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ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION – SUBJECTIVE KNEE FUNCTION, GRAFT FAILURE AND REVISION SURGERY

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Anterior cruciate ligament reconstruction – subjective knee function, graft failure and revision surgery

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

An anterior cruciate ligament (ACL) tear is a severe knee injury, which leads to increased knee laxity and often functional instability. An ACL reconstruction (ACLR) is generally recommended to patients who desire to return to pivoting sports. Surgery is also recommended in cases of persistent instability during activities of daily living. An ACL tear is commonly associated with meniscal and/or cartilage injuries. Patients with an ACL tear, especially if combined with cartilage and/ or meniscal injuries, have a high risk of developing knee osteoarthritis in the long term.

One major problem after ACLR is the risk of graft failure and/or contralateral ACL injury. Revision and contralateral ACLR are relatively common in clinical practice.

This thesis consists of five cohort studies with data obtained from our registry (Capio Artro Clinic, Stockholm, Sweden). The overall aims were to identify factors affecting objective and subjective outcomes after ACLR, the risk of associated (cartilage and meniscus) injuries and meniscus repair at the time of primary ACLR, as well as evaluating and comparing the subjective and objective outcomes of revision and contralateral ACLR with those of primary ACLR.

Study I evaluated risk factors for abnormal (KT-1000 STS > 5 mm) anteroposterior knee laxity after primary ACLR. A total of 5,462 patients were included. Younger (< 30 years) age, preoperative STS difference > 5 mm, medial meniscus resection and the use of an HT autograft over a BPTB autograft increased the odds of abnormal knee laxity 6 months after ACLR. Female gender, medial meniscus repair, lateral meniscus resection or repair did not affect the risk of having abnormal knee laxity after primary ACLR.

Study II compared knee laxity (KT-1000) and functional knee outcome (KOOS) between primary and revision ACLR. A total of 200 patients who underwent primary ACLR with an HT autograft followed by revision ACLR with a BPTB autograft were identified. Comparisons of knee laxity and functional knee outcome were based on a cohort of 118 and 73 patients respectively. Revision ACLR restored knee laxity to a level comparable with that of primary ACLR, but it resulted in a significantly inferior functional knee outcome.

In **Study III**, the primary aim was to evaluate the effect of delayed ACLR on cartilage injuries, meniscus injuries, meniscus repair and abnormal knee laxity at the time of primary ACLR. A second aim was to study the effect of other variables (age, gender, BMI) on the same outcomes. The study included 3,976 patients and established several associations between time from injury to surgery, patient characteristics, associated injuries, meniscus repair and knee laxity. The main findings were that a time from injury to surgery longer than 12 months increased the odds of cartilage and medial meniscus tears, whereas a time from injury to surgery longer than 6 months increased the odds of abnormal (STS > 5mm) knee laxity at the time of ACLR and reduced the chance of medial meniscus repair.

In **Study IV** the aims were: 1) to evaluate the rate of patients reporting a PASS 2 years after ACLR; 2) to determine a wide range of preoperative, intraoperative and postoperative factors

that might affect the achievement of a PASS. Patients with a complete KOOS at 2 years were included (n = 2,335). A PASS on 4 KOOS subscales was reported by more than 60% of the patients.
Among the non-modifiable factors, older age (≥ 30 years) and female gender were those that most affected (positively and negatively respectively) the chance of achieving a PASS. Among the modifiable factors, quadriceps strength and the SLH test performance 6 months after ACLR were those that most affected (increased) the chance of achieving a PASS.

Study V evaluated and compared the results of primary and contralateral ACLR in terms of knee laxity (KT-1000) and functional knee outcome (KOOS). A total of 326 patients with primary and contralateral ACLR were identified. A cohort of 226 patients for whom instrumented (KT-1000) laxity measurements were available and a cohort of 256 patients for whom KOOS values were available for both surgeries were included for analysis. The findings of the study showed that there were no significant differences between primary and contralateral ACLR with regard to the investigated outcomes. We therefore concluded that contralateral ACLR produces predictable results in terms of knee laxity and functional knee outcome, as they do not differ from those of primary ACLR.

In conclusion, several factors are associated with abnormal knee laxity (STS > 5 mm, graft failure) after ACLR. They are younger (< 30 years) age, preoperative STS > 5 mm, medial meniscus resection and the use of an HT autograft over a BPTB autograft. A time from injury to ACLR > 6 months is associated with a preoperative STS > 5 mm which is in turn an important risk factor for abnormal postoperative knee laxity. Delay in ACLR is also associated with increased odds of medial meniscus and cartilage injuries and a reduced likelihood of medial meniscus repair. Both ACL graft rupture and contralateral ACL tear are devastating events for the ACLR patient. However, even though both revision ACLR and contralateral ACLR restore knee laxity, revision ACLR is associated with a significantly inferior functional knee outcome compared with primary ACLR. On the other hand, contralateral ACLR produces a functional knee outcome comparable to that of primary ACLR. Finally, there are several factors associated with subjective knee outcome (2 years PASS) after primary ACLR. Older age (≥ 30 years) and female gender are the non-modifiable factors that most affect (positively and negatively respectively) the chance of achieving a PASS. Quadriceps strength and the SLH test performance 6 months after ACLR are the modifiable factors that most affect (increase) the chance of achieving a PASS. This highlights the fundamental role of rehabilitation after ACLR.

LIST OF SCIENTIFIC PAPERS

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

I. **Risk factors for abnormal anteroposterior knee laxity after primary anterior cruciate ligament reconstruction**
Cristiani R, Forssblad M, Engström B, Edman G, Stålman A
Arthroscopy 2018; 34(8):2478 – 2484

II. **Revision anterior cruciate ligament reconstruction restores knee laxity but shows inferior functional knee outcome compared with primary reconstruction**
Cristiani R, Engström B, Edman G, Forssblad M, Stålman A
Knee Surg Sports Traumatol Arthrosc 2019; 27(1):137-145

III. **Delayed anterior cruciate ligament reconstruction increases the risk of abnormal pre-reconstruction laxity, cartilage and medial meniscus injuries**
Cristiani R, Janarv PM, Engström B, Edman G, Forsblad M, Stålman A
Arthroscopy 2021; 37(4):1214-1220;

IV. **Age, gender, quadriceps strength and hop test performance are the most important factors affecting the achievement of a patient-acceptable symptom state after ACL reconstruction**
Cristiani R, Mikkelsen C, Edman G, Forssblad M, Engström B, Stålman A
Knee Surg Sports Traumatol Arthrosc 2020; 28(2):369-380

V. **Knee laxity and functional knee outcome after contralateral ACLR are comparable to those after primary ACLR**
Cristiani R, Viheriävaara S, Janarv PM, Edman G, Forssblad M, Stålman A
Knee Surg Sports Traumatol Arthrosc 2021; 29(11):3864-3870

OTHER PAPERS BY THE AUTHOR NOT INCLUDED IN THE THESIS

VI. **Meniscus repair does not result in an inferior short-term outcome compared with meniscus resection: an analysis of 5,378 patients with primary anterior cruciate ligament reconstruction**
Cristiani R, Parling A, Forssblad M, Edman G, Engström B, Stålman A
Arthroscopy 2020; 36(4):1145 – 1153

VII. **Only one patient out of five achieves symmetrical knee function 6 months after primary anterior cruciate ligament reconstruction**
Cristiani R, Mikkelsen C, Forssblad M, Engström B, Stålman A
Knee Surg Sports Traumatol Arthrosc 2019; 27(11):3461 – 3470

VIII. **Regarding "Editorial commentary: meniscal repair-Why bother?"**
Cristiani R, Forssblad M, Edman G, Engström B, Stålman A
Arthroscopy 2020; 36(7):1794 – 1795

IX. **Contralateral knee hyperextension is associated with increased anterior tibial translation and fewer meniscal injuries in the anterior cruciate ligament-injured knee**
Sundemo D, Mikkelsen C, Cristiani R, Forssblad M, Senorski EH, Samuelsson K, Stålman A
Knee Surg Sports Traumatol Arthrosc 2018; 26(10):3020 – 3028

X. **Increased knee laxity with hamstring tendon autograft compared to patellar tendon autograft: a cohort study of 5462 patients with primary anterior cruciate ligament reconstruction**
Cristiani R, Sarakatsianos V, Engström B, Samuelsson K, Forssblad M, Stålman A
Knee Surg Sports Traumatol Arthrosc 2019; 27(2):381 – 388

XI. **Medial meniscus resection increases and medial meniscus repair preserves anterior knee laxity: a cohort study of 4497 patients with primary anterior cruciate ligament reconstruction**
Cristiani R, Rönnblad E, Engström B, Forssblad M, Stålman A
Am J Sports Med 2018; 46(2): 357 – 362

XII. **Meniscal repair results in inferior short-term outcomes compared with meniscal resection: a cohort study of 6398 patients with primary anterior cruciate ligament reconstruction**
Svantesson E, Cristiani R, Hamrin Senorski E, Forssblad M, Samuelsson K, Stålman A
Knee Surg Sports Traumatol Arthrosc 2018; 26(8): 2251 – 2258

XIII. **One sixth of primary anterior cruciate ligament reconstructions may undergo reoperation due to complications or new injuries within 2 years**
Lord L, Cristiani R, Edman G, Forssblad M, Stålman A

XIV. **Autograft type affects muscle strength and hop performance after ACL reconstruction. A randomized controlled trial comparing patellar tendon and hamstring tendon autografts with standard or accelerated rehabilitation**
Cristiani R, Mikkelsen C, Wange P, Olsson D, Stålman A, Engström B

XV. **Age, time from injury to surgery and quadriceps strength affect the risk of revision surgery after primary ACL reconstruction**
Cristiani R, Forssblad M, Edman G, Eriksson K, Stålman A

XVI. **Age, time from injury to surgery and hop performance after primary ACLR affect the risk of contralateral ACLR**
Cristiani R, Forssblad M, Edman G, Eriksson K, Stålman A

ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ACLR	Anterior Cruciate Ligament Reconstruction
ADL	Activities of Daily Living
ALL	Antero-Lateral Ligament
ALS	Antero-Lateral Structures
ANOVA	Analysis of variance
ATT	Anterior Tibial Translation
BMI	Body Mass Index
BPTB	Bone-Patellar Tendon-Bone
CI	Confidence Interval
EQ-5D	European Quality of Life Five Dimensions
HT	Hamstring Tendon
IKDC	International Knee Documentation Committee
KOOS	Knee injury and Osteoarthritis Outcome Score
LCL	Lateral Collateral Ligament
LET	Lateral Extra-articular Tenodesis
LM	Lateral meniscus
LSI	Limb Symmetry Index
MCL	Medial Collateral Ligament
MM	Medial meniscus
MIC	Minimal Important Change
MRI	Magnetic Resonance Imaging
NKLR	Norwegian Knee Ligament Registry
OA	Osteoarthritis
OR	Odds Ratio
PASS	Patient-Acceptable Symptom State
PCL	Posterior Cruciate Ligament
PROMs	Patient-Reported Outcome Measurements
QoL	Quality of Life
RCT	Randomized Controlled Trial
ROM	Range of Motion
SD	Standard Deviation

SE   Standard Error

SLH   Single leg hop

STS   Side-To-Side

SNKLR   Swedish National Knee Ligament Registry

WHO   World Health Organization

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1. THE ANTERIOR CRUCIATE LIGAMENT

1.1 Anatomy and biomechanics

The anterior cruciate ligament (ACL) is an essential ligament in the knee joint, which originates from the medial aspect of the lateral femoral condyle and attaches on a broad, anterior area on the tibia. It is intra-articular but extra-synovial. The attachment sites on the femur and tibia are normally referred to as "footprints" and are the most important landmarks when performing an ACL reconstruction (ACLR). The femoral footprint is an oval area located in the posterior (knee at 20-30 degrees of flexion/full extension) or inferior (knee at 90 degrees of flexion) medial surface of the lateral femoral condyle (Figure 1).
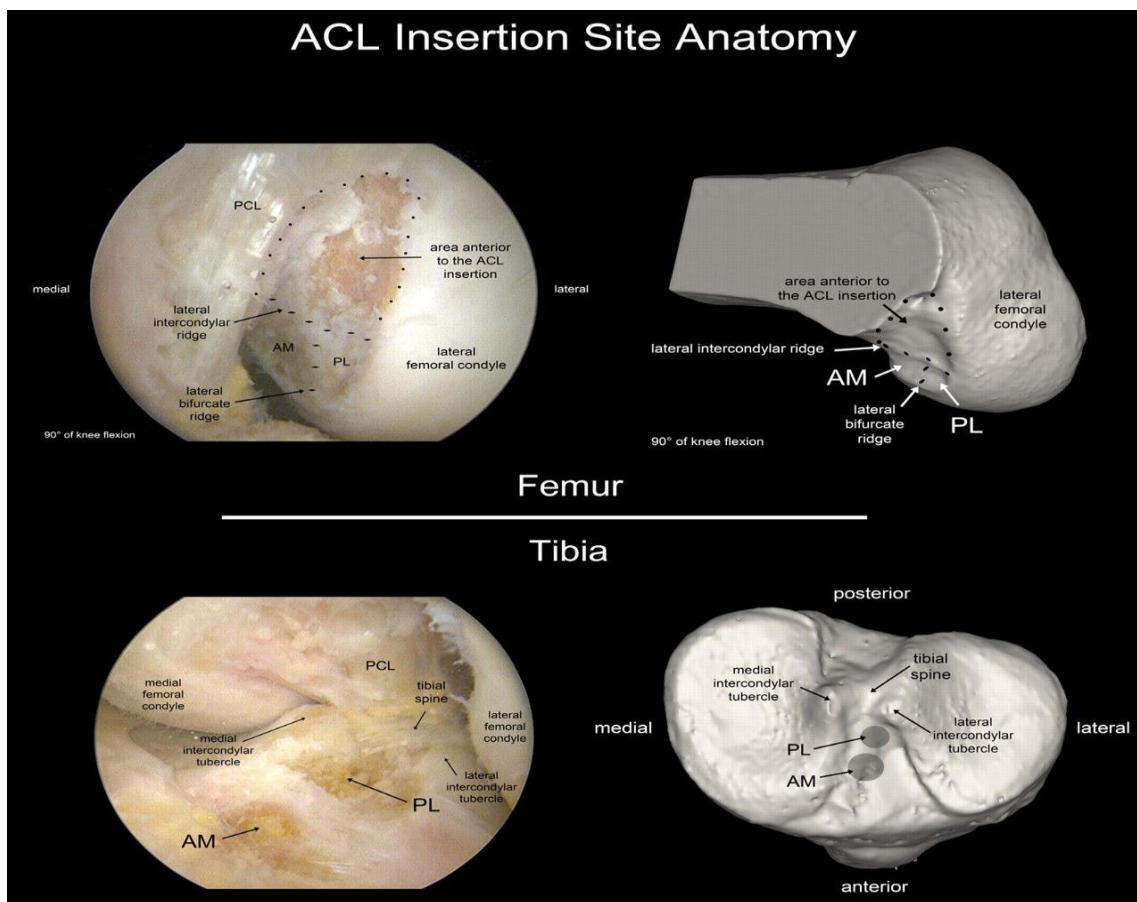
Figure 1. Arthroscopic and 3D CT scan ACL footprints anatomy with illustrations of the insertions of the anteromedial (AM) and posterolateral (PL) bundles (reprinted with permission from Wolters Kluwer. Forsythe et al.[48])

The tibial footprint is a wide, C-shaped or oval area adjacent to the anterior horn of the lateral meniscus (Figure 2). Footprint anatomy presents large variations between individuals. It is of great importance to accurately localize and map these landmarks in each patient when performing an anatomic ACLR. The average width of the ACL is 10-11 mm [58,143]. Its length varies widely (22 to 41 mm) [9].

