typical symptomatic picture presented by patients includes general pain, swelling and limitations in range of motion.[391] The most important finding in the light of this thesis is that patients who have sustained an ACL injury run a considerably increased risk of developing post-traumatic osteoarthritis of the knee.[284] In some cases, the first radiographic signs of osteoarthritis have been reported before the age of 40.[289] This puts patients who have sustained ACL injuries at risk of total knee replacements, considering that the onset of degenerative joint changes will occur 15 to 20 years earilier than in the general patient with osteoarthritis.[221]

Although osteoarthritis can be referred to many times as a clinical diagnosis, in research, a plain radiograph of the weight-bearing knee with measurements of joint space width is commonly used to define the development of osteoarthritis.[268] In terms of patients who have sustained an ACL injury, more than 50% of them are expected to develop knee-joint osteoarthritis 10 to 20 years after the injury.[260 285] Patients with a concomitant intra-articular injury, especially a meniscal injury, run a particularly high risk.[285] The varying incidence of post-traumatic osteoarthritis reported in patients after an ACL injury may also be due to the fact that there is no gold standard for the radiological assessment of knee osteoarthritis. Several classifications have been proposed and are commonly used; they include the Ahlbäck,[6] Fairbank,[91] IKDC[143] and the Kellgren and Lawrence classification.[171]

Treatment involving an ACL reconstruction aims to stabilize the knee joint and protect the menisci and hyaline cartilage from secondary injuries, with the expectation that this will also reduce the risk of developing osteoarthritis.[229] Most of the recent literature does not support the belief that ACL reconstruction will delay or prevent the development of osteoarthritis compared with non-surgical treatment,[204 224 371] but there are some conflicting results on the topic.[199] Interestingly, patients who are stronger and display symmetrical knee extension strength report having less osteoarthritis-related symptoms.[262] This stresses the need to ensure the thorough rehabilitation of patients who have sustained a severe injury to the knee, such as an ACL injury.[263] In addition, there are implications suggesting that all patients should be recommended specific rehabilitation with the aim of strengthening the knee extensors and should have an evaluation of knee extension strength as part of the rehabilitation after a knee injury or when presenting osteoarthritis-related symptoms.[284] When assessing the development of osteoarthritis, it is probably best to regard radiographic signs and clinical symptoms as two distinctly different yet complementary factors, since the correlation is weak.[261]

6.5.3. BETTER AND POORER OUTCOMES

To date, there are more than 19,000 publications in PubMed on the topic of ACL. In the light of this, it is evident that there is a need for a better understanding of what is a good and a poor outcome after this severe knee injury. Numerous of different outcomes have been used and, from a clinical point of view, it is difficult to determine the way in which these patients are best assessed. Another crucial limitation of the current state of the literature is the sparse number of studies using an interdisciplinary approach to treating and evaluating patient who have sustained an ACL injury or undergone an ACL reconstruction.

A few attempts to determine a better or a poorer outcome based on previous objective tests or PROMs have been presented in the literature.[35 79 156 166] The aim of this thesis is to increase our understanding of the patients who do well, and less well, by characterizing and predicting outcome after ACL reconstruction. An example of this is to use the PASS, which uses already valid and reliable outcome measurements but directly relates the results to the patients' perspective of an acceptable outcome.

Question

How do preoperative patient-related, surgery-related and injury-related factors influence the development of osteoarthritis after an ACL reconstruction?

6.6. RATIONALE FOR THIS THESIS

The rationale for this thesis is the perspective of improving the care of patients who sustain an ACL injury, in particular patients who also undergo an ACL reconstruction as part of the treatment regimen. Neither in the clinical setting nor in research will these patients depend on the knowledge of one medical profession. Like running a relay, playing football, working in construction or doing research, the treatment of patients with an ACL injury should be based on a team effort. The physical therapist and orthopedic surgeon, together with and, most importantly, the patient are all in the starting line-up. This thesis is an attempt to bridge parts of the gaps in knowledge presented in this introduction and present an approach to conducting interdisciplinary research between physical therapists and orthopedic surgeons. As part of Study I, we present a method for establishing a rehabilitation outcome register which, in Studies V-VII, we integrate with a register comprising data related to orthopedic surgery and intra-operative data. Consequently, common confounding factors presented in the literature on patients with ACL injury can be dealt with. For example, studies that evaluate surgical aspects of the treatment of patients with an ACL injury often report not having controlled for sports participation or rehabilitation.[330] In the same way, studies that evaluate functional outcome, e.g. muscular strength, seldom include sufficient surgery-related aspects as covariates. To increase our understanding of the factors that may affect the patient-reported outcome after ACL, Study II summarizes findings from the Scandinavian knee ligament registers.

With this in mind, Studies III-IX in this thesis aim to determine predictors or risk factors for better and poorer outcome after ACL reconstruction. Various outcomes relevant to patients who have undergone ACL reconstruction are used. The primary focus is studying preoperative characteristics, intra-operative findings and their effect on the short- and long-term outcome. Identifying both the patient that does well and the patient who fares less well after an ACL reconstruction may help to guide the selection of treatment in the future, especially as most of the studied variables are from a time point at which the patient still has the option of selecting a treatment regimen. The expected results may also help the everyday clinician, physical therapist and orthopedic surgeon to set realistic expectations for patients. Based on the study designs, using primarily register data, the results will be strengthened by their reflection of daily practice but be limited in their stringency. Nevertheless, the results will raise new hypotheses that, in the spirit of further research, may impact clinical care for the better for patients who have sustained an ACL injury.

07

AIMS

OVERALL AIMS

The overall aims are divided into three content areas, each reflected by one theme in this thesis.

1. To determine factors that affect patient-reported outcome after ACL reconstruction and present a rehabilitation-based register capable of dealing with these factors

2. To determine short-term patient-related, surgery-related and injury-related predictors of short-term outcome after an ACL reconstruction

3. To determine patient-related, surgery-related and injury-related predictors of long-term outcome after an ACL reconstruction

SPECIFIC AIMS

Theme one: creating a foundation for research

Study I To utilize a rehabilitation outcome register to characterize patients who return to pre-injury knee-strenuous sports after an ACL reconstruction

Study II To present an overview of evidence from the Scandinavian national knee ligament registers with regard to the effect of patient-related, surgery-related and injury-related factors on patient-reported outcome after an ACL reconstruction. Moreover, to determine the reporting quality of the published studies from the registers and identify areas in need of future research

Theme two: short-term predictors

Study III To determine whether the surgical technique of single-bundle ACL reconstruction, the visualization of anatomic surgical factors and the presence of concomitant injuries at primary ACL reconstruction are able to predict patient-reported success and failure in the SNKLR

Study IV To determine whether patient-related factors, concomitant injuries and preoperative knee laxity are able to predict a PASS in the IKDC-SKF at the one- and two-year follow-up after ACL reconstruction in a multicenter cohort

Study V To determine the proportion of patients who perceive an acceptable level of knee function one year after ACL reconstruction and to determine which patient demographics, concomitant injuries and graft choices may influence this

Study VI To determine whether patient characteristics, intra-operatively identified concomitant injuries and graft choices at primary ACL reconstruction are associated with the recovery of muscle function across a battery of tests one year after an ACL reconstruction

Study VII To determine factors that are able to predict a return to sport one year after an ACL reconstruction in terms of patient characteristics, intra-operatively identified concomitant injuries and graft choices

Theme three: long-term predictors

Study VIII To determine preoperative predictors of acceptable knee function and the development of osteoarthritis 16 years after an ACL reconstruction

Study IX To determine 10-year predictors of knee function after an ACL reconstruction in the SNKLR

08

METHODS

8.1. EVIDENCE-BASED MEDICINE

Evidence-based medicine (EBM) has become the goal for clinical practice and is a frequently used term in modern medicine and research, reflecting well-founded information on diagnosis, treatment, prevention and prognosis.[124] The recent use of the concept of EBM is based to a great extent on Sackett et al.'s[296] publication from McMaster University from 1986. In this publication, the authors described the concept as "the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients". In turn, EBM builds upon three fundamental pillars: the best available research, clinical experience and the patient's perspective.[297]

In the light of the development of EBM, there are two principles that are most important in order to define what good research should strive for. The first is internal validity, which describes the contingent relationship between two variables; i.e. the relationship between an intervention or exposure and an outcome.[214 215] Internal validity can be reflected by the power of a study, patient allocation and the blinding of patients and assessors. The second principle is external validity, which refers to the consistency or replicability of results within a given population or setting.[124 264]

8.1.1 TYPES OF STUDIES – HIERARCHY OF EVIDENCE

The hierarchy of evidence is an essential part of EBM and refers to the amount of potential bias when a certain study design is utilized. The least risk of bias can be expected from level 1 studies and the risk of bias increases with each step on the hierarchical list.[226] There are, however, multiple versions of the hierarchy for level of evidence. The most commonly referred to is the version available from the Oxford Centre for Evidence-Based Medicine website, www.cebm.net. As exemplified in Figure 20, this system categorizes a study from one to five on the basis of its design and potential risk of bias. In addition, if a study has used features such as randomization and prospective follow-up and permits the replication of evidence, this is considered to reduce the risk of bias in the study, thereby entailing a higher level of scientific evidence.[226] The higher the level of evidence, the more reproducibility, applicability and generalizability there is to the everyday patient.[90] Nevertheless, the suggested levels of evidence are important not only to determine whether one study is of higher scientific quality than another but also to facilitate the clinician's immediate understanding of how much weight the results of the study should be given.[90]

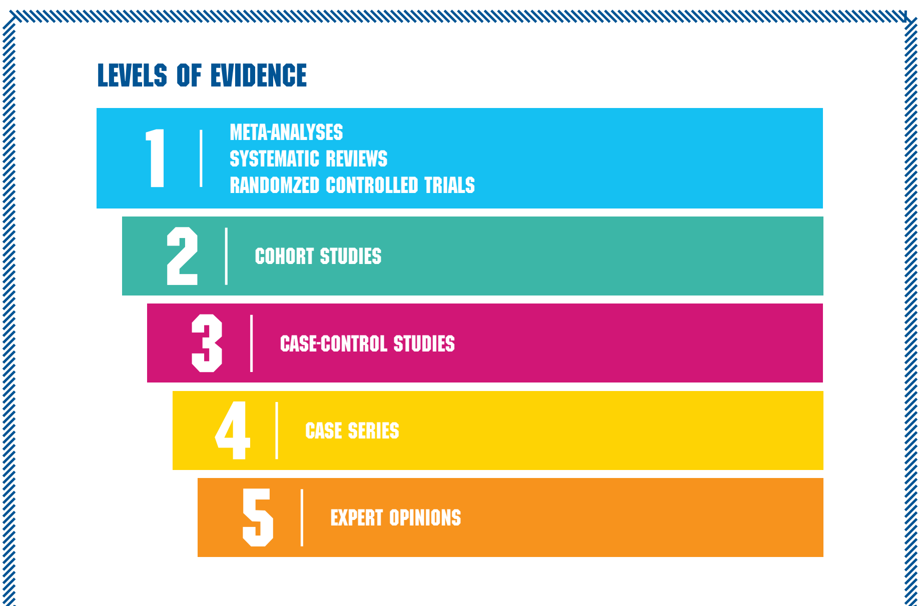

FIGURE 20

The hierarchy of evidence.

8.1.2. SYSTEMATIC REVIEWS

A systematic review is a structured literature review addressing a specific question that is to be answered by analysis of evidence. The Cochrane Collaboration defines the systematic review as: “A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies”.[123] In other words, a systematic review is the name of a *literature review* or *overview* of a specific literature search, based on study selection with strict predefined inclusion and exclusion criteria.[28 140] Data from the included articles should be extracted in a standardized manner with a following quality appraisal of all included studies. Finally, a qualitative or quantitative synthesis of data from the included studies should be performed.[28 140] The most essential part of the systematic review is the literature search with the following inclusion of articles, where all collected articles must be eligible for inclusion, regardless of positive, negative or inconclusive results presented in the studies.[236]

In Study II, a best-of-synthesis, or data-synthesis, approach was used. This methodology refers to the qualitative synthesis of data in a systematic review when an area of research contains studies with a variety of methods that are not suitable for traditional statistical modeling, i.e. meta-analysis.[236] Data-synthesis methodology aims qualitatively to determine the effect of a number of variables on a defined outcome.[18] Meta-analysis and data synthesis are two different yet complementary approaches to synthesizing data in a systematic review.

8.1.3. RANDOMIZED CONTROLLED TRIALS

The RCT is regarded by many as the “gold standard” for conducting research when it comes to testing new medical interventions.[17] RCTs have become the standard that must be met by the pharmaceutical industry in the process of establishing the level of efficacy and safety of a new product.[302] The randomization refers to the fact that participants in the study are allocated at random to receive one of several clinical interventions, also ensuring that known or unknown confounders are distributed equally.[107 314] One of the interventions used in an RCT is the standard of comparison or control.[17] The control may be a standard practice, a placebo, or no interventions at all. The primary goal of conducting an RCT is to test whether an intervention works by comparing it with a control condition (either no intervention or an alternative intervention). Secondary goals may include the identification of factors influencing the effects of the intervention and understanding the processes through which an intervention influences change.[107 127 314]

8.1.4. COHORT STUDIES

Characteristically, a cohort study follows a non-randomized design, where outcomes in a group with a given exposure, e.g. an ACL graft, are compared with outcomes in a similar group with another exposure or without an exposure. This type of study is also referred to as a controlled, prospective, observational study and should not be confused with other types of design, such as a non-randomized controlled trial or a case-control study, which are different in terms of methodology, statistical analysis and levels of evidence.[313] Data are typically collected at the baseline of the study, after which the two groups are followed until a follow-up assessment is carried out and the outcomes are compared. Because of the lack of randomization in a cohort study, these studies are limited in terms of the generalizability of their results.[334] In other words, the cohort study does not control for the distribution of known or unknown factors (confounders) that can potentially affect the outcome. However, the cohort study does take account of the effect of an exposure on an outcome, which allows for estimations of incidences, risks and number needed to treat.[313]

8.1.5. REGISTER STUDIES

A register study is a special type of cohort study based on large-scale register data. Sweden and other countries in Scandinavia are well known for their high-quality national quality registers, thanks to the use of personal identification numbers.[2 82] In general, registers contain large patient populations with a representative cohort of individuals from a real-world patient population, which increases the statistical inference and generalizability of the results (high external validity) but might be subjected to less internal validity compared with an RCT. In other words, the register-based study may be better at determining the effectiveness of an intervention in "real-world" scenarios, i.e. the extent to which an intervention produces an outcome in ordinary day-to-day circumstances.[2] RCTs, on the other hand, are regarded as the "gold standard" and are considered the most suitable tool for making the most precise estimates of treatment effect, efficacy, i.e. the extent to which a beneficial result is produced under ideal conditions.[152 291]

Data are preferably collected prospectively in the register, which makes register-based studies neither retrospective nor subject to recall bias. The register-based design also aims to reduce possible detection bias, systematic differences in outcome assessments between study groups, because patients and examiners may not be aware of future purposes and outcomes in the studies that are produced. Moreover, the completeness of the register helps to manage possible attrition bias, i.e. systematic differences in withdrawals between study groups, in cases where completeness is kept at a high level.[334] Because of this, register-based cohort studies are essential when studying the rate and outcomes of adverse events, such as ACL graft ruptures and revision.[121]

THE SWEDISH NATIONAL KNEE LIGAMENT REGISTER

The SNKLR is a nationwide database that utilizes a web-based protocol for data registration. The protocol consists of two parts; one surgeon-reported section and one patient-reported section. The surgeon enters information about the physical activity performed at the time of injury, time from injury to reconstruction, graft selection and surgical fixation techniques. The data on previous surgery in the reconstructed knee, the contralateral knee and all concomitant injuries are also registered. All surgical procedures performed on the injured knee, including meniscal surgery and treatment for chondral lesions, are reported. Revisions and repeated surgery for other reasons are registered as separate entries in the register. The coverage (proportion of participating units in relation to all eligible units) and completeness (proportion of target population in the register) are 92.9% and > 90% respectively, with a 50-70% response rate on the patient-reported outcome one and two years after ACL reconstruction.[82] There are similar nationwide knee ligament registers in Denmark and Norway. The SNKLR was used in Studies II, IV-VII and IX. The Scandinavian registers were used in Study II.

PROJECT ACL

Project ACL is a local rehabilitation outcome register used primarily by physical therapists. At present, more than 1,600 patients have been included in the project and data have been collected from over 4,000 assessments, comprising approximate answers from 25,000 PROMs and 12,000 tests of muscle function. Project ACL utilizes a web-based platform for regular assessments with PROMs and tests of muscle function for patients who have sustained an ACL injury. Assessments are made after a predefined schedule of follow-up at 10 weeks, four months, eight months, 12 months, 18 months, 24 months, yearly up to five years and every five years after index ACL injury or reconstructive surgery. The PROMs and tests of muscle function used in the project are described in the indroduction for this thesis.

After every assessment in the project, the results are registered in the Project ACL database. In addition, a personal report for the patient is automatically generated and is available online to the patient. The scope of Project ACL is to be user friendly and every patient therefore has the opportunity to make his/her personal report available to the responsible ortopedic surgeon and/or physical therapist. Accordingly, the patient's participation in Project ACL can aid the responsible ortopedic surgeon and physical therapist in the evaluation and progression of rehabilitation. Moreover, mean statistics from all test results in Project ACL are automatically updated and are available online to support the evaluation of rehabilitation, available from www.projektkorsband.se. This methodology has ensured a high level of compliance in the assessments, approximately 80-85%. Project ACL was used in Studies I and V-VII.

8.2. THEME ONE: CREATING A FOUNDATION FOR RESEARCH

STUDY I

Study design

Cross-sectional cohort study

Patients and Methods

The study was performed as a prospective observational register study based on data from the pilot version of Project ACL. Patients who underwent primary ACL reconstruction between 1 June 2009 and 23 January 2015 were eligible for inclusion. Eligible patients had discontinued their rehabilitation six to 18 months after ACL reconstruction and data from the follow-up closest in time to the patients' discharge from the physical therapy setting were used. All patients had a pre-injury self-reported physical activity level on the Tegner activity scale of 6 or higher, i.e. participating in knee-strenuous sport. Patients still undergoing rehabilitation were excluded, as well as patients younger than 15 years, or older than 30 years. Ethical approval was obtained from the Regional Ethical Review Board in Gothenburg, Sweden (registration number: 265-13).

A total of 157 patients were included in the study (Table 3). Cross-sectional data from the final evaluation of muscle function and PROMs were used. The battery of tests consisted of two reliable and valid isotonic tests for muscular strength, to reflect quadriceps and hamstring muscular power in knee extension and knee flexion.[252] The strength tests were performed in a knee-extension and knee-flexion weight training machine (Precor, Competition Line, Borås, Sweden). The average power was recorded through a linear encoder and calculated by Muscle Lab, a computerized muscle function measurement system (Ergotest Technology, Oslo, Norway). Tests were performed between 0° and 110° of knee flexion. Three reliable and valid single-leg tests were used for hop performance [133]: the vertical jump, the hop for distance and the side hop. The results were presented as absolute values accounting for body weight and as an LSI [254].

In terms of patient-reported outcome, four validated PROMs, the KOOS[288], K-SES

[344], Tegner activity scale [341] and PAS, [344] were used to evaluate differences in patients who had and had not returned to sport. [67 95 208] Patients were asked to report their level of physical activity on the Tegner activity scale and PAS for pre-injury, present and future goals of participation.

TABLE 3. Patient demographics Study I.

Demographics	Women (n = 77) ($\bar{x}$±SD or median and range)	Men (n = 80) ($\bar{x}$±SD or median and range)
Age	21.2 ± 3.5 years	23.4 ± 4.3 years
Height	168.8 ± 5.8 cm	181.4 ± 6.1 cm
Weight	64.3 ± 11.9 kg	79.0 ± 9.7 kg
Level of physical activity $_{\text{pre-injury}}$	8 (6-10)	9 (6-10)
Intensity and volume of physical activity $_{\text{pre-injury}}$	4 (2-4)	4 (2-4)

Outcome

Return to sport was used as the primary outcome and was defined in two ways: 1. patients who had returned to their pre-injury level of the Tegner activity scale ± 1[116 193 194] but a minimum of Tegner activity scale 6 and 2. patients who had returned to a Tegner activity scale of 6 or higher, i.e. a knee-strenuous sport.

STUDY II

Study design

Systematic review

Methods

The literature search of this systematic review was performed by an expert in electronic search methods at the Health Technology Assessment Center at the Sahlgrenska University Hospital Library on 5 January 2017. An updated search took place as close to the finalization of the study as possible, on 9 May 2017, and the following databases were searched; PubMed (MEDLINE), EMBASE, The Cochrane Library and AMED. Search terms were mapped to relevant MeSH terms or subject headings where possible. Two reviewers independently screened titles, abstracts and full-text articles for eligibility. A total of 186 studies were identified in the search of which 37 met the inclusion criteria (Figure 21). A modified version of the Downs and Black checklist was applied for quality appraisal (Table 4). Studies published from the Scandinavian registers from their establishment in 2004 and onward that reported patient-reported outcome and provide information on concomitant injuries were eligible. The summary of results from the original publications was organized (synthesized) under the following sections: *patient-related factors, surgery-related factors* and *injury-related factors*. To increase the readability, the results were summarized under sub-headings according to specific topics related to the original studies e.g. *"HT autograft versus PT autograft"*. In cases where the studies overlapped, most emphasis was placed on the study with the highest quality and the largest cohort.

