Generalized Joint Hypermobility and Specific Knee Laxity

Aspects of Influence on the Anterior Cruciate Ligament-injured Knee

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”The last thing my wife
would ever want from
me would be a thesis“

David Wennergren

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Abstract

Injury to the anterior cruciate ligament (ACL) is one of the most serious sports-related injuries, with significant short- and long-term morbidity. The research involving the investigation of risk factors for ACL injury and predictors of outcome after ACL reconstruction is extensive. Generalized joint hypermobility (GJH) and specific knee laxity are factors that have been associated with an increased risk of ACL injury and inferior postoperative outcome, but the state of the evidence is unclear and the availiable information is limited. This thesis consists of five studies with the overall aim of investigating how two main concepts, GJH and specific knee laxity, affect the outcome after ACL reconstruction and how the two concepts affect each other.

Study I is a comprehensive systematic review aiming to investigate the influence of GJH on ACL injury risk and postoperative outcome and to compare the performance of different types of graft used in ACL reconstruction in patients with GJH. Study I comprised 21 studies. While the data synthesis indentified GJH as a risk factor for ACL injury in males, the results were conflicting in females. Moreover, there was limited evidence indicating that GJH is associated with increased postoperative knee laxity after ACL reconstruction. There was limited yet consistent evidence showing that GJH was associated with inferior patient-reported outcome after ACL reconstruction. Finally, there was limited, consistent evidence indicating that patellar tendon autografts produce improved graft performance in comparison to hamstring tendon autografts, in terms of knee laxity and patient-reported outcome. Study II is a register-based cohort study comprising 142 patients undergoing ACL reconstruction. The outcome variables were assessed one year after ACL reconstruction and were analyzed using two methods: (1) dichotomization based on the presence of GJH and (2) linear regression to investigate continuous associations with the Beighton score. Interestingly, and contrary to the hypothesis, the analysis revealed that the KOOS sports and recreation subscale was associated with the continuous Beighton score. Functional performance, evaluated with hop and strength tests, was acceptable, regardless of the presence of GJH. Study III is an international multicenter cohort study investigating the correlation between the Beighton score and rotatory knee laxity in 96 ACL-injured patients. Rotatory knee laxity was evaluated using the instrumented pivot-shift test, using two devices to quantify laxity. The study reported that no correlations between GJH and quantitative rotatory knee laxity were observed in the ACL-injured knee. However, in the contralateral healthy knee, a weak yet significant correlation was observed. Study IV is a retrospective register-based cohort study comprising 8,502 patients undergoing ACL reconstruction. The patients were divided into subgroups based on the degree of hyperextension of the contralateral healthy knee: normal (≤0°), mild (1°-5°), moderate (6-10°) and severe (>10°). The degree of contralateral hyperextension was analyzed in relation to anterior tibial translation (ATT), using the KT-1000 arthrometer, and in relation to the frequency of concomitant intra-articular injuries in the ACL-injured knee. The ATT was examined six months postoperatively. The study identified an association between contralateral knee hyperextension and greater ATT in the ACL injured knee. Interestingly, there was an inverse relationship between the degree of contralateral hyperextension and the frequency of meniscal injuries. Study V is a retrospective cohort study, based on two previous randomized, controlled cohorts, comprising 147 patients undergoing ACL reconstruction. The study assessed the influence of increased knee laxity, assessed two years postoperatively, on clinical outcome variables 16 years postoperatively. This study determined that increased ATT, measured with the Lachman test and the anterior drawer test, was associated with inferior patient-reported outcome 16 years postoperatively. Moreover, increased rotatory knee laxity, measured with the pivot-shift test, was associated with inferior patient-reported outcome and a lower level of physical activity after 16 years.

Taken together, this thesis provides an overview of all the currently available studies on the subject of the influence of GJH on ACL injury risk and postoperative outcome. It further demonstrates that acceptable short-term functional results could be found in patients with GJH after ACL reconstruction, something not previously evaluated, and that patients with increased hypermobility may have short-term subjectively perceived advantages. Moreover, the thesis provides the first correlation analysis between quantitative pivot shift and GJH, finding no association in the ACL-injured knee but a weak correlation in the contralateral healthy knee. Knee hyperextension, a part of GJH, is demonstrated to be associated with increased anterior knee laxity. As identified by Study V, increased anterior and rotatory knee laxity is associated with inferior long-term patient-reported outcome and a lower level of activity after 16 years, results that elucidate the importance of reducing postoperative knee laxity. Considering the accumulated evidence from the current thesis, reduction of postoperative knee laxity is probably particularly important in the susceptible group of individuals with GJH.

Sammanfattning på svenska

SAMMANFATTNING PÅ SVENSKA

Skada på det främre korsbandet är en av de mest allvarliga idrottsrelaterade skadorna, med betydande morbiditet både på kort och på lång sikt. Det finns rikligt med forskning som syftar till att studera riskfaktorer och prediktorer för främre korsbandsskada. Generell överrörlighet (GJH) och specifik knäledslaxitet är faktorer som har associerats till ökad risk för främre korsbandsskada och försämrat postoperativt utfall, men det saknas en sammanfattande översikt över området och mycket information saknas fortfarande. Denna avhandling består av fem studier med det övergripande målet att undersöka hur två olika koncept, GJH och specifik knäledslaxitet, påverkar utfallet efter rekonstruktion av det främre korsbandet, och hur de olika koncepten påverkar varandra.

Studie I är en systematisk översiktsartikel med målet att utvärdera inflytandet av GJH på risken för främre korsbandsskada, eventuell påverkan på postoperativt utfall och för att jämföra hur olika korsbandstransplantat presterar hos korsbandsopererade patienter med GJH. Studie I inkluderar 21 studier. Sammantaget framkom att GJH är en riskfaktor för främre korsbandsskada hos män, medan resultaten är mer tvetydiga för kvinnor. Vidare fanns det begränsad evidens som indikerar att GJH associeras med ökad postoperativ knäledslaxitet efter korsbandsrekonstruktion. Dessutom identifierades begränsad men samstämmig evidens som visade att GJH associerades med sämre patient-rapporterat utfall efter främre korsbandsrekonstruktion. Slutligen identifierades begränsad, men samstämmig evidens som indikerar att transplantat från knäskålsenan producerar bättre resultat än transplantat från baksidan av låret, vad gäller postoperativ knäledslaxitet och patient-rapporterat utfall. Studie II är en register-baserad kohortstudie bestående av 142 patienter som genomgått korsbandsrekonstruktion. Utfallsvariablerna undersöktes ett år efter korsbandsrekonstruktion och analyserades med två metoder: (1) genom dikotomisering baserad på eventuell förekomst av GJH och (2) genom linjär regressionsanalys där utfall analyseras i förhållande till kontinuerlig Beighton score. Analysen påvisade att subskalan för KOOS sports and recreation, en typ av patient-rapporterat utfall, associerades med kontinuerlig Beighton score. Hopp- och styrketester visade acceptabelt utfall oavsett om GJH förelåg eller ej. Studie II är en internationell multicenter studie som undersöker korrelationen mellan Beighton score och rotatorisk knäledslaxitet i 96 korsbandsskadade patienter. Rotatorisk laxitet utvärderades med kvantitativt pivot-shift test, genom användandet av två olika apparaturer som kvantifierar laxitet. Ingen korrelation kunde identifieras i det skadade knät, men i det friska kontralaterala knät observerades en svag men signifikant korrelation mellan kvantitativ rotatorisk laxitet och Beighton score. Studie IV är en retrospektiv register-baserad kohortstudie som inkluderar 8502 patienter som genomgått främre korsbandsrekonstruktion. Patienterna delades upp i subgrupper baserat på graden av knäledshyperextension i det kontralaterala knät; normal (≤0°), lätt (1°-5°), moderat (6-10°) och svår (>10°). Graden av kontralateral hyperextension analyserades i relation till anterior (främre) translation av tibia (ATT), vilken utvärderades med en KT-1000 arthrometer, och i relation till frekvensen av övriga intra-artikulära skador. Undersökningen av ATT utfördes sex månader efter främre korsbandsrekonstruktion. Denna studie identifierade en association mellan kontralateral hyperextension och ökad ATT i det skadade knät. Intressant nog fann man också att en att ökad kontralateral hyperextension korrelerar med lägre frekvens av meniskskador. Studie V är en retrospektiv kohortstudie, baserad på två tidigare randomiserade kontrollerade studier, bestående av 147 patienter som tidigare genomgått främre korsbandsrekonstruktion. Denna studie undersökte hur ökad knäledslaxitet två år efter operation påverkar utfallet 16 år efter operation. Studien identifierade att ökad ATT, undersökt med Lachmans test och främre draglåda, associerade med sämre patient-rapporterat utfall 16 år postoperativt. Vidare noterades att ökad rotatorisk knäledslaxitet associerade med sämre patient-rapporterat utfall och en lägre grad av fysisk aktivitet efter 16 år.

Sammanfattningsvis ger avhandlingen en översikt av tillgängliga studier som utvärderar inflytandet av GJH på risken för främre korsbansskada, samt på hur GJH påverkar postoperativt utfall efter främre korsbandsrekonstruktion. Vidare rapporteras att acceptabla och jämförbara funktionella resultat är att förvänta i det korta perspektivet hos patienter med GJH som genomgått korsbandsrekonstruktion. Avhandlingen presenterar den första korrelationsanalysen mellan kvantitativ rotatorisk knäledslaxitet och GJH, utan att finna någon korrelation i det skadade knät. Däremot kunde en svag men signifikant korrelation identifieras i det friska, kontralaterala knät. Hyperextension av knäleden, vilket ingår som ett kriterie i GJH, undersöktes i en studie där man fann en association med ökad främre knäledslaxtiet. I enlighet med vad som identifierades i den sista studien i avhandlingen, så är ökad främre knäledslaxitet associerad med betydande morbiditet. Både ökad främre samt rotatorisk knäledslaxitet var associerade med sämre patient-rapporterat utfall i det längre perspektivet, utvärderat 16 år efter korsbandsrekonstruktion. Detta illustrerar vikten av att minimera postoperativ knäledslaxitet, och särskilt viktigt tycks det vara hos patienter med GJH.

SAMMANFATTNING PÅ SVENSKA

List of papers

LIST OF PAPERS

This thesis is based on the following studies, referred to hereafter using Roman numerals.

I Generalized joint hypermobility increases ACL injury risk and is associated with inferior postoperative outcome – A systematic review
Sundemo D, Hamrin Senorski E, Karlsson L, Horvath A, Karlsson J, Ayeni O, Juul-Kristensen B, Samuelsson K. *Manuscript under revision for BMJ Open Sport & Exercise Medicine*

II Sport-specific patient-reported outcome is positively associated with Beighton score in patients one year after ACL reconstruction
Sundemo D, Karlsson J, Samuelsson K, Beischer S, Thomeé R, Thomeé C, Hamrin Senorski E. *Manuscript*

III Correlation between quantitative pivot shift and generalized joint laxity: a prospective multicenter study of ACL ruptures
Sundemo D, Blom A, Hoshino Y, Kuroda R, Lopomo N.F, Zaffagnini S, Musahl V, Irrgang JJ, Karlsson J, Samuelsson, K and The PIVOT Study Group
Knee Surgery Sports Traumatology Arthroscopy. 2018 26(8):2362-2370

IV 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, Hamrin Senorski E, Svantesson E, Samuelsson K, Stålman A. *Knee Surgery Sports Traumatology Arthroscopy. 2018 26(10):3020-3028*

V Increased postoperative manual knee laxity at 2 years results in inferior long-term subjective outcome after anterior cruciate ligament reconstruction
Sundemo D, Sernert N, Kartus J, Hamrin Senorski E, Svantesson E, Karlsson J, Samuelsson K.
American Journal of Sports Medicine. 2018 46(11):2632-2645

Other papers by the author not included in the thesis

OTHER PAPERS BY THE AUTHOR NOT INCLUDED IN THE THESIS

VI Objective measures on knee instability: dynamic tests: a review of devices for assessment of dynamic knee laxity through utilization of the pivot shift test
Sundemo D, Alentorn-Geli E, Hoshino Y, Musahl V, Karlsson J, Samuelsson K.
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American Journal of Sports Medicine. 2016 44(9):2304-13.

VIII Double-bundle anterior cruciate ligament reconstruction is superior to single-bundle reconstruction in terms of revision frequency: a study of 22,460 patients from the Swedish National Knee Ligament Register
Svantesson E, Sundemo D, Hamrin Senorski E, Alentorn-Geli E, Musahl V, Fu FH, Desai N, Stålman A, Samuelsson K.
Knee Surgery Sports Traumatology Arthroscopy. 2017 25(12):3884-3891.

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Desai N, Andernord D, Sundemo D, Alentorn-Geli E, Musahl V, Fu F, Forssblad M, Samuelsson K.
Knee Surgery Sports Traumatology Arthroscopy. 2017 25(5):1542-1554.

X Adolescents and female patients are at increased risk for contralateral anterior cruciate ligament reconstruction: a cohort study from the Swedish National Knee Ligament Register based on 17,682 patients
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Knee Surgery Sports Traumatology Arthroscopy. 2017 25(12):3938-3944.

XI No differences in subjective knee function between surgical techniques of anterior cruciate ligament reconstruction at 2-year follow-up: a cohort study from the Swedish National Knee Ligament Register
Hamrin Senorski E, Sundemo D, Murawski CD, Alentorn-Geli E, Musahl V, Fu F, Desai N, Stålman A, Samuelsson K.
Knee Surgery Sports Traumatology Arthroscopy. 2017 25(12):3945-3954.

XII Ten-year risk factors for inferior knee injury and osteoarthritis outcome score after anterior cruciate ligament reconstruction: a study of 874 patients from the Swedish National Knee Ligament Register
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Orthopedic Journal of Sports Medicine. 2018 18;6(12):2325967118812364.

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Sundemo D, Mårtensson J, Hamrin Senorski E, Svantesson E, Kartus J, Sernert N, Karlsson J, Samuelsson K.
Knee Surgery Sports Traumatology Arthroscopy. E-publication ahead of print 2019.

XVII Young age and high BMI are predictors of early revision surgery after primary anterior cruciate ligament reconstruction: a cohort study from the Swedish and Norwegian knee ligament registries based on 30,747 patients
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Knee Surgery Sports Traumatology Arthroscopy. E-publication ahead of print 2019.

XVIII Strength in numbers? The fragility index of studies from the Scandinavian knee ligament registries
Svantesson E, Hamrin Senorski E, Danielsson A, Sundemo D, Westin O, Ayeni OR, Samuelsson K.
Knee Surgery Sports Traumatology Arthroscopy. E-publication ahead of print 2019.

Abbreviations

ACL	Anterior cruciate ligament
ALL	Anterolateral ligament
AM	Anteromedial
ATT	Anterior tibial translation
DB	Double-bundle
EBM	Evidence-based medicine
EDS-HT	Ehlers-Danlos, hypermobility type
GJH	Generalized joint hypermobility
HCTD	Hereditary connective tissue disorder
hEDS	Hypermobile Ehlers-Danlos
HSS	Hospital for Special Surgery
HT	Hamstring tendon
IAS	Image analysis system
ICC	Intraclass correlation coefficient
ICEDS	International Consortium of the Ehlers-Danlos Syndromes
JH	Joint hypermobility
JHS	Joint hypermobility syndrome
KHE	Knee hyperextension
KOOS	Knee injury and Osteoarthritis Outcome Score
LCL	Lateral collateral ligament
LET	Lateral extra-articular tenodesis
LJH	Localized joint hypermobility
LSI	Limb symmetry index
MCL	Medial collateral ligament
MDC	Minimal detectable change
MIC	Minimal important change
MINORS	Methodological Index for Non-Randomized Studies
OA	Osteoarthritis
PASS	Patient-acceptable symptom state
PCL	Posterior cruciate ligament
PL	Posterolateral
PT	Patellar tendon
QPS	Quantitative pivot-shift test
QT	Quadriceps tendon
RSA	Radiostereometry
SD	Standard deviation
5PQ	Five-part questionnaire

Brief definitions

BRIEF DEFINITIONS

ACL reconstruction	A surgical procedure aiming to restore the native anatomy of the anterior cruciate ligament using a tissue graft
Allograft	A graft harvested from a deceased donor
Autograft	A graft harvested from the patient undergoing the surgical procedure
Beighton score	A method used to assess the hyperextensibility of several synovial joints. The method was presented by Beighton, Solomon and Soskolne in 1973 and is the most commonly used method to evaluate generalized joint hypermobility
Brighton criteria	Criteria historically used to define the presence of the Joint Hypermobility Syndrome. The Brighton criteria involve using the Beighton score to assess hypermobility but also include questions relating to arthralgia, back pain, abnormal scarring and so forth
Case-control study	A study with a retrospective design, comparing the outcome of individuals who experience exposure (cases) with that of individuals who are not exposed (controls) to a specific factor (for example, ACL injury)
Cohort study	A longitudinal study involving a cohort (a group of individuals sharing defining characteristics) that is observed over time, enabling the comparison of individuals with a certain exposure with individuals who are unexposed
Confidence interval	A range of values with a predefined probability that the true value lies within the particular range

Confounding factor	A factor that influences both the independent and the dependent variable and which, as a result, may produce a statistical correlation between two variables that in reality have no causal relationship
Contralateral	Relating to the other side of the body
Cut-off value	A predefined limit, within a range of values, that determines whether or not an individual is considered to have a particular condition
Generalized joint hypermobility	A term used to define the hypermobility of several synovial joints, usually in five or more joints. Various methods are used to define generalized joint hypermobility, although the Beighton score is the most common
Goniometer	An instrument used to measure angles of flexion extension of the joints of the body
Graft failure	Insufficiency of the ACL graft, caused by graft rupture or some other biological or technical cause of impaired function of the graft
Hereditary connective tissue disorder	Includes disorders of inheritable origin, of which several have been genetically mapped to identify the accountable mutations. This group includes diseases such as Marfan syndrome, osteogenesis imperfecta, Loeys-Dietz syndrome, to name just a few
Incidence	The probability of the occurrence of a certain condition in a population during a specified period of time
Injury allowance point	A method sometimes used when assessing the Beighton score in patients with a significant injury to one of the joints included in the Beighton score examination. Patients with a significant injury on one side of the body may be awarded an injury allowance point if the contralateral healthy joint meets the prerequisite limit needed to acquire a Beighton score point on that side. Consequently, patients with an ACL injury that have a hypermobile contralateral healthy knee would gain two Beighton score points for the assessment of the knees, one for each knee

Ipsilateral	Relating to the same side of the body
Joint hypermobility	A general term used to describe the hyperextensibility of the synovial joints, with the ability to extend beyond the normal physiological range of motion
Localized joint hypermobility	A term used to define individuals with hypermobility present in only a few joints, normally fewer than five
Odds	The ratio of the probability of the occurrence of an event, to that of an alternative event, in a group with a certain exposure
P value	A probability value, indicating the probability of the result that was observed, or the probability of a more extreme result, if the null-hypothesis is true
Power	The probability that the null-hypothesis is rejected, given that the alternative hypothesis is true
Predictor	A term defining a variable that has a significant association with the occurrence of an outcome
Prevalence	The proportion of a population with a certain condition
Quantitative pivot-shift test	Instrumented pivot-shift test that is quantified with a technological device
Randomized study	A study in which the participants have been randomized to a specific treatment, thereby avoiding the risk of selection bias
Reliability	The consistency of a method, meaning the ability of a method to produce consistent results under consistent conditions

Systematic review	A review article, using a systematized search and selection method to review all the available literature within a specific field
Type I error	The faulty rejection of the null hypothesis if the null hypothesis is true
Type II error	The faulty retention of the null hypothesis if the alternative hypothesis is true
Validity	The extent to which an observation reflects the intended construct, thus accurately corresponding to the real-world situation
Villefranche criteria	Criteria historically used to define the condition known as Ehlers-Danlos, hypermobility type. The criteria consist of an assessment of the Beighton score, but they also involve criteria relating to the hyperextensibility of the skin, recurring joint dislocations, chronic joint or limb pain and so forth

BRIEF DEFINITIONS

1 Introduction

Generalized Joint Hypermobility and Specific Knee Laxity

Aspects of Influence on the Anterior Cruciate Ligament-injured Knee

The anterior cruciate ligament

History

Figure 1 Galen of Pergamon, lithograph by Pierre Roche Vigneron [a]

The history of the anterior cruciate ligament (ACL) spans from ancient times to modern advanced arthroscopic surgery. It was first mentioned approximately 5,000 years ago in the Smith Papyrus. [115] Hippocrates (460-377 BC), often referred to as the father of medicine, suggested that instability subsequent to knee trauma was caused by ruptured internal ligaments. [230] He was succeeded by another Greek, Galen of Pergamon (201-131 BC), physician to the Roman emperor, who was the first to describe the anatomy of the knee joint in detail (Figure 1). Moreover, he named the cruciate ligaments "ligamenta genu cruciata", based on their appearance. [73] After a long silence, lasting almost 2,000 years, the scientific community rediscovered the cruciate ligaments during the 19th century. In 1836, two German brothers, Wilhelm and Eduard Weber, provided a detailed anatomic description of the ACL, including a review of the two fiber bundles, and concluded that the sectioning of the ACL led to increased anteroposterior laxity. [230] A decade later, a professor of surgery at Lyon University, Adameé Bonnet, described the three signs of ligamentous injury of the knee; hemarthrosis, a snapping noise and loss of function. He advised non-surgical treatment consisting of the application of cold packs and early physical activation. [229] The surgical repair of the ACL was first performed in 1895 by Sir Arthur Mayo-Robson of Leeds (1853-1933) using a catgut suture. Six years later, the patient described his leg as "perfectly strong" and he was able to walk and run without a limp. Moreover, Sir Mayo-Robson concluded that no abnormal mobility was present and that the patient had full extension, while flexion was somewhat limited. [210] Between 1914 and 1920, the use of autologous tissue emerged as a graft for the ACL, using a technique that in many ways resembles that of today. [229]

[a] Picture taken, with permission, from https://commons.wikimedia.org/wiki/File:Galen_detail.jpg the 24th of July 2019.

