From the Department of Clinical Science and Education, Södersjukhuset
Karolinska Institutet, Stockholm, Sweden

ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION
Studies on morbidity, function and health-related quality of life

Björn Barenius

Stockholm, 2012

Published by Karolinska Institutet. Printed by Larserics Digital Print AB.

ISBN 978-91-7457-896-6

To my grandfather, Ernfrid, who longed for the journey to academic knowledge,
and my family for loving support.

ABSTRACT

The aim of this thesis was to investigate the effects of graft choice, time between injury and reconstruction and injuries to the menisci on knee function and the health-related quality of life after an anterior cruciate ligament (ACL) reconstruction.

In *Study I*, 153 patients were assessed at a mean 8 years after randomisation to an ACL reconstruction with a bone-patellar tendon-bone or four-strand semitendinosus tendon graft. The results for laxity, functional tests, functional scores and health-related quality of life were similar for the graft types. The bone-patellar tendon-bone graft was associated with more morbidity from kneeling, knee-walking and disturbed sensitivity. Patients having reconstructions before six months from injury had higher Tegner activity scores, and patients with a meniscus procedure before, or at the reconstruction, had worse outcomes.

In *Study II*, 135 patients from the same randomised controlled trial as in *Study I* were assessed for prevalence of radiological osteoarthritis after a mean of 14 years. The prevalence of osteoarthritis was higher after anterior cruciate ligament reconstruction compared to the healthy non-injured limb and medial compartment osteoarthritis was most common. No difference between graft types was found. Meniscus resection and overweight two years after the reconstruction increased the risk of osteoarthritis. Osteoarthritis affected the health-related quality of life and most patients with osteoarthritis were symptomatic.

In *Study III*, 10 patients with a four-strand semitendinosus tendon and 10 patients with a four-strand semitendinosus and gracilis tendon graft were assessed after a mean of 36 months following an ACL reconstruction. No difference in rotational range of motion between the graft types was found by gait analysis and no other differences in functional scores, laxity, return to sport activities or flexion strength.

In *Study IV*, increased time between injury and ACL reconstruction was found to increase the risk for a medial meniscus injury among 8584 patients from the Swedish National Knee Ligament Register. After two years an outcome assessment according to the Knee Osteoarthritis Outcome Score (KOOS) was available for 3556 patients. The results were stratified to a high KOOS defined as functional recovery and a low KOOS defined as treatment failure. The chance for a functional recovery was higher for males and for hamstring tendon grafts and lower for patients with a previous meniscus procedure or a notchplasty at reconstruction. The risk of treatment failure was higher for patients with a previous meniscus procedure or a medial meniscus procedure at the time of reconstruction and lower for the hamstring tendon grafts and individuals between 35 and 54 years old. For a subpopulation of 556 patients, a high pre-injury Tegner activity score increased the risk of treatment failure.

In conclusion, time between injury and reconstruction affect the results after ACL reconstruction as a result of the increasing frequency of additional injuries occurring with time. Graft-related morbidity affects the short- and long-term results. Meniscus injuries influence the short- and long-term results and the prevalence of osteoarthritis after ACL reconstruction, especially if a resection is needed.

Key words: anterior cruciate ligament (ACL), morbidity, health-related quality of life (HRQoL), knee osteoarthritis outcome score (KOOS), osteoarthritis, functional recovery, treatment failure, additional injuries, activity level, predictors.

LIST OF ORIGINAL PAPERS

This thesis is based on the following studies, which will be referred to in the text by their Roman numbers (*Studies I-IV*)

I. Quality of life and clinical outcome after anterior cruciate ligament reconstruction using patellar tendon graft or quadrupled semitendinosus graft: An 8-year follow-up of a randomized controlled trial. **B Barenius, M Nordlander, S Ponzer, J Tidermark, K Eriksson**, *Am J Sports Med vol. 38 (8) pp. 1533-41*

II. Increased risk of osteoarthritis after ACL reconstruction: A 14-year follow-up study of a randomized controlled trial. **B Barenius, S Ponzer, A Shalabi, R Bujak, L Norlén, K Eriksson,** submitted

III. Hamstring tendon anterior cruciate ligament reconstruction: Does gracilis tendon harvest matter? **B Barenius, K Webster, J McClelland, J Feller,** Accepted for publication. *Int Orthop*

IV. Functional recovery after anterior cruciate ligament reconstruction, a study of health-related quality of life based on the Swedish National Knee Ligament Register. **B Barenius, M Forssblad, B Engström, K Eriksson**, *Knee Surg Sports Traumatol Arthrosc E-pub 2012/8/14*

PREFACE

PERSONAL REFLECTION

What is so interesting about the anterior cruciate ligament that so many are willing to spend so much time trying to figure out all there is to know about it? To that question, I have no answer. But for me, it started with a good knee function. I have always enjoyed skiing, climbing and mountaineering. As a small kid I climbed to the top of every tree I could find, and sometimes fell down, but never broke anything. When alpine skiing got too boring I tried free heel skiing and loved it. I can't tell how many times I have got caught by a bush or branch underneath the snow and landed headfirst twisting the caught knee with great force, but no ligament in the knees ever gave way. During my early residency to become an orthopaedic surgeon in a small village close to Jotunheimen in Norway, I met people who had injured their knees and had to change the way they lived. What an impact such a tiny ligament can have! Can the quality of life be good again without pumping powder down an uncharted slope of perfectly spaced birch trees? I'm not sure. I guess you can refocus and adapt. If it had happened to me while I was at my peak of performance in skiing, I would have been ready to go through a lot to get back. But what is the best way to reconstruct the anterior cruciate ligament? And what if I had a meniscus injury? How would that affect my return to skiing? If I had got a weak quadriceps muscle after the surgery and could not ski because of that? If I couldn't ski anymore because the knee was painful and swollen ten years after the surgery? If my knee still felt unstable during skiing even though the surgeon said it was perfect, what would my health-related quality of life be then?

WHAT DOES THIS THESIS ADD?

Additional meniscus injuries requiring resection were found to have a major influence on the health-related quality of life after an anterior cruciate ligament (ACL) reconstruction both in the short- and long-term. Increasing time between injury and reconstruction (TIR) was found to be a risk factor for additional injuries. The ACL reconstruction did not protect the injured knee from osteoarthritis. The results of this thesis have put the initial patient consultation after the injury in focus. The patients desired activity level, compliance with activity modification and goals in the short- and long-term have to be assessed thoroughly. The results outlined in the thesis suggest that patients with clinically unstable knees can benefit from a reconstruction before an additional injury has occurred, but should be cautioned that the stability gained can potentially have negative effects on the knee joint in the long-term.

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LIST OF ABBREVIATIONS

ACL	Anterior cruciate ligament
ADB	Anatomic double bundle
ASB	Anatomic single bundle
AP	Anteroposterior
BMI	Body mass index
BMI2y	BMI at the 2-year follow up.
BPTB	Bone patella tendon bone graft, abbr. used in *Studies I and II*
BQT	Bone quadriceps tendon
CI	Confidence interval
Cl	Contralateral
CSB	Conventional single bundle (transtibial)
EQ-5D™	EuroQol, a generic HRQoL score
FR	Functional recovery, abbr. used in *Study IV*
HRQoL	Health-related quality of life
HT	Hamstring tendons
ITT	Intention-to-treat principle
ICC	Intraclass correlation coefficient
KL	Kellgren & Lawrence radiological OA classification
KOOS	Knee Osteoarthritis Outcome Score
ADL	Activities of daily life, subscale in KOOS
Sp/Rec	Function in sport and recreation, subscale in KOOS
Pain	Symptoms of pain, subscale in KOOS
Symptoms	Other symptoms than pain, subscale in KOOS
QoL	Knee-related quality of life, subscale in KOOS
Lbs.	Pounds
LCL	Lateral collateral ligament
MCL	Medial collateral ligament
N	Newton
Nm	Newtonmeter
OA	Osteoarthritis
OR	Odds ratio
PF	Patellofemoral joint compartment in the knee
PT	The abbreviation used for bone patella tendon bone graft in *Studies III and IV*

RCT	Randomized controlled trial
ROM	Range of motion
RR	Relative risk
SD	Standard deviation
SF-36	Short form 36
PF	Physical functioning, subscale in SF-36, abbr. used in *Study I*
RP	Role physical, subscale in SF-36, abbr. used in *Study I*
BP	Bodily pain, subscale in SF-36, abbr. used in *Study I*
GH	General health, subscale in SF-36, abbr. used in *Study I*
VT	Vitality, subscale in SF-36, abbr. used in *Study I*
SF	Social functioning, subscale in SF-36, abbr. used in *Study I*
RE	Role emotional, subscale in SF-36, abbr. used in *Study I*
MH	Mental health, subscale in SF-36, abbr. used in *Study I*
ST	Semitendinosus tendon
ST<4	Semitendinosus tendon graft with less than 4 strands, abbr. used in *Study IV*
ST 4	Semitendinosus tendon graft with 4 or more strands, abbr. used in *Study IV*
ST/G	Semitendinosus and gracilis tendon, abbr. used in *Study III*
ST/Gr	Semitendinosus and gracilis tendon
ST/Gr<4	Semitendinosus and gracilis tendon graft with less than 4 strands, abbr. used in *Study IV*
ST/Gr 4	Semitendinosus and gracilis tendon graft with 4 or more strands, abbr. used in *Study IV*
TF	Treatment failure, abbr. used in *Study IV*
TIR	Time between injury and ACL reconstruction
TKA	Total knee arthroplasty
VAS	Visual analogue scale, (0-100) 100 best
VAS1	VAS question, ‘How does your knee function?’
VAS2	VAS question, ’How does your knee affect your level of activity?’
VIF	Variance inflation factor

DEFINITIONS

Functional recovery (FR)	Definition of a level of the Knee Osteoarthritis Outcome Score (KOOS) representing patients with a functional recovery after their ACL reconstruction, used in *Study IV*. FR was defined as a KOOS above 90 for Pain, 84 for Symptoms, 91 for ADL, 80 for Sport/Rec and 81 for QoL.
Treatment failure (TF)	Definition of a level of KOOS representing patients with treatment failure after their ACL reconstruction, used in *Study IV*. TF was defined as a KOOS, QoL <44.
KL≥2	Definition of radiological osteoarthritis used in *Study II.* Grade 2 or more in the Kellgren & Lawrence radiological OA classification.
Symptomatic knee problems	A definition according to a level of KOOS combined with radiological osteoarthritis in *Study II* to assess symptomatic osteoarthritis. Patients with a KOOS ≤ 87.5 for the subscale QoL combined with a score on any two subscales below the cut off levels ≤ 86.1 for pain, ≤ 85.7 for symptoms, ≤ 86.8 for ADL and ≤ 85.0 for Sports/Rec, were defined as having symptomatic knee problems.

For further information regarding the KOOS definitions see section 6.9.1 page 24

1 INTRODUCTION

1.1 THE ANTERIOR CRUCIATE LIGAMENT RUPTURE AND THE NEED FOR SURGICAL RECONSTRUCTION

The anterior cruciate ligament (ACL) is the knee joint's primary restraint on anterior translation of the tibia in regard to the femur and a secondary restraint on internal rotation of the tibia. A rupture of the ligament frequently happens because of hyperextension and rotation in the knee on a fixed foot: for example, a contact situation in soccer. Another common cause is external rotation and valgus force on a flexed knee: for example, when the ski is trapped in downhill skiing. The result is often an unstable knee joint where the combined translational and rotational instability leads to the knee joint 'giving way' during pivoting motions, such as a sudden change of direction needed during soccer or during a simple procedure as rounding a corner when walking. The impact of the injury differs. In Sweden a cruciate ligament injury has an incidence of 78 per 100 000 persons, with 36% receiving surgical treatment.[153] Some people can live without a functional ACL and not experience instability, such persons are usually referred to as 'copers'.[155] However, this usually requires a modification of the person's activity,[117] and some are not satisfied with their knee function.[53] Recurrent 'giving way' and secondary injuries to the menisci and cartilage are a risk with non-operative treatment. [63,117,155] There are indications that ACL reconstructions decrease the risk of secondary injuries.[159] Recurrent 'giving way' episodes define a person as a 'non-coper', an indication for ACL reconstructive surgery. When surgeons rate the result after ACL reconstructions the results are usually good,[172] but when patients rate their results it is usually not as good as the surgeons' rating,[87] and the overall result after surgery, compared to non-operative treatment, might not be better.[66,212]

2 REVIEW OF LITERATURE

The patients who have decided to treat their ACL injury with a reconstruction want their knee function back in order to return to a desired level of activity with minimal side effects and no long-term disability. Many factors contribute to the prognosis.

2.1 THE UNSTABLE KNEE AND ACL RECONSTRUCTION

The patient's main problem after an ACL injury is instability, so the main goal of an ACL reconstruction is to restore normal stability.[208] In order to decrease the risk of long-term deterioration of the cartilage, the reconstruction should restore normal kinematics to the knee as well.[15,65] With the transtibial approach usually used at the beginning of the era of arthroscopic reconstruction, an 'isometric' position was sought. Where 'Isometric' means the position of the tunnels in which the graft would receive the same tension forces for all knee angles. In relation to the native footprint of the ACL, this usually resulted in a posterior placement of the tibial tunnel and a posterior and high placement of the femoral tunnel.[94] The native ACL has long fibres in the anterior part and short fibres in the posterior part, and different fibres are tight in different knee joint angles. The ACL is usually considered to have two functional bundles, an anteromedial bundle, tight in flexion, and a posterolateral bundle, tight in extension. The vertical graft resulting from the 'isometric' position restored anteroposterior (AP) laxity but did not effectively restore the rotational component of the instability.[69] The double bundle procedure was developed to achieve a reconstruction more closely resembling the native ACL to achieve better rotational stability.[208] The knowledge gained during the development of the double bundle reconstruction has also led to more knowledge of anatomical ACL reconstruction and the rediscovery of a more anatomical single bundle procedure, but without the drawbacks of open surgery.[85,149,188] The rotational instability is assessed in the clinical setting with the pivot shift test.[70] For the rotational stability to be assessed on a scientific level, a quantifiable method of rotation is needed. A number of methods have been developed, but no clear consensus on the most accurate or 'real-life resembling' test method has been reached.[17,73,98,142,207] It is not clear that the double bundle procedure restores rotational stability better than a single bundle procedure.[90,91,143,147,216] Karlsson et al. recently published a review of anatomical single and double bundle ACL reconstructions. They concluded that more reliable, accurate, precise and validated outcome measures are needed to evaluate the results of these new techniques.[105]

2.2 THE GRAFTS USED IN ACL RECONSTRUCTION

The ACL does not heal and, so far, all methods of repair or augmentation with synthetic material have failed.[12,52,188,189] In the United States of America allograft use is common, but in Europe and Scandinavia the allograft is often reserved for multi-ligament reconstructions and is not used routinely for primary ACL reconstruction.[92,133]

Furthermore, there are indications of less stability and higher failure rates after allograft reconstructions.[26,171] The most frequently used autografts are the bone-patella tendon-bone (BPTB), the bone-quadriceps tendon (BQT) and the hamstring tendon (HT) grafts. The HT graft can be further classified into the semitendinosus and gracilis tendon (ST/Gr) graft or the graft using the semitendinosus tendon (ST) alone. The HT grafts are often reported according to the number of strands included in them. The most frequently used one in Scandinavia being the four-strand ST/Gr.[24] The morbidity after quadriceps tendon harvest is reported to be low, but there are few published studies.[72,77] The BPTB autograft was considered to be the gold standard in ACL reconstruction during the latter part of the 20th century.[68,188] Since then a shift has taken place with the HT graft now being the most frequently used one, at least in Scandinavia.[79] The comparisons between the BPTB and HT grafts are numerous.[29,60,100,124,169,185] However, a recent Cochrane review concluded that there was insufficient evidence to draw conclusions about differences between the BPTB and hamstring tendon graft for the long-term outcome, and the ST/Gr and ST grafts were not separated in the analysis.[148] BPTB grafts resulted in more stable knees but with more anterior knee problems and problems from kneeling, loss of extension range of motion (ROM) and a trend towards loss of extension strength, while the HT had an increased risk of flexion strength loss and a trend towards a loss of flexion ROM.[148] Other meta-analyses have not found a difference in stability.[33,170] Comparisons between BPTB and ST[51,54,128] and between ST and ST/Gr are more rare.[76,151,206]

2.3 THE 'RIGHT' TIME FOR AN ACL RECONSTRUCTION

In the era of Drs Palmer and O'Donoghue an ACL injury was treated with an acute operative procedure.[158,164] The tradition of acute or subacute surgical treatment of the ACL injury was maintained until a number of reports of arthrofibrosis after acute ACL reconstructions led to a paradigm shift.[140,198,199,220] At present most surgeons recommend the ROM to be close to normal before the reconstruction.[49] This usually results in a period between injury and the reconstruction of more than three weeks. In Sweden a tradition of a trial period to assess the effect of non-operative treatment and the regulated health-care system leading to waiting lists, have resulted in a mean period between an ACL injury and reconstruction of more than one year.[231] However, there is evidence of an increasing frequency of meniscus injuries and cartilage lesions with increasing time between injury and the ACL reconstruction,[25,40,41,45,106,110,165] and worse results after reconstruction with an additional injury.[197] There are also reports of better results after reconstruction if it is done early on.[4,25,54,101] Instability during the time between injury and reconstruction can cause changes in knee kinematics and laxity in secondary constraints that are not restored with a reconstruction,[35,73] but with a reconstruction performed within 10 weeks from the injury, abnormal kinematic motion might be avoided.[98] With the less invasive surgical technique used today, the risk of complications due to early surgery also seems less serious.[34]

2.4 THE SUBJECTIVE OUTCOME AFTER AN ACL RECONSTRUCTION

The surgeon rates success after an ACL reconstruction from objective measurements like residual laxity and ROM. The patients' experience of their knee function is assessed mainly via questionnaires regarding functions in daily life and sports. During the history of ACL research a myriad of scores and questionnaires has been developed.[82,132,156,210,225] Many of the early scores used had problems with internal validity and were not comparable.[82] The International Knee Documentation Committee (IKDC) form was developed to resolve that problem. The IKDC evaluation form from 1982 has had widespread use and is validated.[82] However, it has been shown to have little evaluation value over time,[174] and, as all scores, it is susceptible to interview bias.[87] Health-related quality of life (HRQoL) questionnaires were developed for self-administration and are validated.[56,116,195] They are therefore useful for comparing the impact of different conditions The EuroQol (EQ-5D™), are easy for the patient to answer, containing only five questions.[36,56] The EQ-5D™ has been used with good results in hip fracture research and is an outcome measure of the Scandinavian Knee Ligament Registers.[213,231] The Short-Form 36 (SF-36) is a well-documented HRQoL questionnaire.[202] It has been used in the evaluation of many diseases and there are published reference populations for many countries.[219] At the moment, the most used HRQoL questionnaire in ACL research is the Knee Osteoarthritis Outcome Score (KOOS).[180] The KOOS is knee-specific and validated;[181] there is two published reference populations for Sweden,[67,166] it is used as an outcome measure of the Scandinavian Knee Ligament Registers,[79] and it has been shown to be reliable for measuring change over time.[179]

2.5 THE ACTIVITY LEVEL AFTER AN ACL RECONSTRUCTION

One way to measure knee function in real-life situations is to assess at what level of activity the patient can function after the ACL reconstruction. A number of questionnaires have been developed to assess this.[137,154] The Tegner activity score is a frequently used score in Europe.[210] The activity level is often reported before injury, pre-operatively, at the time of evaluation and also the desired activity level at the time of evaluation. The pre-injury activity level has been reported to affect the subjective outcome after an ACL reconstruction.[136] Most studies find a significant increase after reconstruction compared to preoperatively.[51,54,123,134] However, few patients return to pre-injury levels of activity and there are differences between genders.[123,134,138] The activity level might also decrease with age.[14,117] Another way to measure activity is frequency of patients returning to their pre-injury sport. The frequency reported is in line with the results for the Tegner activity score, i.e. few patients return to their pre-injury sport.[18,21]

2.6 THE LONG-TERM EFFECT OF AN ACL INJURY

An ACL injury increases the risk of posttraumatic secondary osteoarthritis (OA).[218] Factors influencing primary OA such as age and BMI have also been linked to the causality of secondary OA.[47,176] Previous studies have shown meniscus injuries and particularly meniscus injuries requiring resection to be associated with secondary OA.[57,145,176,230] Some reports suggest a preventive effect of meniscus sutures for secondary OA.[177,230] There are a number of theories concerning the aetiology of OA after an ACL injury. It has been reported that a mechanical instability could result in early onset OA.[131] That the osseous homeostasis of the knee joint is changed after an ACL injury and reconstruction has been shown by Dye et al.[50] In addition, Andriacchi et al. have studied the altered load characteristics of the cartilage.[16,39] Even though many factors have been studied and the epidemiological connection between a traumatic knee injury and a post-traumatic secondary OA is clear, the mechanism responsible for secondary OA after an ACL injury is unknown. [38,39,61,65,182,226]

The prevalence of reported OA after ACL injuries varies a great deal between different studies. Most long-term radiographic follow-ups after an ACL rupture report increased prevalence of OA compared to uninjured knees.[104,131,218] The protective effect of an ACL reconstruction is unclear, varying from reports of results of a protective effect of the reconstruction to reports of a higher risk for OA after a reconstruction.[45,63,86,88,111,127,131,145,146,150,152,160-162,218,228] Many authors have reported the effect of an additional meniscus injury and meniscus resection on the prevalence of OA after an ACL reconstruction.[43,45,102,108,127,145,160] The effect of time between injury and reconstruction on the prevalence of OA is not as clear.[101,102,129]

Choice of graft for the ACL reconstruction has also been considered to influence long-term radiographic OA, but no clear consensus can be found in the literature. Keays et al. found more tibiofemoral OA after BPTB reconstructions than after HT reconstructions.[108] Leys et al. found a higher incidence of patellofemoral OA when comparing BPTB with HT,[126] and Sajovic et al. found more OA for the BPTB graft than for the HT graft.[184] Other studies have failed to show any graft-specific differences in any of the compartments.[88,129,228] In general, RCTs with a radiological assessment at a minimum of 10 years after anterior cruciate ligament reconstructions are rare and most previous studies are either retrospective or comparisons between different cohorts.