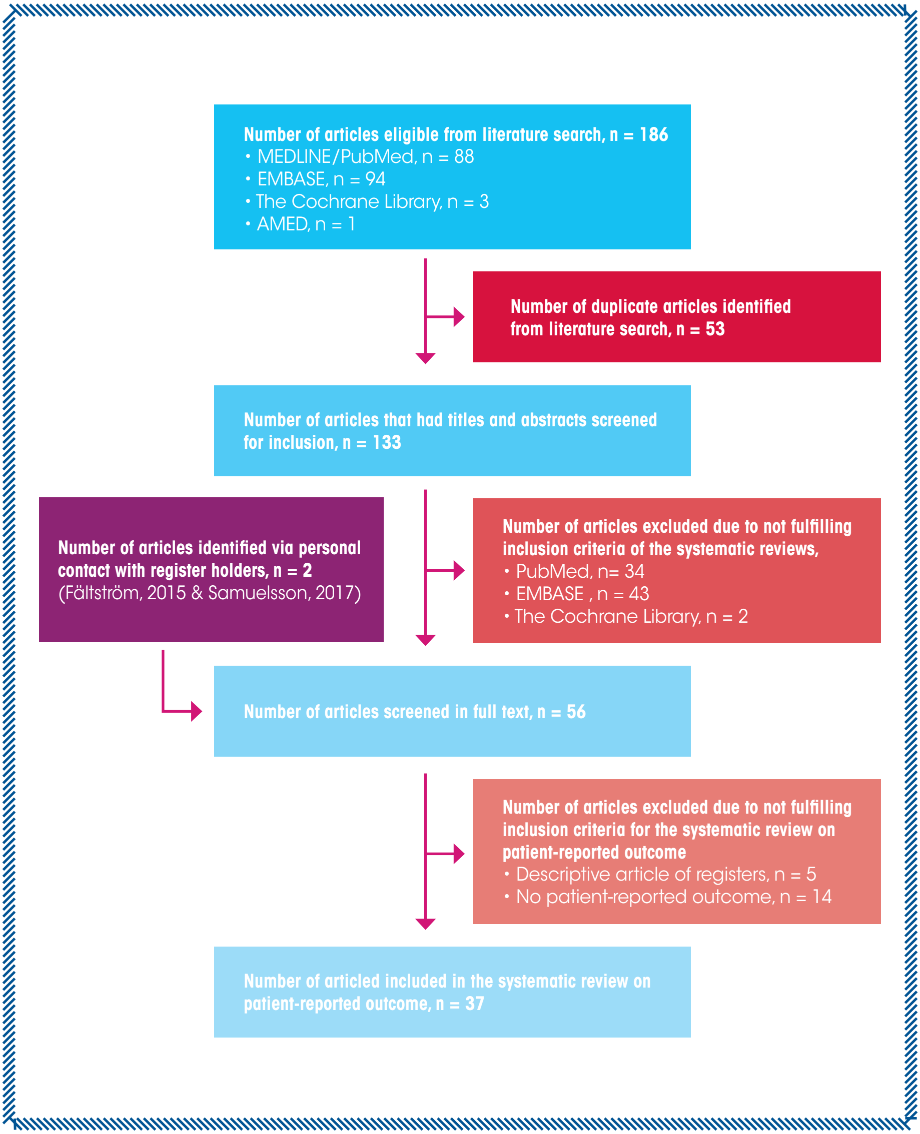

FIGURE 21

Flow-chart of inclusion and exclusion of studies in Study II.

TABLE 4. Modified version of the Downs and Black checklist used in Study II.	
Items included	**Items excluded**
Item 1: Is the hypothesis/aim/objective of the study clearly described?	Item 14: Was an attempt made to blind study subjects to the intervention they have received?
Item 2: Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Item 15: Was an attempt made to blind those measuring the main outcomes of the intervention?
Item 3: Are the characteristics of the patients included in the study clearly described?	Item 21: Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
Item 4: Are the interventions of interest clearly described?	Item 23: Were study subjects randomized to intervention groups?
Item 5: Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Item 24: Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
Item 6: Are the main findings of the study clearly described?	Item 27: Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance was < 5%
Item 7: Does the study provide estimates of the random variability in the data for the main outcomes?	
Item 8: Have all important adverse events that may be a consequence of the intervention been reported?	
Item 9: Have the characteristics of patients lost to follow-up been described?	
Item 10: Have actual probability values been reported (e.g. 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?	
Item 11: Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	
Item 12: Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	
Item 13: Were the staff, places and facilities where the patients were treated representative of the treatment the majority of patients received?	
Item 16: If any of the results of the study were based on "data dredging", was this made clear?	
Item 17: In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or, in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	
Item 18: Were the statistical tests used to assess the main outcomes appropriate?	
Item 19: Was compliance with the intervention/s reliable?	
Item 20: Were the main outcome measurements used accurate (valid and reliable)?	
Item 22: Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period?	
Item 25: Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	
Item 26: Were losses of patients to follow-up taken into account?	

Outcome

All patient-reported outcomes reported from the Scandinavian knee ligament registers, including the KOOS, EQ-5D and the Tegner activity scale.

8.3. THEME TWO: SHORT-TERM PREDICTORS

STUDY III

Study design

Multicenter prospective cohort

Patients and Methods

This study was conducted as a multicenter, prospective cohort study – the Prospective International Validation of Outcome Technology (PIVOT) trial. Four centers participated in this trial, all applying the same study protocol. Patients who underwent single-bundle ACL reconstruction with HT autografts within one year of injury were eligible for inclusion. To be included, the patient had to be between 14-50 years of age and have sustained an injury to at least one of the ACL bundles. The exclusion criteria were as follows: 1) prior ligament surgery on the involved knee; 2) concomitant posterior cruciate ligament injury or collateral ligament injury of grade III; 3) any current or previous knee injury or surgery to the contralateral knee; 4) Kellgren & Lawrence score higher than 2 assessed by radiographic imaging; 5) presence of any condition that would hinder the patient from participation in level I and level II activities (Table 5). Moreover, the patients in the current study had to have complete data on the IKDC-SKF at the one- or two-year follow-ups. The Institutional Review Board approved study performance across all centres, and informed written consent was collected from participating patients prior to enrolment.

The patients who were included underwent a preoperative clinical examination, in both the awake state and under general anesthesia, by sports medicine fellowship-trained orthopedic surgeons. During the awake assessment, the rolimeter[30] and the Lachman test were applied to assess static knee laxity and passive and active knee range of motion was determined. Dynamic knee laxity was assessed by the pivot-shift test, which was performed according to a standardized technique across all four participating centers.[240] The pivot-shift test was performed preoperatively and under anesthesia on both the involved and the non-involved knees. The test was first graded subjectively by the surgeon, according to the IKDC knee ligament rating system.[143] Subsequently, translation of the lateral tibial plateau during the pivot-shift was quantified by an image analysis system, in which adhesive skin markers were placed on three specific anatomic locations. A camera in a computer tablet (iPad, Apple Inc. Cupertino, CA, USA), which enabled the tracking of the color contrast of the markers, was used to capture the performance of the test. A software application analyzes the video and calculates the anteroposterior translation between the femur and the lateral tibial compartment based on the movement of the markers. The tibial acceleration was determined using another non-invasive system, which implements a wireless inertial sensor (KiRA, Orthkey Italia Srl., Italy), which was affixed to the lateral aspect of the proximal tibia through a hypoallergenic strap.[206] The tibial acceleration was calculated from the inertial sensor via computer tablet software analysis (KiRA).[383]

TABLE 5. Patient demographics stratified by achieving a patient-acceptable symptom state in Study III.				
	IKDC-PASS one-year follow-up		IKDC-PASS two-year follow-up	
	Yes (n = 67)	No (n = 19)	Yes (n = 39)	No (n = 11)
Age at reconstruction	24.1 ± 8.9	27.3 ± 10.4	23.7 ± 9.4	24.7 ± 9.2
Patient sex				
Female	28 (41.8%)	9 (47.4%)	17 (43.6%)	4 (36.4%)
Injured knee				
Right	34 (50.7%)	10 (52.6%)	22 (43.6%)	5 (45.5%)
Meniscus involvement				
Lesion in either meniscus	41 (61.2%)	12 (63.2%)	21 (53.8%)	9 (81.8%)
Normal – no lesion	26 (38.8%)	7 (36.8%)	18 (46.2%)	2 (18.2%)
Articular cartilage defect				
No articular cartilage defect	56 (83.6%)	17 (89.5%)	32 (82.1%)	10 (90.9%)
Lesion in any surface	11 (16.4%)	2 (10.5%)	7 (17.9%)	1 (9.1%)
ACL status				
Partial or mixed tear	8 (11.9%)	3 (15.8%)	7 (17.9%)	1 (9.1%)
Complete tear both bundles	59 (88.1%)	16 (84.2%)	32 (82.1%)	10 (90.9%)
Work type				
Mostly sedentary	15 (22.4%)	5 (26.3%)	5 (12.8%)	2 (18.2)
Sedentary, substantial walking	12 (17.9%)	4 (21.1%)	7 (17.9%)	2 (18.2)
Moderately active	21 (31.3%)	5 (26.3%)	15 (38.5%)	2 (18.2)
Demanding physical activity	19 (28.4%)	5 (26.3%)	12 (30.8%)	5 (45.5%)
Prior level of activity				
Very strenuous	49 (73.1%)	14 (73.7%)	26 (66.7%)	10 (90.9%)
Strenuous	16 (23.9%)	1 (5.3%)	11 (28.2%)	0 (0.0%)
Moderate activities	1 (1.5%)	4 (21.1%)	2 (5.1%)	1 (9.1%)
Frequency of activity				
4 - 7 times a week	39 (59.1%)	7 (38.9%)	22 (97.4%)	6 (54.5%)
1 - 3 times a week	21 (31.8%)	8 (44.4%)	11 (28.2%)	3 (27.3%)
1 - 3 times a month	6 (9.1%)	3 (16.7%)	6 (15.4%)	2 (18.2%)
Time from injury to surgery (d)	129.5 ± 82.3	123.4 ± 99.7	142.9 ± 78.8	122.7 ± 103.4

Outcome

Achieving a PASS in the IKDC-SKF one and two years after ACL reconstruction was used as a dependent outcome.

STUDY IV

Study design

Register-based cohort

Patients and Methods

This cohort study was based on data from the SNKLR during the period of 1 January 2005 through 31 December 2014. Patients who underwent primary single-bundle ACL reconstruction with HT were included. Follow-up started on the date of the primary ACL reconstruction and ended at the two-year follow-up, so patients with incomplete data in the KOOS at the two-year follow-up were excluded. Patients who underwent contralateral ACL or revision ACL surgery before the two-year follow-up were excluded. Details on surgical technique were collected using an online questionnaire, the AARSC, comprising 17 essential items, covering the utilization of accessory medial portal drilling, anatomic tunnel placement, the visualization of insertion sites and pertinent landmarks. The surgical techniques of single-bundle ACL reconstruction, concomitant injuries and surgical factors were used as variables of interest for the analyses in this study. A multivariable logistic regression model adjusted for age and patient sex was used to determine predictors of patient-reported success and failure, i.e. 20th and 80th percentile respectively, in the KOOS4 two years after ACL reconstruction. A total of 6,889 patients were included in the study (Table 6). The Regional Ethical Review Board in Stockholm approved the study (ID number: 2011/337-31/3).

TABLE 6. Patient demographics in Study IV.

Patient sex	**n (%)**
Female	3,461 (50.2%)
Concomitant injuries	
Meniscal injury	2,929 (42.5%)
Chondral injury	1,855 (26.9%)
Medial collateral ligament injury	178 (2.6%)
Lateral collateral ligament injury	41 (0.6%)
Surgical technique of ACL reconstruction	
Transportal reference	2,256
Transportal anatomic	1,503
Transtibial anatomic	944
Transtibial partial-anatomic	702
Transtibial non-anatomic	581

Outcome

Patient-reported success and patient-reported failure in the KOOS4, defined as reporting in the top and bottom quintile of the KOOS4 respectively, two years after ACL reconstruction, were used as dependent outcomes in the regression analyses.

STUDY V

Study design

Register-based cohort study including two registers

Patients and Methods

This study was based on data collected prospectively from Project ACL and the SNKLR. Patients registered in Project ACL who had patient-reported data from the one-year follow-up were eligible for inclusion. For the identified patients, additional intra-operative and surgical information was extracted from the SNKLR, including data on concomitant injuries and graft choice. Only patients who underwent primary unilateral ACL reconstruction and had no previous knee surgery were included in the study. Patients were excluded if they had an early postoperative infection. Of the 1,156 patients registered in Project ACL at the time of extraction, 1 January 2017, 456 patients were considered eligible and 343 of them met the final inclusion criteria. Baseline demographics are presented in Table 7. Included and excluded in Studies V-VII based on the combined data from Project ACL and the SNKLR are presented in Figure 22. Ethical approval was obtained from the Regional Ethical Review Board in Gothenburg (registration number 265-13, T023-17).

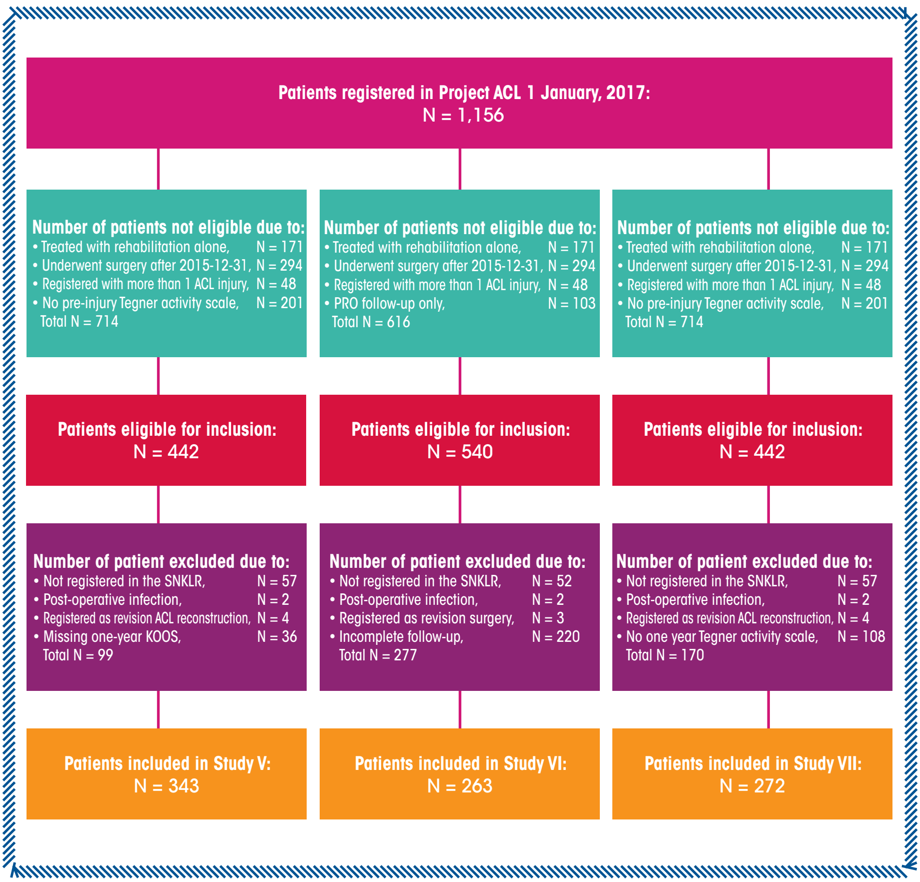

FIGURE 22

Patient inclusion and exclusion in Studies 5-7.

TABLE 7. Baseline data and drop-out analysis in Study V.			
	Included (n = 343)	Excluded (n = 99)	p-value
Patient demographics			
Female	176 (51.3%)	64 (56.6%)	0.38
Age at index ACL injury	26.8 (10.3)	25.5 (9.8)	0.19
Age at index ACL reconstruction	28.1 (10.6)	26.3 (10.0)	0.080
Height [cm]	174.4 (9.5)	172.9 (21.3)	0.67
Weight [kg]	73.9 (15.7)	70.6 (19.4)	0.33
BMI [kg/m2]	24.2 (4.5)	23.4 (4.5)	0.43
Surgery-related factors			
Graft choice			
Hamstring tendon	300 (87.5%)	38 (88.4%)	
Patellar tendon	37 (10.8%)	5 (11.6%)	
Other	6 (1.7%)	0 (0%)	
Concomitant injuries			
Medial meniscus	81 (23.6%)	11 (24.4%)	
Lateral meniscus	95 (27.7%)	12 (26.7%)	
Meniscus (medial or lateral)	154 (44.9%)	21 (46.7%)	
Cartilage	93 (27.1%)	13 (28.9%)	
Medial collateral ligament	16 (4.7%)	3 (6.7%)	
Lateral collateral ligament	1 (0.3%)	0 (0.0%)	
Activity			
Soccer	139 (40.6%)	21 (46.7%)	0.54
Tegner activity scale$_{preinjury}$ ≥6	269 (78.4%)	63 (84.0%)	0.36

For categorical variables, n (%) is presented. For continuous variables, the mean (SD) /median (Q1; Q3)/n = is presented. For comparisons between groups, Fisher's exact test (lowest one-sided p-value multiplied by 2) was used for dichotomous variables and the Mann-Whitney U-test was used for continuous variables.

Outcome

Achieving a PASS in the KOOS subscales, with the addition of a continuous analysis of the KOOS4, were used as dependent outcomes in the regression models. The corresponding PASS cut-offs for the subscales of the KOOS are as follows: pain ≥ 88.9, symptoms ≥ 57.1, ADL = 100, sport and recreation ≥ 75.0 and QoL ≥ 62.5.

STUDY VI

Study design

Register-based cohort including two registers

Patients and Methods

This cohort study was based on data collected prospectively from two registers, Project ACL and the SNKLR. Patients in Project ACL with results from all five tests of muscle function at the one-year follow-up after reconstruction were eligible for inclusion. The battery of tests consisted of strength measurements with a concentric isokinetic test of knee extension and knee flexion at 90 degrees per second using a Biodex System 4 (Biodex Medical Systems, Shirley, New York, USA).[353] Hop tests consisted of the one-legged hop for distance, vertical jump (Muscle lab, Ergotest Technology, Oslo, Norway) and side-hop test. For the eligible patients, additional intra-operative and surgical information was extracted from the SNKLR, including data on concomitant injuries and graft choice. Only patients who underwent primary unilateral ACL reconstruction and had undergone no previous knee surgery were included in the study. Patients were excluded if they had an early postoperative infection. Of the 1,156 patients registered in Project ACL at the time of extraction, 1 January 2016, 540 patients were considered eligible and 263 of them met the final inclusion criteria. Baseline demographics are presented in Table 8.

TABLE 8. Baseline data and drop-out analysis in Study VI.

	Included cohort (n = 263)	Excluded (n = 277)	p-value
Patient demographics			
Female	124 (47.1%)	154 (55.6%)	0.06
Age at index ACL injury	26.7 (10.3)	26.5 (10.3)	0.64
Age at index ACL reconstruction	28.0 (10.5)	27.1 (10.3)	0.19
Height [cm]	174.8 (9.6)	174.4 (9.1)	0.67
Weight [kg]	73.7 (13.0)	73.5 (13.5)	0.66
BMI [kg/m2]	24.1 (2.8)	24.1 (3.2)	0.88
Surgery-related factors			
Graft choice			
Hamstring tendon	232 (88.9%)	154 (90.1%)	
Patellar tendon	29 (11.1%)	17 (9.9%)	0.83
Concomitant injuries			
Medial meniscus	57 (21.7%)	43 (24.3%)	0.60
Lateral meniscus	72 (27.4%)	53 (29.9%)	0.63
Articular cartilage	75 (27.0%)	47 (26.9%)	0.73
Medial collateral ligament	13 (4.9%)	11 (6.2%)	0.71
Lateral collateral ligament	1 (0.4%)	2 (1.1%)	0.71
Meniscus (medial or lateral)	116 (44.1%)	82 (46.3%)	0.72
Activity			
Soccer	105 (39.9%)	107 (45.5%)	0.24
Tegner activity scale$_{preinjury}$ ≥6	198 (78.0%)	98 (85.2%)	0.13

For categorical variables, n (%) is presented. For continuous variables, the mean (SD)/median (Q1; Q3)/n = is presented. For comparisons between groups, Fisher's exact test (lowest one-sided p-value multiplied by 2) was used for dichotomous variables and the Mann-Whitney U-test was used for continuous variables.

Outcome

Achieving an LSI of ≥ 90% across the battery of five tests was used as the primary outcome and the dependent outcome in the prediction models. Additional models were performed using the achievement of an LSI of ≥ 90% in the knee extension and knee flexion tests respectively as dependent outcomes.