The ACL is the principal stabilizer against the anterior displacement and internal rotation of the tibia [71]. However, it should not be regarded as a passive structure. The ACL contains several neural structures [24,127], which register proprioceptive information relating to the position of the knee in the space and in relation to the other segments of the lower limb.
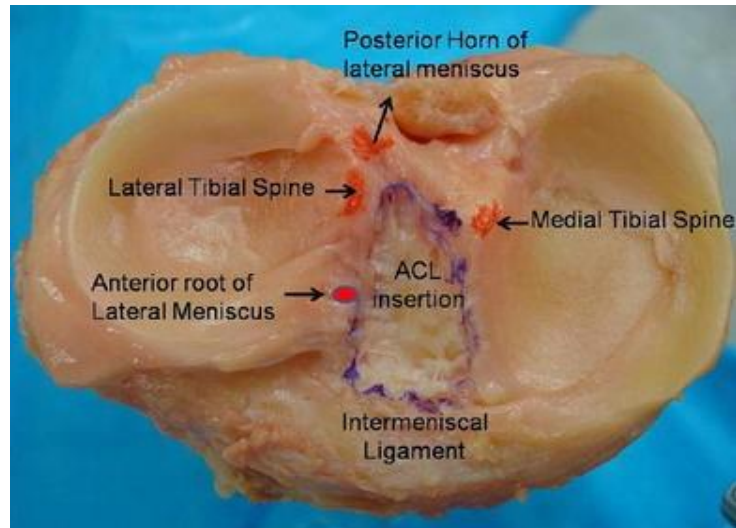
Figure 2. Anatomy of the ACL tibial footprint and its relationships with landmarks (reprinted with permission from Springer. Ferretti et al.[45])

The ACL is traditionally divided into two functional bundles, defined by their tibial insertion. The anteromedial (AM) bundle originates from the posterior (knee at 90 degrees of flexion) area of the femoral footprint and attaches on the anteromedial portion of the tibial footprint. The posterolateral (PL) bundle originates from the anterior (knee at 90 degrees of flexion) part of the femoral footprint and inserts on the posterolateral portion of the tibial footprint (Figure 3).
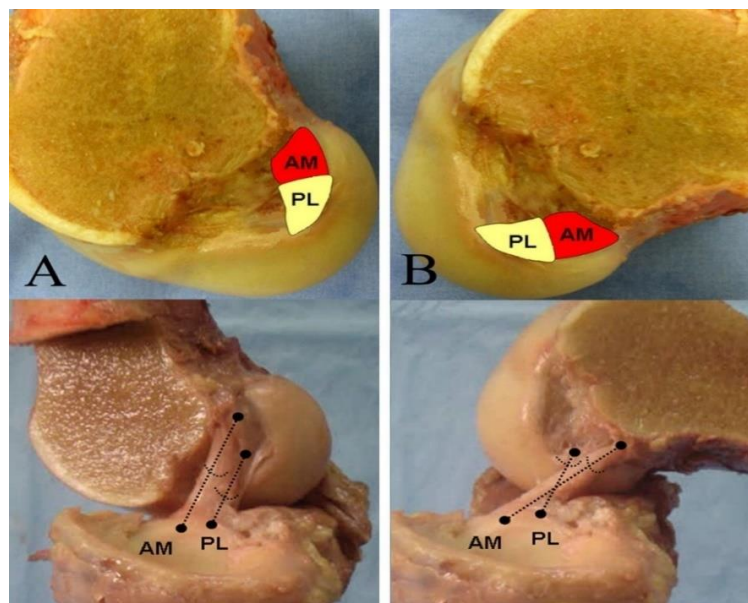
Figure 3. Illustration of the femoral and tibial footprints of the anteromedial (AM) and posterolateral (PL) bundles and their relationship in extension and flexion (reprinted with permission from Wolters Kluwer. Chhabra et al.[27])

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Increasing importance has been placed on this anatomical division over the last years. The two distinct bundles have been proposed to have different biomechanical roles. It has been suggested that the AM bundle progressively tightens in flexion, whereas the PL bundle progressively tightens in extension [27,167]. The PL bundle has also been suggested to play a major role in resisting internal rotation [27,167]. The emphasis placed on the biomechanical roles of the two bundles evolved over the years in the development of the double-bundle technique. However, it is still not clear whether this technique offers some advantages in comparison with an anatomic single-bundle technique [2,25,104,105,137].

The ultimate failure load of the native ACL has been reported to be approximately 2,160 N [162]. However, this value is significantly dependent on age, decreasing substantially for patients over 40 years [162]. Finally, it must be remembered that there are other ligamentous structures (MCL, LCL and in particular ALL structures) which act in synergy with the ACL and are secondary restrainers of the anterior displacement and internal rotation of the tibia [22,81]. Failure to recognize and address additional pathological laxities at the time of ACLR has been widely recognized as one of the most frequent causes of graft failure after ACLR. The menisci have also been recognized as important restrainers of both anterior tibial translation and internal tibial rotation [36,112].

1.2 Epidemiology of ACL injuries

An ACL tear is a common injury in sports medicine. In Sweden, the annual incidence of an ACL tear is estimated to be 0.8/1000 inhabitants aged between 10 and 64 years [116] and approximately 3,500 ACLRs are performed annually [152]. In Scandinavia, the most common activities performed at ACL injury are football, alpine skiing and handball [63]. It is well-known, from several studies, that female athletes have a significantly higher risk of ACL injuries in comparison with male athletes practicing the same sport [12,19,72,125].

Most ACL tears occur in combination with a non-contact trauma. The classic mechanisms associated with an ACL tear are a valgus-external-rotation trauma or, less frequently, a varus-internal-rotation trauma. An ACL injury can also occur after a knee hyperextension.

ACL tears are almost never isolated. Back in 1993, Terry et al. [151] showed that 93% of patients with an ACL injury also had injuries to the antero-lateral structures and that these injuries made an important contribution to abnormal anterior tibial translation and internal tibial rotation. Nowadays, great emphasis is placed on these structures and appropriate reconstructive techniques in an attempt to restore these abnormal knee motions to a level as close as possible to that of the un-injured knee [54]. Meniscal injuries are also extremely common in the ACL-injured knee. Kvist et al. [85] reported that more than 40% of patients have an associated meniscal injury at the time of primary ACLR. Collateral ligament injuries are also common in combination with ACL injuries [89].

Unfortunately, patients who undergo ACLR have a greater risk, compared with healthy knee people, of having another ACL injury in the same knee (ACL graft tear) or in the contralateral knee (contralateral ACL tear). [122]. Many patients with an ACL graft tear or a contralateral ACL tear undergo surgery. Lind et al. [94], with data from the Danish knee ligament reconstruction registry, reported a revision rate of 4.1% 5 years after primary ACLR. Kvist et al. [85] with data from the SNKLR, reported a similar rate (3.8%) for contralateral ACLR at

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the same length of follow-up. Revision ACLR and contralateral ACLR are devastating events for the patients, as they both require a repeat of the long postoperative rehabilitation. It is important to have reliable information about the expected outcome after revision and contralateral ACLR. For clinicians, patient counselling is essential.

1.3 Diagnosis

1.3.1 Anamnesis and physical examination

Patient history plays an essential part in the diagnosis. The vast majority of patients describe a sudden onset of pain, usually associated with a popping sensation, after a pivoting movement. This is generally followed by the rapid onset of joint effusion (hemarthrosis). The patient is unable to continue his/her physical activity.

The physical examination is crucial in the diagnostic process. In many cases (especially if not acute), a thorough physical examination is sufficient to make a diagnosis of an ACL tear. There is a large variability in physiological laxity among individuals and the examination of the normal, un-injured knee first is, therefore, recommended. The classic Lachman and pivot shift tests are normally performed. The Lachman test has been reported to have a significantly higher sensitivity compared with the pivot shift test [17]. The status of the antero-lateral structures strongly affects the amount of anterior and rotatory laxity in the ACL-injured knee [22,81,151]. This might, in part, explain the large inter-individual variability in pathological knee laxities when examining different patients with an ACL injury.

It is extremely important to perform a comprehensive clinical examination of the knee to rule out associated pathological laxities due to PCL (medial tibial step off, posterior drawer test), MCL (valgus stress 0°-30°) or LCL/PLC (varus stress 0°-30°, dial test) injuries. Failure to recognize and address associated injuries is one of the most known causes of graft failure after ACLR [133].

1.3.2 MRI

MRI is commonly used and it has high sensitivity and specificity [124] for diagnosing ACL tears (Figure 4).

Figure 4. MRI image (sagittal T2 projection) showing an ACL tear with associated joint effusion and bone marrow edema in the posterolateral tibial plateau

The MRI plays also an important role in diagnosing associated injures in the ACL-injured knee, which have an important impact on the prognosis and the treatment decision-making process [136].

1.3.3 KT-1000 Arthrometer

The KT-1000 arthrometer (MEDmetric, San Diego, CA) is a very useful instrument for the diagnosis of ACL tears. The KT-1000 arthrometer is more precise than the clinical Lachman test as it offers a quantitative evaluation of anterior tibial displacement [159]. Instrumented laxity measurement is also very useful after ACLR, as it measures and quantifies the anterior restraint provided by the ACL graft to the tibia [99]. Arthrometric laxity measurement has been used in this thesis as an outcome measurement after ACLR (Studies I, II and V) and before ACLR (Study III). A more detailed explanation of its role in the ACL-injured knee is given in the paragraph entitled "Outcomes".

1.4 Treatment

The treatment of ACL injuries is still a topic of great discussion. Generally, it can be divided into surgical and non-surgical (rehabilitation alone). Several factors must be considered when choosing the treatment. The approach must be individualized depending on the characteristics of the patient and the injury. For instance, a concomitant meniscus injury is a factor that strongly supports an ACLR [136]. It is widely accepted that ACLR should be highly recommended to patients involved in pivoting activities. For patients who are not involved in pivoting activities, an initial trial of non-surgical treatment could be recommended, but it should be remembered that, to-date, we do not have any reliable tools to predict which patients will become "copers" after rehabilitation treatment [136]. In Sweden, about 50% of all patients with an ACL injury undergo surgery [152]. Generally (unless clear indication for ACLR due to associated injuries and/or wish to return to pivoting activities), after an initial evaluation and discussion with the patient, a contact with a physical therapist is established and a close clinical follow-up is settled. In case of persistent instability, "giving ways", or inability to return to the desired level of activity, ACLR is recommended.

1.4.1   ACL Reconstruction

Surgical technique

The goal (from a surgical perspective) of an ACLR is the restoration of knee laxity to a level as close as possible to that of the native ACL-intact knee, taking into account graft morbidity and patient expectations. Many technical aspects of ACLR have evolved over the years. However, the most important change that occurred was the transition from an "isometric" to an "anatomic" ACLR technique. Surgeons in the 1980s and 1990s strived to place the femoral tunnel in an isometric position [31,118,160]. The aim was that the graft would experience "no"-minimal length changes during the range of motion. Over the years, several studies [1,77,113] showed that an anatomically placed femoral tunnel resulted in a better restoration of knee laxity compared with a placement at the isometric point. This led many ACL surgeons to a transition from a trans-tibial femoral drilling technique to an independent femoral drilling

technique through the antero-medial portal, which has been shown to lead to superior biomechanical and clinical outcomes [16,26].