3 AIMS OF THE THESIS

Study I

The primary aim of this study was to compare mid- to long-term outcomes after ACL reconstruction randomised to a BPTB or a four-strand ST graft. The outcome was measured by physical examination, instrumented laxity, functional scores and the HRQoL scores SF-36 and KOOS.

Secondary aims were to compare subgroups of patients; early reconstruction (< 6 months) vs late reconstruction, meniscus injury at diagnostic arthroscopy and/or index ACL reconstruction or no meniscus injury and a meniscus injury treated surgically compared to no meniscus injury.

Study II

The primary aim was to compare long-term prevalence of OA after ACL reconstruction randomised to a BPTB or a four-strand ST graft.

Secondary aims were to assess predictors for OA after ACL reconstruction and compare the activity level and HRQoL for patients with or without OA.

Study III

The primary aim was to compare ACL reconstructions with a four-strand ST graft or a four-strand ST/Gr for differences in harvest-related morbidity and residual rotational laxity.

Study IV

The primary aim was to assess predictors for a functional recovery according to a defined level according to KOOS.

Secondary aims were to characterise patients with a functional recovery or treatment failure according to a defined level of KOOS, and to assess the effect of time between injury and the ACL reconstruction on the outcome according to KOOS and the frequency of additional injuries to menisci and cartilage found at the time of reconstruction.

4 STUDY POPULATIONS

4.1 *STUDIES I AND II*

Between 1995 and 1997, 180 patients were included in a two-centre randomised controlled trial (RCT). Inclusion criteria were primary unilateral ACL insufficiency with a time between injury and reconstruction of at least two months, age between 15 and 45, no injury to the PCL in the involved knee or previous ligament surgery on the involved or contralateral knee. Inclusion was effectuated after a diagnostic arthroscopy verifying the ACL injury. The patients were randomised to an ACL reconstruction with an ipsilateral BPTB or four-strand ST graft. The randomisation was done with sealed envelopes in 160 patients and a draw between the methods in 20. Sixteen patients were found not to fulfil the inclusion criteria and were excluded. The remaining 164 patients received their allocated treatment.

4.1.1 *Study I*

After a mean of 8.4 years (SD = 0.98) after the reconstruction, 93% (153 of 164) of the patients (78 BPTB and 75 ST) were evaluated. Patients lost to follow-up are specified in Figure 1. The mean age at injury was 26 years (SD=7), with no difference between the graft groups. In *Study I* the ST group was older, mean 35 years (SD=7.5), than the BPTB group, mean 33 years (SD=6.3), p=0.021. There was still a preponderance of female gender in the BPTB group with 62% of the women, compared to 38% in the ST group, p=0.016. In both groups 23 additional procedures had been performed since the reconstruction. There were two graft ruptures that had been revised in both groups, and 3 ST and 7 BPTB reported contralateral (cl) ACL injuries. Five had been reconstructed, 3 ST and 2 BPTB (4 males and 1 female).

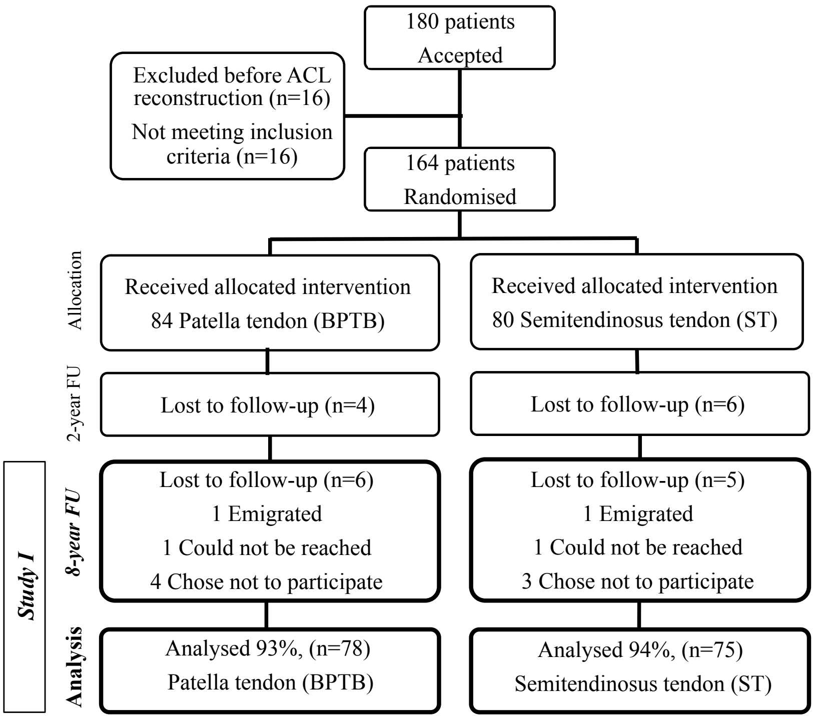
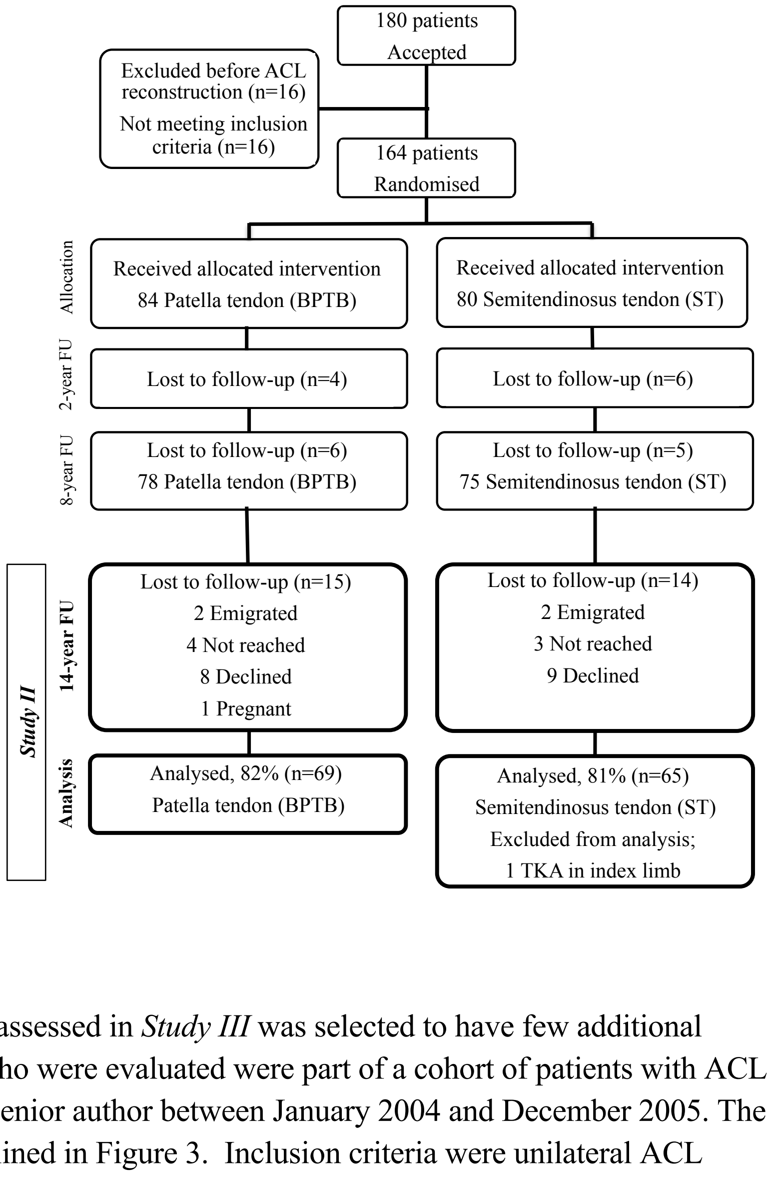


Figure 1
Flowchart for patients in *Study I*

4.1.2 Study II

In *Study II* the same study population as in *Study I* was contacted again to assess long-term prevalence of OA. Patients lost to follow-up are specified in Figure 2. Eighty-two per cent (135 of 164) of the patients (69 BPTB and 66 ST) were evaluated after a mean of 14.1 years (SD=0.5) after the reconstruction. One patient was excluded from the analysis due to a total knee arthroplasty (TKA) in the index limb. As in *Study I,* the ST group was older at the time of follow-up, mean 42 years (SD=7) than the BPTB group, mean 39 years (SD=6), p=0.031. There was still a preponderance of female gender in the BPTB group with the same distribution as in *Study I.* The BPTB group comprised 62% of all the females, vs 38% in the ST group, p=0.046. Periods between injury and *Study II* and between injury and reconstruction were similar for the graft groups.

Figure 2
Flowchart for patients in *Study II*



4.2 STUDY III

The patient population assessed in *Study III* was selected to have few additional injuries. The patients who were evaluated were part of a cohort of patients with ACL reconstructions by the senior author between January 2004 and December 2005. The selection process is outlined in Figure 3. Inclusion criteria were unilateral ACL reconstruction performed within 6 months from injury, age between 18 and 40 at the time of injury, fixation with a metal interference screw in the tibia, and the required graft type was a four-stranded semitendinosus (ST) tendon only or a four-stranded semitendinosus and gracilis (ST/Gr) tendon. Exclusion criteria were concomitant additional PCL injury or collateral ligament injury requiring treatment, a cartilage injury of a severity more than Noyes N2A,[156] additional procedures after the reconstruction or additional injuries after the reconstruction resulting in a graft rupture or cl ACL injury. Patients with a patella tendon graft or current symptoms due to hip or ankle problems were also excluded.

In order to minimise the frequency of additional injuries, patients without additional injuries who satisfied the inclusion criteria were contacted before patients with additional injuries. The patients contacted by letter were subsequently contacted by phone and interviewed. The phone interview included questions regarding injuries sustained after the reconstruction or other injuries pertaining to the exclusion criteria. If the patient satisfied the criteria for inclusion and accepted participation after the phone interview, the study evaluation was done at the gait laboratory. One patient was excluded at the time of the study evaluation after a cl ACL injury was diagnosed. Twenty patients were analysed, 10 with a four-strand ST graft and 10 with a four-strand ST/Gr graft. There were two females in both groups. The mean age at injury was 26 years (SD=8)and the period between injury and reconstruction and the period between reconstruction and *Study III* were similar for the graft groups. The patients in the ST group were taller, 179 cm (SD=6) than those in the ST/Gr group, 173 cm (SD=5), p=0.03. There were 3 lateral meniscus injuries with 1 partial resection and 2 cartilage injuries in the ST/Gr group and 2 lateral meniscus injuries, a stable MCL tear and a cartilage injury in the ST group.

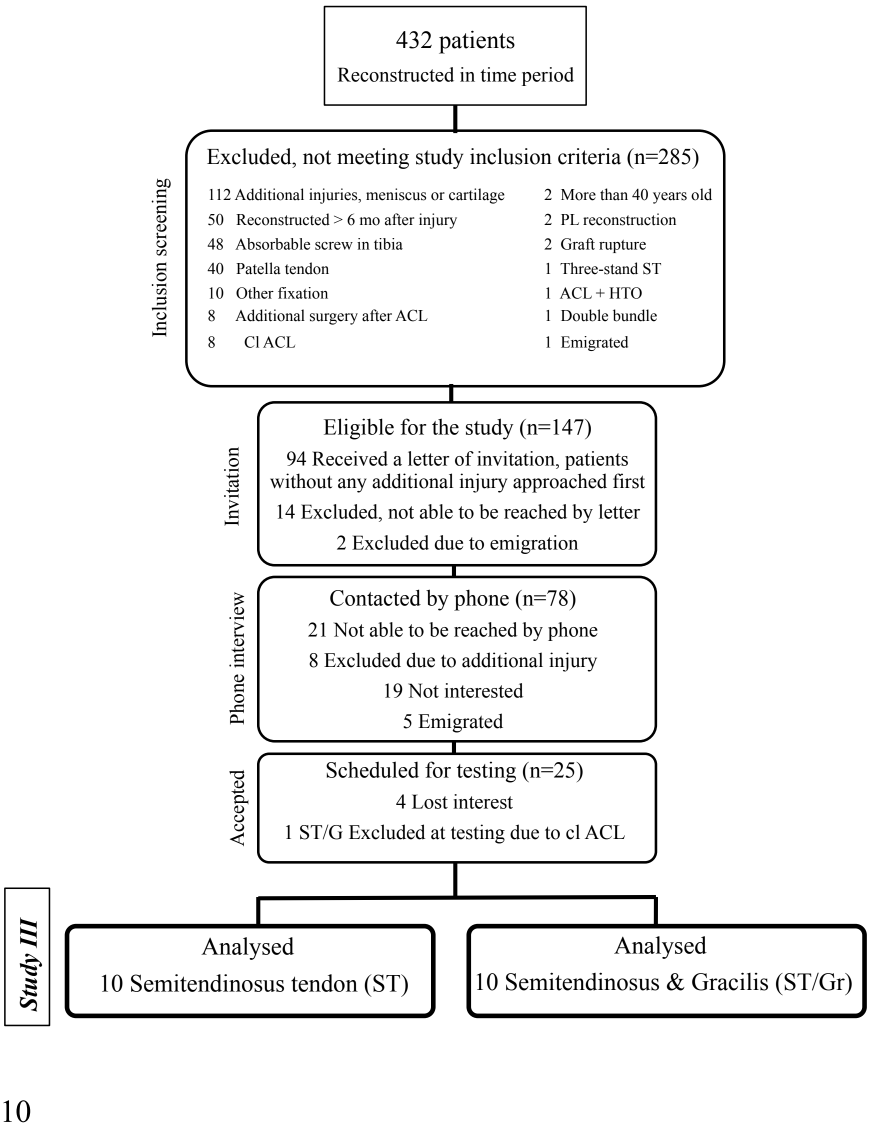
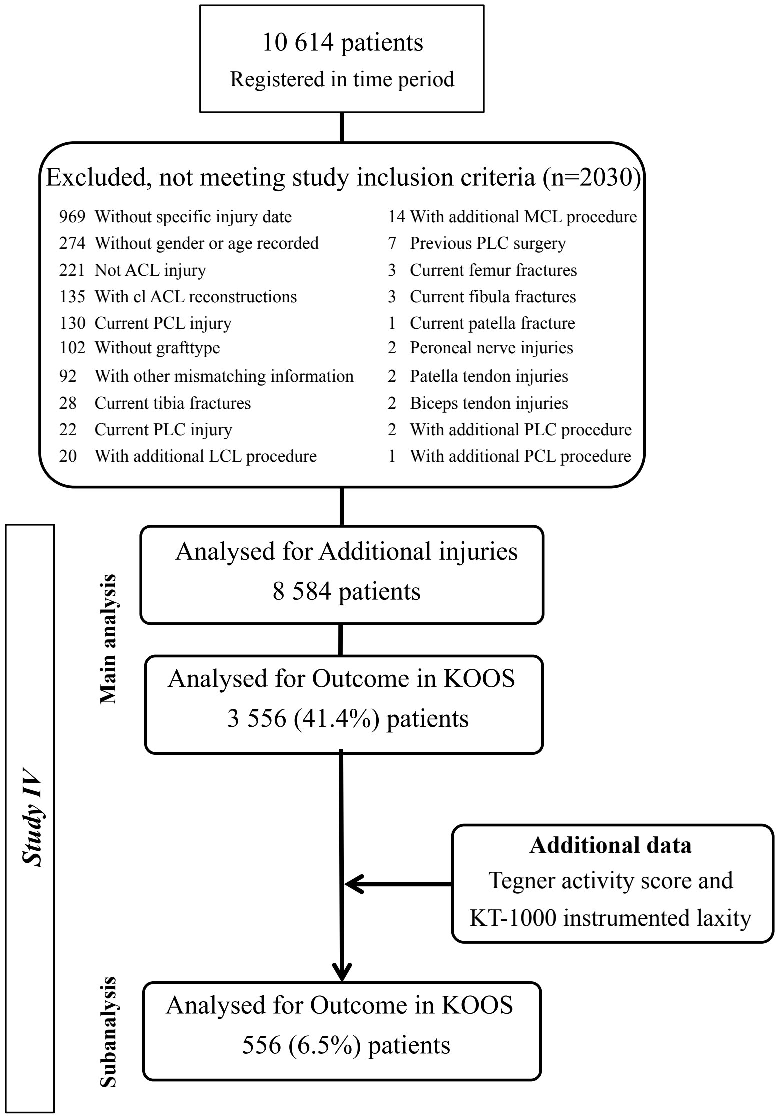


Figure 3 Flowchart for patients in *Study III*

4.3 STUDY IV

The patients included in *Study IV* were all registered as having an ACL injury in the Swedish National Knee Ligament Register between the start of the register in 2005 and the end of the study-period of 2008. The database was evaluated to exclude misclassification. In order to assess outcome after primary ACL reconstruction in relation to time between injury and reconstruction, patients in the register without a defined injury date and with other major injuries in addition to an ACL injury were excluded (Figure 4). The exclusion process left 8584 patients, and this cohort was analysed regarding additional injuries. There were 57.1% males, 57.8% were between 18 and 34 years old at the time of injury and 59.8% had reconstructions within one year after the injury. A cohort of 3556 (41.4%) of the patients had answered a complete KOOS two years after their reconstruction. This cohort was analysed regarding outcome in the KOOS. In this cohort there were 51.3% males and 54.9% were between 18 and 34 years old and 59.6% had reconstructions within one year after the injury. The impact of activity level and laxity on the outcome of KOOS was analysed for a cohort of 556 patients, with a complete KOOS and additional data regarding activity and laxity. In this cohort there were 51.4% males and 49.5% were between 18 and 34 years old and 66.2% had reconstructions within one year after the injury.