STUDY VII

Study design

Register-based cohort including two registers

Patients and Methods

This study was based on a prospective cohort with combined data from two registers, Project ACL and the SNKLR. Patients registered in Project ACL, who had been evaluated one year after ACL reconstruction, were eligible for inclusion. For the identified patients, additional intra-operative and surgical information found in the SNKLR was extracted, including data reported on concomitant injuries and graft choice. Only patients who underwent primary unilateral ACL reconstruction and had undergone no previous knee surgery were considered. Patients were excluded if they had an early postoperative infection reported in Project ACL or the SNKLR. For final analysis, only patients with a pre-injury Tegner activity scale of ≥ 6, i.e. participation in a knee-strenuous sport, were included. Of the 1,156 patients registered in Project ACL at the time of extraction, 1 January 2016, 442 patients were considered eligible and 272 of them met the final inclusion criteria. Baseline demographics are presented in Table 9.

TABLE 9. Patient characteristics and drop-out analysis in Study VII.

Variables	Total cohort (n = 272)	Excluded (n = 170)	p-value
Patient demographics			
Female	138 (50.7%)	82 (48.2%)	0.68
Age at index ACL injury	25.0 (9.2)	25.3 (9.2)	0.77
Age at index ACL reconstruction	26.0 (9.5)	26.2 (9.6)	0.89
Height [cm]	174.7 (9.6)	175.7 (9.8)	0.24
Weight [kg]	72.6 (12.0)	75.0 (15.1)	0.23
BMI [kg/m2]	23.8 (2.9)	24.1 (3.3)	0.52
Surgery-related factors			
Graft choice			
Hamstring tendon	234 (86.0%)	91 (91.0%)	
Patellar tendon	34 (12.5%)	9 (9.0%)	0.43
Other	4 (1.5%)	0 (0.0%)	
Concomitant injuries			
Medial meniscus	60 (22.1%)	24 (23.5%)	0.86
Lateral meniscus	77 (28.3%)	35 (34.3%)	0.32
Cartilage	65 (23.9%)	27 (26.5%)	0.70
Medial collateral ligament	12 (4.4%)	7 (6.9%)	0.47
Lateral collateral ligament	1 (0.4%)	1 (0.4%)	0.94
Meniscus (medial or lateral)	122 (44.9%)	53 (52.0%)	0.27
Activity			
Soccer	122 (44.9%)	76 (53.1%)	0.13
Tegner activity scale$_{preinjury}$ [0-10] Median (Q1; Q3)	8.0 (7.0; 9.0)	8.0 (7.0; 9.0)	0.27

For categorical variables, n (%) is presented. For continuous variables, the mean (SD)/median (Q1; Q3)/n = is presented. For comparisons between groups, Fisher's exact test (lowest one-sided p-value multiplied by 2) was used for dichotomous variables and the Mann-Whitney U-test was used for continuous variables.

Outcome
Return to sport one year after ACL reconstruction, defined as a Tegner activity scale of ≥ 6, i.e. participating in knee-strenuous sport, was used as the dependent outcome in the regression model.

8.4. THEME THREE: LONG-TERM PREDICTORS

STUDY VIII

Study design
Long-term prospective cohort based on two randomized controlled trials

Patients and Methods
This study is an exploratory analysis of data from two previous RCTs[43 81 192] that comprised 193 patients who underwent unilateral arthroscopic ACL reconstruction with ipsilateral HT or PT autografts. In the original studies,[81 192] patients were eligible if they had an isolated unilateral ACL rupture and no more than minor meniscal or chondral lesions. Patients who suffered multiligament injuries, major meniscal injuries, chondral lesions requiring surgical treatment or had a previous ACL reconstruction were excluded. ACL reconstructions were performed by six experienced senior surgeons between September 1995 and January 2000. Patients were randomized using non-transparent sealed envelopes to ACL reconstruction with either an HT autograft or a PT autograft (Table 10). All the patients gave their written informed consent and the Regional Ethical Review Board in Gothenburg approved the long-term follow-up of these patients (ID number: 986-12).

In the original studies, the patients underwent ACL reconstruction under general anesthesia and were given preoperative antibiotic prophylaxis. Reconstructions were performed using a TT or medial portal technique using either a PT or an HT autograft. All the patients underwent a similar rehabilitation program designed by their local physical therapist, with immediate full weight-bearing and full range of motion.[318] No brace was used. During the first six weeks, external loads were not permitted from 30 degrees of knee flexion to hyperextension. Closed chain exercises were started immediately postoperatively. Running was permitted at three months postoperatively.

In the preoperative assessment, the KT-1000 arthrometer[68] was used for the assessment of anteroposterior knee laxity. Range of motion was measured to the nearest 5° using a goniometer. The Lysholm score[341] and Tegner activity scale[341] were used to assess knee function and level of physical activity. To evaluate muscle function, the one-leg-hop test was used. An independent physical therapist, not involved in the patients' rehabilitation, performed a preoperative assessment, including the Lachman test[275] and the pivot-shift test.[108] In addition, the presence of concomitant injuries was recorded by the operating surgeon. At the long-term follow-up, a similar assessment was made. In addition, the IKDC[157] evaluation system was used as one of the primary outcomes.

As part of the long-term follow-up, standard weight-bearing radiographic examinations were performed. Frontal and lateral side projections of both knees were obtained. In addition, the skyline view of the patellofemoral joint was examined. The Kellgren-Lawrence classification was used to assess the obtained projections and osteoarthritis was defined as a Kellgren-Lawrence grade of ≥ 2 (i.e. significant osteophytes and/or a cartilage reduction of up to 50%).[91 171] All assessments were performed by an independent experienced senior musculoskeletal radiologist.

TABLE 10. Baseline demographics, characteristics and drop-out analysis in Study VIII.			
Variables	Included cohort (n = 124)	Excluded (n = 23)	p-value
Patient demographics and characteristics			
Female	45 (36.3%)	7 (30.4%)	0.77
Age at ACL reconstruction	27.9 (8.3)	24.2 (7.5)	0.028
Cause of ACL injury			
Contact sport	82 (70.7%)	18 (81.8%)	
Non-contact sport	18 (15.5%)	2 (9.1%)	
Activities of daily living	4 (3.4%)	0 (0.0%)	
Work	1 (0.9%)	0 (0.0%)	
Other	11 (9.5%)	2 (9.1%)	0.77
Time from injury to ACL reconstruction			
0-12 months	57 (49.6%)	10 (45.5%)	
> 12 months	58 (50.4%)	12 (54.5%)	
Months between injury and ACL reconstruction	35.3 (57.2)	30.8 (40.9)	
Intra-operative data			
Type of autograft			
Bone-patellar tendon-bone	51 (41.1%)	10 (43.5%)	
Hamstring tendon	73 (58.9%)	13 (56.5%)	1.00
Concomitant injuries, dichotomous Yes	85 (69.1%)	12 (52.2%)	0.18
Preoperative clinical assessment			
Range of motion side-to-side difference knee extension	0 (-10; 25) n = 115	5 (0; 20) n = 22	0.031
Range of motion side-to-side difference knee flexion	-5 (-30; 55) n = 115	-8 (-45; 15) n = 22	0.067
KT-1000 89N side-to-side difference	4.2 (4.0) n = 114	4.4 (3.7) n = 21	0.69
Lachman test			
0	1 (0.9%)	0 (0.0%)	
1	25 (21.9%)	4 (18.2%)	
2	63 (55.3%)	9 (40.9%)	
3	25 (21.9%)	9 (40.9%)	0.14
Pivot-shift test			
0	12 (10.8%)	4 (18.2%)	
1	80 (72.1%)	14 (63.6%)	
2	17 (15.3%)	4 (18.2%)	
3	2 (1.8%)	0 (0.0%)	0.55
One-leg-hop test (limb symmetry index)	74.2 (28.1) 85.0 (0.0; 113.0) (65.0; 91.0) n = 114	80.4 (21.8) 86.0 (0.0; 103.0) (69.0; 93.0) n = 22	0.42
Preoperative patient-reported outcome			
Lysholm score	69.9 (15) n = 115	72.9 (9.6) n = 22	0.45
Tegner activity scale pre-injury			
3	1 (0.9%)	0 (0.0%)	
4	1 (0.9%)	0 (0.0%)	
5	7 (6.1%)	0 (0.0%)	
6	9 (7.9%)	3 (13.6%)	
7	24 (21.1%)	3 (13.6%)	
8	14 (12.3%)	1 (4.5%)	
9	55 (48.2%)	14 (63.6%)	
10	3 (2.6%)	1 (4.5%)	0.20

For categorical variables, n (%) is presented. For continuous variables, the mean (SD)/median (min; max)/(Q1; Q3)/n= is presented. For comparisons between groups, Fisher´s exact test (lowest one-sided p value multiplied by 2) was used for dichotomous variables, the Mantel-Haenszel chi -square test was used for ordered categorical variables, the chi-square test was used for non-ordered categorical variables and the Mann-Whitney U-test was used for continuous variables.

Outcome

The PASS of the IKDC and the development of osteoarthritis, defined as a Kellgren-Lawrence of ≥ 2, were used a primary outcomes and dependent outcomes in the prediction models.

STUDY IX

Study design

Long-term register-based prospective cohort

Patients and Methods

Prospectively collected data were extracted from the SNKLR on 31 December 2016. Patients who underwent ACL reconstruction between 1 January 2005 and 31 December 2006 were eligible for enrolment. If no data from the ten-year follow-up of the KOOS were available or if the patients' first entry in the SNKLR was a revision ACL reconstruction, the patients were excluded. All baseline patient demographics and surgery-related factors were extracted for patients who met the inclusion criteria (Table 11).

The variables of interest covered five categories: patient demographics, injury pattern, activity that led to injury, surgery-related factors including graft fixation methods and preoperative patient-reported outcome. Patient demographics comprised patient sex, age at ACL reconstruction, height, weight, body mass index, cigarette smoking and the use of smokeless tobacco. Injury pattern covered information related to the registered ACL reconstruction (primary/revision) and all concomitant injuries. Information on the location and severity (International Cartilage Repair Society, ICRS, grades)[52] of articular cartilage injuries was extracted, but only the presence and ICRS of these injuries were further analyzed. Collateral ligament injuries were assessed by including data on injuries that led to reconstructive treatment, i.e. grade 3 injuries. In the SNKLR, the activity that led to ACL injury covers sporting activities, as well as work-related activities and ADL. In this study, the most frequently reported sporting activities (soccer, Alpine skiing, handball and floorball) were used and compared with all other activities. The timing of surgery, a patient's total number of ACL reconstructions and graft choice were assessed in surgery-related factors. The category of graft fixation comprised all femoral and tibial fixations used during the time period, but only fixations that were used in more than 10% of the included cohort were analyzed. The preoperative patient-reported outcome comprised the baseline KOOS and EQ-5D.[1] In addition, the PASS[235] was applied to the preoperative KOOS on each subscale and studied further. The Regional Ethical Review Board in Stockholm approved the study (ID number: 2011/337-31/3).

TABLE 11. Patient and surgical characteristics and drop-out analysis in Study IX.			
	Included cohort (n = 874)	No 10-year data (n = 1,251)	p-value
Patient-related characteristics			
Age at injury	26.7 (9.8) n = 805	24.4 (8.8) n = 1,186	
Age at ACL reconstruction	29.2 (10.2) n = 874	26.5 (9.4) n = 1,251	<0.0001
Female	424 (48.5%)	521 (41.6%)	0.0020
Body mass index	24.9 (3.9) n = 420	25.0 (3.4) n = 338	0.32
Height (cm)	173.9 (9.0) n = 421	174.9 (8.8) n = 338	0.16
Weight (kg)	75.7 (14.9) n = 425	76.8 (13.4) n = 340	0.072
Cigarette smoking	26 (6.1%)	21 (6.2%)	1.00
Non-smoking tobacco	69 (16.2%)	65 (19.1%)	0.34
Surgery-related characteristics			
Subsequent ACL reconstruction			
Ipsilateral	n = 4	n = 80	0.0017
Contralateral	n = 3	n = 137	0.0033
Day-care surgery	398 (45.5%)	603 (48.2%)	0.24
Time to surgery			
> 12 months	369 (45.8%)	506 (42.7%)	0.18
Graft choice			
Patellar tendon autograft	116 (13.4%)	123 (10.0%)	
Hamstring tendon autograft	745 (86.3%)	1,108 (89.8%)	
Other	2 (0.2%)	3 (0.2%)	0.048
Meniscal injury (medial and/or lateral)			
Yes	337 (38.6%)	555 (44.4%)	0.0086
Articular cartilage injury			
Yes	282 (32.3%)	330 (26.4%)	0.0038
Articular cartilage injury by ICRS grade			
Grade 1-2 (nearly normal/abnormal)	217 (24.8%)	246 (19.7%)	
Grade 3-4 (severely abnormal)	65 (7.4%)	84 (6.7%)	0.014
Medial collateral ligament injury			
Yes	23 (2.6%)	26 (2.1%)	
Yes, with reconstruction, i.e. grade 3	13 (1.5%)	19 (1.5%)	0.79
Lateral collateral ligament injury			
Yes	5 (0.6%)	3 (0.2%)	
Yes, with reconstruction, i.e. grade 3	10 (1.1%)	8 (0.6%)	0.14

For categorical variables, n (%) is presented. For continuous variables, the mean (SD)/median (min; max)/(Q1; Q3)/n= is presented. For comparisons between groups, Fisher's exact test (lowest one-sided p-value multiplied by 2) was used for dichotomous variables, the Mantel-Haenszel chi-square test was used for ordered categorical variables, the chi-square test was used for non-ordered categorical variables and the Mann-Whitney U-test was used for continuous variables.

Outcome

All subscales of the KOOS, and the additional KOOS4, were used as the primary outcome and dependent outcome in the ten-year risk factor analyses.

09

STATISTICAL METHODS

STUDY I

Descriptive statistics were used for patient demographics and outcomes, reported as the mean, standard deviation and 95% confidence intervals. Between-group comparisons of patient demographics and outcomes were performed with an independent parametric t-test and a non-parametric test, the Mann-Whitney U-test. Statistical analyses were performed using SPSS (version 22, 2013 SPSS Inc., Chicago, IL, USA).

STUDIES III AND IV

The statistical analyses in Studies III and IV were performed in IBM SPSS Statistics (Version 23.0, IBM Corp, Armonk, New York, USA). Descriptive statistics were used for patient demographics and outcomes. Univariable logistic regression models, with the respective primary outcome of each study as the dependent variable, were used and reported as an OR with a 95% confidence interval (CI). In Study III, a multivariable logistic regression model was additionally used with adjustments for significant differences in patient baseline characteristics; age and patient sex. All significance tests were conducted at the 5% significance level.

STUDIES V-VIII

The statistical analyses in Studies V-VIII were performed using the SAS System for Windows, version 9, statistical analysis system (SAS Institute Inc., Cary, North Carolina, USA). Descriptive statistics for patient demographics and outcomes were reported as numbers and percentages for categorical variables. Continuous variables were reported as the mean, standard deviation, median, minimum and maximum. For comparisons between two groups, Fisher's exact test (lowest one-sided p-value multiplied by two) was used for dichotomous variables and the Mann-Whitney U test for continuous variables. Binary logistical regression was performed to analyze the association between predictors and dependent outcome with regard to the respective purpose of each study. The results of the logistic regression models were presented with the odds ratio (OR), 95% CI and p-values. The area under the receiver operating characteristic (ROC) curve was given as a measurement of goodness of fit, using limits of 0.90-1 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair, 0.60-0.70 = poor and 0.50-0.60 = fail.[223] A continuous linear regression was performed to analyze the KOOS4 in Study V. In an attempt to find the best predictive model for the primary outcomes of each study, a stepwise multivariable logistic model was used. Predictors with $p < 0.20$ were entered into the stepwise analyses. All significance tests were two-sided and conducted at the 5% significance level.

STUDY IX

The statistical analyses in Study IX were performed using the SAS statistical analysis system (SAS/STAT, version 14.2, 2016; SAS Institute Inc., Cary, North Carolina, USA). Descriptive statistics for patient demographics and outcomes were reported as count and proportion for categorical variables. Continuous variables were reported with the mean and SD and median with the first and third quartiles. Comparisons between included and excluded patients were performed using Fisher's exact test (lowest one-sided p-value multiplied by two) for dichotomous variables, the Mann-Whitney U test for continuous variables, the Mantel-Haenszel chi-square test for ordered categorical variables and the chi-square test for non-ordered categorical variables. The continuous outcome variables of the study (KOOS subscales and KOOS4) were categorised into quartiles and analyzed first with univariable proportional odds regression models. A forward stepwise proportional odds regression was used to select independent predictors. Only those predictors attaining a p-value of < 0.20 in the univariable analysis were included in the forward stepwise proportional odds regression. The results of the regression models were presented with OR, 95% CI and p-values. All significance tests were two-sided and conducted at the 5% significance level.

10

RESULTS

10.1. THEME ONE: CREATING A FOUNDATION FOR RESEARCH

AIM

To determine factors that affect patient-reported outcome after ACL reconstruction and present a rehabilitation-based register capable of dealing with these factors.

SUMMARY

The results of the first theme show the importance of defining an outcome to understand the influence of other variables of interest. As exemplified in Study I, the way retrun to sport is defined on the Tegner activity scale influences both the proportion of patients who succeeded in returning to sport and also the way other variables, such as muscle function and patient-reported outcome, were reflected by the outcome. In the light of this, when results overlap, i.e. a variable is consistently significant across different definitions of the outcome, this can facilitate the understanding of the importance of that variable. Creating a rehabilitation outcome register is therefore a novel approach with the ability to follow larger numbers of patients, over a long period of time. This may be necessary in order better to understand the complex interactions of factors influencing outcome after ACL injury and reconstruction.

The identification and verification of modifiable factors which could potentially affect patient-reported outcome were especially valuable in Study II. They included avoiding the use of microfracturing and the debridement of full-thickness concomitant cartilage injuries, considering choosing an HT graft over a PT graft and the implementation of structured rehabilitation protocols. In the clinical setting, special emphasis should be placed on targeting these modifiable factors that could affect patient-reported outcome. On the other hand, clinicians and patients should be aware that there are non-modifiable factors that might predispose to inferior results. Younger age at index ACL reconstruction and male sex were the most predominant patient-related factors with a positive influence on patient-reported outcome, while the presence of a full-thickness cartilage injury and meniscal injuries resulted in inferior patient-reported outcomes. Moreover, this review highlighted the sparse evidence from the registers in terms of the outcome for the non-reconstructive treatment of ACL injuries compared with ACL reconstruction. Most importantly, the findings in Study II, based on generalizable data from the large Scandinavian cohorts, create a foundation for research by indicating which variables may influence or confound patient-reported outcome after an ACL reconstruction.

STUDY I

Return to pre-injury Tegner activity scale

Fifty-two of the 157 patients (33%) reported that they had returned to their pre-injury Tegner activity scale ± 1 on average ten months after the ACL reconstruction. No significant differences in the LSI, with values between 90% and 97%, were found in terms of muscle function between patients who had returned and patients who had not returned to their pre-injury Tegner activity scale ± 1. Patient-reported knee function as measured with the KOOS differed significantly, favoring patients who had returned to their pre-injury Tegner activity scale ± 1: pain ($p = 0.038$), symptoms ($p < 0.001$), ADL ($p = 0.003$), sport and recreation ($p < 0.001$) and QoL ($p < 0.001$). These patients also had higher perceived self-efficacy of knee function ($p < 0.01$). Absolute values for the tests of muscle function and hop performance, accounting for body weight, are presented in Table 12.

TABLE 12. Absolute values for tests of muscle function for the injured and uninjured leg in patients that had and had not returned to pre-injury Tegner ±1 in Study I.

Test of muscle function Mean ± SD	Women			Men		
	Returned	Not returned	P-value	Returned	Not returned	P-value
Knee extension IL (W/kg)	3.2 ± 1.0	2.6 ± 0.7	0.010	4.1 ± 0.6	3.9 ± 1.0	0.361
Knee extension NL (W/kg)	3.5 ± 0.9	2.9 ± 0.9	0.014	4.4 ± 0.6	4.4 ± 0.9	0.581
Knee flexion IL (W/kg)	1.9 ± 0.5	1.6 ± 0.4	0.055	2.5 ± 0.5	2.4 ± 0.6	0.163
Knee flexion NL (W/kg)	2.1 ± 0.5	1.8 ± 0.5	0.070	2.9 ± 0.5	2.8 ± 0.4	0.231
Vertical jump IL (cm/kg)	0.23 ± 0.04	0.21 ± 0.06	0.355	0.26 ± 0.07	0.27 ± 0.07	0.721
Vertical jump NL (cm/kg)	0.26 ± 0.04	0.27 ± 0.03	0.728	0.29 ± 0.05	0.27 ± 0.06	0.501
Hop for distance IL (cm/kg)	2.1 ± 0.4	1.9 ± 0.3	0.161	2.0 ± 0.3	2.0 ± 0.3	0.641
Hop for distance NL (cm/kg)	2.1 ± 0.3	2.0 ± 0.3	0.167	2.1 ± 0.4	2.1 ± 0.4	0.735
Side hop IL (n/kg)	0.7 ± 0.2	0.5 ± 0.2	0.012	0.8 ± 0.1	0.7 ± 0.2	0.107
Side hop NL (n/kg)	0.8 ± 0.2	0.6 ± 0.2	0.004	0.8 ± 0.1	0.7 ± 0.1	0.217

IL; injured leg. NL; non-injured leg.