Anatomy and function

THE CRUCIATE LIGAMENTS

The cruciate ligaments form a biomechanical entity which, in combination, maintains the continuous contact between the femoral condyles and the tibial plateau during the range of motion of the knee. [87] Macro-anatomically, the ACL resembles a band, ranging in length between 22 and 41mm. [11] It consists of two distinct structures: the anteromedial (AM) and posterolateral (PL) bundles, terminology based on their respective insertion sites on the tibia. [291] On the tibial side, the AM bundle inserts anteromedially, anterior and lateral to the medial tibial spine, while the PL bundle inserts slightly posterior and lateral to the AM bundle. [63] The AM bundle originates on the posterior and proximal aspect of the medial wall of the lateral femoral condyle, while the PL bundle originates on the posterior and distal aspect of the wall. [291] The two bundles make varying contributions to knee stability at different knee flexion angles. In extension, the PL bundle is taut, while the AM bundle is more lax. With increasing flexion, the PL bundle becomes lax and tension increases in the AM bundle. Biomechanical studies have demonstrated that the transection of the AM bundle leads to increased anterior tibial translation (ATT) at 60° and 90° of knee flexion, while the transection of the PL bundle increases anterior tibial translation at 30° of knee flexion. [291] Moreover, the transection of the PL bundle increases combined rotation at 0° and 30° of flexion, compared with the intact knee and with the isolated transection of the AM bundle. [291] The two bundles thus cooperate to restrict anteroposterior and rotatory knee laxity, dependent on the flexion angle of the knee. The proprioceptive abilities of the ACL are provided by the posterior articular branches of the tibial nerve. Four different types of mechanoreceptor (Ruffini receptors, Vater-Pacini receptors, Golgi-like tension receptors and free nerve endings) contribute to the proprioceptive ability, giving feedback on the postural changes and movements of the knee. [63] The middle genicular artery, originating from the popliteal artery, provides the blood supply to the ACL. [63]

The posterior cruciate ligament (PCL) is exceptionally strong, stronger than the ACL in specimens of comparable age. [12] The PCL originates from the medial femoral condyle and the roof of the intercondylar notch and runs down to the tibia, laterally (Figure 2). The tibial attachment is located at the posterior tibial shelf, between the posterior horns of the medial and lateral menisci. [12] The PCL is 32 to 38 mm long and is three times larger at the insertion sites than at its midsubstance. Like the ACL, the PCL is comprised of two distinct bundles; the anterolateral and the posteromedial bundles. [285] The function of the PCL involves the prevention of posterior displacement of the tibia, relative to the femur. [12]

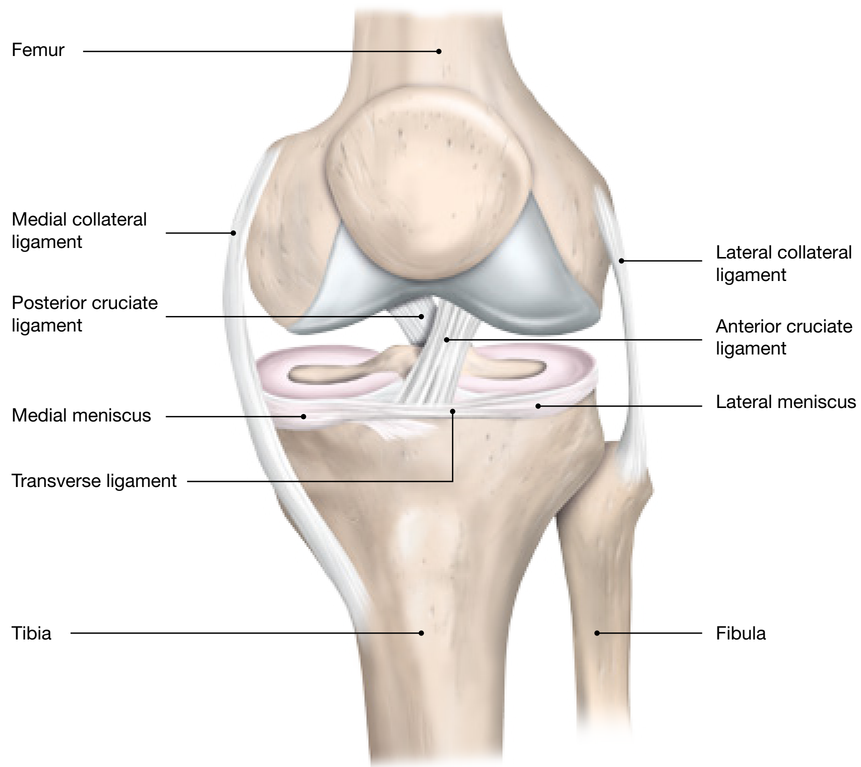

Figure 2 Anterior view of the knee joint, illustrating the cruciate ligaments, the collateral ligaments, the menisci and involved bones.

THE JOINT CAPSULE

The joint capsule has attracted increasing interest in recent years, mainly through discussions relating to the anterolateral structures of the knee and the potential existence of an anterolateral ligament (ALL). [47, 180] There is controversy about whether it is a distinct ligament [47, 284] or instead a sheet of fibrous tissue. [84] A previous anatomical and histological study identified an anterolateral ligament in all 40 examined knees, finding its origin close to the popliteal tendon insertion. From there, it was found to travel to its insertion into the lateral meniscus, posterior to Gerdy's tubercle. [284] However, other researchers have failed to identify a clear ligament structure, using methodology involving primate and fetus dissections, as well as arthroscopic and radiological examination. [180] To summarize, a consensus statement, published in 2019, concluded that the proposed ALL is a capsular structure within Seebacher layer 3 within the anterolateral capsule. Moreover, it was concluded that the morphology of the proposed ALL varies between individuals and that it runs superficial to the lateral collateral ligament (LCL) and attaches between the tibia and the anterior border of the fibular head. [77]

However, the main functions of the joint capsule comprise knee stability and joint encapsulation, thereby containing the synovial fluid intra-articularly. [87] The capsule is attached to the edges of the tibia and femur, circumferentially. [188] The capsule is structured from layers of tissue. Internally, the capsule is lined by a synovial membrane, contributing to the production of intra-articular synovial fluid. Externally, the capsule is composed of a strong, fibrous matrix, mainly containing collagen fibers. [188]

THE COLLATERAL LIGAMENTS

There are two collateral ligaments, the medial and the lateral (Figure 2). The medial collateral ligament (MCL) consists of two parts, the deep MCL and the superficial MCL. The superficial MCL originates from the posterior part of the femoral epicondyle and travels distally, inserting to the medial tibial condyle at the anteroposterior level of the pes anserinus insertion. [16] The superficial MCL is the stronger of the two components, acting as a primary restraint against valgus load and external rotation. [87, 209] The deep portion of the MCL has been described as a thickening of the medial part of the capsule and is divided into two parts, the meniscotibial and the meniscofemoral ligaments. The deep part of the MCL contributes with anteroposterior stability and, to a limited extent, it also counteracts valgus and internal rotation. [16, 87, 209]

The lateral, or fibular, as it is also called, collateral ligament of the knee is one component of a larger biomechanically important part of the knee, the posterolateral corner. The other parts of the posterolateral corner, not discussed in further detail, involve the popliteal tendon, the arcuate popliteal ligament and the joint capsule. [247] The LCL is a chord-like structure, located outside the knee joint capsule. It originates from between the lateral epicondyle and the supracondylar process of the femur and stretches inferiorly to the head of the fibula. [247] Biomechanically, the LCL is the primary restraint to varus movement. [51, 139] There is also evidence indicating that the LCL plays an important role in counteracting the external and internal rotation of the tibia. [55]

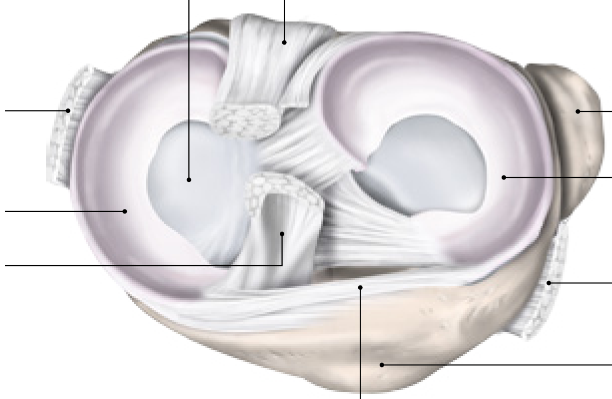

Figure 3 Transverse view of the knee joint seen from above, illustrating the cruciate ligaments, the collateral ligaments, the menisci and the meniscofemoral ligaments.

THE MENISCI

The two menisci, the lateral and the medial, are smooth structures composed of fibroblast and chondrocyte cells and extracellular matrix components (Figure 3). [50] Important stabilizers of the menisci include the MCL, the transverse ligament, the meniscofemoral ligaments and additional anchoring points at the anterior and posterior horns. The ligament of Wrisberg and the ligament of Humphrey, also referred to as the meniscofemoral ligaments, assist in the stabilization of the lateral meniscus. They originate from the femoral condyle, close to the attachment of the PCL, and attach to the posterior horn of the lateral meniscus.[137, 157] Meniscus vascularization is complete at birth, but it diminishes with age, resulting in blood supply to only 10-25% of the tissue, situated in the periphery, at maturity. [52] This is relevant with respect to the healing process, where the avascular central part of the menisci are at risk of suffering permanent degenerative or post-traumatic lesions, due to limited healing capacity. [157] The menisci are versatile organs, contributing both to load transmission and shock absorption and also to the nutrition and lubrication of the intra-articular cartilage. [157] It has recently been demonstrated that the menisci have important stabilizing properties in terms of mitigating anteroposterior and rotatory knee laxity. According to previous studies, the medial meniscus primarily withstands anteroposterior laxity,[152, 156, 236, 250] while the lateral meniscus is an important structure in countering rotatory laxity. [156, 260]

Epidemiology

The anterior cruciate ligament is the most common ligament to be injured in the knee, with a reported injury rate of approximately 80 per 100,000 individuals per year in Sweden. [2] In the United States, ACL reconstruction is the sixth most common orthopedic surgical procedure. [75] It is estimated that around 130,000 reconstructions are performed annually in the United States. [159] In Sweden, the most common activity performed when sustaining an ACL injury is soccer, followed by alpine skiing, floorball and handball. [2]

Etiology

MECHANISM OF INJURY

The discussion relating to the mechanism of ACL injury has been divided into two distinct themes depending on whether or not the injured individual was in physical contact with another individual at the time of injury. The majority of injuries occur without contact, and according to previous studies the rate of non-contact injuries ranges from 70% to 84%. [9] Common activities during injury include a change of direction or cutting maneuvers in combination with deceleration. Moreover, landing from a jump or pivoting with the knee in or near full extension are common mechanisms. [39, 68] The above-mentioned situations include knee joint movements causing knee valgus or varus, internal or external rotation and anterior tibial translation. [9, 39, 160] It has been demonstrated that anterior tibial translation, in combination with forces caused by valgus or internal rotation, lead to increased strain on the ACL, compared with only one isolated force acting on the ACL. [35, 160]

Figure 4 Certain types of footwear and playing surface are regarded as extrinsic risk factors for anterior cruciate ligament injury. [b]

[b] Picture taken, with permission, from https://commons.wikimedia.org/wiki/File:Puma_association_football_shoes.jpg the 24th of July, 2019.

RISK FACTORS FOR ACL INJURY

Traditionally, risk factors for ACL injury are characterized as either intrinsic (from within the individual) or extrinsic (from outside the individual) in nature. There are several significant extrinsic risk factors. For example, the type of footwear is regarded as a contributing factor (Figure 4). The design and position of the cleats may increase rotational traction, thereby increasing the risk of lower extremity injury.[267] Similarly, a playing surface that creates greater shoe-surface friction, such as Bermuda grass (a certain type of natural grass) or artificial grass, has also been associated with an increased risk of ACL injury.[28, 193]

Moreover, there are various intrinsic risk factors that are considered important. A previous review categorized intrinsic risk factors as anatomical, hormonal, neuromuscular or biomechanical risk factors. [9] In creating a foundation for interpreting the results in this thesis, the neuromuscular risk factors are particularly important and will be reviewed in detail. Neuromuscular control has been described as "the unconscious activation of the dynamic restraints surrounding a joint in response to sensory stimuli". [9] In sports participation, the pre-activation of knee joint stabilizing muscles is thought to increase dynamic stability during impact. [93, 220] Specifically, the co-activation of agonist and antagonist muscles, such as the quadriceps and the hamstrings, is important. Using a strain gauge, it has been demonstrated that isolated quadriceps contraction strains the ACL more than the simultaneous co-activation of both quadriceps and hamstrings. [69] Relative hamstring-to-quadriceps weakness may cause increased anterior tibial translation and can, thereby, contribute to an ACL injury. [53] On the other hand, through the co-contraction of quadriceps and hamstring muscles, the knee joint is compressed, thereby limiting anterior tibial translation and more of the valgus moment is absorbed by the articular surfaces, which reduces the strain on the ligaments.[91, 93] Moreover, studies have found that female athletes display a disproportionate activation of their lateral hamstrings during landing[220] and a decreased ratio of medial to lateral quadriceps activation.[183] This combination of factors, observed in females, increases the load on the lateral side of the joint. This may cause an indirect opening on the medial side of the joint, thereby increasing anterior shear force, which further increases the strain on the ACL. [93]

In support of the significance of neuromuscular factors, female soccer and basketball players who sustained ACL injuries were found to have a relative hamstring-to-quadriceps strength deficit, compared with non-injured athletes. [181] Moreover, increased dynamic knee valgus, measured using knee abduction moments, has been associated with an ACL injury. [92] Female athletes with high knee abduction moments have been shown to decrease their knee abduction moments following a neuromuscular training program. [182] This supports the notion that more synchronized quadriceps/hamstring co-contraction limits the valgus moment, which may in turn contribute to an increased ACL injury risk.

Laxity and laxity testing

Knee laxity testing is performed for two principal reasons; the diagnosis of articular injury and the evaluation of postoperative treatment. Knee laxity can be divided by two different properties, the vector of movement (anteroposterior or rotatory laxity) and the evaluation of uniplanar or multiplanar (static or dynamic laxity) laxity (Figure 5).

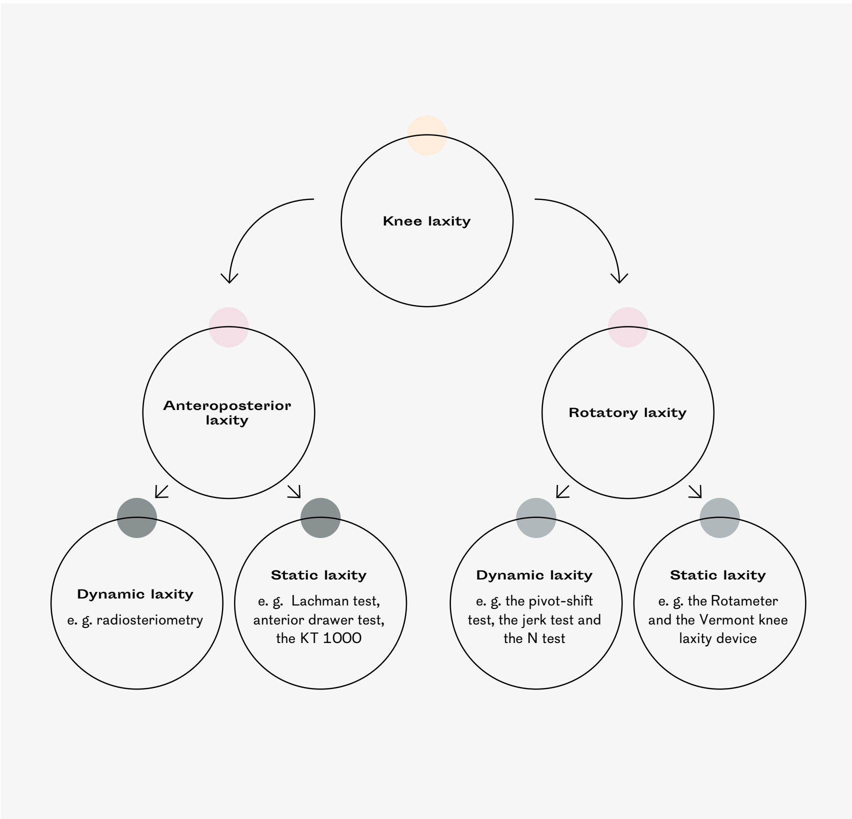

Figure 5 Depicting a structure of available methods to assess knee laxity. Examples are given to illustrate available tests for each respective category.

ANTEROPOSTERIOR KNEE LAXITY

The assessment of anterior knee laxity is an essential part of the diagnosis of an ACL rupture. [199] It is also a frequently used parameter in postoperative assessments after ACL reconstruction, to evaluate treatment results. [34, 38, 144] The assessment of anteroposterior laxity is mainly performed using static assessments, although dynamic assessments, including invasive methods such as radiostereometry (RSA), also exist. The ACL is the primary stabilizer of ATT of the tibia, although other factors contribute to the resistance of ATT. [10] The menisci, particularly the medial meniscus, perform an important stabilizing function in the anteroposterior direction. [152, 156, 236, 250] Female sex has also been reported to influence anterior knee laxity [270] and, according to a recent meta-analysis, the ovulatory phase of the menstrual cycle is associated with increased knee laxity. [90] Moreover, increased knee hyperextension and greater navicular drop have been associated with increased anterior knee laxity. [240] Both high-grade preoperative Lachman and anterior drawer tests have been associated with generalized joint hypermobility (GJH) and chronic ACL injury (in relation to acute injury). [156]

MANUAL ANTEROPOSTERIOR LAXITY ASSESSMENT

Two manual methods, often used in the clinical setting, are the Lachman test and the anterior drawer test, both measuring static anterior laxity (Figure 6). In comparison with other manual clinical tests, the sensitivity of the Lachman test is superior in the diagnosis of ACL injury in the office setting. [277] A meta-analysis reported a sensitivity of 0.81 and 0.91 and a specificity of 0.81 and 0.78 for awake and anesthetized patients respectively. During the examination, the distance of ATT of the injured knee is compared with that of the uninjured knee, since every individual patient is his/her own best reference. To perform the Lachman test, the patient lies supine, with the knee in 20-30° of flexion. The patient is instructed to relax the musculature in the leg in order to reduce the influence of neuromuscular stabilization. The examiner places one hand on the thigh, distally on the femur, and the other on the inside of the proximal tibia. The thigh is held firmly while the tibia is pulled anteriorly. Laxity is subjectively graded by the sensation of laxity perceived in the hands of the examiner. According to the IKDC criteria, laxity is graded as A, B, C and D, corresponding to 0-3 mm, 3-5 mm, 5-10 mm and > 10 mm of ATT, respectively. [89]

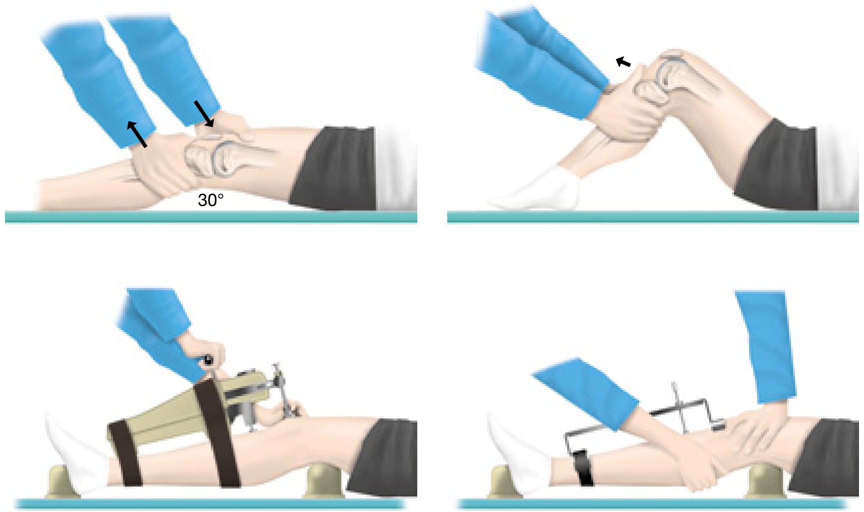

Figure 6 Illustrations of anteroposterior laxity assessment.
Upper left: the Lachman test, **upper right**: the anterior drawer test,
lower left: the KT-1000, **lower right**: the Rolimeter

INSTRUMENTED ANTEROPOSTERIOR LAXITY ASSESSMENT

To enhance the quantification of anterior knee laxity and mitigate subjectivity, various devices have been developed. [27, 60] An instrumented assessment of anterior laxity generally aims to quantify the Lachman test. During the instrumented examinations, the patient lies supine with the knee in 20-30° of flexion, similar to the procedure for the Lachman test. One of the most commonly used devices is the KT arthrometer, the KT-1000 and the KT-2000 (MEDmetric Corp, San Diego, CA, USA, Figure 6). [59] The patient's legs are placed on the thigh support to ensure muscle relaxation before testing. The arthrometer is fixed to the lower leg using a strap. Anterior tibial translation can be measured using a predefined torque, or by the manual maximum test. The reliability of the KT-1000 varies with the examiner's experience[101] and has been considered fair when performed by experienced professionals. [237] Another commonly used quantification device of ATT is the Rolimeter (Aircast Europa, Neubeuern, Germany), a simple metallic device with results comparable to those of the KT-1000 arthrometer in terms of reliability (Figure 7). [27, 234] The device comprises two convex supports and a bar that connects them. The lower support is fastened with a strap. It is not possible to customize or measure the applicable force and a standard manual maximum Lachman test is therefore performed. [27]

ROTATORY KNEE LAXITY

Previously, anteroposterior laxity has been the gold standard for postoperative assessment to evaluate treatment results, although rotatory knee laxity has attracted increasing interest during the past decade. [26, 177] Even though the Lachman test is regarded as the most sensitive test for diagnosing an ACL injury, the pivot-shift test, a test of rotatory knee laxity, is considered the most specific. [199] Rotatory knee laxity can be measured both statically and dynamically, but both are associated with methodological difficulties. [151, 257] Static rotatory knee laxity measures internal and external tibial rotation and can be mechanized using different devices to reduce interrater variability. [151, 171] However, one of the difficulties is determining the starting position of the foot during measurement of rotation. [171] Dynamic rotatory laxity is associated with issues related to intra- and interrater variability, since the tests are performed, and in many situations also interpreted, by human hands. However, dynamic rotatory knee laxity is more closely associated with symptoms of instability and the development of osteoarthritis (OA) than anteroposterior laxity, making rotatory knee laxity an important topic for research. [26, 109, 133, 145]

The cause of the magnitude of rotatory knee laxity in the ACL-injured knee is multifactorial. Factors that have been reported to increase rotatory knee laxity, apart from injury to the ACL, are injuries to the anterolateral complex or the iliotibial tract,[131, 179, 221, 246] injury to the menisci, particularly the lateral meniscus,[156, 175, 179, 246, 260] increased tibial slope [201, 246] and generalized ligamentous laxity.[156]

MANUAL ROTATORY LAXITY ASSESSMENT

Several methods, including the pivot-shift test, the N test and the jerk test, are used to quantify rotatory knee laxity. [130] A previous study identified different biomechanical advantages to both the N test and the pivot-shift test. [130] However, the pivot-shift test is the most frequently used for testing rotatory knee laxity in the literature. [136] The pivot- shift test is performed to diagnose an ACL injury or to quantify rotatory knee laxity. The pivot-shift phenomenon was first reported by Galway et al. and was described as the instant reduction of the anteriorly subluxated lateral tibial plateau, which can be reproduced in ACL-insufficient knees. [74] To perform the pivot-shift test, the patient is placed in the supine position. Using the standardized method of performing the pivot-shift test, the foot of the patient is lifted and rotated internally by the examiner. Next, as the knee joint starts to flex, the examiner applies valgus stress to the joint. The pivot point is reached at approximately 30 degrees of flexion, thus producing a sudden reduction of the tibia, which can be sensed by the examiner. [97] Biomechanically, the lateral tibial plateau dislocates (subluxation) anteriorly when flexion increases. As the pivot point is reached, the iliotibial band pulls the tibia posteriorly, resulting in a posterior reduction movement. [43] The manual pivot shift is clinically graded as A (normal), B (+ glide), C (++ clunk) and D (+++ gross).[89] The quantification of the pivot-shift test is highly subjective, although the inter- and intraexaminer variability can be reduced using a standardized maneuver. [17]

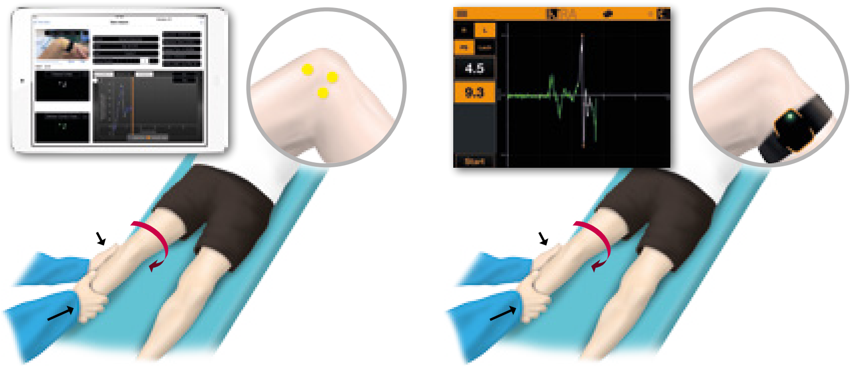

Figure 7, Left: The image analysis system with three colored markers attached to bony landmarks of the lateral part of the knee. The pivot-shift test is performed by the examiner, while an assistant uses a tablet computer to capture the motion of the lateral part of the knee. The contrast of the colored markers is detected by the tablet application and a graph forms, illustrating the change in position. Right: The KiRA, with an inertial sensor attached to the lateral part of the proximal lower leg. The inertial sensor is connected to a tablet computer using Bluetooth technology. Accelerometer data are interpreted by an application installed on the tablet.