One fundamental step in anatomic ACLR is the identification of the femoral and tibial footprints. Large variations in footprint anatomy [135] are present among individuals. A successful ACLR can only be achieved through an in-depth knowledge of the anatomy and an individualized tunnel placement depending on the individual patient´s anatomy. Tunnel malposition is one of the most important causes of failure of an ACLR [103,109,155]. The stumps of the native ACL are the most important landmarks and they should be carefully identified and demarcated during surgery. Other important references for the femoral footprint are the "resident´s ridge", which demarcates the superior (knee at 90 degrees) or anterior (knee at 30 degrees/extension) end of the footprint, and the "bifurcate ridge" between the AM and PL bundle. On the tibia, an important reference is the anterior horn of the lateral meniscus. The ACL tibial footprint has a very close relationship with the meniscal root attachment [88]. Biomechanical studies have shown that the optimal graft placement, for restoring anterior and rotatory laxity, is within the anatomical center of the femoral and tibial footprint [67,117].

Graft choice

Several grafts are used for ACLR. The most commonly used autografts are the HT and BPTB autografts. In Sweden, the most popular graft is the HT autograft (> 80% of primary ACLRs) [152]. There is a never-ending debate among ACL surgeons about which graft is superior to the other. In reality, every graft has its pros and cons and probably there is no graft which fits best to all patients. Every patient might benefit from a different graft and the graft choice should be individualized.

In an RCT [34] comparing muscle strength and SLH performance between HT and BPTB graft in the first 24 months after ACLR, it was found that the BPTB group had an inferior quadriceps strength from 4 to 12 months and a poorer SLH test performance at 4 months compared with the HT group. On the other hand, inferior hamstring strength was found at all post-operative follow-ups in the HT group. Therefore, the strength deficits generated by the harvesting of the different grafts should be considered when choosing the graft for ACLR, as it would be good to avoid specific (quadriceps or hamstring) strength deficits depending on the sport/activity practiced by the patient. Important outcomes of ACLR also include the restoration of knee laxity and the subjective outcome after surgery. The literature is inconsistent regarding the graft potential in terms of restoring knee laxity. Some studies have favored the BPTB graft [11,37,44], whereas others have reported no differences between HT and BPTB graft [93,100]. On the other hand, several studies have reported that the use of a BPTB graft results in a higher risk of anterior knee pain and extension loss [15,60,68]. However, the literature has also reported a lower risk of graft failure and revision surgery for the BPTB graft compared with the HT graft [56,86]. These factors are also important to consider when choosing the graft.

One graft that has gained in popularity in recent years is the quadriceps tendon (QT) autograft. A systematic review and meta-analysis found no differences in clinical outcomes and graft survival between QT, HT and BPTB autografts, however the QT autograft was

associated with significantly less donor-site pain compared with the BPTB autograft [110]. In addition, the QT graft showed a significantly higher failure load and stiffness and almost twice the cross-sectional area compared with the BPTB graft [139].

Another option is the use of an allograft. Allografts are tissues obtained from cadavers. Large variations are present in different countries regarding allograft usage. In Sweden, an allograft for ACLR is used very seldom [152], whereas in the US it is estimated that up to 30-40% of all ACLRs are performed with an allograft [73,101]. The potential benefits of allograft use could be reduced donor-site morbidity, less post-operative knee pain and reduced surgical time [30]. However, they are associated with increased knee laxity and a higher risk of graft failure, especially in younger patients [20,156,168]. Their use should be carefully considered, as they might only provide an alternative in highly selected patients.

Graft choice is a complex decision. There are many factors (biomechanical properties of the graft, work and/or sport practiced by the patient, age, skeletal maturity, associated knee ligament injuries, graft properties in restoration of knee laxity, expected subjective and functional knee outcome etc.) that must be considered and graft choice should be individualized to suit each patient.

1.5 Outcomes

There are several instruments to evaluate the outcome of an ACLR. What is a "successful" ACLR? This is a difficult question to answer, as there are many aspects that should be considered. From a surgical perspective, an objective assessment is essential. The clinical examination is an essential part of this assessment, but it does not provide a precise, quantitative measurement of knee laxity. The KT-1000 arthrometer [38] is the most studied instrument for quantifying anterior knee laxity.

From the patient (and surgeon) perspective, it is essential to evaluate subjective knee outcome. Patient-reported outcome measures (PROMs) evaluate the patient perception of treatment and knee function. Several PROMs for evaluating ACL injuries have been presented. The KOOS [131] is a widely used PROM to evaluate subjective knee function in patients with ACL injuries. The KOOS is also the main PROM used in the SNKLR.

1.5.1 Instrumented laxity measurement – KT-1000 arthrometer

The KT-1000 arthrometer provides a precise, quantitative measurement of the anterior translation of the tibia. It is not only useful for diagnosing an ACL tear and measuring the degree of laxity, but it is also useful after ACLR to quantify the restraint provided by the graft [38]. The patient is placed supine on an examination table. To keep the knee at 20-30 degrees of flexion, a bolster is placed under the thighs. The feet are placed on a footrest and, to avoid muscle contraction and external rotation, a strap is applied around the thighs. The instrument has two pads. One pad is placed on the patella and one on the tibia. The arthrometer is then secured to the tibia with 2 straps. The examiner then pulls on the arthrometer handle and three sounds can be heard consecutively. These sounds correspond to the amount of anterior tibial load applied by the examiner (15 lbs/67 N; 20 lbs/89 N; 30 lbs/134 N). A manual max measurement is usually performed as well. It is important to recalibrate the arthrometer after

each measurement. This is done by pulling-pushing the handle of the arthrometer several times until the "zero", neutral point is found (Figure 5).

Figure 5. KT-1000 measurement (reprinted with permission from Springer. Isberg et al.[74])

The measurement must always be bilateral. The injured or ACL-reconstructed knee is compared with the uninjured knee. The side-to-side (STS) difference in displacement (injured or ACLR knee – uninjured knee) is registered. STS laxity is classified, according to the IKDC examination form [69], in four grades: A) Normal: ≤ 2mm; B) Nearly normal: 3-5 mm; C) Abnormal: 6-10 mm; D) Severely abnormal: > 10 mm. It is recommended that only the standard displacement force of 134 N is used for grading [69].
Instrumented laxity measurement with the KT-1000 arthrometer has proven to be reliable [39,76,95,164].

1.5.2 Knee injury and Osteoarthritis Outcome Score (KOOS)

This PROM has been used extensively to measure subjective knee function before and after ACLR. It was first developed by Roos et al. in 1998 [131]. It is the main PROM in the SNKLR [152]. In general, it is used for knee injuries (ACL injury, meniscus injury, chondral injury) that could lead to the development of OA. It is also used as an outcome measurement in the OA itself.
The KOOS is a questionnaire, consisting of five subscales, which is directly filled in by the patient at the doctor office or, alternatively, on the internet. It takes a few minutes to complete. In total, there are 42 questions in the five subscales of Pain, Symptoms, ADL, Sport/Rec and QoL. The score on each subscale ranges from 0 to 100, where 0 represents "extreme knee problems" and 100 "no knee problems". It is recommended to evaluate each subscale separately [131]. According to Roos et al. [131], the most responsive subscales at follow-up after ACLR are the Sport and Recreation and the QoL subscales. The minimal important change on the subscales is usually considered to be 8-10 points [131]. One possible limitation with the use of the KOOS might be the not straightforward interpretation,

especially with regard to the postoperative scores. A score that might considered as "good" or "successful" by the orthopedic surgeon does not necessarily correspond to "feeling well" from the patient´s perspective. Recently, Muller et al. [111] identified the thresholds for the PASS after ACLR. These scores were established by 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 participations restrictions, do you consider the current state of your knee satisfactory?". These thresholds (Pain $\geq$ 88.9; Symptoms $\geq$ 57.1; ADL = 100; Sport and Recreation $\geq$ 75.0; QoL $\geq$ 62.5) might provide a more straightforward interpretation of the KOOS, as they are more representative of the patient´s knee well-being.

1.5.3 Isokinetic strength measurement and hop test performance

One of the most important goals of ACLR is return to sport. Post-surgical time is only one of the aspects that should be considered for allowing patients to return to sport. Strength tests and hop tests are used in the clinical practice to evaluate readiness to return to sport. The principle is to test muscle strength and the combination of neuromuscular control and proprioceptive function of the ACL reconstructed knee in comparison with the contralateral healthy knee. The results of these tests are normally reported through the limb symmetry index (LSI) (affected leg/healthy leg x 100). An LSI of $\geq$ 90% is generally reported as the goal to reach for return to sport [33,115,153]. One of the most used machines for measuring quadriceps and hamstring strength is the Biodex System 3 (Biodex Medical Systems, Shirley, New York, USA). Testing protocols can differ depending on angular velocities, number of repetitions, ROM as well as mode of contraction. However, patients usually warm-up before the test and are instructed about the modality of the test. Some practical trials are also allowed. The highest values achieved during the test, for both quadriceps and hamstrings, are usually registered.

The single leg hop test is one of the most used hop tests to assess hop performance [33,115.128,153]. It is a very simple test to perform. The patient is asked to stand on one leg and jump straight as far as possible and land on the same leg. It is essential that the landing is stable, otherwise the test is repeated. As for the muscle strength test, patients are instructed previously about the modality of the test and allowed to make some practical trials. Usually, the best trial of each leg is registered.

2. AIMS OF THE THESIS

The overall aims were to identify factors affecting objective and subjective outcomes after ACLR, the risk of associated (cartilage and meniscus) injuries and meniscus repair at the time of primary ACLR. Another aim was to evaluate and compare the subjective and objective outcomes of revision and contralateral ACLR with those of primary ACLR.

Study I The aim of study I was the identification of preoperative and intraoperative factors associated with "graft failure", defined as a KT-1000 STS laxity > 5 mm, after primary ACLR.

Study II The aim of study II was to compare knee laxity (KT-1000) and functional knee outcome (KOOS) between primary and revision ACLR.

Study III The primary aim of study III was to evaluate the effect of the timing of ACLR on cartilage and meniscus injuries, meniscus repair and knee laxity at the time of primary ACLR. However, the effect of other variables (age, gender and BMI) on these outcomes was also evaluated.

Study IV The first aim of study IV was to evaluate the rate of patients achieving an acceptable symptom state, on each of the KOOS subscales, 2 years after primary ACLR. In addition, it evaluated a wide range of preoperative, intraoperative and postoperative factors affecting the achievement of a PASS.

Study V This study aimed to compare knee laxity (KT-1000) and functional knee outcome (KOOS) between primary and contralateral ACLR.

3. METHODS

3.1 Data Sources

Data for all the studies were extracted from our local registry, at Capio Artro Clinic, Stockholm, Sweden. This registry is a part of the SNKLR but contains some additional data. Patients undergoing ACLR at our institution are entered in the registry. Patient and surgical data are registered at baseline. Age, gender, side of injury, BMI, activity at ACL injury, pre-injury Tegner activity level [150], time from injury to surgery, graft used, graft diameter, meniscal and cartilage injuries, as well as meniscal surgery (resection or repair) for both menisci, are the preoperative and intraoperative variables available. Knee laxity (KT-1000 arthrometer) is routinely measured pre-operatively and at 6 months postoperatively. Isokinetic quadriceps and hamstring strength tests, as well as the single-leg-hop test, are performed at the 6-month follow-up. The KOOS is collected preoperatively, one, two and five years after ACLR. Patients are identified by using their unique personal identity number [98].

3.2 Study design

The studies included in this thesis are *Registry-based cohort studies.* Cohort studies follow, over time, a group of patients who undergo a particular intervention. Data are collected at baseline and at one or more follow-ups. A single cohort study might include multiple cohorts, for which data are collected using the same methods during the same period. This creates the opportunity to compare different interventions for otherwise similar groups.
In Scandinavia, there is a well-known tradition of health-related registries [41,114]. The Nordic countries have pioneered ACL registries. The Swedish ACL registry was established in 2005, following Norway and Denmark [152]. The main strengths of registry-based cohort studies are usually the large number and heterogeneity of the included patients. These characteristics usually make the results of these studies highly generalizable and of great value in every-day clinical practice. This is one of the main differences in comparison with randomized controlled trials (RCTs). RCTs are generally made on an homogeneous group of patients. A significant number of patients are in fact excluded from these studies. This can affect the external validity. On the other hand, registries generally have strong external validity, due to the fact that they include a wide, heterogeneous and varied study population [59]. However, randomization is not present in cohort studies and there might be an imbalance in the distribution of potential confounding factors that might affect the outcome. For this reason, statistical methods such as logistic regression analyses and an analysis of variance are also successfully employed in cohort studies [8,108]. These cohort studies are retrospective studies, but they are based on prospectively collected data. As a result, there is no risk of recall bias, due to the prospective registration [59].
Loss to follow-up or attrition remains a well-known phenomenon and the main problem in registry cohort studies [5,85]. Attrition could have three major statistical implications – potential selection bias, reduced generalizability of the results and loss of statistical power [47]. There should not be any pre-established level of what constitutes an "acceptable" follow-up [75]. On the contrary, these potential statistical implications should be considered case by case [32]. In most cases, due to the large sample size, even with a not-optimal follow-up rate, registry studies maintain very satisfactory power and the results are still highly

generalizable. However, loss to follow-up might be a matter of concern when it is not random, which occurs when there is a systematic difference between the included cohort and the lost to follow-up cohort [59]. The extent of the loss to follow-up determines the impact on the potential selection bias. So, in order to increase the validity of registry studies, it is important to prevent the loss to follow-up as much as possible [42,84]. In some cases, the differences between the included cohort and the loss to follow-up cohort are unknown and therefore unmeasurable. However, in registry studies, all patient and surgical data are registered at baseline and, thanks to their unique personal identity number [98], all the data from patients who are lost to follow-up can be easily retrieved and analyzed. To assess the presence of a potential selection bias in the event of a large loss to follow-up, it is important to perform a drop-out analysis [59]. With this analysis, it is possible to show eventual differences in patient characteristics between the included cohort and the loss to follow-up cohort. For instance, an analysis of data in the Swedish ACL registry showed that older age and female gender improve the 2-year KOOS response rate [129]. Differences between patients included and patients lost to follow-up in registry studies may have the potential for selection bias and could influence the results. In many cases these differences may be small and therefore not clinically relevant. However, it is important to be aware of these differences. The inclusion of these baseline characteristics as covariates, for instance, in an analysis of covariance model, with the KOOS as an outcome, would strongly reduce their potential effect on the results [32,35,84].