Return to Tegner activity scale 6 or higher

Of the 157 patients, 84 (54%), 35 women and 49 men, returned to Tegner activity scale 6 or higher. No difference was found for the LSI, with values between 90% and 96%, for the tests of muscle function between patients who had returned and patients who had not returned to knee-strenuous sports. Patient-reported knee function as measured with the KOOS differed significantly between groups, where patients who had returned to knee-strenuous sports had a superior score for symptoms ($p = 0.030$), ADL ($p = 0.017$), sport and recreation ($p < 0.001$) and QoL ($p < 0.001$), compared with patients who had not returned. These patients also reported a higher goal for their future level of physical activity ($p < 0.05$) and higher future level of physical activity ($p < 0.01$). Differences in absolute muscle function accounting for body weight are presented in Table 13.

TABLE 13. Absolute values for tests of muscle function for the injured and uninjured leg in patients that had and had not returned to Tegner Activity Scale 6 or higher, i.e. knee-strenuous sports, in Study I.

Test of muscle function Mean ± SD	Women			Men		
	Returned	Not returned	P-value	Returned	Not returned	P-value
Knee extension IL (W/kg)	3.0 ± 0.9	2.6 ± 0.7	0.032	4.1 ± 0.8	3.8 ± 1.0	0.133
Knee extension NL (W/kg)	3.3 ± 0.8	2.8 ± 0.6	0.024	4.4 ± 0.7	4.3 ± 1.0	0.373
Knee flexion IL (W/kg)	1.8 ± 0.5	1.6 ± 0.4	0.066	2.5 ± 0.4	2.2 ± 0.7	0.039
Knee flexion NL (W/kg)	2.1 ± 0.4	1.7 ± 0.5	0.017	2.9 ± 0.4	2.8 ± 0.5	0.325
Vertical jump IL (cm/kg)	0.22 ± 0.04	0.21 ± 0.07	0.806	0.26 ± 0.06	0.28 ± 0.08	0.458
Vertical jump NL (cm/kg)	0.26 ± 0.04	0.28 ± 0.01	0.391	0.27 ± 0.06	0.29 ± 0.06	0.564
Hop for distance IL (cm/kg)	2.0 ± 0.4	1.9 ± 0.3	0.311	2.0 ± 0.3	2.1 ± 0.3	0.778
Hop for distance NL (cm/kg)	2.1 ± 0.3	2.0 ± 0.3	0.504	2.1 ± 0.3	2.1 ± 0.4	0.708
Side hop IL (n/kg)	0.7 ± 0.2	0.6 ± 0.2	0.214	0.8 ± 0.2	0.7 ± 0.2	0.425
Side hop NL (n/kg)	0.7 ± 0.2	0.6 ± 0.2	0.104	0.8 ± 0.1	0.8 ± 0.1	0.963

IL; injured leg. NL; non-injured leg. * = Significant difference between groups, $p < 0.05$

To summarize, the main findings in this prospective observational register study were that patients who returned to knee-strenuous sports had less impairment during daily activities and sport and recreation, better knee-related QoL and higher self-efficacy of knee function, at an average of 10 months of post-operative rehabilitation.

STUDY II

The literature search yielded a total of 186 identified articles, 88 articles in the PubMed (MEDLINE) database, 94 in EMBASE, three in the Cochrane Library and one in the AMED database. In addition, two studies were identified via the publication lists provided by the register holders. After applying inclusion and exclusion criteria, a total of 37 articles were included in this systematic review.

The Downs and Black score ranged from 9 to 20 points, with a median score of 16 points of a possible 22 points (table found in Study II). Items 8 (adverse events reported) and 19 (compliance reliable) of the Downs and Black were not fulfilled by any study. With the exception of these, the included studies were particularly suboptimal in terms of ensuring the representativeness of the recruited subjects (Item 12) and taking patients lost to follow-up into account for the analysis (Item 26). Fewer than half the included studies fulfilled Item 12 (subjects prepared to participate representatively, reported in 12/37 studies) and Item 26 (loss to follow-up taken into account, reported in 17/37 studies).

The results from the systematic review of factors that affect patient-reported outcome after ACL reconstruction in the Scandinavian knee ligament registers are summarized below, according to the three levels of synthesis: patient-related factors, surgery-related factors and injury-related factors.

PATIENT-RELATED FACTORS

- Two studies from the SNKLR have specifically investigated the effect of patient sex on patient-reported outcome.[5 183] In short, female patients appear to report inferior results in PROMs across all follow-ups.

- Patients of younger age appear to report superior outcome in terms of the KOOS[5 72 94] and Tegner activity scale[94] compared with older patients. However, one of the studies that investigated the effect of both patient sex and age on patient-reported outcome after ACL reconstruction raised the concern that studies only examining the effect of age on outcome may be confounded by the effect of patient sex.[5]

- The effect of smoking on patient-reported outcome has been reported in two studies from the SNKLR.[7 183] Both are consistent in showing that smokers report inferior results from preoperatively to five years after ACL reconstruction in the KOOS and EQ-5D.

- Data on return to sport are not kept in the Scandinavian knee ligament registers, but Fältström et al.[92] utilized the SNKLR and sent out an additional questionnaire to female patients who, before their ACL injury, participated in soccer. Data from 182 players were collected with a median of 18 months from primary ACL reconstruction where 94 (52%) patients had returned to soccer. The most common reason for not returning was “lack of trust in the knee” (28%).

- In a Norwegian cohort study published by Grindem et al.[130], 84 patients who underwent active pre- and postoperative rehabilitation at a specialist clinic as part of the Delaware-Oslo ACL cohort study were compared with 2,690 patients from the Norwegian register not receiving progressive rehabilitation. The intervention cohort showed a significantly better preoperative and two-year KOOS for all subscales.

- One study investigated the association between the use of oral contraceptives and the risk of ACL surgery. [350] The primary finding suggests that the use of oral contraceptives was associated with a reduced likelihood of undergoing an ACL reconstruction.

- An analysis of non-responders, i.e. patients not responding to the surveys administered by the registers, in the Scandinavian knee ligament registers has been performed in two studies.[279 282] Both studies found minor to no differences in patients not responding compared with the responding patients.

SURGERY-RELATED FACTORS

- Patients undergoing primary and revision ACL reconstruction improve on all subscales of the KOOS at the one-, two- and five-year follow-ups compared with the preoperative KOOS.[7 183]

- The KOOS at one year is equivalent to the two-year score in patients undergoing primary ACL reconstruction in the SNKLR, across all subscales and sub-groups of patient sex, age, concomitant injuries and graft choice.[301]

- Patients reporting a low KOOS QoL run an increased risk of undergoing a subsequent ACL reconstruction, [120] where, for instance, patients reporting a KOOS QoL of < 44 points two years after reconstruction have an almost four-fold increase in the risk of undergoing revision ACL reconstruction.

- Patients undergoing revision ACL reconstruction report significantly poorer results on the subscales of the KOOS and EQ-5D on all follow-up occasions compared with those undergoing primary ACL reconstruction.[7 183 201]

- Two studies[183 280] have compared the patient-reported outcome for patients undergoing ACL reconstruction with either an HT or a PT autograft. Both studies consistently report that patients receiving HT autografts report a slightly superior KOOS on all follow-up occasions.

- The diameter of the HT autograft was reported not to influence the KOOS after ACL reconstruction.[323]

- No difference in the KOOS was reported between different drilling techniques (transportal or transtibial) or the surgical technique of single-bundle ACL reconstruction.[136 138 281]

- Patients undergoing double-bundle ACL reconstruction report a slightly lower preoperative KOOS, but they report a similar one- and two-year KOOS.[7 183]

- The administration of NSAIDs to patients undergoing ACL reconstruction does not increase the risk of revision or an inferior KOOS-QoL score at the two-year follow-up.[327] On the other hand, patients that were administered NSAIDs reported significantly higher scores for all KOOS sub-scales at the two-year follow-up.

- A cross-sectional study from the SNKLR matched patients who were not reconstructed with patients with an ACL reconstruction and compared the KOOS and EQ-5D between cohorts at each point of follow-up from baseline to the five-year follow-up.[21] Patients undergoing reconstructive treatment after ACL injury rate their knee function and QoL, measured with the KOOS as superior compared with non-reconstructed patients one to five years after the ACL injury.

INJURY-RELATED FACTORS

- Patients who have sustained concomitant injuries report inferior results on all KOOS subscales preoperatively and at the short-term follow-up at one and two years.[7] However, the results at the medium-term five-year follow-up are inconclusive.

- Males and older patients have a higher frequency of meniscal and chondral injuries.[72]

- A concomitant meniscal injury at the time of ACL reconstruction is present in 35-55%[121 183 200] of patients in the Scandinavian knee ligament registers.

- Patients with concomitant meniscal injuries have an inferior KOOS preoperatively one and two years after ACL reconstruction.[7] In particular, patients who undergo ACL reconstruction with a repair or resection of the medial meniscus, or lateral meniscus repair have a significantly lower preoperative KOOS compared with patients undergoing isolated ACL reconstruction.[188]

- A concomitant cartilage injury at the time of ACL reconstruction is present in 17-27%[121 183 200] of patients in the Scandinavian knee ligament registers.

- Several studies concluded that patients with concomitant full-thickness cartilage lesions (ICRS grade 3-4) report more impairment on all KOOS subscales preoperatively and at short-term follow-ups, one and two years after ACL reconstruction, compared with patients without these lesions.[149 292-294]

- One study comprising a small cohort of patients investigated five to nine years after ACL reconstruction was performed in patients with a concomitant full-thickness cartilage lesion and reported that the recovery of patient-reported knee function was similar to ACL reconstruction performed in patients without concomitant cartilage lesions.[352]

- In terms of the surgical treatment of cartilage injuries, microfracture as treatment showed significant negative effects on patient-reported outcomes two years after ACL reconstruction, with reference to patients who did not receive treatment for concomitant full-thickness cartilage lesions. [295]

- An increased frequency of concomitant injuries has been reported in patients with increased time from ACL injury to surgery.[35 118 293]

10.2. THEME TWO: SHORT-TERM PREDICTORS

AIM

To determine short-term patient-related, surgery-related and injury-related predictors of short-term outcomes after ACL reconstruction.

SUMMARY

In the second theme, preoperative characteristics and intra-operative findings were used to determine different short-term outcomes, i.e. one and two years, after ACL reconstruction. In terms of patient-related predictors, which were particularly studied in Studies V-VII, patient sex and age at the time of ACL reconstruction have a near consistent effect on short-term outcome. Younger patients and males had an increased likelihood of reporting acceptable knee function, recovering symmetrical knee function and returning to sports. In terms of the pre-injury level of physical activity, patients who participated in a higher level of physical activity had an increased likelihood of reporting a superior short-term outcome, compared with patients who did not participate in knee-strenuous activity. However, when only considering the patients who had a knee-strenuous level of activity, the effect on outcome is not consistent.

Surgery-related predictors, especially surgical techniques of single-bundle ACL reconstruction and the choice of an HT or PT autograft, showed little to no effect on one- and two-year outcome after reconstruction. Some favorable results for HT autografts achieving acceptable patient-reported knee function were found in Study V.

Injury-related predictors, especially in terms of concomitant injuries, had an overall negative influence on short-term outcome after ACL reconstruction. This in turn suggests that patients who have sustained concomitant injuries may require more than a year of rehabilitation to recover knee function and return to sport. As illustrated in Studies III-V, patient-reported knee function appears to be impaired in patients who have sustained a concomitant injury one and two years after ACL reconstruction. However, it should be pointed out that the result of inferior patient-reported knee function in the presence of a concomitant injury was not consistent across the studies in this thesis. Study III also suggested that the presence of increased preoperative knee-joint laxity does not negatively influence the short-term likelihood of achieving acceptable knee function after ACL reconstruction, with the possible exception of patients with manually assessed high-grade rotational laxity.

In Study VI, no difference was demonstrated in the likelihood of achieving symmetrical knee function across a battery of five tests between patients with or without concomitant injuries. However, fewer than one in four patients had symmetrical knee function defined as an LSI of ≥ 90% across the battery of tests. When return to sport was used as an outcome in Study VII, the presence of a concomitant meniscus injury and especially a medial collateral ligament injury was negatively associated with return to sport one year after ACL reconstruction with seven-fold odds.

STUDY III

A total of 86 patients had complete data on the IKDC at the one-year follow-up and 67 of them (78%) achieved a PASS. Two-year data were available for 50 patients, of which 39 patients (79%) achieved a PASS. Preoperative knee range of motion and anterior tibial displacement were not able to predict the achievement of a PASS at the one-year follow-up. A low-grade manual pivot-shift according to IKDC grading had increased odds of achieving a PASS at one year (OR = 2.96, [95% CI: 1.01-8.66], p = 0.047), compared with patients who displayed a high-grade pivot shift preoperatively. However, this was not confirmed by the preoperative quantitative pivot shift (QPS) measurements (awake: tibial translation; OR = 0.99, [95% CI: 0.72-1.35], (p = 0.95), acceleration; OR = 1.04, [95% CI: 0.68-1.59], (p = 0.85). Examination under anesthesia (EUA): tibial translation; OR = 1.02, [95% CI: 0.78-1.31], (p = 0.87), acceleration; OR = 1.14 [95% CI: 0.93-1.40], (p = 0.22). All one-year predictors are presented in Table 14. None of the studied variables of patient characteristics, concomitant injuries or knee-joint laxity predicted a PASS at the two-year follow-up.

TABLE 14. Univarible logistic regression model with PASS one year after ACL reconstruction as the dependent variable in Study III.

Predictor	n missing	Reference	Value	Mean ± SD or Freq(%)	OR (95% CI)	P-value
Patient characteristics						
Age at ACL reconstruction	0	Continuous		24.8 ± 9.3	0.97 (0.92-1.02)	0.19
Patient Sex	0	Female*	Male	*37/86 (43.0%)	1.25 (0.45-3.49)	0.67
Freq. of physical activity	2	1-3x/month		9/84 (10.7%)		-
			4-7x/week	46/84 (54.8%)	2.79 (0.56-13.86)	0.21
			1-3x/week	29/84 (34.5%)	1.31 (0.26-6.55)	0.74
Prior level of activity	0	No activity		1/86 (1.2%)	-	-
			Very strenuous	63/86 (73.3%)	0.0 (0.0-infinity)	1.00
			Strenuous activities	17/86 (19.8%)	0.0 (0.0-infinity)	1.00
			Moderate activity	5/86 (5.8%)	0.0 (0.0-infinity)	1.00
Time from injury to surgery	0	Continuous		128 ± 86	1.01 (0.10-1.40)	0.79
Injury characteristics						
Meniscus injury	0	Normal – no lesion*	Lesion in either meniscus	*33/86 (38.4%)	0.92 (0.32-2.64)	0.88
Articular cartilage injury	0	No articular cartilage defect*	Lesion in any surface	*73/86 (84.9%)	1.67 (0.34-8.28)	0.53

ACL injury	0	Complete tear of both bundles*	Partial or mixed	*75/86 (87.2%)	0.72 (0.17-3.01)	0.66
Range of motion						
Passive knee extension	7	Continuous		2 ± 4	0,96 (0.85-1.08)	0.48
Active knee extension	8	Continuous		2 ± 4	1.00 (0.89-1.1.2)	0.99
Passive knee flexion	8	Continuous		135 ± 21	1.01 (0.99-1.103)	0.35
Active knee flexion	7	Continuous		132 ± 21	1.01 (0.99-1.04)	0.27
Objective knee laxity						
Anterior KT-1000 at 30Nm	13	Continuous		10.2 ± 3.1	0.96 (0.79-1.16)	0.64
Anterior KT-1000 man. max.	9	Continuous		10.9 ± 3.6	0.96 (0.82-1.11)	0.55
KT-1000 side-to-side difference at 30Nm	13	Continuous		3.7 ± 2.7	0.91 (0.73-1.14)	0.40
KT-1000 side-to-side difference at min. max.	9	Continuous		4.2 ± 2.8	0.89 (0.73-1.10)	0.29
Lachman dichotomous	4	1-5mm translation*	6mm + translation	*33/82 (40.2%)	1.25 (0.43-3.59)	0.68
Pivot-shift	4	Equal*		*5/82 (6.1%)	-	-
			Gross (3+)	2/82 (2.4%)	0.25 (0.01-8.56)	0.44
			Clunk (2+)	27/82 (32.9%)	0.50 (0.05-5.15)	0.56
			Glide (1+)	48/82 (58.5%)	1.46 (0.14-15.1)	0.75
Pivot-shift dichotomous	4	Low-grade (Grade 0-1)*	High-grade (Grade 2-3)	*53/82 (64.6%)	0.34 (0.12-0.99)	0.047
Accelerometer injured $knee_{preop\text{-}awake}$	11	Continuous		3.58 ± 1.68	0.94 (0.68-1.30)	0.72
IAS injured $knee_{preop\text{-}awake}$	6	Continuous		2.15 ± 1.69	0.85 (0.64-1.13)	0.26
Accelerometer injured $knee_{preop\text{-}EUA}$	13	Continuous		6.05 ± 4.91	1.13 (0.94-1.37)	0.20
IAS injured $knee_{preop\text{-}EUA}$	1	Continuous		2.83 ± 2.10	0.92 (0.74-1.16)	0.50
Accelerometer side-to-side $difference_{preop\text{-}awake}$	13	Continuous		0.80 ± 1.34	1.04 (0.68-1.59)	0.85
IAS side-to-side $difference_{preop\text{-}awake}$	8	Continuous		1.21 ± 1.65	0.99 (0.72-1.35)	0.95
Accelerometer side-to-side $difference_{preop\text{-}EUA}$	13	Continuous		3.12 ± 4.94	1.14 (0.93-1.40)	0.22
IAS side-to-side $difference_{preop\text{-}EUA}$	5	Continuous		1.86 ± 2.13	1.02 (0.78-1.31)	0.87
EUA, examination under anesthesia; Freq, frequency; IAS, image analysis system; Max, maximum; Nm, Newton meters;						

STUDY IV

Patient-reported success

The average KOOS4 in the group of patient-reported success was 89.9 points. No differences in the proportion between surgical techniques or surgical procedures were found. The lowest proportion of patients represented in the 80th percentile had undergone ACL reconstruction using the transtibial (TT) partial-anatomic technique. TT partial-anatomic was therefore used as a reference in the logistic regression model.

The absence of a concomitant injury to the menisci was significantly associated with patient-reported success (OR = 0.81 [95% CI: 0.72-0.92], p = 0.001), as was the absence of cartilage injury (OR = 0.70 [95% CI: 0.61-0.81], p < 0.001). No overall associations with surgical techniques or surgical factors were found. However, an association was found in favor of the TT partial anatomic over the TT anatomic surgical technique (OR = 1.37 [95% CI: 1.07-1.76], p = 0.013), (Table 15).

TABLE 15. Logistic regression model for prediction of patient-reported success adjusted for age and patient sex in Study IV.

Predictor	Odds ratio	95% CI	p-value
Concomitant Injury			
MCL	0.84	0.57-1.25	0.40
LCL	1.30	0.64-2.65	0.48
Meniscus	0.81	0.72-0.92	0.001
Cartilage	0.70	0.61-0.81	< 0.001
Surgical techniques Reference = TT partial-anatomic			0.18
TP reference	1.18	0.95-1.48	0.14
TT non-anatomic	1.22	0.92-1.62	0.16
TT anatomic	1.37	1.07-1.76	0.013
TP anatomic	1.22	0.97-1.54	0.10
Surgical factors			
Landmarks	1.06	0.81-1.38	0.67
Footprints	1.17	0.94-1.46	0.16
Ridges	0.95	0.81-1.10	0.49
Drilling (TT vs TP)	1.04	0.91-1.17	0.60

LCL, lateral collateral ligament; MCL, medial collateral ligament

Patient-reported failure

The average KOOS4 in the patient-reported failure group was 56.2. No differences in the proportion of surgical techniques or surgical procedures were found. The lowest proportion of patients represented in the 20th percentile had undergone ACL reconstruction using the TT non-anatomic technique. TT non-anatomic was therefore used as a reference in the logistic regression model.

The presence of a concomitant cartilage injury was significantly associated with patient-reported failure (OR = 1.27 [95% CI, 1.11-1.44], p = 0.001). No overall associations with surgical techniques or surgical factors were found. However, an association was found in favor of the TT non-anatomic technique compared with the transportal reference surgical technique (OR = 1.37 [95% CI, 1.07-1.76], p = 0.013) (Table 16).