INSTRUMENTED ROTATORY LAXITY ASSESSMENT

The issue of variability in grading rotatory knee laxity has encouraged the development of devices to improve reliability. [257] In essence, the quantification of dynamic rotatory knee laxity is equivalent to quantitative pivot shift (QPS). A number of different methods, including electromagnetic sensor systems, [43, 100] surgical navigation [134, 138], inertial sensors[150, 155] and image analysis systems, are used to quantify the pivot-shift test. [98, 99] With respect to the current thesis, two methods are of particular interest: the inertial KiRA accelerometer[150] (Orthokey, LLC, Lewes, DE, USA) and an image analysis system. [98] The image analysis system uses a software application on an Apple iPad (Apple Inc, Cupertino, California, USA, Figure 7). [98, 150] The image analysis system measures the translation of the lateral compartment

of the knee.[98] The lateral aspect of the knee is captured, using a camera on a tablet computer. Three bony landmarks are marked using brightly colored markers (Color Coding Labels; Avery Dennison Corporation, Pasadena, CA, USA): the tubercle of Gerdy, the lateral femoral epicondyle and the fibular head. The relative two-dimensional movement of the marked structures is captured by the camera and a software program produces a graph plotting the anterior-posterior position of the femur as a function of time. The change in position that occurs during femoral reduction on the tibia, when the knee reaches its pivot point, is captured and the distance of the shift in position is presented in millimeters. [99] The image analysis system has shown excellent reliability, calculated by measuring intraobserver and interobserver intraclass correlation coefficients (ICCs >90). [23, 173] If the tablet is held at a distance between 50 to 175 cm from the knee, with less than 45° degree deviation from the perpendicular position, the image analysis system has an accuracy of 92%. [172] Also, the image analysis system has demonstrated strong correlations with bony movement, meaning there are little skin-to-bone motion artifacts. [172, 176]

The accelerometer, containing an inertial sensor, has been utilized, as recently described by Lopomo et al. [150] The tri-axial sensor is fastened to the lateral aspect of the proximal tibia (Figure 7). This device quantifies the pivot-shift test by measuring the acceleration of the joint during the execution of the maneuver. This device has been tested in terms of reliability, presenting an intraclass correlation coefficient of 0.79. The inertial sensor has a resolution of 0.03 m/s^2. Moreover, it has been shown to have strong correlations with invasive methods, including navigation systems. [149]

Morbidity

INSTABILITY AND LAXITY

The principal indication for ACL surgery is persistent knee instability, hindering physical activity and sports performance. [30, 109, 208] Before modern surgical techniques and rehabilitation programs were developed, an injury to the ACL could be the end of a career in a physically demanding profession or sport. [20] However, even after the implementation of up-to-date surgical and non-surgical ACL treatment, a few studies have reported that the rate of return to sport and a return to the preinjury level of activity are continuously unsatisfactory. [21] Previous studies have reported that, three years after reconstruction, only 65% of soccer players still compete at the same level. [275]Moreover, a meta-analysis including other sports demonstrated that as few as 55% return to competitive level. [21] Further, there is evidence indicating that knee laxity, and rotatory knee laxity in particular, is associated with an increased risk of the development of osteoarthritis and symptoms of instability. [109, 133, 145] Residual instability and an inability to return to the preinjury level of activity after ACL reconstruction are therefore suboptimal [20, 76, 276] and there are lively ongoing scientific discussions about how to reduce postoperative knee laxity, using double-bundle ACL reconstruction or complementary lateral extra-articular tenodesis, for example. [37, 77]

GRAFT RUPTURE

Graft rupture is a dreaded complication. Revision surgery is technically challenging for the surgeon to perform and additional surgery leads to a second period of convalescence and rehabilitation. Graft rupture is equally detrimental in terms of instability, and patients whose professional career depends on a high level of physical activity demand reliable knee stability. Several factors have been associated with graft rupture and ACL revision surgery; they include patient age, type of graft, obesity, smoking, generalized joint hypermobility and competitive level sports. [44, 140, 244, 258, 289]

OSTEOARTHRITIS

Rupture of the ACL leads to an increased risk of developing osteoarthritis. Osteoarthritis leads to functional impairment, pain, swelling and stiffness. Studies have shown that more than 50% of patients sustaining an ACL injury have radiographic signs of OA within 10-20 years. [148, 256] Since many patients are young and active, the affected individuals suffer disabling pain and stiffness in early middle-age [216] and the question of arthroplasty might be considered; an intervention that is generally not recommended for younger patients due to the limited lifespan of current arthroplasties. [65, 204] This in turn leads to high costs in terms of both patient suffering and healthcare expenditure. [224] Studies have reported conflicting evidence in terms of the capability of ACL reconstruction to reduce the risk of OA. [6, 153, 164, 168, 191, 219] However, modern anatomic ACL reconstruction techniques have recently been developed and OA can take decades to develop and, as a result, long-term follow-up studies of modern techniques are warranted to evaluate their effect on the development of OA.

Treatment

The choice of treatment for ACL injury is difficult and treatment must be individualized. [18] There are many potential choices to make; non-surgical or surgical treatment, type of graft, surgical technique, single- or double-bundle reconstruction, fixation method, intra-articular reconstruction only or combined with extra-articular reconstruction. The first choice, the choice of non-surgical or surgical treatment, is perhaps the most important. There is evidence showing that non-surgical treatment, with patients receiving only rehabilitation, is equal or even better for certain patients. [72, 81] The main arguments for selecting surgical reconstruction include patients who have excessive knee laxity, experience of instability or are aiming to return to physically demanding activities. [30, 109, 208] However, as many as 25% of patients experience persistent rotatory knee instability after ACL reconstruction and, for this reason, additional techniques, including double-bundle ACL reconstruction and lateral extra-articular tenodesis, have been developed to mitigate anterolateral laxity.[248] On the other hand, patients with low physical demands or patients who do not perceive issues with instability during their daily lives are better suited to non-surgical treatment, since the surgery itself is costly and is associated with considerable convalescence postoperatively.

REHABILITATION

Rehabilitation is an essential component in the treatment of ACL injury, both in patients undergoing surgery and in patients receiving non-surgical treatment. Rehabilitation after ACL injury can be divided into three phases, the early phase, the late phase and the return-to-sport phase. Recommendations for a return to sport after an ACL reconstruction have been proposed and the recommended rehabilitations time range from nine to 12 months after surgery. [83] However, the time of rehabilitation differs between individuals and the fulfillment of the rehabilitation criteria is a more appropriate method to evaluate the progress in ACL rehabilitation, instead of following a fixed time schedule. [3] Important factors to evaluate in the planning of ACL rehabilitation include the degree of preoperative laxity and concomitant injuries to the menisci and collateral ligaments, which explains why rehabilitation protocols have to be individualized. [3]

Patients undergoing ACL reconstruction should initiate rehabilitation directly after the injury and should continue at least until the moment of return to sport, or even life-long. [3] The early phase of rehabilitation permits immediate full weight-bearing in patients who are able to walk symmetrically, without pain and effusion [278, 283] At an early stage, patients are recommended to initiate isometric quadriceps exercises in order to regain extension strength, but at a rate and strain that does not cause pain. [3] Next, open and closed kinetic chain exercises are introduced by the physical therapist, often around four weeks postoperatively, if tolerated by the patient. [3, 278] The aims of the late phase of rehabilitation include symmetrical functional performance, evaluated with hop tests, and symmetrical knee flexion and extension strength. A limb symmetry index (LSI) above 90% is recommended. The LSI is calculated by dividing the results for the injured limb with the results for the uninjured limb. Further, normal jumping, walking and running biomechanics should be restored. [3, 278] Last, the decision about when to return to sport is difficult and requires interaction between the athlete and the physical therapist. The athlete starts to include sport-specific exercises, including technical training, jumping exercises, sprinting and other activities, depending on the type of athletic activity. [3, 278] A recent study reported that delaying return to sport by one month reduced the re-injury rate by 51%, until the ninth month, when no further risk reduction was observed. [83] Adequate rehabilitation and proper timing are therefore crucial in order to return to sport safely after ACL reconstruction.

Surgical reconstruction

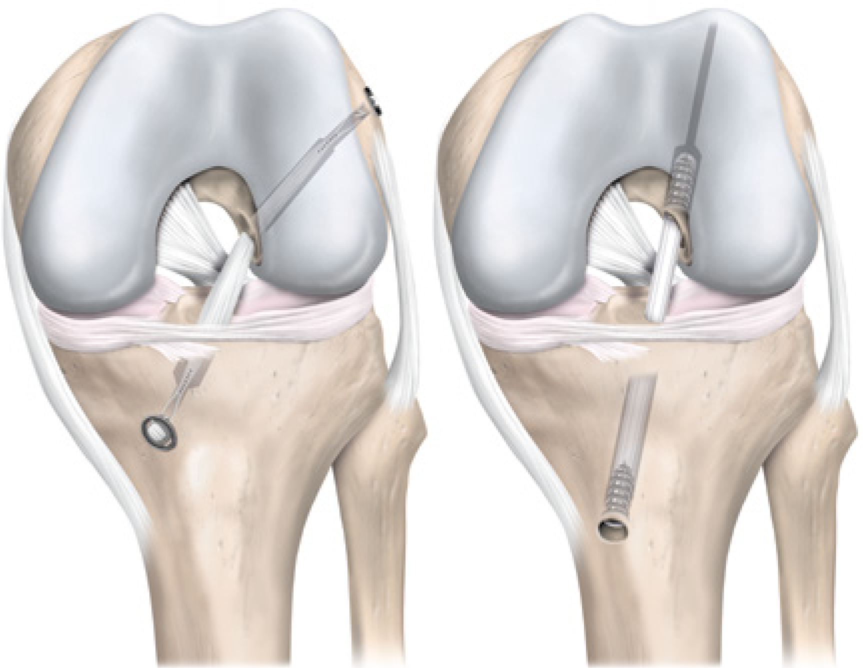

Figure 8 Illustrations of different methods used for ACL reconstruction,
left: anatomic ACL reconstruction using the transportal technique with a more oblique and horizontal graft placement, resembling normal anatomy;
right: isometric transtibial ACL reconstruction with a more vertical graft placement

SURGICAL TECHNIQUE

The historical perspective gives an overview of the transition from conservative treatment to the first attempts at surgical reconstruction. In the modern era, during the last two to three decades, there has been a substantial shift in surgical technique. Surgery has progressed from isometric, non-anatomic ACL reconstruction, frequently performed using transtibial drilling, to arthroscopic techniques designed to emulate native ACL anatomy (Figure 8).[78] Anatomic ACL reconstruction can be performed using different techniques. However, to achieve anatomic reconstruction, the visualization of the insertion sites is paramount. Using a three-portal technique improves the visualization of both femoral and tibial native ACL attachment sites. [19] Intra-articular landmarks are used to guide the placement of the tunnels in the ACL footprints. [18] This enables a more oblique and horizontal placement of the femoral tunnel, thereby creating a graft placement closer to the native anatomy, which will in turn reduce rotatory knee laxity. [18, 102, 143]

Single- vs double-bundle reconstruction

The use of single- and double-bundle (DB) ACL reconstruction is a frequently discussed topic. The theoretical advantage is to better imitate the native ACL anatomy, since the native ACL is composed of two individual bundles making specific contributions to knee stability, depending on the degree of knee flexion. A recent assessment of meta-analyses, including high-level clinical studies, has demonstrated that the DB reconstruction produces less postoperative knee laxity, including an assessment of anteroposterior and pivot-shift testing, but with no significant difference in terms of patient-reported outcomes or the risk of graft failure. [161] Moreover, registry studies have reported contradictory findings in terms of the risk of revision. [4, 259] The disadvantages of DB reconstruction include increased operating time, greater technical difficulty and increased economic cost. [161, 190]

The selection of patients that would benefit from DB reconstruction involves an assessment of preoperative knee laxity. [178] It has been proposed that tibial insertion sites of < 14 mm are appropriate for single-bundle reconstruction, while insertion sites of > 18 mm may benefit from double-bundle reconstruction, as it would cover a larger proportion of the native attachment of the ligament. [18] Another factor is the risk of notch impingement, where a narrow intercondylar notch would not fit a double-bundle reconstruction. Previous recommendations have stated that a shallow notch, less than 12 mm, is not suitable for double-bundle reconstruction due to the risk of impingement. [95]

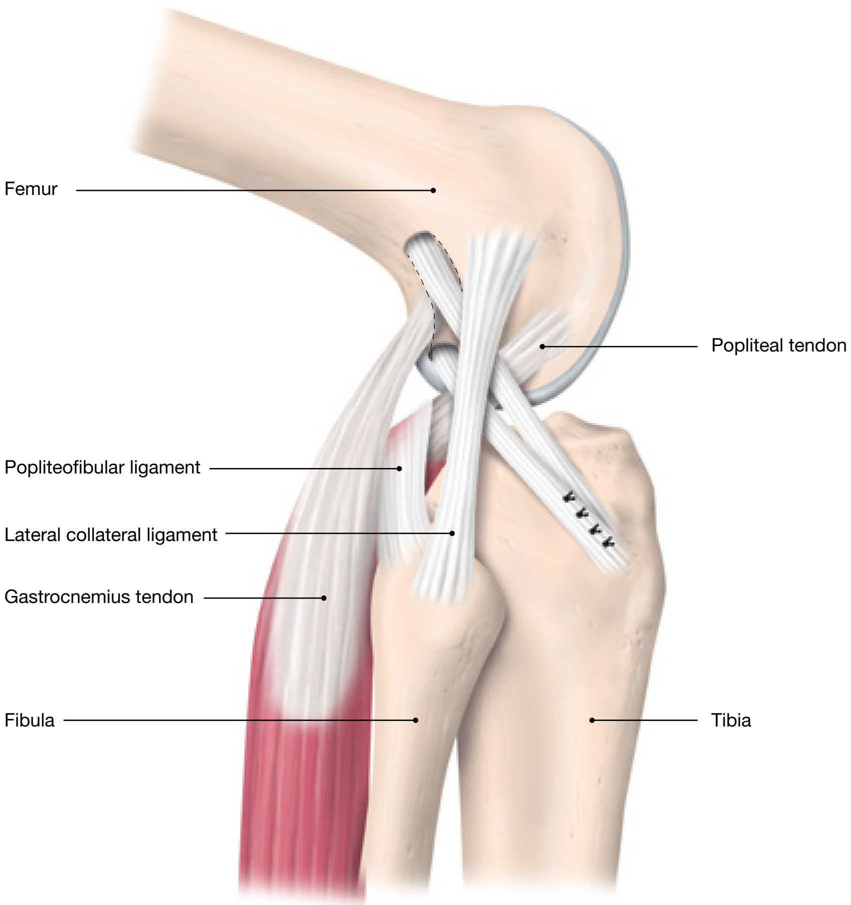

Figure 9 Illustrating a lateral extra-articular tenodesis using the Lemaire technique. A proximal part of the iliotibial band is detached and passed under the lateral collateral ligament, then through a femoral tunnel and again passed deep to the lateral collateral ligament, then fixed distally using sutures, to the iliotibial band.

Lateral extra-articular tenodesis

Lateral extra-articular tenodesis (LET) is not a new surgical procedure, although it has regained interest after many years of limited attention. Presently, various methods for performing LET have been presented (Figure 9). [241] Primarily, rotatory knee laxity has been difficult to remedy using non-anatomic intra-articular reconstruction and LET has been regarded as an alternative to help control anterolateral rotatory laxity. [94, 284] As previously discussed, anatomical studies have identified tissue adjacent to or incorporated in the anterolateral capsule, entitled

the ALL by some [284] and considered by others to be a sheet of fibrous tissue. [84] However, there appears to be consensus on the fact that the anterolateral capsule acts as a secondary stabilizer, in terms of both the anterior translation and rotation of the lateral compartment. [84, 167, 179] A recent meta-analysis reported that ACL reconstruction in combination with LET reduced rotatory knee laxity, although there were no differences in terms of ATT or patient-reported outcomes. The authors of the meta-analysis found methodological flaws, including insufficient sample size, methodological consistency and internal validity of the included studies. [94] Presently, there is an ongoing randomized controlled trial with an adequate sample size that aims to remedy these methodological flaws, a study that could possibly shed further light on this topic. However, there is concern in the scientific community in terms of the risk of over-constraining the knee joint, causing reduced internal tibial rotation, which has been observed in patients with combined ACL reconstruction and LET. [40, 180, 232, 241] Issues related to over-constraint have been reported to be increased knee joint stiffness [118], impaired physiological motion [15, 218] and the development of OA. [218, 226] Nevertheless, more research needs to be conducted to further improve our understanding of over-constraint and clarify indications for the appropriate use of LET. It has been suggested that patients suitable for a LET procedure, in combination with ACL reconstruction, include revision ACL reconstructions, patients with high-grade pivot shift, with GJH, with knee hyperextension and young patients returning to pivoting activities. [77]

TYPE OF GRAFT

In Sweden, there has been a transition from the use of patellar tendon (PT) autografts, as the most frequently used graft, to the increasing use of hamstring tendon (HT) autografts. Since 2005, the use of HT autografts has increased from 80 to 91%, according to the Swedish National Knee Ligament Register. [2] Another graft type that has attracted increasing interest lately is the quadriceps tendon (QT) autograft, used either as a soft-tissue graft or with a bone block at one end. Finally, an allograft, a graft from a deceased donor, can also be used. The use of allografts is more common internationally, although in Sweden they were only used in 1% of cases in 2016. [2]

The properties of different grafts is a thoroughly researched subject. Generally, studies have found that the most common graft types, the HT and the PT grafts, are comparable and viable options for ACL reconstruction, but with their respective advantages and disadvantages. [38, 225] Studies have demonstrated that HT grafts are associated with deficits in flexion strength and increased anteroposterior laxity compared with PT grafts, while the advantage of HT grafts include less donor-site morbidity. [62, 166] Patellar tendon grafts are associated with increased knee pain and knee-walking impairment. [38, 266] However, PT grafts appear to be superior in terms of knee laxity and there are indications of a lower risk of graft rupture when compared with HT grafts. [225, 258, 288] A recent meta-analysis found that QT autografts generate less knee donor morbidity than PT grafts and a better patient-reported outcome than HT grafts, making the QT graft a valid alternative to the more frequently used graft types. [170] The obvious advantage of allografts involves the absence of donor-site morbidity. However, allografts have been associated with increased knee laxity and inferior patient-reported outcomes. [280] Thus, in line with other choices made in ACL treatment, the choice of graft type has to be individualized, considering patient-specific preferences, to adapt to the living situation of the patient.

Assessment of outcome for research purposes

As previously described, injury to the ACL may lead to instability and in the long term lead to the development of osteoarthritis with associated pain, recurrent swelling and stiffness. Various methods have been developed to assess the subjective impairment and functional deficits the aforementioned symptoms produce. A brief review of methods relevant to the current thesis will be provided.