Figure 4 Flowchart for the patients in *Study IV*.



5 ETHICS

All studies were conducted according to the Helsinki Declaration and were approved before initiation by a local ethics committee. *Studies I, II and IV* were approved by the local Ethical Review Board in Stockholm and *Study III* was approved by the Faculty Human Ethics Committee (FHEC) of La Trobe University, Melbourne Australia.

6 METHODS

6.1 METHOD OF ACL RECONSTRUCTION

6.1.1 *Studies I and II*

The surgical technique used for the ACL reconstructions in *Studies I and II* was a one-incision arthroscopic reconstruction using a transtibial approach. Acufex® (Acufex, Microsurgical Inc., Mansfield, MA, USA) femoral and tibial guides were used for tunnel placement. Additional injuries to the menisci were assessed and treated with reinsertion with meniscus arrows, resection or expectancy at the diagnostic procedure and at the reconstruction. Eight experienced surgeons performed the reconstructions; notchplasty and meniscus treatment were carried out according to the surgeon's decision. Cyclic loading of the graft was done with 10 repetitions of full ROM before tibial fixation. The tibial fixation was done in full extension. The ST was harvested through an incision over the pes anserinus with a semi-blunt, semi-circular tendon stripper (Acufex, Microsurgical Inc., Mansfield, MA, USA). To maximise tendon length, approximately 15 mm of periosteum from the insertion to the tibia was harvested with the tendon. The four-strand tendon was fixed to mersilene tapes in both free ends with #2 Ethibond whipstitches. A traction table with 15 lbs. traction was used. The mersilene tape was tied to an Endobutton® (Acufex, Microsurgical Inc., Mansfield, MA, USA) for femoral fixation and the tape was tied to two AO screws with a washer for fixation to the tibia. The BPTB was harvested using the one-incision technique in 64 patients and a two-incision technique in 20 patients. The femoral fixation was done with a 7 x 20 mm titanium interference screw, and the tibia fixation with a similar 9 x 20 mm screw.[54]

6.1.2 *Study III*

The surgical technique for the ACL reconstructions in *Study III* was a one-incision arthroscopic reconstruction using a modified transtibial approach. The tendons were harvested through an oblique 3 to 4-cm incision over the pes anserinus. The semitendinosus tendon was always harvested first and the semitendinosus tendon length was measured. A minimum length of 26 cm for the semitendinosus tendon was required to perform a four-strand ST only reconstruction. The tendon graft was attached with a doubled 3mm Dacron tape to an Endobutton® (Smith and Nephew Endoscopy, Mansfield, MA, USA). The femoral tunnel was drilled using a transtibial technique, but with the starting point of the tunnel identified prior to tibial tunnel preparation, and the starting point of the tibial tunnel more medial and proximal than for a 'traditional' transtibial technique. The surgeon aimed to start the femoral tunnel at the '10 o'clock' orientation on the lateral wall of the intercondylar notch for a right knee, as visualised with the knee at 80° flexion, approximating the centre point of the femoral footprint of the ACL. Cyclic loading of the graft was done with 10 repetitions of full ROM before tibial fixation. The distal end of the graft was fixed with a metallic interference screw with the knee in 70 degrees of flexion with 67 N of traction applied to the graft.

6.1.3 *Study VI*

In the Swedish National Knee Ligament Register, there is no registration of surgical technique such as drill method, portal used or other surgical technique. The graft used, tunnel size and fixation used are recorded. In *Study VI* the grafts evaluated were semitendinosus only with 4 or more strands (ST 4), semitendinosus only with less than 4 strands (ST<4), semitendinosus and gracilis with 4 or more strands (ST/Gr 4), semitendinosus and gracilis with less than 4 strands (ST/Gr<4) and bone-patella tendon-bone (BPTB). In this study the fixation method and tunnel size were not evaluated.

6.2 METHOD OF REHABILITATION

6.2.1 *Studies I and II*

All patients used an unlocked Genu Syncro knee brace® (Syncro Med. GmbH, Linz, Austria) during walking for three weeks. The brace allowed 0–130 degrees of ROM. Full-weight bearing was allowed from the first day, with the assistance of crutches for the first three weeks. ROM and closed chain exercises were started on the first postoperative day with instructions by a physiotherapist. The brace was removed during the exercises. Open-chain exercises and running was allowed after 12 weeks. Before returning to cutting or contact sports, the patient's knee had to be assessed as functionally stable, a one-leg hop index of 90% had to be achieved and at least 6 months should have passed after reconstruction.

6.2.2 *Study III*

No brace was used and full-weight bearing was allowed as tolerated from the first postoperative day. The rehabilitation program encouraged immediate full extension and quadriceps function as soon as possible, with an emphasis on restoration of vastus medialis function. This was achieved through isometric exercises with the knee in full extension and closed-chain exercises during the first three months. The patients were allowed to ride a stationary bicycle after two weeks. Gymnasium exercises were allowed after 6 weeks and running after 10 weeks. Sports-specific drills were allowed after three months. No emphasis was placed on gait retraining.

6.2.3 *Study IV*

The register includes patients from all over Sweden. The rehabilitation after an ACL reconstruction registered in the Swedish National Knee Ligament Register probably ranges from none at all to exceptionally well-monitored individualised rehabilitation with a team of rehabilitation experts in a professional team setting.

6.3 PHYSICAL EXAMINATIONS

6.3.1 Lachman

The Lachman test was used in *Studies I–IV* to grade residual anteroposterior laxity.[188,214] Originally, Lachman was graded as positive if a 'soft end-point' was found, indicating a ruptured ACL, or negative if a 'hard end-point' was found, indicating an intact ACL. In this thesis a 4-grade scale of Lachman was used, with Grade 0 representing normal laxity, Grade 1 almost normal (5 mm side to side difference between limbs), Grade 2 clearly pathological (6–10 mm) and Grade 3 severe laxity (>10 mm).[9]

6.3.2 Pivot shift

The pivot shift test is a widely used clinical test that assesses both the translational and rotational component of instability in the knee joint, which in a real-life situation for the patient is often the cause of a giving way of the knee.[70] However, grading of the pivot shift test by the examiner is highly subjective, and the results cannot be generalised or compared between studies.[3,89,113] The pivot shift test was used to assess residual rotational laxity in *Studies I–IV*. Grade 0 equals an 'absent' pivot shift. Grade 1 is usually described as a 'glide', and Grade 2 as a clear pivoting motion or 'clunk'. Grade 3 represents a subluxating pivoting motion or 'pronounced clunk'.[99] In *Studies II and IV* the pivot shift was dichotomised to no pivot shift for grade 0 or positive for grades 1–3. In *Study III* the pivot shift was graded as nearly normal if there was a 'glide' or if there was any discernible difference in the pivot shift noted between the healthy contralateral limb and the operated limb, i.e. a difference that was 'less' than a glide.

6.3.3 Standing knee flexion angle

The standing knee flexion angle has been suggested to correlate with deep flexion strength, and therefore to be a simple test for strength loss after semitendinosus and gracilis tendon harvest.[1,151] The patient stands on the contralateral limb with the hip in neutral extension. The patient is asked to flex the limb to be tested maximally in the knee joint with the foot held in plantar flexion. The angle of the knee joint is measured with a goniometer (Figure 5). This test was used in *Study III*.

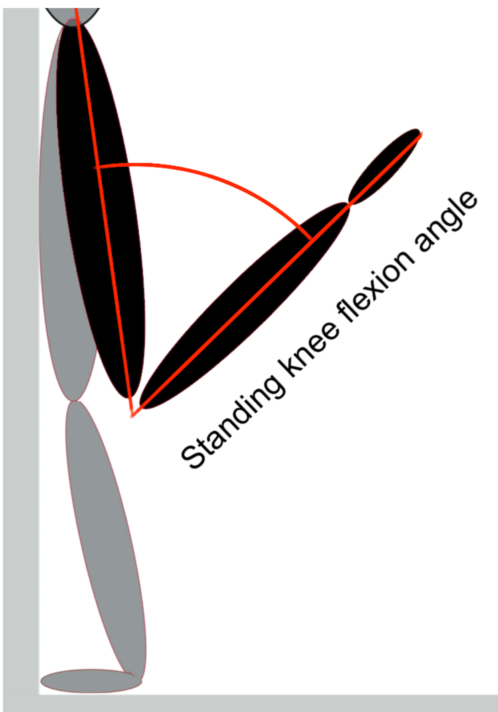


Figure 5
Standing knee flexion angle.
(©Björn Barenius)

6.3.4 Range of motion (ROM)

ROM was measured with a goniometer in *Studies I and III*. In *Study I* ROM was reported as a deficit in flexion and extension with reference to the healthy non-injured limb. In *Study III* the total ROM of the operated limb was compared to that of the healthy non-injured limb, and the deficit in the number of degrees measured was reported.

6.3.5 Area of disturbed sensitivity

In *Study I* the area of skin with disturbed sensitivity after graft harvest was measured in cm^2 according to Kartus.[107]

6.4 INSTRUMENTED LAXITY

6.4.1 KT-1000

The KT-1000 arthrometer (MEDmetric, San Diego, CA, USA) is one of the most frequently used instruments for measuring anteroposterior laxity in the knee joint. The reliability of the KT-1000 has been assessed in a number of studies including radiostereometry (RSA).[7,8,46,64,97] It can be used with different anterior forces applied, the most frequently used ones being 15 lbs. (67 N) and 20 lbs. (89 N). A force of more than 30 lbs. (>134 N) is usually referred to as 'manual max'. A higher applied force has been shown to correlate with higher accuracy of the test.[8,46] In *Studies III and IV* the KT 1000 was used to measure residual anteroposterior laxity after ACL reconstruction, using a manual max force. In *Study III* the instrument was calibrated according to the instructions of the manufacturers before each test.

6.4.2 Rolimeter®

The Rolimeter® is a validated instrument for measuring anteroposterior laxity in the knee joint.[22,173,191] It is used with manual max anterior force applied. It was used in *Study I*. The results are used in *Studies I and II*.

6.4.3 Stryker laxity tester

The Stryker knee laxity tester (OSI Stryker, Kalamazoo, MI, USA) is another validated instrument for measuring anteroposterior laxity in the knee joint.[7,8,84] The device was used at inclusion and at the two-year follow-up of the patient population used in *Studies I and II*. Testing was done at 20 lbs. (89 N) and 40 lbs. (178 N) of load. The results are used in *Studies I and II*.

6.5 FUNCTIONAL TESTS

6.5.1 One-leg hop

The one-leg hop test was used in *Study I*. The patients made three attempts to jump as far as possible with one limb at a time, jumping off and landing on the same leg. The longest jump for each limb was recorded. A percentage of the distance for the index limb with reference to the healthy limb was calculated. A resulting hop index of, for example, 100% would mean that a similar distance was reached with both limbs and, for a lower percentage, a shorter distance for the index limb. The one-leg hop test is a frequently used and reliable test for evaluating neuromuscular control and quadriceps strength.[71,157,193,227] A hop index of more than 85–90% has often been used for ACL-reconstructed patients to be regarded as sufficiently rehabilitated.[23,44,168]

6.5.2 Knee-walking test

To assess donor site morbidity after ACL reconstruction with a BPTB graft, Kartus et al. developed a knee-walking test (Figure 6).[107] The patients kneel with both knees on the floor and walk on their knees with their hands behind their back. The test has four grades: normal, unpleasant, difficult and impossible. It was used in *Study I*.

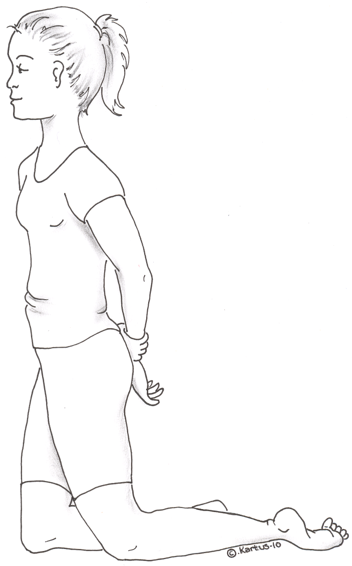


Figure 6
The knee-walking test. Published with the permission of C. Kartus.

6.5.3 Strength test with Biodex dynamometer

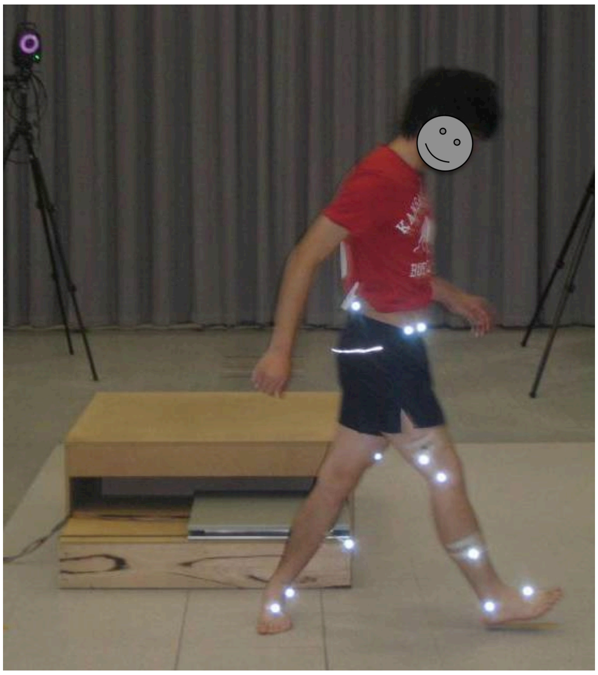
A number of manufacturers have developed instruments for evaluating the quadriceps and hamstring strength after ACL reconstruction in a standardised manner. One validated instrument is the Biodex dynamometer (Biodex Medical Systems Shirley, NY, USA) used in *Study III*.[209] It can be used with the patient to be tested in a number of positions, with a number of angular velocities for measuring isokinetic torque and a number of fixed angles for measuring isometric torque. In *Study III* the dynamometer was used with patients in a seated position. After a 5-minute warm-up on a stationary exercise bicycle, both limbs were tested with the healthy non-injured limb being tested first. The isokinetic test was performed at 60 degrees/s of angular velocity. Each test included five repetitions and the torque value at 90 degrees of flexion during the flexion motion was recorded. The first and last repetitions were excluded to minimise variance due to familiarisation or expectation aspects, and the three remaining values were averaged. A difference in torque was calculated with the healthy non-injured limb as reference. The isometric test was performed at 90 degrees of flexion. For this test, there were three repetitions and all repetition values were averaged.

Figure 7
The Biodex dynamometer used in *Study III*. (©Björn Barenius)

6.6 KINEMATIC EVALUATION

A considerable challenge in ACL research has been to evaluate functional instability after an ACL reconstruction. A number of instruments and evaluation methods have been developed to attempt to quantify the rotational component of the instability.[17,73,98,142,207] One method is the gait analysis used in *Study III*. This method uses infrared cameras at a high frequency. The cameras are used to track the position of a reflective marker in three dimensions in a calibrated volume of space. Using standardised placement of the markers on a patient, the system can calculate motion in a joint in extension/flexion, adduction/abduction and internal/external rotation from the relative position of the markers. The system used in *Study III* was an eight-camera three-dimensional motion analysis system with a sampling rate set to 100Hz (Vicon MX system, Oxford Metrics Ltd, UK). The system was calibrated according to the manufacturer's instructions prior to each data collection session. Measurements of the pelvis and lower limbs were obtained for each patient according to the manufacturer's manual and reflective markers were attached to the lower limbs using the standard Plug-in-Gait marker set.[48,103,163] To obtain a reference point for the knee joint for the markers, a static trial was performed with the patient in quiet standing. For this trial, the knee alignment device (KAD; Motion Lab Systems Inc., Baton Rouge, LA, USA) was used to determine the centre of the knee joint.[224] The markers for the lateral thigh and shin were attached to 6 cm-long wands. The wands were fixed to the skin with Micropore tape (3M, Maplewood, MN, USA) and all other markers were fixed directly to the skin with double-sided tape. Vicon Plug-in-Gait (Oxford Metrics Ltd, UK) biomechanical modelling software was used to process and output the data as kinematic profiles. Lower limb segment trajectories were filtered by fitting Woltring's quintic spline with a mean squared setting of 20 to the data prior to running the biomechanical model. Each patient first completed a minimum of 6 trials of walking at a comfortable pace to warm up and rule out major gait problems. The patients were then required to complete a stair descent and pivot activity (Figure 8). This task has been described previously and we essentially followed the same procedures as Ristanis et al.[175] All patients were instructed to descend and pivot at a self-selected pace as quickly as they could without feeling insecure. The two-step staircase used for the descend stairs and pivot task was made of timber and without handrails. It had a rise of 180mm, tread of 300mm and width of 1 meter. Patients were required to descend from the top step and, after foot contact with the ground, immediately pivot (external rotation on the stance limb) on the landing leg at 90 degrees and walk away from the staircase. A horizontal line was placed on the floor to indicate the direction of the 90-degree turn, which was to the right for the right limb and to the left for the left limb. A minimum of six trials was conducted for each limb with the healthy non-injured limb being tested first. The pivoting period was identified from initial foot contact with the ground with the limb to be tested until foot contact with the ground of the contralateral limb. Tibial rotation profiles were plotted and the maximum and minimum angular displacements were identified from each of the six trials for each subject. The variable of interest was the range of tibial rotation. It was determined by subtracting maximum and minimum angular displacements.[175,222]

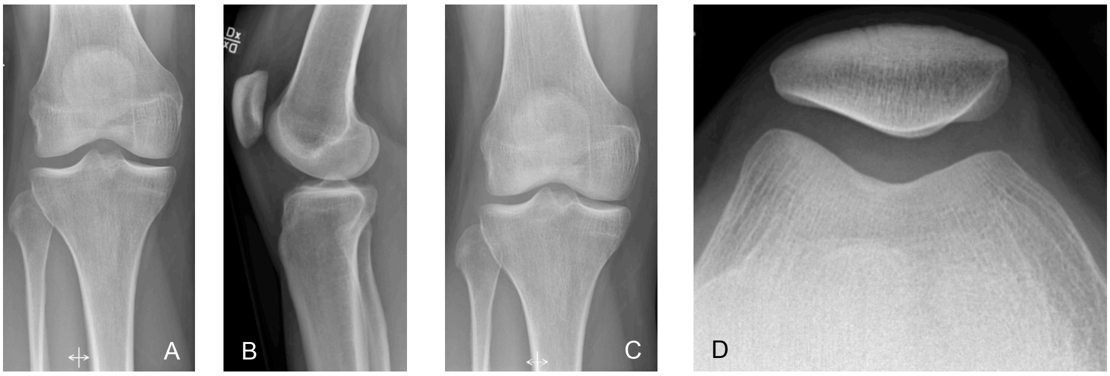
Figure 8
The pivoting task after a stair descent test in a gait laboratory. Note the infrared camera in the upper left corner and the reflective markers on the patient's lower limbs and pelvis. (© Björn Barenius)



6.7 RADIOLOGICAL EVALUATION

In *Study II* a radiological evaluation was performed. The radiographs were taken during weight bearing with anteroposterior and lateral views in full knee extension, an anteroposterior view with 30° of knee flexion and a skyline view of the patellofemoral compartment. Both limbs were examined in all patients (Figure 9).

