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NEW ASPECTS ON TIMING AND GRAFT MORBIDITY IN ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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New aspects on timing and graft morbidity in Anterior Cruciate Ligament Reconstruction
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Nina and Poppy

ABSTRACT

The aim of this thesis was to investigate the effect of different surgical techniques on knee function and outcomes after an anterior cruciate ligament (ACL) reconstruction (ACLR).

In *Study I*, 70 patients with a Tegner level of six or more were assessed after randomisation between acute ACLR (within 8 days after the injury) and delayed ACLR (after normalised range of motion [ROM] 6–10 weeks after the injury) using a four-strand semitendinosus tendon graft. The primary endpoint was range of motion at three months, and in this first study the patients were followed up for six months. The results for stiffness, laxity, functional tests and functional scores were comparable for both groups. Patients who underwent delayed surgery had more muscle hypotrophy in the early phase of the rehabilitation process.

In *Study II*, 70 patients from the same randomised controlled trial as in *Study I* were assessed to compare total number of sick-leave days taken during the first year following an ACL rupture in those undergoing acute and delayed reconstruction as a means of measuring indirect socioeconomic costs. Acute reconstruction resulted in significant fewer sick-leave days during the first year after the injury. Acute and delayed ACL reconstruction provided similar clinical outcomes after 12 months with no significant differences.

In *Study III*, the patients in *Study I* were assessed at 24 months post-surgery. Twelve patients were lost to follow-up, six in each group. While no significant differences regarding outcome measurements between the groups could be found, both groups showed better functional outcome scores compared to the Swedish Knee Ligament Register (SKLR).

In *Study IV*, 140 patients were randomised between ipsilateral (IL) and contralateral (CL) four-strand semitendinosus tendon autograft and followed up for 24 months. The aim was to compare muscle strength and patient reported outcomes following ACLR using a semitendinosus (ST) graft from the IL leg compared to a graft from the CL leg and the primary endpoint was isometric hamstring strength at 6 months The results did not show any measurable subjective differences. The CL group showed early symmetrical strength between the limbs, while the IL group stayed asymmetrical during the whole trial with significant differences between the groups in both isometric and isokinetic strength.

In conclusion, acute ACLR can be performed safely without an increased risk of developing stiffness, and a reconstruction performed before recurrent giving ways occur increases the likelihood of achieving better functional scores. There is also, from a society viewpoint, a potential economic benefit to identifying individuals who would benefit from acute ACL reconstruction. Using a CL autograft is a safe option and could have benefits regarding regaining symmetrical strength between the limbs

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following original articles and manuscript. Every paper will be referred to in the text by their corresponding Roman numerals.

I. Eriksson K, **von Essen C**, Jönhagen S, Barenius B. No risk of arthrofibrosis after acute anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc. 2018 Oct;26(10):2875-2882. doi: 10.1007/s00167-017-4814-1. Epub 2017 Nov 29. PMID: 29188336; PMCID: PMC6154043.

II. **von Essen C**, McCallum S, Barenius B, Eriksson K. Acute reconstruction results in less sick-leave days and as such fewer indirect costs to the individual and society compared to delayed reconstruction for ACL injuries. Knee Surg Sports Traumatol Arthrosc. 2020 Jul;28(7):2044-2052. doi: 10.1007/s00167-019-05397-3. Epub 2019 Feb 14. PMID: 30762087; PMCID: PMC7347679.

III. **von Essen C**, Eriksson K, Barenius B. Acute ACL reconstruction shows superior clinical results and can be performed safely without an increased risk of developing arthrofibrosis. Knee Surg Sports Traumatol Arthrosc. 2020 Jul;28(7):2036-2043. doi: 10.1007/s00167-019-05722-w. Epub 2019 Sep 26. PMID: 31559463; PMCID: PMC7347704.

IV. **von Essen C**, Barenius B, Eriksson K. Utilizing a contralateral hamstring autograft facilitates earlier isokinetic and isometric strength recovery after anterior cruciate ligament reconstruction. Submitted manuscript

LIST OF ABBREVIATIONS

ACL	Anterior cruciate ligament
ACLR	Anterior cruciate ligament reconstruction
ADB	Anatomic double bundle
AF	Arthrofibrosis
AM	Anteromedial
AP	Anteroposterior
BPTB	Bone patella tendon bone graft
CI	Confidence interval
CL	Contralateral
CONSORT	Consolidated Standards of Reporting Trials
DB	Double boundle
FR	Functional Recovery
G	Gracilis tendon
HT	Hamstring tendon
IKDC	International Knee Documentation Committee
KOOS	Knee Injury and Osteoarthritis Outcome Score
Subscales KOOS	
ADL	Activities of daily life
Sp/Rec	Function in sport and recreation
Pain	Symptoms of pain
Symptoms	Other symptoms
QoL	Knee-related quality of life
LCL	Lateral collateral ligament
LSI	Limb Symmetri Index
MCL	Medial collateral ligament
MIC	Minimal Important Change
MRI	Magnetic resonance imaging
OA	Osteoarthritis
PASS	Patient Acceptable Symptom Stage
PCL	Posterior cruciate ligament

PL	Posterolateral
PRO	Patient reported outcome
QALY	Quality-adjusted life-year
QT	Quadriceps tendon
RCT	Randomized controlled trial
ROM	Range of motion
SB	Single bundle
SD	Standard deviation
SES	Socioeconomic Status
SKLR	Swedish national knee ligament register
ST	Semitendinosus tendon
STG	Semitendinosus and gracilis tendon
TF	Treatment Failure
TT	Transtibial

DEFINITIONS

ACL reconstruction	Reconstruction of the anterior cruciate ligament using a tissue or graft
Allograft	Tissue transplanted from one person to another
Autograft	Tissue taken and transferred from one spot to another on the person's body
Bias	Systematic error
Closed kinetic chain exercises	Physical exercise where the motion of a limb can have restricted range of motion
Cohort Study	A prospective observational study where a group of individuals with a common property is monitored over time. Used e.g. in order to study the effect of a particular exposure.
Contralateral	Belonging to or occurring on the opposite side of the body
Effect size	An effect in a study is really just the result, i.e. what was found. If one is looking for the difference between two groups, the effect is the difference found. The effect size measures the strength of the result and is just magnitude based and does not depend on the sample size. Therefore, a significant *p*-value tells us that an intervention works, whereas an effect size tells us how much it works. 0.2 is considered a 'small' effect size, 0.5 represents a 'medium' effect size and 0.8 a 'large' effect size
Functional Recovery	Definition of a level of the Knee Injury and Osteoarthritis Outcome Score (KOOS) representing patients with a functional recovery after their ACL reconstruction, used in *Study III and 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.
Graft failure	Insufficiency of the reconstructed ACL graft

Ipsilateral	Belonging to or occurring on the same side of the body
Instability	A subjective unreliability due to increased looseness compared to normal
Laxity	An objective finding of looseness of the joint
Meta-analysis	A statistical analysis of multiple separate studies adressing the same question in order to test the pooled data for statistical significance
MIC	the smallest measured change in score that patients perceive as being important.
Null hypothesis	A hypothesis used in statistics that proposes that there is no difference between certain characteristics of a population
p-value	Probability value, the probability of observing a at least equal extreme value as the result about the null hypothesis is true. $p < 0.05$ is practice in medical science
PASS	Patient acceptable symptom state (PASS), an acceptable state that corresponds to ‘feeling well’. Thresholds have been defined for both IKDC; 75,9, and for KOOS (Pain = 88.9, Symptoms = 57.1, ADL = 100, Sport = 75.0,QoL = 62.5)
Power	The probability of avoiding a Type II error for a true treatment effect of given magnitude
Prospective	Forward in time
QALY	Quality-adjusted life-years, enables comparisons between therapy areas and provides a more comprehensive picture of the health effects of a treatment. The QALY measure is designed so that a year of life is multiplied by the quality of life during the year of life. The quality of life is between 0 and 1, where 1 corresponds to full health and 0 corresponds to death. A person living five years with full health has the equivalent of 5 QALY, while a person living five years with a 80 percent quality of life weight has 4 QALY (0.8 * 5 = 3)

Randomised clinical trial	A controlled clinical trial in which intervention group (es) is compared with control group (s) and where the study objects drawn / randomised to one of the respective groups and followed prospectively over time. Golden standard for clinical trials.
Retrospective	Backward in time
Revision surgery	Surgery performed to replace a failed ACL implant
Sensitivity	The probability of a positive test result when the positive result is the correct result
Specificity	The probability of negative test result when negative result is the correct result
Systematic review	A review or a literature study focused on a research question that attempts to identify, evaluate, select and compile all high-quality research evidence relevant to the question. The data from the included studies are then collected and analysed
Treatment failure	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.
Type I error	Incorrect rejection of a true null hypothesis ('false positive'), or an overestimation of the relationship
Type II error	Failure to reject a false null hypothesis ('false negative'), often due to lack of power, or an underestimation of the relationship

CONTENTS

1 INTRODUCTION

The anterior cruciate ligament (ACL) prevents the anterior translation of the tibia in regard to the femur as well as the rotation of the tibia. Although a rupture of the ACL frequently happens in contact sport, such as football (US: soccer), it often occurs without contact[1]. The result of an ACL injury is commonly an unstable knee joint where the instability could lead to episodes of ‘giving way’. Some people with a torn ACL do not experience instability or ‘giving way’ they are typically referred to as ‘copers’. However, most of these persons modify their activity and are therefore named ‘adapters’[2]. The ‘non-copers’ are those who cannot return to their previous activity level due to the instability caused by the ruptured ACL. With a torn ACL, there is a risk for recurrent ‘giving ways’ and secondary injuries, such as meniscus or cartilage lesion, as well as other ligament injuries[3-5]. Among active patients, the rate of ‘true copers’ seems to be low. Frobell et al. did a randomised controlled trial (RCT) comparing operative and conservative treatment, and had conservative-to-operative crossover rate of more than 50%, and in a study by Hurd et al.,who had developed an algorithm to classify highly active patients as potential copers, found that within 10 years of the ACL rupture, 83% of the potential ‘copers’ had undergone anterior cruciate ligament reconstruction (ACLR)[6 7]. Therefore, ACLR is the preferred treatment for active patients who wish to return to sport (RTS), and in my opinion it should be performed as soon as possible to prevent downstream effects.

2 BACKGROUND

2.1 ANATOMY OF THE ACL

The knee, or the tibiofemoral joint, is a hinged joint formed between the femur, tibia and patella and involves both rotation and translation. The surfaces of the joint are covered with a layer of hyaline cartilage, which gives the bones a smooth surface and protects the bone. Between the femur and tibia are the menisci, which act as shock absorbers and stabilisers in the knee[8 9]. The knee is dynamically stabilised by muscles and ligaments to hold it in proper alignment.

The ACL is one of four ligaments of the knee, and its primary role, working together with the posterior cruciate ligament (PCL), is to prevent the anteroposterior displacement of the tibia on the femur and secondarily to provide rotational stability[10].

The ACL is an intraarticular extrasynovial structure, originating from mesenchymal cells, and is richly vascularised from the middle genicular artery[11 12]. It consists mainly of parallel collagen 1 fibres and a matrix of different glycoproteins, making a complex, elastic system, allowing it to withstand tension and load[13]. As all people are unique, the anatomies of the ACL differ from knee to knee. The ACL has an average length of 32 mm with an average diameter of 11 mm[14] and runs from the anterior intercondylar spine of the tibia to the medial wall of the lateral femoral condyle[15]. Although regarded as one ligament, the ACL is often described as consisting of two bundles, the anteromedial (AM) and posterolateral (PL)[16 17]. The femoral insertions of the AM and PL bands are often separated by a bony landmark, the bifurcated lateral ridge, which, together with the intercondylar ridge, is used to identify the anatomical position for the femoral tunnel in ACLR. Both the AM and PL prevent anterior translation and internal and external rotation of the tibia in relation to the femur, with the AM band more tense from 30° to 90° and the PL from 0° to 30° of knee flexion[15 18]. Studies have showed that the AM bundle is superior to the PL bundle in terms of anteroposterior and rotational stability[19 20]. A fact worth considering when choosing the tunnel positioning during ACLR.

2.2 EPIDEMIOLOGY

The incidence of ACL injuries varies between 68–80 per 100 000 persons per year in Sweden and worldwide[21-24], and it is suggested that around 50% of ACL injuries in Sweden undergo surgery[25]. The most common age group for ACLR is 15–19 years[1], and even though it has been reported that females have a higher risk for ACL injuries[26 27], males are overrepresented in terms of reconstruction[1].

The vast majority (80%) of ACL injuries happen in non-contact situations, especially cutting or landing[28-30], and football is the most common sport[1]. Koga et al. used a model-based image-matching technique and concluded that the injury occurs close to full knee extension (i.e. axial compression) in combination with valgus force[31]. Quadriceps contraction has also been suggested as a potential contributor to ACL injuries[30]. As a result, there has been a development of prevention exercises and neuromuscular training programmes, which have proven to be effective in reducing ACL injuries[32-34].

An ACL injury is seldom isolated; concomitant structural injuries, such as the menisci, the collateral ligaments or the cartilage, are affected in up to 88% of these injuries[35].

2.3 CLINICAL ASSESSMENT OF ACL INJURIES

While magnetic resonance imaging (MRI) is a valid and non-invasive diagnostic method to find the injury (specificity and sensitivity of 94–98%)[36 37], it is also relevant to assess a suspected ACL injury by evaluating the increased anteroposterior laxity as well as the rotational knee laxity.

The most commonly used physical examinations are described as follows.

The Lachman test

The Lachman test, with reported sensitivity values ranging from 0.63–0.93 and specificity values ranging from 0.55–0.99[38], is performed with the patient's knee in 30° of flexion and is assessed relative to the contralateral (CL) knee. The tibia is pulled forward to assess the amount of anterior translation of the tibia. An intact ACL should prevent forward translational movement, while an ACL injury will demonstrate increased anterior translation without an endpoint. A difference between the legs of more than 2 mm indicates an ACL injury[39 40]. To quantify the anteroposterior laxity, the most common devices are the KT-1000 and the Rolimeter, both of which can be used to determine the movement in millimetres[41 42].

The anterior drawer test

The test is performed with the patient in the supine position with the hip flexed to 45° and the knee flexed to 90° with the feet flat on the ground. The examiner tries to translate the tibia anteriorly to the femur. The test is positive if there is a side-to-side difference. The test has high sensitivity and specificity in chronic conditions but not in acute conditions[39], reported sensitivity values ranging from 0.18–0.92 and specificity values ranging from 0.78–0.98[38].

The pivot shift test

The test is performed by applying valgus stress and axial load while internally rotating the tibia as the knee is slowly moved from extension to flexion. This test is considered positive if the proximal tibia subluxes anteriorly on the distal femur at about 30° of flexion[44]. The test has a sensitivity of 0.18 to 0.48 and a specificity of 0.97 to 0.99[38]. However, the grading of the pivot shift test is highly subjective due to impossibility of comparing grading between studies[45 46]. In these studies, the pivot shift was graded either normal or not.

2.4 TREATMENT

The aim of any treatment of an ACL injury is to reduce the feeling of instability and to restore the function of the knee. The treatment can be surgical or non-surgical, both with rehabilitation.