3.3 Participants

Study I

In this study, 7,185 patients who underwent primary ACLR (2000-2015) were assessed for eligibility. Patients with a contralateral ACL injury or reconstruction and patients with missing pre- or post-operative KT-1000 measurements were excluded. The final study population was composed of a total of 5,462 patients with pre- and post-operative instrumented laxity measurements available. Patient characteristics are reported in Table 1.

Table 1. Patient Characteristics (n = 5462 patients)

		Mean ± SD postoperative STS difference, *mm*
Preoperative variables		
Age at surgery, y, mean ± SD	28.1 ± 10.3 (range, 9 to 63)	
Aged younger than 30 years	20.9 ± 4.7; 3223 (59)	1.9 ± 2.2
Aged 30 years or older	38.6 ± 6.6; 2239 (41)	1.5 ± 2.2
Gender		
Male	3051 (55.8)	1.7 ± 2.2
Female	2411 (44.2)	1.9 ± 2.2
Pre-operative STS difference		
> 5 mm	1208 (22.1)	3.0 ± 2.3
≤ 5 mm	4254 (77.9)	1.4 ± 2.0
Intraoperative variables		
Graft type		
HT autograft	4770 (87.3)	1.8 ± 2.2
BPTB autograft	692 (12.7)	1.2 ± 2.1
No meniscus surgery	3435 (62.9)	1.6 ± 2.1
Medial meniscus surgery		
Resection	777 (14.2)	2.2 ± 2.5
Repair	266 (4.9)	1.7 ± 2.3
Lateral meniscus surgery		
Resection	824 (15.1)	1.9 ± 2.2
Repair	160 (2.9)	1.9 ± 2.1

Data are reported as n (%), unless otherwise indicated. SD, standard deviation; HT, hamstring tendon; BPTB, bone patellar tendon bone; STS, side-to-side; *mm*, millimeter

Study II

Study II included the same patients who consecutively underwent primary HT and revision BPTB autograft ACLR (2000-2015). Other inclusion criteria were no associated ligament injuries, no contralateral ACL injuries/reconstruction and graft rupture as the cause of revision. From a total of 200 patients, two cohorts (one for the comparison of knee laxity and one for the comparison of functional knee outcome) were generated. The patient flowchart is displayed in Figure 6. Patient demographics for the knee laxity and the functional knee outcome cohort are reported in Tables 2 and 3.
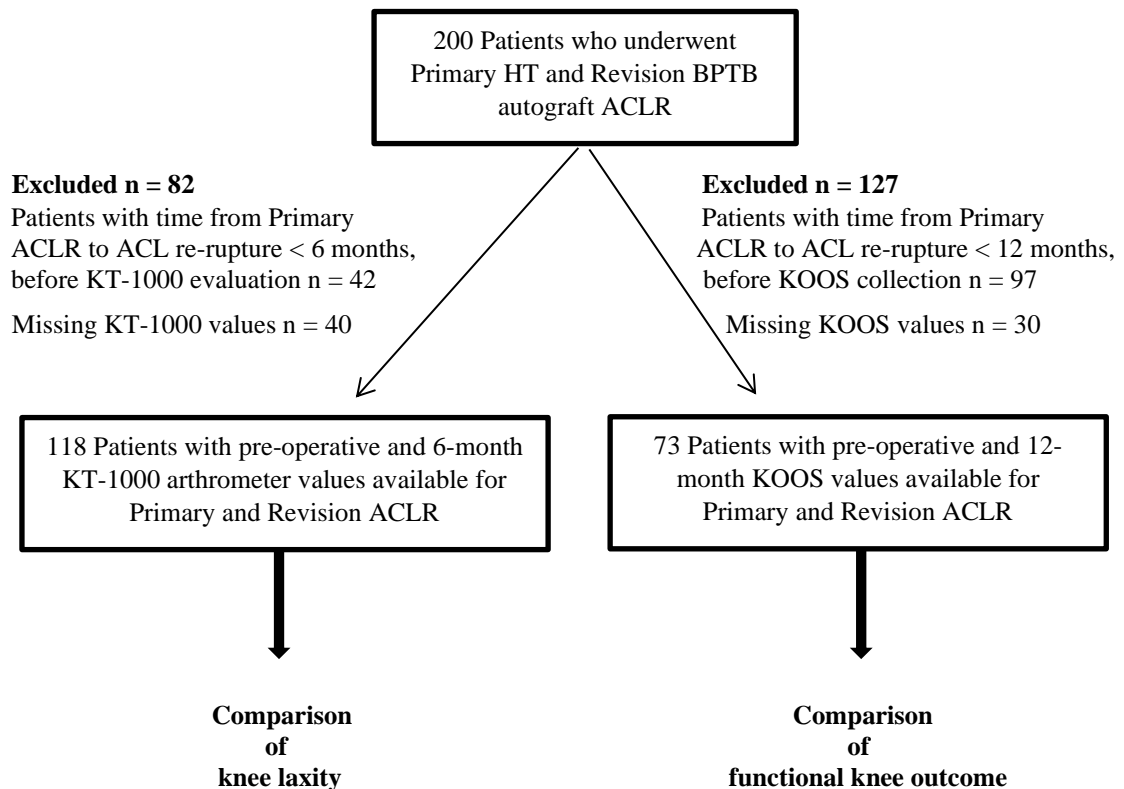
Figure 6. Patient flowchart.

Table 2 Patient Demographics (Knee laxity cohort)

Variable		Primary ACLR	Revision ACLR	Total[*]
Sex, male/female, n (%)	60/58 (51.0/49.0)			
Injured side, right/left	64/54			
Age at surgery, y ± SD		21.7 ± 7.1	24.3 ± 7.5	
Cause				
Soccer		57 (48.3)	46 (39.0)	
Alpine skiing		19 (16.1)	17 (14.4)	
Floorball		13 (11.0)	10 (8.5)	
Handball		8 (6.8)	6 (5.1)	
Other sports		13 (11.0)	26 (22.0)	
Other		8 (6.8)	13 (11.0)	
Associated procedures, n (%)				
MM resection		19 (16.0)	7 (5.9)	26 (21.9)
LM resection		14 (11.7)	11 (9.2)	25 (20.9)
MM repair		3 (2.5)	8 (6.7)	11 (9.2)
LM repair		6 (5.0)	4 (3.3)	10 (8.3)
MM repair + LM resection		3 (2.5)	1 (0.8)	4 (3.3)
MM resection + LM resection		1 (0.8)	1 (0.8)	2 (1.6)
MM repair + LM repair			1 (0.8)	1 (0.8)
Chondral lesions, n (%)		16 (13.6)	22 (18.6)	38 (32.2)
Fixation methods, n (%)				
Femur				
Endobutton		118 (100)	67 (56.8)	
Interference screw		/	51 (43.2)	
Tibia				
AO screw with washer		110 (93.2)	/	
Interference screw		8 (6.8)	118 (100)	
Mean time intervals for primary and revision ACLR, months (range)				
From injury to primary ACLR	7.2 (0.5 – 74.8)			
From primary ACLR to ACL graft rupture	22.7 (6.5 – 82.0)			
From ACL graft rupture to revision ACLR	9.0 (1.0 – 80.2)			

ACLR, anterior cruciate ligament reconstruction; ACL, anterior cruciate ligament; SD, standard deviation; MM, medial meniscus; LM, lateral meniscus

[*]Total amount of meniscal procedures performed and chondral lesions found at primary and revision ACLR.

Table 3 Patient Demographics (Functional knee outcome cohort)

Variable		Primary ACLR	Revision ACLR	Total[*]
Sex, male/female, n (%)	40/33 (54.7/44.3)			
Injured side, right/left	42/31			
Age at surgery, y ± SD		21.6 ± 7.0	24.7 ± 7.3	
Cause				
Soccer		33 (45.2)	23 (31.5)	
Alpine skiing		12 (16.4)	11 (15.0)	
Floorball		10 (13.7)	9 (12.3)	
Handball		4 (5.5)	3 (4.2)	
Other sport		10 (13.7)	18 (24.7)	
Other		4 (5.5)	9 (12.3)	
Associated procedures, n (%)				
MM resection		10 (13.5)	5 (6.7)	15 (20.2)
LM resection		8 (10.8)	5 (6.7)	13 (17.5)
MM repair		3 (4.0)	3 (4.0)	6 (8.0)
LM repair		2 (2.7)	3 (4.0)	5 (6.7)
MM repair + LM resection		3 (4.0)	1 (1.3)	4 (5.3)
MM resection + LM resection		1 (1.3)	1 (1.3)	2 (2.6)
Chondral lesions, n (%)		10 (13.5)	14 (18.9)	24 (32.4)
Fixation methods, n (%)				
Femur				
Endobutton		73 (100)	40 (54.8)	
Interference screw		/	33 (45.2)	
Tibia				
AO screw with washer		67 (91.8)	/	
Interference screw		6 (8.2)	73 (100)	
Mean time intervals for primary and revision ACLR, months (range)				
From injury to primary ACLR	5.9 (0.5 – 35.2)			
From primary ACLR to ACL graft rupture	29.9 (13.0 – 82.6)			
From ACL graft rupture to revision ACLR	8.2 (0.5 – 48.0)			

ACLR, anterior cruciate ligament reconstruction; ACL, anterior cruciate ligament; SD, standard deviation; MM, medial meniscus; LM, lateral meniscus
[*]Total amount of meniscal procedures performed and chondral lesions found at primary and revision ACLR.

Study III

In this study, patients who underwent primary ACLR between 2005 and 2017, with no concomitant ligament injuries, were assessed for eligibility. Only patients with a complete data set available were included. Patients with a contralateral ACL injury or reconstruction were excluded. The final population included in the analysis was composed of 3,976 patients. A detailed summary of patient characteristics is presented in Table 4.

Table 4. Patient Characteristics (n = 3,976 Patients)

		Cartilage Injury	MM Injury	LM Injury	MM Resection	MM Repair	LM Resection	LM Repair	STS Difference > 5 mm
		660 (16.6)	899 (22.6)	908 (22.8)	556 (14.0)	245 (6.2)	624 (15.7)	161 (4.0)	952 (23.9)
Surgical timing, months, mean ± SD	14.5 ± 10.3	20.9 ± 33.4	18.9 ± 29.4	12.7 ± 23.3	23.9 ± 34.4	10.5 ± 14.2	13.3 ± 25.0	11.2 ± 17.5	17.0 ± 28.0
0-3	719 (18.1)	88 (12.2)	132 (18.3)	215 (29.9)	56 (7.8)	56 (7.8)	147 (20.4)	36 (5.0)	151 (21.0)
3-6	1122 (28.2)	151 (13.5)	218 (19.4)	262 (23.3)	106 (9.5)	74 (6.6)	179 (15.9)	51 (4.5)	230 (20.5)
6-12	1101 (27.7)	178 (16.2)	224 (20.3)	229 (20.8)	146 (13.3)	60 (5.5)	155 (14.1)	41 (3.7)	271 (24.6)
12-24	517 (13.0)	108 (20.9)	143 (27.7)	98 (18.9)	97 (18.8)	32 (6.2)	68 (13.1)	13 (2.5)	140 (27.1)
>24	517 (13.0)	135 (26.1)	182 (35.2)	104 (20.1)	151 (29.2)	23 (4.5)	75 (14.5)	20 (3.9)	160 (30.9)
Gender									
Male	2138 (53.8)	370 (56.1)	520 (57.9)	545 (60.0)	348 (62.6)	121 (49.4)	391 (62.7)	83 (51.5)	521 (54.7)
Female	1838 (46.2)	290 (43.9)	379 (42.1)	363 (40.0)	208 (37.4)	124 (50.6)	233 (37.3)	78 (48.5)	431 (45.3)
Age at surgery, years mean ± SD	28.6 ± 10.6	33.8 ± 10.9	30.2 ± 11.2	27.0 ± 10.2	33.2 ± 11.2	24.3 ± 9.0	28.1 ± 10.1	22.6 ± 9.2	27.9 ± 10.5
≥ 30 years	1661 (41.8)	414 (62.7)	474 (52.7)	327 (36.0)	316 (56.8)	69 (28.2)	249 (39.9)	32 (19.9)	375 (39.4)
< 30 years	2315 (58.2)	246 (37.3)	425 (47.3)	581 (64.0)	240 (43.2)	176 (71.8)	375 (60.1)	129 (80.1)	577 (60.6)
BMI, Kg/m^2, mean ± SD	24.2 ± 3.6	24.8 ± 3.5	24.5 ± 3.5	24.3 ± 3.7	25.0 ± 3.4	23.6 ± 3.6	24.6 ± 3.7	23.5 ± 4.1	23.8 ± 3.5
≥ 25	1347 (33.9)	266 (40.3)	341 (37.9)	321 (35.3)	246 (44.3)	62 (25.3)	240 (38.5)	45 (27.9)	267 (28.1)
< 25	2629 (66.1)	394 (59.7)	558 (62.1)	587 (64.7)	310 (55.7)	183 (74.7)	384 (61.5)	116 (72.1)	685 (71.9)

NOTE. Data are reported as n (%), unless otherwise indicated. The rates of cartilage and meniscus injuries, meniscus resection and repair, and STS difference > 5 mm in the surgical timing groups are reported in relation to the number of patients present in the specific timing group to show their trend with a longer time from injury to surgery interval.
BMI, body mass index; LM, lateral meniscus; MM, medial meniscus; SD, standard deviation; STS, side-to-side.