Figure 9
The radiological views. (A) Anteroposterior, (B) lateral, (C) anteroposterior with 30° of knee flexion and (D) patellofemoral. (© Björn Barenius)



6.7.1 Radiological osteoarthritis (OA)

The level of OA was graded according to the classification systems of Kellgren & Lawrence,[109] Ahlbäck[2] and Fairbank.[57] The Ahlbäck and the Kellgren & Lawrence classifications are presented in Table 1. The AP view is used for the Fairbank classification. One point is given for flattening of the femur condyle, one point for a ridge formation and one point for joint space narrowing. Three is the maximum score for each compartment with a total maximum of six points for the tibiofemoral joint. Ahlbäck grade 1 was defined as a Kellgren & Lawrence grade 3, as seen in Table 1.[167] Three independent radiologists evaluated all the radiographs. We defined OA as a consensus of at least two of the three radiologists on a Kellgren & Lawrence grade of 2 or more.

Table 1
Ahlbäck and Kellgren & Lawrence (KL) classification with corresponding grades as used in *Study II.*

Ahlbäck Grade	Ahlbäck definition	KL Grade	KL definition
		Grade 1	Minute osteophyte, doubtful significance
		Grade 2	Definite osteophyte, no or minimal joint space narrowing
Grade 1	Joint space narrowing (joint space < 3mm)	Grade 3	Moderate joint space narrowing
Grade 2	Joint space obliteration	Grade 4	Greatly impaired joint space and subchondral sclerosis
Grade 3	Minor bone attrition (0–5 mm)		
Grade 4	Moderate bone attrition (5–10 mm)		
Grade 5	Severe bone attrition (>10 mm)		

6.7.2 Patella height

The Insall-Salvati index was used to measure patella height in *Study II*.[93] The senior author in *Study II* did all the measurements. The index is calculated by dividing the length of the patella tendon (TL) by the length of the patella (PL) as measured on a lateral view radiograph (Figure 10). The Insall-Salvati index for a normal patella height ranges between 0.8 and 1.2. An index below 0.8 represents a patella baja and above 1.2 a patella alta.[93] In *Study II* we defined patella infera as an index difference of more than 0.05 with a lower index in the ACL reconstructed limb than in the contralateral knee.

Figure 10
Insall-Salvati index. The ratio between tendon length (TL) and patella length (PL). (© Björn Barenius)

6.8 FUNCTIONAL SCORES

6.8.1 IKDC classification

The International Knee Documentation Committee (IKDC) developed an evaluation form to classify the outcome after knee ligament injuries.[82] The standard evaluation form consists of eight groups or problem areas: the patient's subjective assessment, symptoms, ROM, ligament examination, compartment findings, donor site pathology, radiological findings and functional tests. The first four groups are used for the final overall IKDC rating. Every evaluation point is rated as normal (A), nearly normal (B), abnormal (C) or severely abnormal (D). The lowest rating in every problem area determines the rating for that problem area. The lowest rated problem area determines the final overall IKDC rating. Results for the final overall IKDC rating and the ratings for the three objective problem areas are reported in *Study I*. In *Study II* the final overall IKDC grade from the 2-year follow-up was dichotomised to AB or CD and evaluated as a predictor of OA.

6.8.2 IKDC subjective knee form score (IKDC 2000)

In 2001 a new IKDC evaluation form was developed.[95] The IKDC 2000 Knee Form includes a demographic form, a current health assessment form, a subjective knee evaluation form, a knee history form, a surgical documentation form and a knee examination form. The subjective knee evaluation form used in *Study III* has been validated and found reliable.[95] It comprises an aggregated score with 10 items. Item 10 relates to knee function prior to injury and current knee function and is not included in the score. The item scores for items 1–9 are summed up and transformed into a scale from 0 to 100. A score of 100 is interpreted to mean no limitation in ADL or sport activities and no symptoms.

6.8.3 Lysholm score

The Lysholm score was used in *Study I.* [210] It is an aggregated functional score with 8 functions graded for a total maximum score of 100. The eight functions are: Limp (with maximum 5 points), Support (5 points), Locking (15 points), Instability (25 points), Pain (25 points), Swelling (10 points), Stair climbing (10 points) and Squatting (5 points). A result of less than 65 is often regarded as poor, 65–83 as fair, 84–94 as good and 95–100 as excellent.[11,53,87]

6.8.4 Tegner activity score

The Tegner activity score is a widely used score to grade numerically sport and work activities on a scale from 0 to 10 (Table 2). The score was presented by Tegner and Lysholm in 1985 and was meant to be used in combination with the Lysholm score.[210] The Tegner score was used in combination with the Lysholm score in *Study I* and separately in *Studies II and IV*. The patients assessed their activity level before injury and at the current follow-up and indicated a desired activity level at the current follow-up. The interval from 7 to10 corresponds to competitive sports, 4 to 6 to recreational sports and 0 to 3 to activities of daily life.

Table 2
Tegner activity score.

Tegner Activity	Definition of Activity
10	Competitive sports: Soccer – national and international elite
9	Competitive sports: Soccer – lower divisions, Ice Hockey, Wrestling, Gymnastics
8	Competitive sports: Bandy, Squash, Badminton, Athletics (Jumping & similar.), Downhill skiing
7	Competitive sports: Tennis, Athletics (running), Motor Cross, Speedway, Handball, Basketball Recreational sports: Soccer, Bandy, Ice Hockey, Squash, Athletics (Jumping), Cross-country Track Finding (competitive and recreational)
6	Recreational sports: Tennis, Badminton, Handball, Basketball, Downhill Skiing, Jogging at least 5 times per week
5	Competitive sports: Cycling, Cross-country Skiing Recreational sports: Jogging on uneven ground at least twice weekly Work: Heavy Labour (i.e. building, forestry)
4	Recreational sports: Cycling, Cross-country Skiing, Jogging on uneven ground at least twice weekly Work: Moderately Heavy Labour (i.e. truck driving, heavy domestic work)
3	Competitive & recreational sports: Swimming, Walking in forest possible Work: Light Labour (e.g., nursing)
2	Walking on uneven ground possible but impossible to walk in forest Work: Light Labour
1	Walking on even ground possible Work: Sedentary
0	Sick leave or disability pension due to knee problems

6.8.5 Werner patellofemoral score

A modified patellofemoral score of Werner et al. was used in *Study I* (Table 3).[225] The Werner patellofemoral score is an aggregated functional score covering eight functions with a maximum score of 50 points. In the modified score used, the maximum score is 55 points with a modification of the eight functions tested. Pain is graded in two functions with a maximum total of 30 points and the original functions Limp, Feeling of instability and Swelling have been omitted and a function of Sitting with bent knees for more than 30 minutes has been introduced.

Table 3
Modified patellofemoral score according to Werner

Maximum score 55 points (best)			
Pain		**Sitting with bent knees** (more than 30 min.)	
Never	5	No problems	5
Light and infrequent	3	Light problems	4
Constant	0	Difficulties	2
		Unable	0
Pain, occasional		**Squatting**	
Never	20	No problems	5
During or after running	15	Light problems	4
When stair-walking	12	Difficulties	2
After walking > 2 km	9	Unable	0
After walking < 2 km	6		
When walking	3		
At rest	0		
Stair-walking, up stairs		**Kneeling**	
No problems	5	No problems	5
Light problems	4	Light problems	4
Difficulties	2	Difficulties	2
Unable	0	Unable	0
Stair-walking, down stairs		**Catching**	
No problems	5	Never	5
Light problems	4	Sometimes	3
Difficulties	2	Frequent	0
Unable	0		

6.8.6 VAS 1 and VAS 2

In *Study I and II* the patients rated their knee function after the reconstruction on a visual analog scale from 0 – 100 (0 worst possible score, 100 best possible score). VAS 1 was the question ‘How does your knee function?’ and VAS 2 ‘How does your knee function affect your activity level?’
In *Study II* the patients were asked only VAS 1.

6.9 HEALTH-RELATED QUALITY OF LIFE EVALUATION

6.9.1 Knee Osteoarthritis Outcome Score (KOOS)

The KOOS is a knee-specific HRQoL instrument that was developed to assess the patient's opinion about their knees and associated problems. KOOS consists of five subscales: Pain, Other symptoms (Symptoms), Function in daily living (ADL), Function in sport and recreation (Sp/Rec), and Knee-related quality of life (QoL).[180] The patients answer 9 questions to assess Pain, 7 questions to assess Symptoms, 17 questions regarding ADL, 5 questions regarding Sp/Rec and 4 questions regarding QoL. All questions are graded from 0 to 4 points. A normalised score for each subscale is then calculated with a maximum of 100 points indicating no symptoms and 0 points indicating extreme symptoms. KOOS has been used in a number of studies to assess HRQoL after ACL injuries.[25,75,117,130,136] KOOS provides an outcome measure for all of the Scandinavian Knee Ligament Registers.[79] It was used in *Studies I, II and IV.*

6.9.1.1 Symptomatic OA

In *Study II* Lohmander et al.'s definition of symptomatic knee problems according to KOOS was used.[131] Patients with a KOOS below 87.5 for the subscale QoL combined with a score below the cut of level for any two of the other subscales, ≤ 86.1 for pain, ≤ 85.7 for symptoms, ≤ 86.8 for ADL, ≤ 85.0 for Sports/Rec, were defined as having symptomatic knee problems (Figure 11). Patients with symptomatic knee problems according to this definition and radiological OA were defined as having symptomatic OA.

6.9.1.2 Functional recovery

In *Study IV* we defined a level of KOOS that the patients had to score above to be considered to have a functional recovery (FR). We based our definition on a published Swedish reference population.[166] The FR level was defined as the lower threshold for the 95% CI of 18–34-year-old males. Subsequently, for the patient to be classified as being in FR, all KOOS subclasses had to be above the following scores: 90 for Pain, 84 for Symptoms, 91 for ADL, 80 for Sp/Rec and 81 for QoL (Figure 11).

6.9.1.3 Treatment failure

In *Study IV* a previously published definition of treatment failure (TF) according to KOOS was used.[66] A patient with a score below 44 on the subscale QoL was defined as being in TF (Figure 11).

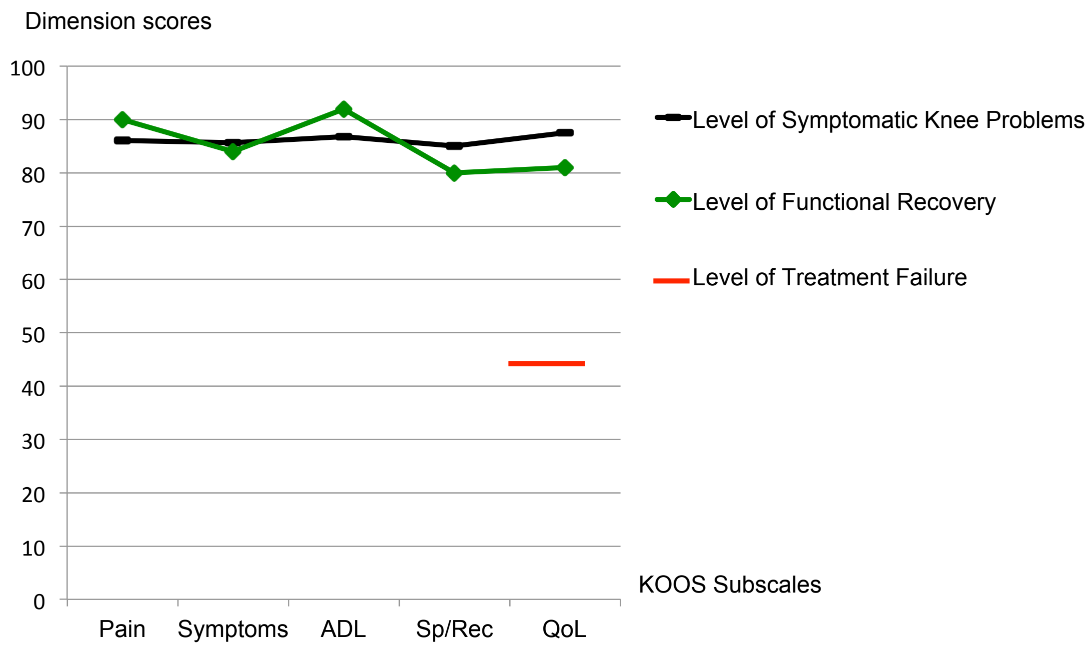


Figure 11
KOOS definitions: Level of Symptomatic Knee Problems: any subscale score below black line, Level of FR: all subscale scores above green line, Level of TF subscale: QoL scores below red line.

6.9.2 Short Form 36 (SF-36)

The SF-36 is an HRQoL instrument comprising 36 items concerning physical and mental function.[202] Ten of the items require recoding. Raw scale scores are computed by summing up across items. The raw scale scores are then transformed into a final score of 0–100 on the eight subscales: Physical Functioning (PF), Role Limitations due to Physical Function (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Limitations due to Emotional Problems (RE) and Mental Health (MH). The SF-36 was used in *Study I*.

6.10 OTHER SUBJECTIVE PATIENT EVALUATIONS

6.10.1 Experienced sensory loss

In *Study I*, the patient's subjective experience of disturbed sensitivity after the graft harvest was analysed with the question 'Do you experience a sensory loss?' The answer was graded at 3 levels: (1) No sensory loss, (2) Disturbed sensitivity and (3) Lost sensitivity.

6.10.2 Harvest-related hamstring problems

In *Study III* the patients were asked if they had experienced hamstring pain or other hamstring problems after their ACL reconstruction. They were asked in what situations they had their problems and if they had received any diagnosis or treatment for the problem.

7 STATISTICAL METHODS

The statistical software SPSS™ was used in all studies. In *Studies II and IV* the statistical software R v 2.14.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for analyses of collinearity, interactions, consistency and goodness of fit. In all studies the tests were two-sided and the results were considered significant at $p < 0.05$. In all studies descriptive statistics for nominal variables were analysed using the $\chi 2$ test or the Fisher exact test for expected distributions of 5 or less. Ordinal variables and non-normally distributed interval and ratio scale variables were evaluated with the Mann-Whitney U test, and Student's t test was used for normally distributed interval and ratio scale variables in independent groups. The related samples t test and the Wilcoxon matched-pair signed-rank test were used for variables with measurements from more than one time point. In addition to these tests other statistical methods were used in some studies. They are presented below.

7.1 STUDY I

The Tegner activity score, the Lysholm score, VAS 1 (How does your knee function?) and VAS 2 (How does your knee affect your activity level?) are presented as medians with range values and were analysed as ordinal variables.

7.2 STUDY II

Logistic regression modelling was used to assess predictors of OA, estimated by odds ratios (OR) with 95% confidence intervals (CI). A p value of less than 0.1 after univariable regression was used to select variables to be included in the multivariable analysis. Age at injury was determined to be more interesting than age at the follow-up as a predictor, and only age at injury was included in the multivariable analysis. Time since reconstruction was not included in the multivariable analysis due to its low predictive value. When predictors of the same type were significant only the strongest predictor in the univariable analysis was evaluated in the multivariate analysis in order to minimise interactions. When the Tegner activity score was included in a regression the variable was categorised to 0-3, 4-6 or 7-10. The inter-rater correlation coefficient to assess inter-rater reliability was calculated using Fleiss' kappa for n raters. An Intraclass correlation coefficient (ICC) for the Insall-Salvati index measurement was calculated for 10% of the patients in *Study II*. There was no indication of multicollinearity, no outliers affecting the models and no interactions were found that changed the significance of the models. Discrimination of the models was tested with c-statistics and goodness of fit with Hosmer & Lemeshow's test.

7.3 STUDY IV

Univariable logistic regression was used to evaluate possible predictors before the final multivariable logistic regression model was chosen. A p value of less than 0.1 after univariable regression was used to select variables to be included in the multivariable analysis. As a consistency analysis, age and waiting time before surgery as continuous variables were also modelled using restricted cubic splines to evaluate whether or not these variables had non-linear effects. The final multivariable regression models were further analysed. All two-way interactions between all included variables were tested. The Cessie van Houwelingen goodness-of-fit test was used to test the validity of the final models of multivariable logistic regression and discrimination was tested using c-statistics. Multicollinearity was investigated using the variance inflation factor (VIF).

8 EVALUATION OF METHODS

8.1 GAIT ANALYSIS

One of the limitations of marker-based gait analysis in measuring knee rotation motion is that it may be subject to error due to marker misplacement and artefacts from skin movement. The artefact from skin movement on markers decreases the sensitivity and possibly makes measurements of rotation in the knee joint unreliable due to measuring close to the margin of error. Benoit et al. showed that a marker fixed in bone was more reliable than a skin marker, using RSA as a reference, they found large interindividual variation in rotational excursion and larger absolute values with skin markers in healthy subjects.[27,28] Bone-fixed markers have mainly been used earlier to improve the reliability of the gait analysis error correction.[6] Isberg et al. used RSA to measure rotational laxity.[98] However, the invasive nature of RSA and bone-fixed markers limits their usefulness for testing real-life situations. The error arising from marker misplacement is substantially reduced when the assessors are experienced.[141] Therefore, to minimise this error in *Study III,* all measurements were done by the same two assessors with over 10 years of experience in gait analysis. Good repeatability of data from these assessors has been reported.[222] There are now a number of publications on rotational laxity after ACL reconstruction using marker-based gait analysis.[73,120,147,175,215,221,224] They all report comparable values regarding rotational laxity. Even if the reported values do not reflect the true knee kinematics, the correlation and repeatability between studies are good. With the limitations of the method in mind, gait analysis is a useful way to test knee laxity with pivoting tasks in simulated real-life situations to compare different ACL reconstructive methods.

8.2 RADIOLOGICAL OA

One reason for the variety in prevalence of OA after ACL reconstruction is the definition of radiological OA according to different grading systems. The most usual radiographic classification systems for grading osteoarthritic changes in the knee joint after ACL injury are those of Kellgren and Lawrence,[109] Ahlbäck,[2] Fairbank,[57] and the IKDC.[82] Cartilage loss and osteophyte formation are both features of a degenerative process in the knee joint. Systems that take both cartilage thickness and other radiological signs, such as osteophytes and cysts, into account have higher validity in the OA definition.[122] Regardless of the classification system used, they all have an inter-observer variation due to the subjective interpretation of each radiographic appearance. In *Study II* three radiologists classified the radiological OA according to Kellgren and Lawrence, Ahlbäck and Fairbank. There were two radiologists specialised in skeletal radiology and one with another speciality. The use of three radiologists should increase the specificity of the diagnosed radiological OA in *Study II*. However, the subjective interpretation of each radiographic appearance is still present. This is apparent in *Study II*, where the intercorrelation coefficient between the radiologist pairs differs and the combined intercorrelation coefficient for the three radiologists is low.

The intracorrelation coefficient for the Insall-Salvati index was good with ICC of 0.85 for the index limb and 0.91 for the non-injured limb.

8.3 STRENGTH TESTING WITH BIODEX®

Strength tests are influenced by compliance with the testing apparatus, placement of the test subject, experience of the testing situation, psychological aspects around the testing situation, injuries and other influencing factors. Strength test results show wide variance, and large numbers of test subjects are needed to avoid type I and type II errors. The strength test results from *Study III* should be interpreted with caution.