Who will benefit from ACLR is still debated as the long-term outcome after ACLR compared to conservative treatment has not been proven to be better[6 47 48]. Many patients never go back to their pre-injury activity level, and many patients develop osteoarthritis (OA) of the knee irrespective of treatment[4 49-52]. However, it is well established that ACLR decreases pathologic laxity and reduces episodes of instability[5 6 53].

A general opinion is that high-level athletes, in particular those engaging in pivoting sports, are likely to benefit from ACLR as well as those suffering from recurrent 'giving ways', hence persons having a higher risk for subsequent meniscal or chondral injuries[25 54].

Frobell et al.[6 47] published a randomised controlled trial (RCT) on the subject, comparing initial ACL reconstruction with rehabilitation alone and a choice of later reconstruction. They found no differences between the groups and therefore concluded that rehabilitation alone should be regarded as the primary treatment after an ACL injury, but these findings need to be viewed in the context that nearly 50% of the participants with an ACL rupture remained symptomatic following rehabilitation and later opted for ACLR. Similarly, a recent Cochrane review concluded that there is not enough evidence to suggest that the two options are equally effective[55].

2.4.1 Surgical treatment

2.4.1.1 Position of the graft

The main problem for the patient is instability, so the main goal of ACLR is restoring normal stability[56]. A few decades ago, at the beginning of the arthroscopic ACLR era, a transtibial (TT) approach for reconstructing the ACL was used, and the objective was an 'isometric' position, where the aim was to achieve the same tension force on the graft at all angles. This meant placing the graft in a more non-anatomical vertical position, with a posterior placement of the tibial tunnel and the femoral tunnel both high and posterior[57 58]; however, this position did not to the same degree restore rotational stability[59]. This led to a transition to instead strive for an anatomical replacement of the ruptured ACL using an accessory AM portal for reaming the femoral tunnel. This can be done by either a single-bundle (SB) or a double-bundle (DB) technique, where the DB tries to mimic the ACL according to its AM and PL bundles. Both these techniques restore the kinematics in the knee [60-62] and have also proven to be better than the TT technique in improving rotational stability[33 34 63] although studies do not show that the DB procedure restores rotational stability better than the SB procedure[57 64-66].

2.4.1.2 *Grafts used in ACLR*

The most widely used autografts for reconstruction of the ACL include the patellar tendon (BPTB), the hamstring tendon (HT) and the quadriceps tendon (QT), all of which have their own advantages and disadvantages. There are numerous studies that have evaluated the results between the three, but for the most part, they show comparable results in terms of successfully stabilising the knee[67-70], but BTBP grafts are considered to create more donor site morbidity compared to HT grafts[71-73]. In addition to autografts, there is also the option for allografts.

Additionally, studies examining which graft to choose have found that the surgeon's recommendation was the primary influencer[74 75].

The BPTB autograft is still considered the gold standard in ACLR[76 77], but at least in Sweden the HT has replaced it as the most commonly used graft[21].

Patella tendon (BTPB) autograft

Among the advantages of the BTPB is the ease of harvest, and the bone plugs at both ends facilitate graft fixation. Its most significant disadvantage is donor site morbidity. Anterior knee pain is common with BTPB, at around 50%, and kneeling pain, around 65%, at two-year follow-up[78 79]. An extension deficit can be seen up to three years postoperatively, but all of these morbidities usually disappear over time[78]. Other rare complications are patella fractures (incidence 0.4–1.3%) and patella tendon ruptures (incidence 0.18–0.25%)[70].

Hamstring tendon (HT) autograft

HT grafts are mostly reported based on the number of strands included in the grafts and can be further classified into semitendinosus and gracilis (STG) or just semitendinosus (ST). The extent to which HT graft size matters in regard to failure rate is still unclear; evidence indicates that the graft diameter should be at least 8 mm[80-82], and two studies showed a linear correlation that the likelihood of revision surgery decrease with every 0.5-mm increase of diameter in the HT graft size up to a graft size of 10 mm[82 83]. HT also has some donor site morbidities, which include both sensory and strength deficits. The sensory deficit is typically related to the incision, where branches of the saphenous nerve is easy to disrupt[84]. The main drawback of HT harvesting is the considerable deficit in knee flexion and tibial internal rotation strength[85] and might therefore be less suitable for patients dependent on deep flexion strength, such as wrestlers, gymnasts and other high-level athletes. The HT will in most cases regenerate after harvest although functional deficit may persist for at least two years[84 86-89]. The ST and G tendons insert at the pes anserinus region, and if they do not regenerate at full length, the biomechanics in the knee might change.

Quadriceps tendon (QT) autograft

QT has gained popularity in recent years[90]. Harvest of the QT can be done with or without a bone block, and the morbidity has been reported as low[73]. The most commonly reported morbidities are anterior knee pain and strength deficit, and more rare reports include bleeding and haematoma formation, cosmetic deformities of the distal thigh and patella fracture[73 91]. In a systematic review, the anterior knee pain was less frequently seen with QT compared to BPTB, and in regard to strength, there was no difference between QT and BPTB. Additionally, QT had greater flexion strength over HT but less knee extension strength[91].

Allograft

An allograft is a tissue transplanted from another person. In Europe, the allograft is not routinely used for primary ACLR, but it is common in the USA[92]. There are also indications of less stability and higher failure rates after ACLR with allografts, especially in the younger population[93 94].

Contralateral (CL) graft

Clinical observation when using the CL leg for donor graft with revisions of ACLR has raised the possibility to use it as a good donor candidate for primary reconstruction[95-98]. The CL BPTB has been widely used and studied for primary reconstruction with good results[98-100]. However, as for CL HT, the first reported study was by Yasuda[101], who mainly aimed to distinguish the morbidity caused by STG harvest. To my knowledge, the only other study undertaken on this subject is an RCT by McRae et al.[102], also using STG; however, this study could not demonstrate any drawbacks or benefits.

Andernord et al. studied the association of harvest site and the future need for CL reconstruction and found an increased risk among female patients who underwent ACLR with a CL HT graft[96]. One explanation could be that females depend more on their hamstring performance on the ACL than their male counterparts[103]. However, there were few patients, and no other study has showed the same association.

2.5 WHEN IS THE RIGHT TIME TO PERFORM ACLR?

At the beginning of the ACLR era, ACLR was considered an acute procedure[104 105], but at the beginning of 1990s, Shelbourne and colleagues[106 107] evaluated the effect of the timing of surgery after acute ACLR and found a significant increase in arthrofibrosis(AF) in patients who underwent surgery within the first week of injury. This led to a paradigm shift that is largely still in effect today. According to this paradigm, ACLR should be performed when ROM has normalised, usually at least three weeks after injury[108]. However, several studies have shown a similar postoperative ROM regardless of when surgery was performed[109-111].

Sweden has embraced a treatment algorithm, which means that most patients first receive non-surgical treatment, thereby extending the time to surgery[112]. This is in line with the studies by Frobell et al.[6 47]. An advantage of delaying surgery is that the patients can prepare for the reconstruction and establish realistic recovery goals and, so-called ‘copers’ can also be identified. However, there is evidence that early ACLR can facilitate better results, including earlier RTS and work, and has been reported to be more cost effective, while there is also evidence that increased time between injury and surgical intervention is associated with an increased incidence of concomitant injuries[3 5 113-119].

There is, however, no clear definition in regard of the time from injury to reconstruction what early or delayed reconstruction is. This lack of definition is leading to conflicting evidence of risks and benefits. Andernord et al. pointed out in a systematic review that early ACLR ranged from two days to seven months, while delayed ranged from three weeks to 24 months[109]. Other, more recent meta-analyses also had broad or overlapping cut-offs[120 121], which makes it impossible to draw any conclusions regarding timing. Two other recent meta-analyses, which had a clearer definition of acute and delayed reconstruction, within three weeks as according to Shelbourne, could not find any differences between the groups[122 123].

2.6 OUTCOME

While the surgeon rates success from objective measures, such as laxity, ROM and muscle function, the subjective measures from the patient's perspective are usually assessed via questionnaires, often referred to as patient-reported outcomes (PROs). As there are more than 54 outcome scores for ACL ruptures[124], it is important to use those that are validated and possible to compare with other studies. One of the first validated forms was the International Knee Documentation Committee (IKDC) form, designed in 1982 and which has had widespread use since then[125]. Health-related quality of life (HRQoL) questionnaires were developed for self-administration, and the one used the most within ACL research is currently the Knee Injury and Osteoarthritis Outcome Score (KOOS), which is specific to knee injuries and is validated and used in the SKLR as an outcome measure[126 127]. While a certain score in KOOS might be satisfactory for the surgeon, it does not have to correlate to the patient's wellbeing. Therefore, Barenius et al. suggested threshold values for what they defined as functional recovery (FR), and these values were based on the lower threshold for 95% confidence interval of 18–34-year-old males in a Swedish reference population two years post-surgery[128]. Another study by Muller et al. defined threshold values for what they named patient-acceptable symptom state (PASS), and the values were defined by a study population of 251 patients answering the question – 'Taking into account all the activity you have during your daily life, your level of pain, and also your activity limitations and participation restrictions, do you consider the current state of your knee satisfactory?' – one to five years after ACLR[129]. The values for the subscales differ between PASS and FR and thresholds are not interchangeable. While FR is equivalent to a return to a nearly pre-injury KOOS level, hence harder to obtain, PASS is a measure of what the patient finds an acceptable state. In the national cohort by Barenius, only one-fifth of the patients were in FR after two years, while in a recent study by Cristiani et al., more than 60% reported PASS on four of the five subscales in KOOS[128 130]. Another study, by Ingelsrud et al., conducted similar research in which they asked patients from the Norwegian knee ligament register about their acceptable symptom state[131]. The patients were categorised into three groups – those with acceptable symptoms, those who felt that their treatment had failed and a third category for those who were indecisive. This study showed acceptable symptoms in 66%, even if the cut-offs used in this study were similar to the ones in Barenius study for pain, symptoms and ADL they were lower for Sport/Rec and QoL. For QoL a score of 72 would be enough to reach an acceptable state compared to 81 in the study by Barenius. One reason for this could be that Barenius only extracted data from the register, whereas the Norwegian study asked the question directly. For PROs, Ingelsrud also confirmed that the subscales for Sport/Rec and QoL are the most important and defined the minimal important change (MIC) after ACLR. In a study from 2018, they found that that the MIC values for Sport/Rec and QoL were 12 and 18, respectively[132].

While treatment failure (TF) is as important as success, it has been a bit overlooked in the literature. In the Barenius study, the cut-off value for TF was set as subscale QoL < 44. This value is from a study by Frobell, randomising between surgical vs non-surgical treatment after an ACL injury[47]. The value of 44 was one criterion for crossover from non-surgical to surgical treatment. In the cohort by Barenius, 30% of the patients were defined as TF. In Ingelsrud's study, the KOOS subscale QoL value for TF was < 28, and therefore only 13% in this cohort study was regarded as TF[131].

2.6.1 Rerupture rate and CL injuries

An ACL graft tear or a CL ACL injury is detrimental to patient outcomes following ACLR. From the results of systematic reviews, one can expect a failure rate between 3.5 and 7% of the autografts[133-135]. Younger patients, especially adolescents, run an even higher risk of another ACL injury[136 137]. There may be many reasons for this although younger patients RTS with frequent pivoting movements, such as football, at a higher rate than older patients[137 138]. By exposing the knee to a higher degree of pivoting movements, the knee will be at a higher risk of an injury and could explain why younger patients run a greater risk for a subsequent ACL injury. In a more recent study, Grindem et al. concluded that age itself was not associated with a second ACL inury[139]. They found that, independent of age, return to high-level pivoting sports within the first year resulted in a six-times-higher risk for another ACL injury and that younger patients are more likely to return to this activity level and therefore ran a higher risk for a rerupture. By making sure the patients had gained symmetrical strength and delaying the return for at least nine months, the risk for a rerupture decreased[140]. Although females run a higher risk for a primary ACL injury, studies have not shown sex to be a risk factor for a reinjury[138 141 142]. This could be explained by the fact that women seem to return to a lower level of activity[143]. The exact rate of re-tears is difficult to determine as there are many unrecorded – some might cope with occasional giving-way, while others are no longer as active as before and therefore are not bothered by the graft rupture. Most graft failures occur during the first year after reconstruction, which could be due to an inadequate incorporation process of the graft[144 145].

Revision surgery could be another outcome measure as it might represent patients with clinical symptoms of a re-tear. The rates of revision surgery have been reported at 2–3% within the first two to three years[146 147] and an overall revision rate of approximately 4% in both the Danish ACL Reconstruction Register and SKLR[146 148]. Sadly, the outcome after a revision surgery is often less successful[149].

In terms of CL ACL injury, the numbers are between 12–14%[133 135 150]. It often occurs during the first three years after the first ACLR, and risk factors are age, sex and activity at the primary ACLR[96 144 150 151].

2.6.2 Return to sport (RTS)

The majority of patients undergoing ACLR are active in sports and want to return to their pre-injury activity level although this is not a guarantee even after surgery. A recent meta-analysis by Ardern et al.[143] reported that only two-thirds manage to return to their previous level, however 82% returned to some type of sport participation. Other systemic reviews looking at high-performance athletes showed that most returned to their pre-injury level, with rates varying between 78 and 90%[152-154].

2.7 ARTHROFIBROSIS

Arthrofibrosis (AF) is abnormal internal scarring inside the joint and can occur in almost any joint[155]. The fibrotic scarring is caused by an inflammatory response, leading to an uncontrolled myofibroblast proliferation with reduced normal aptosis. This in turn makes a lot of extracellular matrix composed of collagen, which causes sticky adhesion and contracts tendons and bursa and makes the knee lose its ROM[156]. Why AF occurs is still unknown but seems to have a physical trigger, such as surgery, and certain procedures have an increased risk, especially ACLR[157 158]. The incidence of AF after ACLR ranges between 2 and 35%, and the difference might be the lack of uniformity in defining AF[157 158]. Shelbourne et al. developed the most common classification in use in 1996. They defined AF as a 5° loss of extension and proposed a classification system based on flexion and extension loss[159] (see Table 1). An international panel of experts developed a more recent classification in which a restricted ROM in flexion or extension or both must be present for a diagnosis of AF[160]. The severity is then graded according to loss of movement based on the deviation from full flexion or extension as mild, moderate and severe flexion range (90°–100°, 70°–89°, < 70°) and/or extension restriction (5°–10°, 11°–20°, > 20°)[160]. Mayr et al. proposed another classification; AF should be defined if scar tissue is found in at least one compartment of the joint and affects the ROM[161]. These definitions are objective cut-offs, but other studies use subjective restriction of ROM as a definition of AF, which makes it unclear the severity of the AF and therefore hard to review the literature and to determine risk factors for AF[162]. Other reasons for ROM problems can be poor surgical technique, poor graft positioning and inappropriate width of the graft[158]. The aim of investigating a patient with a stiff knee after surgery is to exclude other causes of stiffness. CT or plain radiography can show malpositioning or patella infera. An infection should also be excluded. MRI can show scar tissue but is not totally reliable in the diagnosis of AF[160]. If there are no other causes of stiffness, an arthroscopy may be performed to support the clinical diagnosis. Patients requiring intervention range from 0.5% to 5.4% in different studies, and females carry a higher risk[158 163 164]. One could define AF as early, within 3–6 months, or late, > 6months, and treatment depends on this. If motion loss develops early, NSAID and/or intra-articular steroid injections can be used, and a trial of intensive physiotherapy might help in regaining ROM[165]. If this fails, manipulation under anaesthesia (MUA)[165] can be performed. Patients with late AF or patients resistant to non-operative treatment usually require arthroscopic treatment[160 166].