Study IV

In *Study IV*, a total of 5,231 patients who underwent primary ACLR (2005-2015) were identified. Patients with contralateral ACL injuries or reconstruction and revision ACLR were excluded. A cohort of 4,794 patients was eligible for inclusion. From this cohort, 2,459 patients were excluded due to missing KOOS data 2 years after surgery. A total of 2,335 patients had KOOS data at the 2-year follow-up and were analyzed. Patient characteristics and drop-out analysis are detailed in Table 5.

Table 5 Patient characteristics and dropout analysis

	Included cohort (n = 2,335)	No two-year KOOS data (n = 2,459)	*P* value
Pre-operative factors			
Age at surgery, yrs, mean ± SD	29.7 ± 10.9	28.3 ± 9.9	< 0.001
Age younger than 30 yrs	20.9 ± 4.6; 1233 (52.8)	21.4 ± 4.6; 1475 (59.9)	
Age 30 yrs or older	39.5 ± 6.7; 1102 (47.2)	38.5 ± 6.4; 984 (40.1)	
Gender			< 0.001
Male	1182 (50.6)	1508 (61.3)	
Female	1153 (49.4)	951 (38.7)	
Time from injury to surgery, months, mean ± SD	15.1 ± 8.7	16.9 ± 9.8	n.s.
≤ 3 months	381 (17.7)	352 (16.2)	
> 3 months	1769 (82.3)	1821 (83.8)	
	n = 2150	n = 2173	
Pre-injury Tegner activity level, median (range)	7 (1-10)	7 (1-10)	n.s.
High, ≥ 6	1749 (87.4)	1897 (89.1)	
Low, < 6	252 (12.6)	232 (10.9)	
	n = 2001	n = 2129	
Intra-operative factors			
Graft type			n.s.
HT autograft	2100 (89.9)	2182 (88.7)	
BPTB autograft	235 (10.1)	277 (11.3)	
No meniscus surgery	1528 (65.4)	1473 (59.9)	
Medial meniscus surgery			
Resection	321 (13.7)	379 (15.4)	n.s.
Repair	95 (4.0)	128 (5.2)	n.s.
Lateral meniscus surgery			
Resection	326 (13.9)	395 (16.1)	0.04
Repair	65 (2.8)	84 (3.4)	n.s.
			n.s.
Cartilage injury			
Yes	469 (20.0)	478 (19.4)	
No	1866 (80.0)	1981 (80.6)	

Post-operative factors (six months)

Isokinetic quadriceps strength			n.s.
LSI ≥ 90%	758 (32.5)	713 (34.3)	
LSI < 90%	1575 (67.5)	1367 (65.7)	
	n = 2333	n = 2080	
Isokinetic hamstring strength			n.s.
LSI ≥ 90%	1120 (48.0)	963 (46.3)	
LSI < 90%	1210 (52.0)	1115 (53.7)	
	n = 2330	n = 2078	
Single-leg-hop test			n.s.
LSI ≥ 90%	1335 (65.5)	1210 (66.9)	
LSI < 90%	704 (34.5)	596 (33.1)	
	n = 2039	n = 1806	

Data are reported as n (%), unless otherwise indicated.
KOOS, Knee injury and Osteoarthritis Outcome Score; SD, standard deviation; HT, hamstring tendon; BPTB, bone patellar tendon bone; LSI, limb symmetry index

Study V

Study V is based on patients who underwent bilateral ACLR (primary and contralateral ACLR at two different time points) during 2001-2017. Patients with an HT or a BPTB autograft ACLR were included. A total of 326 patients were identified. Patient characteristics are reported in Table 6. Two cohorts (one for the comparison of knee laxity and one for the comparison of functional knee outcome) were generated. The patient flowchart is shown in Figure 7.
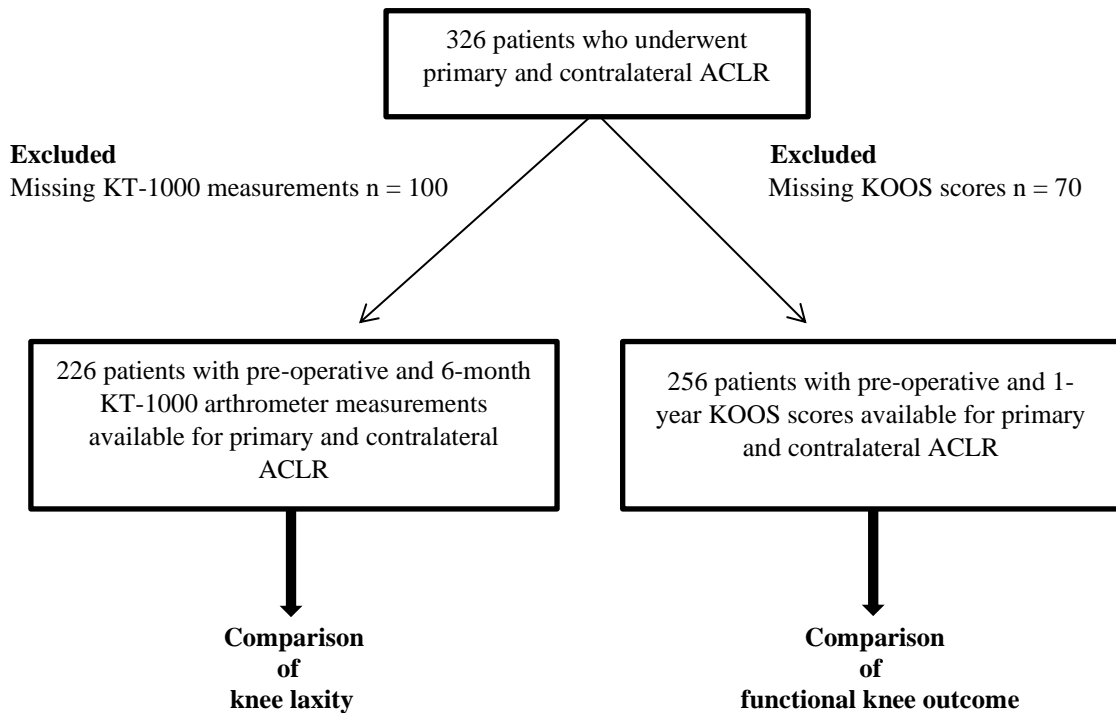
Table 6 Patient characteristics

Variable		Primary ACLR	Contralateral ACLR
Gender, male/female, *n* (%)	156/170 (47.9/52.1)		
Injured side, right/left, *n* (%)	153/173 (46.9/53.1)		
Age at surgery, years ± SD		23.9 ± 9.4	27.9 ± 10.1
Activity at injury, *n* (%)			
Football		123 (37.7)	135 (41.4)
Alpine skiing		43 (13.2)	50 (15.3)
Floorball		20 (6.1)	27 (8.3)
Handball		19 (5.8)	16 (4.9)
Other sports[*]		49 (15.0)	48 (14.7)
Other		25 (7.7)	32 (9.8)
Missing		47 (14.4)	18 (5.5)
Graft, *n* (%)			
HT autograft		261 (80.1)	280 (85.9)
BPTB autograft		65 (19.9)	46 (14.1)
Associated meniscal procedures, *n* (%)			
MM resection		40 (12.3)	43 (13.2)
LM resection		45 (13.8)	54 (16.6)
MM repair		13 (4.0)	19 (5.8)
LM repair		9 (2.8)	10 (3.1)
Cartilage injuries, *n* (%)		48 (14.7)	52 (16.0)
Time intervals, months ± SD			
From injury to ACLR		10.8 ± 18.2 (n = 258)	10.0 ± 19.2 (n = 287)
From primary to contralateral ACLR	48.3 ± 39.4		

ACLR, anterior cruciate ligament reconstruction; BPTB, bone-patellar tendon-bone; HT, hamstring tendons; LM, lateral meniscus; MM, medial meniscus; SD, standard deviation

[*]Basketball, rugby, dancing, motocross, gymnastics, boxing, ice hockey, tennis, volleyball

Figure 7. Patient flowchart

```
                    ┌─────────────────────────────┐
                    │   326 patients who underwent │
                    │  primary and contralateral ACLR │
                    └─────────────────────────────┘
```

Excluded   **Excluded**
Missing KT-1000 measurements n = 100   Missing KOOS scores n = 70

```
┌───────────────────────────────┐      ┌───────────────────────────────┐
│ 226 patients with pre-operative│      │ 256 patients with pre-operative│
│ and 6-month KT-1000 arthrometer│      │ and 1-year KOOS scores         │
│ measurements available for     │      │ available for primary and      │
│ primary and contralateral ACLR │      │ contralateral ACLR             │
└───────────────────────────────┘      └───────────────────────────────┘
```

        Comparison   **Comparison**
            of   **of**
        knee laxity   **functional knee outcome**

3.4 Outcome measurements

Study I

The outcome was the postoperative (6-month) difference in displacement (STS difference) between the ACL-reconstructed knee and the healthy knee. Knee laxity was classified according to the IKDC examination form [69]. Abnormal knee laxity was defined as an STS difference > 5 mm (IKDC grades C and D).

Study II and V

The outcomes of these studies were knee laxity (KT-1000 arthrometer) and functional knee outcome (KOOS). Data on laxity measurements (pre-op and 6-month post-op) and KOOS (pre-op and 1-year post-op) were reviewed. *Study II* was based on a comparison between primary and revision ACLR, whereas *Study V* was based on a comparison between primary and contralateral ACLR.

Study III

There were several end points in this study. The dependent variables were: cartilage injury, MM injury, LM injury, MM repair, LM repair and abnormal (STS > 5 mm) pre-reconstruction laxity.

Study IV

The outcome of this study was the achievement of a PASS, in each KOOS subscale, 2 years after ACLR. The achievement of a PASS was assessed on the basis of the threshold values identified by Muller et al. [111]: Pain $\geq$ 88.9; Symptoms $\geq$ 57.1; ADL = 100; Sport and Recreation $\geq$ 75.0; and QoL $\geq$ 62.5.

3.5 Statistical analysis

All the statistical analyses were conducted using IBM SPSS Statistics (SPSS Inc, Armonk, New York, USA). All the variables were summarized with standard descriptive statistics such as frequency, mean and SDs. The distributions were checked for severe deviations from a normal distribution. Logistic regression analyses were used in *Studies I, III* and *IV*. An ANOVA for repeated measurements was used in *Studies II* and *V*. The level of significance in all analyses was 5% (2-tailed).

Study I

The dependent variable was a post-operative STS laxity > 5 mm. The independent variables were: age < 30 years, female gender, pre-operative STS laxity > 5 mm, HT graft, medial meniscus resection, medial meniscus repair, lateral meniscus resection and lateral meniscus repair. The results of the logistic regression analysis were expressed as odds ratio (OR) with 95% confidence intervals (CI).

Study II

Comparisons between primary and revision ACLR in terms of pre-operative, post-operative and laxity reduction or functional knee outcome improvement from pre-op to post-op were made with an analysis of variance (ANOVA) for repeated measurements. Differences in the distribution of "surgical failures" (STS laxity > 5 mm) between primary and revision ACLR were analyzed with Pearson´s x^2-test.

Study III

The main outcome variables of this study were: cartilage injury, MM injury, LM injury, MM repair and LM repair. The dependent variables were: time from injury to surgery (0-3, 3-6, 6-12, 12-24, and > 24 months), age $\geq$ 30 years, BMI $\geq$ 25 [163].
The 0- to 3-month group was chosen as the reference timing group. The other timing groups were compared with this group. The number of MM, LM and cartilage injuries were analyzed in relation to the number of patients in each specific timing group. The number of MM and LM repairs were analyzed in relation to the number of patients in each specific timing group with an MM or LM injury respectively.
Another outcome variable was abnormal pre-reconstruction laxity (STS difference > 5 mm). For this analysis, the same independent variables described above were used plus MM and LM injury, as it has been shown that they could potentially affect knee laxity in the ACL-deficient knee [6,97,142]. The results of the logistic regression analyses were reported with ORs and 95% CIs.

Study IV

The dependent variable in this study was the achievement of a PASS, in each KOOS subscale, 2 years after primary ACLR. The independent variables were: age ≥ 30 years, female gender, delayed (> 3 months) ACLR, pre-injury Tegner activity level ≥ 6, HT autograft (vs. BPTB autograft), MM resection, MM repair, LM resection, LM repair, cartilage injury, postoperative (6-month) quadriceps strength LSI $\geq 90\%$, hamstring strength LSI $\geq 90\%$ and SLH test performance LSI $\geq 90\%$. The results of the logistic regression analyses were expressed as ORs with 95% CIs. For comparisons between the included and the loss to follow-up cohort, Pearson´s Chi-square test was used.

Study V

Comparisons between primary and contralateral ACLR in terms of pre-operative, post-operative and laxity reduction or functional knee outcome improvement from pre-op to post-op were made with an analysis of variance (ANOVA) for repeated measurements.

3.6 Ethics

All the studies included in the present thesis are registry based. The data for all the studies were extracted from the Capio Artro Clinic registry, which is a part of the SNKLR. The SNKLR is regulated by the Patient Data Act – Patientdatalag (PDL) (2008:355) and the General Data Protection Regulation (GDPR), EU 2016/679. The studies were approved by the regional ethics committee, Karolinska Institutet, Stockholm, Sweden, diary number 2016/1613-31/2. For this type of study, informed consent is not required. The data are retrospectively collected and presented at group level with a minimal risk of the patients being identified. Each author declared no possible conflict of interest in connection with any of the studies.

4. RESULTS

FACTORS AFFECTING THE RISK OF ABNORMAL LAXITY AFTER ACLR (STUDY I)

A total of 223 patients (223/5,462 = 4.1%) had abnormal (STS > 5 mm) laxity postoperatively. Factors that increased the odds of having abnormal knee laxity were age < 30 years, preoperative STS > 5 mm, the use of an HT graft and MM resection. Female gender, MM repair, LM resection or repair were not correlated with abnormal knee laxity.