8.4 INSTRUMENTED LAXITY

The devices used are reliable, but a direct comparison between them is not accurate, which makes a comparison of laxity over time in *Studies I and II* unreliable.[84]

9 SUMMARY OF PAPERS

9.1 STUDY I

9.1.1 Introduction

There are few RCTs with patient-assessed HRQoL that report mid- to long-term results for ACL reconstruction with the BPTB graft, the previous gold standard procedure, compared to the currently more frequently used hamstring tendon ACL reconstruction. The aim of the study was to compare the clinical outcome and HRQoL at least 6 years after ACL reconstruction with a ST or BPTB graft. The hypothesis was that the ST reconstruction would perform as well or better than the BPTB.

9.1.2 Material and Methods

During 1995–97, 164 patients were randomised to receive ACL reconstruction with an ipsilateral BPTB or a four-strand ST graft. For fixation, an Endobutton® on the femoral side and a suture over a post for the tibia was used in the ST group and interference screw on the femoral and tibial sides for the BPTB group. At a mean of 8.4 years (SD = 0.98) after the reconstruction, 153 (93%) patients (78 BPTB and 75 ST) were evaluated by an independent physical therapist. The evaluation included a physical examination comprising ROM, Lachman, pivot shift, patient rating of sensory loss, and knee function with two VAS questions, instrumented laxity with the Rolimeter®, functional tests with a one-leg hop and the knee-walking test according to Kartus. Functional scores were the Lysholm, Tegner activity score, the modified Werner patellofemoral score and the IKDC. HRQoL was assessed with SF-36 and KOOS.

9.1.3 Results

Fifty-seven per cent of all males were in the ST group at the follow-up compared to 43% in the BPTB group (p=0.016); otherwise, the groups were similar regarding demographic data. The mean age at follow-up was 34 years (SD=7). The graft groups were similar in all comparisons except for the Kartus knee-walking test, with more problems in the BPTB group, i.e. 24 patients with no problems, 22 with slight problems, 22 with moderate problems and 10 with severe problems, compared to 46, 17, 6 and 6 in the ST group (p<0.001) and the function kneeling reflected in the Werner patellofemoral score with 19 patients with no problem with kneeling, 23 with light problems, 31 with moderate problems and 5 unable to kneel in the BPTB group and 25, 32, 16 and 2 in the ST group (p<0.001). The BPTB group also reported more pronounced sensory loss than the ST group. The patients with early reconstructions (< 6 months) had fewer meniscus injuries, 37% vs 62% in those with late reconstructions (p=0.008), the early reconstructed also had a higher activity level, median 6 vs 3 (p<0.001). KOOS showed no clinical difference for early vs late reconstruction with a difference of 5 points for ADL, Sp/rec and 6.5 points for QoL, but a statistical difference for ADL (Figure 12). There were significant differences in the SF-36 for the subscales PF, BP and SF (Figure13).

9.1.4 Conclusion

The hypothesis was proved with a similar result found for the ST and the BPTB graft in regard to stability, functional tests, functional scores and HRQoL, but with more donor site-related morbidity still present after 8 years in the BPTB group.

In this study patients having reconstructions after less than 6 months had sustained fewer meniscus injuries, were more active and had a better HRQoL according to SF-36 than those with late reconstructions.

Figure 12
Mean KOOS scores for patients with reconstructions less than 6 months from injury, green line, and patients with reconstructions after ≥ 6 months, blue line. The yellow arrow represents what is considered to be a clinically significant difference in KOOS.

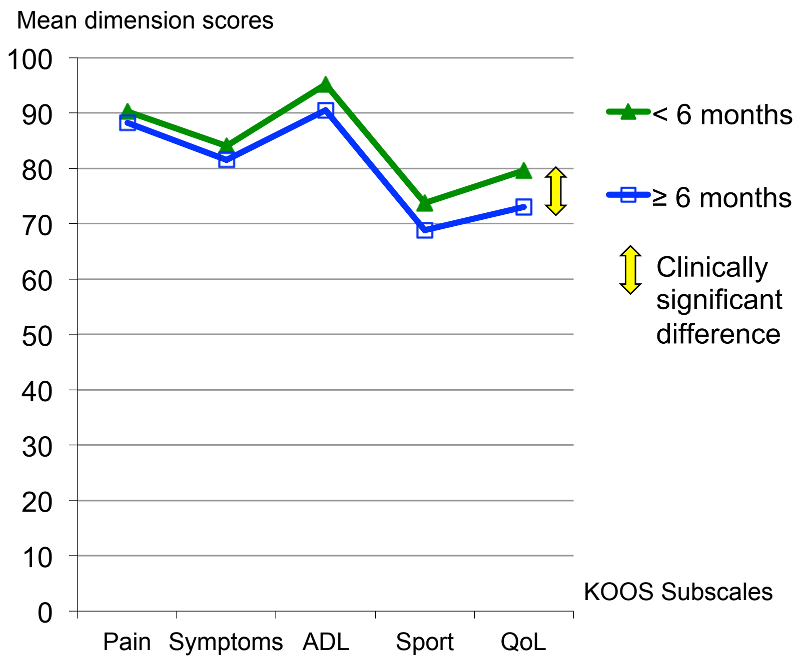
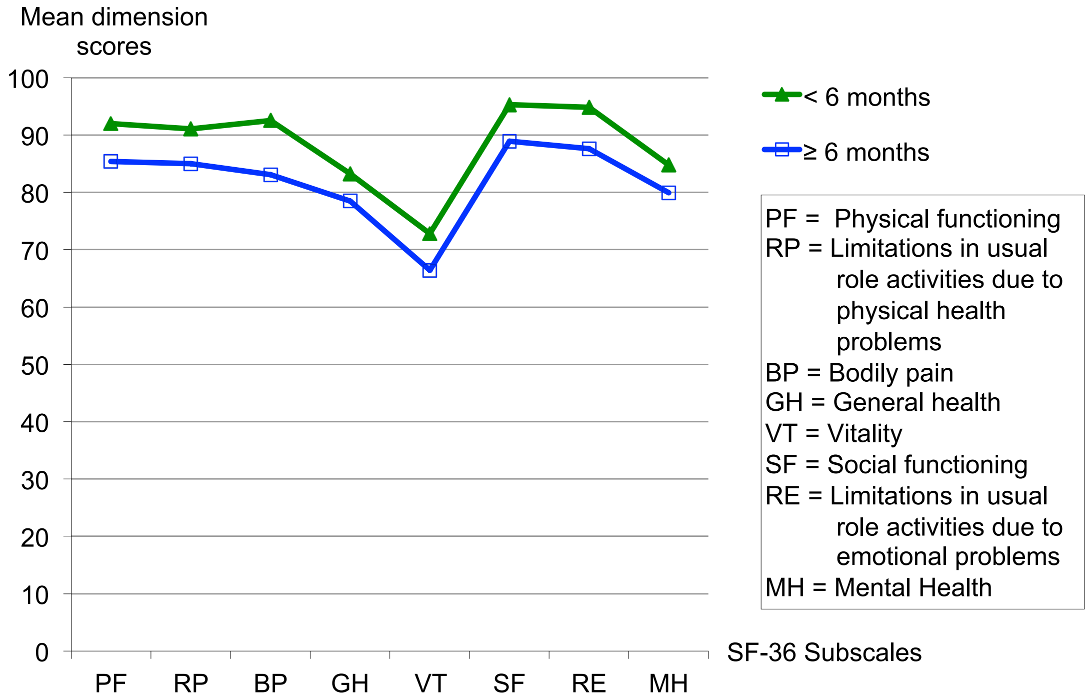


Figure 13
Mean SF-36 results for patients with reconstructions less than 6 months from injury, green line, and patients reconstructed after ≥ 6 months, blue line.



9.2 STUDY II

9.2.1 Introduction

The true prevalence of OA after an ACL injury and the effect of an ACL reconstruction on the prevalence of OA are unclear. The reported prevalence varies and there are few long-term follow-ups of randomised studies. The aim of this study was to compare the prevalence of radiological OA after an ACL reconstruction at a minimum of 10 years after randomisation to an ACL reconstruction with a BPTB or ST graft. The hypothesis was that the grafts would have similar prevalences of OA. A secondary aim was to assess predictors of OA.

9.2.2 Material and Methods

The same study population as in *Study I* was used. At a mean of 14.1 years (SD=0.5) after the reconstruction, 135 (82%) patients (69 BPTB and 66 ST) were available for an evaluation. One patient was excluded from the analysis due to a TKA in the index limb. The evaluation included the Tegner activity score, KOOS, VAS 1 and a radiological examination of both limbs with an AP view in extension and 30° of flexion a lateral view in extension and a skyline view of the PF compartment. Patella height was assessed with the Insall-Salvati index. Radiological OA was classified according to Ahlbäck, KL and Fairbank by three independent radiologists. Ahlbäck grade 1 was defined as similar to KL grade 3. Radiological OA in the study was defined as a consensus of at least two of the three radiologists of KL≥2. Variables from the inclusion, index reconstruction and two-year follow-up were assessed for their predictive value regarding OA in the medial, lateral and PF compartments. Symptomatic OA was evaluated using a definition of symptomatic knee problems according to KOOS in addition to the radiological findings.

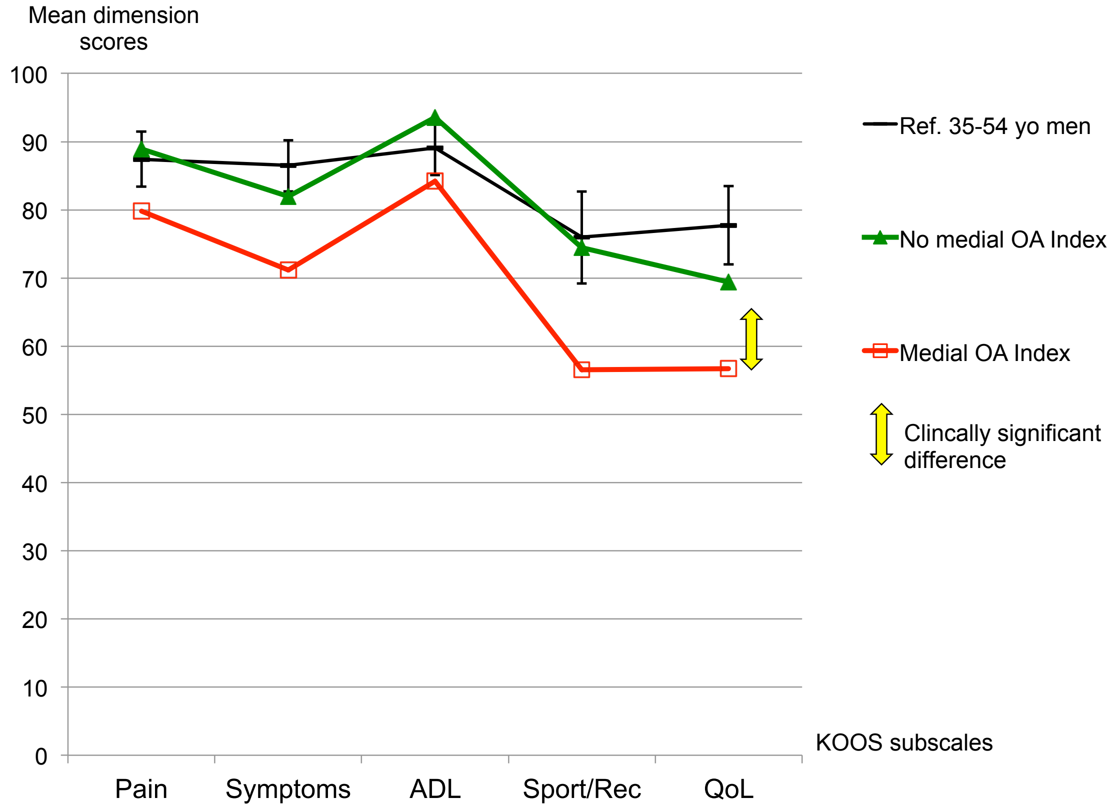
9.2.3 Results

The difference in gender between the graft groups was still present in this study population, 49% females in the BPTB group vs 32% in the ST group (p=0.046). There were more lateral meniscus resections in the ST group, 32%, compared to 15% in the BPTB group (p=0.015), and a higher prevalence of OA in the lateral compartment in the ST group, 31%, compared to 16% in the BPTB group (p=0.042); otherwise, the graft groups were similar in all comparisons. For all compartments, a higher prevalence of OA was found for the ACL reconstructed limb compared to the initially healthy contralateral limb (p<0.05 for all comparisons). Time between injury and reconstruction was not found to be a predictor of OA, but was a predictor for an injury and a resection of the medial meniscus. In the multivariable analysis of predictors of OA, graft type was not a predictor. Medial meniscus resection was a predictor of medial compartment OA with an OR of 3.6 (95% CI 1.4–9.2) and lateral meniscus resection for lateral compartment OA, with an OR of 4.5 (95% CI 1.8–11.5). BMI≥25 at the 2-year follow-up was a predictor of medial compartment OA, with an OR of 3.1 (95% CI 1.2–7.9), and PF compartment OA with an OR of 2.8 (95% CI 1.1–6.9). A majority of patients with OA was symptomatic. Medial compartment OA in the index limb resulted in a statistically and clinically significantly lower KOOS (Figure 14).

9.2.4 Conclusion

Our hypothesis was proved with a similar prevalence of OA found in both graft groups. The ACL reconstruction did not protect the knee joint from OA. A meniscus injury requiring resection was the strongest predictor of OA. An ACL reconstruction might decrease the risk of OA in patients with instability if the reconstruction is performed before an additional meniscus injury has occurred.

Figure 14
Mean KOOS for patients without medial compartment OA, green line, and with medial compartment OA in the index limb, red line. The black line with error bars represents a reference population of 35-54 years old men with 95% CI.[166] The yellow arrow represents a clinically significant difference in KOOS.



9.3 STUDY III

9.3.1 Introduction

Graft harvest-related morbidity is one of the factors considered when outcomes after ACL reconstruction are analysed. The persisting problems with kneeling, knee standing, loss of sensitivity and anterior knee pain after BPTB harvest are partly responsible for the rapid decline in the use of this graft. The hamstring graft most frequently used now also has graft-related morbidity, with muscle weakness in flexion frequently being reported. There are reports that the morbidity is less if the gracilis is spared and only the semitendinosus tendon is used. The aim of this study was to compare single bundle ACL reconstructions using the ST/Gr or ST graft, with regard to morbidity and function, including rotational stability. Our hypothesis was that the ST graft would provide a more stable reconstruction with less morbidity.

9.3.2 Material and Methods

Twenty patients (10 ST and 10 ST/Gr) agreed to be evaluated at a mean 36 (range 27–45) months after their ACL reconstruction. They were selected to have few additional injuries, no current hip or ankle problems and no history of giving way after the reconstruction. The evaluation consisted of a physical examination with ROM and laxity measured by Lachman, pivot shift and KT-1000. The IKDC2000 subjective knee evaluation form was used and the patients were asked questions regarding instability, sport activity and hamstring problems. Strength was measured with a Biodex dynamometer. Rotational stability was assessed with three dimensional gait analysis during a 90-degree pivot task after descending a stair. The tibial rotational range of motion was evaluated.

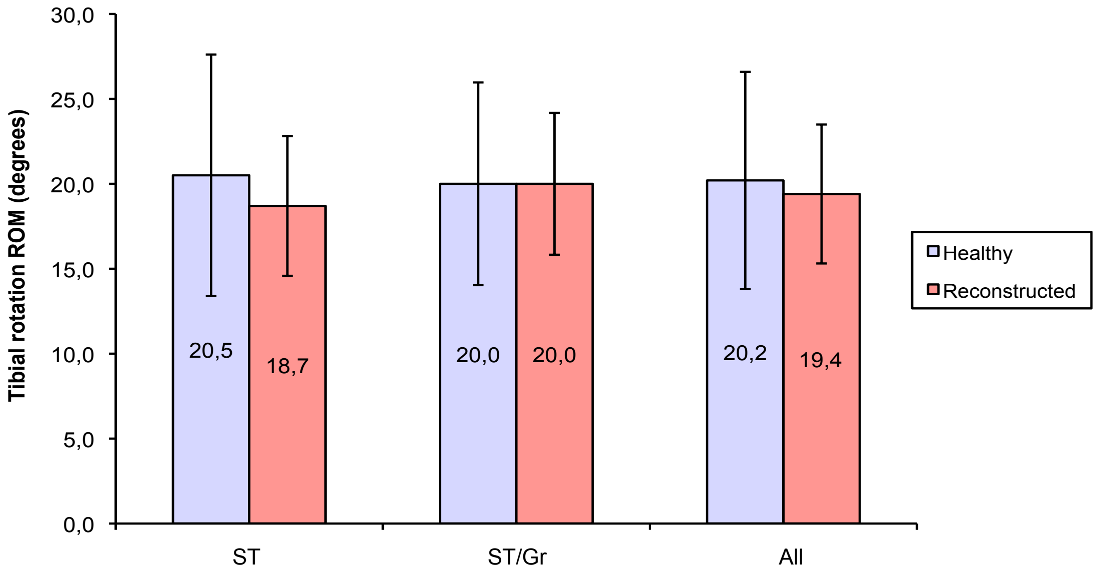
9.3.3 Results

The groups were similar regarding age and gender, time between injury and reconstruction, time between reconstruction and follow-up and additional injuries. The ST group was taller. The ST graft had a larger diameter (mean 8.7 mm, SD = 1) than the ST/Gr graft (mean 7.5 mm, SD = 1), (p=0.01). Patients had decreased flexion strength in their ACL-reconstructed limb between 20% and 36% at 90 degrees of flexion and had lost some active flexion ROM but there was no difference between the graft groups. No difference in laxity or the IKDC2000 score was found. The rotational stability was similar between the groups and was comparable to that of the healthy non-injured limb for both graft groups (Figure 15). Episodic hamstring problems were frequent after the reconstruction and were reported by 11 of 20 patients (55%). Ten per cent of the patients reported persistent hamstring problems.

9.3.4 Conclusion

In this study a hamstring ACL reconstruction had persistent donor site morbidity from decreased deep flexion strength and hamstring problems of varying types. The stability was similar between the graft groups and the hypothesis of higher morbidity in the ST/Gr group could not be proved.

Figure 15
Range (SD) of tibial rotation measured by gait analysis in degrees. Blue columns, healthy non-injured limb; red columns, ACL reconstructed limb. (ST) semitendinosus tendon group, (ST/Gr) semitendinosus and gracilis tendon group, (All) combined data for the whole cohort.



9.4 STUDY IV

9.4.1 Introduction

The effect of additional injures on the outcome after ACL reconstruction might be hard to evaluate in most studies due to sample size. The experience of many ACL surgeons is that the time between injury and reconstruction (TIR) matters for the frequency of additional injuries found at the time of reconstruction and the outcome after the reconstruction. The aim of this study was to evaluate the effect of TIR and additional injuries on the outcome after ACL reconstruction in a large cohort. The hypothesis was that early reconstructions would be more frequent among the patients with the highest KOOS outcome and that they would have fewer additional injuries.

9.4.2 Material and Methods

A cohort from 2005 to 2008 from the Swedish National Knee Ligament Register was used. After exclusion of 2030 patients with a revision ACL, a multiligament injury, a cl ACL injury or a PCL injury or patients without a defined injury date, 8584 patients were included in the study. A complete KOOS was recorded for 3556 (41.4%) of the patients two years after the reconstruction. To assess predictors of a high or low KOOS result, we defined a level of KOOS required to be in functional recovery of above 90 for the subscale Pain, 84 for Symptoms, 91 for ADL, 80 for Sp/Rec and 81 for QoL and used a previous definition of treatment failure as a KOOS subscale QoL≤44. A number of variables were assessed for their predictive value regarding functional recovery and treatment failure. For 556 patients, data regarding activity levels and instrumented laxity using the KT-1000 were available and these patients were also assessed for the predictive value of laxity and activity in regard to functional recovery or treatment failure. The effect of different variables on the frequency of additional injuries to the meniscus and cartilage was assessed in an analysis of all the 8584 patients.