Table 1: Classification of arthrofibrosis

Arthrofibrosis	Extension Loss	Flexion Loss	Patellar Tightness (Yes/No)	Patella Baja (Yes/No)
Type 1	<10°	None	No	No
Type 2	>10°	None	No	No
Type 3	>10°	>25°	Yes	No
Type 4	>10°	≥30°	Yes	Yes

Adapted from Shelbourne et al.[159]

A 'cyclops lesion' is special localised fibrosus noduli which occur in the intercondylar notch with a pattern histologically different than that of AF and should therefore not be mistaken for AF[167]. The incidence range from 1.9–10.9% and can occur after ACLR and can cause knee extension loss[168]. It has been suggested that the debris from the tibia tunnel or microtrauma to the graft stimulates cyclops lesions[169]. A recent systematic review identified knee stiffness before ACLR, a narrow intercondylar notch and a tibial tunnel position too anterior as risk factors for developing cyclops lesions[168]. A cyclops lesion, if symptomatic, is treated with arthroscopic removal[158 167] and can be detected with MRI[170]

2.8 OSTEOARTHRITIS (OA)

Patients with an ACL injury run a much higher risk of developing post-traumatic OA over the long term, up to 20 years from injury; a 10-fold increased risk has been reported[4 171]. Studies also show that meniscus injuries are associated with a higher rate of secondary OA[4 172-174]. There are reports suggesting that meniscus sutures to some extent prevent secondary OA[175 176]. Even though no treatment for an ACL injury has shown to reduce the risk for OA, there are indications that factors protecting the knee from subsequent injuries, such as early ACLR[54], and an increased focus on saving the meniscus[176] might be beneficial in reducing the risk of secondary OA[177]. It will be interesting to see what the future holds.

2.9 HEALTHCARE SYSTEM AND SOCIOECONOMICS

Healthcare in Sweden is largely tax-funded and decentralised. It is a system where everyone has equal access to healthcare services. The central government, country councils and municipalities are in charge of and responsible for the healthcare services. The coverage is extensive, and patients only pay small fees when visiting a doctor, with a maximum of 1,100 SEK per 12 months. Private healthcare is also available but is rather small although expanding each year.

If a person cannot work in Sweden due to sickness or injury, he or she can obtain compensation with a sick leave benefit. The system is regulated by Swedish law and for the first day of illness, a qualifying deduction is made which corresponds to 20 % of a normal week's salary. After this first day one will obtain sick pay. As an employee, you receive sick pay from your employer up to and including day 14; after that, the money comes from the Swedish Social Insurance Agency (Försäkringskassan). The patient needs to submit a medical certificate to his or her employer after one week. There is, however, a time limit for sick leave pay; during the first 90 days, the patient is entitled to the pay if he or she is unable to cope with their normal work. For the next 90 days, the patient can get sick leave pay if he or she is unable to cope with their normal work or any other work the employer can offer. The sick leave pay is usually 80% of the worker's salary, with a maximum of 804 SEK per day, but many employers offer a form of insurance to ensure a higher salary if a person gets sick[178].

To evaluate the cost effectiveness of a treatment, quality-adjusted life-year (QALY) can be used. QALY was developed to facilitate comparison between treatments or interventions. By converting a treatment to a common unit, comparison can be made in terms of cost per standardised effect. QALY measures the benefit of an intervention to a patient over their lifetime; it measures the years a patient might gain as well as the quality of life during those years[179]. Further, taking into account to the total cost and the outcomes associated with the treatment (QALY gain) provides a value of cost per QALY. This makes it possible to compare treatments based on the total costs of their outcomes, and different countries have different threshold values of what counts as cost-effective[179].

As ACL tears usually affect young people, there are large potential economic losses when suffering an injury. Although it is hard to generalise studies due to differences in healthcare systems, there are studies showing that ACLR seems to be more cost-saving and cost-effective than rehabilitation[113 180 181]. In a recent study comparing competitive athletes, the incremental cost-effectiveness ratio of ACLR was approximately $22,000 per QALY gained[182].

2.9.1 Sick leave in other countries

Sick pay and sick leave vary from country to country. Some countries require employers to pay for the sick leave days (Australia, the Netherlands, New Zealand, Switzerland and the United Kingdom), while others have a social insurance system that covers sick pay using tax revenue (Canada, France, Ireland, Italy and Japan). Most countries use a combination of employer mandates and social insurance (Austria, Belgium, Denmark, Finland, Germany, Greece, Iceland, Luxembourg, Norway, Spain and Sweden). A waiting period is often employed, ranging from one to nine days, and represents a period where no money is paid out. There are also forms of insurance that can entitle the patient to more sick leave and other benefits.[183]

Among the more generous countries is the Netherlands, where workers can be absent up to 104 weeks and receive 70% of their salary for the whole period. The employers are obliged to cover that cost during the whole period, but not longer than the duration of the contract. There is also an upper ceiling of €200 per day. German workers are entitled to 100% of their earnings for the first six weeks and 70% thereafter. The first six weeks are covered by the employer and the rest by the state[183].

In the UK, employees have no statutory right to receive their contractual pay during time spent away from work on sick leave. They may, however, have a right to receive statutory sick pay ('SSP') at a fixed amount set by the government, which is currently £95.85 per week, with the first three days unpaid up to 28 weeks[184].

There is no national requirement in the USA to offer paid sick leave though many states have their own laws on this. However, the Family and Medical Leave Act (FMLA) requires companies with more than 50 employees to allow them unpaid time off for medical leave or to care for a family member. The rules and regulations vary for different states. For example, workers in Massachusetts receive one hour of paid sick time for every 30 hours they work. Workers in New York are given 40 hours of paid sick leave per year. Alternatively, in a minority of jurisdictions (for example, California, Connecticut and Massachusetts), employers are required to provide paid sick leave for employees[185].

As for Australia, employees are entitled to 10 days of leave each year, and if the worker does not use the days, they carries over into the next year. Employees also can take unpaid sick leave for up to three months[183].

3 AIMS

The overall aim of this thesis was to investigate the influence of different surgical strategies on the outcome after ACLR.

3.1 STUDY I

The aim of the study was to determine if it is safe to reconstruct the ACL within eight days after the injury compared to delayed ACLR after normalised ROM 6–10 weeks after the injury. The primary endpoint was ROM at three months.

Secondary aims were to compare early functional outcomes between the groups. Physical examination, instrumented laxity, functional scores and Lysholm and KOOS measured the outcome.

3.2 STUDY II

The aim of the study was to compare the total number of sick-leave days taken the first year following an ACL rupture in those undergoing acute and delayed reconstruction as a means of measuring socioeconomic costs.

Secondary aims were to compare early functional outcomes between the groups at 12 months.

3.3 STUDY III

The aim of the study was to compare acute ACLR within eight days of injury with delayed reconstruction after normalised ROM 6–10 weeks after injury in regard to outcomes when assessed at a minimum of 24 months post-surgery.

3.4 STUDY IV

The aim of the study was to compare ACLR using ST graft harvested from the ipsilateral (IL) leg compared with those where the ST graft is harvested from the CL leg. The primary endpoint was isometric hamstring strength at six months.

Secondary aims were to compare patient-reported and functional outcomes between the groups over 24 months. Physical examination, instrumented laxity, functional scores and Lysholm and KOOS measured the outcome

4 STUDY POPULATION

4.1 STUDIES I–III

Between 2006 and 2013, 70 patients were included in a one-centre RCT. Patients presenting at the emergency department with a severe knee injury were assessed with MRI within three days of the injury. If there was an ACL injury, the patient was evaluated for participation in the trial. A total of 920 patients were assessed for eligibility. Inclusion criteria were primary unilateral ACL rupture, age between 18 and 40 years and no previous injury on the involved or CL knee. Further criteria were no additional injuries on MRI indicating a need for an acute procedure nor PCL-insufficiency, LCL or MCL injury greater than grade one and no sign of OA. The study was designed to include patients with a high demand for stability in the knee; therefore, an inclusion criterion was a Tegner activity level of at least six, which is recreational sport (tennis, alpine skiing, etc.).

If the patient fulfilled the prerequisites, a research nurse performed the randomisation with sealed envelopes in batches of 20, and the patients were randomised to ACLR within eight days of injury or delayed reconstruction after normalised ROM 6–10 weeks after the injury.

The demographics of the study groups are presented in Tables 2–3. One patient dropped out before reconstruction in the delayed group due to waiting time. Preoperatively, there were no significant differences between the study groups. Both groups were similar in terms of gender, age at the time of surgery and the number and type of associated injuries.

Table 2: Descriptives of the study population

Variables	**Total (n=69)**	**Acute ACLR (n=34)**	**Delayed ACLR (n=35)**	**Sign**
Age at inclusion mean ±SD	26.9 ± 6.1	27.7 ± 6.5	26.1 ± 5.7	n.s.
Gender: females n (%)	21 (31)	10 (30)	11 (31)	n.s.
Height cm mean ±SD	177 ± 9	177 ± 9	178 ± 9	n.s.
Weight kg mean ±SD	77 ± 11	76 ± 11	78 ± 12	n.s.
Smoker n (%)	4 (6)	2 (6)	2 (6)	n.s.
Highest education n (%)				n.s.

High school/college	35 (55)	20 (65)	15 (45)	
University	29 (45)	11 (35)	18 (54)	
Type of activity when injured n (%)				n.s.
Football	27 (38)	14 (41)	13 (37)	
Indoor floorball	16 (24)	6 (18)	10 (29)	
Alpine ski/snowboard	10 (15)	7 (20)	3 (8)	
Handball	5 (7)	1 (3)	4 (11)	
Wrestling/MMA	3 (5)	3 (9)	0	
Gymnastics	2 (3)	2 (6)	0	
Ice hockey	1 (2)	0	1 (3)	
Am. football	1 (2)	0	1 (3)	
Badminton	1 (2)	0	1 (3)	
Basketball	1 (2)	0	1 (3)	
Dance	1 (2)	1 (3)	0	
Tennis	1 (2)	0	1 (3)	

Patient demographics at baseline are displayed as mean ± SD, number and percentage, respectively

Table 3: Demographics

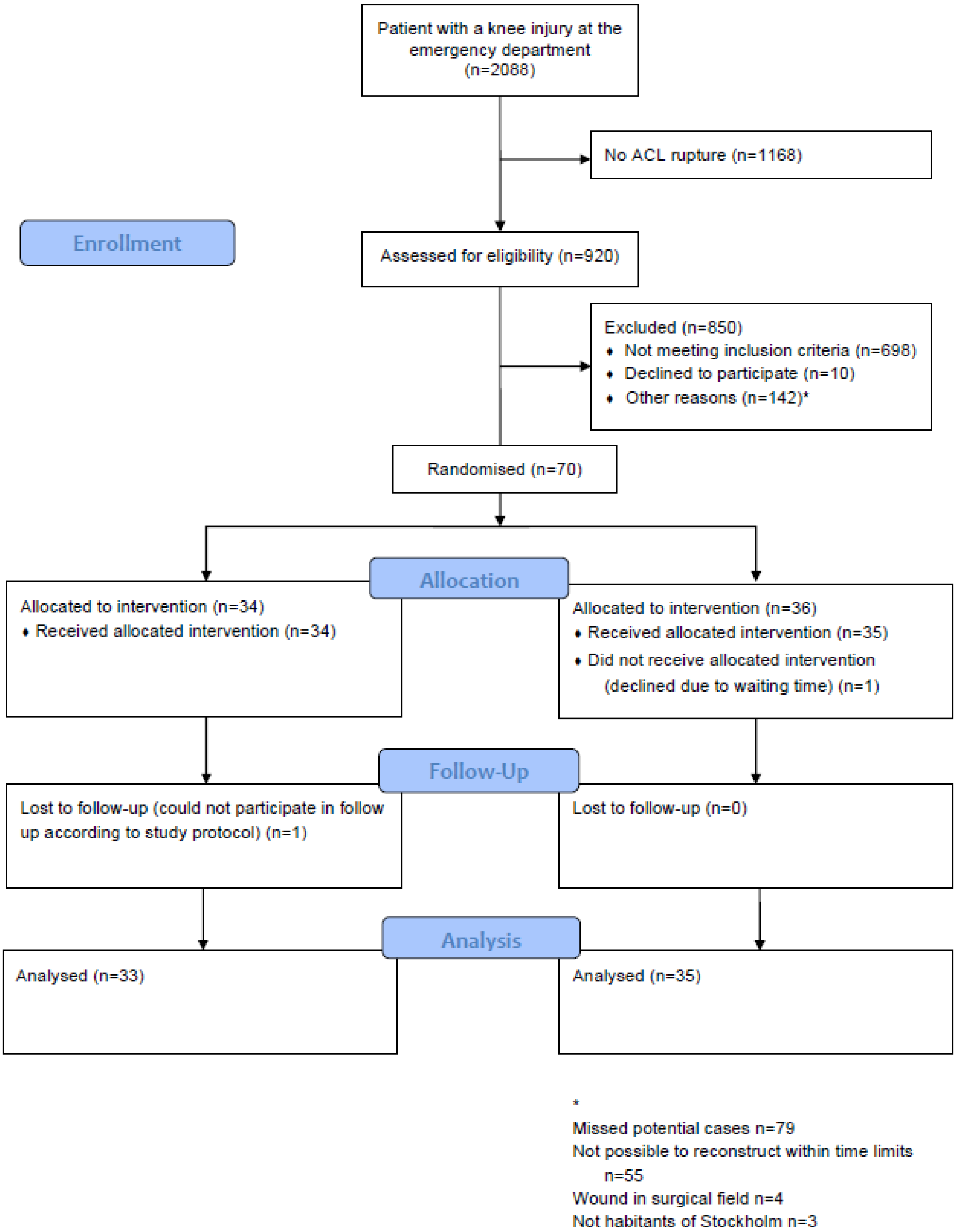
Variable		**Acute ACLR (n=34)**	**Delayed ACLR (n=35)**	**Sign**
Time injury-recon	d ± SD	5 ± 2	55 ± 8	< 0.01
OP time	min ± SD	93 ± 20	83 ± 18	n.s.
Graft diameter	mm ± SD	8.8 ± 0.8	8.6 ± 0.8	n.s.
Additional injury	n (%)	21 (66)	15 (47)	n.s.
Medial meniscus	n (%)	7 (21)	2 (6)	n.s.
Lateral meniscus	n (%)	13 (39)	10 (29)	n.s.
Sutures	n (%)	3 (9)	1 (3)	n.s.
Cartilage inj.	n (%)	10 (29)	4 (11)	n.s.
Transtibial technique	n (%)	12 (35)	10 (29)	n.s.
Anteromedial technique	n (%)	22 (65)	25 (71)	n.s.

Patient demographics at baseline for patients who underwent ACLR are displayed as mean ± SD, number and percentage, respectively. Statistical significant ($p < 0.05$) values were only seen for the time from injury to reconstruction.