TABLE 16. Logistic regression model for prediction of patient-reported failure adjusted for age and patient sex in Study IV.			
Predictor	Odds ratio	95% CI	p-value
Concomitant Injury			
MCL	1.09	0.76-1.57	0.64
LCL	1.87	0.97-3.62	0.06
Meniscus	1.1	0.98-1.24	0.12
Cartilage	1.27	1.11-1.44	< 0.001
Surgical techniques Reference = TT non-anatomic			0.12
TP reference	1.29	1.01-1.63	0.04
TT non-anatomic	1.09	0.83-1.42	0.56
TT anatomic	1.35	1.02-1.78	0.04
TP anatomic	1.21	0.94-1.55	0.14
Surgical factors			
Landmarks	1.00	0.77-1.30	0.99
Footprints	0.98	0.79-1.21	0.85
Ridges	1.08	0.92-1.26	0.36
Drilling (TT vs TP)	1.06	0.94-1.20	0.36
LCL, lateral collateral ligament; MCL, medial collateral ligament			

STUDY V

The proportion of patients achieving a PASS varied between 40-85% on the KOOS subscales one year after reconstruction. There was an overall lack of consistency related to the effect of concomitant knee injuries and graft choice on acceptable knee function based on the results of the regression modeling. The lack of consistency in these findings is also highlighted by the poor capacity of any model to explain the variance in the outcome; none of the area under the ROC curve (AUC) results that showed predictive capacity no better than chance and none of the R-squared values was above 2%. However, younger age at reconstruction and males had favorable odds of achieving acceptable knee function across the KOOS subscales. Increased odds of achieving a PASS in the KOOS sport and recreation was found for patients who had no cartilage injury; it was 1.63-fold ([95% CI; 1.01-2.64], p = 0.045). Additionally, there was 0.41-fold ([95% CI; 0.19-0.85], p = 0.017) decrease in the odds of achieving a PASS in the KOOS QoL in patients receiving a PT autograft (Table 17). In the multivariable analysis, increased odds of achieving a PASS in the KOOS QoL were associated with the absence of meniscus injury, OR = 1.62 [95% CI; 1.04-2.54], p = 0.035) and lower odds were found for PT autografts (OR = 0.38 [95% CI; 0.18-0.80], p = 0.011).

TABLE 17. Univariable and adjusted regression analyses with the patient-acceptable symptom state on the Knee injury and Osteoarthritis Outcome Score subscale of quality of life as a dependent outcome in Study V.

				Univariable*			Adjusted**	
Tentative predictors	n missing	Value	PASS KOOS QoL (≥62.5)	OR (95%CI) KOOS QoL ≥62.5	p-value	Area under ROC curve (95%CI)	OR (95%CI) KOOS QoL ≥62.5	p-value
Patient sex	0	Female	82 (46.6%)					
		Male	91 (54.5%)	1.37 (0.90-2.10)	0.14	0.54 (0.49-0.59)		
Age at index ACL recon-struction (OR per 10 units)	0	12-<25 years	85 (54.8%)					
		25-<35 years	51 (45.5%)					
		35-58 years	37 (48.7%)	0.92 (0.76-1.13)	0.45	0.54 (0.48-0.60)		
Tegner activity level preoperative [0-10]	0	1-<6	38 (51.4%)					
		6-10	135 (50.2%)	0.99 (0.89-1.09)	0.78	0.51 (0.45-0.57)		
Medial meniscus injury	0	Yes	35 (43.2%)					
		No	138 (52.7%)	1.46 (0.89-2.42)	0.14	0.53 (0.49-0.58)	1.42 (0.85-2.36)	0.18
Lateral meniscus injury	0	Yes	44 (46.3%)					
		No	129 (52.0%)	1.26 (0.78-2.02)	0.35	0.52 (0.48-0.57)	1.37 (0.84-2.22)	0.21
Meniscus in-jury (medial or lateral)	0	Yes	71 (46.1%)					
		No	102 (54.0%)	1.37 (0.89-2.10)	0.15	0.54 (0.49-0.59)	1.44 (0.93-2.23)	0.099
Cartilage injury	0	Yes	45 (48.4%)					
		No	128 (51.2%)	1.12 (0.70-1.80)	0.64	0.51 (0.46-0.56)	1.10 (0.66-1.84)	0.71
Medial collateral ligament injury	0	Yes	8 (50.0%)					
		No	165 (50.5%)	1.02 (0.37-2.78)	0.97	0.50 (0.48-0.52)	0.92 (0.33-2.56)	0.88
LCL colleratal ligament injury	0	Yes	0 (0.0%)					
		No	173 (50.6%)	554826 (0.00-infinity)	0.99	0.50 (0.50-0.51)	668066 (0.00-infinity)	0.99
Graft choice	6	Ham-string tendon	158 (52.7%)					
		Patellar tendon	12 (32.4%)	0.43 (0.21-0.89)	0.023	0.54 (0.51-0.57)	0.41 (0.19-0.85)	0.017

P-values, OR and area under ROC curve are based on original values and not on stratified groups. OR is the ratio for the odds of an increase in the predictor of one unit. *) All tests are performed with univariable logistic regression. **) Adjusting for age at index ACL reconstruction, patient sex and preoperative Tegner activity scale [0-10] using logistic regression.

STUDY VI

No patient demographic or intra-operative predictors were found to be significant when attempting to predict the achievement of symmetrical muscle function, defined as an LSI of ≥ 90%, across the battery of tests consisting of knee extension and flexion strength, vertical jump, hop for distance and the side-hop test (Figure 23). In the analysis of achieving symmetrical knee extension strength, a concomitant lateral meniscus injury and a PT autograft reduced the odds of achieving an LSI of ≥ 90% in knee extension strength, OR = 0.49 ([95% CI; 0.25-0.97], p = 0.039] and OR = 0.30 ([95% CI; 0.14-0.67], p = 0.0033) respectively. In addition, reduced odds of recovering knee extension strength were found in older patients, OR = 0.76 ([95% CI; 0.60-0.98], p = 0.034). A higher pre-injury level of physical activity increased the odds of recovering knee flexion strength, OR = 1.14([95% CI; 1.01-1.29], p = 0.037).

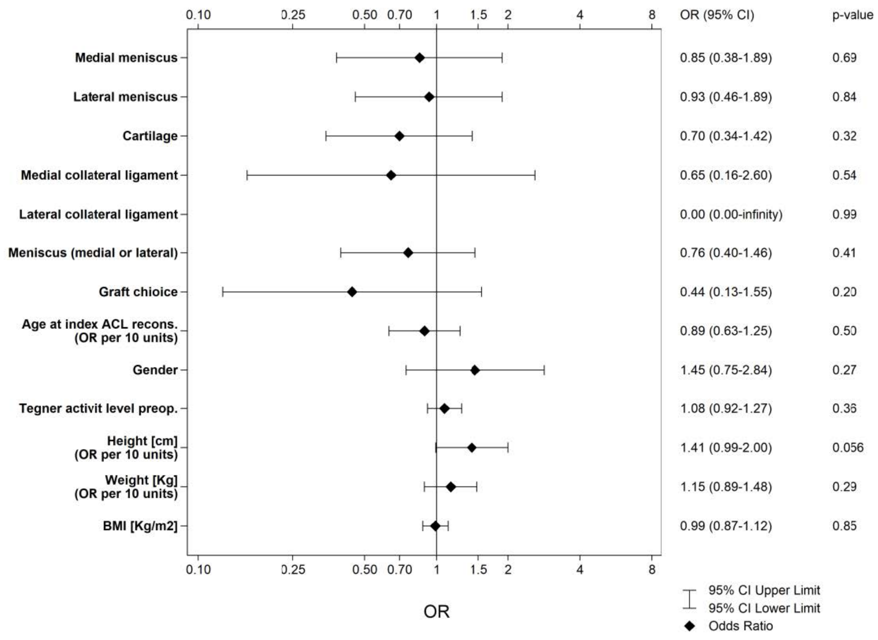

FIGURE 23

Odds ratio, 95% confidence intervals and p-values for a limb symmetry index of ≥ 90 % in all five tests of strength. An OR of > 1 indicates a result favoring the absence of a concomitant injury. For graft choice, an OR of < 1 indicates that the result favors an HT autograft, while an OR of > 1 favors a PT autograft.

STUDY VII

In Study VII, a total of 155 patients (57%) returned to sport one year after ACL reconstruction. In the multivariable analyses of the study, an increase in the odds of return to sport was found in patients of male sex OR = 2.58 ([95% CI; 1.43-4.65], p = 0.0016), and in patients with a higher preoperative level of physical activity, OR = 1.45 ([95% CI; 1.13-1.87], p = 0.0038). A higher age at ACL reconstruction reduced the odds of returning to sport, OR = 0.43 ([95% CI; 0.30-0.63], p < 0.0001), indicating that younger age at the time of reconstruction was favorable for a return to sport (OR = 2.32 [95% CI; 1.59-3.33], p < 0.0001). Moreover, patients who did not have a medial collateral ligament injury had higher odds of returning to sport, OR = 7.61 ([95% CI; 1.42-40.87], p = 0.018), as well as patients with no meniscus injury (lateral or medial), OR = 1.92 ([95% CI; 1.10-3.36], p = 0.023) (Figure 24). The area under the ROC curve with 95% CI for a multivariable model to predict return to sport was considered to have a fair goodness of fit (0.78, 95% CI; 0.72-0.83).

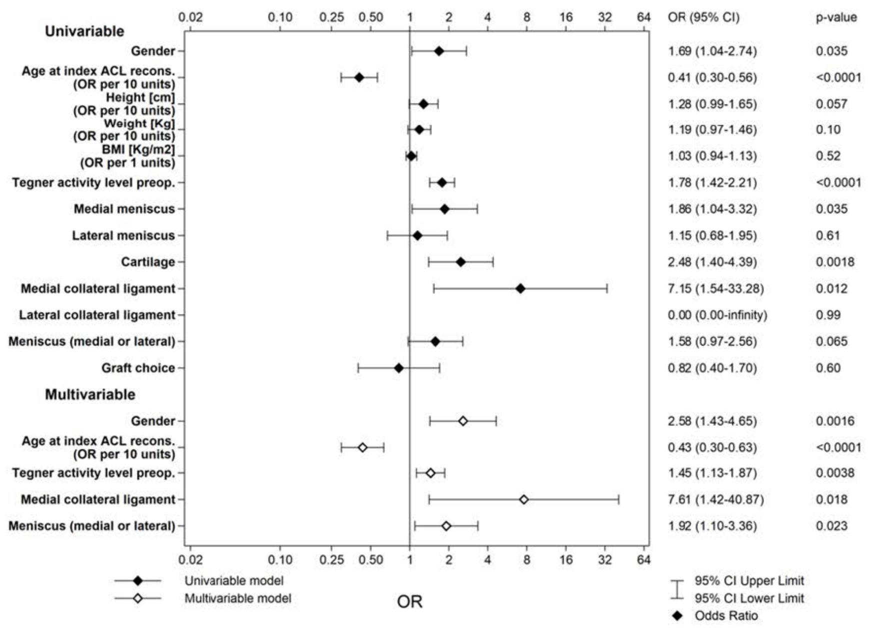

FIGURE 24

Logistic regression models, OR and 95% confidence intervals for return to sport. An OR of > 1 indicates an effect favoring a return to sport. In terms of concomitant injuries, an OR of > 1 indicates a result favoring the absence of concomitant injury. For age at ACL reconstruction, an OR of > 1 indicates a result favoring older age. For graft choice, an OR of < 1 indicates a result favoring an HT autograft, while an OR of > 1 favors a PT autograft.

10.3. THEME THREE: LONG-TERM PREDICTORS

AIM

To determine patient-related, surgery-related and injury-related predictors of long-term outcome after ACL ligament reconstruction.

SUMMARY

Studies VIII and IX aimed to determine the long-term outcomes in the light of patient-reported outcome and the development of osteoarthritis. In terms of patient-related factors, older age at the time of ACL reconstruction and a higher preoperative body mass index appear negatively to influence long-term patient-reported outcome after reconstruction. In addition, patients who reported perceiving less preoperative pain and less impairment in daily activities report superior long-term knee function.

Surgery-related predictors, i.e. graft choice and fixation methods, had limited to no effect on long-term outcome. However, the methods most commonly used for the femoral graft fixation appeared to have a positive effect on patient-reported outcome.

In terms of injury-related predictors, a concomitant articular cartilage injury in particular was determined to be a risk factor for inferior long-term outcome. For instance, every increase in the ICRS grade of severity entailed a further risk of reporting inferior knee function in Study IX. In addition, Study VIII suggested that patients who had more than a year waiting between the ACL injury and reconstruction had increased odds of developing osteoarthritis.

STUDY VIII

Predicting a patient-acceptable symptom state

Half the cohort (n = 62) reported an IKDC score above the PASS cut-off. No patient demographic or preoperative patient-reported outcome was statistically significant when attempting to predict a PASS of the IKDC at 16 years after ACL reconstruction. In the univariable analyses, patients with a concomitant injury at the index operation and greater preoperative anteroposterior translation (Lachman test) had increased odds of a PASS in the IKDC, OR = 2.22 ([95% CI; 1.01-4.88], p = 0.048) and OR = 2.02 ([95% CI; 1.14-3.58], p = 0.016) respectively. These results were consistent in the multivariable analysis; the presence of a concomitant injury, OR = 2.61 ([95% CI; 1.10-6.21], p = 0.030), and Lachman test, OR = 1.87 ([95% CI; 1.05-3.35], p = 0.034) respectively (Figure 25). The goodness of fit of the multivariable model in predicting a PASS in the IKDC was poor, AUC = 0.67 (0.58-0.77).

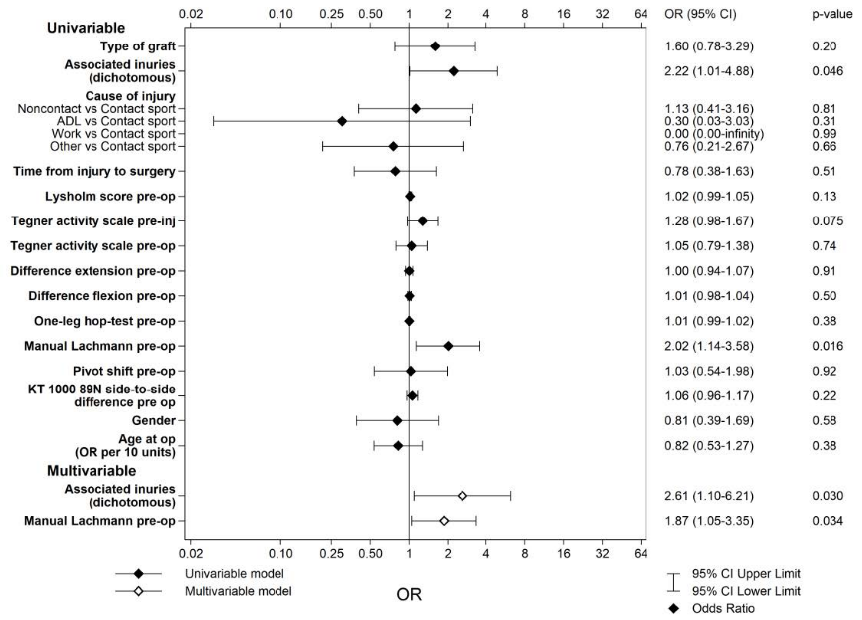

FIGURE 25

Univariable and multivariable regression models, OR and 95% confidence intervals for the achievement of a PASS in the IKDC. An OR of > 1 indicates a result favoring achieving a PASS. For age at index ACL, an OR of > 1 indicates a result favoring older age. For graft choice, an OR of < 1 indicates a result favoring an HT autograft, while an OR of > 1 favors a PT autograft.

A total of 49 patients (43%) had developed osteoarthritis, as defined by a Kellgren-Lawence score of ≥ 2. The pre-injury or preoperative level of activity was not statistically significant when attempting to predict the development of osteoarthritis 16 years after ACL reconstruction. In the univariable analysis, the presence of a concomitant injury and more than one year between ACL injury and index surgery increased the odds of developing osteoarthritis, OR = 2.29 ([95% CI; 1.01-5.19], p = 0.048) and OR = 2.49 ([95% CI; 1.16-5.32], p = 0.019) respectively. In addition, older age at the time of ACL reconstruction showed a 2.22-fold ([95% CI; 1.35-3.66], p = 0.0016) increase in the odds of developing osteoarthritis. The time between ACL injury and reconstruction and older age at ACL reconstruction were consistently significant in the multivariable analysis, OR = 2.25 ([95% CI; 1.02-5.00], p = 0.046) and OR = 2.28 ([95% CI; 1.34-3.86], p = 0.0023) (Figure 26). The goodness of fit of the multivariable model in predicting osteoarthritis was fair, AUC = 0.71 (0.61-0.80).

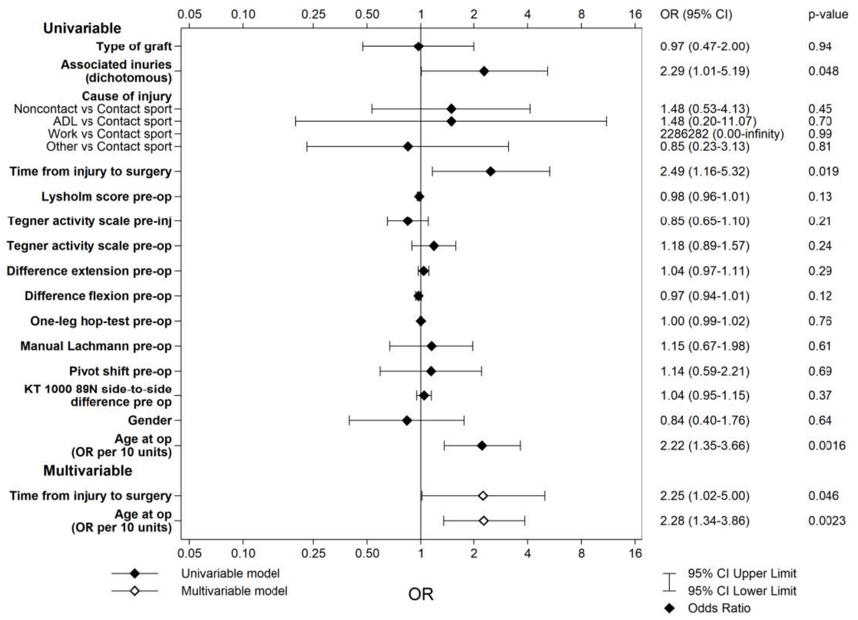

FIGURE 26

Univariable and multivariable regression models, OR and 95% confidence intervals for the development of osteoarthritis. An OR of > 1 indicates a result favoring the development of osteoarthritis. For age at index ACL, an OR of > 1 indicates a result favoring older age. For graft choice, an OR of < 1 indicates a result favoring an HT autograft, while an OR of > 1 favors a PT autograft.

STUDY IX

A total of 2,125 patients were eligible for the study and 874 patients (41%) fulfilled the inclusion criteria with a 10-year follow-up of the KOOS after ACL reconstruction in the SNKLR. The preoperative and 10-year outcome of the KOOS and EQ-5D are presented in Figure 27.

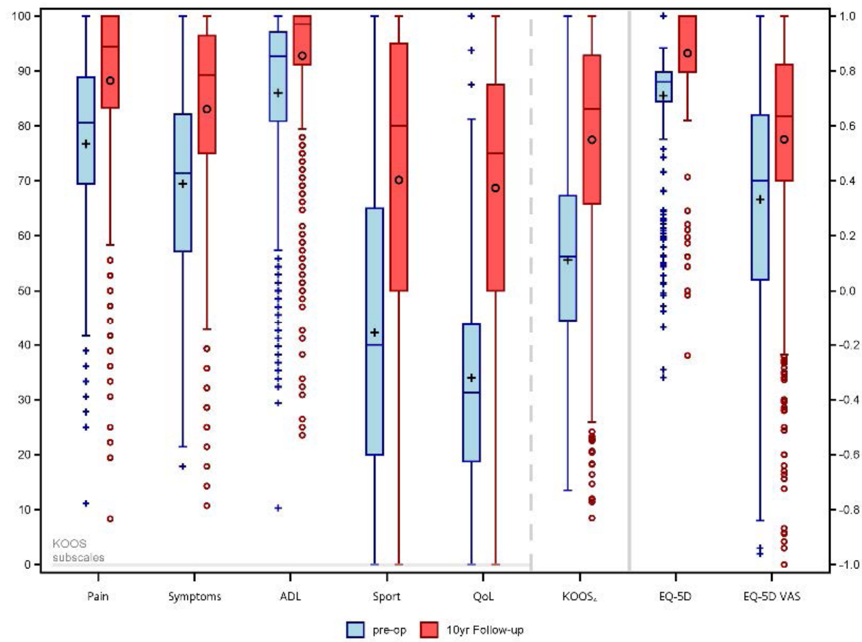

FIGURE 27

Preoperative and 10-year KOOS and EQ5-D in Study IX. The results are presented as box plots with preoperative scores in blue and 10-year outcome in red. The KOOS is presented on the left Y axis and EQ5-D on the right.

In patients without a failure to achieve a 10-year follow-up, no patient-related or surgery-related predictors were significant across all KOOS subscales. The presence of a concomitant articular cartilage injury resulted in inferior KOOS symptoms, sport, QoL and the KOOS4, OR 0.64-0.80 ($p < 0.05$) for every two-step increase in ICRS grade. A higher preoperative KOOS pain increased the odds of a higher KOOS on the subscales of pain, symptoms, sport and the KOOS4. In addition, a higher preoperative KOOS ADL favored a higher 10-year KOOS on three subscales. Interestingly, no patient-related factor, historical factor, time to surgery-related factor or tibial fixation favored the 10-year KOOS. In terms of the KOOS QoL, a older age at reconstruction, the absence of a meniscus and articular cartilage injury and sustaining an injury during Alpine skiing and a higher preoperative KOOS ADL and QoL were favorable for a higher 10-year outcome. The key risk factors that were identified and covered several KOOS subscales were consistently significant in the validation model, including patient demographics, despite the loss of more than 400 patients. In this additional model, a preoperative higher body mass index proved to be a significant risk factor on three of five KOOS subscales and the KOOS4. All significant risk factors are presented in Table 18.

TABLE 18. Significant risk factors for ten-year Knee injury and Osteoarthritis Outcome Score in Study IX.