9.4.3 Results

Two years after the ACL reconstruction 19.7% of the patients were in functional recovery and 28.9% in treatment failure. The strongest predictor for FR was graft type and the strongest negative predictor was previous meniscus surgery (Figure 16). The strongest predictors for treatment failure were medial meniscus surgery at the time of reconstruction and previous meniscus surgery; the strongest negative predictor was graft type (Figure 17). Increasing TIR increased the risk of medial meniscus injury and cartilage lesions found at the time of reconstruction. Lateral meniscus injuries found at the reconstruction were more frequent for patients having reconstructions < 3months from injury, patients with an additional collateral ligament injury and among males.

9.4.4 Conclusion

The hypothesis was only partly proven as time between injury and reconstruction only increased the risk of additional injuries found at the time of reconstruction and did not affect the outcome directly. However, the chain of events with increasing additional injuries with increasing time between injury and reconstruction and less functional recovery and more treatment failure for patients requiring surgery for additional injuries led us to conclude that timing does matter for the outcome. Patients with instability should undergo reconstruction before ‘giving way’ has led to additional injuries in order to increase the chance of a functional recovery.

Figure 16

Functional recovery (FR), multivariable model. Odds ratios (OR) for all predictors included in the model presented with 95% CI and p value. For stratified predictors, the reference value is presented in parentheses.

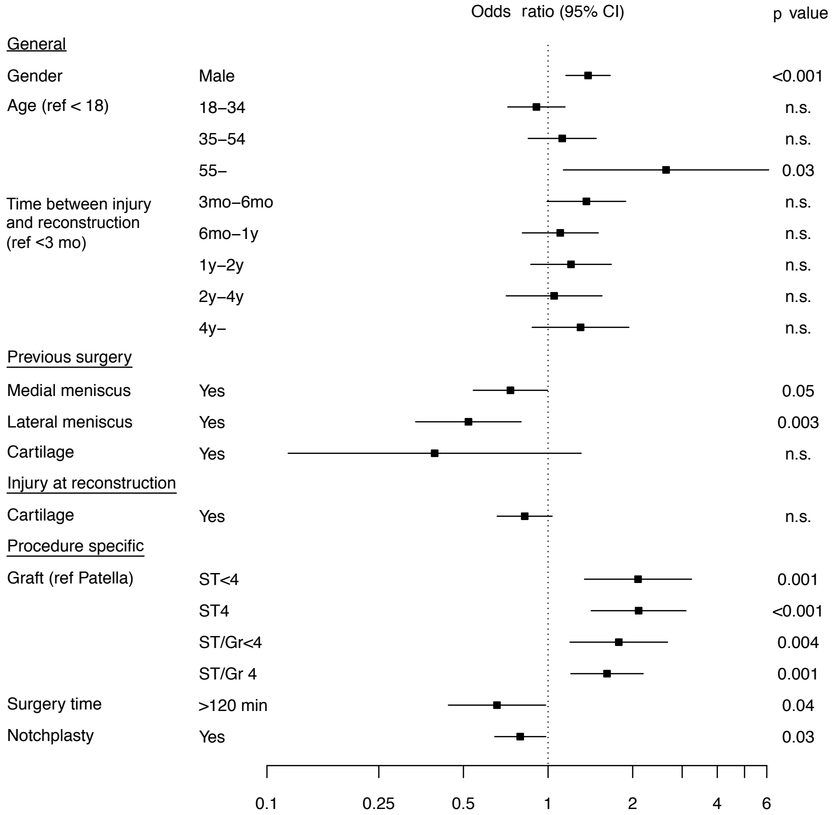
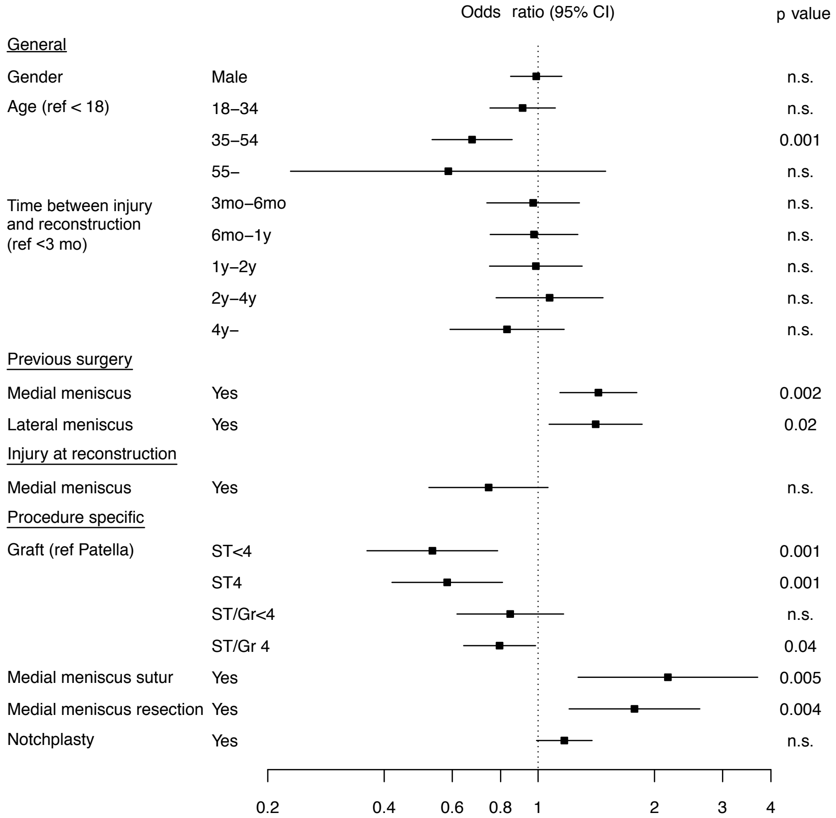


Figure 17

Treatment failure (TF), multivariable model. Odds ratio (OR) for all predictors included in the model presented with 95% CI and p value. For stratified predictors the reference value is presented in parentheses.



10 ADDITIONAL RESULTS

Results in his section are referred to as '*add. results*' in the discussion.

In *Study I* the distribution of lost sensitivity was presented. The area in cm^2 of disturbed or lost sensitivity was also measured. For the 57 patients with disturbed or lost sensitivity in the BPTB group, the median area was 27 cm^2 (1–162 cm^2) and, for the 48 patients in the ST group, 60 cm^2 (3–480 cm^2), p<0.01.

KOOS and IKDC results according to the Tegner activity scores in *Study I*, dichotomised to 0–6 or 7–10, are presented in Table 4.

Table 4
IKDC and KOOS results at the 8-year follow-up according to the Tegner activity score.

	Tegner 0–6 (n=118)	Tegner 7–10 (n=33)	p value
IKDC n (%)			0.018
A	11 (9)	7 (20)	
B	61 (51)	20 (59)	
C	32 (27)	5 (15)	
D	15 (13)	2 (6)	
KOOS mean (SD)			
Pain	87 (14)	94 (7)	0.009
Symptoms	81 (17)	86 (15)	n.s.
ADL	91 (13)	96 (7)	0.02
Sp/Rec	67 (27)	81 (17)	0.006
QoL	73 (20)	83 (16)	0.005

The subpopulation of patients having reconstructions less than 6 months after injury assessed in *Study I* were analysed for Tegner activity scores in *Study II*. In *Study I* patients having reconstructions < 6 months after the injury irrespective of graft type maintained their activity level better than after later reconstruction, patients having reconstructions < 6 months after injury had a Tegner activity score median of 6 while those with reconstructions ≥ 6 months after injury had a Tegner activity score median of 3 (p<0.001). This difference was not found at the 14-year follow-up (<6 months), median 5, and (≥6 months), median 4 (p=0.057).

When all patients with a bilateral OA, any additional procedure after the index reconstruction or an additional meniscus injury in the cohort of *Study II* was excluded, the prevalence of OA was still higher in the ACL-reconstructed limb. After exclusion there were 50 patients; none had medial compartment OA in the cl limb, but 18 (36%) patients had medial compartment OA in the ACL-injured limb, p<0.001.

In *Study II* the preoperative radiological findings or radiological findings at the two-year follow-up had low predictive value for OA after 14 years. This was due to the low compliance and frequency of findings at the earlier radiological evaluations. However, from a descriptive point of view, the seven patients with radiological narrowing of the medial or PF compartment two years after the ACL reconstruction are of interest and are presented as a case series.

Case 1 No OA
A male, 35 years old at the time of injury, had two thirds of both of his menisci resected and underwent reconstruction with a BPTB graft after 14 months. After two years his BMI was below 25 and he had no pivot shift after 2 or 8 years, but a positive Lachman. At the time of *Study II* he was 50 years old and 15 years after the reconstruction, he had had no procedure after the index surgery. He was symptomatic according to the KOOS definition of symptomatic knee problems. He had a VAS1 of 54, EQ-5D of 1, Tegner activity score of 5 and desired level of 6, and no OA (KL<2).

Cases 2–6 are presented in Table 5.

Case 7, TKA
A male, 37 years old at the time of injury. He showed a narrowing of medial cartilage on preoperative radiographs, had one third of his medial meniscus resected at the arthroscopy and index surgery and underwent reconstruction with an ST graft after 8 years and 4 months at the age of 45. After two years his BMI was above 25, he had no pivot shift after 2 or 8 years, and no Lachman. At the time of *Study II* he was 60 years old (14 years after the reconstruction); he had an osteotomy 8 years after the reconstruction and, finally, a TKA in the index limb. He was symptomatic according to the KOOS definition of symptomatic knee problems. He had a VAS1 of 11, EQ-5D of 0.12, Tegner activity score of 1 and desired level of 6, and no OA (KL<2) in the healthy non-injured limb.

Table 5
Presentation of results at the 14-year follow-up of patients with cartilage narrowing at the 2-year follow-up Cases 2–6. OA according to KL≥2.

	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	Male	Male	Female	Male	Female
Age at injury	40	32	31	29	34
Med. meniscus resection	1/3	1/2	-	Suture	-
Lat. meniscus resection	1/3	Suture	-	-	-
Time, Injury–Recon. (months)	18	9	6	14 y 5 mo	13
Graft	ST	BPTB	BPTB	BPTB	BPTB
BMI≥25 at 2 y fu	-	-	-	-	>30
Lachman 2 y or 8 y	+	+	-	+	-
Pivot shift 2 y or 8 y	+	+	-	-	-
Additional procedure	-	Scope & shave	-	Medial meniscus resection	-
Age at *Study II*	56	47	47	44	49
Time, Reconstruction–*Study II*	14.6	13.5	13.6	14	14.1
Symptomatic acc. to KOOS	-	+	-	+	+
VAS1 at 14 y	96	53	100	0	26
EQ-5D	1	0.8	1	0	0.16
Tegner activity score	2	6	3	0	1
Desired Tegner	3	7	3	6	3
Medial comp OA index	+	+	+	+	+
Contralateral OA, any comp.	+	-	-	-	+

In *Study IV,* when the pre-injury level of Tegner activity was dichotomised to 0–6 or 7–10 the increased risk of treatment failure for patients with level 7–10 with reference to patients with level 0–6 was OR=1.8 with a 95% CI of 1.1–2.7, p=0.012. Time between injury and reconstruction was longer for patients with a medial meniscus resection at the time of reconstruction, mean 949 days (SD=1448), compared to patients without a medial meniscus resection, mean 559 days (SD=988), p<0.001. Time between injury and reconstruction was shorter for patients with a medial meniscus suture at the time of reconstruction, mean 463 days (SD=687), compared to patients without, mean 626 days (SD=1094), p<0.001.

In *Study IV* no analysis of the type of fixation was done. The effect of femoral fixation close to the joint line or using a suspensory system is not clear. The cohort in *Study IV* was analysed according to fixation in the femur and tibia. For a functional recovery, the results for the femoral fixation are presented in Table 6. When the fixation of the femur was dichotomised to suspensory (Endobutton®) or close to the joint line (Rigidfix®, Interference screw and Transfix®) the OR for a functional recovery with 'close to joint line' as reference was OR=1.4 for an Endobutton® with a 95% CI of 1.2–1.7, p<0.001. Results for femoral fixation and treatment failure are presented in Table 7. Using the same dichotomisation and reference as for functional recovery, the OR for treatment failure was 0.8 for an Endobutton® with a 95% CI of 0.67–0.97, p=0.025.

Table 6
Functional recovery and femoral fixation with Endobutton® as reference, univariable analysis. *Add. results* for the cohort of *Study IV.*

	n	OR	95% CI	p value
Endobutton (reference)	713			0.003
Other	10	0.3	0.04–2.7	n.s.
AO screw	5	2.1	0.3–12.4	n.s.
Clamp	8	0.4	0.05–3.6	n.s.
Retrobutton®	32	0.9	0.4–2.0	n.s.
Rigidfix®	1379	0.8	0.6–1.0	0.026
Interference screw	848	0.6	0.4–0.7	<0.0001
Transfix®	539	0.7	0.6–0.7	0.022

Table 7
Treatment failure and femoral fixation with Endobutton® as reference. Univariable analysis. *Add. results* for the cohort of *Study IV.*

	n	OR	95% CI	p value
Endobutton (reference)	713			0.038
Other	10	1.9	0.5–7.0	n.s.
AO-screw	5	0.7	0.08–6.6	n.s.
Clamp	8	1.8	0.4–7.4	n.s.
Retrobutton®	32	1.5	0.7–3.2	n.s.
Rigidfix®	1379	1.1	0.9–1.4	n.s.
Interference screw	848	1.5	1.1–1.8	0.001
Transfix®	539	1.2	0.9–1.5	n.s.

More methods are used for tibial fixation, both 'suspensory' types of methods (screw and washer, the Cobra® device, Endobutton®, a clamp and the AO screw) and fixation inside the tunnel (Intrafix®, Rigidfix®, metal and resorbable interference screws). The results for the tibial fixation are presented in Table 8. With a dichotomisation between the 'tunnel-fixed' and 'suspensory' methods, 'suspensory' methods were again positive predictors of a functional recovery. For a functional recovery with fixation inside the tunnel as reference, 'suspensory methods' had an OR=1.2 with a 95% CI of 1.02–1.5, p=0.028. Using the same dichotomisation, no differences were found for treatment failure.

In the multivariable regression model, femoral fixation or tibial fixation was not a predictor of functional recovery or treatment failure.

Table 8
Functional recovery and tibial fixation, metal interference screw as reference. Univariable analysis. *Add. results* for the cohort of *Study IV*.

	n	OR	95% CI	p value
Metal interference screw (Reference)	1313			0.008
Other	44	1.3	0.6–2.7	n.s.
AO screw	327	1.5	1.1–2.0	0.004
Cobra®	39	2.8	1.4–5.4	0.002
Endobutton®	10	3.0	0.8–10.6	n.s.
Intrafix®	896	1.0	0.8–1.2	n.s.
Clamp	27	0.6	0.2–1.9	n.s.
Resorbable interference screw	124	1.4	0.9–2.2	n.s.
Retroscrew®	117	1.0	0.6–1.7	n.s.
Rigidfix®	232	1.3	0.9–1.8	n.s.
Screw and washer	392	1.0	0.8–1.4	n.s.

11 GENERAL DISCUSSION

Even though the need for an ACL reconstruction is still a matter of debate as stated in the Introduction, the focus of this thesis has been on factors influencing the result after an ACL reconstruction from the patient's perspective. It has been on factors of morbidity, such as donor site symptoms or a meniscus injury, on factors of function, such as residual instability or the ability to do a one-leg hop, and on factors related to the patient's subjective evaluation, such as the desired level of activity and health-related quality of life (HRQoL).

11.1 GRAFT CHOICE AND ASPECTS OF MORBIDITY

The main goal of ACL reconstructive surgery is a stable knee joint. Before the best graft for an ACL reconstruction can be chosen, differences in stability after an ACL reconstruction using different types of grafts have to be analysed. In a meta-analysis of 24 trials in 18 cohorts with a total of 1512 patients, Biau et al. found similar stability with a BPTB and the HT graft according to the Lachman test, but the BPTB graft resulted in more anterior knee pain, loss of extension and more problems with kneeling.[33] Biau et al. questioned their own results due to the poor quality of the studies included. In another meta-analysis, Biau et al. attempted to raise the level of evidence by pooling individual patient data from six RCTs for a total of 423 patients. BPTB and HT were compared according to the pivot shift and they found a decreased risk of a positive pivot shift after a BPTB graft.[31] However, ST and ST/Gr grafts were not separated and HT grafts with 2–5 strands were included. A recent Cochrane report by Mohtadi et al. used data from 19 studies with a total of 1597 patients and found more stability with BPTB than HT grafts.[148] In *Study I* no difference in stability between BPTB and ST grafts was found.[25] This is in line with other RCTs comparing ST or ST/Gr with a BPTB graft.[81,128,134,139,185,196] The results in *Study I* and in the literature indicate that clinically measurable stability can be achieved with a BPTB, a ST/Gr and a ST graft, but large cohorts indicate that the BPTB might give more stability. The selection of the best graft to use then depends mostly on the morbidity created by the graft harvest produce. An allograft clearly has the lowest donor site morbidity, but other aspects of allograft use make this graft choice controversial and in Sweden it is rarely used in primary ACL reconstructions.[133,171] Thus, this graft type will not be discussed further. Eight years after reconstruction the BPTB graft still had more donor site morbidity from kneeling and knee-walking according to Kartus et al.,[107] more frequent disturbed or lost sensitivity and more pronounced loss of skin sensation on subjective evaluation of disturbed sensitivity (*Study I*).[25] This is in line with previous studies and meta-analyses.[33,55,60,134,139,148,170,196] However, if there was a disturbed sensitivity patients with an ST graft had disturbances of a larger area (*add. result*). That the BPTB harvest affects the infrapatellar nerve and its branches and the ST graft harvest might cause injury to the saphenous nerve might be one explanation for the difference in area. Further morbidity for the BPTB graft with loss of extension and for the HT graft with loss of flexion has been reported,[60,148,196] as well as long-term strength deficits in extension for the BPTB graft [10,134,148] and flexion for the HT graft.[134,139,148,151] In *Study I* there were no differences between the graft groups regarding loss of ROM or functional strength measured by the one-leg hop; similar results were found by Sajovic et al. and Maletis et al. in their RCTs comparing the BPTB graft with the ST/Gr graft and by Mohtadi et al. in their Cochrane report.[25,134,148,185] Thus, no clear evidence regarding differences in ROM and functional strength between BPTB and ST/Gr or ST grafts exists. The morbidity after ST or ST/Gr harvest has been studied further. There are indications that the additional gracilis harvest results in more deep flexion and rotational strength loss than harvest of only the semitendinosus,[1,76,186,192] and that the difference might be tested with active knee flexion against gravity.[151] In *Study III* no difference in flexion strength or active knee flexion angle was found between ST and ST/Gr, contradicting previous results. Other recent studies have also failed to show any difference in deep flexion strength or the active knee flexion angle.[19,76] Measuring the active knee flexion angle is probably not the optimal way to evaluate deep flexion strength loss, but the lack of differences might also be an effect of sample size. The difference in morbidity between an ST or ST/Gr graft harvest is probably small in comparison to all other factors that contribute to the final result after an ACL reconstruction, and the findings of a higher OR for a functional recovery and a lower OR for treatment failure for the ST graft than for the ST/Gr graft in *Study IV* might indicate that there is a difference, but that the sample sizes of previous studies have been too small to find the true difference.[24]