Patient-reported outcome

THE KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE

One frequently used patient-reported outcome is the Knee injury and Osteoarthritis Outcome Score (KOOS).[215] The KOOS consists of five individual subscales involving assessment of pain, other symptoms, function in daily living, knee-related quality of life and function in sport and recreation. The subscales are individually scored from 0 (worst) to 100 (best). The purpose of the KOOS is to evaluate patients' experience of their knees and associated symptoms and can be used both in the short term and in the long term. [54] The test-retest reliability is adequate for the pain, symptoms, quality of life and sports and recreation subscales, but it is regarded as lower for the function in daily living subscale. [54] Subscale-specific values for the minimal important change (MIC) have been determined. [103] The subscales of sports and recreation and knee-related quality of life have been recommended for use after ACL reconstruction, with MIC values of 12.1 and 18.3 respectively. [103]

TEGNER ACTIVITY SCALE

The Tegner activity scale grades the level of activity, taking account of both occupational strain and sports activity. [261] The scale ranges from the least knee-strenuous

activity (0) to the most knee-strenuous activity (10). The Tegner activity scale has been found to have acceptable floor and ceiling effects. Test-retest reliability with an ICC of 0.82 and a minimal detectable change (MDC) of 1 has been reported. [41]

LYSHOLM SCORE

First published in 1982, the Lysholm score is a widely used patient-reported outcome measurement aiming to assess the patient's opinion of functional signs of instability. [154] With the updated Lysholm score, published in 1985, the following parameters were assessed: limp, support, locking, instability, pain, swelling, stair-climbing and squatting. [261] The total score ranges from 0 (worst) to 100 (best). Test-retest reliability with an ICC of 0.94 and an MDC of 8.9 has been reported. [41] The overall Lysholm score has acceptable floor and ceiling effects and acceptable internal consistency. [41]

INTERNATIONAL KNEE DOCUMENTATION COMMITTEE SUBJECTIVE KNEE FORM

The International Knee Documentation Committee Subjective Knee Form (IKDC-SKF) was first presented in 2001 and has since been used frequently in the assessment of traumatic knee injuries. [104] The questionnaire comprises a total of 18 symptoms assessing knee pain and function and is scored from 0 (worst) to 100 (best). An MDC of 12.8 has been reported for the IKDC-SKF. [105] Moreover, an MIC of 11.5 has been suggested, with a sensitivity of 0.82 and a specificity of 0.64. [105] Apart from the continuous analysis of the IKDC-SKF, it can also be analyzed in relation to the Patient Acceptable Symptom State (PASS). [174] A positive answer to the following question is interpreted as the achievement of PASS: "Taking account of all the activity you have during your daily life, your level of pain and also your activity limitations and participation restrictions, do you consider the current state of your knee satisfactory?". An IKDC-SKF score of above 75.9 has been proposed as the achievement of PASS, with a sensitivity and specificity of 0.83 and 0.96 respectively. [174]

FUNCTIONAL TESTS

Functional tests comprise tests of both strength and coordination. One important measurement is the LSI, previously described, where the results for the injured limb are related to the results for the uninjured (healthy) limb.

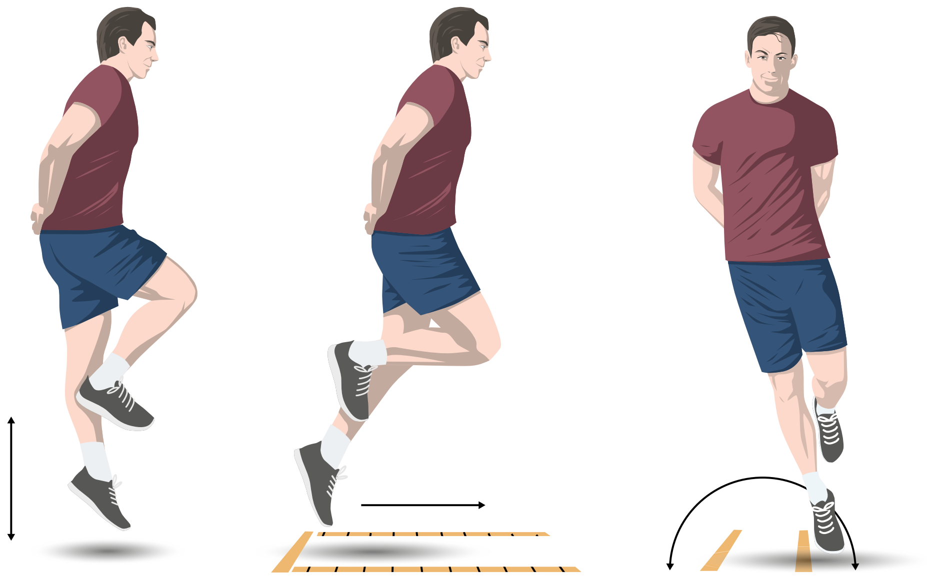

Figure 10 Illustrations of three hop performance tests used in the assessment of rehabilitation progression after an anterior cruciate ligament injury. From left to right: vertical-hop test, single-legged hop test for distance and the side-hop test.

HOP TESTS

There are three hop tests which are of specific importance to the current thesis: the vertical hop, the single-legged hop for distance and the side-hop test (Figure 10). To perform the vertical-hop test, the patient stands on one leg with his/her hands on his/her back, and is then asked to jump as high as possible. The vertical height is calculated using the air time. In the current thesis, the Muscle Lab (Ergotest Technology, Oslo, Norway) was used. Acceptable reliability with an ICC between 0.74-0.98 has been reported. [142]

To perform the single-legged hop test for distance, the patient starts on one leg with his/her hands on his/her back. The patient is instructed to jump as far as possible. Acceptable reliability with an ICC of 0.94-0.95 has been reported. [85]

To perform the side-hop test, the patient stands on one leg with his/her hands on his/her back. The patient is instructed to jump as many times as possible, between two lines set 40 cm apart, during a total test time of 30 seconds. An ICC of 0.87-0.95 has been reported for the side-hop test. [85]

MUSCLE STRENGTH

Assessment of muscular strength is an important part of ACL rehabilitation. More specifically, isokinetic dynamometry is often used in assessments after ACL injury due to the reliability and reproducibility of the method. [271] In the current thesis, concentric knee extension and flexion strength was tested during three repetitions at an angular velocity of 90°/second, at a predefined range of motion of 0-90°, measuring peak torque using a Biodex System 4 (Biodex Medical Systems, Shirley, New York, USA).

RADIOLOGY

The use of radiology in postoperative assessments of ACL injuries aims to quantify the development of post-traumatic osteoarthritis. One of the most frequently used methods is the Kellgren-Lawrence classification. The Kellgren-Lawrence classifies OA on a scale from 0 (best) to 4 (worst), assessing joint space narrowing, osteophytes, sclerosis and bony deformity.[117] Interobserver reliability of 0.51-0.89 has been reported in previous studies. [287] The sum of knee OA classified using the Kellgren-Lawrence classification has been assessed in terms of correlations with arthroscopic findings of OA (anteroposterior projection reliability: 0.30, Rosenberg projection reliability: 0.42). [287]

The Fairbank classification system evaluates patellofemoral OA and the development of osteophytes. [67] The reliability has been reported to range between 0.36-0.44, depending on the radiographic projection used. [287] The summarized OA using the Fairbank classification has been correlated with arthroscopic findings of OA (anteroposterior projection reliability: 0.32, Rosenberg projection reliability: 0.36).

Generalized joint hypermobility

Definition and diagnosis

DEFINITION OF JOINT HYPERMOBILITY AND JOINT HYPERMOBILITY SYNDROMES

Joint hypermobility (JH) is defined merely by hyperextensibility of the synovial joints, with the ability to extend, passively and/or actively, beyond the normal physiologic range of motion. Joint hypermobility may be present in isolation, in combination with symptoms or as a feature of a clearly defined syndrome, such as hereditary connective tissue disorders (HCTD) (Figure 11). Common synonyms of JH include joint laxity and joint hyperlaxity. The assessment of JH comprises the examination of subjects using specific measurement devices or techniques, such as a goniometer.[46]

Joint hypermobility can be divided into two principal groups, localized joint hypermobility (LJH) and GJH. If JH is present in only few joints, normally fewer than five, it can be defined as LJH. Localized joint hypermobility may affect large or small joints and may be bilateral; knee hyperextension or genu recurvatum is a typical example. It may be either congenital or acquired. Possible reasons for acquired LJH include previous trauma or surgery, joint disease or training. [46] If JH is more widely distributed, usually in five or more joints, this is indicative of GJH. The congenital form of GJH is more common, although it may be acquired due to conditions such as degenerative joint disease, hypothyroidism or other endocrine disorders. [46] Several different methods are used to define GJH, although the most common is probably the Beighton score. [114]

The nosology of conditions with hypermobility is complex for the uninitiated. Historically, asymptomatic, non-syndromic individuals with hypermobility were merely mentioned as individuals with GJH. Previously, patients who did not have a more severe HCTD but were symptomatic were often diagnosed with either joint hypermobility syndrome (JHS) or Ehlers-Danlos, hypermobility type (EDS-HT), assuming they fulfilled the respective criteria. The terms of these two "benign" hypermobility conditions originated from different groups, JHS defined by the Brighton criteria[80] and EDS-HT defined using the Villefranche criteria[31], but they are currently often regarded as interchangeable due to their phenotypic similarities. [96, 205] Several earlier studies have utilized these criteria to define hypermobility, making them continuously relevant, although, since the latest consensus meeting of the International Consortium of the Ehlers-Danlos Syndromes (ICEDS) held in

2017, these terms are obsolete in terms of the future classification of conditions with hypermobility. Instead, several of the patients with previous JHS or EDS-HT diagnoses will be tested against the criteria for the newly presented hypermobile Ehlers-Danlos (hEDS). [158] If these stricter criteria are not fulfilled in hypermobile, symptomatic patients, the exclusion diagnosis *hypermobility spectrum disorders* will apply (Figure 11). [46]

Figure 11 Illustrating the relationship between conditions associated with joint hypermobility. The first group of individuals have joint hypermobliity but are asymptomatic and do not fulfill the criteria for any syndrome associated with hypermobility. The second group, entitled "well-defined syndromic hypermobility", comprises individuals with a specific diagnosis of a hypermobility syndrome, including patients with hereditary connective tissue disorders, such as Ehlers-Danlos spectrum disorders, Marfan syndrome, Loeys-Dietz syndrome and osteogeneis imperfecta, but also individuals with the more benign hypermobile Ehlers-Danlos. The third group consists of patients with hypermobility and symptoms, such as musculosceletal pain or neurodevelopmental manifestations, but who do not fulfill the criteria for a specific syndrome. This third group, entitled "hypermobility spectrum disorders", is intended as a descriptive and exclusion diagnosis.

METHODS FOR DIAGNOSING GENERALIZED JOINT HYPERMOBILITY

Beighton score

Background

The Beighton score is a common, versatile method used to define GJH. The most frequently used method, using a nine-point scale, is an elaboration based on previous work. [33] Originally, Carter and Wilkinson [45] published a method used to evaluate joint hypermobility in 1964. This method was modified by Beighton and Horan in 1969, presenting a five-point scale using the average extension of a bilateral test to define hypermobility in each individual joint. [32] Finally, in a study investigating the articular mobility of a population of 1,081 inhabitants of the Tswana village, situated about 60 miles north-west of Johannesburg, South Africa, the nine-point Beighton score was presented (Figure 12). In that study, published in 1973 by Beighton, Solomon and Soskolne, the authors presented the method that is most frequently used and that is also currently used to define GJH in the diagnosis of Ehlers-Danlos spectrum disorders [158].

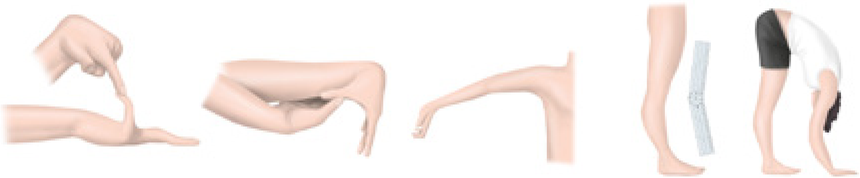

Figure 12 Picture illustrating the tests included in the Beighton score. Four joints are examined bilaterally using a goniometer; with the patient's palm and forearm resting on a flat surface with the elbow flexed at 90°, if the fifth metacarpophalangeal joint can be hyperextended above 90°, one point is awarded (1). With the patient's arm stretched forward and with the hand pronated, if the thumb can be passively moved to touch the ipsilateral forearm, one point is awarded (2). With the patient's arm stretched to the side, with the hand supine, if the elbow hyperextends more than 10°, one point is awarded (3). With the patient standing, if the knee hyperextend more than 10°, one point is awarded (4). Last, with the patient's knees kept straight and with the feet together, if the patient can bend forward to place the whole palm of both hands flat on the floor in front of the feet, one point is awarded. The total Beighton score scale ranges from 0 to 9 points.

Reliability and validity

The reliability and validity of the Beighton score has been the subject of investigation. [113, 114] A recent systematic review summarized the evidence in this regard. [114] The validity of the Beighton score, compared with other evaluation methods, demonstrated limited positive or conflicting evidence, based on three original studies. The validity of the Beighton score in relation to range of motion, association with pain, association with injuries and association with different diseases was also reviewed with different levels of conflicting evidence. It was concluded that, based on the reliability and validity synthesis, the use of the Beighton score was acceptable. [114] However, the procedure of the Beighton score evaluation has to be standardized in order to mitigate variability. It has been recommended that the photos in the study, published in 1973 by Beighton et al., should be used to standardize the testing procedure for clinical use. [33, 113, 114]

Cut-off value

Different cut-off values have been proposed and utilized in the literature. Two influential cut-off values can be derived from two formerly used hypermobility conditions; JHS, diagnosed using the Brighton criteria, and EDS-HT, using the Villefranche criteria. For adults, according to Brighton criteria, a cut-off of 4 of 9 [80] was used to define hypermobility, while a cut-off of 5 of 9 was implemented in the Villefranche criteria. [31]

In the latest consensus meeting, held by the ICEDS, individualized cut-off values were implemented to define GJH in patients with a suspected hEDS diagnosis (Table 1). In patients with an acquired impairment to joint hypermobility, caused by past injury or surgery, affecting the total Beighton score, it is suggested that historical information should be used. This historical information can be obtained using the five-part questionnaire (5PQ)[86]. If the Beighton score is one score below the sex- and age-specific cut-off and the 5PQ is positive (meaning a minimum of two positive items), the diagnosis of GJH can be determined.

In addition, studies assessing GJH in patients with musculoskeletal injuries have previously used an *injury allowance point.* [251] An injury allowance point can be awarded to patients with a positive hypermobility test on one side of a bilateral test, but with previous significant injury to the non-hypermobile joint. Injured joints can therefore be assumed to have been equivalent, in terms of joint extension, to the contralateral healthy joint preinjury. Even though an injury allowance point has been used in the literature, it should be stated that it was not included as a recommended method in the latest 2017 consensus meeting of the ICEDS. [158]

Table 1. Individualized generalized joint hypermobility cut-off

Demographic group	Cut-off
Pre-pubertal children and adolescents	≥ 6
Pubertal men and women up to the age of 50	≥ 5
Men and women over the age of 50	≥ 4

Cut-off values depending on demographic characteristics in the determination of generalized joint hypermobility as part of the hypermobile Ehlers-Danlos syndrome, as proposed by the International Consortium on the Ehlers-Danlos Syndromes. In patients with an acquired impairment to joint hypermobility, historical information using the five-part questionnaire can be used.

OTHER METHODS

Different methods have been used to define GJH. A recent systematic review found six primary clinical assessment methods for the classification of GJH, four clinical assessment methods (Beighton score, Carter and Wilkinson[45], Hospital del Mar[42], Rotes-Querol[217]) and two questionnaire-based methods (5PQ[86] and Beighton score self-reported[186]).[114] According to the systematic review, all the other clinical tests apart from the Beighton score lacked satisfactory data relating to reliability and validity. Questionnaire-based methods offer an opportunity to enable larger, more cost-effective epidemiological studies. However, the current evidence states that, in terms of the reliability and validity of the 5PQ, there is conflicting or limited supporting evidence. In terms of the self-reported Beighton score, there was unknown evidence in terms of validity, [114] although it has been found to be reliable in patients with femoro-acetabular impingement. [186]

Epidemiology

Epidemiological research has revealed a considerable variation in in prevalence of GJH between studies. Important aspects affecting the magnitude of GJH involve differences in age, sex and race, factors that are known to affect the degree of hypermobility. [207, 268] Joint range is known to decrease with age [249] and Beighton score has been reported to have an inverse relationship with age. [206] However, the variations in assessment methods and definitions of GJH also affect the results. [206, 207] A previous review reported a prevalence of 2-57% of GJH in different populations. [207] Studies have shown that both Arabic[8] (males/females %: 25/39) and African populations (males/females %: 35/57) have a high prevalence of GJH. Moreover, both adults and children of Chinese origin have an increased prevalence of GJH when compared with Caucasians. A recent large study reported a prevalence of 13% of self-reported GJH in a general Danish population. [110]

Hypermobility appears to be more frequent in certain occupational groups. For example, a recent study showed that 72% of ballet dancers had GJH. [48] Moreover, previous studies have verified an increased prevalence of hypermobility in ballet dancers. [162] In part, this may be due to acquired hypermobility, supported by the fact that the accomplishment of the palm-to-floor test correlates with the duration of an active career as a ballet dancer. [132] However, joints not subjected to stretching have also demonstrated increased hypermobility in ballet dancers, indicating increased hypermobility to be due, at least in part, to genetic predisposition. [162] It has been suggested that hypermobility offers an advantage within certain occupations causing, through natural selection, individuals with

hypermobility to exceed their peers, thereby causing an increased prevalence of GJH in these groups. [79]

Morbidity

As previously discussed, GJH is only a descriptive term for increased synovial joint extension over what is considered normal for that particular individual. GJH can thus be present, and is often mandatory, in several connective tissue disorders. Not surprisingly, patients with GJH and established syndromic diagnoses can experience different symptoms, including hypertrophic scarring, hernias, vaginal/rectal prolapse, and cardio-valvular problems, since it is part of the diagnostic criteria for some of the conditions. [158] However, GJH has also been associated with a number of different symptoms in the absence of more severe connective tissue disorders. A recent study of the general Danish population reported that individuals with self-reported GJH had twice the odds of having knee joint symptoms, such as pain, compared with controls. [110] Approximately one third of individuals with self-reported GJH declared that knee joint symptoms prevented them from performing their usual activities at home and/or outside the home. Moreover, several studies have found associations between GJH and the development of OA, although the results appear to be inconclusive at present. [57, 61, 70, 235] However, it has been suggested that a cross-sectional investigation of both OA and GJH at older age may be difficult to interpret, as hypermobility might be a marker of fitness, associated with less OA.[61]

Rehabilitation

Rehabilitation plays an important role in the management of patients with GJH. [66] The prevalence of hEDS/JHS in adults with musculoskeletal complaints in outpatient clinics has been reported to vary between 30-55%. [66] Pain found in multiple locations is common in patients with hEDS/JHS and there are indications that the neuropathic pain component may be overrepresented. [213] Hyperalgesia, possibly caused by a sensitized central nervous system, has been associated with hEDS/JHS, which underlines the importance of adapted and gradually increased physical therapy. [211] The basis of evidence for rehabilitative management is limited, as recently concluded in a best-evidence review assessing physical therapy treatment in patients with hEDS/JHS. [66] Especially in adults, high-quality evidence is lacking, with the publication of only one RCT assessing different rehabilitation regimens. This randomized, controlled study found reduced knee pain and increased proprioception in patients receiving training involving balance, plyometrics and proprioception, compared with a control group with no treatment or intervention. [222]

Based mainly on clinical experience, physical therapists use strategies such as education, reassurance, hydrotherapy and relaxation training, although higher quality evidence for these treatments is lacking. It has been suggested that treatment, in patients with hEDS/JHS, should be individualized to reduce the risk of increased musculoskeletal pain and avoid central sensitization. [66, 212] A careful and gradual increase in rehabilitation intensity has been recommended to reduce the risk of injury and overtraining, since this could lower confidence in the physical therapist and in the patient. Moreover, in higher levels of physical activity and sports, a gradual return to activity has been recommended and the training load should be monitored to ensure a safe recovery. [66]

Neuromuscular function

The neuromuscular function of individuals with GJH differs from that in individuals without GJH. The rate of torque development in isometric knee flexion is higher in girls with GJH than in their non-hypermobile counterparts. [107] Further, the knee extensor rate of force has been found to be higher in adults with GJH. [163] As described by Jensen et al., the rate of force and torque is an important factor when jumping [279] and it has been demonstrated that children with GJH are superior at performing vertical counter-movement jumps. [112] The rate of torque development is regarded as an important factor for joint stabilization,[49] which is in turn regarded as particularly important for individuals with GJH, since the increase in joint laxity may cause the perception of joint instability. It has therefore been suggested that the increased rate of force development seen in individuals with GJH is due to the neuromuscular compensation of joint hypermobility, not as a direct cause of GJH. [107] However, the hamstring-to-quadriceps strength ratio, a factor that has been associated with ACL injury, is lower in adults with GJH. [112] Moreover, children with GJH have less semitendinosus activity, both before and after landing, compared with children without GJH. [111] The alterations in neuromuscular recruitment and function may be partly due to the inferior proprioceptive capabilities found in individuals with GJH. [243] More imprecise feedback by the proprioceptive sensors may in turn lead to a more imprecise reactionary movement of the limbs.

Generalized joint hypermobility and the ACL

Studies have assessed the influence of GJH on ACL injury risk and postoperative outcome during the last few decades. [5] Several systematic reviews have been conducted with the aim of reviewing risk factors for ACL injury, in which generalized joint hypermobility has been included in a few of the reviews. [9, 58, 195, 197] However, GJH has been treated as one factor among others, which explains why important

publications assessing GJH in the context of ACL injury risk have been missed in previous reviews.

RISK FACTOR FOR INJURY AND REVISION SURGERY

A systematic review concluded that GJH was a significant risk factor for knee joint injury, in general. [195] Several studies report an association between GJH and ACL injury risk specifically. [7, 203, 270] On the other hand, there are also studies reporting no association between GJH and ACL injury risk[255] and one study even reported that less hypermobility was associated with ACL injury risk.[239] This leads to an uncertain foundation of evidence, since an updated and comprehensive systematic review is missing.