4.1.1 Study I

In the study, 70 patients were included and randomised, and one dropped out due to waiting time. Therefore, 69 patients were analysed at six months. As seen in Tables 2–3, no differences were found between the groups except the time from injury to reconstruction. The CONSORT flowchart is shown in Figure 1.

Figure 1. *CONSORT flowchart of Study I*



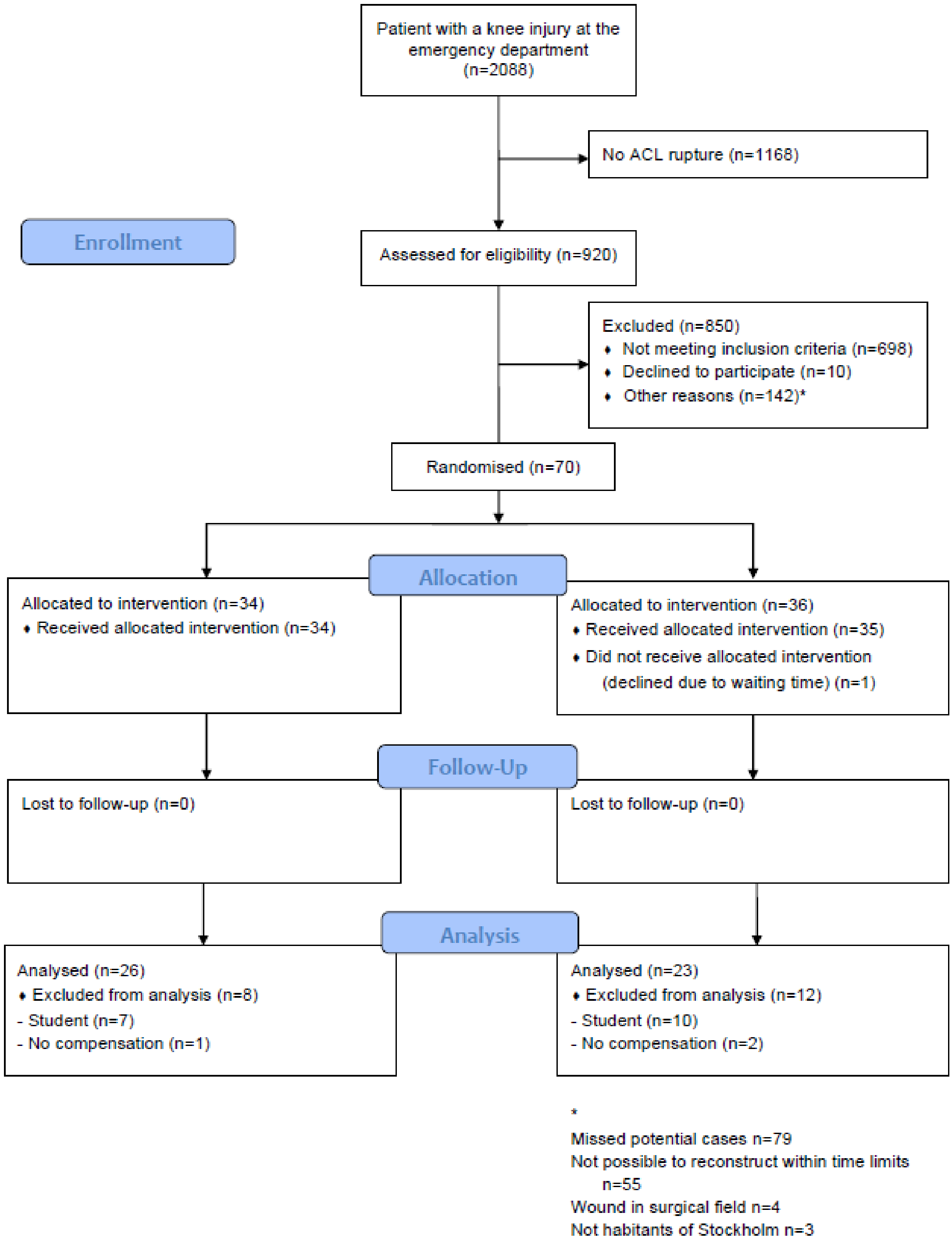
4.1.2 Study II

In *Study II*, the same study population as in *Study I* was assessed to compare total number of sick-leave days taken the first year following an ACL rupture in those undergoing acute and delayed reconstruction. The CONSORT flowchart is shown in Figure 2. No patients were lost in this follow-up. Eight patients in the acute group and 12 in the delayed group did not receive sick-leave and were therefore excluded. In regard to type of labour, there were no differences between the groups; see Table 4.

Table 4: Occupation for study participants

Main occupation n (%)	Total (n=69)	Acute ACLR (n=34)	Delayed ACLR (n=35)	Sign.
Working	49 (71)	26 (76)	23 (66)	n.s.
Heavy manual labor	12 (24)	8 (31)	4 (17)	n.s.
Light manual labor	20 (41)	10 (38)	10 (43)	n.s.
Office work	17 (35)	8 (31)	9 (39)	n.s.
No compensation	3 (4)	1(3)	2 (6)	n.s.
Student	17 (25)	7 (21)	10 (29)	n.s.

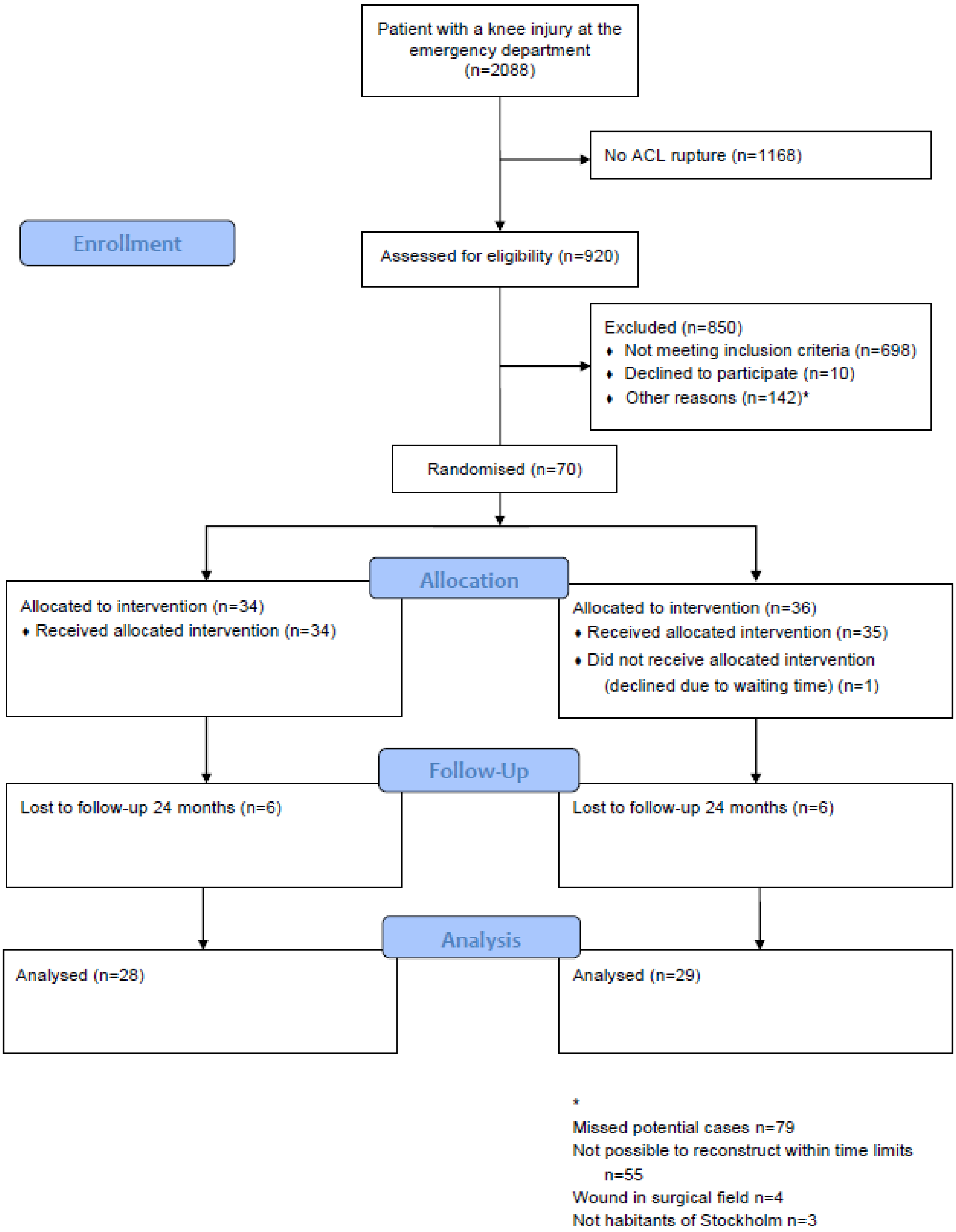
Figure 2. *CONSORT flowchart of Study II*



4.1.3 Study III

In *Study III*, the same study population as in *Study I* and *Study II* was assessed to look at and compare outcomes when assessed at a minimum of 24 months post-surgery. Twelve (17%) patients were lost to follow-up with no significant difference between groups (6 vs 6). There was no difference in mean follow-up time between the groups.

Figure 3. *CONSORT flowchart of Study III*



4.2 STUDY IV

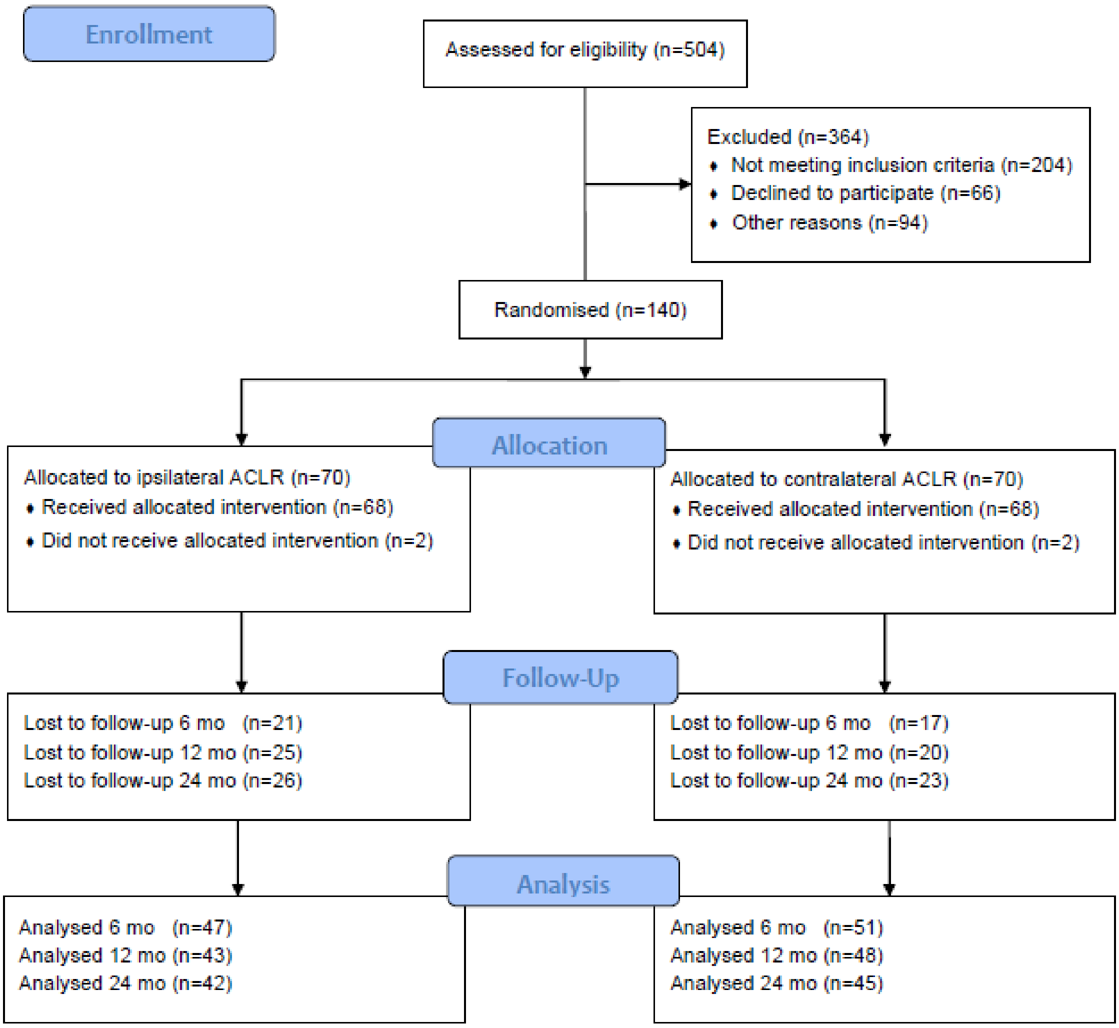
Between 2013 and 2017, an orthopaedic team screened all patients presenting with an isolated ACL injury at the orthopaedic outpatient clinic. If they met the inclusion criteria, they were asked to participate in a one-centre RCT. In total, 504 patients were assessed for eligibility, and 140 patients were included. The inclusion criteria were a primary ACL injury in a knee-healthy person between 18 and 50 years of age with no additional injuries on MRI indicating a need for an acute procedure. The patients were randomised between IL and CL four-stranded ST autograft. The primary endpoint was isometric hamstring strength at six months. The patients were followed up at 6, 12 and 24 months; patients lost to follow-up are specified in the CONSORT diagram in Figure 4. The descriptives and demographic data of the study population were obtained at baseline and included patient age, gender, time from injury to surgery and concomitant injuries. They are presented in Table 5 with no significant differences.

Table 5: Desctriptives and demographic data of study population

Variable	**Total (*n*=137)**	**Ipsilateral ACLR *n*=68**	**Contralateral ACLR *n*=69**	**Sign**
Age at inclusion, mean ± SD	33.1 ± 9	33.0± 9	31.1± 9	n.s.
Gender: female, n (%)	58 (42)	33 (48)	25(38)	n.s.
BMI mean ± SD	25.1± 3,4	25.2± 3,6	24.9± 2,9	n.s.
Time injury-recon median months (range)		5.8(1-188)	5.1(0.7-250)	n.s.
ST/G n(%)	8 (6)	4(6)	4(6)	n.s.
Additional injury n (%)	82(60)	41(60)	41(60)	n.s.
Medial meniscus n (%)	57(40)	29(42)	28(40)	n.s.
Lateral meniscus n (%)	31(22)	19(28)	12(17)	n.s.
Sutures n (%)	36(26)	16(24)	20(29)	n.s.
Cartilage inj n (%)	21(15)	7(10)	14(20)	n.s.

ACL=anterior cruciate ligament Reconstruction CL=uninjured contralateral limb
Patient demographics at baseline for patients with an ACL tear are displayed as mean ± SD, number and percentage, respectively.