11.2 METHODS OF RECONSTRUCTION AND ASPECTS OF STABILITY

The transtibial approach for femoral drilling was used in *Studies I–III*. During the period 2005–2008 (*Study IV*), it is probable that the majority of the reconstructions in Sweden were done using a transtibial technique, but some surgeons probably used the anteromedial portal for the femoral drilling and some had started with double-bundle procedures, and some were aware of the debate regarding anatomic reconstruction and were in the process of changing their technique.[232] A notchplasty decreased the chance of a functional recovery, indicating that a non-anatomic positioning of the graft, which required a notchplasty lowered the chances of a complete recovery (*Study IV*).[24] There are no other variables in the register indicating graft placement, so no further analysis was possible. The point of fixation has been a matter of concern, with reports of adverse effects with “suspensory’ fixation methods.[58,187] The ACL reconstructions of *Studies I* and *II* have a non-anatomical placement, a suspensory fixation both in the tibia and femur for the ST and tunnel fixation in both tunnels for the BPTB. No difference in Lachman, pivot shift or instrumented laxity with Rolimeter® was found in *Study I,*[25] contradicting the results of elongation of the graft and increasing laxity found by Scheffler et al.[187] ‘Suspensory’ or ‘ close to joint line’ fixation was not a predictor of treatment failure or functional recovery (*add. results*). This result is in line with the findings of Schultz and Carr, who reported good results with extra cortical fixation, and of Kong et al., who found no difference in outcome after ACL reconstructions fixated with the Endobutton® or the Crosspin®.[115,190] Andersson et al. reviewed the literature regarding fixation and reported more tunnel widening with 'suspensory' fixation but no differences in outcome compared to 'close to joint line' fixation.[13] No data regarding tunnel widening is available for *Study IV*, but the results for outcome *(add. results)* is in line with the results in the literature.[13,115,190]

Similar stabilities measured by Lachman, pivot shift and KT-1000 were found with an ST or ST/Gr reconstruction (*Study III*). Tibial internal ranges of motion measured by gait analysis were similar between ACL-reconstructed limbs and healthy non-injured limbs during an external pivot after descending a stair (*Study III*). The results from *Study III* contradict the results of Georgoulis et al., who found a residual rotational laxity after ACL reconstruction with an ST/Gr graft, resulting in a larger rotational range measured by gait analysis compared to the non-injured limb and healthy controls.[74] Misonoo et al. tested 44 patients 12 months after ACL reconstruction, 22 double-bundle and 22 single-bundle reconstructions and compared them with 22 healthy controls.[147] They used strength testing to verify completed rehabilitation before the pivot test. The pivot test included a drop and an angled cutting motion. Their ACL reconstructed limbs had significantly reduced rotational range compared to the healthy limb, and approximately 5 degrees less rotational range compared to the results in *Study III*. There was no difference between double- or single- bundle reconstructions. Before the more demanding double-bundle procedure is proclaimed as the 'gold standard' for restoration of stability after an ACL injury, the effect a single-bundle reconstruction has on rotational stability has to be thoroughly assessed. In a recent study Webster et al. found that a more anatomic femoral placement of a single-bundle reconstruction could restore rotational stability compared to a healthy control group in a high-demand pivoting task.[223] The results after double-bundle procedures are not clearly superior. Hussein et al. have published results showing no difference in rotational stability after ACL reconstructions with individualised anatomic single-bundle (ASB) or anatomic double-bundle (ADB) measured by pivot shift.[90] They also published results from another study where the ADB was superior to a transtibial conventional single-bundle (CSB) or ASB reconstruction for AP and rotational stability.[91] In their second study the instrumented laxity was measured by KT-1000 and showed a mean 1.2 mm side-to-side difference in the ADB group, 1.6 mm in the ASB group and 2.0 mm in the CSB group ($p=0.002$). Rotational stability was measured in per cent negative pivot shift: ADB 93.1%, ASB 66.7% and CSB only 41.7%, significant differences between all groups ($p<0.01$). The authors concluded that the results were significant but may not be clinically relevant. In *Study I* there were 76% negative pivot shifts 8 years after a non-anatomic reconstruction.[25] Thus, the results of Hussein et al. and *Study I* corroborate reports of questioned reliability of the pivot shift as a measure of rotational stability.[3,25,89-91,113] The results presented in this thesis and the presented literature indicate that, with current tests and measuring methods, a non-anatomic reconstruction might produce stable knees as measured by AP-laxity and current rotational tests. Fixation does not seem to matter for stability, but the graft type and non-anatomic placement might affect the subjective outcome. This is in line with the review by Karlsson et al.[105]

11.3 ADDITIONAL INJURIES AND ASPECTS OF TIMING

The experience of most surgeons is that the outcome after an ACL reconstruction depends a lot on the additional injuries the knee has sustained before the reconstruction. It is clear that, in the long term, a meniscus resection will result in cartilage narrowing and OA,[57,230] and the amount of meniscus resected correlates with the cartilage changes.[14,176] The effect of a meniscus injury on the outcome after ACL reconstruction in the short to mid-term has not been as thoroughly studied. In their cohort of 482 patients after ACL reconstructions, Shelbourne et al. found an 85% normal or nearly normal IKDC rating with no meniscus resection after 7.6 years;[197] for patients with a partial or total medial meniscus resection, the same rating was 63% and with resection of both menisci, 60%. They also found more laxity with KT-1000 among patients with any type of medial meniscus resection, and the subjective score was lower when a cartilage lesion was present at the reconstruction. This is in line with the results of *Study IV*. In that study, two years after reconstruction the chance for a functional recovery was lower after previous meniscus surgery, and the risk for treatment failure was increased with previous meniscus surgery. The risk for treatment failure was highest if a medial meniscus procedure was required at the time of reconstruction; for medial resection OR for treatment failure was 1.8 and for suture OR was 2.2.[24] Røtterud et al. studied full-thickness cartilage lesions in the Norwegian National Knee Ligament Register and found less improvement with the ACL reconstruction among patients with a full-thickness cartilage injury than among patients without.[183] In *study IV* there was no effect of a cartilage lesion on the chance of a functional recovery or the risk of a treatment failure. One explanation could be that the compliance with registration of cartilage lesions is low in the Swedish National Knee Ligament Register; another explanation could be that all types of cartilage lesions were treated equally in *Study IV*. There is also a concern that recurrent giving way can result in increased laxity in secondary restraints, causing residual laxity even after a successful ACL reconstruction.[37,59,98] Isberg et al. showed that if the ACL is reconstructed within 10 weeks of injury before giving way had occurred, normal knee kinematics could be maintained.[98] The effect of time between injury and surgery on the frequency of additional injuries found at surgery has been studied. There are numerous reports of a higher frequency of meniscus injuries and cartilage lesions found at the time of ACL reconstruction with a longer time between injury and reconstruction (TIR).[40,41,45,54,78,106,110,165,197] In *Study IV* there was a higher risk of a medial meniscus injury or a cartilage lesion with a TIR of more than 1 year: for the medial meniscus, the OR was 1.6 and, for a cartilage lesion, OR was 1.5. A lateral meniscus injury was less frequent with a TIR of >3 months, OR 0.7.[24] The mean time between injury and reconstruction was higher for patients with a medial meniscus resection than for those without (*add. results*). This concurs with the results of Cipolla et al.,[42] who found a 71.5% intact medial meniscus in ACL-injured patients undergoing surgery within one week after the injury, and only in 25.5% in chronic patients; the chronic patients had various times between injury and surgery, but all had more than one week. A resection of the medial meniscus was required in 43% of the chronic patients and, in 7% of them a previous meniscus resection had been done. For the lateral meniscus, only 39% of the patients had an intact meniscus if surgery was performed within one week and the figure for the chronic patients was 58%. Cipolla et al. concluded that the lateral meniscus injury found in acute reconstructions is associated with the ACL rupturing trauma and is mostly stable and self-healing and that the medial meniscus injury is the result of instability and giving way during the time between injury and reconstruction and are often unrepairable. This might also be one explanation for why a medial meniscus suture was a predictor of failure in *Study IV*; the mean time between injury and reconstruction for patients with a medial meniscus suture at the time of reconstruction was 463 days (*add. results*). The time between injury and repair and the repair methods used during the study period could influence the prognosis for a meniscus suture and affect the outcome of the reconstruction negatively.[200,217] That TIR in itself affects the outcome after an ACL reconstruction is not clear. Karlsson et al. found that a subacute reconstruction resulted in a retained higher activity level in an RCT comparing subacute (TIR 2–12 weeks) and late reconstruction (TIR 12–14 months).[106] In the two-year results for the RCT used in *Study I*, Eriksson et al. found that patients reconstructed with a TIR of <5 months had a higher final IKDC rating than patients with TIR ≥ 5months.[54] Frobell et al. found no difference in KOOS improvement from injury to the two-year follow-up in patients randomised to early reconstruction (TIR< 10 weeks) or non-operative treatment and optional late reconstruction (TIR mean 11.6 months).[66] In *Study I* patients with TIR <6 months had retained a higher Tegner activity score compared to patients with TIR ≥6 months, but no other clear differences were found, which is in line with the findings of Karlsson et al.[25,106] In *Study IV* no effect of TIR on outcome in functional recovery or treatment failure could be found, these results support the findings of Frobell et al.[24,66] However, with the results in *Studies I and IV* and the previously discussed results regarding outcome after an additional injury and the effect of TIR on the frequency of additional injuries found at reconstruction, the argument could be made that TIR affects the outcome after an ACL reconstruction through the additional injuries sustained during TIR. That it is instability with 'giving way' that results in additional injuries, not TIR in itself, is supported by the literature. [42,63,106] The study by Frobell et al. has received some criticism as there are differences in the frequency of meniscus injuries and events of instability found in the groups, but this difference did not affect the result after two years.[66] One explanation for why no difference was found between the groups in that study, which would concur with the results in *Study IV*, is that the effect of a meniscus injury might not be apparent after only two years.

11.4 LEVEL OF ACTIVITY, AND HEALTH-RELATED QUALITY OF LIFE

In Sweden it is customary to inform the patient of the expected outcome of a reconstruction and the risks associated with it. If the surgeon feels that a reconstruction is indicated, the decision to go through with the reconstruction is the patient's, which seems fair, as they are the ones taking the risks. In many cases a period of non-operative treatment with rehabilitation is recommended before the decision on a reconstruction is taken. This might explain why Sweden has a high frequency of non-operative treatment. Similar treatment algorithms are recommended in other European countries.[144] The patients that undergo an ACL reconstruction are usually convinced that they need their knee stability back to be able to put a desired amount of demand on their knee and to function on the activity level they desire. Thorstensson et al. interviewed patients participating in an RCT randomised between rehabilitation and reconstruction.[212] They interviewed patients who requested a reconstruction in the rehabilitation arm of the study: 'Many described a lack of trust in their knee' and 'Patients believed that surgery would provide joint stability'.[212] The majority of patients receiving an ACL reconstruction in Sweden are between 15 and 30 years old, and the ACL injury is mainly suffered during sport participation of some kind.[231] A modification of one's activity level is often required to function without an ACL,[117] and a high activity level with high knee demand is detrimental to the knee without stability.[63] Swirtun et al. showed that patients with a high activity level often choose a reconstruction and base their decision on assumptions about future problems.[203] It has been shown that the level of activity attained after the reconstruction is related to the patient's satisfaction with the outcome of the reconstruction.[114] To be able to return to the desired level of activity is also related to a successful rehabilitation, with a restored functional strength and no major donor site morbidity.[30,83,112,118] One way to measure the activity level is the frequency of patients who return to sports. In *Study III* 90% of the patients had returned to some kind of sport activity. Ardern et al. has studied return to sports. In a meta-analysis of 5770 patients in 48 studies, they found that 90% of the patients were assessed to have normal or nearly normal laxity and strength, and 85% were normal or nearly normal in the IKDC evaluation. However, only 44% returned to a competitive sport and 63% to their pre-injury level of participation and 82% to some kind of sport participation at a mean of 41.5 months after reconstruction. In a case series of 314 patients the investigators found 45% at their pre-injury level and 29% participating in a competitive sport after a mean of 40 months after reconstruction, and 54 of 90 who changed their sport participation after the reconstruction did so because of knee function, Ardern et al. concluded that psychological factors may be a contributing cause to the low rate of return to sports in spite of good objective knee function.[18,20] However, the type of sport was not specified, and one cause of the differences found in the frequency of returning to sports can be inconsistencies due to different knee demands in the sports in question. The Tegner activity score used in *Studies I, II and IV* takes knee demand into account. A level 10 score requires a knee function sufficient to play national or international league soccer.[210] In *Study I* the activity level had decreased from the two-year follow-up from a median of 6 in the BPTB group and 5 in the ST group to a median of 5 in the BPTB and 4 in the ST group after 8 years, with no statistical difference between the groups.[25] This level of activity was maintained to *Study II* at 14 years; median 4 in the BPTB and ST groups. In *Study I* subjects with early reconstructions maintained a higher activity level than those with later reconstructions, in line with the results of Karlsson et al.[106] This difference was not found at the 14-year follow-up (*add. results*).

Knee-specific scores and HRQoL scores are usually used to evaluate the impact of knee function on the activity level and other aspects of the patient's life. EQ-5D is an outcome measure in the Swedish National Knee Ligament Register and used in *Studies*

II and IV. EQ-5D has been used with good results in hip fracture research.[213] However, the impact of the ACL injury on EQ-5D was too small to characterise the study populations accurately in *Studies II and IV*.[24] One cause of this might be that ACL injured patients are usually very healthy apart from their injury. In *Study I* no difference between graft groups was found for Lysholm, IKDC, KOOS or SF-36,[25] and no differences for KOOS in *Study II*. This is in line with other RCTs comparing BPTB and HT. Sajovic found no difference five years after BPTB or ST/Gr reconstruction in Lysholm or IKDC evaluations.[185] After 11 years they found no difference in Lysholm, IKDC or SF-36 evaluations.[184] Biau et al. found no difference in final IKDC results in their meta-analysis of BPTB and HT.[32] There might be no difference or the measuring methods or study designs are inadequate for measuring the true difference.

Both the knee specific IKDC score and the HRQoL score KOOS have been validated.[96,179,194] There has been a concern that the sensitivity of KOOS might be too low to detect symptoms and disabilities of patients with an ACL injury.[80,205] Tanner et al. compared 11 knee-specific instruments, including the KOOS and IKDC. The IKDC form was found to include more questions that the patients graded as important in assessing their problems after an ACL injury and the KOOS was superior to the IKDC for patients with mild OA. Both the IKDC and the KOOS were found to contain many items important to patients.[205] Hambly et al. compared IKDC and KOOS, and they found the subscales Sp/Rec and QoL to be the most important to the patients.[80] KOOS has been used for other conditions than ACL injury and found to be valid,[181] and for KOOS there are reference populations for high-level athletes and different age groups.[67,166] KOOS has been shown to be sensitive to changes over time,[178] which has been questioned concerning the IKDC.[174] In *Study II* the IKDC evaluation showed further improvement in the final rating from the 2-year to 8-yearfollow-up. This could be an effect of coping or reorientation to another life as the Tegner activity score decreased in the same time period, or it could be an effect of the IKDC instrument not measuring change over time well, and a third explanation is that the knee function was actually better after 8 years due to less knee demand with a lower level of activity. Ten points has been proposed as a clinically significant change in KOOS,[179] a level of difference seldom found in ACL studies. The compounded and normalised score presented by the KOOS in five subscales also makes a further analysis of the causes of the result difficult.[82] The causality behind a level of KOOS is not discernible. Stratifying the results according to levels of KOOS could be one way to characterise populations with different levels of KOOS. Lohmander et al. defined symptomatic knee problems according to a level of KOOS.[131] Patients with any subscale score below the cut-off level were defined as having a symptomatic knee problem. Frobell et al. defined treatment failure as a KOOS subscale QoL below 44.[66] To our knowledge, no such definition has been elaborated for a high KOOS result after an ACL reconstruction before *Study IV*.[24]

Does a high KOOS level correlate with a high activity level and a stable functioning knee? This question is hard to answer. In *Study IV* a higher Tegner activity score at the time of reconstruction or 6 months after reconstruction increased the chance of a functional recovery, and a higher activity level before the injury increased the risk of treatment failure. The results regarding functional recovery could indicate that a well functioning rehabilitation before and after the reconstruction is beneficial for the outcome after two years. These results are in line with Kvist's review of rehabilitations and results presented by Langford et al., namely that as the post reconstruction rehabilitation progressed, patients experienced fewer negative emotions regarding their injury and more positive emotions about returning to their sport.[118,121] A high pre-injury activity level did not correlate with a high KOOS two years after the reconstruction in *Study IV*. In *Study I* patients with a Tegner activity score of 7–10 had higher final IKDC and KOOS scores than patients with an activity level of 0–6 (*add. results*). Månsson et al. found a higher KOOS for patients with a higher preoperative Tegner activity score,[136] and Kocher et al. found a correlation between less patient satisfaction with a lower level of activity.[114] For the patients in *Study IV,* a pre-injury Tegner activity score of 7–10 was a strong predictor of treatment failure (*add. results*). That a high pre-injury level of activity increases the risk of failure seems logical, as the demand on the knee is even greater for such a patient to return to a subjectively acceptable level. However, the effect of the activity level should be interpreted with care for *Study IV* because the KOOS and activity level were not measured at the same point in time and because there were inconsistencies in the activity data. Also, the more frequent treatment failure among patients with high pre-injury activity in *Study IV* doesn't have to be contradictory to the results in *Study I*, or the results of Månsson et al. and Kocher et al. as the activity level at the time of the KOOS evaluation is not known.[24,114,136] Swirtun et al. did not find a difference in outcome in the total KOOS after reconstruction depending on the Tegner activity score, but a low score for embitterment on the Swedish universities' Scale of Personality Questionnaire, correlated with a better KOOS.[204] Kvist et al. found a correlation between fear of reinjury and the knee-related quality of life (KOOS subscale QoL).[119] Thomée et al. have shown that the patient's level of self-efficacy before surgery can predict knee function scores one year after reconstruction (KOOS subscale Sp/Rec),[211] Thus, the psychological influence on the outcome after an ACL reconstruction is clear.[119,121,204,211]

That a high KOOS would correspond to a knee function allowing the desired activity level seems probable, and perhaps a high KOOS would correspond to favourable personality traits and result in a higher frequency of return to the desired sport compared to a low KOOS. That patients not achieving their desired level of activity would rate their HRQoL lower and that the risk of not achieving the desired level of activity would be higher among patients with a high pre-injury activity level also seems probable. Further studies are needed to resolve this issue. The results from *Studies I and IV* and the results reported by Kocher et al. and Månsson et al. also indicate that combining KOOS with an activity level score is necessary to analyse the causes of the KOOS result more thoroughly.[114,136]

11.5 LONG-TERM RESULTS, ASPECTS OF OSTEOARTHRITIS

In *Study II* an ACL reconstruction did not protect the knee from OA. If all patients with additional injuries and procedures were excluded, the reconstruction still could not protect the injured knee from OA (*add. results*). This is in line with most of the current literature. Li et al. found 39% radiographic OA in the reconstructed limb eight years after the reconstruction vs. 11.5% in the cl limb; a high BMI and medial meniscus resection and medial compartment chondrosis were predictors of OA.[127] Murray et al. reported OA according to the IKDC radiographic evaluation. They found 15% A, 51% B, 19% C and 14% D in the reconstructed limb and 26% A, 50% B, 17% C and 7% D in the cl limb.[150] Holm et al. found 55–64% OA 10 years after reconstruction according to KL≥2 and in the cl limb the prevalence was 22–28%.[88] Øiestad et al. found 71% OA according to KL≥2 for ACL-reconstructed limbs after 10–15 years and 25% in the cl limb.[161] The patients in *Study II* and in the studies by Li, Murray, Holm and Øiestad et al. had reconstructions between 1986 and 2002.[88,127,150,161] It is probable that the majority of the patients had a non-anatomic reconstruction. At the present time, for most studies conducted using a modern anatomic technique, less then 8 years would have passed since reconstruction. Wipfler et al. have reported 9-year results after their anatomic ACL reconstruction with BPTB and compared it with an ST/Gr graft. The size and location of cartilage lesions was analysed according to the International Cartilage Repair Society (ICRS) evaluation package after non-weight bearing limb MRI scans. They found a difference only for grade 3 or 4 lesions, which were more frequent in the BPTB group vs the cl limb.[228] These five studies describe the problem of making good comparisons of reports on OA in different studies. Three studies used the Kellgren & Lawrence classification, but with two different cut-off levels for radiological OA. One used IKDC and one ICRS. Different classification systems and definitions of the cut-off level for OA, combined with different times to follow-up have resulted in reported OA prevalences from 9% by Ferretti et al. 6 years after reconstruction to 84% after 20 years reported by Maletius et al..[62,135] In *Study II* OA was classified according to KL≥2, but defined as a consensus of at least two of the three involved radiologists. The prevalences found in *Study II* are similar to the levels found by Holm et al. and Øiestad et al. with the same radiological cut-off level for OA and the same time between reconstruction and follow-up.[88,161] Based on the results of *Study II* and the results from studies with similar definitions and design, an estimated prevalence of radiological OA according to KL≥2 of 70% 10–15 years after a non-anatomical reconstruction for a group of patients with additional injuries included seems probable. It is also probable that the non-anatomic reconstruction from 10–15 years ago can not protect the knee from OA, and this is in line with current theories of changed cartilage load and insufficient repair capabilities of chondrocytes as a cause of OA.[16,39,45,88,127,150,161,229] It is clear from the literature that an additional injury increases the risk of OA.[43,45,102,108,127,145,160] Previous studies have reported that a high BMI along with the ACL injury is a risk factor for radiological OA; this is in conformity with the results of *Study II*.[5,45,47,111,125,127,176]

Symptomatic OA has also been defined in a number of ways: for example, according to additional questions, radiological grade of OA and to levels of KOOS.