ASSOCIATION WITH KNEE LAXITY

The significance of knee laxity in the diagnosis and morbidity of the ACL-injured patient has been previously reviewed in the introduction to the current thesis. With the aim of finding factors that predict or are associated with pre- and postoperative knee laxity, the influence of GJH has been evaluated. In one study, comprising 2,318 patients, the authors found that GJH was associated with a high-grade Lachman test, a high-grade anterior drawer test and a high-grade pivot-shift test. However, the authors used an uncommon and unspecific method for the determination of GJH. [156]

EFFECT ON POSTOPERATIVE OUTCOME

Few studies have assessed the influence of GJH on postoperative outcome in patients undergoing ACL reconstruction. There are studies indicating that GJH is associated with increased postoperative intermediate-term knee laxity and inferior patient-reported outcomes (including the Lysholm score, IKDC and Cincinnati knee rating system scores) in patients with an ACL injury. [122, 124, 140] However, only a few studies have been published, which explains why additional studies, including patients with other demographic backgrounds, are warranted. [121, 122, 126]

Knee hyperextension

DEFINITION AND DIAGNOSIS

Knee hyperextension is not a universally predefined term with a distinct cut-off value. In contrast to GJH, where the ICEDS has structured the definition of the GJH concept, knee hyperextension (KHE) has not been clearly defined. Knee hyperextension is generally examined using a goniometer, although other methods, such as measurements of heel height,[140] have also been used (Figure 13) . In the literature, various cut-off values have been used to define KHE; knee extension beyond neutral, [184, 227, 254] equal to or beyond five degrees,[56] equal to 10 degrees and beyond[5, 169] or beyond 10 degrees. [33, 128, 272] Moreover, self-reported KHE has been evaluated, using the following question: "Can you hyperextend one or both your knees?". Individuals who answered yes to the question above were said to have selfreported KHE. [110]

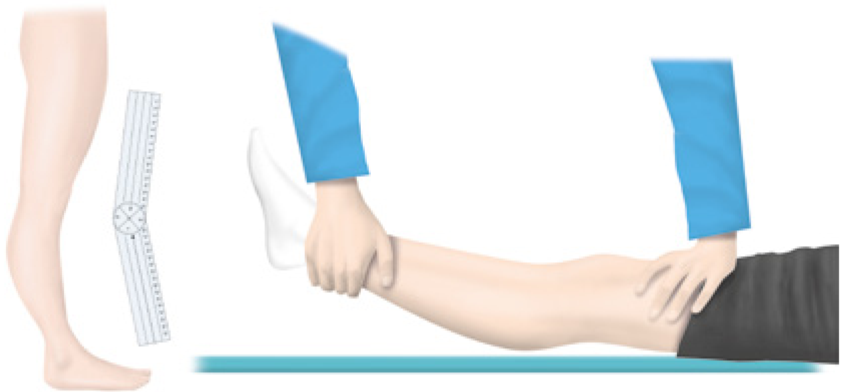

Figure 13 Illustrations of measurements of knee hyperextension. Left: knee hyperextension is measured with the patient standing, using a goniometer to quantify hyperextension. Right: heel height is measured with the patient supine on the examination table. Using passive hyperextension, the heel height is measured from the table to the heel.

EPIDEMIOLOGY

There is a lack of studies assessing the prevalence of KHE in the general population. However, a Danish population-based epidemiological study, comprising 1,006 randomly selected adults, reported that 23% had self-reported KHE. The prevalence of KHE was higher in females. [110] In a study of 1,145 ACL-injured patients, the prevalence of individuals with KHE was 374 (33%), but this population does not necessarily reflect the prevalence in the general population, since this was a subset of patients with an ACL injury. [56]

KNEE HYPEREXTENSION AND THE ACL

Risk factor for ACL injury and graft failure

There is evidence showing that KHE is associated with primary ACL injury. Myer et al. found that a positive measurement of KHE increased the odds of ACL-injured status fivefold (95% CI 1.2-18.4).[184] Moreover, there is further supporting evidence

showing that KHE is associated with the risk of ACL injury, [140, 227, 272] although one of the studies did not confirm that KHE was a risk factor for ACL injury in males, only in females. [272]

In terms of the association between KHE and graft tear, the evidence is conflicting. In a prospective study, comprising 1,145 patients, preoperative symmetrical KHE (≥5°) increased the risk of ACL graft failure (OR 2.1, 95% CI 1.1-4.7, p=0.03).[56] On the other hand, a study published by Benner et al., comprising 553 patients, found different results. Benner et al. assessed KHE of the ACL-injured knee and were unable to find an association between knee hyperextension and the risk of subsequent graft rupture.[34] Larson et al. published a study showing a significant association between graft failure and heel height (Figure 13), but they did not find any association with classical goniometer-mediated KHE. [140]

Association with knee laxity

In terms of anteroposterior laxity, a previously mentioned study by Benner et al. found no association between ATT and KHE in the ACL-injured knee. [34] However, another study found a significant association between KHE and ATT, assessed using the KT-2000. [128] Rotatory knee laxity and its association with KHE has also been evaluated. A recent study, published in 2019, assessing 54 ACL-injured patients, found that knee hyperextension was associated with QPS, quantified using the KiRA device. The mean (±SD) degree of passive knee extension was 2.3 ± 4.5 in the QPS-negative group, compared with 6.8 ± 6.6 in the QPS-positive group. [223] However, using RSA, functional knee laxity and ATT have been evaluated during walking and running and they were not found to be associated with KHE. [187]

Effect on postoperative outcome

In one clinical study, comprising 368 patients undergoing ACL reconstruction, preoperative KHE was predictive of postoperative pivot shift at the one-year follow-up. [269] Another study reported that KHE was correlated with inferior postoperative patient-reported outcome measurements, including the Lysholm score and the IKDC score. [128] Last, using a knee scoring system evaluating knee laxity, functional and patient-reported outcome, Aglietti et al. found inferior results for ACL injured individuals with contralateral KHE. [5]

Rationale for this thesis

The rationale for this thesis is to extend our understanding of two main concepts, specific knee laxity and GJH. The thesis aims to investigate how these concepts affect the ACL-injured individual and how they are related to each other. In terms of the influence of GJH on ACL injury risk and postoperative outcome, several studies have been published, but the knowledge is dispersed and a few studies appear to have been forgotten and are seldom cited in studies assessing GJH. In the literature, GJH is frequently regarded as a risk factor for ACL injury. However, there is uncertainty about what the aggregated evidence indicates, whether GJH affects males and females differently, how it affects graft rupture risk and post-ACL reconstruction outcome. Thus, to create a foundation for research, a systematic review was conducted as Study I. To contribute to the limited evidence investigating the influence of GJH on postoperative outcome, Study II was conducted. Study II utilizes a rehabilitation outcome register to assess patients with ACL injury and subsequent ACL reconstruction. This study provides unique data in terms of postoperative strength and functional performance that have previously not been evaluated in ACL-injured patients, with regard to GJH. This enables a comparison of postoperative rehabilitation development in patients with and without GJH, important information that could be used to produce adapted rehabilitation programs for individuals with GJH. Study III bridges the two concepts in the current thesis, investigating a potential relationship between instrumented rotatory knee laxity and GJH in ACL-injured individuals. Since GJH and knee laxity are thought to affect both ACL injury risk and postoperative outcome individually, an investigation of the relationship between the two could produce interesting novel information. On the same inter-conceptual notion, Study IV aims to evaluate whether knee hyperextension in the contralateral knee is related to increased knee laxity in the ACL-injured knee. Finally, Study V mainly focuses on specific knee laxity and how it affects long-term functional and patient-reported outcome and the development of OA. As described in the introduction, there is large-scale focus on the quantification of knee laxity in the scientific community. Novel surgical techniques and procedures, including the use of DB ACL reconstruction and LET, are driven by the aim to reduce knee laxity, although there are no previous studies reporting how knee laxity affects patient outcome in the long term.

2 Aims

Generalized Joint Hypermobility and Specific Knee Laxity

Aspects of Influence on the Anterior Cruciate Ligament-injured Knee

DAVID SUNDEMO

The overall aim of the thesis is to determine how specific knee laxity and GJH affect the ACL-injured individual and how knee laxity and GJH are related to each other.

Specific aims

Study I The primary aim was to investigate the influence of GJH on ACL injury risk using a qualitative synthesis of the studies identified in the systematic review. The secondary purpose was to investigate the influence of GJH on postoperative outcome (including graft-failure risk, knee laxity and patient-reported outcome) and to compare the performance of different graft types in patients with GJH.

Study II The primary aim of this study, using a rehabilitation register, was to determine whether GJH influences postoperative results on the sports and recreation subscale on the Knee injury and Osteoarthritis Outcome Score (KOOS). The secondary aim was to assess additional postoperative parameters including return to sport, patient-reported outcome, hop tests and muscular strength.

Study III The aim of this international multicenter study was to determine whether ACL-injured knees and healthy contralateral knees demonstrate a higher degree of quantitative rotatory knee laxity, depending on the level of GJH.

Study IV The primary aim of this study, using a clinical research register, was to determine the association between hyperextension of the contralateral healthy knee and increased ATT in the ACL-injured knee. The secondary aim of the study was to investigate the potential relationship between contralateral knee hyperextension and concomitant cartilage and meniscal injuries lägg till: in the ACL-injured knee.

Study V The aim of this study was to investigate whether increased knee laxity at two years after ACL reconstruction, measured using the Lachman test, the anterior drawer test, the pivot-shift test and the KT-1000, is associated with an inferior clinical outcome and an increase in the development of OA in the long term.

3 Methods

Generalized Joint Hypermobility and Specific Knee Laxity

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Clinical study design

The selection of the type of clinical study design is an important part of gathering evidence for an hypothesis. The type of clinical study design describes how trials and experiments are performed. The design of a clinical study is tailored to suit the purpose of the scientific question; it may be observational, epidemiological, diagnostic or therapeutic. The clinical study design affects, and is affected by, the umbrella term "evidence-based medicine (EBM)". In short, EBM is a scientific approach designed to improve medical decision-making by using high-quality evidence from well-designed, well-executed research. To grade the quality of evidence, several hierarchical structures of level of evidence have therefore been presented. One of the most frequently used is the Oxford Centre for Evidence-Based Medicine, found at the website www.cebm.net. It is a complex structure, with different study designs overlapping several levels of evidence, where the conduct of the study, including the assessment of risk of bias, also affects the ultimate evidence level. Generally, the randomization of participants in therapeutic studies, the blinding of participants and examiners in all relevant studies and a prospective study design are related to a higher level of evidence.

Systematic reviews

A systematic review is conducted to summarize and weigh the currently available evidence related to a specific scientific question. Systematic reviews relate to the highest level of available evidence, but they are ultimately defined by the underlying evidence they include in the synthesis of the data. [165] A straight qualitative synthesis can be performed, or it can be combined with a quantitative meta-analysis if the underlying evidence is deemed adequate for that type of analysis. [165] To ensure methodological stringency, several journals require a systematic review to be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [165] The transparency of the methodology used in the conduct of the review is important, to ensure that a replication of the study can be performed. A predefined scientific question is posed and clear inclusion and exclusion criteria are stated prior to a literature search. [165] Then, a systematic, replicable literature search is conducted involving one or several databases. The screening of studies is often performed by two different researchers, to reduce the risk of missing relevant studies. Ultimately, the included studies are synthesized by the authors and, if applicable, a quantitative meta-analysis can be conducted. [24]

Cohort studies

A cohort study is a type of longitudinal observational study that follows participants with a common characteristic (for example, ACL injury) from a defined baseline. [290] It can be used for epidemiological research, to investigate the impact of suspected risk factors on an outcome. Cohort studies can be either prospective, where the study question is posed prior to the gathering of data, or retrospective, where already existing information in registers or databases is extracted for research purposes. [290] Data are collected at baseline and participants are subsequently reevaluated on several occasions, where the dispersion of outcomes is investigated. The disadvantage of the non-randomized study design in cohort studies is that it is impossible to control for unknown confounders, although known confounders, supposing that these variables are available for analysis, can be considered post-hoc using certain statistical methods. [198]

Register studies

A register study is a certain type of cohort study, often with access to large amounts of data. Population-based, nationwide registers, available in several disciplines in Sweden, have certain advantages. [2, 108] Nationwide registers with good coverage and completeness have high external validity, meaning that the results of the study are generalizable to the underlying population to which the study aims to extrapolate the results. One disadvantage of register studies is the internal validity. Since register studies often involve several health centers, connected to the day-to-day production of healthcare, there is a higher risk of variation in procedures and assessments of outcome, than in randomized, controlled trials.

PROJECT ACL

Project ACL is used as the information source for Study II. Project ACL was initiated in September 2014. Structurally, the register uses an internet-based platform to obtain patient-reported outcomes and to summon participants to clinical tests, involving tests of GJH, muscular strength and functional performance (hop tests). The patient-reported outcomes that are regularly obtained are the Physical Activity Scale[263], the Tegner Activity Scale[261], the Knee Self Efficacy Scale[264], the KOOS[215], the KOOS-Child[194], the European Quality 5 Dimensions 3 levels[1] and the ACL Return to Sport after Injury Scale[281]. The follow-up program involves assessments at 10 weeks, four months, eight months, 12 months, 18 months and 24 months and

then every year up to five years, followed by every five years after ACL injury or reconstructive surgery. All the participants have access to their test data and can compare their progress with the mean progress of all the participants. This feature, in combination with the user-friendly interface of the database, has generated a compliance of 80-85%.

Study I

Study design

Systematic review with qualitative synthesis

Methods

Study I was conducted as a systematic review and was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[252] All clinical studies, written in English, assessing GJH in relation to ACL injury were considered for inclusion in the review. In terms of study design, review articles, expert opinions, cadaver studies, animal studies and case-report studies were excluded from analysis.

The literature search was performed by an expert medical librarian, first on 6 February 2018, after which an updated search was conducted on 11 January 2019. Three databases were searched (MEDLINE/PubMed, EMBASE and the Cochrane Library). The search string involved two concepts, relating to ACL injury and hypermobility respectively (Table 2).

All the titles, abstracts and full-text articles were independently reviewed by two authors. All the studies selected after the screening of title and abstract were then read in full text for the assessment of eligibility. In the event of disagreement, consensus discussions were held.

A critical review of study quality was conducted using the Methodological Index for Non-Randomized Studies (MINORS).[242] The quality of the included studies was independently graded by two authors. In the event of disagreement, consensus discussions were held. The MINORS assessment involves eight items relating to non-comparative studies and twelve items for comparative studies. Originally, the MINORS assessment was created to assess longitudinal observational studies. However, Study I included several case-control studies, making items 6 and 7 irrelevant, and these items were therefore excluded for studies with a case-control study design. Items are graded on a scale from 0 to 2 points. Consequently, non-comparative, case-control and comparative studies can be awarded a maximum total of 16, 20 and 24 points, respectively. The quality of the results of non-comparative studies can be understood as follows; 0-4, very low quality; 5-8, low quality; 9-12, fair quality and 13-16, high quality. [119] Moreover, for comparative studies, the scores correspond to the following: 0-6, very low quality; 7-12, low quality; 13-18, fair quality and 19-24, high quality. [119] There is no predefined cut-off value for case-control studies using the MINORS score. A qualitative data synthesis was performed, summarizing the aggregated evidence for each respective aim.

Table 2 Search string for Study I

PubMed	
#1	anterior cruciate ligament* OR ACL
#2	"Anterior Cruciate Ligament"[Mesh]
#3	"Anterior Cruciate Ligament Injuries"[Mesh]
#4	#1 OR #2 OR #3
#5	laxity OR hypermobility OR GJH OR GJL OR Beighton OR generalized OR generalised
#6	#4 AND #5
Embase	
#1	'anterior cruciate ligament*':ti,ab,kw OR 'acl':ti,ab,kw
#2	'anterior cruciate ligament'/exp OR 'anterior cruciate ligament injury'/exp
#3	#1 OR #2
#4	'laxity':ti,ab,kw OR 'hypermobility':ti,ab,kw OR 'gjh':ti,ab,kw OR 'gjl':ti,ab,kw OR 'beighton':ti,ab,kw OR 'generalized':ti,ab,kw OR 'generalised':ti,ab,kw
#5	#3 AND #4
Cochrane	
#1	anterior cruciate ligament* or ACL:ti,ab,kw
#2	laxity or hypermobility or GJH or GJL or beighton or generalized or generalised:ti,ab,kw
#3	#1 AND #2

ACL = anterior cruciate ligament, GJH generalized joint hypermobility, GJL generalized joint laxity

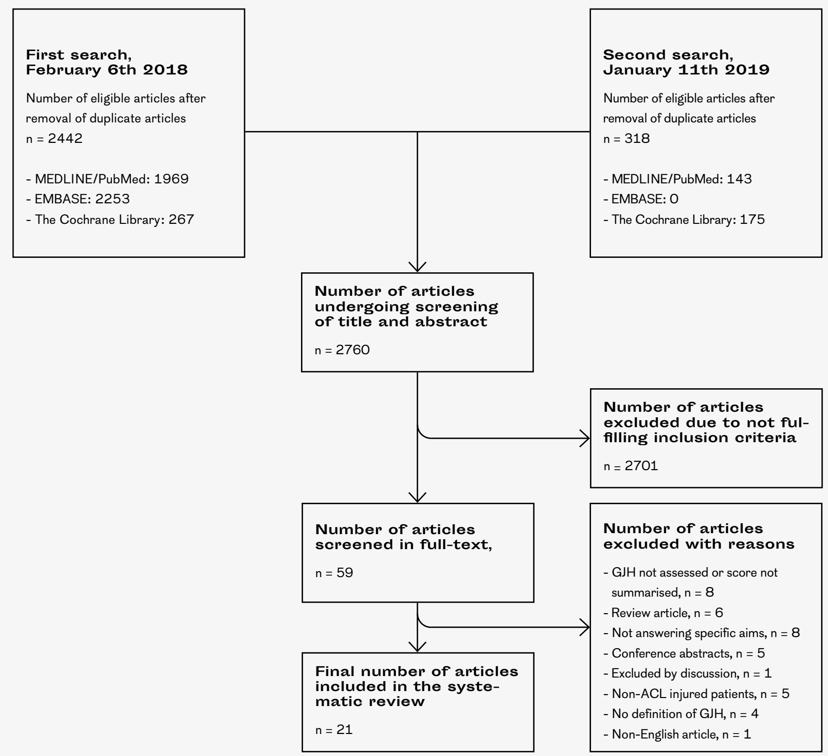

Figure 14 Flow chart of study selection. GJH = generalized joint hypermobility, ACL = anterior cruciate ligament

Outcome

The assessment of the primary aim, risk of ACL failure, was reported according to the definition of failure utilized in each respective study. Postoperative outcomes (including graft failure, knee laxity, patient-reported outcome and osteoarthritis) were not pre-specified in detail to ensure inclusion of all the possible data currently available.

Study II

Study design

Prospective register-based cohort study

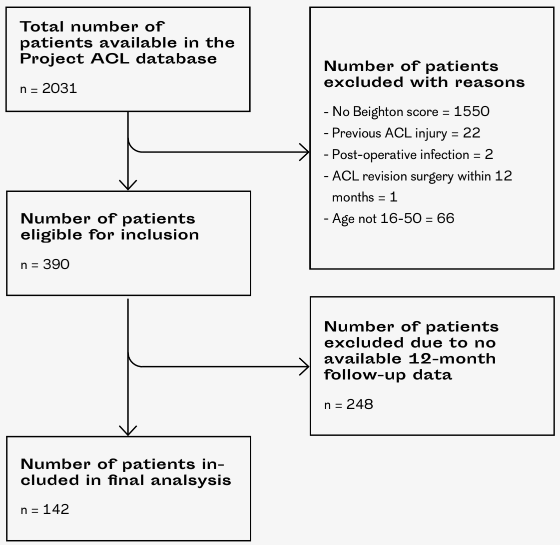

Figure 15 Flow chart of patients. ACL = anterior cruciate ligament

Patients and methods

In Study II, patients that were recruited to a prospective rehabilitation registry, Project ACL, were included (Figure 15). Eligibility criteria included: age 16-50 years, primary ACL reconstruction and available one-year follow-up data. Patients who did not have available data evaluating GJH were excluded. Written information was distributed to all patients and written informed consent was obtained. Ethical approval was given by the Regional Ethical Review Board (registration nos. 265-13, T023-17).

As previously described, Project ACL is comprised of two parts, a web-based platform used to obtain patient-reported outcome variables and a clinical part comprising tests that evaluate muscular strength and hop tests. The clinical tests and assessments of GJH were evaluated by physical therapists. The evaluation of GJH, using the Beighton score, started in January 2019. In order to improve inter- and intra-rater reliability, all the physical therapists were trained in how to perform the Beighton score evaluation. An injury allowance point was used to assess probable preinjury hypermobility of the injured knee. The cut-off for the definition of GJH was used in accordance with the 2017 ICEDS consensus meeting. As the patients were aged between 16-50, a cut-off of ≥ 5 was used.

Table 3. Tests of muscle function

	Degrees of movement	Practice trials	Test trials	Rest between repetitions, s	Units
Knee extension	90-0°	10 (50%) 10 (75%) 2 (90%)	3-4	40	Newton/meter
Knee flexion	0-90°	10 (50%) 10 (75%) 2 (90%)	3-4	40	Newton/meter
Vertical-hop test		2	3	20	Centimeters
Single-legged hop for distance		2	3-5	20	Centimeters
Side-hop test			30 seconds per side	180	Number of hops

S = seconds, % represents the percentage of maximum force during the particular practice trial

Outcome

The sports and recreation subscale of the KOOS was used as the primary outcome. Secondary outcomes included the following: $KOOS_4$, the other KOOS subscales and the Tegner Activity Scale. [261] Moreover, knee extension and flexion strength and hop tests were regarded as secondary outcomes. The hop tests comprised the vertical-hop test, the single-legged hop test for distance and the side-hop test (Table 3). [85, 189] The LSI, dividing the results for the injured limb by the results for the contralateral limb, was used to evaluate the rehabilitation progression of both strength and hop tests. As stated in the introduction, an LSI above 90% was considered acceptable. [29, 265]

Statistical methods

Descriptive statistics of the baseline parameters were reported using the number and percentage for categorical variables. The mean, standard deviation, median and range were presented for continuous variables. For ordered categorical variables, the median and range were used. Between-group comparisons were analyzed using the following methods: Fisher's exact test (dichotomous variables), the Mantel-Haenszel chi-square test (ordered categorical variables), the chi-square exact test (non-ordered categorical variables) and Fisher's non-parametric permutation test (continuous variables). Moreover, Fisher's non-parametric permutation test was used for continuous variables at the one-year follow-up. In addition, univariable and adjusted linear regression analysis were executed for all outcomes. The analysis is presented using beta values, 95% confidence intervals, p-values and R-square numbers. The factors of sex, age and type of graft were used in the multivariable, adjusted analysis.

A post-hoc power analysis of the dichotomous analysis of the primary outcome revealed a power of 0.34. The observed difference in the means and standard deviations of the groups in the current study was used in the analysis. Statistical significance was set at $p = 0.05$.