Figure 4. *CONSORT flowchart of Study IV*



5 METHODS

5.1 STUDY DESIGN

5.1.1 Randomised Controlled Trial (RCT)

RCTs are thought to represent the highest quality of evidence[186]. The key aspect of any RCT is the use of a control group, to which the experimental group is compared, and randomisation, which means that the participants are randomly assigned to the interventions. Randomisation ensures that the participants in each group have a similar distribution of characteristics to ensure that the groups are comparable in terms of known and unknown confounders.

To reduce the risk of a RCT being underpowered, both the sample size and the power of the study need to be considered. A power analysis gives the researcher a way to establish the sample size required to study the expected difference between the groups. If the expected differences are small, a large sample size is needed to find the difference. If a study is underpowered, there is a risk of a type-II error, therefore failing to reject a false null-hypothesis.

Even though RCTs are considered the most accepted study design, this does not mean that they can ensure external validity. External validity refers to how the results can be generalised to other populations. An RCT often consists of homogenous populations and usually recruited with strict criteria, which make studies less applicable to other populations.

5.2 SURGICAL TECHNIQUE

5.2.1 Studies I–III

The same surgical techniques were used for the ACLRs in Studies I–III. All patients underwent arthroscopic ACLR by four experienced surgeons. Additional injuries to the menisci were assessed and treated with resection, reinsertion with meniscus sutures or expectancy. The ST was harvested through an incision over pes anserinus, and a minimum length of 26 cm for the ST tendon was required to perform a four-strand ST-only reconstruction with a free periostal flap attached. If not sufficient in diameter, the gracilis tendon was harvested as well. The technique used for the first 22 patients in these studies was a TT approach, while the remaining 47 used an AM approach. This change was made due to the evolution of the surgical technique at the time. When using the TT approach, the tibia was drilled first, and then the femur was drilled with a TT drilling technique with an angle of 45°. With the knee in 80–90° of flexion, the surgeon aimed for a femur entry point at 10 or 2 o'clock on the lateral wall using an offset guide of 5–7 mm. Using the AM approach, the surgeon drilled the femoral tunnel using an accessory medial portal, aiming for the centre of the femoral footprint. On the femoral side, the graft was attached with Endobutton Continuous Loop® (Smith & Nephew, Inc., Andover, MA 01810, USA). The cyclic loading of the graft was done with 20 repetitions of full ROM before tibial fixation, which was performed with a metal interference screw, RCI® (Smith & Nephew, Inc., Andover, MA 01810, USA), or Soft Screw® (Arthrex Inc., Naples, Florida 34108, USA) in 90° of flexion. The distal fixation was also reinforced with osteosutures.

5.2.2 Study IV

The surgical technique for the ACLR in *Study IV* was the same for the two groups except for the harvesting site. Two experienced surgeons performed the reconstructions. Firstly, a diagnostic arthroscopy was performed. The ST tendon was then harvested through an AM longitudinal incision, and only if the ST tendon was not sufficient in length of 26 cm or diameter of 8 mm, the gracilis tendon was harvested as well. A free periostal flap was extracted from the same incision. The ST tendon was quadruple over two adjustable loops with a free periostal flap attached. On the femoral side, the surgeons used a Tightrope RT™ (Arthrex, Inc., Naples, FL) and for the tibial side Tightrope ABS™ (Arthrex, Inc., Naples, FL); the graft construct was secured with sutures of nr. 2 FibreWire™ (Arthrex, Inc., Naples, FL). The femoral tunnel was drilled using an accessory AM portal, and the ACL insertion site was marked with an awl aimed at the centre of the ACL insertion site in order to place the centre of the tunnel just behind the bifurcate ridge about 8–10 mm from the posterior cartilage with the knee in 90° of flexion. On the tibial side, the centre of the tunnel was placed in alignment with the anterior horn of the lateral meniscus. For the tibial cortical fixation, a 'TightropeButton'™ (Arthrex, Inc., Naples, FL) was used. The tensioning of the construct was performed by tightening the loops according to surgeon preference.

5.3 REHABILITATION

5.3.1 Studies I–III

All patients used the same rehabilitation protocol and were treated at one physiotherapy centre to ensure all patients got the same postoperative treatment. Full weight bearing and ROM were permitted immediately as well as closed kinetic chain exercises. Open chain exercises were allowed after six weeks and running after 14 weeks. The patients were allowed to resume sport activity after Biodex® testing showed 90% strength in the injured leg compared to the CL leg but never earlier than six months. If the meniscus was sutured, the patient wore a brace for six weeks with limited ROM; otherwise, the rehabilitation was the same.

5.3.2 Study IV

The same guidelines were used for all patients as in *Study I-III,* but the patients chose where to do their physiotherapy by themselves. The patients were permitted immediate full weight-bearing and full ROM. If the meniscus required suturing, the knee was fixed in a brace with limited ROM for six months, 0–60° for four weeks and 0–90° for another two weeks.

Closed kinetic chain exercises were started immediately postoperatively. Open chain exercises were allowed after six weeks, running was permitted at three months and contact sports at nine months at the earliest, provided that the patient had regained full functional stability and Biodex® testing showed 90% strength in the injured leg compared to the CL leg.

5.4 CLINICAL EXAMINATIONS

Range of motion (ROM)

The patients were examined using a goniometer along the scale 0–180°. The uninjured leg was used as a reference and evaluated first. The maximum range of active ROM was measured, and the examiners also noted any cases of hyperextension.

The Lachman test

The Lachman test, with reported sensitivity values ranging from 0.63–0.93 and specificity values ranging from 0.55–0.99[38], is performed with the patient's knee in 30° of flexion and is assessed relative to the CL knee. The tibia is pulled forward to assess the amount of anterior translation of the tibia. An intact ACL should prevent forward translational movement, while an ACL injury will demonstrate increased anterior translation without an endpoint. A difference between the legs of more than 2 mm indicates an ACL injury[39 40]. To quantify the anteroposterior laxity, the most common devices are the KT-1000 and the Rolimeter; both can be used to determine the movement in millimetres[41 42]. The studies use the grade normal or not.

The pivot shift test

The pivot-shift test is performed by applying valgus stress and axial load while internally rotating the tibia as the knee is slowly moved from extension to flexion. This test is considered positive if the proximal tibia subluxates anteriorly on the distal femur at about 30° of flexion[44]. The test has a sensitivity of 0.18–0.48 and a specificity of 0.97–0.99[38]. However, the grading of the pivot shift test is highly subjective, therefore impossible to compare grading between studies[45 46]. In these studies, the pivot shift was either graded normal or not.

5.5 INSTRUMENTED LAXITY

Rolimeter®

Rolimeter® is a validated instrument that quantifies anterioposterior knee laxity[41 42]. The Rolimeter® is used by fixating to the patient's leg with a single adjustable ankle strap distally. There is a curved proximal plate that should be placed on the centre of the patella. The examiner then puts one hand on this to stabilise the patella and in turn fixate the femur. A metal stylus is then placed on the patient's tibial tuberosity. A modified Lachman test is then performed as the examiner applies full manual force. The anterior displacement of the stylus can then be read directly with no possibility for failure of calibration or machine error. It has been validated and compared to the KT-1000 with similar results[187].

5.6 FUNCTIONAL TESTS

One-leg hop test

This is a reliable multifunctional assessment for evaluating joint mobility, muscle strength, coordination and timing. To conduct the test, the patient stands on one leg and is asked to jump as far as possible and still be able to stick the landing on the same leg. The distance is then calculated in relation to the healthy limb and an index of more than 85% has been used as a limit for patients to be regarded rehabilitated after ACLR[188-190].

Strength using the Biodex dynamometer

A dynamometer provides an objective measurement of muscle strength; although it can be criticised for lacking functional relevance to sport and training, it is still regarded as the 'golden standard'. There are several different on the market. In the studies conducted, the Biodex (Biodex Medical Systems, Shirley, NY, USA) is used. The Biodex dynamometer (Biodex Medical Systems, Shirley, NY, USA) is a validated instrument[191]. It can be used in a number of angular velocities for measuring isokinetic torque and a number of fixed angles for measuring isometric torque. Usually, the test person does three repetitions, and the values are then averaged in the system. When performing the Biodex test, the patient sits in an upright chair with his/her leg strapped to a movable part of the testing machine. The patient is instructed to fully straighten and then fully bend the knee for multiple repetitions. The test results are used to objectively compare the surgical to the non-surgical side as well as to compare the quadriceps and hamstring muscles in the same leg. One limitation is that the patient is in a sitting position, which restricts the flexion from going further than 100°. This makes it impossible to assess strength in deep flexion.

5.7 FUNCTIONAL SCORES

The International Knee Documentation Committee (IKDC) classification

The IKDC developed an evaluation form to classify the knee after an injury. The standard form consists of the following eight problems: 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, and every point is rated A–D (normal to severely abnormal)[125].

IKDC subjective knee form score (IKDC 2000)

Developed in 2001, it is a subjective knee evaluation form, revised from the original IKDC form, regarding function, symptoms and sports activity. It contains 11 questions and a total score range from 0 to 100, with higher scores indicating better results. It is validated, but the IKDC2000 has not been shown to be reliable for the longitudinal evaluation of function at more than one time point[125 192].

Lysholm score

This instrument focuses mainly on symptoms and complaints but not functions in sport and recreational activities. The scale consists of eight items with 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[193-195].

Tegner activity level

The Tegner activity level is used for grading sport and work activities on a scale from 0 to 10 and is meant to be used together with the Lysholm score as a complement[195].

VAS 1 and VAS 2

These questions were used to rate the patients knee function on a visual analogue scale ranging from 0–100, with 0 being the worst possible score and 100 the 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?’

5.8 HEALTH-RELATED QUALITY OF LIFE (HRQOL) EVALUTAION

Knee Injury and Osteoarthritis Outcome Score (KOOS)

The KOOS is a valid, knee-specific widely used self-administered questionnaire. It is used as an outcome measure in the SKLR[21] and can be used to measure change over time[126 127]. It contains 42 questions in five subscales of pain (9 items), other symptoms (7 items), activities in daily living (ADL) (17 items), function in sport and recreation (5 items) and knee-related quality of life (QoL) (4 items). All questions are graded from 0 to 4 points. A normalised score for each subscale is then calculated, with scores range from 0 to 100, with higher score indicating better results. Barenius et al.[128] defined based on a Swedish population both FR and TF. For FR, all subscales had to be above 90 for pain, 84 for symptoms, 91 for ADL, 80 for sp/rec and 81 for QoL, and TF was defined as a score below 44 on QoL.

5.9 STATISTICAL METHODS

The data in all studies were analysed using SPSS version 22 or 25 (IBM, Armonk, NY, USA) for Macintosh.

Mean and SD or median and range were calculated for descriptive statistics depending on the normality of the data. Statistical significance was defined as $p < 0.05$ for all analyses and was two-sided in all studies. To compare between groups, the Student’s t-test (quantitative, normally distributed data), Mann-Whitney U-test (ordinal data or non-normal distributions), chi-squared test and Fisher’s exact test (nominal data) were used as appropriate.

Power analyses were conducted for *Studies I, III* and *IV* to estimate enough number of patients to include in the different studies. In *Studies I* and *III,* the sample size calculation was based on the primary outcome variable ROM at three months post-surgery, and the number of interest was 5° loss of extension according to a previous study. From clinical experience the normal range at three months is 110–135°, which stipulates a mean of 122.5. The computation assumes that the mean difference is 5 (corresponding to means of 122.5 vs 117.5), and the common within-group standard deviation is 7.0. The sample size required was 64 patients, 32 patients in each group calculated with use of a study power of 80% and a type-1 error (α) of 0.05.

In *Study IV,* the primary endpoint was isometric hamstring strength at six months. To detect a difference of 10% (SD ± 15) with a study power of 80% and a type-1 error (α) of 0.05, the study would need at least 37 patients in each group.

In *Study II,* a post hoc power analysis using G*Power 3.1.9.2 (Franz Paul, Kiel, Germany) was used to determine the effect size and power of the study. Based on the results at one year in the study population, an effect size of 0.73 was calculated, with *α* set at 0.05 and a two-sided test, the power of the study was calculated to 71%.

5.10 ETHICS

When performing any type of research, especially when testing new methods, the researcher must value the potential benefits against the harm one could cause to the patients. Before research is conducted, approval from an ethical committee is required. The regional Ethical Review Board in Stockholm has evaluated and approved all studies in this thesis (Dnr I-III 2006/404-31/3/2008/1541-32; Dnr IV 2013/1398-31/2) and was conducted according to the Declaration of Helsinki. This states, for example, that participation is voluntary and that the study participants can withdraw from participation at any time. Prior to study participation, the participants are provided with information about the study both orally and in writing, and written informed consent is obtained. To protect the integrity of the participants, each patient is given a study-specific ID number that is used throughout the data collection and data analysis.

6 SUMMARY OF PAPERS

6.1 STUDY I

6.1.1 Introduction

Historically, acute ACLR has been avoided due to reports of early rehabilitation problems with stiffness. The aim of the RCT was to assess the impact of the time between injury and reconstruction on the ROM after ACL surgery. The hypothesis was that with modern techniques it is safe and can be beneficial to reconstruct the ACL in the acute phase.

6.1.2 Material and methods

During the period 2006–2013, 70 patients with a high recreational activity level, a Tegner level of six or more, were randomised to receive ACL reconstruction with a four-strand ST graft within eight days of injury or after normalised ROM 6–10 weeks after injury. For fixation, an Endobutton® in the femur and a metallic interference screw in the tibia were used. The rehabilitation training was performed at the same physiotherapy centre for all patients. A power analysis indicated a need of 64 patients to find a 5° difference in ROM at three months. For the first three months, the patients were followed weekly by SMS with the question 'How is your knee working?' ROM was assessed after three months as the primary outcome. The follow-up at six months included a Biodex strength test, Lachman, Rolimeter, pivot shift, one leg hop, IKDC, KOOS, Lysholm and Tegner activity level.

6.1.3 Results

Seventy percent of the patients were males, the mean age at the time of inclusion was 27 years (18–41) and the pre-injury Tegner level was median 9 (5–10), with no differences between the groups. One patient in the delayed group dropped out before surgery. In total, 64 patients (91%) were assessed at three months.

At the three-month follow-up, the patients were assessed for the primary variable, with no significant differences in any range of motion demonstrated between the groups.
At the six-month follow-up, the delayed group had significantly more muscle atrophy of the quadriceps compared to the CL leg. Furthermore, significantly higher proportions of patients in the acute group passed the one leg hop test (47 vs 21%, $p < 0.05$). Additionally, no significant differences between the groups were found in the other clinical assessments nor in terms of associated injuries.

6.1.4 Conclusion

Acute ACLR can be performed safely without an increased risk of developing stiffness. There are potential benefits as patients who underwent acute surgery had less muscle hypotrophy in the early phase of the rehabilitation process.

6.2 STUDY II

6.2.1 Introduction

As an ACL injury is a functionally disabling injury and often prevents patients from returning to work from the time of the injury to the time of reconstruction, acute ACLR may facilitate an earlier return to work. Measuring sick-leave days for the first year after an ACL injury is an easy way to measure socioeconomic costs. It was hypothesised that an acute ACLR results in fewer sick-leave days without inferior PROs.