Øiestad et al. found 46% symptomatic OA in a cohort of ACL reconstructed patients 10–15 years after reconstruction, with additional injuries included, and 32% for isolated ACL injuries according to KL≥2 and affirmed knee pain the last 4 weeks according to a question.[160] Struewer et al. defined KL≥3 as symptomatic OA and reported 23% 13.5 years after a BPTB reconstruction.[201] With their definition of symptomatic knee problems according to a cut-off level of KOOS, Lohmander et al. found 42% symptomatic OA in the ACL-injured limb in a cohort of female soccer players 12 years after ACL injury.[131] In *Study II* the definition of Lohmander et al. was used and the prevalence of symptomatic OA was 39% for the medial compartment. The results from *Study II* are in agreement with Lohmander et al., who used the same definition; again the problem of comparing results from different studies is apparent.

Some authors have reported a higher prevalence of OA with longer time between injury and reconstruction.[102,129] In *Study II* time between injury and reconstruction did not affect the prevalence of OA, but the frequency of meniscus injuries increased with time and a meniscus resection was the strongest predictor of OA. The same argument as in *Study IV* can be applied in *Study II*, i.e. that time between injury and reconstruction increases the risk of 'giving way' and subsequently the outcome after reconstruction by way of additional injuries to the cartilage and menisci. However, it should not be forgotten that the mechanism of OA is not known and that these studies only relate to statistical probabilities.[65] One patient (*case 1, add. results*) might not get OA even after a non-anatomic ACL reconstruction done 14 months after injury with two thirds of both menisci resected but be symptomatic, while another (*case 4, add. results*) undergoing reconstruction within 6 months from the injury and with no additional injuries or procedures can have radiological OA but is non-symptomatic.

11.6 FINAL CONSIDERATIONS, CLINICAL RELEVANCE AND FUTURE PERSPECTIVES

In this thesis stability measured by Lachman, pivot shift, instrumented laxity and rotational range with gait analysis were not strong predictors of outcome after an ACL reconstruction in the short or long-term. The methods used have all been questioned regarding sensitivity and specificity. At the moment, few inexpensive, reliable, easy-to-use and real-life-simulating methods exist. Hopefully, the research in pivot shift instruments will be fruitful and it will be interesting to follow the refining work on gait analysis and the development of dynamic CT, MRI and RSA. To facilitate comparisons of further research on dynamic instability after ACL injury with these resource-demanding methods, it would be helpful to have an agreed set of defined pivoting tests for different demands. However, most patients with an instability can describe their problem by means of a knee-specific questionnaire, relate their activity level to their knee function and assess the impact on their health-related quality of life. The Scandinavian knee ligament registers are able to collect large study populations in which analyses of subpopulations can reveal information that it is impossible to detect in smaller study populations. The results from the Danish Knee Ligament Register will be followed with interest as they already record the Tegner activity score and KOOS, making a further analysis of the outcome according to activity level possible. The impact of personality traits and other psychological factors on the outcome after ACL injuries should not be forgotten and, compared to the number of studies relating to graft types, laxity and other objective measures of outcome, this field has not received much interest. To study the effect of socioeconomic factors on the outcome after an ACL reconstruction by cross-referencing the Swedish National Knee Ligament Register with other National registers would be interesting. From the patient's perspective, it seems that morbidity has a major influence on outcome. The results in this thesis suggest that although it is hard to find differences in outcome after ACL reconstructions due to donor site morbidity, there are differences that can be found in large enough cohorts. Fixation does not seem to be a major factor for outcome. The use of only the semitendinosus tendon for primary ACL reconstructions can be recommended due to the good stability achieved and the least amount of donor site morbidity of autografts. From the results in this thesis and the literature, it is clear that injuries to the medial meniscus increase with time between injury and reconstruction and that medial meniscus injuries are probably the result of recurrent giving way. The lateral meniscus is different from the medial meniscus and so is the mechanism of injury and prognosis after a lateral meniscus injury. That lateral meniscus injuries are related to the initial trauma and have a high potential to heal seems probable. The results indicate that the full impact of a meniscus injury might not be apparent two years after the reconstruction. It would be interesting to perform the same analysis as in *Study IV* for the five-year results from the Swedish National Knee Ligament Register. The medial and lateral compartment OA was strongly associated with meniscus resection. In theory, prevention of OA could be achieved with an ACL reconstruction before giving way has occurred and care is taken not to resect a stable lateral meniscus tear. However, there is evidence enough today that an ACL reconstruction does not give protection from OA and ACL-injured patients should be informed of the risk of future OA before a reconstruction. The long-term results after modern anatomic ACL reconstructions will be interesting to follow. Will these methods recreate normal knee kinematics sufficiently to protect the knee from OA even with a return to high knee demand activities? The results in this thesis and the current literature suggest that an anatomic single bundle with a semitendinosus tendon graft performed before an additional injury has occurred is a good way to treat an ACL injury. To decrease the morbidity in the injured limb further, graft harvest from the contralateral limb could be suggested. For patients presenting immediately after the ACL rupturing trauma with additional meniscus injuries, subacute ACL reconstruction and meniscus repair could be a possible treatment option. Early surgery could result in better outcome for the meniscus repair and ACL reconstruction if the surgery was performed in the first week after the injury, and with manageable risk for complications, due to modern surgical techniques. Well-designed studies of early reconstructions are needed to resolve these questions.

With the current knowledge, ideally, the "non-coper' after an ACL injury should be identified before the first giving way to minimise the risk of additional injuries, decrease the morbidity and perhaps the risk of future OA. On the other hand, a potential 'coper' is identified after a period of rehabilitation and successful activity modification.

To select patients that will benefit from surgical treatment remains a challenge for the ACL reconstruction surgeon.

O'Donoghue's classic paper from 1950 still has validity:

'*An early decision as to treatment*
must be made immediately after examination.
Surgery should not be reserved for those cases
in which conservative treatment has failed.'

12 CONCLUSIONS

Studies I–III

- The BPTB and ST graft yield similar results, including the risk of OA in the long-term, but the BPTB carries an increased risk for graft site morbidity related to kneeling and knee-walking. No differences between the ST and ST/Gr graft were found.
- A non-anatomic ACL reconstruction does not protect the knee from OA, and the OA after an ACL reconstruction is often symptomatic.
- An injury to the menisci in need of treatment affects the long-term result and risk of OA.
- Overweight after the reconstruction might be a risk factor for OA.

Study IV

- Medial meniscus injuries and cartilage lesions increase with the time between injury and reconstruction, the chance for a functional recovery is less for patients with a previous meniscus procedure and the risk for a treatment failure is higher for patients with a previous meniscus procedure or a medial meniscus procedure at the time of reconstruction.
- The chance for a functional recovery after an ACL reconstruction is higher for males and for all types of HT grafts compared to the BPTB graft and the risk for a treatment failure after an ACL reconstruction is lower if an ST or four-strand ST/Gr graft is used.
- A notchplasty decreases the chance for a functional recovery.
- Patients with a high activity level before injury have a higher risk for treatment failure.

13 SAMMANFATTNING PÅ SVENSKA

En främre korsbandsskada ger ofta dålig knäfunktion på grund av instabilitet. Det kan resultera i knä-vikningar som kan skada menisker eller broskytor i knäleden. Det främre korsbandet läker inte, så behandlingen för instabilitet efter en främre korsbandsskada är en rekonstruktion med ett transplantat. I Sverige är det vanligen ett fritt kroppseget transplantat som används. Vanligt använda transplantat är knäskålssenan med en benbit från underbenet och knäskålen, eller en eller flera senor från den bakre lårmuskeln. Resultatet efter en korsbandsskada bedöms ofta av ortopeden utifrån hur stabilt knäet har blivit, återhämtning av styrka och återgång i idrott. Effekten av tilläggsskador, tidpunkt för rekonstruktionen och mer sjuklighet av transplantattagningen är inte så studerat.

Syftet med studierna i denna avhandling var att jämföra den effekt olika typer av kroppsegna transplantat, tiden mellan skadan och rekonstruktionen samt tilläggsskador på meniskerna har på knäfunktionen och den upplevda hälsorelaterade livskvaliteten efter rekonstruktionen.

I *Studie I* gjordes en lång tidsuppföljning av 153 patienter i medeltal åtta år efter att de fått en främre korsbandsrekonstruktion. De lottades ursprungligen mellan ett knäskålssene-transplantat eller ett fyr-skänklat semitendinosussene-transplantat i en prospektiv randomiserad studie. Ingen skillnad mellan transplantattyperna påvisades vid klinisk undersökning av stabilitet, funktionella tester, funktionella frågeformulär eller frågeformulär om hälsorelaterad livskvalitet. Patienter med kortare tid än sex månader mellan skada och korsbandsrekonstruktion hade högre aktivitetsnivå efter 8 år enligt frågeformuläret Tegner aktivitets nivå. Patienter med tilläggsskador på meniskerna hade sämre utfall efter rekonstruktionen.

I *Studie II* undersöktes 135 patienter från samma patientpopulation som i *Studie I* efter att ytterligare 6 år hade gått. Efter i medeltal 14 år från korsbandsrekonstruktionen undersöktes förekomsten av röntgenologisk ledsvikt (artros). Artros var vanligare i det korsbandsrekonstruerade benet än i det initialt oskadade benet. Artros var vanligast i ledkammaren på knäets insida. Det var ingen skillnad i frekvens av artros mellan transplantattyperna efter justering för antalet meniskresektioner. Om en del av menisken tagits bort på grund av en tilläggsskada innan eller i samband med korsbandsrekonstruktionen ökade risken för artros i den ledkammare menisken hörde till. Övervikt definierat som ett "Body mass index" (BMI) över 25 två år efter korsbandsrekonstruktionen var också en riskfaktor för artros. Förekomst av artros påverkade den hälsorelaterade livskvaliteten och de flesta patienter med röntgenologisk artros hade också besvär från knäleden.

I *Studie III* utvärderades tio patienter med ett fyr-skänklat semitendinosussene-transplantat och tio patienter med ett fyr-skänklat semitendinosus och gracilissene-transplantat 36 månader efter korsbandsrekonstruktionen. Rörelseomfånget vid rotation i knäleden bedömdes med gånganalys, böjstyrka med ett styrketest i sittande och patienterna fick besvara frågeformulär om knäfunktion och återgång i idrott. Inga skillnader mellan transplantattyperna påvisades.

I *Studie IV* analyserades resultat från det Svenska korsbandsregistret. Hos 8584 patienter som fick en främre korsbandsrekonstruktion mellan 2005 och 2008, påvisades att frekvensen av meniskskador på menisken på knäets insida och förändringar på broskytorna ökade med tiden mellan skada och rekonstruktion. Två år efter rekonstruktionen hade 3556 patienter av de 8584 svarat på det hälso relaterade livskvalitets-formuläret Knee Osteoarthritis Outcome Score (KOOS). Livskvalitet resultateten utvärderades utifrån en definition av ett högt värde på KOOS kallat funktionellt återhämtning och ett lågt värde av KOOS kallat behandlingssvikt. Chansen för en funktionell återhämtning var större för män och för alla transplantattyper från den bakre lårmuskeln, och chansen för funktionell återhämtning var lägre för patienter med en tilläggsskada på menisker som resulterat i ett operativt ingrepp innan korsbandsrekonstruktionen eller att korsbandsfåran i lårbenet vidgats i samband med korsbandsrekonstruktionen så kallad "notchplastik". Risken för behandlingssvikt var större för patienter med en tilläggsskada på menisker som resulterat i ett operativt ingrepp innan korsbandsrekonstruktionen eller en operativ åtgärd på menisken på knäets insida i samband med korsbandsrekonstruktionen, och risken för behandlingssvikt var lägre för patienter mellan 35 och 54 år gamla vid tidpunkten för rekonstruktionen och om rekonstruktionen utfördes med transplantat från den bakre lårmuskeln. För 556 patienter i studien fanns även aktivitetsnivå enligt Tegner registrerat, en hög Tegner aktivitetsnivå innan skadan ökade risken för behandlingssvikt.

Konklusion: Tiden mellan skada och rekonstruktion påverkade resultatet efter en korsbandsrekonstruktion via ökad frekvens av tilläggsskador med ökad tid. Transplantattypen påverkade resultatet efter en korsbandsrekonstruktion via mer sjuklighet i kroppsdelen den togs ifrån både på kort och lång sikt. En tilläggsskada i en menisk påverkade resultatet efter en korsbandsrekonstruktion både på kort och lång sikt och förekomsten av artros efter korsbandsrekonstruktionen, speciellt om tilläggsskadan gjort att en del av menisken tagits bort.

14 ACKNOWLEDGEMENTS

Many individuals have contributed to the making of this thesis. I would like to thank all of you, mentioned or not; it would not have been possible (or as much fun) without your participation. I would especially like to express my gratitude to:

Kalle Eriksson, My main supervisor, for introducing me to the 'right way' to do an ACL reconstruction (ST 4 with periost-flap), for sharing your enthusiasm, experience and vision of ACL research, for patience when all my other projects interfered with the research, for always aiming for the best, and for your friendship.
Sari Ponzer, My co-supervisor and current boss, for giving me the time (and money) to complete this project, for your insight into the world of research, your unrivalled speed and capacity to be of assistance with all aspects of research and at the same time being an understanding boss.
Julian Feller, Co-author and 'the man' of ACL reconstructions in Melbourne, for sharing your expertise, knowledge and for your hospitality during my fellowship. For setting an example of how a well functioning knee surgery business can produce research, and for your firm guidance in getting the best out of *Study III*. Go Magpies!
Kate Webster, Co-author and research supervisor at the gait laboratory of La Trobe University, for a wonderful time in Melbourne, for introducing me to gait analysis, and for all your work with *Study III*.
Björn Engström, My mentor and co-author, for sharing your perspective of ACL surgery and research, for your ability to always give feedback in a positive manner.
Magnus Forssblad, Co-author and father of the Swedish National Knee Ligament Register, for sharing the register data with me, and for always having quick responses to my questions.
Jan Tidermark, Co-author, for sharing your experience and critical view in research needed for evidence based medicine, and for your structuring of the manuscript in *Study I*.
Martin Nordlander, Co-author, all hail to the most stubborn physiotherapist I know for tracking and coercing so many patients to participate in *Study I*.
Jodie McClelland, Co-author, for almost making me understand gait analysis, frequently helping me out, for your friendship, good laughs and for being one of the nine people who listened to me in Rio.
Adel Shalabi, Robert Bujak, and **Louise Norlén**, my radiologists and co-authors, for your classification work.
Tina Levander and **Elisabeth Skogman**, my research nurses, for doing the daily hard work of clinical research with a smile, keeping the study patients logistics in order and for all the patient phone calls and for always calling and coercing one more time. It could not have been done without you!
Clare Ardern, for your help with strength testing and your enthusiasm for research even on Saturday mornings.
Jo Wittwer, for excellent help in the gait lab and for your dry humour.
All the patients involved in the research, for sharing your time and experience of your ACL injury with me.

Göran Modin, My former boss, for given me the time and opportunity to initiate and pursue this research.
Ricard Miedel, My most recent former boss, for continuing support in the pursuit of research time and courses, for your friendship, good talks and for always sheltering me from the wind on the bike.
Ulric Willers and **Richard Blomfeldt**, for all your extra work in my absence.
Hans Törnqvist, for being an inspiring senior orthopaedic surgeon.
Hylton Menz, Deputy Director of the Musculoskeletal Research Centre, for inviting me into the research group and for your epic movember moustache.
Lina Benson, for statistical help with *Studies II and IV,* and for always making me check once more that I really understood what I had calculated and why.
Gunnar Edman, for statistical help with *Study IV* and fruitful discussions regarding the definition of remission.
Isaac Austin, for excellent linguistic refinement of *Study I, II* and the Thesis.
Tim Whitehead, for your generosity and for showing me that ACL research is a lot like a Rock and Roll band on tour.
Anneli Andersson my world best secretary for keeping tabs on my schedule and patient appointments and together with **Monica Linder** always helping me out with my research stuff in the last second.
Solveig Nettelbladt, for always having a check- and send-list, and for calmly helping out with last minutes applications and all other research events.
Sektion 24 and **Tina**^{2}, My closest colleagues and friends at the orthopaedic department, for your patience with me during this time when my mind has been elsewhere, and for not hunting me more.
Christian, Simon, Orlando and **all other colleagues** and **friends** in the Orthopaedic department, for a stimulating working environment, good times in and off the workplace. I'm looking forward to working with you all again.
The 'wine gang', **Klas, Niklas, Fredrik, Carl-Magnus, Patrick** and **Petter**, for many of the good moments in life, with good wine and good friends most problems can be forgotten at least for a while.
The 'cycle gang' Peter, **Henrik**, **Ricard**, **Per**, **Christian**, **Buster**, **Evelina**, **Sami, Piotr, Niklas** and **Mikael**, for other good moments in life enjoyed on a saddle.
Thomas Marmolin brother in law and close friend, for continous computer support.
Birgitta and **Bengt Eriksson**, my parents for providing me with a good platform in life, and for your unconditional love.
Ulla and **Hans Marmolin**, my parents in laws for understanding my need for doing this research, and for your support.
And finally my family, **Allan**, **Ingmar** and **Folke** my best boys in the world, thank you for your patience, 'the work' is finally done, and **Susanne** my love, for understanding and supporting me, and for staying with me on the rollercoaster of life.

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16 ORIGINAL PAPERS (I – IV)