KNEE LAXITY AND FUNCTIONAL KNEE OUTCOME – PRIMARY VS REVISION AND CONTRALATERAL ACLR (STUDIES II & V)

Study II revealed no differences between primary and revision ACLR in terms of mean preop and postop STS difference and ATT reduction. However, a higher frequency of "surgical failures" (postoperative STS difference > 5 mm) (8.4% vs. 5.0%; *P* = 0.02) was found after primary ACLR.

Revision ACLR showed higher scores in four KOOS subscales pre-operatively: Symptoms (*P* = 0.003), Pain (*P* = 0.01), Sport and Recreation (*P* = 0.006) and QoL (*P* = 0.04). However, primary ACLR showed a significantly greater improvement from preop to postop in all subscales and the postoperative scores were higher in the Pain (*P* = 0.04), ADL (*P* = 0.002) and Sport and Recreation (*P* < 0.001) subscales.

In *Study V*, no differences were found between primary and contralateral ACLR in terms of mean preoperative and postoperative ATT and ATT reduction. Similarly, no differences between the surgeries were found with regard to preoperative and postoperative KOOS scores as well as the improvement in the KOOS from preoperative to postoperative.

EFFECT OF DELAY IN ACLR, AGE, GENDER AND BMI ON CARTILAGE INJURIES, MENISCUS INJURIES, MENISCUS REPAIR AND ABNORMAL PRERECONSTRUCTION LAXITY (STUDY III)

Several important associations were found in this study.

Cartilage and meniscus injuries

The odds of cartilage injuries increased with a delay (> 12 months) in ACLR and age ≥ 30 years. The odds of MM injuries increased with a delay (> 12 months) in ACLR, male gender and age ≥ 30 years, whereas the odds of LM injuries decreased with a delay (> 3 months) in ACLR and age ≥ 30 years but increased with male gender.

MM or LM repair

The odds of MM repair decreased with a delay (> 6 months) in ACLR, whereas time from injury to surgery had no effect on the odds of LM repair. Age ≥ 30 years reduced the odds of both MM and LM repair.

Pre-reconstruction laxity

The odds of having abnormal pre-reconstruction laxity increased with a delay (> 6 months) in ACLR and the presence of a MM injury, whereas it was reduced by a BMI of ≥ 25.

THE PATIENT-ACCEPTABLE SYMPTOM STATE AFTER PRIMARY ACLR (STUDY IV)

There was a significant variation in the rate of patients who achieved an acceptable symptom state, in the different KOOS subscales, at the 2-year follow-up. The rate varied from 45.6% for the ADL subscale to 93.6% for the Symptoms subscale.
Several factors had a varying impact on the likelihood of achieving a PASS in the different subscales:

- Age ≥ 30 years and 6-month quadriceps strength LSI ≥ 90%: increased the odds in all subscales.
- Female gender: reduced the odds in the Pain, ADL and Sport/Rec subscales.
- MM repair: reduced the odds in the Pain subscale.
- HT vs. BPTB autograft: increased the odds in the Sport/Rec subscale.
- Cartilage injury: reduced the odds in the Sport/Rec subscale.
- 6-month SLH test performance LSI ≥ 90%: increased the odds in the ADL, Sport/Rec and QoL subscales.

5. SUMMARY OF PAPERS

STUDY I

Introduction

The way patient demographics (age and gender) and intraoperative (graft, meniscus resection or repair) factors affect knee laxity after ACLR is still debated. Moreover, the influence of preoperative knee laxity on postoperative knee laxity is not well studied. The purpose was to investigate if age, gender, preoperative knee laxity, graft choice, MM or LM resection or repair affected the odds of having abnormal knee laxity after ACLR. The hypothesis was that younger age, female gender, knee laxity before ACLR, the use of an HT autograft over a BPTB autograft and meniscus resection increased the odds of abnormal knee laxity after ACLR.

Material and Methods

In total, 5,462 patients with primary ACLR were included in the analysis. Knee laxity was measured preoperatively and at the 6-month follow-up using the KT-1000 arthrometer (134-N). Relationships between age < 30 years, female gender, preoperative STS laxity > 5 mm, HT graft, MM resection, MM repair, LM resection, LM repair and postoperative STS laxity > 5 mm were analyzed with a logistic regression analysis.

Results

A total of 223 patients (223/5,462 = 4.1%) had abnormal (STS > 5 mm) laxity postoperatively. Factors that increased the odds of having abnormal knee laxity were: age < 30 years, STS laxity > 5 mm before ACLR, HT graft and MM resection. Female gender, MM repair, LM resection or repair were not correlated with abnormal postoperative laxity.

Conclusion

Abnormal knee laxity after ACLR was associated with age < 30 years, STS laxity > 5 mm before surgery, HT autograft and MM resection.

STUDY II

Introduction

Previous studies comparing primary and revision ACLR are based on a matched group-analysis and include several grafts for both surgeries. The purpose of this study was to compare, in the same patients, knee laxity and subjective outcome among primary and revision ACLR, performed with an HT autograft and a BPTB autograft respectively. The hypothesis was that knee laxity would be comparable between primary and revision ACLR, but that revision ACLR would result in an inferior functional knee outcome.

Material and Methods

In total, 118 and 73 patients with primary HT autograft and revision BPTB autograft ACLR were used for the comparison of knee laxity and subjective knee outcome, respectively. For both surgeries, instrumented knee laxity (KT-1000 134-N) was measured preoperatively and at the 6-month follow-up. The KOOS was collected preoperatively and at the 1-year follow-up. An ANOVA for repeated measurements was used for comparisons between the surgeries.

Results

No differences were found between primary and revision ACLR in terms of the mean preop and postop STS difference and ATT reduction. However, a higher frequency of "surgical failures" (postoperative STS difference > 5 mm) was found after primary ACLR. Revision ACLR showed higher scores in four KOOS subscales pre-operatively: Symptoms, Pain, Sport/Rec and QoL. However, primary ACLR showed a significantly greater improvement from preop to postop in all subscales. Moreover, the scores in the Pain, ADL and Sport/Rec subscales were significantly higher postoperatively.

Conclusion

There were no significant differences in terms of knee laxity between primary ACLR performed with an HT autograft and revision ACLR performed with a BPTB autograft. However, the subjective outcome was inferior after revision ACLR.

STUDY III

Introduction

There is still no consensus regarding the optimal surgical timing in reducing the prevalence of meniscus and cartilage injuries. Moreover, there is a lack of literature regarding the potential effects of time from injury to surgery on knee laxity and the odds of meniscus repair. Other variables such as age, gender and BMI may also affect the odds of meniscus injuries, cartilage injuries and meniscus repair, as well as having an impact on knee laxity. The purpose of this study was to evaluate relationships between surgical timing, age, gender, BMI and concomitant intra-articular (cartilage and meniscus) injuries, the likelihood of meniscus repair and abnormal (STS laxity > 5 mm) laxity at the time of ACLR. The main hypothesis was that a delay in ACLR would increase the odds of concomitant intra-articular (meniscus and cartilage) injuries and abnormal pre-reconstruction laxity, whereas it would reduce the likelihood of meniscus repair.

Material and Methods

In total, 3,976 patients who underwent primary ACLR and had a complete data set available were included. Logistic regression analyses were performed with time from injury to ACLR, gender, age and BMI as independent variables and cartilage injury, MM injury, LM injury, MM repair and LM repair as dependent variables. An additional logistic regression analysis was performed with the same independent variables plus MM injury and LM injury, and abnormal pre-reconstruction laxity (STS difference > 5 mm) as the dependent variable.

Results

Cartilage and meniscus injuries. The odds of cartilage injuries increased with a delay (> 12 months) in ACLR and age ≥ 30 years. The odds of MM injuries increased with a delay (> 12 months) in ACLR, male gender and age ≥ 30 years, whereas the odds of LM injuries decreased with delayed (> 3 months) ACLR and age ≥ 30 years but increased with male gender.

MM and LM repair. The odds of MM repair decreased with a delay (> 6 months) in ACLR, whereas time from injury to surgery had no effect on the likelihood of LM repair. Age ≥ 30 years reduced the odds of both MM and LM repair.

Pre-reconstruction laxity. The odds of abnormal pre-reconstruction laxity were increased with delayed (> 6 months) ACLR and the presence of a MM injury, whereas they were reduced by a BMI of ≥ 25.

Conclusion

Increased odds of cartilage and MM injuries were found with a time from injury to surgery ≥ 12 months. Increased odds of abnormal (STS > 5 mm) laxity and reduced odds of MM repairs were found with a delay in ACLR of ≥ 6 months.

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STUDY IV

Introduction

Knowledge is limited about the percentage of patients achieving an acceptable symptom state and the factors affecting its achievement after primary ACLR in a large cohort. The purpose of this study was to evaluate the rate of patients achieving a PASS 2 years after ACLR and to make a comprehensive analysis of the factors affecting its achievement.

Material and Methods

In total, 2,335 patients with primary ACLR and a complete 2-year postoperative KOOS were included. The outcome was the achievement of a PASS in each KOOS subscale. Associations between preoperative (age, gender, surgical timing, pre-injury Tegner), intraoperative (graft, MM resection, MM repair, LM resection, LM repair, cartilage injury) and postoperative (6 month) (quadriceps strength, hamstring strength, SLH test performance) factors and the outcome variable were assessed with a logistic regression analysis.

Results

A significant variation was found in the rate of patients achieving a PASS among the KOOS subscales (Pain 68.3%, Symptoms 93.6%, ADL 45.6%, Sport/Rec 62.6% and QoL 69.0%). Several factors had a varying impact on the different subscales: 1) Age $\geq$ 30 years and 6-month quadriceps strength LSI $\geq$ 90% increased the odds across all subscales; 2) Female gender reduced the odds in the Pain, ADL and Sport/Rec subscales; 3) MM repair reduced the odds in the Pain subscale; 4) HT autograft increased the odds in the Sport/Rec subscale; 5) Cartilage injury reduced the odds in the Sport/Rec subscale; 6) 6-month SLH test performance LSI $\geq$ 90% increased the odds in the ADL, Sport/Rec and QoL subscales.

Conclusion

A percentage of patients greater than 60% achieved a PASS in four subscales. Older age and female gender consistently increased and reduced respectively the likelihood of achieving an acceptable symptom state across the subscales. Quadriceps strength and hop performance (at 6 months) were the modifiable factors that consistently increased the opportunity to achieve an acceptable symptom state 2 years after surgery.

STUDY V

Introduction

There is lack of literature comparing primary and contralateral ACLR. The purpose of this study was to compare laxity and subjective outcome between primary and contralateral ACLR. It was hypothesized that these outcomes would be comparable between the surgeries.

Material and methods

In total, 226 and 256 patients with primary and contralateral ACLR were used for the comparison of knee laxity and subjective knee outcome respectively. For both surgeries, instrumented knee laxity (KT-1000 134-N) was measured preoperatively and at the 6-month follow-up. The KOOS was collected preoperatively and at the 1-year follow-up. An ANOVA for repeated measurements was used for comparisons between the surgeries.

Results

No differences were found between primary and contralateral ACLR in terms of mean preop, postop and ATT reduction. Similarly, no differences between the surgeries were found in the preoperative, improvement preop to postop, and postoperative KOOS scores.

Conclusion

Contralateral ACLR showed comparable results to those of primary ACLR in terms of knee laxity and subjective knee outcome.

6. DISCUSSION

6.1 ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION AND KNEE LAXITY

Restoration of knee laxity is an important goal of an ACLR. The measurement of knee laxity can be broadly divided into manual and instrumented. The main advantage of the instrumented measurement is that it offers a precise, quantitative evaluation of knee laxity [159]. Manual tests are subject to high variability among examiners and are greatly affected by clinical skills [134].

Patients undergoing ACLR are heterogeneous. There is wide variation in terms of patient characteristics, time from injury to surgery and associated meniscal injuries. Graft choice also varies widely between surgeons.

The different graft potential in restoring knee laxity, for the two most commonly used autografts (HTs and BPTB), has always been controversial. Over the years, many studies comparing knee laxity between the two grafts have reported contradictory findings [4,18,50,70,161]. Several meta-analyses, comprising a large number of patients have attempted to answer this question, but they have also reported contrasting results. Goldblatt et al. [61] reported KT-1000 manual-max measurements for a total of 182 patients (91 HT, 91 BPTB) and concluded that the BPTB graft was superior to the HT graft in restoring knee laxity. Similarly, in a later publication, Li et al. [92], who analyzed the KT-1000 measurements (89-N) of 518 patients (276 HT, 242 BPTB), also found results favoring the BPTB autograft. On the contrary, Xie et al. [166], in a more recent meta-analysis, found no significant differences between the grafts. In *Study I*, which included 5,462 primary ACLRs (4,770 HT, 692 BPTB), the use of an HT autograft was found to increase the odds (OR, 1.83; 95% CI, 1.08 -3.11; P =.025) of having abnormal knee laxity after ACLR. A recent study [37] also showed that the use of a BPTB autograft resulted in a larger ATT reduction and significantly reduced postoperative STS difference compared with the use of an HT autograft. There have been some concerns in the literature regarding the lack of rigid fixation, tendon-to-bone healing and slower ligamentization with the HT graft [52,106]. This might explain the differences between the two grafts in restoring knee laxity [37].