6.2.2 Material and methods

The same study population as in *Study I* was used. Data from the Swedish Social Insurance Agency, Försäkringskassan, were obtained for information about the number of sick-leave days due to the knee injury and over the following 12 months and compared between the two groups. Only sick-leave days based on a diagnosis of ACL injury were included in the study. The follow-up at 12 months also included a Biodex strength test, Lachman, Rolimeter, pivot shift, one leg hop, IKDC, KOOS, Lysholm and Tegner activity level.

6.2.3 Results

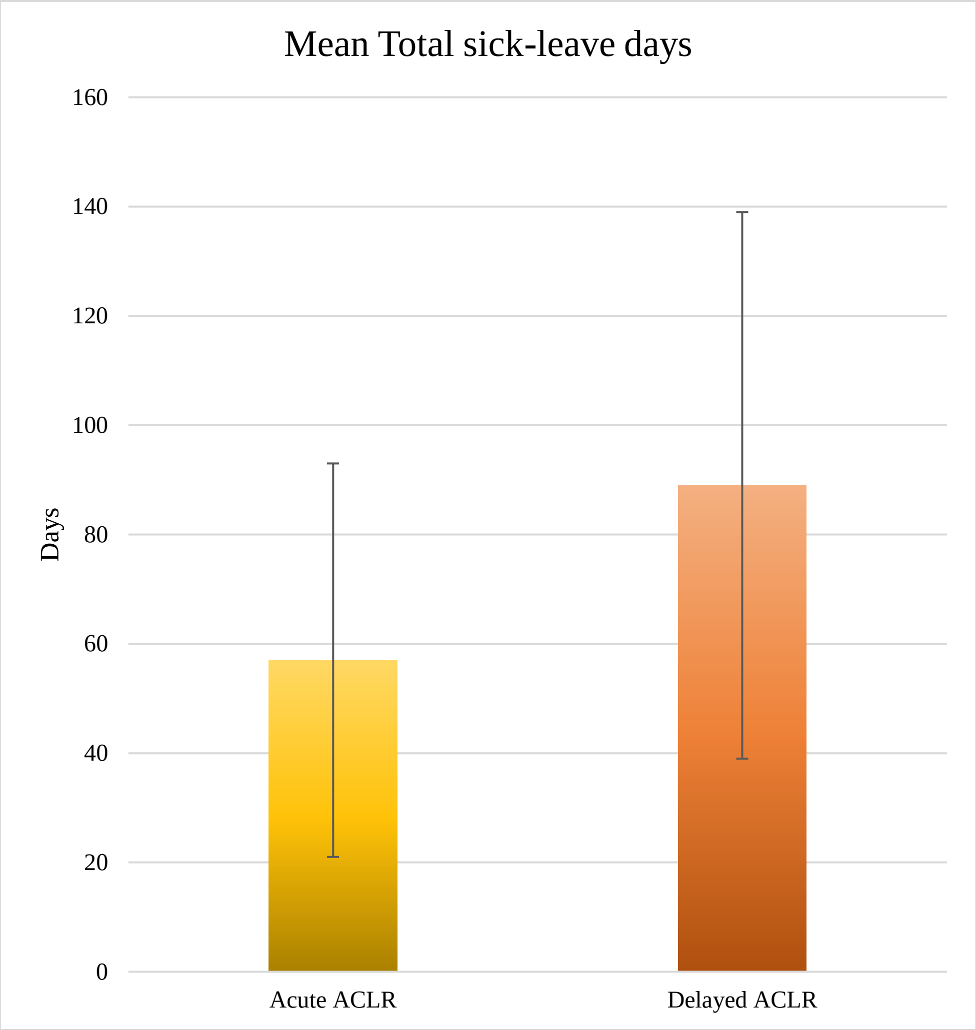
All patients were assessed regarding the number of sick-leave days. Three patients (4%) did not claim sick-leave compensation due to self-employment, and another 17 (25%) were students and therefore not eligible for sick-leave compensation. The remaining 49 (71%) were distributed by 26 in the acute group and 23 in the delayed group, accordingly. There were no differences between the groups regarding line of work. The mean number of sick-leave days for the acute group was significantly lower (M=57, SD=36) compared to the delayed group (M=89, SD=50; $p < 0.05$), Figure 5. The delayed group also had a different distribution of the days – one continuous or two separate periods, depending on type of work. There were no significant differences between the groups in any other assessment.

6.2.4 Conclusion

On an individual level, acute ACLR resulted in fewer sick-leave days. From a societal viewpoint, there is a potential economic benefit in identifying individuals who would benefit from acute ACLR. The groups also showed comparable clinical outcomes one year after surgery.

Figure 5.

Mean total number of sick-leave days during the first year after the injury.



6.3 STUDY III

6.3.1 Introduction

ACL tears are common injuries, and ACL reconstructions, regardless of the technique and graft source, are considered safe and effective procedures. Injury-to-surgery time still remains controversial. There have been recommendations to delay ACLR due to the risk of AF even though several studies have shown acute ACLR to be a safe option. In an initial study with the primary endpoint of ROM at three months showed no significant differences regarding ROM or clinical outcome at six months. The aim of this study was to assess two groups randomised to acute ACLR within eight days or after 6–10 weeks when ROM was normalised at a minimum of 24 months post-surgery. It was hypothesised that an acute ACLR would not result in inferior PROs nor a higher frequency of ROM deficits.

6.3.2 Material and methods

The same study population as in *Study I* was used. The follow-up at six months included a Biodex strength test, Lachman, Rolimeter, pivot shift, one leg hop, IKDC, KOOS, Lysholm and Tegner activity level as well as VAS 1 & 2. ACL graft failures, CL ACL ruptures and meniscal repair failures requiring revision meniscus surgeries were recorded during the trial period.

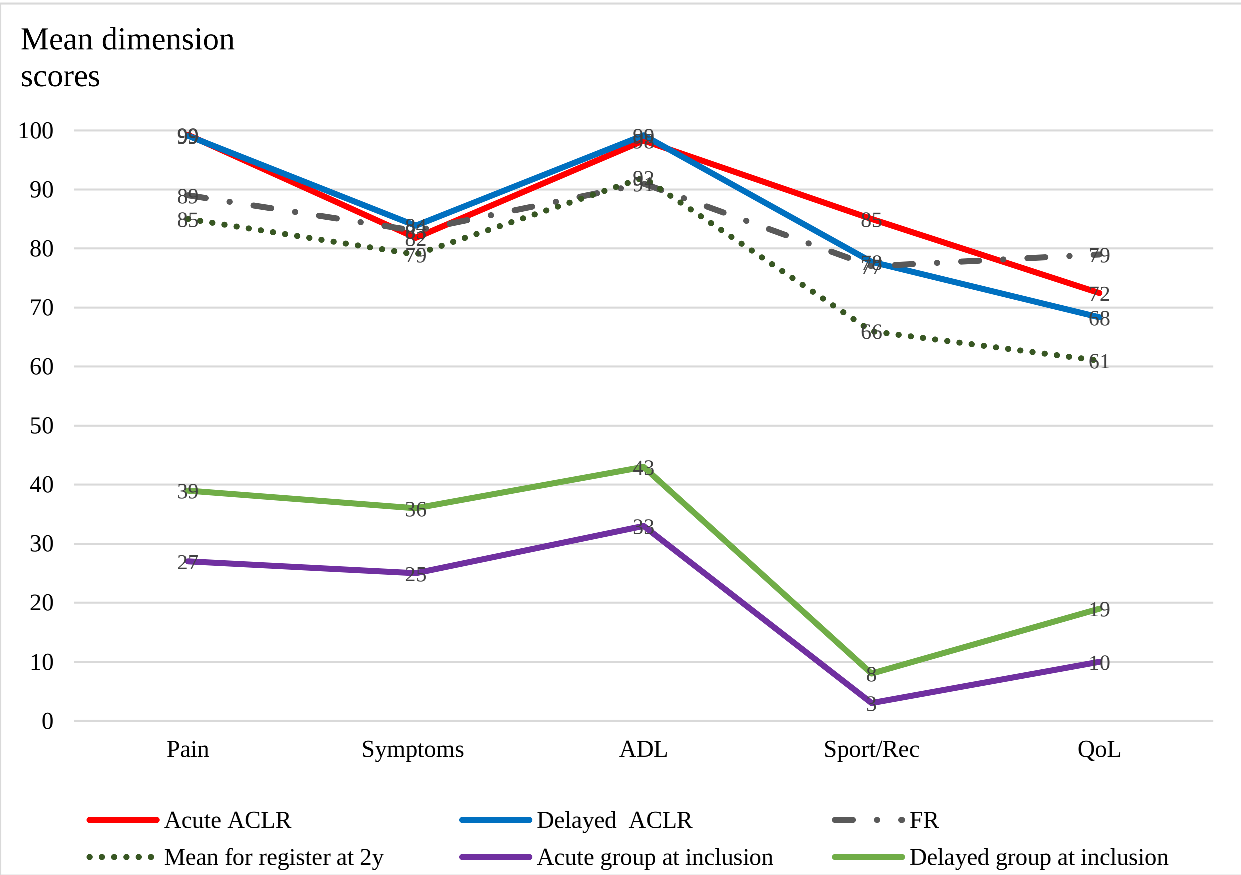
6.3.3 Results

Twelve (17%) patients were lost to follow-up, with no significant difference between groups (6 vs 6). Early extension deficit seen at three months had resolved. The patients in the acute group perceived their knee function as better than those in the delayed group (VAS 1 & 2, p=0.016 and p=0.022, respectively), and the median Tegner level was restored to pre-injury and desired levels for both groups. KOOS showed a significant improvement in all subscales from the preoperative status, Figure 6, and the FR rate was near 40%, which is almost double that in the SKLR, with no differences between the two groups. Also, TF was reduced to half of that in SKLR. There was no increased risk for additional surgery whether the reconstruction was performed acute or delayed.

6.3.4 Conclusion

The study provides further evidence that acute ACL reconstruction can be performed safely without an increased risk of developing stiffness.

Figure 6: *Mean KOOS scores*



Score range from 0 to 100, with higher scores indicating better results. Mean KOOS scores show significant improvement, but no significant difference between the groups.

6.4 STUDY IV

6.4.1 Introduction

When performing ACLR, the surgeon usually uses an autograft from the same, IL, leg. Taking the graft from the uninjured, CL, leg would theoretically mean that the injured leg does not need to suffer any additional damage in connection with ACLR. There are a few studies using BTPB from the CL leg for primary ACLR and numerous on revisions with good results. There are only two studies that have been published using a hamstring graft, and in both cases the studies used an STG graft. Using only the ST does not compromise strength and function as much as harvesting both tendons. The aim of the RCT was to assess the impact of ST graft harvest from the CL leg compared to the IL leg when performing ACLR. The hypothesis was that using a CL ST graft is safe and can be beneficial regarding strength recovery as the knee does not take on a double hit.

6.4.2 Material and methods

Between 2013 and 2017, 140 patients were randomised to receive ACL reconstruction with a four-strand ST graft harvested from either the IL or the CL leg. Two surgeons performed all ACL reconstructions with the same technique. The graft fixation on the femoral side was done using an adjustable loop Tightrope™. The fixation on the tibial side was done using a Tightrope ABS. The rehabilitation was standardised but free of choice for the patient. A power analysis indicated a need of 74 patients to find a mean 10% difference in isometric hamstring strength at six months. A Biodex strength test was performed at six months as the primary outcome. The follow-up at six, 12 and 24 months included a Biodex strength test, Lachman, Rolimeter, pivot shift, one leg hop, IKDC, KOOS, Lysholm and Tegner activity level.

6.4.3 Results

A total of 140 patients were initially included in the study. For the primary outcome at six months, 38 patients were lost to follow-up, and for final analysis, an additional seven patients were lost, which left 95 patients (46 in the IL group and 49 in CL group). Both groups were comparable in terms of demographic details and preoperative scores and findings.

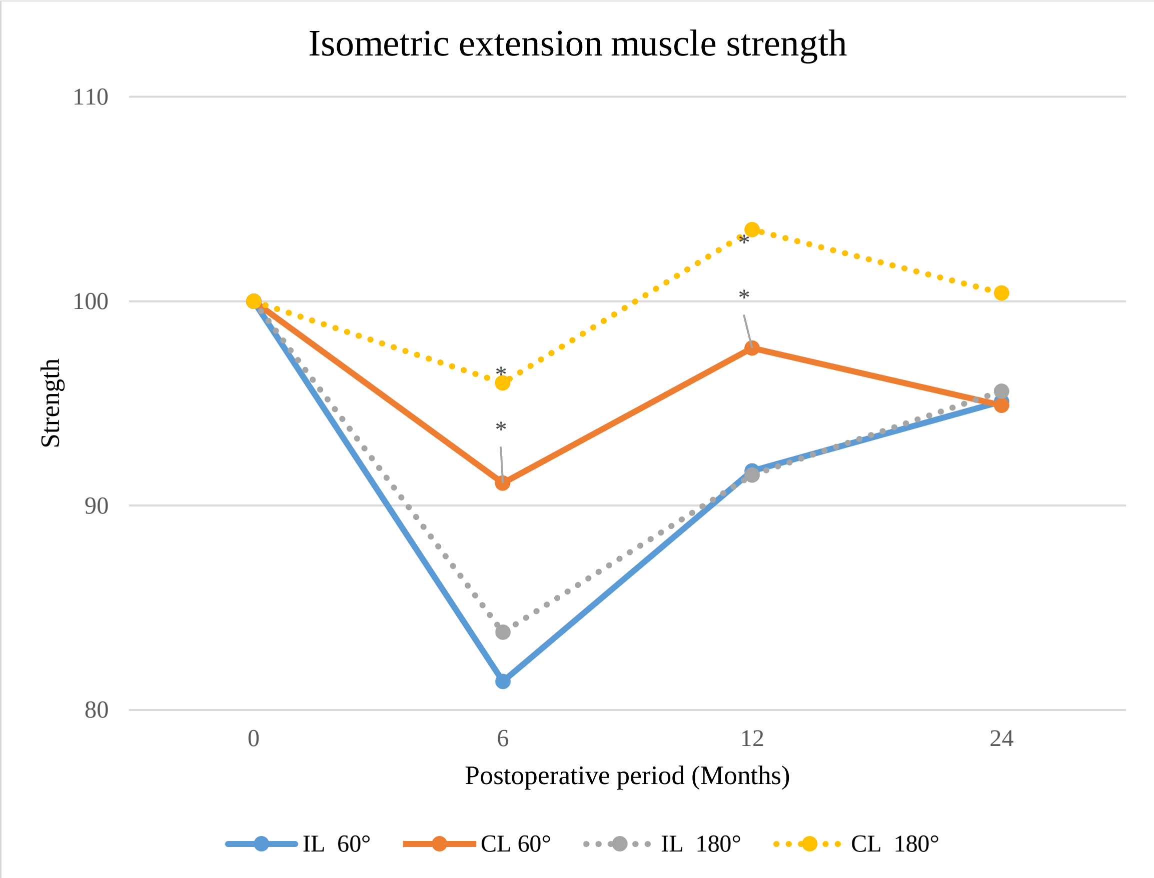
At the six-month follow-up, the patients were assessed for the primary variable, with the CL group significantly stronger in isometric hamstring strength and continuing to be so at 12 months as well. However, at 24 months, no difference in isometric strength could be seen, Figure 7. Regarding isokinetic flexion muscle strength and total work in flexion, the IL group was significantly weaker in all velocities during the trial period, Figure 8 and 9. No differences were found between the groups in the other clinical assessments.