KOOS Pain	KOOS Symptoms	KOOS ADL	KOOS Sport	KOOS QoL	$KOOS_4$
	Articular cartilage ICRS grade		Articular cartilage ICRS grade	Articular cartilage ICRS grade	Articular cartilage ICRS grade
Body mass index		Body mass index	Body mass index		Body mass index
Lower preoperative KOOS Pain	Lower preoperative KOOS Pain		Lower preoperative KOOS Pain		Lower preoperative KOOS Pain
	Injury sustained from other than Alpine skiing			Injury sustained from other than Alpine skiing	Injury sustained from other than Alpine skiing
	Lower preoperative KOOS ADL	Lower preoperative KOOS ADL		Lower preoperative KOOS ADL	
Injury sustained in other than floorball			Injury sustained in other than floorball		
			Metal screw as femoral graft fixation		Metal screw as femoral graft fixation
Other/uncommon femoral graft fixation			Other/uncommon femoral graft fixation		
		Preoperatively not achieving a PASS in KOOS Pain	Preoperatively not achieving a PASS in KOOS QoL	Older age at reconstruction	Preoperatively not achieving a PASS in KOOS Symptoms
				Meniscal injury	Lower preoperative EQ5-D
				Preoperative KOOS QoL	

11

DISCUSSION

The overall aim of this thesis was to determine short- and long-term predictors of outcome after ACL reconstruction. The presented themes aimed to emphasize three different areas of outcome after ACL reconstruction, reflected by the nine studies that are included: the general picture, short-term predictors and long-term predictors. In the following section, the aim is to discuss the findings in each individual theme and determine how the themes relate to one another across the subjects of patient-related, surgery-related and injury-related factors.

11.1. THEME ONE: CREATING A FOUNDATION FOR RESEARCH

Medical research is very much dependent on using validated and reliable outcomes in order to draw explicit conclusions that may alter or improve the care of patients. However, in medical research, it is often difficult to determine what the primary outcome is, how outcomes should be valued against each other and what might be the optimal and clinically relevant outcome. Because of this, there is wide use of different outcomes related to the various professions involved and the expectations of the patient. The first theme in this thesis aimed to generate a general understanding of the factors that may potentially affect patient-reported outcome after an ACL reconstruction, primarily in terms of patient-reported knee function and return to sport. Less explicitly, Study I also illustrated differences in results related to various definitions of return to sport. This concept also indicates the impact of a variable when it is consistent across the different definitions of an outcome. Study II is the first systematic review of patient-reported outcome from the large Scandinavian knee ligament registers. The studies based on these registers have strong external validity due to their inclusion of tens of thousands of patients, despite their methodological lack of generalizability relating to their non-randomized design. Nevertheless, the information from these large cohort register studies is an important foundation to include for the planning of future studies.

DEFINING RETURN TO SPORT

Returning to sport is one of the most commonly used outcomes in sports medicine research, including after ACL injury and reconstruction. The outcome covers the level of patient participation in the International Classification of Functioning, Disability and Health[360] and is therefore regarded as an important patient-related outcome measurement. Return to sport has been defined in various ways throughout the literature by using a single question or by different physical activity rating measurements such as the Tegner activity scale[341] or the Marx activity score.[218] Consequently, it is important to remember that these definitions may cover different levels of return and frequencies of participation. This issue has been highlighted by a comprehensive systematic review of the topic of return to sport after ACL reconstruction reporting that 81% of patients will return to some type of sport, 65% of patients to their pre-injury sport and 55% of patients will participate in competitive sport.[22]

In Study I, two different definitions of return to sport were used: firstly, patients who had returned to their pre-injury level of Tegner activity scale ± 1[116 193 194] but a minimum level of 6 on the Tegner activity scale and, secondly, patients who had returned to a Tegner activity scale of 6 or higher, i.e. a knee-strenuous sport. The rationale for using two different definitions was that return to a pre-injury Tegner activity scale ± 1 could exclude patients who actually do return successfully to a knee-strenuous sport. A broader definition of return, i.e. return to a Tegner activity scale of 6 or higher, was therefore chosen. For example, a patient with a pre-injury Tegner of 10 who only returned to a score of 6, 7 or 8 would be classified as unsuccessful, using return to pre-injury Tegner ± 1, despite the fact that this patient had returned successfully to a knee-strenuous sport. The use of return to a Tegner activity scale of 6 or higher resulted in an increase in the return rate, which is in agreement with the literature.[24] It appears evident that the Tegner activity scale can be used to determine a return to sport. At a Tegner activity scale of 6 and higher, no more work-related activities options are left in the PROM. Including patients with a Tegner activity scale of 6 or higher and also using this "cut-off" as an outcome will ensure that the patients are participating in some type of sport. This concept was also used in Study VII. However, the concept of defining return to sport in such a manner is limited by not including patients in less knee-strenuous activities, such as running. In addition, this definition does not include an objective or subjective measurement of the level of participation,[19] ranging from return to participating in sport to return to performing in sports (illustrated in the introduction). Because of this, single questions that directly ask about these issues may be a further advantage in the evaluation of return to sport.

PSYCHOLOGICAL FACTORS AFTER ACL RECONSTRUCTION

In recent years, increasing interest has been shown in the evaluation of so-called psychological factors in sports medicine, reflected by various PROMs. The rationale of using psychological outcomes has shed further light on the patients' perception of treatment outcome. The outcomes also cover areas that are not easily assessed by the standard objective measurement frequently used throughout medical research. In Study I, differences in psychological factors in relation to return to sport were highlighted, where patients who had not returned to a knee-strenuous sport had a lower future knee self-efficacy, potentially affecting patients' motivation to reach a sufficient level of physical activity.[324] It is well established that there are differences in psychological factors between patients who have and have not returned to sport after an ACL reconstruction.[20] The reason for this difference may be related to personality traits or perceived fears, but no or very few studies have exclusively determined the impact of psychological factors on outcome. For instance, psychological factors in patients who have undergone ACL reconstruction have not been addressed in patients who have recovered muscle function and have clinically acceptable knee stability.

The outcome of self-efficacy has been modified to suit the population of ACL-injured patients and has yielded interesting results. In Study I, the lower self-efficacy results found in patients who had not returned to sport correlated with lower goals for future level of physical activity, which is an interesting finding requiring further confirmation.[345]

Regardless of the definition of return to sport used in Study I, patients who had returned, as well as those who had not, had LSI values for muscle function around 90%, which is usually regarded as satisfactory.[148 346] This supports the current discussion relating to the fact that the recovery of muscle function alone is regarded as insufficient as a return-to-sport criterion.[346] There is a consensus statement in the literature suggesting that a score of at least 85% of the maximum of a PROMs should be used as part of the return-to-sport criteria.[208] Based on the results of Study I, it is suggested that, when evaluating return to sport after an ACL reconstruction, the physical therapist should both think further than the LSI values and try to incorporate absolute strength measurements,[87 131] as well as always including psychological factors.

PATIENT-RELATED FACTORS IDENTIFIED IN THE SCANDINAVIAN KNEE LIGAMENT REGISTERS

In Study II, the systematic review of the Scandinavian knee ligament registers, the younger age at ACL reconstruction and males were confirmed as affecting patient-reported outcome after reconstruction. [5 7 72 94 183] The results corroborate the present evidence in the literature and suggest that age and patient sex as patient-related factors should be considered as confounders when analyzing the patient-reported outcome in patients after an ACL reconstruction.[338] In clinical terms, these factors are non-modifiable but still just as important in order to set realistic and appropriate expectations for physical therapists and patients after an ACL reconstruction. The finding of superior outcomes in patient sex and age-related subgroups raises further questions about whether treatment can be improved for the group at risk of an inferior outcome, or whether special concern is necessary when treating these patients. This may also be relevant in concern of reducing the numbers subsequent ACL injuries, where females and younger patients have been identified as running an increased risk.[9 12 13 137 250 270 362]

In terms of modifiable patient-related factors, there were consistent results in Study II showing that smoking negatively affected patient-reported outcome.[7 183] It appears appropriate to advise and support the cessation of smoking before an ACL reconstruction is planned.

The possible positive effects of specialized rehabilitation were underlined by a study identified in the systematic review (Study II). Grindem at al.[130] showed that preoperative and postoperative patient-reported knee function were improved in patients who received specialized and controlled preoperative and postoperative rehabilitation compared with standard care represented by the Norwegian Knee Ligament Register (NKLR). This highlights the potential benefits of improved outcome after structured rehabilitation before an ACL reconstruction. For instance, Eitzen et al.[80] found that preoperative asymmetry in quadriceps strength of more than 20% predicted a poorer functional outcome two years after ACL reconstruction. In addition, a study from the SNKLR reported that a lower preoperative KOOS Symptoms was a predictor of ACL revision,[93] implying that clinicians should be advised to keep patients in structured rehabilitation until an acceptable KOOS level is achieved and before ACL reconstruction is performed. In terms of postoperative outcome, symmetrical hop tests have been associated with superior self-reported knee function one and two years after ACL reconstruction[202] and return to sport.[22] Despite the important implications of these findings, very few studies consider including pre- and postoperative measurements of muscle function in ACL research. It can therefore be argued that the rehabilitation outcome register presented in Study I, which is capable of combining data with the SNKLR, is an important and novel approach for further studies.

SURGERY-RELATED FACTORS IDENTIFIED IN THE SCANDINAVIAN KNEE LIGAMENT REGISTERS

In terms of surgery-related factors in Study II, it is evident that patients who undergo an ACL reconstruction with HT autografts report superior results in the KOOS compared with patients with PT autografts.[183 280] However, this difference may be explained by the higher proportion of HT autografts used in the registers.[113] In addition, Gifstad et al.[113] reported increased revision rates for HT autografts compared with PT autografts in younger patients participating in pivoting sports. The RCTs on the topic comparing the two graft selections have not been able to report any differences in patient-reported knee function in either short- or long-term follow-ups.[228 300] Independent of graft choice, ACL reconstruction has been shown to improve overall patient-reported knee function reflected by the KOOS after both primary and revision surgery.[7 83 119 121 183 200 279] Rehabilitation most likely also plays an important role in explaining the postoperative improvement in patient-reported outcome, but, unfortunately, the Scandinavian knee ligament registers do not include any rehabilitation-related data.

In terms of the surgical techniques used, no or only minor differences in the KOOS have been reported from the registers.[7 138 183 279 281 335] Unfortunately, information about the indications for the choice of surgical technique is not collected in the registers. It should also be borne in mind that the KOOS instrument may not be able to discriminate between surgical techniques. Several other outcomes, such as graft rupture, knee-joint laxity and rotational stability, should be included in the total evaluation of surgical techniques.

TREATED WITH REHABILITATION ALONE, ALSO KNOWN AS NON-RECONSTRUCTIVE TREATMENT

Patients treated with rehabilitation alone will be referred to as non-reconstructed, since the Scandinavian knee ligament registers do not have any data related to rehabilitation. Ardern et al.[21] have published a study with a cross-sectional pair-matched analysis of non-reconstructed and ACL-reconstructed patients up to the five-year follow-up. The study concluded that patients treated without ACL reconstruction have inferior results on all the subscales of the KOOS at all follow-ups. However, only in the KOOS subscale of sport and recreation at the one-year follow-up did the difference between the treated groups exceed the minimal clinical important difference (MCID) for the KOOS.[287] This contradicts what has previously been reported from RCTs, suggesting no difference in subjective knee function between treatment types.[104 105 229] This discrepancy may be explained by the standard national clinical setting reflected by register studies, entailing a selection bias and a non-randomized study design in Ardern et al.'s study. In the RCTs using an evidence-based rehabilitation protocol, patients treated non-surgically have been reported to achieve results comparable to those of patients treated with ACL reconstruction.[104 271]

INJURY-RELATED FACTORS IDENTIFIED IN THE SCANDINAVIAN KNEE LIGAMENT REGISTERS

The summary of Study II underlined the fact that concomitant meniscal and articular cartilage injuries at ACL reconstruction are common findings in the Scandinavian knee ligament registers, especially among patients of male gender and older age.[7 72 293] Studies identified from the systematic review also suggested that patients who wait for more than one year from the ACL injury to reconstruction might also have a higher proportion of concomitant injuries.[11 13 35 118] Information in terms of the indications for time from injury to reconstruction is not collected in the registers and time itself may not therefore be the reason for the increased number of injuries found in these patients. Patients with concomitant injuries to menisci or articular cartilage report inferior results in the KOOS preoperatively and at the one- and two-year follow-ups compared with patients with an isolated ACL injury.[7] These differences decline at the medium-term follow-up, a minimum of five years after ACL reconstruction, and this can potentially be explained by an adaptation of lifestyle and physical activity among patients.

Patients with meniscal pathology have been reported to run an increased risk of long-term impairment in terms of function and also regarding the development of osteoarthritis, especially after the resection of the menisci.[8 259 285] The recent short-term study from the NKLR suggests that impairment after meniscal resection takes time to develop and, contrary to the long-term reports, meniscal resection may even result in superior short-term results compared with meniscal repair. In terms of concomitant cartilage injuries, most studies from the registers have investigated full-thickness cartilage injuries independent of location and have found an association with a poorer patient-reported outcome.[27 292-294] Taken together, the results of Study II suggest that concomitant knee injuries and time from ACL injury to reconstruction, as well as the treatment and location of concomitant injuries, appear to have an influence on the patient-reported outcome after ACL reconstruction. It is therefore recommended that concomitant injuries should be evaluated in relation to outcome in ACL research. Large cohorts are, however, needed in order to assess the complex area of concomitant injuries in a correct manner.

THEME 1 – SUMMARY

Factors related to the patient, the surgical treatment and rehabilitation and the presence of other injuries in the knee joint appear to affect the patient-reported outcome. To facilitate setting realistic expectations in patients, it could be very helpful to be aware of the potential influences related to outcomes after ACL reconstruction. Modifiable factors that favor superior patient-reported outcome include not smoking, pre- and postoperative specialized rehabilitation, using an HT autograft and, indirectly, less time between ACL injury and reconstruction. Non-modifiable factors that favor a superior patient-reported outcome include male sex, younger age and not having sustained a concomitant intra-articular injury.

11.1. THEME TWO: SHORT-TERM PREDICTORS

The second theme will be primarily discussed in terms of the outcomes and the influence of different variables on each outcome. An overall statement on the effect of predictors on short-term outcomes after ACL reconstruction will be given at the end of this theme.

"Short term" often refers to the first and second year after ACL reconstruction. During this period of time, the patients are usually in frequent contact with the medical professions, especially the physical therapist. The clinicians should be aware of the specific characteristics related to the patient, the surgical treatment and the injury as a guide to the interpretation of symptoms and in order to set realistic expectations of outcome. This theme aims to provide short-term prognostic factors for patients after an ACL reconstruction. It is important to remember that the results of research most often determine the general picture of the condition of interest, i.e. it may not represent the truth in every detail for a particular patient. The timeframe of this theme in the thesis covers the time during which a patient regularly meets physical therapists but also transitions to returning to sport or training alone. Key points of this theme include factors related to when extra periods of rehabilitation or medical care may improve outcome after an ACL reconstruction.

PREOPERATIVE KNEE-JOINT LAXITY

Increased knee-joint laxity, i.e. a larger side-to-side difference in both anteroposterior and rotational laxity, may indicate a more severe injury, potentially including injuries to several structures in the knee joint.[238 239 339] There are continuous discussions related to whether the magnitude of increased knee laxity affects the postoperative outcome after ACL reconstruction.[144 209] In order to further determine the relationship with preoperative knee-joint laxity, non-invasive technology for the quantitative assessment of the pivot shift, as used in Study III, was developed to reduce the intra- and inter-rater variability of the test. Interestingly, the preoperative QPS did not predict a PASS in the IKDC-SKF at any time point during the follow-up in the study. There was, however, an increased likelihood of achieving an acceptable symptom state in the IKDC-SKF for the preoperative low-grade pivot-shift group, compared with the high-grade group, at the one-year follow-up in Study III. On the other hand, the increased odds of achieving a PASS in patients with a preoperative low-grade pivot shift were not significant at the two-year follow-up. The manual low grading of the pivot shift correlates well with low QPS[239] and it is therefore theoretically likely that the QPS technology might be superior at detecting small discrepancies within the "low-grade group". In addition, the analysis of QPS as a continuous variable is more precise compared with the dichotomized analysis of the subjectively graded pivot shift. Because of this, it appears that more interest should be paid to the effect of postoperative knee laxity on patient-reported outcome after ACL reconstruction and QPS technology appears to be an advantage.

Perhaps more importantly, the QPS assessment of preoperative and postoperative knee-joint laxity may shed more light on our understanding of the risk of ACL graft ruptures. It is generally agreed that an ACL reconstruction should provide axial and rotational stability. However, the optimal method for achieving this remains controversial. It has, however, been suggested that so-called non-anatomically placed grafts are exposed to minor forces compared with "anatomically" placed grafts,[167] thereby potentially making them less subject to rerupture.[76]

SHORT-TERM KNEE FUNCTION

The use of patient-reported outcome has become an essential part of the evaluation of any treatment or condition in medicine. According to EBM, the use of PROMs is one way to highlight the patients' perspective of treatment outcome.[90] In terms of knee function, a wide range of different outcome measurements has been established in the literature, including the KOOS[288] and IKDC-SKF,[157] which were used in this thesis. Despite the frequent use of these outcomes, they still entail difficulties when they are interpreted, especially in the clinical setting. Typically, PROMs cover various questions relating to the function and activity of the International Classification of Functioning, Disability and Health.[360] The outcome measurements commonly used after an ACL injury are also considered more knee generic than condition specific, limiting relevant discriminability in the evaluation of these patients. Because of this, the PASS was used in this thesis in Studies III, V and VIII. The PASS enables a patient-relevant cut-off in determining when the outcome of a treatment has been acceptable.[62 235] The PASS can be generated in relation to any PROMs by asking patients: "Taking account of all the activity you have during your daily life, your level of pain and also your activity limitations and participation restrictions, do you consider the current state of your knee satisfactory?"[235] Based on the patients replying "yes" to this question, a PASS can be calculated from the same patients' response to a PROM. In addition to the PASS, Study IV used the top and bottom quintile as a measurement of the KOOS as a reflection of superior and inferior outcome. The purpose of using these definitions was to determine a superior, acceptable, or inferior outcome in the commonly used measurements of patient-reported knee function.

It is well established that, in the continuous analyses of various PROMs, patients who have undergone an ACL reconstruction will generally report impaired knee function in comparison with a knee-healthy counterpart.[35 183 201 210 294] On average, this is also true when considering patients with concomitant injuries within the group of patients who have undergone ACL reconstruction, where a meniscal injury or a chondral lesion has been identified as the cause of impaired knee function in the short term.[36 85 183 188 294] The overall important conclusion of Studies III and V is that more than half of patients undergoing ACL reconstruction will report acceptable knee function one and two years after an ACL reconstruction. These results are somewhat better compared with what other studies have reported as a measurement of treatment success in the short term.[35 156] Whether the results presented in this thesis are a better estimate of the proportion of patients who are satisfied with the treatment will need to be further addressed. The discrepancies between studies may also be related to the different definitions used to determine success, similar to the issue of determining return to sport.

In terms of patient-related factors that influence one- and two-year knee function after an ACL reconstruction, this thesis identified male sex and younger age as characteristics positively affecting knee function. In Study V, these factors showed an almost consistent effect on the PASS on all the KOOS subscales and the continuous analysis of the KOOS4.

Interestingly, a similar pattern, where males and younger patients appear to report superior knee function, has been reported in continuous analyses of the KOOS.[5 72 94] On the other hand, the effects of patient sex and age were insignificant in Study III. These differences may be related to the different outcomes used in these studies, the PASS in the KOOS and IKDC-SKF respectively. The much smaller cohort in Study III compared with Study V may affect these differences. Nevertheless, the overall interpretation in relation to the findings in Study II suggests that patient sex and age should be regarded as important patient-related factors to account for when evaluating patient-reported knee function. In terms of the patients' preinjury level of physical activity, this did not result in a significant effect on patient-reported knee function, either in Study III or in Study V. Clinical awareness of this fact could facilitate the setting of realistic expectations and also implies areas that need to be further addressed in rehabilitation.

In terms of surgery-related factors, they were primarily assessed in Study V by determining the influence of HT and PT autografts. The study suggested that an HT autograft was associated with increased odds of achieving a PASS on the KOOS subscales of pain, knee-related QoL and the continuous analysis of the KOOS4. In general, the use of a PT autograft is associated with more early harvest-site morbidity than the HT autograft,[54 361] which may explain these early results, but the differences between grafts may diminish over time. However the distribution of PT and HT autografts selected for primary reconstruction in Study V was skewed and may have influenced the favorable outcome for HT grafts (PT n = 41 and HT n = 334). The difference between grafts found in this study appears to be an artifact possibly related to the fact that more than 95% of patients in the SNKLR undergo primary ACL reconstruction with an HT autograft, thereby creating a selection bias, albeit representative of a Swedish cohort.[183] In contrast to other reports on this topic, a Cochrane review found no differences between graft choices in relation to knee function in a balanced cohort in the short- or long-term follow-up.[228] In addition, on the topic of surgery-related factors, Study IV, which included the top and bottom quintiles of the two-year KOOS4, showed no effect on detailed aspects of the technique of single-bundle ACL reconstruction on knee function.