The role of the menisci in controlling knee laxity in the ACLR-knee has also been controversial in both cadaveric [96,107,119] and clinical [7,78,141,165] studies. For instance, Shelbourne and Gray [141], in a long-term follow-up of 482 ACLRs, reported that patients with intact or repaired menisci have significantly less laxity (KT-1000 man-max) than patients with medial or medial and lateral meniscus resection. On the contrary, Kartus et al. [78] and Wu et al. [165] did not find any difference in postoperative laxity (KT-1000 89-N and KT-2000 man-max, respectively) between patients with intact or deficient menisci. The large sample in *Study I,* which allowed a robust logistic regression analysis and the evaluation of four separate conditions of the menisci (MM resection, MM repair, LM resection, LM repair) as possible risk factors for abnormal knee laxity after ACLR, showed that only MM resection increased that risk. MM repair and the condition of the LM did not affect the risk of abnormal postoperative knee laxity. Another study performed at our institution [36], which reviewed KT-1000 measurements of 4,497 primary ACLRs, supported these findings showing

that MM resection increases knee laxity, whereas MM repair restores laxity to the same level as an intact meniscus. In addition, the condition of the LM (resection or repair) had no significant effect on knee laxity. The different role of the menisci in controlling knee laxity might be due to differences in the anatomy and geometry between the two structures, with the LM having no posterior "wedge effect" [91] to prevent the anterior translation of the tibia compared with the MM. However, the LM is thought to be more important in controlling pivoting laxity [46, 112].

In *Study I*, another factor associated with abnormal postoperative laxity was younger (< 30 years) age. We hypothesized that this finding could have two reasons: on one side younger patients may, theoretically, perform more intense rehabilitation compared with their older counterparts and this might cause the elongation of the graft. At the same time, it is also possible that the lower risk of having abnormal postoperative laxity in older patients is the result of progressive degenerative changes that might lead to a "stiffer" knee. Similar results were found by Marchand et al. [102], who reported greater laxity after ACLR with age < 20 years.

Another aspect that has been discussed in the literature is the influence of preoperative laxity on postoperative laxity. Ahn et al. [7] and Hamada et al. [65] found no association between laxity before and after ACLR. On the contrary, Signorelli et al. [144], assessed the knee with six different tests and found an association between pre- and post-reconstruction laxity, even though the postoperative anterior knee laxity at 30 degrees was the least affected by the preoperative knee laxity. In *Study I*, preoperative STS laxity > 5 mm was the most important risk factor for having abnormal (STS > 5 mm) knee laxity after ACLR. This suggests a strong correlation between laxity before and after ACLR. The restoration of normal laxity is less likely in patients with high preoperative laxity values. Interestingly, in *Study III*, a delay in ACLR of > 6 months was associated with an increased risk of abnormal (STS > 5 mm) pre-reconstruction laxity and a delay of > 12 or > 24 months further increased that risk. The change in knee kinematics in the ACL-injured knee may put the other stabilizing structures under more stress, with a risk of stretching [145]. Kent et al. [79] showed that the secondary ligaments carry increased forces in the ACL-deficient knee compared with the ACL-intact knee.

To summarize, *Studies I* and *III* showed that age < 30 years, preoperative STS > 5 mm, HT graft, MM resection and a delay in ACLR of > 6 months (which led to an increased risk of preoperative STS > 5 mm) increased the risk of abnormal postoperative knee laxity.

Some studies [37,62,154] found no association between anterior laxity and subjective knee outcome. However, knee laxity after ACLR might be important for several other reasons. Struewer et al. [147] reported an association between the development of OA and KT-1000 measurements. Some authors reported that graft failure, revision ACLR and additional knee surgery are more common with an HT autograft compared with a BPTB autograft [50,56,57,138]. One possible explanation might be that the increased knee laxity obtained with the HT graft may produce a higher "stress" on the other knee structures and on the graft itself, which would in turn be exposed to a greater risk of injury and failure respectively. A BPTB graft might be more suitable for patients who demand higher knee stability and/or present one or more risk factors (younger age, preoperative STS > 5 mm, MM resection) for having abnormal laxity after ACLR.

The meniscus is an essential structure for preserving knee laxity in the ACLR-knee and should be repaired whenever possible. In a cadaveric model, Papageorgiou et al. [119] showed a substantial (33-55%) increase in the ACL graft in-situ forces after MM resection. In a clinical study, Robb et al. [130] reported a clear association between meniscal status and the failure of the reconstruction. Failure of the ACL graft was strongly associated with meniscus resection, whereas patients with meniscus repair had no increased risk of failure. The changes in knee kinematics produced by meniscus resection might be responsible for a higher "stress" in the ACL graft, which predisposes to graft failure.

Another important consideration relates to the timing of ACLR. Delayed ACLR (> 6 months) increases the risk of a preoperative STS > 5 mm (*Study III)*, which is in turn the most important risk factor for having abnormal postoperative knee laxity (*Study I*). These findings suggest that an ACLR should be performed early, at the latest within 6 months from the injury. If an ACL injured patient does not undergo early ACLR, a close clinical follow-up should be established during the first months after the injury in order to identify promptly the eventual need for an ACLR.

Finally, younger patients might benefit from modifications to the postoperative management in order to reduce the risk of postoperative abnormal knee laxity. Delayed weight bearing, knee bracing and a slower rehabilitation have been suggested [102].

6.2 REVISION AND CONTRALATERAL ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

ACL graft ruptures and contralateral ACL injuries are serious and common problems in clinical practice. After ACLR, patients have a higher risk of new ACL injuries in the ipsilateral or contralateral knee in comparison with knee-healthy people [122]. Paterno et al. [121] reported that 25.4% of a cohort of young, active patients who came back to pivoting sports after ACLR reported a new ACL injury (ipsilateral or contralateral) during the first postoperative year. Many patients with an ACL graft tear or a contralateral ACL tear undergo surgery. Revision ACLR and contralateral ACLR are devastating events for the patients, since they both require a repeat of the long postoperative rehabilitation.

In the literature, limited information is available regarding the outcome of revision and contralateral ACLR. There are studies comparing revision ACLR with primary ACLR [55,80,90,158], but they are based on a matched-group comparison and are not homogeneous since they include different grafts for both surgeries. These characteristics do not enable to draw definitive conclusions about the outcome of revision ACLR in comparison with that of primary ACLR. Several studies [10,53,157] have identified risk factors for contralateral ACL injury and reconstruction, but there is a paucity of studies comparing the outcomes between primary and contralateral ACLR.

As for clinicians, patient counselling is essential. In *Study II*, we compared the same patients who underwent primary and revision ACLR. All the primary ACLRs were performed with an HT autograft and all the revision ACLRs were performed with a BPTB autograft. This scenario mimics what happens in the real clinical setting and is therefore more likely to make an accurate comparison between primary and revision ACLR. In *Study V*, we analyzed

patients with bilateral ACLR. The outcome of contralateral ACLR was compared with that of primary ACLR.

In *Study II,* no significant differences in knee laxity between primary and revision ACLR were found, apart from the higher (8.4% vs. 5.0%) rate of surgical failures (STS > 5 mm) after primary ACLR. This finding, which is in accordance with the findings in *Study I*, might be related to the previously discussed differences in the fixation and biological properties of the HT autograft compared with the BPTB autograft. All the primary ACLRs, in *Study II*, were performed with an HT autograft, whereas all the revision ACLRs were performed with a BTPB autograft. Regarding functional knee outcome, it is interesting to note that the patients reported higher preoperative KOOS scores for revision ACLR. Similar findings were reported by Weiler et al. [158], who reported a higher preoperative Lysholm score for revision ACLR. It might be hypothesized that the injury to the ACL graft has less impact on the subjective knee function than the first ACL injury. The improvement from preoperatively to postoperatively was greater for primary ACLR than for revision ACLR in all subscales. Finally, the postoperative KOOS scores were higher for primary ACLR in the Pain, ADL and Sport/Rec subscales. However, probably only the difference in the Sport/Rec subscale (14.7 points) represents a clinically relevant difference. The other differences in favor of primary ACLR in the Pain (3.5 points) and ADL (3.2 points) subscales are probably too small to be considered clinically important.

In *Study V*, contralateral ACLR resulted in laxity and functional knee outcome comparable to primary ACLR. No significant differences were found for preoperative, postoperative or improvement from preop to postop values for the KT-1000 measurements or for the KOOS subscales scores.

These findings suggest that, even if an ACL graft rupture or a contralateral ACL tear are both very serious complications, undergoing contralateral ACLR appears to be a less catastrophic event than undergoing revision ACLR. There are several potential explanations for these results. First, in *Study II*, patients had more meniscal and chondral injuries after revision ACLR. Secondly, patients who underwent revision ACLR sustained two severe injuries (first an ACL injury and then an ACL graft rupture) and underwent two surgeries (ACLR and revision ACLR). Moreover, two different grafts were harvested from the same knee (HT and BPTB) and, as a result, both the flexor and the extensor mechanisms were affected [64,158]. Finally, it could be hypothesized that the choice of the graft played a significant role. All the revision ACLRs were performed with a BTPB graft. The increased "donor morbidity site" associated with the BPTB graft is well-known [50,92,166]. A study performed at our institution [37], comparing primary ACLR performed with HT and BPTB autograft showed that patients in the HT group improved significantly more from pre-op to the 1-year follow-up in four of the five KOOS subscales compared with the BPTB group. The largest difference in improvement was found for the Sport/Rec subscale. Similarly, in *Study IV,* the use of an HT graft (vs. BPTB graft) increased the odds of achieving a PASS in the Sport/Rec subscale 2 years after ACLR.

6.3 TIME FROM INJURY TO SURGERY, MENISCUS AND CARTILAGE INJURIES AND LIKELIHOOD OF MENISCUS REPAIR

The deleterious effects of meniscus and cartilage injuries at the time of primary ACLR are well-known. These injuries have a negative effect on subjective and objective knee outcomes and strongly contribute to the development of osteoarthritis [140,141,169].

It is generally accepted that a longer time from injury to ACLR may place these structures at risk. An ACL injury alters the joint biomechanics increasing shear forces on the cartilage and menisci [146]. In addition, the "giving-ways" episodes eventually experienced by ACL-injured patients may also put these structures at risk of injury [82]. There is still, however, no clear consensus about how long would be "acceptable" to wait without a significant increase in the risk of associated injuries. Time to surgery intervals ranging from 6 weeks [82] to 12 months [21,29,49] have been reported in previous studies. Patients may choose to delay ACLR for several reasons. Moreover, conservative treatment, with the option of delayed ACLR, might be initially pursued. It is therefore important to have some general guidelines regarding how long, from injury to ACLR, it would be "safe" to wait.

In *Study III*, it was found that the risk of cartilage and MM injury increased with a time from injury to ACLR > 12 months. On the contrary, the risk of having a LM injury decreased with delayed (> 3 months) ACLR. The higher risk of injury with delayed ACLR for the MM might be due to the anatomic and geometric features of this structure, which we discussed in *Study I*. The MM, especially the posterior horn, has a "wedge effect" and acts as a secondary stabilizer to anterior tibial translation [36]. Papageorgiou et al. [119] showed that the stress forces on the MM are doubled after transection of the ACL in comparison with the intact ACL state. There is a biomechanical interdependence between the ACL and the MM. The insufficiency of one structure increases the stresses on the other and vice versa [119]. The LM is far more mobile than the MM [23] and has no posterior "wedge effect" to limit anterior tibial translation [91]. These characteristics are probably responsible for the lower susceptibility of this structure to ACL deficiency. In fact, the odds of LM injuries decreased with increased time from injury to surgery. Most LM injuries occur at the time of the ACL injury [43] and probably have a good chance of healing over time, as the LM might not experience the same biomechanical loads as the MM. Barenius et al. [13] also reported that delayed ACLR (> 3 months) reduced the likelihood of LM injuries.

In the event of concomitant meniscus injuries at the time of primary ACLR, it is well accepted that every effort should be made to preserve meniscal tissue whenever possible. Meniscus resection has deleterious effects on subjective knee function and the development of osteoarthritis [14]. Meniscus repair is associated with superior subjective and radiological outcomes [83,123] and is essential for restoring knee laxity in the ACL-reconstructed knee [36]. In the recent literature, only a few studies have evaluated how time from injury to ACLR affects the likelihood of performing meniscus repair. Everhart et al. [43] and Chhadia et al. [28] reported a decreased odds of MM repair with a delay in ACLR of > 2 or > 3 months respectively. Similarly, we found that delaying ACLR has a negative impact on the likelihood of performing MM repair. In *Study III*, reduced odds of MM repair with a delayed (> 6 months) ACLR were found. Conversely, the likelihood of LM repair was not affected by a delay in ACLR. These differences might be explained, once again, by the different

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biomechanical roles of the menisci. As described above, the MM, unlike the LM, is an essential stabilizer to ATT [36]. Delayed ACLR might increase the stresses on the MM over time and lead to additional injuries, reducing the probability of repair.

In the light of these findings, ACLR should be performed early and not beyond 6 months from the injury. Delaying ACLR might expose the knee to an increased risk of cartilage injuries and MM injuries and, at the same time, reduce the likelihood of MM repair. In addition, a longer waiting time might also affect joint kinematics, increasing the risk of abnormal (STS > 5mm) preoperative knee laxity, which is in turn the most important risk factor for abnormal postoperative laxity (*Study I*).

In *Study III*, demographic variables were also evaluated as possible risk factors for cartilage injuries, meniscus injures and the likelihood of meniscus repair. Male gender increased the risk of MM and LM injuries, in our cohort. This may be related to a potentially higher activity level and more severe trauma in male patients [28]. As expected, older age (≥ 30 years) was associated with an increased risk of cartilage and MM injuries. Similar findings were reported by Brambilla et al. [21] and might be due to the progressive degenerative joint changes. On the contrary, older age (≥ 30 years) strongly reduced the likelihood of MM and LM repair. This finding might have two explanations. First, meniscal tissue in older patients might be less amenable to repair because of inferior quality due to the progressive degenerative changes. At the same time, surgeons might be much more prone to repair the meniscus in younger (< 30 years) patients due to the well-known negative effects of meniscus resection in the long-term [83,123].