The mean Lysholm, Tegner and IKDC scores at all time points after surgery were significantly improved as compared with mean preoperative scores in both the groups with no difference between them. FR rate was in line with the SKLR. Failure of ACLR was observed in two patients in each group. All cases of failure were due to significant re-injuries. One case of CL ACL injury was found in the CL group.

6.4.4 Conclusion

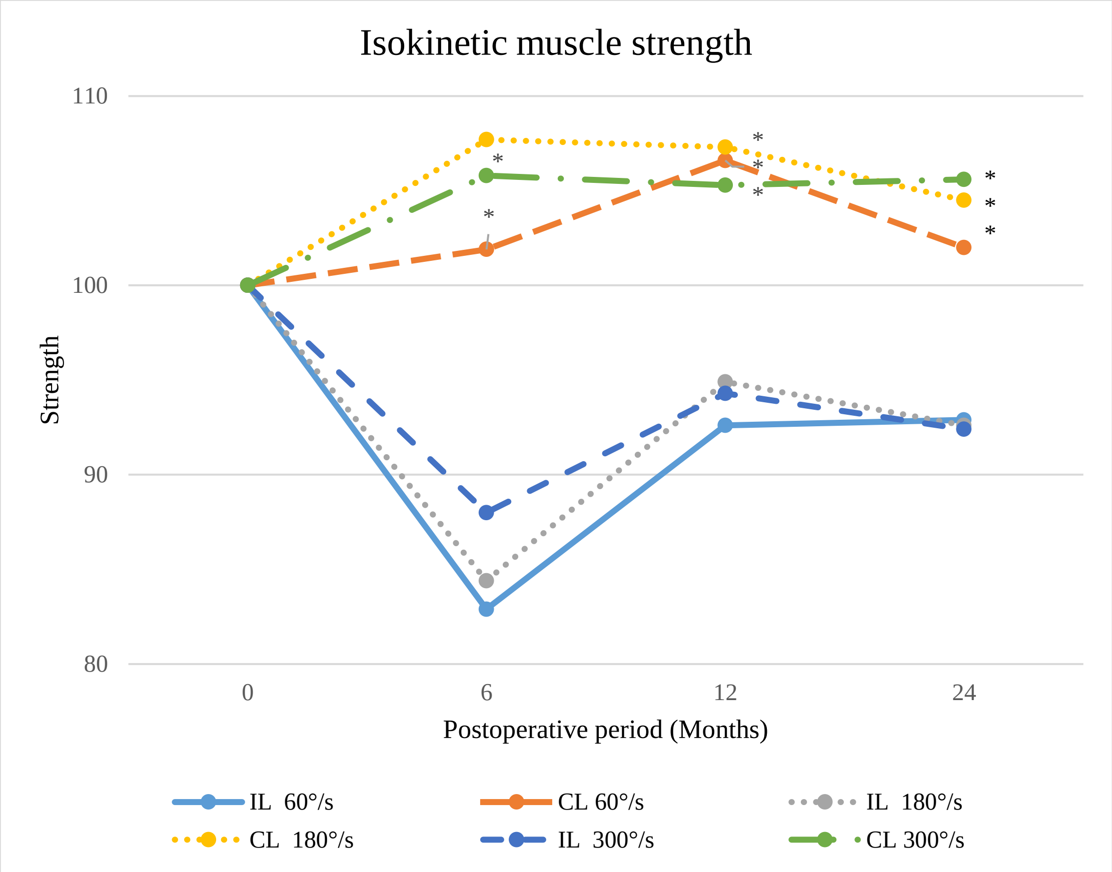
CL graft harvest is a safe option with potential benefits and no measurable disadvantages. The CL group showed early symmetrical strength between the limbs, while the IL group stayed asymmetrical during the whole trial.

Figure 7.



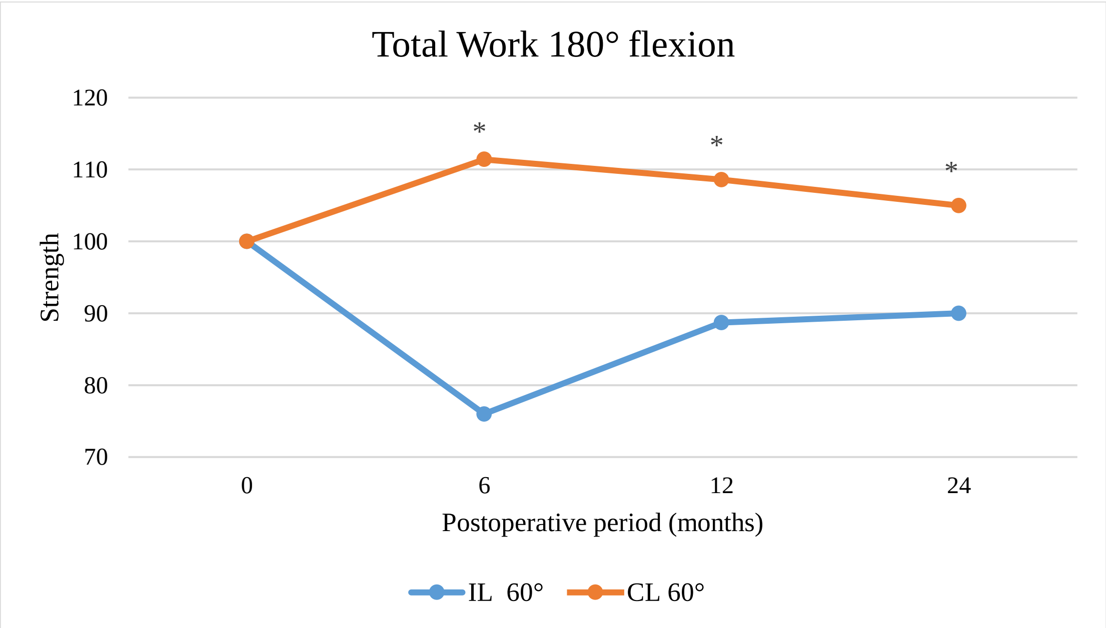
*The average isometric extension muscle strength after surgery displayed as mean percentage with ref. contralateral leg set at 100. *, p <0.05*

Figure 8.



*The average isokinetic flexion muscle strength after surgery displayed as mean percentage with reference cl leg set at 100. *, p<0.05*

Figure 9.



*The average total work at 180° after surgery displayed as mean percentage with reference contralateral leg set at 100. *, p<0.05*

7 STRENGTH AND LIMITATION

In general, there is a limitation in this thesis that the first three studies are quite similar as they assess the same study population.

As for strength testing, there are many factors that may influence the results. The test subjects are influenced by their experience of the situation and psychological aspects surrounding the testing situation. There are variances between results, and there is a need of enough subjects to have reliable results. For these reasons, the strength testing in *Studies I–III* should be interpreted with some caution. In *Study IV,* however, there should be enough subjects according to the power calculation made.

Regarding all the studies, they are only what one could describe as short-term follow-ups although two years has been described as a minimum follow-up time period[196]. For the follow-up period in *Study I,* it was clearly defined in the study aims that the primary endpoint was ROM at three months. The follow-up for 24 months in *Study III* instead answered other important questions, such as reruptures, revisions and activity level.

7.1 STUDY I AND III

The strengths of the studies were the prospective, randomised design and that the patients in the groups were comparable in terms of age, gender and pre-injury Tegner activity level. Further, the patients were reconstructed using the same type of graft and had the same supervised rehabilitation programme.

Potential limitations are the limited number of patients; though there were sufficient numbers according to the power analysis, there is still a possibility for a type 1 error to occur. Another limitation is the change in surgical method (TT vs AM portal drilling). The studies also offer only short-term results, as mentioned above. Another limitation is that the study population is very specific, and one could argue that the results are due to the specific type of subjects in the study and making it hard to generalise the results to all patients with an ACL injury. The knee outcome scores in *Study I* should also be interpreted carefully as at least a one-year follow-up is required to obtain meaningful measures[197].

7.2 STUDY II

The main limitation is that the power analysis was performed to detect loss of ROM and not sick-leave days. The post hoc analysis did, however, show a high effect size, which supports the likelihood of the results being true. Sick-leave days are a blunt measure for socioeconomic costs as there are several other factors that affect the total cost of ACLR. We did not have a non-operative counterpart for comparison, and our study focused only on individuals with at least a moderate activity level, thus making it hard to generalise.

7.3 STUDY IV

The major strength of this study is that it is a randomised trial with only two experienced orthopaedic surgeons performing ACLR with the same standardised technique. The groups were comparable in terms of age, gender and additional injuries, and both subjective and objective measurements were made. The study population is also easy to generalise as the inclusion criteria are not as slim as those in the other studies.

One limitation of the study is that the rehabilitation was not supervised, so it cannot be determined whether all patients got the same rehabilitation. Another weakness of the study is the loss of follow-up. A big loss of follow-ups was anticipated, and the number of participants in the study were included accordingly. There is a common opinion that a dropout rate of more than 20% is a threat to the validity and the power of a study[196]. In this case, the dropout rate was 33% for the final analysis although enough subjects were analysed according to the present power analysis. In a comparison with the characteristics of those who completed the study versus those who did not, there were no differences. Another limitation is that we did not use a 'battery of tests' that have been suggested to better assess functional assessments and to discriminate between the injured and non-injured leg, instead used only one hop test[198]. Another potential limitation is that the possible reduction in the strength of the CL leg when harvesting the HT will inflate the symmetrical index, thereby leading to a misrepresentation of the functional ability of the injured limb. As described, there are only short-term follow-ups for 24 months. However, the study includes clinical examinations, PROs, activity level and verified reinjures.

8 DISCUSSION

The overarching aim of this doctoral thesis was to develop a better understanding as to whether we can improve subjective and objective outcomes after ACLR with different strategies and mind sets, and the focal point has been on the patient's perspective. To achieve this, the doctoral thesis is based on four studies, all of them RCTs.

Even though the ACL injury is one of the most studied in the field of orthopaedics, there is still debate regarding everything from timing to graft choice and even whether surgery is necessary. What is certain is that the main goal for all treatment is a stable knee joint with as little morbidity as possible.

8.1 TIMING OF ACLR

As previously stated, the ideal timing for ACLR has not been identified and is still under debate. In *Studies I–III,* 'acute' or 'early' was defined within eight days after the injury and 'delayed' after 6–10 weeks. The most important findings in the *Studies I–III* were that at the three-month follow-up, no significant differences in ROM between groups were evident and that at six months postoperatively, the 'delayed' group had more muscular hypotrophy of the quadriceps. Additionally, at 12 and 24 months, PROs were similar. There is, however, no clear and accepted definition in the literature as to what should be regarded as early and delayed ACLR. There has been opposing evidence on the risks and benefits of early reconstruction, in which early surgery was classified as ranging from within two days to seven months and delayed surgery as ranging from three weeks to 24 years after the injury[109 199]. In more recent meta-analyses surgery within three weeks has been defined as early, avoiding overlaps between the groups, and these studies could report good final outcomes without a higher risk of complications, in line with the studies in these thesis[111 122 123]. The average time between injury and reconstruction in the SKLR is between 400 and 500 days (13–17 months)[200], and there are also differences between countries[1]. The majority of ACLRs were performed within six months in the UK and the US and after six months in the Scandinavian countries. There might be several reasons for this. One reason could be that Sweden has embraced a treatment algorithm where most patients first receive non-surgical treatment to explore whether they are copers, thereby extending the time to surgery. This is in line with both the traditional dogma that surgery should be delayed for at least six weeks to decrease swelling and regain ROM as well as adequate time for decision-making and to prepare the patients both mentally and physically, as not every patient needs surgery[106 201]. The risk for AF has been one of the main reasons to delay treatment[106 161], but *Studies I–III* did not find an increase in AF. This is in line with other more recently published high-level trials[122 123]. The studies that advocated delayed surgery due to AF were all done during the 1990s, with different rehabilitation, arthrotomy techniques and nonanatomic graft positioning[106 161]. The evolution of rehabilitation and surgical techniques has made it safer to perform early ACLR. AF following ACLR is a major complication, but another aspect is what should be classified as AF. In *Studies I–III*, the primary outcome was ROM at three months, and the power calculation was made from a definition of AF as 5° loss of extension from a study by Shelbourne et al.[159]. It was not until recently that a more modern classification was made, and it can be hard to evaluate other studies in regard to what really should be classified as AF[160]. Another reason is logistics and waiting lists, the latter due to lack of resources.

The decision to reconstruct the ACL should be individualised. Not all patients need ACLR even if it has traditionally been recommended for young, healthy patients with the desire to engage in pivoting sports. Frobell et al. conducted a prospective randomised trial comparing early ACLR (i.e. within 10 weeks) with optional delayed reconstruction (both with the inclusion of structured rehabilitation) and reported no significant differences between the groups according to KOOS, Tegner activity level or meniscal tears requiring surgery or OA findings at two and five years[6 47]. However, patients that required meniscal fixation were excluded, and half of the patients in the optional delayed group opted for reconstruction during the trial. In addition, the non-operative group showed greater knee laxity as well as more meniscal injuries (13 vs 1).

Delaying ACLR might increase the risk for more damage to the knee. *Studies I–III* did not find any differences between the groups regarding additional injuries, but the literature reports evidence of increased risk of damage over time. Granan et al. found an increased risk of meniscal tears for every month passed[25]. Other studies have also reported significantly more meniscal and cartilage injuries when delaying surgery[54 202 203]. In contrast, a recent systematic review by Ekås et al. could not find evidence that surgery decreases the risk for a new meniscal tear[204]. Further, the presence of meniscal or cartilage injuries in combination with an ACL tear contributes to the development of OA[4 205]. ACL injuries are associated with a higher risk for OA regardless treatment[206]. However, when a meniscal injury was present, the prevalence of OA increased between 21–48%, further highlighting the importance of not sustaining further injuries[205]. There are also data suggesting that ACLR can to some degree prevent OA development[177 206]. None of the studies in the thesis have long-term results, but saving the meniscus and keeping the kinematic might save the knee further and in the long term reduce the risk for OA.

Due to the Swedish healthcare system, an acute reconstruction within one week of injury is not always possible, but most patients can be evaluated within the first week after the injury. Non-operative treatment of an ACL injury can be discussed in less active patients and then the need for surgery can be re-evaluated within a reasonable timeframe so that the patient, if not a ‘coper’, can be reconstructed before additional injuries to the knee are sustained. However, not offering a young and active athlete patient an early ACLR is not an acceptable option. Of course, there is a risk of overtreatment, but in the best case scenario, the surgery will save the menisci from further damage. If a decision for ACLR has been made, there is no reason to wait.