Study III

Study design

Prospective cohort study

Patients and methods

Study III is a publication emanating from a prospective observational international multi-center study designed with the aim of examining patients over a period of 24 months, although the current study only involves an analysis of preoperative parameters. The inclusion criteria were as follows: age 14-50 years of age, scheduled for ACL reconstruction within one year of injury, regular participant in level I (American football, basketball or soccer) or level II (racquet sports, skiing or manual labor occupations) activities. Patients were excluded if they had any of

the following: grade 3 or 4 cartilage lesions in the knee, previous ligament surgery in the involved knee, concomitant PCL injury, inflammatory arthritic condition, other injury to the lower extremities affecting the ability to participate in level I or II activities or previous surgery or injury to the contralateral knee. Orthopedic surgeons, with sports medicine fellowship training, performed all the intraoperative examinations and reconstructions between December 2012 and February 2015. Generalized joint hypermobility was evaluated using the Beighton score and a cut-off value of ≥ 5 was used for the definition of hypermobility. Examinations of knee laxity were executed both with patients awake and when they were under anesthesia. A total of six examiners performed all the pre- and intraoperative tests across all sites. Examiners were not blinded with regard to which knee was being examined. The pivot-shift test was executed using the standardized technique and was quantified both subjectively, according to the IKDC criteria,[89] and using quantitative measurement devices. Moreover, general baseline data in terms of age, sex, sports activity level and patient-reported outcome were obtained.

Ethical approval was granted by institutional review boards at all the respective international centers (reference number: 1008-12) and written, informed consent was obtained from all the patients.

Outcome

The primary outcome was to analyze how GJH correlated to instrumented rotatory knee laxity, or QPS. The QPS was evaluated using two devices, previously described in detail in the introduction; the KiRA accelerometer[150] and the image analysis system. [98] Both devices were used with patients awake and under anesthesia. The QPS was analyzed both in relation to continuous Beighton score and in relation to the dichotomized groups, based on the existence of GJH.

Statistical methods

Descriptive statistics were presented using numbers and percentages for categorical variables. The mean and standard deviations were used for continuous variables. Differences in preoperative parameters between the Beighton score subgroups were made using the Pearson chi-square test or the Mann-Whitney U-test. Outcomes were analyzed using both correlation analysis and subgroup analysis. The Spearman correlation was used to assess correlations between QPS and Beighton score. To illustrate the dispersion of the outcome data from the subgroups, the median and interquartile range were used. The Mann-Whitney U-test was used to analyze the outcome data in relation to the subgroups. In addition, a multivariate regression analysis of the Beighton score subgroups was executed, presenting odds ratios and confidence intervals. Sample size analysis was not conducted for the outcomes in the current study. Statistical significance was set at p = 0.05.

Study IV

Study design

Retrospective cohort study

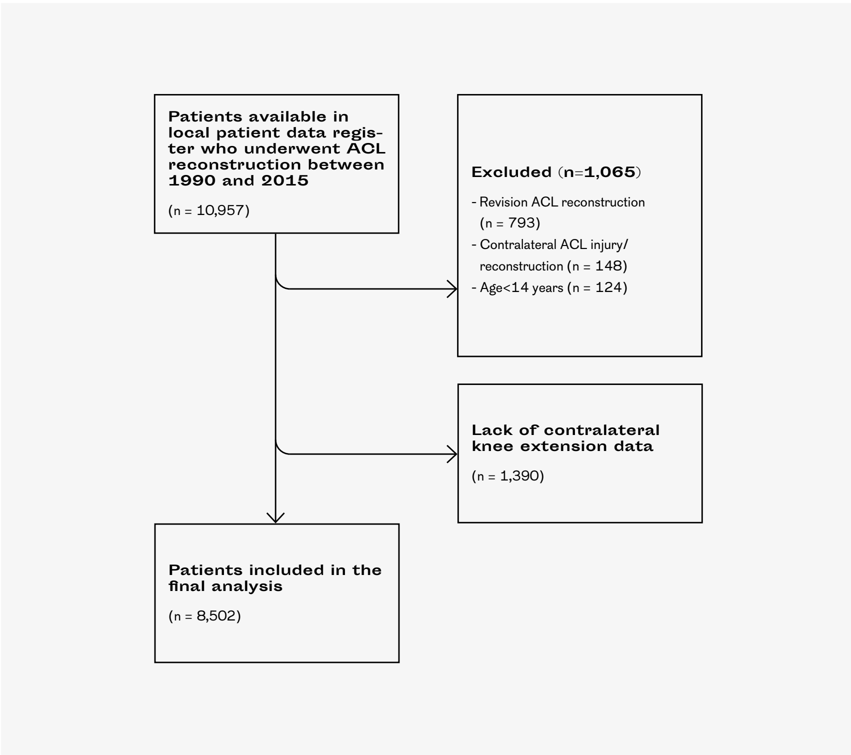

Figure 16 Flow chart of included patients. ACL = anterior cruciate ligament

Patients and methods

Using a register-based retrospective study design, Study IV had available information on a total of 10,957 patients who underwent ACL reconstruction between February 1990 and December 2015 at the Capio Artro Clinic, Stockholm, Sweden (Figure 16). The inclusion criteria were: patient age > 14 and ACL reconstruction using either a PT or an HT autograft. The exclusion criteria were: a previous ipsilateral or contralateral ACL injury. The organization of the clinical research register at the Capio Artro Clinic ensures complete coverage of data relating to previous contra- or ipsilateral surgery, concomitant knee injuries, graft choice, fixation method and other potential simultaneous interventions. The Regional Ethics Committee at Karolinska Institutet approved the study (2016/1613-31/2).

In terms of surgical technique, the central third of the PT was harvested, with two bone blocks, to create PT autografts. The HT grafts comprised a triple or quadruple semitendinosus autograft, accompanied by an additional gracilis tendon if the semitendinosus graft was considered insufficient in size. Meniscal lesions, suitable for suturing, were repaired with either a FAST-FIX suture anchor device (Smith and Nephew, Andover, Mass, USA) or using an outside-in technique with a PDS 0 (Ethicon, Inc, Sommerville, NJ, USA), depending on the location of the lesion.

Rehabilitation was standardized, with all patients following a rehabilitation protocol. The use of full range of motion and immediate full weight-bearing was allowed, in patients with isolated ACL reconstruction or meniscal resection. Closed kinetic exercises were employed for quadriceps strengthening during the first three months postoperatively. Return to sport was individualized, although a return to sport before six months was discouraged.

Physical examinations were performed on two occasions, preoperatively and six months postoperatively. The extent of range of motion was determined using a goniometer. In addition, ATT was evaluated using a KT-1000. At 20 degrees of flexion, an anterior load of 134-N was applied. A minimum of three measurements were made and the median value, in millimeters, was registered. For the purpose of analysis, four subgroups with a gradual increase in contralateral knee hyperextension were created. Groups with no hyperextension (Group A, ≤ 0°), mild (Group B, 1-5°), moderate (Group C, 6-10°) and severe hyperextension (Group D, > 10°) were created. Hyperextension of the contralateral knee was used to determine subgroup placement since it was regarded as a better representative of the preinjury range of motion of the injured knee.

Outcome

All outcomes were analyzed in relation to the subgroups of different degrees of contralateral knee hyperextension. The primary outcome was to evaluate ATT. Specifically, differences in absolute ATT and ATT side-to-side difference, meaning the difference in ATT between the injured and the contralateral knee, were evaluated. Further, by analyzing the changes in pre- to postoperative side-to-side differences in ATT, a comparison between the subgroups in terms of postoperative ATT reduction was conducted. Finally, the difference in concomitant cartilage and meniscus injuries between the groups was analyzed.

Statistical methods

Descriptive statistics of categorical variables were presented with numbers and percentages. Means, standard deviations, medians and range were presented for continuous variables. Analyses of demographic variables were performed using Fisher's exact test and the Mann-Whitney U test for dichotomous and continuous variables respectively. Concomitant meniscal and cartilage injuries were analyzed using multivariate logistic regression analysis, adjusted for age and sex. Correspondingly, in the analysis of KT-1000 data, multivariate logistic regression was used to identify differences between the reference group (Group A) and the other subgroups. The covariates of age, sex, graft choice and meniscal injuries were used in the multivariate analysis of the KT-1000 analysis. Significance was set at $p = 0.05$.

Study V

Study design

Retrospective cohort based on two prospective randomized, controlled trials

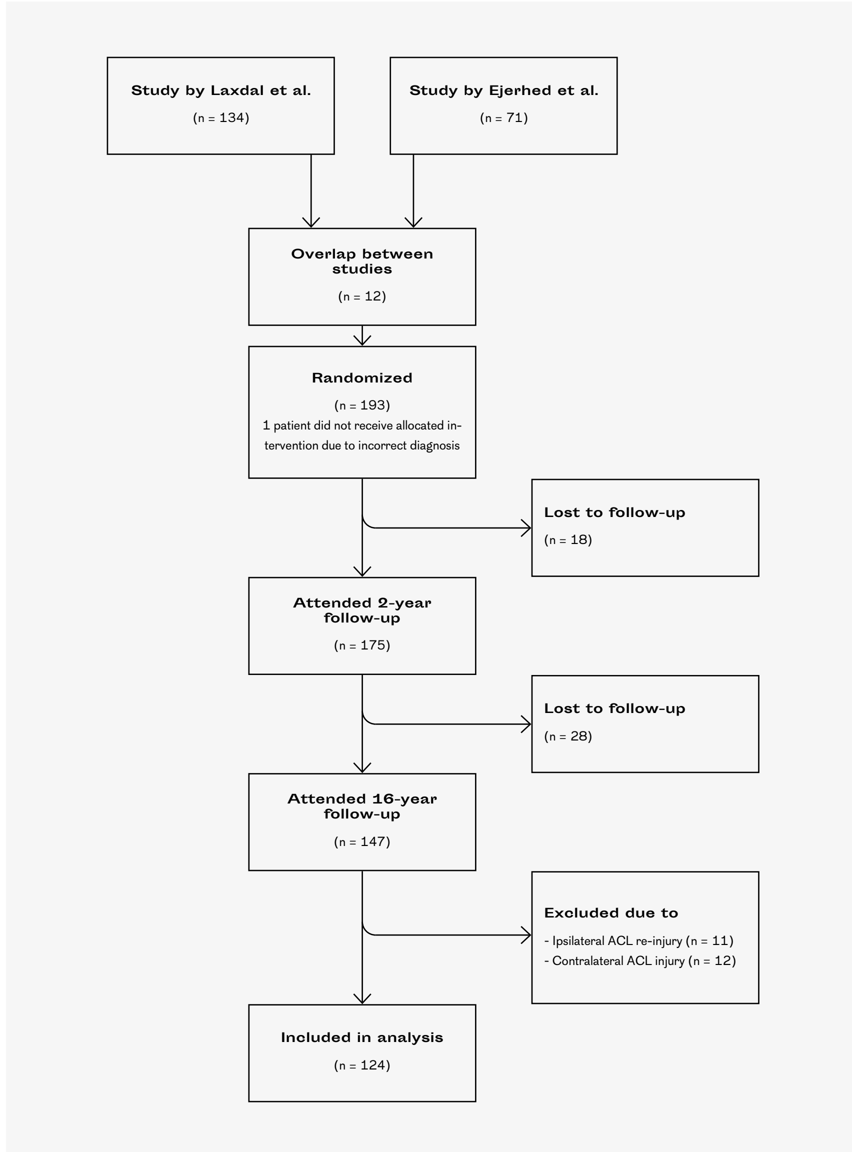

Figure 17 Flow chart of included patients. ACL = anterior cruciate ligament

Patients and methods

Study V is based on two previous prospective, randomized, controlled studies[64, 142] assessing differences between HT and PT autografts. The original studies involved 193 patients, undergoing ACL reconstruction between 1995 and 2000 (Figure 17). The inclusion criteria were: ACL injury and no more than minor chondral lesions (Outerbridge grades 1 to 2). The exclusion criteria were: previous ACL injury, contralateral ACL injury and multiligament injuries. Ethical approval was granted by the Human Ethics Committee at Gothenburg University and Stockholm University and written informed consent was obtained from all patients.

At the time of surgery, anatomic ACL reconstruction was not employed. The transtibial approach was used for all PT reconstruction. To construct the ACL transplant, the central third of the PT was harvested. The femoral tunnel was drilled aiming at the 10:00 to 10:30 o'clock position. The HT reconstructions were performed using either the transtibial or the transportal technique, using a medial portal. Reconstructions using HT grafts used either triple or quadruple semitendinosus autografts, or a combination of semitendinosus and gracilis tendons. Like PT reconstructions, surgeons aimed at the 10:00 to 10:30 o'clock position in reconstructions using HT autografts.

Similar rehabilitation protocols were employed for all patients. Full range of motion and full immediate weight-bearing were allowed. Closed kinetic exercises were started directly postoperatively. After three and six months, running and contact sports respectively were allowed in patients with adequate functional stability, strength, coordination and balance.

Physical examinations were performed preoperatively, two and 16 years postoperatively. Knee laxity at the two-year follow-up was selected as a predictor of long-term outcome, since ligamentization and early graft failure would have occurred during that time. Manual knee laxity was evaluated using the Lachman test, the anterior drawer test and the pivot-shift test. Instrumented ATT was assessed using the KT-1000 arthrometer at 89 N of force. Moreover, radiographic assessment of the knees was performed at the 16-year follow-up. Projections of the frontal sides, the lateral sides and the skyline view of the patellofemoral joint were obtained.

Outcome

Outcomes were assessed at the 16-year follow-up. To assess functional performance, the LSI of the single-legged hop test was evaluated. Patient-reported outcomes

involved the IKDC-SKF, the Tegner activity scale and the Lysholm score. [262] The IKDC-SKF was analyzed both using the continuous scores and by using the PASS. [174] A score above 75.9 has been suggested as the achievement of PASS (sensitivity 0.83, specificity 0.96), which was used in the current study. The Lysholm score was interpreted as follows: (≤64), fair (65-83), good (84-94) and excellent (95-100). [262] Moreover, a classification of OA was made by a senior radiologist, using the Kellgren-Lawrence and the cumulative Fairbank methodology.[147], [67, 117]

Statistical methods

Descriptive statistics are presented using the means and standard deviations for continuous variables. Ordinal data are presented using medians and first and third quartiles. An analysis of dichotomous variables was executed using Fisher's exact test. Ordered categorical variables were analyzed using the Mantel-Haenszel chi-square test. Continuous variables were analyzed using the Mann-Whitney U-test. The manual laxity tests were dichotomized into subgroups with negative (0) or positive (1, 2 or 3) knee laxity. The KT-1000 arthrometer data were analyzed using the Spearman correlation. Statistical significance was set at 0.05.

4 Results

Generalized Joint Hypermobility and Specific Knee Laxity

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Study I

A total of 2,760 studies were found in the initial search and 59 studies were read in full text. Finally, 21 studies contained information relating to the aim of the study and were included in the qualitative synthesis (Figure 14 and Table 4).

The MINORS score means (range) were 9 (9-9), 13 (7-18) and 15 (12-19) for non-comparative studies, case-control studies and comparative studies respectively. The main methodological strengths of the included studies were the reporting of a clearly stated aim (item 1), the inclusion of consecutive patients (item 2), the use of appropriate endpoints (item 4), a follow-up of more than two years (item 6) and the use of adequate and contemporary control groups (items 9 and 10). The methodological weaknesses of the included studies involve the uneven reporting of the timing of data collection; if prospectively or retrospectively collected (item 3). Moreover, the demographic baseline equivalence (item 11) was unevenly reported. Further, only six studies used multivariate, or partly multivariable analyses, considering the influence of potential confounders on the investigated outcome. [88, 128, 135, 239, 270, 272] Moreover, only eight studies performed prospective sample size analysis, while one study appears to have performed a post-hoc power analysis. [272]

Table 4. Articles included in the final review

Authors	Year	Study group characteristics	Patients (male)	Mean age, years	Mean follow-up time, years	Percentage with non-contact injury	Hyper-mobile patients, n (%)	Evaluation method
Akhtar et al. [7]	2015	Primary ACL injury	139 (100)	28	NA	NI	52 (37)[P]	BS [Q]
		ACL revision	44 (29)	28	NA	NI	25 (57) [P]	
		Controls	70 (57)	33	NA	NA	11 (16) [P]	
Anderson et al. [14]	1987	Unilateral ACL injury	17 (10)	23	NA	NI	NI	BS [Q]
		Bilateral ACL injury	14 (8)	26		NI	NI	
		Controls	17 (10)	27		NA	NI	

Table continues to p. 85 →

Authors	Year	Study group characteristics	Patients (male)	Mean age, years	Mean follow-up time, years	Percentage with non-contact injury	Hypermobile patients, n (%)	Evaluation method
Astur et al. [25]	2018	ACL injury	107 (82)	32.9 SD ± 11.9	0.5	NI	17 (15.9)	BS [Q]
		ACL and meniscal injury	75 (60)		0.5		17 (36.2)	
		Meniscal injury	60 (54)		0.25		11 (25.6)	
Harner et al. [88]	1994	Bilateral ACL injury	31 (22)	29	NA	100	NI	Modified and Horan method
		Controls	23 (13)	29	NA	NA	NI	
Kim et al. [120]	2009	Single-bundle PT graft	32 (14)	29	2 [T]	NI	All patients	Beighton and Horan
		Double-bundle QT graft	29 (11)	25	2 [T]		All patients	
Kim et al. [125] (only subgroup with GJH presented)	2008	Single-bundle PT graft	20 (7)	28	2 [T]	NI	All patients	Beighton and Horan
		Single-bundle HT graft	11 (3)	30	2 [T]		All patients	
Kim et al. [128]	2009	Single-bundle PT graft or single-bundle HT graft	272 (175)	29	2 [T]	NI	NA	Beighton and Horan
Kim et al. [123]	2018	Non-hypermobile with PT graft	122 (97) [R]	29.9±10.6	2 [T]	NI	None	BS [Q]
		Non-hypermobile with HT graft	53 (42) [R]	31.1±10.6	2 [T]		None	
		Hypermobile with PT graft	41 (29) [R]	29.4±10.5	2 [T]		All	
		Hypermobile with HT graft	21 (15) [R]	28.5±8.0	2 [T]		All	
Kim et al. [124 S]	2018	Hypermobile ACL reconstructed	27 (19)	29.5±10.2	8 [T]	NI	33	BS [Q]
		Non-hypermobile ACL reconstructed	81 (63)	28.7±10.4	8 [T]		67	
Kramer et al. [135]	2007	ACL injury	33 (0)	21	NA	NI	NI	BS
		Controls	33 (0)	19	NA	NA	NI	

Authors	Year	Study group characteristics	Patients (male)	Mean age, years	Mean follow-up time, years	Percentage with non-contact injury	Hypermobile patients, n (%)	Evaluation method
Larson et al. [141]	2017	Hypermobile ACL reconstructed	41 (9)	23	5.7	NI	41	BS [Q]
		Non-hypermobile ACL reconstructed	142 (72)	28	6.2		0	
Motohashi et al. [169]	2004	Unilateral ACL injury	161 (54)	19.8 (range 12-45)	3.3 (range 1.1-7.4)	NI	NA	Method according to Fukubayashi et al.
		Bilateral ACL injury	10 (0)	18.2 (range 13-24)		90%	NA	
		Controls	95 (0)	15.6 SD ± 1.4	NA	NA	NA	
Ramesh et al. [202]	2005	ACL injury	169 (137)	Range 18-34	NA	75.4%	72 (42.6)	BS
		Controls	65 (NI)	NI, age and sex matched	NA	NA	14 (21.5)	
Scerpella et al. [227]	2005	ACL injury	36 (14)	Males: 22.7 SD ± 3.4 Females: 21.5 SD ± 2.5	NA	100	NA	BS and a modified version
		Controls	181 (89)	Males: 20.1 SD ± 1.4 Females: 19.5 SD ± 1.2	NA	NA	NA	
Sgaglione et al. [238]	1990	ACL primary suture repair	70 (38)	25.8 SD ± 0.8	3.2 SD ± 0.15	NI	26 (37)	Beighton and Horan [Q]
Shimozaki et al. [239]	2018	ACL injury	12 (0)	15.4 SD ± 0.3	3	12	NA [U]	BS
		Controls	156 (0)	15.5 SD ± 0.3	3	NA	NA [U]	
Stijak et al. [253]	2014	ACL injury	29 (29)	26.6	NA	100	NI	BS [Q]
		Controls	29 (29)	27.1	NA	NA	NI	
Stijak et al. [255]	2014	ACL injury	12 (0)	24.2	NA	100	NI	BS [Q]
		Controls	12 (0)	24.8	NA	NA	NI	
Uhorchak et al. [270]	2003	ACL injury	24 (16)	18.4 (range 17-23)	4 (both groups)	100	NA	BS [Q]
		Uninjured controls	835 (723)			NA	NA	
Vacek et al. [272]	2016	ACL injury	109 (36)	NI	NA	100	NI	BS
		Controls	227	NI	NA	NA	NI	
Vaishya et al. [273]	2013	ACL injury group	210 (135)	24.6 ± 0.9	NA	NI	127 (60.5)	BS
		Controls	90 (55)	NI. Matched for age and sex	NA	NA	23 (25.5)	

ACL = anterior cruciate ligament, BS = Beighton score, HT = hamstring tendon, NA = not applicable, NI = no information, PT = patellar tendon, QT = quadriceps tendon, SD = standard deviation

[P] Using the > 4 cut-off limit. [Q] with modifications, [R] the presented patients were followed up for two years, fewer patients were examined at the five-year follow-up. [S] Only the patients in the eight-year follow-up were included, as the same patients from the two- and five-year follow-ups are presented in the following article by Kim et al. [123]. The exact follow-up time was not disclosed. [U] Patients not dichotomized into hypermobile/non-hypermobile

Unilateral ACL injury

The effect of GJH on the risk of unilateral ACL injury was assessed in ten studies. Five of these ten studies analyzed the influence of GJH in groups with both sexes,[7, 14, 202, 270, 273] all showing significant associations between GJH and ACL injury.

Males were analyzed separately in four studies. In three of four, significant associations were found between ACL injury and GJH.[253, 270, 272] In the fourth study, two methods were used to define GJH; one showed a significant association with ACL injury, while the other did not. [227]

Six studies analyzed females separately. Two studies reported significant positive associations between GJH and ACL injury, [270,135] two studies did not report significant associations[255, 272] and another study reported that less hypermobility increased the risk of ACL injury.[239] The last study used two methods to define hypermobility, one method showing a significant association, while the other did not (table availiable in Study I in the appendix). [227]

Taken together, there was consistent evidence of an association between GJH and the risk of unilateral ACL injury in males, while in females the results were conflicting.

Bilateral ACL injury

Bilateral ACL injury was evaluated in five studies. One study reported that patients with bilateral ACL injuries had higher hypermobility scores in comparison with patients with unilateral ACL injuries. [169] The other four studies reported no significant association between the incidence of bilateral or contralateral ACL injury and GJH (table availiable in Study I in the appendix).[14, 123, 124, 141]

Taken together, there was insufficient evidence to draw any conclusions in terms of the influence of GJH on bilateral ACL injury risk.