6.4 SUBJECTIVE KNEE FUNCTION AFTER PRIMARY ACL RECONSTRUCTION

An ACL tear is a major knee injury, which might have a serious impact on subjective knee function. Several PROMs have been described in the literature and are routinely used in clinical practice to measure subjective knee function after ACL injury and ACLR. The KOOS is one of the most commonly used PROMs and is the main PROM in the Swedish ACL registry [152]. One of the problems with the KOOS is the not straightforward interpretation. A postoperative score that might be interpreted by us, orthopedic surgeons, as a success might not necessarily correspond to a patient feeling well.

Some attempts have been made to overcome this limitation of using the KOOS. Barenius et al. [13], in a registry-based study, used the concepts of "functional recovery" and "treatment failure" to better define the subjective outcome after ACLR. "Functional recovery" was defined as the lower threshold for the 95% CI of 18-34 years old males in the Swedish reference population [120]. The corresponding KOOS subscale scores were all to be as follows: Pain > 90, Symptoms > 84, ADL > 91, Sport/Rec > 80, QoL > 81. On the contrary, a QoL score < 44 defined a "treatment failure" [51]. Another, modern approach facilitating the interpretation of the KOOS after ACLR was recently introduced by Muller et al. [111]. The authors established the thresholds for the PASS between 1 and 5 years after ACLR. Patients were asked a simple question which "summarizes" their subjective knee function as a whole: "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?". The corresponding identified KOOS subscale scores were: Pain ≥

88.9; Symptoms ≥ 57.1; ADL = 100; Sport/Rec ≥ 75.0, QoL ≥ 62.5. This relatively simple approach of examining the KOOS might have the advantage of better reflecting how the patient perceives his/her treatment.

In *Study IV*, the rate of patients achieving a PASS in each KOOS subscale 2 years after primary ACLR was assessed. Moreover, a comprehensive evaluation of several preoperative, intraoperative and postoperative factors potentially affecting the achievement of a PASS was performed. The PASS was achieved by more than 60% of the patients in 4 subscales. However, a great variation was found between the KOOS subscales (Pain 68.3%; Symptoms 93.6%; ADL 45.6%; Sport/Recreation 62.6%; QoL 69.0%). The factors that most affected the achievement of a PASS were age, the results of the isokinetic quadriceps strength test and the SLH test 6 months after surgery. In particular, age ≥ 30 years and a quadriceps strength LSI of ≥ 90% increased the likelihood of achieving a PASS in all subscales, while a SLH test performance LSI of ≥ 90% increased the odds in the ADL, Sport/Rec and QoL subscales. The literature is inconsistent regarding the effect of age on the subjective outcome after ACLR. Ageberg et al. [3] reported that age had no effect on the KOOS subscale scores 2 years after ACLR. Hamrin Senorski et al. [66] reported that younger age increased the odds of achieving a PASS 1 year after ACLR. Conversely, Desai et al. [40], in line with the results in our study, showed that older age was associated with higher KOOS subscale scores after ACLR. It can be hypothesized [*Study IV*, 40] that younger patients are less frequently satisfied after ACLR compared with their older counterparts, as they might have higher functional requests from their knees due to their potential higher activity level. Another important conclusion to draw from *Study IV* is that performing strength and hop tests 6 months after ACLR is not only important in evaluating readiness to return to sport. We showed that these tests are also important in predicting subjective knee outcome through the achievement of a PASS at the 2-year follow-up. Information gained from these tests would therefore be of great importance for clinicians to identify patients who require targeted rehabilitation interventions to address strength and hop deficiencies in order to increase subjective knee function and the likelihood of achieving a PASS at a later follow-up.

Muscle strength and hop performance are modifiable by rehabilitation. This study highlights the importance of rehabilitation after ACLR in order to achieve a better subjective outcome. Female gender was a factor that reduced the likelihood of achieving a PASS in 3 subscales (Pain, ADL and Sport/Rec). Several studies [3,40,66,149] showed inferior subjective outcomes in females after ACLR. Ageberg et al. [3] previously hypothesized that gender-related differences regarding subjective knee outcome after ACLR might be due to differences in muscle knee function compared with males. However, our multivariable logistic regression analysis, which included quadriceps and hamstring strength tests and the SLH test as independent variables, revealed that female gender was an independent factor for the PASS. The reason why females report inferior subjective outcomes compared with males after ACLR needs to be investigated. In a recent large meta-analysis, Tan et al. [149] reported no differences regarding objective outcomes between males and females.

Study IV also showed that the use of an HT autograft over a BPTB autograft increased the odds of achieving a PASS in the Sport/Rec subscale 2 years after ACLR. Previous studies have reported that the BPTB autograft is associated with a greater anterior knee pain [92,166]. The "donor-site morbidity" related to the use of the BPTB autograft might explain our results.

A previous study [37] from our research group also reported inferior KOOS subscales scores 1 year after primary ACLR performed with a BPTB autograft compared with ACLR with an HT autograft.

Interestingly, MM repair reduced the likelihood of achieving a PASS in the Pain subscales. Two previous large registry studies found similar results. Svantesson et al. [148], using the Capio Artro Clinic registry, reported inferior results (Lysholm score at 6 months and KOOS subscale scores at 1 year) after primary ACLR for patients who underwent concomitant meniscus repair. LaPrade et al. [87], using data from the NKLR, reported that the 2-year postoperative KOOS scores were significantly inferior in patients who underwent concomitant MM repair in comparison with patients with isolated ACLR. The authors found no differences between isolated ACLR and ACLR with MM resection or LM repair or resection. It should, however, be noted that both studies did not account for failures of meniscus repair at follow-up. An analysis of medical records and the exclusion of patients who underwent subsequent surgery due to the failure of the meniscus repair was not performed. *Study IV* may suffer from the same bias. A later study [35] performed by our research group found no differences in 1- and 2-year KOOS subscale scores irrespective of the meniscus treatment (resection or repair). In this study, patients who underwent meniscus resection at follow-up due to the failure of the meniscus repair performed at the primary ACLR were identified and analyzed separately. The results showed that there were no differences in terms of KOOS scores between patients with a successful meniscus repair and patients with isolated ACLR or ACLR and meniscus resection. Patients with a failed meniscus repair, who underwent meniscus resection at follow-up, reported inferior KOOS subscale scores in comparison with patients with a successful meniscus repair.

Finally, as expected, even a cartilage injury at the time of ACLR had a negative effect on subjective knee outcome, reducing the likelihood of achieving a PASS in the Sport/Rec subscale 2 years after primary ACLR. However, cartilage injury had no impact on the achievement of a PASS on other subscales. The Sport/Rec subscale is one of the most responsive after ACLR [131]. Probably, a 2-year follow-up is not long enough to see the impact of a cartilage injury on other KOOS subscale scores, which are less sensitive. In *Study IV,* even MM or LM resection did not have any effect on the likelihood of achieving a PASS. Again, this follow-up is probably not enough to appreciate the deleterious effects of the loss of meniscal tissue on subjective knee function.

7. CONCLUSIONS

Study I. Younger age (less than 30 years), preoperative STS difference > 5 mm, the use of an HT autograft over a BPTB autograft and medial meniscus resection increase the risk of abnormal laxity (STS difference > 5 mm) after ACLR.

Study II. Revision ACLR performed with a BPTB autograft restores knee laxity (KT-1000 arthrometer) but results in an inferior subjective knee outcome (KOOS subscale scores) in comparison with primary ACLR performed with an HT autograft.

Study III. A longer waiting time from injury to ACLR has negative effects on associated injuries and knee laxity. The odds of medial meniscus and cartilage injuries increased with a delay of more than 12 months. Increased odds of abnormal pre-reconstruction laxity (STS > 5 mm) and a reduced likelihood of medial meniscus repair were associated with a delay of more than 6 months.

Study IV. A PASS was achieved by more than 60% of the patients in 4 KOOS subscales 2 years after ACLR. However, there was a great variation in the rate of patients achieving a PASS in the different KOOS subscales. Among the factors affecting the achievement of a PASS, age, quadriceps strength and hop test performance were the most important. Older age (> 30 years) and symmetrical quadriceps strength (6 months after ACLR) increased the likelihood of achieving a PASS in all KOOS subscales. SLH test performance ≥ 90% (6 months after ACLR) increased the likelihood of achieving a PASS in the ADL, Sport/Rec and QoL subscales.

Study V. Contralateral ACLR shows results comparable to those of primary ACLR in terms of knee laxity (KT-1000 arthrometer) and subjective knee outcome (KOOS subscale scores).

8. POPULAR SCIENCE SUMMARY OF THE THESIS

The anterior cruciate ligament (ACL) is an essential ligament in the knee, functioning as a joint stabilizer. ACL injuries are very common, especially in young people active in sports. In the event of an ACL injury, a decision should be made about pursuing non-surgical (rehabilitation, with the option of delayed surgery) or surgical (ACL reconstruction) treatment. ACL reconstruction is generally recommended to patients active in pivoting (twisting) sports and/or patients who have a feeling of knee instability. The torn ACL is usually replaced with a tendon harvested from the patient. The most used tendons are the hamstrings (tendons at the back of the thigh) or the patellar tendon (tendon which attaches to the kneecap and the tibia). Frequently, the ACL injured knee has associated (meniscus and cartilage) injuries. If present, these injuries, are usually treated at the time of ACL reconstruction.

The results of surgery can be evaluated objectively (clinical examination and laxity measurement) and subjectively (specific questionnaires that patients are asked to answer before and after surgery).

Unfortunately, after ACL reconstruction, patients have a higher risk (compared with healthy knee subjects) of suffering an additional ACL injury on the same or the contralateral knee. In fact, reoperation of the ACL (revision ACL reconstruction) and reconstruction of the contralateral ACL (contralateral ACL reconstruction) are relatively common events in clinical practice.

This thesis is based on registry data on several thousands of patients who underwent ACL reconstruction at Capio Artro Clinic, Stockholm, Sweden. By analyzing these data, it has been possible to study several factors associated with objective (knee laxity) and subjective (patient´s perception of treatment/knee function) results after primary ACLR, the impact of timing of ACLR on associated (meniscus and cartilage) injuries, the chance of meniscus repair and knee laxity. Finally, the results of revision and contralateral ACLR have been compared with those of primary ACLR.

The studies in this thesis have shown that:
- Knee laxity after ACL reconstruction is affected by age at surgery, the choice of the tendon used to reconstruct the ACL, the status of the medial meniscus, the laxity before ACL reconstruction and the time from injury to surgery
- Delay in ACL reconstruction increases the risk of associated (meniscus and cartilage) injuries and reduces the opportunity to repair an injury to the medial meniscus
- Older ($\geq$ 30 years) age and female gender are the non-modifiable factors that most affect (positively and negatively respectively) subjective knee outcome after ACL reconstruction. Quadriceps strength and hop performance 6 months after ACL reconstruction are the modifiable factors that most affect (increase) the subjective knee outcome 2 years after ACL reconstruction.
- Revision ACL reconstruction restores knee laxity to a level comparable to that of the primary ACL reconstruction but results in an inferior subjective knee outcome. On the other hand, contralateral ACL reconstruction produces equivalent results in terms of knee laxity and subjective knee outcome compared with primary ACL reconstruction.

With the knowledge acquired from the studies included in this thesis, it is possible to improve the objective and subjective outcome after primary ACLR and to carefully counsel patients about the expected outcome after revision and contralateral ACLR.

9. POINTS OF PERSPECTIVES

The ACL is probably one of the most studied topics in orthopedics and sports medicine. However, despite thousands of published studies on ACL injuries and their treatment, there are still many controversies. Indications for ACLR, timing of surgery, graft choice, fixation methods, post-operative rehabilitation and- the timing and criteria for returning to sports are only some examples. This "chaos" is probably due in part to the many low-quality published studies and the contrasting results found in the literature.

There are several potential areas of future research to improve the treatment of ACL injuries, ranging from anatomy, biomechanics-kinematics, injury prevention to surgical techniques and post-operative management. However, two outcomes of ACLR are highlighted in this thesis. One is objective, the KT-1000 arthrometer laxity measurement. The other one is subjective, the KOOS questionnaire.

Even though the KT-1000 arthrometer was developed in the 1980s, it is still the most used and validated instrument for measuring knee laxity before and after ACLR. It is difficult to believe that, despite the tremendous technological innovations in all fields of medicine in past years, we are still using an instrument that was developed almost 30 years ago. The KT-1000 arthrometer is no longer commercially available. An interesting device that has recently been developed is the KiRA (Kinematic Rapid Assessment). The Kira is an accelerometer that can be used to measure both anterior and rotational knee laxity. However, recent studies report contrasting results for the KiRA in quantifying anterior tibial translation in a manner similar to the KT-1000 arthrometer [126,132]. There is a need for more research to develop devices that can help us obtain a reliable quantification of anterior and rotational laxity before and after ACLR.

The KOOS is a widely used PROM before and after ACLR. However, it is not specific to ACL injuries, as it could be used for meniscus and chondral injuries and for osteoarthritis as well. There are probably only 2 subscales that are the most responsive at follow-up after ACLR [131], the Sport and Recreation and QoL subscales. In spite of this, the KOOS is the main PROM in the Scandinavian ACL registries. It would be useful to introduce a more specific PROM for ACL injuries in the registries. Thomas S. Kuhn, an American and historian philosopher, said "The answers you get depend on the questions you ask".

Finally, every effort should be made in the future to try to improve the response rate to the PROMs in the registries. Attrition is still a major problem in registry studies. Some analyses of subjective knee outcome might be biased due to the low response rate.

In conclusion, as researchers, we should always keep our curiosity high and try to find new and more effective methods to evaluate the results of our ACLRs and find answers to the many questions we still have. A lot is known, but a lot is unknown!

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