In terms of injury-related factors, Studies III-V assess the presence of concomitant injuries on the PASS of the IKDC-SKF, the KOOS subscales and the top and bottom quintiles of the two-year KOOS4. Like previous studies that have reported a negative association between the presence of meniscal and articular injuries and patient-reported knee function, Study V showed an overall tendency, suggesting that the presence of concomitant injuries reduces the likelihood of achieving a PASS one year after an ACL reconstruction. However, there was almost no consistency across the regression models in terms of associations with different concomitant injuries and the KOOS subscales. Importantly, the lack of consistency in these findings is also highlighted by the poor capacity of any models to explain the variation in the outcome in Study V; none of the AUC results showed a predictive capacity better than chance and none of the R-squared values was above 2%. These results are strengthened by the findings in Study IV, which showed a positive influence on knee function in the absence of both meniscal and cartilage injuries. However, Study III, which primarily determined the effect of preoperative knee laxity, did not find any effect of the dichotomization of concomitant injuries and one- and two-year knee function. The considerably smaller cohort in Study III most likely contributes to this discrepancy in results, but the fact that this study did not include multivariable regression modeling accounting for differences related to patient characteristics also contributed. Extra-articular knee injuries did not appear significantly to affect one- and two-year patient-reported outcome, with the exception of an absence of medial collateral ligament injury, which had a strong positive effect on the PASS in KOOS Pain. The effect on only one subscale of the KOOS may be negligible, but this finding is interesting in the light of the effect of a medial collateral ligament injury found in Study VII. There are only a small number of studies including the presence and severity of a medial collateral ligament injury in patients who have undergone an ACL reconstruction.

The overall interpretation of the findings in this theme with regard to injury-related factors is that they need to be accounted for in research and clinical practice. These findings also have external validity, since they confirm the findings from the MOON cohort, where Cox et al.[64] showed that meniscal injuries and grade 3 and 4 articular cartilage lesions in various regions at the index ACL reconstruction predicted poorer subjective knee function in the KOOS and IKDC-SKF six years after the reconstruction. In clinical terms, patients who have undergone ACL reconstruction and present concomitant knee injuries need appropriate information in order to set realistic short-term expectations for their recovery. There is a need for better treatment options in terms of rehabilitation, and most likely also surgery, to improve patient outcome in this group.

RECOVERY OF MUSCLE FUNCTION

One key feature of the rehabilitation after ACL injury and reconstruction is the muscle strength of the lower extremities. The general picture has always been that strong muscles around the knee joint are protective and aid in the appropriate loading of the joint. Because of this, many different strength measurements have been presented, more or less clinician friendly, assessing various types of strength.[222 353] These tests all share the fact that they have not been specifically validated in relation to outcome after ACL injury or reconstruction. In recent years, however, achieving and maintaining symmetrical knee function has been associated with less risk of subsequent ACL injury[132 184] and less osteoarthritis-related symptoms.[261 285] This has made the recovery of muscle function, across a battery of tests, an important benchmark after ACL reconstruction, but little attention has been paid to the factors that may alter a patient's likelihood of achieving satisfactory knee function. In Study VI, patients with concomitant intra-articular injuries did not have unfavorable odds of achieving an LSI of ≥ 90% in five tests of muscle function one year after ACL reconstruction. It is important to remember that all the logistic regression models in Study VI resulted in no better than a poor goodness of fit, which indicates that other factors that were not included in the analyses contribute to achieving a symmetrical performance across a battery of tests. The study also revealed that a remarkably low proportion of patients, fewer than one in four, were able to achieve symmetrical results in all five tests of muscle function one year after surgery. Similar results have, however, been reported previously and together imply that restoring muscular capacity may take longer than the time that is commonly implied as a reference,[74 117 347 366 392] which also has important implications for return to sport.[132]

In terms of injury-related factors, the presence of concomitant injury did not influence the likelihood of recovering muscle function one year after an ACL reconstruction. This finding will need confirmation, considering that no multivariable analyses were performed. The use of only univariable analyses to assess a specific concomitant injury entails a risk of using biased reference groups including other injuries. In addition, the goodness-of-fit analyses suggested room for improvement where, most likely, preoperative muscle function[80] and psychological factors[100] might improve the explanatory capacity of the models. However, the lack of an association between concomitant injuries and the recovery of muscle function may also contribute to the fact that achieving symmetrical muscle function across a battery of tests is a difficult short-term goal to attain after ACL reconstruction.[346] With regard to the findings in Study VI, one year may be sufficient to recover from the short-term impairment, especially from the intra-articular concomitant injuries. These results need to be further confirmed by future studies. Until then, clinicians should remain aware of the limited sensory innervation of these structures[50 51 85 227 370] and the potential long-term consequences these injuries have for knee health.[259]

In the additional analyses of knee extension strength, patients who were operated on using an HT autograft and had a lateral meniscus injury had favorable odds of achieving symmetrical knee extension strength. There is no explicit reason for why these surgery- and injury-related factors would have a favorable effect on recovering symmetrical knee extension strength. However, the analyses did not account for differences attributed to differences in rehabilitation or pain, where a patient with either a lateral meniscus injury or receiving a PT graft may have been subjected to a more careful approach in rehabilitation. The analysis of the knee flexion test in Study VI revealed that a higher pre-injury level of physical activity increased the odds of recovering knee flexion strength. Some concerns must be acknowlegded related to the potential ceiling effect of the seated knee extension test.[347]

RETURN TO SPORT

The outcome of return to sport is one of the most patient-relevant outcomes in the recreational and athletic populations after ACL reconstruction. Additionally, the time at which a patient is ready to return to sport continues to be one of the most pronounced challenges in sports traumatology.[19 319 346] Returning to sport is a delicate balance between ensuring a recovery of sufficient muscular capacity and minimizing the risk of subsequent injury. Timing may also play an important role in understanding subsequent injuries, considering the results from Grindem et al.[132] who reported a 51% reduction in secondary surgery for each month that a return to sport was delayed during the first nine months after ACL reconstruction. Interestingly, Feucht et al.[97] reported that patient expectations are high after ACL reconstruction, where 91% of patients expect to have returned to sport one year after surgery. In Study VII, 57% of patients made a return to sport at one year after ACL reconstruction. This number is surprisingly low compared with what has been reported in younger and general ACL-reconstructed populations,[22] but it may be related to the follow-up time. It appears important to stress that a longer period of rehabilitation might be necessary for a return to sport compared with the 9-12 months; a timeframe that is recommended.[32 132 346] In clinical terms, realistic goals are important in order to avoid dissatisfaction and loss of motivation among these patients.[145]

What influences a successful outcome, such as return to sport, after ACL reconstruction is dependent on many different factors.[19 208 266] Some of the previous literature has, however, failed to take account of differences in results (after ACL reconstruction) caused by the presence of concomitant knee injuries. Concomitant injuries constitute additional damage to the patients' knee joint, but the impairment these injuries entail may vary among patients and the different types of injury.[64 266] Study VII is one of the first studies to address this question by including both relevant physical therapy data Project ACL and relevant orthopedic surgery data (the SNKLR). The study suggests that the absence of concomitant meniscal injury and medial collateral injury in patients who have undergone an ACL reconstruction resulted in favorable odds of returning to sport one year after reconstruction. Interestingly, the ACL and the medial collateral ligament, together with neuromuscular control, have been reported to contribute synergistically to resisting knee valgus when landing.[278] Because of this, it is possible that these patients may experience more instability in their knee joint, causing them to delay or prevent a return to sport in the short term.[359] On the other hand, meniscal and cartilage injuries, which were also found to have a negative effect on return to sport in Study VII, may cause pain or swelling in the patients' knees and therefore constitute a different reason for impairment.[51 85 172] Taken together, the results of Study VII imply that patients with certain characteristics and with concomitant injuries need a longer period of rehabilitation after an ACL reconstruction before they are ready for a return to some type of sport. However, it is evident that the results from Study VII need confirmation.

Study VII also confirmed important patient-related factors for returning to sport after an ACL reconstruction: younger age,[169 198] male sex[23] and a higher pre-injury level of sports participation.[22 116] In clinical terms, these factors are very important to consider in the individual treatment of patients after an ACL reconstruction. For instance, younger age at the time of an ACL reconstruction has frequently been reported to be associated with superior outcome, in terms of returning to sport and patient-reported knee function after ACL reconstruction.[5 22 23] However, this group of patients also run an increased risk of additional ACL injury.[362] Because of this, a clinician may have to consider prolonging the rehabilitation period for these patients (despite a pleasing early outcome). It is also possible that patient age can act as a proxy for other factors such as life commitments, which may influence the time or the level at which a patient chooses to participate in sport, less explicitly explaining the favorable outcome and increased risk in younger patients.[22 198]

THEME TWO – SUMMARY

Factors related to the patient, the surgical treatment and rehabilitation and the presence of other injuries in the knee joint appear to have the potential to affect the short-term outcomes after ACL reconstruction covered by this thesis. In terms of patient-related factors, male sex and younger age have a positive influence on returning to sport and patient-reported knee function in the short term but not on recovering symmetrical knee function. A higher pre-injury level of physical activity is positively associated with returning to sport. In terms of surgery-related factors, the use of an HT autograft appears to have a positive effect on patient-reported knee function. The general picture of injury-related factors suggests that patients who have sustained concomitant injuries run the risk of inferior outcome across patient-reported knee function and returning to sport after ACL reconstruction. This relates, in particular, to patients who have sustained a meniscal or medial collateral ligament injury.

11.3. THEME THREE: LONG-TERM PREDICTORS

As in discussion of the second theme, the results of the third theme will primarily be discussed in terms of the outcomes covered and the effect of each of the studied variables on each outcome. An overall statement on the effect of predictors on long-term outcomes after ACL reconstruction will be given, together with statements on the differences found in short- and long-term predictors.

"Long term" often refers to a follow-up of at least ten years after a treatment or event. In the case of the present theme, follow-ups of the two studies were made ten and 16 years after the ACL reconstruction. Probably the most important aspect of the long-term follow-up is that it presents what happens to the patients in the long run, many years after the primary treatment period. The outcome of the long-term follow-up can potentially influence primary treatment options, as an inferior long-term outcome may sometimes not be reflected at all in the short term. As a clinician, it is fundamental to acknowledge the patients' goals when selecting treatment. A great deal of respect must, however, be paid to the potential long-term consequences, which the patient might not consider at all. Nonetheless, patients who have sustained an ACL rupture, with or without undergoing an ACL reconstruction, will run an increased risk of developing post-traumatic osteoarthritis and are perhaps future candidates for a total knee arthroplasty.

DEVELOPMENT OF OSTEOARTHRITIS

Osteoarthritis is the degenerative change in articular cartilage typically presenting after joint injuries but also in cases of inappropriate joint loading over time. The presentation of this condition often involves pain and swelling of the joint, indirectly impairing function. However, some patients who present with radiographic signs of osteoarthritis do not perceive symptoms, suggesting that the condition should be considered and reported as two entities; radiographic and symptomatic osteoarthritis.[8 260] Study VIII in this thesis is one of several verifying the increased presence of osteoarthritis after an ACL reconstruction at 10-20 years of follow-up.[36 259 260 285 289 316] In terms of patient-related factors, older age at the time of ACL reconstruction had a more than two-fold increase in the odds of developing osteoarthritis, which is consistent with previous studies.[45 98 213] This finding is not surprising, since older patients may already have had degenerative changes present at the time of injury and at surgery and have been reported to have a higher presence of concomitant injuries.[66 69 75] Interestingly, patient sex did not have an influence on the development of osteoarthritis, considering the general short-term differences identified in theme two and the higher frequency of concomitant injuries usually seen in males.[72]

In terms of surgery-related factors, waiting to undergo an ACL reconstruction for longer than one year after injury also carried a more than two-fold increase in the risk of developing osteoarthritis. However, these results should be considered with caution, since the reasons for the differences in time to surgery were not recorded. In spite of this, a recent systematic review supports the notion that early ACL reconstruction, in patients who require reconstruction, may be beneficial across several outcomes compared with a delayed reconstruction.[196]

In terms of injury-related factors in Study VIII, the presence of concomitant injuries did not entail an increased risk in the development of osteoarthritis 16 years after an ACL reconstruction. This is surprising, considering the strong evidence and association between concomitant intra-articular injuries and the development of osteoarthritis.[64 84 259] The discrepancy between Study VIII and the literature may be attributed to the dichotomization of concomitant injuries used in the analyses, where less severe injuries may have underestimated the effect of certain concomitant injuries (supported by the significant effect in the univariable analysis in Study VIII). In addition, it should be noted that only minor meniscal and chondral lesions were included, i.e. more severe injuries such as Outerbridge[53] grade 3 and 4 were excluded from the analyses. A larger cohort would have allowed for the inclusion of the type of concomitant injury (e.g. articular cartilage, meniscus), severity, size and treatment. It should also be noted that the multivariable regression model was only considered fair in goodness of fit, indicating that other factors not accounted for in Study VIII have an important effect on the development of posttraumatic osteoarthritis.

Moreover, preoperative knee laxity and functional performance, assessed with the one-leg-hop test, were used in Study VIII but did not affect the development of osteoarthritis. Future modeling in order to understand the complexity associated with the development of osteoarthritis should include postoperative outcomes as potential risk factors. For instance, postoperative symmetrical quadriceps function has been reported to be associated with less impairment in the precence of osteoarthritis,[262 285] which could imply that ensuring the postoperative symmetry of knee function is of greater importance than preoperative muscle function to minimize the impairment caused by osteoarthritis. The recovery of muscle function, rehabilitation, a maintained level of physical activity and concomitant injuries are potential factors that may increase our understanding of the development of this secondary outcome after ACL reconstruction.[262 284] Because of this, it is not possible to determine whether the treatment in Study VIII (surgery and structured rehabilitation) had a beneficial effect on reducing the impairment due to osteoarthritis.

LONG-TERM KNEE FUNCTION

Long-term knee function is evaluated with the same outcome measurements that were used in theme two of this thesis. The patient-reported perception of treatment outcome is essential, but it is not clear whether the results of a short-term follow-up are comparable with those of a long-term follow-up. Concern has been voiced about minor changes seen over time in PROMs after an ACL reconstruction, indicating that the responsiveness of these outcomes may not be as good as suggested.[301 329] One potential source of this limitation may be related to that the validation and responsiveness of various outcomes are only assessed in the short term. Nevertheless, a long-term evaluation with these PROMs is necessary in order to understand treatment outcome. In addition, to improve treatment outcome after an ACL reconstruction and assess an individually expected outcome, a large spectrum of potential risk factors must be evaluated simultaneously.[210] In order to do this, the large number of patients in the Scandinavian knee ligament registers allows for in-depth statistical modeling, including the pertinent patient-, surgery- and injury-related factors, enabling an improved understanding of the factors that influence the long-term outcome.[334] Study IX is the first study from the Scandinavian knee ligament registers to determine the long-term predictors of knee function ten years after an ACL reconstruction. Regarding patients reporting acceptable knee function, more than half these patients reported achieving a PASS across almost all subscales of the KOOS ten years after an ACL reconstruction. In a similar fashion, the results of Study VII also showed that approximately one in two patients reported acceptable knee function. Interestingly, one third of the patients in Study VIII who reported achieving a PASS had developed radiographic signs of osteoarthritis, highlighting the differences in radiographic and symptomatic presentation. Approximately half the cohorts in Studies III and V, with short-term follow-up, also reported achieving a PASS, which prompts the question of what influences the perception of attaining acceptable knee function. Of course, the patients' demands in relation to the level of physical activity typically decrease ten to 16 years down the line, which may partly explain similar results. However, it should be pointed out that the PASS for the KOOS and IKDC-SKF is only established for one to six years after ACL reconstruction.[235] Whether the same cut-offs can be used for long-term follow-ups is yet to be determined. However, considering that the same PROMs are used, the results give some insight into the way the long-term outcome relates to the short-term acceptable outcome.

One unanticipated result of both Studies VIII and IX was that no patient-related risk factor was consistently able to predict long-term knee function. In terms of short-term results, as reported in the second theme of this thesis, being male and being younger at the time of reconstruction were patient-related factors more frequently associated with improved outcome.[5 11 23 338] However, considering the highlighted long-term results, the effect of these factors may diminish over time. One limitation of Study IX was the large proportion of patients for whom patient demographic data were missing, which entailed the exclusion of these factors in the multivariable modeling. A sub-analysis including all patient-related factors was, however, performed in Study IX. This analysis showed that a higher body mass index appeared to have a negative effect on long-term knee function. Although this result requires confirmation, it suggests that interventions to reduce preoperative body mass index may have a positive effect on long-term knee function. Nonetheless, severe knee injuries have been associated with obesity with an almost fourfold increase in the risk three to ten years after surgery.[367]

In terms of surgery-related factors, the third theme in this thesis did not identify any overall impact of the studied variables on the outcome of patient-reported knee function in connection with osteoarthritis. The results of Study IX suggested that the use of uncommon and older femoral graft fixation methods increases the risk of inferior patient-reported knee function. However, since these methods are uncommon, especially in recent years, this does not appear to be an area where much can be improved with regard to function. Like previous studies, the differences related to the selection of an HT or PT graft diminish over time, where comparable outcomes are observed in terms of knee function and osteoarthritis.[43 151 298 361]

In terms of injury-related factors, Study IX identified an articular cartilage injury as being strongly associated with an inferior KOOS on several subscales ten years after ACL reconstruction. This has previously been established, but the results of Studies VIII and IX add to the external validity of these results.[64 285 294] For instance, the MOON group recently conducted a ten-year risk factor analysis on an American cohort of 1,592 patients and the study confirmed the significant negative effect of grade 3-4 cartilage lesions on the long-term KOOS.[329] Although not assessed in Study IX, articular cartilage injuries are commonly associated with an increased risk of developing post-traumatic osteoarthritis[64 260] and this may also help to explain the negative effect on the KOOS seen in Study IX. In contrast, meniscal injuries, which also increase the risk of developing osteoarthritis,[36 64 260 329] were not found to be a risk factor for inferior knee function in Study IX. However, the meniscal injuries were assessed dichotomously and this may have underestimated (like Study VIII) the difference between resection and repair as treatment. In a short-term follow-up from the NKLR, LaPrade et al.[188] found only small differences between different locations and treatments of meniscal injuries, which could imply that the KOOS as a PROM may not be able to discriminate differences between these types of injuries. Future studies may consider focusing on the effect of the location and treatment of intra-articular injuries to further improve our understanding of these potential risk factors, but a larger cohort size compared with Studies VIII and IX will be needed.

As pointed out in the introduction and method section of this thesis, risk factors with a consistent effect across at least two "independent" scales of an outcome are more likely to be more clinically meaningful. These risk factors should be explored by clinicians to improve ACL reconstruction outcomes. This was illustrated in the results of Study IX. Interestingly, the risk factors identified in Study IX included the preoperative KOOS subscales of pain and ADL. As structured preoperative rehabilitation has been shown to improve the preoperative KOOS,[130] clinicians should be advised to ensure that patients are well prepared before undergoing ACL reconstruction, in order to improve both short- and long-term outcomes. It is yet to be established whether specific cut-off values for the preoperative KOOS and a superior postoperative outcome can be defined. To summarize Study IX and the third theme in this thesis, potential modifications to risk factors include identifying optimal interventions for grades 3-4 articular cartilage injuries, interventions to lower levels of perceived pain, interventions to reduce limitations in ADL and potentially lowering the preoperative body mass index.

THEME THREE – SUMMARY

Factors related to the patient, the surgical treatment and rehabilitation, together with the presence of other injuries to the knee joint, appear to have the potential to affect the long-term outcomes after ACL reconstruction. To facilitate setting realistic expectations in patients after ACL reconstruction, it is important to acknowledge the long-term consequences of the injury. In terms of patient-related factors, a minor effect on long-term knee function and osteoarthritis appears to be related to patient characteristics. A lower preoperative body mass index may, however, be an important attribute in understanding which patients perceive superior long-term knee function. Surgery-related factors showed no clinically relevant effect on the long-term outcomes that were studied. Finally, the presence of concomitant injuries appears to have a negative influence on long-term outcome, where full-thickness cartilage lesions are regarded as risk factors that need to be addressed.

12

LIMITATIONS

12.1. GENERAL METHODOLOGICAL LIMITATIONS

THE KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE

To minimize error and increase the relevance of the results obtained by using PROMs, these measurements should consist of condition-specific items.[61] This is easy to understand when exemplified by the illogical use of an elbow PROM in a patient with knee problems. The impact of misuse is more difficult to understand in cases where a questionnaire designed to determine outcome in patients with osteoarthritis is used on patients with an ACL injury – for instance, if the Western Ontario and McMaster Universities Arthritis Index (WOMAC)[39 109] is used in patients with an ACL injury. In such cases, the inappropriate use of a PROM could potentially distort the results of the study, making it difficult to detect differences.

There are several examples in the literature where the selection of treatment, rehabilitation versus surgery or placebo, has been assessed with a PROM and resulted in non-significant differences between groups.[37 104 105 321] In these studies, it is essential that the PROMs that are used have undergone rigorous validation to the target condition, if the results are to be able to determine which type of treatment is superior to another. However, there are several examples where the PROM being used has not been validated against the target population.