Graft failure

A total of four studies reported the frequency of graft failure. Two studies, using a quadruple HT autograft, a PT autograft, a fascia-lata autograft or an allograft reported significant positive associations with hypermobility.[7, 141] In the two studies, using either PT or HT autografts, which did not report significant associations, the graft failure rate was consistently higher in the hypermobile group, irrespective of graft type (table availiable in Study I in the appendix).

Taken together, there was insufficient evidence to draw conclusions in terms of the influence of GJH on graft failure risk.

Knee laxity

Two studies assessed postoperative laxity using the Lachman test and the pivot-shift test. Using the Lachman test at follow-up after five-[123] and eight[124] years, increased laxity was reported in patients with GJH, regardless of whether PT or HT grafts were used. Increased laxity evaluated using the pivot-shift test was observed in patients with PT grafts at the five- and eight-year follow-ups in patients with GJH[123, 124] but not in patients with HT autografts.[123]

Instrumented ATT was assessed in three studies. The mean side-to-side difference using the KT-2000 was significantly increased in patients with GJH at both five and eight years postoperatively.[123, 124] One study, using the KT-1000, reported no difference in ATT between groups (table availiable in Study I in the appendix).[141]

Taken together, there was limited evidence associating GJH with increased knee laxity five and eight years postoperatively.

Patient-reported outcome

The results for the Lysholm and IKDC scores were reported in four comparative studies, showing inferior outcomes in patients with GJH at two,[123, 128] five,[123] six[141] and eight[124] years postoperatively. Moreover, using the Cincinnati knee rating system, inferior outcomes for patients with GJH were reported at six years postoperatively. [141] The level of physical activity, using the Tegner activity scale, was assessed in one non-comparative study of patients with GJH at six months postoperatively. In this study, no correlation between hypermobility and the level of activity was found (table availiable in Study I in the appendix). [25]

Taken together, there was limited yet consistent evidence of inferior patient-reported outcomes in patients with GJH and previous ACL reconstruction. There was insufficient evidence in terms of the effect of GJH on the postoperative level of physical activity.

Osteoarthritis

Osteoarthritis was evaluated, using radiography, in two comparative studies. No significant differences in the incidence of OA between patients with and without GJH were found after two, five or eight years (table availiable in Study I in the appendix). [123, 124]

Taken together, there was limited evidence reporting no effect of GJH on the development of OA in the short- to mid-term perspective.

Graft choice in patients with GJH

Four studies evaluated the effect of graft choice in ACL-reconstructed patients with GJH, all from the same research group. Knee laxity was assessed using four different methods. One study reported that, using the Lachman test, a DB-QT autograft was superior to a patellar-tendon PT autograft.[120] Patellar tendon and HT autografts were compared in two studies, reporting superior results for the PT in one study[125] at two years postoperatively, but, at five years, there was no difference between the grafts[123]. Evaluating the pivot-shift test, one study demonstrated better results using PT autografts compared with HT autografts at two years postoperatively[125]. Using the KT-2000, one study reported better results using DB-QT autografts compared with PT autografts.[120] Consistently superior results, in terms of instrumented ATT, were observed for the PT autograft in three studies compared with the HT autograft,[120, 125] although, in one of the studies, no statistical analysis was performed.[128]

In terms of the Lysholm score, there was no difference between the DB-QT autografts and PT autografts.[120] Better Lysholm scores were reported for patients using the PT autograft, at two and five years postoperatively, compared with patients receiving the HT autograft.[123, 125] The two studies assessing the Hospital for Special Surgery (HSS) and the IKDC (classified as A, B, C and D) did not report any significant differences with regard to graft type.[120, 125] The continuous IKDC score was, however, better in patients receiving the PT autograft compared with patients with the HT autograft in one study, both two and five years postoperatively (table availiable in Study I in the appendix).[123]

Taken together, there was limited yet consistent evidence that PT autografts were superior to HT autografts in patients with GJH, with PT autografts showing a reduced risk of anteroposterior laxity and improved patient-reported outcome.

Study II

Patient data were available for 2,031 patients in the Project ACL database, of which 142 were eligible for inclusion and had one-year follow-up data (Figure 15). Eleven (2 males) patients presented with GJH, while 131 did not (73 males), with significantly more females in the group with GJH. Patients with GJH were younger (24.1 vs. 27.8 years), although the difference was not statistically significant (Table 5).

Table 5. Baseline parameters of included patients

	Total (n=142)	Beighton score 0-4 (n=131)	Beighton score 5-9 (n=11)	p-value
Sex				
Female	67 (47.2%)	58 (44.3%)	9 (81.8%)	
Male	75 (52.8%)	73 (55.7%)	2 (18.2%)	0.035
Age at index operation	27.6 (9.1) 25.8 (16.1; 50.1) n=142	27.8 (9.2) 26.1 (16.1; 50.1) n=131	24.1 (6.6) 22.0 (16.9; 38.6) n=11	0.19
Height [cm]	174.5 (9.1) 174.0 (156.0; 195.0) n=142	174.7 (9.1) 175.0 (156.0; 195.0) n=131	171.6 (9.3) 169.0 (160.0; 190.0) n=11	0.29
Weight [kg]	73.4 (12.8) 72.5 (45.0; 108.0) n=142	73.7 (13.0) 73.0 (45.0; 108.0) n=131	68.7 (9.1) 67.0 (55.0; 85.0) n=11	0.22
BMI [kg/m2]	24.0 (2.9) 23.8 (18.0; 33.1) n=142	24.0 (3.0) 24.0 (18.0; 33.1) n=131	23.3 (1.9) 23.2 (20.3; 26.5) n=11	0.42
TYPE OF GRAFT				
Hamstring tendon autograft	124 (87.9%)	115 (88.5%)	9 (81.8%)	
Patellar tendon autograft	13 (9.2%)	11 (8.5%)	2 (18.2%)	
Allograft	2 (1.4%)	2 (1.5%)	0	
Other	1 (0.7%)	1 (0.8%)	0	
Quadriceps tendon autograft	1 (0.7%)	1 (0.8%)	0	0.71
PATIENT-REPORTED OUTCOME				
KOOS Sports and recreation	42.4 (23.8) 44.0 (0.0; 100.0) n=44	40.7 (23.4) 43.0 (0.0; 100.0) n=39	56.0 (24.6) 65.0 (25.0; 80.0) n=5	0.18

Table continues to p. 90 →

	Total (n=142)	Beighton score 0-4 (n=131)	Beighton score 5-9 (n=11)	p-value
KOOS Pain	75.6 (15.6) 78.0 (33.0; 97.0) n=44	74.7 (15.8) 78.0 (33.0; 94.0) n=39	82.8 (13.2) 89.0 (64.0; 97.0) n=5	0.28
KOOS Symptoms	67.5 (22.4) 68.0 (18.0; 100.0) n=44	65.7 (22.9) 68.0 (18.0; 100.0) n=39	81.6 (10.3) 79.0 (68.0; 96.0) n=5	0.13
KOOS Daily living	87.5 (14.8) 92.0 (40.0; 100.0) n=44	86.6 (15.3) 91.0 (40.0; 100.0) n=39	94.6 (8.8) 99.0 (79.0; 100.0) n=5	0.25
KOOS Quality of life	38.5 (19.1) 38.0 (0.0; 75.0) n=44	35.7 (17.9) 38.0 (0.0; 69.0) n=39	60.2 (14.3) 63.0 (38.0; 75.0) n=5	0.0052
KOOS4	56.0 (17.4) 58.1 (21.0; 90.8) n=44	54.2 (17.3) 57.8 (21.0; 90.8) n=39	70.2 (11.9) 74.0 (51.5; 80.3) n=5	0.051
HOP TESTS				
LSI single-legged hop test	86.7 (19.4) 93.9 (27.0; 100.0) n=14	86.0 (20.0) 93.0 (27.0; 100.0) n=13	95.6 n=1	0.57
LSI vertical jump	81.7 (23.9) 86.8 (20.0; 117.0) n=15	81.9 (25.8) 87.9 (20.0; 117.0) n=13	80.4 (5.5) 80.4 (76.5; 84.2) n=2	0.93
LSI side-hop test	88.4 (18.8) 89.3 (60.0; 115.4) n=7	90.4 (19.7) 92.9 (60.0; 115.4) n=6	76.3 n=1	0.57
MUSCULAR STRENGTH				
LSI quadriceps strength	88.4 (20.7) 91.4 (38.5; 156.2) n=42	89.0 (21.8) 92.4 (38.5; 156.2) n=36	84.7 (12.8) 88.1 (64.1; 97.9) n=6	0.64
LSI hamstring strength	97.6 (14.2) 97.0 (63.3; 125.8) n=42	99.0 (13.9) 98.2 (74.8; 125.8) n=36	89.4 (14.5) 92.6 (63.3; 103.6) n=6	0.13

KOOS = Knee injury and Osteoarthritis Outcome Score, LSI = limb symmetry index
For categorical variables, n (%) is presented.
For continuous variables, the mean (SD)/median (min; max)/n = is presented.

Patient-reported outcome

Dichotomized analysis revealed that patients with GJH obtained higher scores when evaluating KOOS sports and recreation (mean 81.5 vs. 67.5, p=0.076), although the difference was not statistically significant (Table 6).

The linear regression analysis revealed that the primary outcome, KOOS sports and recreation, was positively associated with the continuous analysis of the Beighton

score, for the univariable (beta 2.56 [95% CI 0.38-4.74], R-square 0.04, p-value 0.02) and the adjusted (beta 2.30 [95% CI 0.10-4.49], p-value 0.04) analyses (Table 7).

Table 6. Dichotomous analysis of investigated outcomes at 12 months

Outcome parameters at one year postoperatively	Total (n=142)	Beighton score 0-4 (n=131)	Beighton score 5-9 (n=11)	p-value
PATIENT-REPORTED OUTCOME				
KOOS Sports and recreation	68.6 (23.7) 70.0 (0.0; 100.0) n=128	67.5 (23.8) 70.0 (0.0; 100.0) n=118	81.5 (19.2) 87.5 (45.0; 100.0) n=10	0.076
KOOS Pain	85.4 (12.9) 89.0 (33.0; 100.0) n=128	85.2 (13.0) 89.0 (33.0; 100.0) n=118	86.9 (12.0) 90.5 (58.0; 97.0) n=10	0.71
KOOS Symptoms	76.6 (16.9) 82.0 (25.0; 100.0) n=128	76.3 (17.2) 82.0 (25.0; 100.0) n=118	80.3 (12.5) 80.5 (61.0; 96.0) n=10	0.49
KOOS Daily living	93.1 (12.1) 99.0 (31.0; 100.0) n=127	92.8 (12.4) 97.0 (31.0; 100.0) n=117	96.6 (8.2) 100.0 (74.0; 100.0) n=10	0.35
KOOS Quality of life	59.5 (19.4) 63.0 (0.0; 100.0) n=128	58.7 (19.3) 59.5 (0.0; 100.0) n=118	68.8 (18.5) 72.0 (44.0; 100.0) n=10	0.12
KOOS4	72.5 (15.8) 73.4 (27.8; 100.0) n=128	71.9 (15.9) 73.0 (27.8; 100.0) n=118	79.4 (12.9) 82.9 (54.3; 92.8) n=10	0.16
Tegner Activity Scale	6.00 (1.00; 10.00) n=128	6.00 (1.00; 10.00) n=118	8.00 (1.00; 10.00) n=10	0.13
HOP TESTS				
LSI Single-legged hop test	94.0 (12.4) 95.7 (47.8; 134.2) n=116	93.9 (12.4) 95.7 (47.8; 134.2) n=107	95.7 (12.6) 97.8 (72.2; 110.9) n=9	0.66
LSI Vertical jump	89.3 (15.5) 89.3 (49.4; 131.7) n=117	89.2 (15.6) 89.1 (49.4; 131.7) n=108	91.5 (15.0) 92.2 (65.3; 110.8) n=9	0.67
LSI Side-hop test	98.6 (18.0) 98.5 (57.1; 171.4) n=105	98.4 (18.3) 98.5 (57.1; 171.4) n=97	100.2 (14.4) 98.3 (84.2; 125.0) n=8	0.79
MUSCULAR STRENGTH				
LSI Quadriceps strength	93.8 (13.6) 93.9 (36.4; 154.8) n=129	93.8 (13.9) 93.9 (36.4; 154.8) n=118	94.3 (9.6) 96.9 (73.8; 105.2) n=11	0.89
LSI Hamstring strength	97.3 (14.4) 99.3 (7.8; 133.3) n=129	97.5 (14.7) 99.6 (7.8; 133.3) n=118	95.2 (10.7) 94.1 (83.8; 115.6) n=11	0.59

KOOS = Knee injury and Osteoarthritis Outcome Score, LSI = limb symmetry index
For continuous variables, the mean (standard deviation)/median (min; max)/n = is presented.

Hop tests and muscular strength

There were no associations with continuous Beighton score or the presence of GJH and the single-legged hop test for distance, the vertical-jump test, the side-hop test and the tests of muscular strength (Tables 6 and 7). Both the mean and the median values of all analyses of the hop tests exceeded an LSI of 90%, except for the vertical-jump test in the group without GJH (Table 6).

Table 7. Linear regression analysis of investigated outcomes

	Univariable*			Adjusted**	
Outcome parameters one year postoperatively	**Beta (95% CI)**	**p-value**	**R-square**	**Beta (95% CI)**	**p-value**
PATIENT-REPORTED OUTCOME					
KOOS Sports and recreation	2.56 (0.38;4.74)	0.022	0.04	2.30 (0.10;4.49)	0.040
KOOS Pain	0.69 (-0.51;1.90)	0.26	0.01	0.38 (-0.87;1.62)	0.55
KOOS Symptoms	1.25 (-0.32;2.82)	0.12	0.02	0.89 (-0.73;2.52)	0.28
KOOS Daily life	1.24 (0.11;2.37)	0.032	0.04	0.98 (-0.20;2.15)	0.10
KOOS Quality of life	1.52 (-0.29;3.33)	0.100	0.02	1.15 (-0.73;3.02)	0.23
KOOS[4]	1.51 (0.04;2.97)	0.044	0.03	1.18 (-0.32;2.68)	0.12
Tegner Activity Scale	0.19 (-0.04;0.41)	0.10	0.02	0.13 (-0.09;0.35)	0.23
HOP TESTS					
LSI Single-legged hop test	0.45 (-0.75;1.65)	0.46	0.01	0.38 (-0.85;1.61)	0.54
LSI Vertical jump	0.76 (-0.72;2.24)	0.31	0.01	0.49 (-0.99;1.98)	0.51
LSI Side-hop test	0.16 (-1.71;2.04)	0.86	0.00	0.25 (-1.69;2.18)	0.80
MUSCULAR STRENGTH					
LSI Quadriceps strength	0.17 (-1.03;1.37)	0.78	0.00	0.13 (-1.08;1.34)	0.83
LSI Hamstring strength	0.08 (-1.20;1.35)	0.91	0.00	-0.05 (-1.37;1.27)	0.94

CI = confidence interval, KOOS = Knee injury and Osteoarthritis Outcome Score, LSI = limb symmetry index
P-values, beta and R-square are based on original values and not on stratified groups.
*) All tests are performed with univariable linear regression.
**) Adjusting for sex, graft (surgery) and age at index operation using linear regression

Study III

A total of 103 patients were involved in the study. Eighty-nine (86%) patients had complete ACL ruptures and the remaining 14 (14%) patients suffered partial ruptures. Beighton score data were missing for seven patients, leading to their exclusion from the analysis. Complete data sets for 96 (93%) patients were analyzed. Of the included patients, there were 40 (42%) females and 56 (58%) males (Table 8).

Table 8. Descriptive statistics, baseline data and concomitant meniscal injuries

	All patients	Beighton score 0-4	Beighton score 5-9	p-value	N
Sex (female/male)	40/56	31/52 (37.3/62.7%)	9/4 (69.2/30.8%)	p = 0.03*	96
Age (mean, ± SD)	24.6 (±9.1)	25.5 (±9.5)	18.9 (±11.8)	p = 0.047*	96
Medial meniscus (normal/lesion)	58/38 (60.4/39.6)	50/33 (60.2/39.8%)	8/5 (61.5/38.5%)	p = 0.93 (n.s.)	96
Lateral meniscus (normal/lesion)	58/38 (60.4/39.6)	53/30 (63.9/36.1%)	5/8 (38.5/61.5%)	p = 0.82 (n.s.)	96
CORS (mean, ± SD)	29.4 (±14.9)	29.2 (±15.3)	30.6 (±11.8)	p = 0.40 (n.s.)	96
MAS (mean, ± SD)	11.3 (±5.2)	10.7 (±5.4)	14.9 (±2.2)	p = 0.003*	96
IKDC 2000 (mean, ± SD)	58.1 (±15.7)	58.4 (±15.7)	55.8 (±16.2)	p = 0.55 (n.s.)	96
ADLS (mean, ± SD)	79.8 (±15.7)	80.3 (±15.7)	76.7 (16.4)	p = 0.42 (n.s.)	96

CORS = Cincinnati Occupational Rating Scale, MAS = Marx Activity Scale, IKDC = International Knee Documentation Committee, ADLS = Activities of Daily Living Scale of the Knee Outcome Survey, SD = Standard deviation
* Denotes statistical significance, p-values are provided for analysis of the difference between the Beighton score subgroups N.s. = non-significant

The mean age of all the patients was 24.6 years. As a group, female patients had significantly higher Beighton scores when compared with male patients (p = 0.03). There was a difference showing that the patients in the subgroup with low Beighton scores were significantly older than the patients in the high Beighton score group (p = 0.047). The group with high Beighton scores had a higher level of activity measured with the Marx Activity Scale (p=0.003, Table 8).

Quantification using the image analysis system or the accelerometer in awake patients did not reveal any significant correlations with Beighton score (Table 9).

Table 9. Correlation with Beighton score, preoperative awake patients

	Correlation (rho)	p-value	N
IAS – involved knee	-0.022	0.837 (n.s.)	92
IAS – non-involved knee	-0.117	0.278 (n.s.)	88
IAS – side-to-side difference	0.035	0.744 (n.s.)	88
Accelerometer – involved knee	-0.079	0.475 (n.s.)	84
Accelerometer – non-involved knee	-0.154	0.169 (n.s.)	82
Accelerometer – side-to-side difference	-0.004	0.970 (n.s.)	82

IAS = Image analysis system N.s = non-significant * Denotes statistical significance

In anesthetized patients, there were no significant correlations between QPS, using the image analysis system, and the level of Beighton score when analyzing the involved knee or the side-to-side difference (Table 10). However, when analyzing the non-involved side, a significant correlation was found (r = 0.235, p = 0.024). Using the accelerometer, no significant correlations could be established with patients under anesthesia (Table 10). Comparing the subgroups with high and low Beighton scores, there was no significant difference either when using the image analysis system or when using the accelerometer. The results did not reach statistical significance either when patients were awake or when they were under anesthesia (tables availiable in Study III in the appendix). Multivariate analysis, adjusted for meniscal injuries, age and sex, revealed that the image analysis system was associated with the level of Beighton score in the non-involved knee in anesthetized patients. No other analysis, using multivariate statistics, was significant (Table 11).

Table 10. Correlation with Beighton score, preoperative anesthetized patients

	Correlation (rho)	p-value	N
IAS – involved knee	0.106	0.309 (n.s.)	95
IAS – non-involved knee	0.235*	0.024*	92
IAS – side-to-side difference	-0.032	0.762 (n.s.)	92
Accelerometer – involved knee	0.138	0.217 (n.s.)	82
Accelerometer – non-involved knee	0.027	0.812 (n.s.)	82
Accelerometer – side-to-side difference	0.125	0.265 (n.s.)	82

IAS = Image analysis system N.s = non-significant * Denotes statistical significance

Table 11. Beighton score, multivariate analysis of preoperative anesthetized patients

	OR	OR CI (95%)	p-value
IAS – involved knee	1.07	0.81-1.41	0.650 (n.s.)
IAS – non-involved knee	1.86	1.10-3.17	0.022*
IAS – side-to-side difference	0.85	0.60-1.19	0.333 (n.s.)
Accelerometer – involved knee	1.06	0.93-1.19	0.387 (n.s.)
Accelerometer – non-involved knee	1.40	0.84-2.32	0.196 (n.s.)
Accelerometer – side-to-side difference	1.04	0.92-1.16	0.556 (n.s.)

IAS = Image analysis system OR = Odds Ratio CI = Confidence Interval N.s.= non-significant * Denotes statistical significance. Multivariate analysis adjusted for meniscal injuries, age and sex

Study IV

The local patient data registry contained information about 10,957 patients of which 1,065 (9.7%) patients were excluded.

Table 12. Demographics of contralateral knee extension subgroups

	Subgroups based on contralateral knee extension									
	Group A (HE <= 0°)	Group B (HE 1-5°)			Group C (HE 6 - 10°)			Group D (HE > 10°)		
Out-come variables			Diff between groups, mean (95% CI)	p-value		Diff between groups, mean (95% CI)	p-value		Diff between groups, mean (95% CI)	p-value
Age, years	29 (10.2) 28 (14; 90) n=4335	27.5 (9.6) 26 (14; 66) n=3331	1.48 (1.03; 1.91)	<0.0001	26.8 (9.4) 26 (14; 79) n=771	2.19 (1.46; 2.91)	<0.0001	25.6 (8.1) 24 (15; 48) n=65	3.37 (1.34; 5.34)	0.013
Patient sex										
Male	2,612 (60.3%)	1,778 (53.4%)	6.9 (4.6; 9.1)		402 (52.1%)	8.1 (4.2; 12.0)		34 (52.3%)	7.9 (-5.1; 21.0)	
Female	1,723 (39.7%)	1,553 (46.6%)	-6.9 (-9.1; -4.6)	<0.0001	369 (47.9%)	-8.1 (-12.0; -4.2)	0.0003	31 (47.7%)	-7.9 (-21.0; 5.1)	n.s.
Tendon										
Patellar tendon	1,145 (26.4%)	1,278 (38.4%)	-12.0 (-14.1; -9.8)		328 (42.5%)	-16.1 (-19.9; -12.3)		33 (50.8%)	-24.4 (-37.4; -11.4)	
Hamstring tendon	3,190 (73.6%)	2,053 (61.6%)	12.0 (9.8; 14.1)	<0.0001	443 (57.5%)	16.1 (12.3; 19.9)	<0.0001	32 (49.2%)	24.4 (11.4; 37.4)	<0.0001

Diff: difference, HE: hyperextension
For categorical variables, n (%) is presented.
For continuous variables, the mean (SD)/median (min; max)/n= is presented.