8.2 ACTIVITY LEVEL AND PROS

In general, the outcome after ACLR is largely dependent on the secondary injuries the knee has sustained during the time from the injury to the reconstruction. But how do we measure outcome, and what can be regarded as success? There are of course the objective measurements, such as laxity, reruptures and concomitant injuries, but these do not take in to account how the patients feel. A successful treatment surely means different things to different people. For an elite athlete, success might be returning to sport participation as soon as possible, while to others success is defined as performing at the same level as before the injury. For the surgeon, an objective stabile knee can define success. PRO highlights the patient's perception of the treatment. The two most commonly used PROs after an ACL injury are the KOOS and the IKDC-SKF, both which are validated[126 207]. Moreover, both have advantages and disadvantages. KOOS covers five subscales (pain, symptoms, ADL, sp/rec and QoL) but was originally developed for OA and its progression. It contains many questions, 42, several that might seem a bit 'easy' for the patient, and does not include specific items relating to instability. The IKDC form has fewer items to answer and was associated with more questions that the patients felt important in recognizing their difficulties after an ACL injury[208]. A comparison between IKDC and KOOS found the subscales sp/rec and QoL to be the most important to the patients[209]. However, the results can be difficult for the clinician to understand and interpret. A clinically meaningful change in PRO may not be associated with an acceptable state corresponding to 'feeling well'. In *Study III,* the term functional recovery (FR) is used, a score defined by Barenius et al. as a KOOS value above the lower threshold for the 95% CI of 18–34-year-old males in a Swedish reference population for all subscales[128]. FR is equivalent to a return to a nearly pre-injury KOOS level, setting the bar high. In *Study III,* FR rate was almost 40% for both groups, and that is almost double of that in the SKLR[128]. Barenius et al. could not find that time between the injury and reconstruction was a negative predictor for FR, but the outcome was influenced by additional injuries, often sustained during the waiting period. This could explain why FR was so high in *Study III* as both groups were reconstructed before experiencing episodes of giving way and therefore did not sustain additional injuries to the already injured knee. Although not as glamorous, TF should be regarded as important as success. In *Study III,* a KOOS QoL subscale value of < 44 points was used as a cut-off for TF. This value originates from a study by Frobell et al. in which it was used as a criterion for crossover from non-surgical to surgical treatment and was also used in the study by Barenius et al.[47 128]. In *Study III,* the TF rate was half of that of the SKLR, which further highlights the importance of avoiding additional injuries to the knee[128]. More recently, another study defined thresholds for PASS for each subscale of the KOOS and IKDC by asking the patients if the state of their knee was satisfactory, and several studies have since applied these values[129 130 210]. The thresholds for PASS are lower than that of FR and are therefore easier to pass. Ingelsrud conducted a similar study on defining TF, asking the patients if they thought their treatment had failed, and got a threshold of KOOS QoL subscale < 28[131]. If the threshold used by Ingelsrud and Muller was to be applied on the patients in *Study III*, 72% would reach the PASS criteria, no difference between the groups and only 5% TF – this in comparison with the study by Cristiani, where 60% achieved PASS, and with Ingelsrud, where 13% failed[130 131]. In *Study IV,* PASS was achieved for 57% within the KOOS subscales, which is in line with the previous studies, and TF 7%, which is better than the study from Ingelsrud[130 131]. The patient group in *Study IV* might not be young, high-level athletes struggling to get back to high-level sport but rather patients trying to cope with the potential limitations of their reconstructed ACL status.

As the main goal after treatment of an ACL injury often is the RTS, a way to measure outcome is to look at the activity level and to what extent patients RTS. While an objective good knee function is important for the RTS, there are other psychological factors to consider as well. The Tegner activity score does grade the activity level but not activity exposure, and thus, although patients may have reached a similar Tegner level, they may have never returned to the same level of play as before the injury[195]. In all studies, there was a distinguishable difference between pre-injury and pre-surgery activity level. In *Study III,* the median Tegner activity level was restored for both groups, and more than 93% of the patients had returned to recreational sports within two years. In *Study IV,* the activity level had decreased at the two-year follow-up from a median of 7 and 8, respectively, to 5 for both groups. This is in line with a meta-analysis by Ardern et al. in which only 55% returned to a competitive sport and 63% to their pre-injury Tegner level even though almost 90% had a nearly normal IKDC[143 211]. Another aspect and difference between the two study populations in *Studies III* and *IV* is that in *Study III* the patients were younger, composed of more men and had a higher pre-injury Tegner level, all of which are important factors for RTS after an ACL injury[211-214]. Another factor that influences the RTS is concomitant injuries[215]. In *Study IV,* there were more treatments for meniscus, another reason for not delaying ACLR.

8.3 MUSCLE FUNCTION

Strong muscles around the knee protect the joint and are a key factor in the rehabilitation after ACLR in order to RTS. There is no clear consensus to determine when patients can RTS after ACLR, but time after surgery, stability and symmetrical muscle strength have been reported as key factors[198 216 217]. A recent study showed that for every month RTS was delayed from six up to nine months postoperatively, the re-injury incidence was reduced by 51%[140]. Symmetry between the injured and uninjured legs, often referred to as the limb symmetry index (LSI), has been defined as ≥ 90% of muscle function, and this cut-off has been reported to decrease the risk of another ACL injury after RTS[140 198]. Using an autograft impairs either the knee extensor or flexor mechanism, depending on graft[218]. The HT graft preserves quadriceps function but weakness of the hamstring has been reported with inferior knee function after ACLR[219 220]. The HT also has a stabilising effect in valgus stress[221]. Studies also suggest that decreased hamstring strength in combination with higher quadriceps strength might be a factor for ACL rupture[222 223]. In *Studies I–IV,* strength measurements were performed using a Biodex System (Biodex Medical Systems, Shirley, New York, USA) and the one leg hop test. In *Study I,* the acute reconstruction group had less muscular hypotrophy of the thigh muscles, and a significantly higher proportion of patients passed the one leg hop test. This might indicate that ACLR before extrinsic quadriceps inhibition might help preserve muscles and function. It would be of great value to compare the difference between early and delayed surgery in terms of recovery time from an ACL injury.

In *Study IV*, using an ST graft from the CL leg resulted in improved flexion muscle strength and symmetrical strength between the limbs as early as six months post-surgery, while in the IL group the asymmetry remained after two years. Several other studies have reported asymmetry more than two years after surgery[198 224 225]. Avoiding a double hit to the already injured knee might lessen the burden to restore muscle strength. Muscle strength is a critical factor for the outcome after ACL reconstruction, and attaining symmetrical knee function should be considered a cardinal aim of rehabilitation due to the preventive effects of secondary injuries.

8.4 ASPECTS OF ECONOMY

As ACLR is one of the most commonly performed orthopaedic procedures, in Sweden alone about 4000 per year, there has been an interest in determining the value of the intervention by ACLR and developing value-based healthcare[200]. Mather et al. and Farshad et al. both used economic modelling to compare ACLR to non-operative treatment and found ACLR to be more cost-effective[113 180 226]. Stewart et al. compared competitive athletes in another cost-effectiveness analysis, and the incremental cost-effectiveness ratio(ICER) of an ACLR in comparison to physical therapy was approximately $22,000 per QALY-year[182]. There are, though, limitations to these models as they do not measure any indirect costs, such as missed workdays and loss of productivity. Kiadaliri et al. conducted an analysis of the cost-effectiveness of early versus optional delayed ACLR and could not show any economic benefits of early ACLR over a five-year period[227]. There are, however, some questions regarding the calculation of the number of sick-leave days, too, as 23 of 59 patients in the optional delayed group were dismissed in the calculation. Marcano et al. showed in a recently published study a trend that ACLR, especially earlier operative treatment, was associated with a more positive change in income compared with conservative treatment[228]. In *Study II*, a delayed ACLR resulted in significantly more sick-leave days (89 vs 57 days) within the first year compared with an acute ACLR, resulting in higher indirect costs. The result might be generalisable for countries with healthcare systems and guidelines similar to those of Sweden, but there could be big differences depending on how the healthcare system is financed.

9 CONCLUSIONS

9.1 STUDY I

- Acute ACLR can be performed safely without an increased risk of developing stiffness within the first three months.
- Patients who underwent acute surgery had less muscle hypotrophy of the thigh muscles in the early phase of the rehabilitation process.
- This support that clinicians can make the optimal decision for each individual patient.

9.2 STUDY II

- Patients who underwent acute reconstruction required significantly less sick-leave compensation than those who underwent delayed reconstruction and had fewer indirect costs after ACLR. From a society viewpoint, there is a potential economic benefit to identifying individuals who would benefit from acute ACLR.
- Acute and delayed ACL reconstruction provided comparable clinical outcomes after 12 months with no significant differences.

9.3 STUDY III

- Acute ACL reconstruction can be performed safely without an increased risk of developing stiffness and other adverse effects.
- Acute or early ACLR, which is performed before recurrent giving ways occur, increases the likelihood of achieving FR.
- Rehabilitation should be focused postoperatively rather than preoperatively.

9.4 STUDY IV

- CL graft harvest is a safe option with potential benefits.
- There are no measurable subjective or objective disadvantages.
- The CL group showed early symmetrical strength between the limbs.
- The IL group remained asymmetrical during the trial.

10 FUTURE PERSPECTIVE

The incidences of ACL injuries have risen in recent years, and ACLR has become more of a standard procedure. Despite being one of the most studied injuries, there are still controversies in the field of ACL research. Moreover, due to the large number of publications, there can be confusion when interpreting the results.

To start, research would gain a great deal from consensus. To achieve qualitative research, consensus should be reached as to which outcome assessments should be used to obtain valid, reliable measures that reflect both subjective and objective outcomes. This is important to be able to compare studies. Future studies should define AF more precisely as well as define what should be regarded as early ACLR.

As every patient is unique, it is important to individualise ACL treatment. By doing so, we can hopefully improve the outcome and reduce negative consequences. However, individualised ACLR accounts not only for the anatomy but also for graft choice, timing and activity. The results in this thesis suggest that early surgery results in better outcome and that prevention of OA could be achieved with ACLR before giving way occurs. It would be interesting to see more well-designed studies of early reconstruction with an anatomical reconstruction and look at the long-term data to better understand the effect on the development of OA.

As part of individualising the treatment after an ACL injury, non-reconstructed patients need to be addressed in the same manner as the reconstructed. These patients need to be studied across a range of outcomes to improve the understanding on who will benefit from each treatment. There is also a need of larger, non-biased RCTs comparing modern ACLR with conservative treatment.

Another thrilling development is registry-based RCTs (R-RCTs). These are randomised trials that use a clinical registry for outcome reporting. R-RCTs make it possible to recruit a large number of unselected patients with great external validity at a low cost, which has been demonstrated in cardiology[229]. As the follow-up also relies on registries, the impact on regular healthcare is minimal. R-RCTs could be very valuable for comparing treatments already in use in clinical practice. If integrated into the SKLR, one could compare treatments that usually would need very large sample sizes, such as graft choice, timing and fixation method.

Nordenvall et al. conducted a highly interesting study showing that socioeconomic status (SES) had an impact on treatment after an ACL injury[230]. The same research group performed another study using SES as an alternative outcome when evaluating symptomatic surgery[228]. It would be intriguing to develop this further and also address different socioeconomic factors in the same way. There are great possibilities to use national registers to answer difficult questions. In the study by Nordenvall, a higher SES increases the likelihood of undergoing operative treatment[230]. One reason could be that patients with a lower SES do not have the possibility to afford sick leave. It would also be interesting to look at the differences of sick-leave days between reconstructed and non-reconstructed patients and whether there are any differences depending on social class or geography by cross-referencing the registers. Another question that needs to be answered is whether ACLR allows for a sooner return to work in general.

Other important aspects for further research regard activity and RTS after ACL treatment. The Panther symposium has done tremendous work in defining the different stages of the RTS continuum after an ACL injury, including emphasising the importance of a multidisciplinary approach[217]. The outcome measurements are still a bit blunt, and a better measurement should be validated. From the results in this thesis, CL ST graft harvest promotes earlier muscle symmetry, and it would be interesting to look at the donor site morbidity after harvest as well as to study whether the early symmetry might facilitate a faster and higher RTS rate in a more active study population.

As discussed, PROs can illuminate differences in treatment outcomes. There are, however, very few studies that have evaluated the effect of patients' expectations on PROs, and in the area of ACL surgery there are no studies to date that have successfully described the relationship between patient expectations and postoperative PROs. To define the effect of patient expectations on PROs after ACL treatment is a very important subject to research in order to improve the patient experience after treatment. Despite the fact that the Internet can provide incalculable information, it is not clear how much of the information the patients really understand. This is an area that is not researched and could provide important information about the discrepancy between the patient's and doctor's view and on the expectations from the treatment.

Even though we have learned a great deal, we must be humble in regard to the fact that we do not have all the answers and that what we know not to be the truth might change in the future. Future research needs to focus on using classic high-level studies with modern methodology and large register studies.

11 POPULAR SCIENCE SUMMARY

An ACL injury is a serious knee injury that often affects younger individuals in connection with sports. The sports where the injury is most common are football, handball, floorball, alpine skiing and basketball. People who sustain an ACL injury are often forced to end a sports career prematurely. The injury can cause lifelong discomfort and often leads to early development of knee OA regardless of how it is treated. An ACL injury can either be treated surgically, when creating a new cruciate ligament using a piece of tendon from another part of the knee, or without surgery, when working through structured physiotherapy to train the stability of the knee.

Clinical practice has been to usually wait at least six to eight weeks after the injury before surgically reconstructing the ACL. The reason for this is that it has been considered important to regain normal mobility in the injured knee before surgery. This routine is based on experiences from a time when ACL surgery was performed with an open technique (which is no longer used), and it was then found that stiffness in the operated knee was more common in those who underwent acute surgery. However, when delaying surgery there is a higher risk for other injuries to the knee, such as injuries to the cartilage and the meniscus. Traditionally, tendons used for reconstruction have been removed from the already injured leg. There have been indications that reconstruction using muscle tendons taken from the healthy leg has less harmful effects and a faster return to normal function after surgery, but no one has studied this further.

The present dissertation is based on two randomised clinical trials and aims to answer questions regarding the timing of an ACL reconstruction and graft choice.

Studies I–III

In these studies, 70 highly active patients were randomly drawn to either early or delayed ACL reconstruction and compared for both subjective and objective measurements, with a focus on timing, and followed for two years after surgery. Early was defined within one week after the trauma and delayed when the patients had gained normal movement of the knee, which took 6–10 weeks. The difference between the groups regarding sick-leave days during the first year was also assessed as a measurement of indirect costs.

No differences regarding outcome measurements or stiffness could be found between the groups, yet at the six-month follow-up, the early group had preserved more muscles around the knee. Additionally, the delayed group had significantly more sick-leave days within the first year, demonstrating that early ACL reconstruction is more cost-effective.

Study IV

A total of 140 patients were randomly drawn to either ACL reconstruction with a tendon from the already injured leg or from the healthy leg. The patients were followed for 24 months after surgery. There were no comparable subjective differences between the two groups, but the group in which the tendon was removed from the uninjured leg had symmetrical muscle strength after only six months, while the group in which the tendon was removed from the already damaged leg did not regain strength symmetry after two years. The group in which the tendon was removed from the uninjured leg was also significantly stronger when performing strength measurements.

The dissertation shows that the previous belief that patients should wait a couple of months before an ACL reconstruction can be performed is not true; rather it can be performed safely immediately without any major risk of stiffness. From a societal perspective, it is cost-effective to find the patients who need an ACL reconstruction as soon as possible. Using a tendon from the uninjured leg might have benefits regarding regaining early symmetrical strength and is a safe option.

In conclusion, if a decision for an ACL reconstruction has been made, there is no reason to wait.

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