The use of the KOOS in patients after an ACL injury and reconstruction is one such example.[104 105] The KOOS is an extension of the WOMAC[39] (covers the subscales of pain, symptom and limitations in ADL) and is primarily validated for patients with osteoarthritis of the knee joint. Despite including the subscales of sport and QoL, the KOOS has been determined to have inadequate measurement properties in the three original WOMAC subscales when used for patients after ACL reconstruction.[61 179] In addition, the hybrid version of the KOOS, the KOOS4, which is added up to produce a total score, has not undergone a validation to enable it to be used as a separate score.[60 61]

This is problematic, because it may limit the ability to detect differences in treatments and limits the responsiveness of the KOOS.[179] The potential wash-out of treatment effects, inadequate measurement properties and the risk of type-1 errors when using an outcome of this kind have been addressed by previous studies.[61 301 329] Including questions that are not relevant or fail to cover important aspects/limitations of the target condition is worrying. Several questions on the KOOS have a ceiling effect when used in patients after ACL reconstruction, i.e. the task of the item is too easy for the patient.[104] One example of this is the question relating to putting on or taking off a pair of socks.[288] The KOOS can also be regarded as limited as is it does not include questions relating to instability, which is one of the most common symptoms and indications for reconstruction in patients with an ACL injury. Awareness of the limitations of the KOOS for patients after an ACL injury or reconstruction is important in order not to distort the results from research or at a clinic.

LIMB SYMMETRY INDEX

The LSI is one of the most common ways of presenting the outcome of tests of muscle function after an ACL injury and reconstruction. [74 254] The purpose of presenting this ratio between the injured and uninjured leg is to facilitate an understanding of the results. However, there is a possible overestimation of results when using the LSI to evaluate the recovery of knee function, even in the light of the rigorous return-to-sport criteria commonly used, i.e. an LSI of ≥ 90% in multiple tests or the recovery of pre-injury status.[74 117 366] For instance, Wellstandt et al.[366] evaluated the results of the uninvolved leg as a reference standard for symmetry indices used in return-to-sport testing. Based on performance tests conducted at an early stage after the ACL injury, the authors estimated pre-injury levels of muscular strength and performance. The authors concluded that these estimated levels may be a better reference for the recovery of muscle function, considering the decrease in strength in the uninvolved leg that usually occurs during rehabilitation.[366] Like other studies, the reduction in the strength or performance of the uninvolved leg will inflate the LSIs over time, thereby leading to a misrepresentation of the functional ability of the injured limb. [117 366]

Another important concern relating to the presentation of this outcome is that the LSI ratio is based on two independent tests, one on each limb, with their own variability. The LSI is therefore subject to uncertain variability which can over- or underestimate the true discrepancy in performance between the patient's limbs. Despite the LSI's shortcomings, the return-to-sport criteria for achieving symmetrical function across a battery of tests have been associated with a large increase in the risk of knee re-injury.[208 346] So, achieving this landmark after an ACL reconstruction can arguably be regarded as a fundamental goal of rehabilitation because of its protective effects in terms of secondary injuries. However, it remains to be confirmed whether this goal is sufficient to ensure a safe return to sport and limit long-term impairments.

12.2. STUDY-RELATED LIMITATIONS

STUDY I

The methodological limitations of Study I included the fact that no randomization of patients or sample size calculation was performed. No data on surgical factors, concomitant injuries or compliance with rehabilitation were included in this study. Moreover, no blinding of patients, caregivers or assessors was used in the study. The loss of data from the follow-up of the hop test, due to patients being judged as unable to perform the tests, limits the opportunity to draw conclusions from the hop-test results. In addition, rehabilitation programs were individualized to suit the patients.

STUDY II

The main limitation of Study II related to the quality assessment, where no standardized and validated checklist exists for register studies. Study quality in this systematic review was assessed using a modified version of the Downs and Black checklist (see method section) for non-randomized and cohort studies, which is primarily designed to assess the reporting quality of a study. All but one studies had a score between 12 to 20 of 22 possible points, which indicates that studies from the Scandinavian knee ligament registers generally display high reporting quality. The studies with the lowest scores had a cross-sectional design or included relatively small patient cohorts, which automatically yields lower scores on the Downs and Black. Moreover, no cut-off for the determination of quality exists for the Downs and Black checklist.

The results of Study II may also be limited by not including studies of higher quality, such as level 1 RCTs, which are not possible to conduct based on registers. This potential limitation should have been minimized by the large number of studies included in the systematic review, as well as the cohort sizes. The large cohorts do, however, increase the risk of multiple significance. In the Scandinavian knee ligament registers, the same PROMs are used, e.g. the KOOS, which results in a high level of consistency among studies and results. In addition, the results of the included studies were extracted according to the way the results were presented in each study, thereby minimizing loss of data but introducing potential limitations by not accounting for bias in the interpretation of the results from the original studies. Taking account of the number of studies with similar research questions, this limitation should have been reduced when summarizing an overview and interpreting the published data from the Scandinavian knee ligament registers.

STUDY III

The main limitations of Study III include the lack of blinding for the examiners to the results of the image analysis technique and inertial sensor, as the data were collected. To minimize the potential bias caused by a lack of blinding, the IKDC clinical grade for the pivot-shift test was assigned before revealing the results of the quantitative assessments. In addition, the collection of data can be limited by differences in the execution of the pivot-shift test across examiners at the four international sites, despite the standardized methodology used to evaluate rotatory knee laxity. Finally, there was no standardized rehabilitation protocol, which could play a major role in the patients' perception of knee function at the follow-up. This study consists of a relatively small cohort of patients with a limited follow-up rate and no à priori sample size calculation was performed due to the study design.

STUDY IV

The most distinctive potential limitation of Study IV was the incomplete response to the questionnaire sent out to the surgeons and any recall bias. Nevertheless, the retrospective collection of detailed surgical data was necessary to obtain information relating to items in the AARCS. To minimize recall bias, responders were only asked to answer the questions if they were sure of the date, by specifying specific years and not months, on which they adopted or abandoned the surgical technique in question. Moreover, all the patients who underwent surgery during time periods when the surgeon was "in between" surgical techniques were not included.[71] There were also a large number of patients in the SNKLR with incomplete data and they were therefore excluded from the study. Further limitations of Study IV are that rehabilitation and pre-injury sports participation were not controlled.

STUDY V

The most important potential limitations of Study V included the fact that the univariable analyses of the presence of a concomitant injury are limited by the fact that the reference group, i.e. patients without the concomitant injury of interest, may include patients with other concomitant injuries, thereby reducing the effect of the model. A large number of regression models were also conducted, increasing the risk of multiple significance and type-1 errors. In addition, differences in treatment regimens during surgery and rehabilitation could have minimized the influence of the concomitant injuries.[378] Only a small proportion of patients had a concomitant injury to the medial (n = 18) or the lateral (n = 1) collateral ligaments and the small number of patients with these injuries in the cohort may limit the ability to draw conclusions, with regard to these injuries and their association with acceptable knee function. In terms of concomitant meniscal and cartilage injuries, no information relating to size, severity or treatment was included, which could be regarded as a limitation.

STUDY VI

The limitations of Study VI included the fact that the reference group in the univariable analyses consisted of all the included patients who did not have the concomitant injury of interest and, as a result, the analyses may be biased, underestimating the effect of an additional injury, as the reference group may have included patients with other concomitant injuries. In addition, the preoperative results for muscle function were not available for all the included patients, as strength differences in patients with and without concomitant injuries may have been present before they were treated with reconstructive surgery. The presence of concomitant injures was analyzed dichotomously at reconstruction and no attention was therefore paid to the potential differences in the surgical and rehabilitation treatments. Moreover, the lack of data relating to the size and severity of concomitant injuries may mean that the dichotomous analysis of concomitant injuries was not sensitive enough to identify differences in the recovery of muscle function and could be regarded as a limitation in the study. In addition, a very small proportion of patients had an injury to either the medial (n=18) or the lateral (n=1) collateral ligaments, which limits the ability to draw conclusions related to these injuries. Finally, the low values of the ROC curve analyses suggested that none of the predictors in the study can be regarded as strong, despite their potential influence on clinical practice.

STUDY VII

The limitations of Study VII include the fact that the reference group in the univariable analyses consisted of all the included patients who did not have the concomitant injury of interest and, as a result, the analyses may be biased, underestimating the effect of an additional injury, as the reference group may have included patients with other concomitant injuries (like Studies V and VI). For instance, in the univariable analysis of the effect of meniscal injuries on RTS, the reference group, i.e. patients without meniscal injuries, may, for example, have included patients with a concomitant cartilage injury who might have similar, equal, or even larger limitations, thereby making the results for the reference group misleading. The presence of concomitant injures was also analyzed dichotomously at index reconstruction (yes/no) and no account was taken of the potential differences in the surgical and rehabilitation treatment of these injuries. There is no consensus when it comes to the type of treatment that should be used in the presence of concomitant injuries.[46 172 294 295 312] In addition, no information on the localization and severity of concomitant injuries was included and this could potentially bias the results. Moreover, for some of the predictors, only a small proportion of patients was represented in certain variables, e.g. lateral collateral ligament injury (n=1) and PT autograft (n=34), and this could limit the ability to draw conclusions, with regard to concomitant injuries and their association with the recovery of knee function.

STUDY VIII

The limitations of Study VIII include its merger of two cohorts. The follow-up rate in these original studies was only 76% and the further exclusion of patients due to sustaining an additional ACL injury are further limitations. In addition, the study design, with regression modeling, did not allow for a standard sample size calculation or power analysis. The use of both the transtibial and medial portal approaches to drill the femoral tunnel can also be regarded as a limitation. The fact that a more active approach in modern rehabilitation, with a combination of both open and closed kinetic chain exercises, is used immediately after ACL reconstruction is another consideration. Finally, the KT-1000 arthrometer anterior side-to-side difference was measured at only 89 N preoperatively, as opposed to 134 N and the manual maximum at follow-up.

STUDY IX

The main limitation of Study IX was the sub-optimal follow-up of patient-reported outcome in the SNKLR. There are no data in the SNKLR on structural imaging (radiological or magnetic resonance imaging evaluation), but this would be desirable in order to confirm the state of the meniscus and articular cartilage and the development of osteoarthritis. In addition, there are no data on rehabilitation or activity level, which may positively or negatively influence knee function. Patients who were unfortunate enough to undergo a revision or a contralateral ACL reconstruction were excluded from this study, as no ten-year data are available at the moment. Future studies should aim to include a larger cohort to determine the effect of combinations and locations of concomitant injuries, treatment, injury patterns from different activities and additional surgeries.

12.3. AREAS NOT COVERED BY THIS THESIS

GRAFT FAILURE

The most important limitation, which needs to be acknowledged, is that none of the included studies aims to determine predictors of subsequent ACL injury. Subsequent ACL injury can be considered as the most definite type of treatment failure. Whether or not the results of the present thesis are applicable to the population of patients who are unfortunate enough to sustain a subsequent ACL injury cannot be determined. It should be pointed out that these patients were not included in any of the nine studies.

POSTOPERATIVE RESIDUAL LAXITY

The ACL reconstruction aims to reduce the patients' knee laxity. A postoperative assessment of either anteroposterior or rotational knee-joint laxity was not included in this thesis. Including a measurement of postoperative knee-joint laxity would have created a further opportunity to determine whether the treatment with ACL reconstruction was successful. However, it has not been established whether a clinically stable knee is associated with superior patient-reported knee function, the recovery of muscle function or a return to sport after an ACL reconstruction.

LONG-TERM OBJECTIVE KNEE FUNCTION AND ACTIVITY LEVEL

This thesis did not cover the evaluation of long-term muscle function and activity level. The extent to which the results for muscle function may help us to understand the long-term outcomes after ACL reconstruction, such as subsequent ACL injuries or patient-perceived treatment failure, has not been established.

TREATMENT WITH REHABILITATION ALONE

Patients treated with only rehabilitation were not included in this thesis, with the exception of the one study identified in Study II. Unfortunately, not including these patients means that no explicit comparisons can be made between treatment regimens.

13

CONCLUSIONS

13.1 THEME ONE – CREATING A FOUNDATION RESEARCH

STUDY I

- The patients who returned to knee-strenuous sport were characterized as having fewer symptoms and less impairment during daily activities, sport and recreation, compared with patients who had not returned to knee-strenuous sport ten months after an ACL reconstruction.
- The patients who had returned to knee-strenuous sport also reported a higher frequency and intensity of physical activity, higher knee self-efficacy and higher knee-related quality of life.

STUDY II

- Both primary and revision ACL reconstruction improve patient-reported knee function compared with preoperative status.

- Patients of younger age and male sex, receiving HT autografts and having no concomitant injuries, reported superior results in terms of patient-reported outcomes.

- No clinically relevant differences in patient-reported knee function were found with regard to the surgical techniques for ACL reconstruction that are available.

13.2. THEME TWO – SHORT-TERM PREDICTORS

STUDY III

- Almost 80% of patients were able to achieve acceptable patient-reported knee function one and two years after anatomic single-bundle ACL reconstruction.

- The presence of a preoperative low-grade pivot shift increased the odds of achieving an acceptable level of knee function compared with a high-grade pivot shift one year after an ACL reconstruction.

- The measurements of QPS were not associated with achieving a patient-reported acceptable knee function.

STUDY IV

- The surgical technique of single-bundle ACL reconstruction was not predictive of patient-reported knee function, two years after reconstruction in a cohort from the SNKLR.

- Patient-reported success was associated with the absence of concomitant injury to the menisci and cartilage.

- The presence of a concomitant cartilage injury predicted a patient-reported failure.

STUDY V

- More than half the patients reported an acceptable symptom state on four of five KOOS subscales one year after an ACL reconstruction.

- Younger age at the time of reconstruction and male sex increased the likelihood of achieving acceptable levels of patient-reported knee function one year after an ACL reconstruction.

- There was a lack of consistency related to the effect of concomitant knee injuries and graft choice on acceptable knee function.

STUDY VI

- No negative effect on the one-year recovery of symmetrical performance in five tests of muscle function was found in the presence of concomitant injuries.

- Fewer than one in four patients in the cohort achieved an LSI of ≥ 90% across the battery of tests.

- Patients of younger age who underwent reconstruction with an HT autograft obtained favorable results in terms of recovering knee extension strength.

- The graft choice of ACL reconstruction did not influence the possibility of achieving an LSI of ≥ 90% across all five tests of muscle function one year after the ACL reconstruction.

STUDY VII

- Patients of male sex, younger age, a higher pre-injury level of physical activity, with no concomitant injury reported to the medial collateral ligament or the meniscus, had higher odds of returning to sport one year after an ACL reconstruction.

13.3. THEME THREE – LONG-TERM PREDICTORS

STUDY VIII

- Patients who were older at the time of ACL reconstruction and had waited for more than a year between the injury and reconstruction ran an increased risk of having developed osteoarthritis on average 16 years after the reconstruction.

- One in two patients reported acceptable long-term knee function, but no risk factor for poorer patient-reported knee function was identified.

STUDY IX

- This ten-year risk factor analysis identified several factors that can affect long-term knee function after ACL reconstruction.

- Potential modifications to risk factors include identifying optimal interventions for grades 3-4 articular cartilage pathology, ensuring lower levels of perceived pain, minimizing limitations in ADL and potentially lowering the preoperative body mass index.

14

FUTURE PERSPECTIVES

At the beginning of 2018, there were more than 19,000 publications on patients with ACL injuries in the PubMed database. Despite the large amount of research, there are still controversies in terms of the selection of treatment for these patients. Future research needs to focus on continuing and improving the interprofessional assessment of patients with an ACL injury. We also need to balance stringency and relevance in future research using classic high-level studies (RCTs or prospective cohorts) with modern methodology and large register studies.

Where do we begin? With the present thesis in mind, we need to improve our understanding of why there is still such a large proportion of patients that will be unfortunate and sustain a subsequent ACL injury after their ACL reconstruction. This is an area in which several authors have already published a fair amount of work, but more interprofessional work should be performed. In research, we often forget that a risk factor only entails an increased risk when the patient is subject to the exposure. So, only studying a surgery-related factor or a strength measurement is not enough to improve our understanding of why many patients sustain a subsequent ACL injury. There is also a need to better understand the consequences of subsequent ACL injuries in the short- and long-term perspectives, since the reasons for sustaining an injury of this kind likely differ as time passes from injury or reconstruction. In addition, both high-level RCT´s and large register studies should preferably be used to address and understand the rare event of a subsequent ACL injury.

We also need to address patients who are treated with rehabilitation alone to further develop individualized treatment programs after an ACL injury. Based on what has been presented in the literature, there appears to be a bias in the selection of treatment after an ACL injury. Most patients are treated with ACL reconstruction and rehabilitation. The number of patients selected for each treatment is more evenly distributed in the Scandinavian countries compared with other large geographical areas in Europe and the US, but there is still room to improve our understanding of the criteria for selecting treatment. The patients who have rehabilitation alone as treatment need to be studied across various outcomes, in a fashion similar to that used in this thesis, to improve our understanding of who will and will not benefit from this treatment regimen. Having acquired a basic understanding of the respective treatments, we should further address the selection of treatment with high-level RCTs using specific outcomes that are relevant to the patient, orthopedic surgeon and physical therapist.

On many occasions, the general literature on patients with an ACL injury can be confusing, not only because of the large numbers of publications, but also because of the large number of outcomes used to address this heterogeneous group of patients. Determining which of the commonly used outcomes have the most relevant impact on the treatment of patients with an ACL injury is an interesting and promising area of research. Nonetheless, acquiring further evidence-based knowledge and developing new methods to evaluate these patients can help the field of research to reach consensus.

Finally, it is well established that ACL injuries are most frequent in younger individuals. These patients are highly motivated and are generally eager to return to sport. At the same time, the young patients who have sustained an ACL injury run a high risk of sustaining a subsequent ACL injury. In addition, they are primary candidates for developing early-onset osteoarthritis, knowing the generally increased risk of degenerative knee joint changes after ACL injury. Because of the differences in the risk of suffering an ACL injury and a subsequent injury in younger patients, these patients may not be fully comparable with their older counterparts. There is an evident need for an increased understanding of why the younger individual runs an increased risk of primary and secondary ACL injury, as well as understanding what can help to improve outcomes in these patients. I truly believe that we have learned a lot throughout the years of conducting research on the topic of patients with an ACL injury, but the time has now come to challenge our beliefs and work hard to push the field even further.

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STUDY I

Return to knee-strenuous sport after anterior cruciate ligament reconstruction: a report from a rehabilitation outcome registry of patient characteristics

Hamrin Senorski E, Samuelsson K, Thomee C, Beischer S, Karlsson J, Thomee R

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STUDY II

Factors that affect patient-reported outcome after anterior cruciate ligament reconstruction – a systematic review of the Scandinavian knee ligament registers

Hamrin Senorski E, Svantesson E, Baldari A, Ayeni OR, Engebretsen L, Franceschi F, Karlsson J, Samuelsson K

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STUDY III

Preoperative knee laxity measurements predict the achievement of a patient-acceptable symptom state after ACL reconstruction: a prospective multicenter study

Hamrin Senorski E, Svantesson E, Sundemo D, Musahl V, Zaffagnini S, Kuroda R, Karlsson J, Samuelsson K

Journal of ISAKOS, 2018, doi:10.1136/jisakos-2017-000186

STUDY IV

Increased odds of patient-reported success at 2 years after anterior cruciate ligament reconstruction in patients without cartilage lesions: a cohort study from the Swedish National Knee Ligament Register

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Knee Surgery Sports Traumatology Arthroscopy, 2017, doi:10.1007/s00167-017-4592-9

STUDY V

Factors affecting the achievement of a patient acceptable symptom state one year after ACL reconstruction - A cohort study on 343 patients from two registries

Hamrin Senorski E, Svantesson E, Beischer S, Grassi A, Krupic F, Thomeé R, Samuelsson K

Orthopaedic Journal of Sports Medicine, 2018, Accepted

STUDY VI

Concomitant injuries may not reduce the likelihood of achieving symmetrical muscle function one year after anterior cruciate ligament reconstruction – a prospective observational study based on 263 patients

Hamrin Senorski E, Svantesson E, Beischer S, Thomeé C, Grassi A, Krupic F, Thomeé R, Karlsson J, Samuelsson K

Knee Surgery Sports Traumatology Arthroscopy, 2018, doi:10.1007/s00167-018-4845-2

STUDY VII

Low one-year return to sport rate after anterior cruciate ligament reconstruction regardless of patient and surgical factors – A prospective cohort study on 272 patients

Hamrin Senorski E, Svantesson E, Beischer S, Thomeé C, Thomeé R, Karlsson J, Samuelsson K

American Journal of Sports Medicine, 2018, Accepted

STUDY VIII

Preoperative predictors of 16-year acceptable knee function and osteoarthritis after anterior cruciate ligament reconstruction – an analysis based on 147 patients from two randomised controlled trials

Hamrin Senorski E, Sundemo D, Svantesson E, Sernert N, Kartus J, Karlsson J, Samuelsson K

Manuscript

STUDY IX

Ten-year risk factors of the Knee injury and Osteoarthritis Outcome Score after anterior cruciate ligament reconstruction: a study of 874 patients from the Swedish National Knee Ligament Register

Hamrin Senorski E, Svantesson E, Spindler K, Alentorn-Geli E, Sundemo D, Westin O, Karlsson J, Samuelsson K

Manuscript

APPENDICES