Data relating to range of motion for the contralateral knee were available for 8,502 (77.6%) of the patients fulfilling the inclusion criteria and all these patients were included in the final analysis (Figure 16). The largest subgroup comprised patients with no hyperextension (Group A, 4,335 patients). Groups B, C and D comprised 3,331, 771 and 65 patients respectively. A PT autograft was more frequently used in patients with hyperextension (Group B: 38.4%, p< 0.0001, Group C: 42.5%, p< 0.0001, Group D: 50.8%, p< 0.0001) than in patients without (Group A: 26.4%, Table 12). An analysis of meniscal injuries, including injuries to both the medial and the lateral menisci, showed that injuries were proportionally more frequent in patients with no hyperextension (Group A: 34.1%) compared with patients with an increasing degree of hyperextension (Group B: 27.1%, p< 0.0001, Group C: 27.0%, p=0.0003, Group D: 18.5%, p=0.012, Table 13).

Table 13. Concomitant meniscal and chondral injuries

	Subgroups based on contralateral knee extension									
	Group A (HE <= 0°)	Group B (HE 1-5°)			Group C (HE 6 - 10°)			Group D (HE > 10°)		
Outcome variables			Diff between groups, mean (95% CI)	p-value		Diff between groups, mean (95% CI)	p-value		Diff between groups, mean (95% CI)	p-value
Cartilage injury										
Yes	678 (15.6%)	404 (12.1%)	3.5 (1.9; 5.1)		92 (11.9%)	3.7 (1.1; 6.3)		7 (10.8%)	4.9 (-3.5; 13.3)	
No	3,657 (84.4%)	2,927 (87.9%)	-3.5 (-5.1; -1.9)	0.0015	679 (88.1%)	-3.7 (-6.3; -1.1)	n.s.	58 (89.2%)	-4.9 (-13.3; 3.5)	n.s.
Medial meniscus injury										
Yes	911 (21.0%)	527 (15.8%)	5.2 (3.4; 7.0)		124 (16.1%)	4.9 (2.0; 7.9)		7 (10.8%)	10.2 (1.8; 18.7)	
No	3,424 (79.0%)	2,804 (84.2%)	-5.2 (-7.0; -3.4)	<0.0001	647 (83.9%)	-4.9 (-7.9; -2.0)	0.0062	58 (89.2%)	-10.2 (-18.7; -1.8)	n.s.
Lateral meniscus injury										
Yes	827 (19.1%)	527 (15.8%)	3.3 (1.5; 5.0)		115 (14.9%)	4.2 (1.3; 7.0)		7 (10.8%)	8.3 (-0.1; 16.7)	
No	3,508 (80.9%)	2,804 (84.2%)	-3.3 (-5.0; -1.5)	0.0002	656 (85.1%)	-4.2 (-7.0; -1.3)	0.0043	58 (89.2%)	-8.3 (-16.7; 0.1)	n.s.
Meniscal injury, dichotomous										
Yes	1,479 (34.1%)	903 (27.1%)	7.0 (4.9; 9.1)		208 (27.0%)	7.1 (3.6; 10.7)		12 (18.5%)	15.7 (5.3; 26.0)	
No	2,856 (65.9%)	2,428 (72.9%)	-7.0 (-9.1; -4.9)	<0.0001	563 (73.0%)	-7.1 (-10.7; -3.6)	0.0003	53 (81.5%)	-15.7 (-26.0; -5.3)	0.012

Diff: difference, HE: hyperextension
For categorical variables, n (%) is presented.
For continuous variables, the mean (SD)/median (min; max)/n= is presented.
Comparisons were made between control Group A and the other groups using multivariate logistic regression analysis adjusting for age and sex.

The mean preoperative ATT of the contralateral knee was significantly greater for Groups B and C compared with Group A. Similarly, an analysis of the preoperative ATT of the ACL-injured knee revealed a significantly greater ATT for Groups B and C compared with Group A (Table 14). An analysis of the ATT of the injured knee six months postoperatively revealed a gradual increase in ATT, from 8.2 mm (Group A) to 8.5, (Group B) 8.5 (Group C) and 9.1 (Group D). An analysis of preoperative or six-month postoperative differences in side-to-side measurements of the injured knee did not reveal any significant differences between the subgroups (Table 14).

Table 14. KT-1000 outcome variables with regard to contralateral extension subgroups

	Subgroups based on contralateral knee extension									
	Group A (HE <= 0°)	Group B (HE 1-5°)			Group C (HE 6 - 10°)			Group D (HE > 10°)		
Outcome variables	Mean (mm)	Mean (mm)	95% CI	p-value	Mean (mm)	95% CI	p-value	Mean (mm)	95% CI	p-value
KT-1000 preoperative, contralateral knee	6.5	6.8	(0.14-0.42)	<0.0001	6.9	(0.17-0.68)	0.0002	6.3	(-1.01-0.60)	n.s.
KT-1000 preoperative, injured knee	10.1	10.3	(0.06-0.42)	0.0055	10.6	(0.23-0.89)	0.0004	10.0	(-1.08-0.96)	n.s.
KT-1000 six months postoperative, injured knee	8.2	8.5	(0.13-0.45)	<0.0001	8.5	(0.02-0.60)	0.035	9.1	(-0.08-1.77)	n.s.
KT-1000 preoperative, side-to-side difference	3.5	3.5	(-0.22-0.14)	n.s.	3.7	(-0.19-0.45)	n.s.	3.7	(-0.88-1.14)	n.s.
KT-1000 six months postoperative, side-to-side difference	1.7	1.8	(-0.06-0.23)	n.s.	1.7	(-0.21-0.30)	n.s.	2.4	(-0.08-1.56)	n.s.
KT-1000 reduction from pre-operative to postoperative side-to-side difference	-1.8	-1.7	(-0.09-0.28)	n.s.	-1.9	(-0.41-0.24)	n.s.	-1.4	(-0.62-1.43)	n.s.

The analysis was adjusted for age, sex, type of graft and meniscal injury (dichotomous). Comparisons were made between control Group A and the other groups using multivariate logistic regression analysis. CI: confidence interval, HE: hyperextension

Study V

At the long-term follow-up, 147 (76%) patients were examined. Graft rupture and contralateral ACL injury occurred in 11 and 12 patients respectively during the total follow-up period (Figure 17). For analysis purposes, these patients were excluded. The 124 patients included in the analysis had a mean age of 27.9 (± 8.3) years at the time of surgery.

Table 15. Demographic data, included patients and patients excluded due to ACL re-injury or contralateral ACL injury

Variable	All included patients	Patients excluded due to ACL re-injury during follow-up	Patients excluded due to contralateral ACL injury during follow-up
Age at reconstruction, years			
Mean ± SD	27.9 ± 8.3	24.7 ± 9.3	23.8 ± 5.8
Range	14 - 59	15-45	17-39
N	124	11	12
Sex, male/female (%)	79 (63) /45 (37)	8 (73) / 3 (27)	8 (67)/4 (33)
N	124	11	12
Long-term follow-up period, years			
Mean ± SD	16.4 ± 1.2	16.6 ± 1.2	16.0 ± 1.6
Range	13.3 - 18.7	14.8 - 18.8	13.3 - 18.0
N	124	11	12
Associated injuries at surgery, yes (%)	85 (69)	5 (45)	7 (58)
Medial meniscus	37 (30)	1 (9)	7 (58)
Lateral meniscus	51 (42)	4 (36)	2 (17)
Osteochondral lesion	13 (11)	0	1 (8)
Other*	4 (3)	2 (18)	0
n	123	11	12
Type of graft, HT/PT (%)	73 (59) /51 (41)	7 (64) /4 (36)	6 (50) /6 (50)
N	124	11	12
Surgical portal technique (%)			
Transtibial	78 (63)	7 (64)	7 (58)
Transportal	46 (37)	4 (36)	5 (42)
N	124	11	12

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Lysholm score			
Preoperative			
Mean ± SD	69.9 ± 15.0	73.6 ± 10.1	72.3 ± 9.6
Range	14 - 99	58 - 85	54-86
n	115	10	12
Two-year follow-up			
Mean ± SD	87.7 ± 13.5	80.4 ± 25.9	89.5 ± 12.6
Range	37-100	22-100	60 - 100
n	110	8	10
Tegner activity scale			
Preoperative			
Median (Q1:Q3)	4 (3:5)	4 (3.75:6.75)	4 (3.25-5)
Range	1 - 8	3 - 9	3 - 6
n	114	10	12
Two-year follow-up			
Median (Q1:Q3)	6 (5:7)	6.5 (4.25:9)	7 (6:9)
Range	2 - 10	2 - 9	3 - 9
n	110	8	10
Single-legged hop test, LSI			
Preoperative			
Mean ± SD	79.8 ± 20.0	87.4 ± 10.5	81.8 ± 14.0
Range	10-113	67-103	57-99
n	106	9	12
Two-year follow-up			
Mean ± SD	91.2 ± 15.3	92.4 ± 12.0	98.9 ± 17.4
Range	38-122	76-105	69.0-123
n	110	5	10
New surgery during long-term follow-up, injured side, yes (%)	55 (44)	11 (100)	8 (67)
ACL re-injury	0	11 (100)	0
Meniscus	30 (24)	0	5 (42)
Cartilage	4 (3)	0	1 (8)
Implant problems	4 (3)	0	0
Septic knee	2 (2)	0	0
Posterior cruciate ligament injury	1 (1)	0	0
Extension deficit	0	0	1 (8)
Other	14 (11)	0	1 (8)
N	124	11	12

HT = hamstring tendon, PT = patellar tendon, SD = standard deviation, Q1 = first quartile, Q3 = third quartile, LSI = limb symmetry index, n = number of patients with available data for the particular analysis *Other injury includes synovitis or minor injury to the meniscus, requiring no more than meniscus shaving.

Knee laxity at the two-year follow-up

Increased laxity, examined with the Lachman test, was observed in 47 (42%) patients. Only four (4%) patients presented with grade 2 laxity and one (1%) patient presented with grade 3 laxity. Examined using the anterior drawer test, two (2%) patients presented with grade 2 laxity and no patient presented with a grade 3 anterior drawer test. Seven (6%) patients presented with positive pivot-shift tests, all with grade 1 (Table 16).

Table 16. Knee laxity measurements at two years postoperatively, all patients

Knee laxity variable		**Missing**
Lachman test, positive (%)	47 (42)	11
0	66	
1 (3-5 mm)	42	
2 (6-10 mm)	4	
3 (>10 mm)	1	
Anterior drawer, positive (%)	26 (23)	13
0	85	
1 (3-5 mm)	24	
2 (6-10 mm)	2	
3 (>10 mm)	0	
Pivot-shift test, positive (%)	7 (6)	13
0 (normal)	104	
1 (glide)	7	
2 (clunk)	0	
3 (gross)	0	
KT-1000 side-to-side difference 89 N, mm		
Mean ± SD	1.9 ± 2.7	14
Range	-4 – 11.5	

SD = Standard deviation

The Lachman test

A negative Lachman test at two years was associated with better Lysholm scores (85.2 ± 11.9, vs. 76.9 ± 17.8, p=0.0064) and IKDC-SKF scores (76.3 ± 19.4 vs. 67.8 ± 19.3, p=0.011) at the 16-year follow-up. A negative Lachman test was also associated with a better chance of achieving IKDC-SKF PASS (40 vs. 18, p=0.031). The following outcomes at the 16-year follow-up did not have any associations with the Lachman test after two years: the presence of OA, the single-legged hop test and the Tegner activity scale (Table 17).

Table 17. The Lachman test: baseline comparison and long-term outcome for dichotomized subgroups

	Outcome variable	**Positive Lachman test at two years**	**Negative Lachman test at two years**	**P-value**
	Age at reconstruction, years			
	Mean ± SD	29.6 ± 9.3	26.7 ± 7.7	0.068
	Range	14-52	15-59	
	N	47	66	
Demographic comparison between dichotomized subgroups	**Sex, male/female (%)**	32 (68)/15 (32)	40 (61)/26 (39)	0.54
	n	47	66	
	Type of graft, HT/PT (%)	25 (53)/22 (47)	40 (61)/26 (39)	0.55
	N	47	66	
	Associated injuries at surgery, yes (%)			
	Medial meniscus	32 (68)	48 (73)	0.74
	Lateral meniscus	20 (43)	17 (26)	0.09
	Osteochondral lesion	20 (43)	30 (46)	0.91
	Other*	7 (15)	5 (8)	0.35
	N	0	1 (2)	1.00
		47	66	
	New surgery during long-term follow-up, injured side, yes (%)	23 (49)	26 (39)	0.41
	Meniscus (medial and/or lateral)	13 (28)	15 (39)	0.70
	Osteochondral lesion			
	Implant problems	1 (2)	2 (3)	1.00
	Septic knee	0	4 (6)	0.22
	Posterior cruciate ligament	1 (2)	1 (2)	1.00
	Extension deficit	1 (2)	0	0.83
	Other	0	0	1.00
	N	7 (15)	4 (6)	0.22
		47	66	
	Long-term follow-up period, years			
	Mean ± SD			
	Range	16.5 ± 1.2	16.2 ± 1.2	0.18
	N	14.0-18.7	13.3-18.6	
		47	66	
	Lysholm score			
	Preoperative			
	Mean ± SD	67.4 ± 13.5	71.8 ± 16.0	.037**
	Range	34-95	14-99	
	n	47	66	
	Two-year follow-up			0.14
	Mean ± SD	85.1 ± 15.6	89.9 ± 11.6	
	Range	37-100	46-100	
	N	47	62	
	Tegner activity scale			
	Preoperative			
	Median (Q1:Q3)	3 (3:4)	4 (3:5)	0.38
	Range	2-7	1-8	
	n	47	66	
	Two-year follow-up			0.055
	Median (Q1:Q3)	6 (4:7)	7 (5:8)	
	Range	2-9	2-10	
	N	47	62	

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	Single-legged hop test			
	Preoperative			
	Mean ± SD	77.8 ± 21.1	81.1 ± 19.4	0.45
	Range	10-108	13-113	
	n	44	60	
	Two-year follow-up			0.23
	Mean ± SD	88.4 ± 17.3	93.3 ± 13.4	
	Range	38-116	63-122	
	N	47	62	
Long-term outcome variables	**IKDC-SKF**			
	Mean ± SD	67.8 ± 19.3	76.3 ± 19.4	0.011**
	Range	11.5-100	12.6-100	
	Achievement of PASS, yes (%)	18 (38)	40 (61)	0.031**
	N	47	66	
	Lysholm score			
	Mean ± SD	76.9 ± 17.8	85.2 ± 11.9	0.0064**
	Range	8-100	32-100	
	Knee function***	Fair	Good	
	N	47	66	
	Tegner activity scale			
	Median (Q1:Q3)	4 (3:5)	4 (3:5)	0.44
	Range	0-8	1-10	
	N	47	66	
	Single-legged hop test			
	Mean ± SD	84.5 ± 33.1	87.4 ± 26.0	0.28
	Range	0-184	0-124	
	N	46	66	
	Osteoarthritis			
	Kellgren-Lawrence			
	Median (Q1:Q3)	1 (0:2)	1 (0:2)	0.45
	Range	0-4	0-4	
	n	47	66	
	Cumulative Fairbanks			0.42
	Median (Q1:Q3)	2.5 (1:4)	2 (1:3)	
	Range	0-6	0-6	
	N	47	66	

HT = hamstring tendon, PT = patellar tendon, SD = standard deviation, Q1 = first quartile, Q3 = third quartile, LSI = limb symmetry index, PASS = Patient Acceptable Symptom State, n = number of patients with available data for the particular analysis *Other injury includes synovitis or minor injury to the meniscus, requiring no more than meniscus shaving. **Denotes statistical significance ***Graded knee function according to Tegner et al. [262]

The anterior drawer test

At the 16-year follow-up, better IKDC-SKF (75.3 ± 18.7 vs. 62.9 ± 20.2, p=0.0046) and Lysholm scores (84.1 ± 12.1 vs. 72.6 ± 20.2 p=0.0043) were observed in the group with a negative anterior drawer test at the two-year follow-up. There were no differences in evaluations of the Tegner activity scale, the single-legged hop test or OA at the 16-year follow-up (Table 18).

Table 18. The anterior drawer test: baseline comparison and long-term outcome for dichotomized subgroups

	Outcome variable	Positive anterior drawer test at two years	Negative anterior drawer test at two years	P-value
	Age at reconstruction, years			
	Mean ± SD	29.7 ± 9.2	27.4 ± 8.3	0.34
	Range	16-52	14-59	
	n	26	85	
	Sex, male/female	15 (58)/11 (42)	55 (65)/30 (35)	0.67
	n	26	85	
	Type of graft, HT/PT	17 (65)/9 (35)	47 (55)/38 (45)	0.50
	n	26	85	
	Associated injuries at surgery, yes (%)	16 (62)	63 (74)	0.32
	Medial meniscus	7 (27)	30 (35)	0.59
	Lateral meniscus	11 (42)	39 (46)	0.93
	Osteochondral lesion	4 (15)	4 (5)	0.47
	Other*	1 (4)	1 (1)	1.00
	n	26	85	
	New surgery during long-term follow-up, injured side, yes (%)	14 (54)	35/50	0.36
	Meniscus (medial and/or lateral)	6 (23)	22 (26)	0.99
	Osteochondral lesion	0	3 (4)	0.47
	Implant problems	1 (4)	3 (4)	1.00
	Septic knee	1 (4)	1 (1)	0.83
	Posterior cruciate ligament	0	1 (1)	1.00
	Extension deficit	0	0	1.00
	Other	6 (23)	5 (6)	0.038**
	n	26	85	
	Long-term follow-up period, years			
	Mean ± SD	16.4 ± 1.2	16.3 ± 1.2	0.95
	Range	14.0-18.7	13.3-18.6	
	n	26	85	

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	Lysholm score			
	Preoperative			
	Mean ± SD	68.5 ± 16.1	70.2 ± 14.9	0.65
	Range	34-94	14-99	
	n	26	85	
	Two-year follow-up			
	Mean ± SD	84.7 ± 17.3	88.5 ± 12.4	0.55
	Range	37-100	46-100	
	n	24	83	
	Tegner activity scale			
	Preoperative			
	Median (Q1:Q3)	4 (3:4)	4 (3:4)	0.65
	Range	2-7	1-8	
	n	26	85	
	Two-year follow-up			0.16
	Median (Q1:Q3)	6 (4:7)	6 (5:8)	
	Range	3-9	2-10	
	n	24	83	
	Single-legged hop test			
	Preoperative			
	Mean ± SD	79.0 ± 18.7	79.6 ± 20.8	0.53
	Range	29-108	10-113	
	n	24	78	
	Two-year follow-up			0.83
	Mean ± SD	89.4 ± 19.6	91.6 ± 14.2	
	Range	38-110	52-122	
	n	24	83	
Long-term outcome variables	**IKDC-SKF**			
	Mean ± SD	62.9 ± 20.2	75.3 ± 18.7	0.0046**
	Range	11.5-100	12.6-100	
	Achievement of PASS, yes (%)	7 (27)	49 (58)	0.011**
	n	26	85	
	Lysholm score			
	Mean ± SD	72.6 ± 20.2	84.1 ± 12.1	0.0043**
	Range	8-100	32-100	
	Knee function***	Fair	Good	
	n	26	85	
	Tegner activity scale			
	Median (Q1:Q3)	4 (3:5)	4 (3:5)	0.40
	Range	0-7	1-10	
	n	26	85	
	Single-legged hop test			
	Mean ± SD	83.0 ± 40.1	86.7 ± 25.3	0.84
	Range	0-184	0-142	
	n	25	85	
	Osteoarthritis			
	Kellgren-Lawrence			
	Median (Q1:Q3)	1 (1:2)	1 (0:2)	
	Range	0-4	0-4	0.39
	n	26	85	
	Cumulative Fairbanks			
	Median (Q1:Q3)	2 (1:5)	2 (1:3)	0.26
	Range	0-6	0-6	
	n	26	85	

HT = hamstring tendon, PT = patellar tendon, SD = standard deviation, Q1 = first quartile, Q3 = third quartile, LSI = limb symmetry index, PASS = Patient Acceptable Symptom State, n = number of patients with available data for the particular analysis *Other injury includes synovitis or minor injury to the meniscus, requiring no more than meniscus shaving. **Denotes statistical significance ***Graded knee function according to Tegner et al. 262

The pivot-shift test

A negative pivot-shift test at the two-year follow-up was associated with better IKDC-SKF scores (74.5 ± 18.8 vs. 46.9 ± 17.8, p=0.0014) and Lysholm scores (83.3 ± 13.4 vs. 58.9 ± 23.0, p=0.0007) and with a better Tegner activity scale (4 [3:5] vs. 3 [1:4], p=0.033). Moreover, a larger proportion of the patients with a negative pivot-shift test achieved IKDC-SKF PASS (57 vs. 0, p=0.011) after 16 years. There were no significant differences for the single-legged hop test or the presence of OA at the 16-year follow-up (Table 19).

Table 19. The pivot-shift test: baseline comparison and long-term outcome for dichotomized subgroups

	Outcome variable	Positive pivot-shift test at two years	Negative pivot-shift test at two years	P-value
Demographic comparison between dichotomized subgroups	**Age at reconstruction, years**			
	Mean ± SD	29.3 ± 7.9	27.9 ± 8.7	0.55
	Range	16-40	14-59	
	n	7	104	
	Sex, male/female (%)	3 (43)/4 (57)	67 (64)/37 (36)	0.45
	n	7	104	
	Type of graft, HT/PT (%)	6 (86)/1 (14)	58 (56)/46 (44)	0.24
		7	104	
	Associated injuries at surgery, yes (%)	5 (71)	73 (70)	1.0
	Medial meniscus	0	36 (35)	0.12
	Lateral meniscus	4 (57)	44 (42)	0.70
	Osteochondral lesion	3 (43)	9 (9)	0.054
	Other*	0	1 (1)	1.00
	n	7	104	
	New surgery during long-term follow-up, injured side, yes (%)	5 (71)	43 (41)	0.25
	Meniscus (medial and/or lateral)	2 (29)	26 (25)	1.00
	Osteochondral lesion	0	3 (3)	1.00
	Implant problems	0	4 (4)	1.00
	Septic knee	0	2 (2)	1.00
	Posterior cruciate ligament	2 (29)	0	0.13
	Extension deficit	0	0	1.00
	Other	2 (29)	8 (8)	0.24
	n	7	104	
	Long-term follow-up period, years			
	Mean ± SD	15.7 ± 1.7	16.4 ± 1.2	0.29
	Range	14.0-18.1	13.3-18.7	
	n	7	104	

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	Lysholm score			
	Preoperative			
	Mean ± SD	68.4 ± 15.3	70.2 ± 15.3	0.91
	Range	43-85	14-99	
	n	7	104	
	Two-year follow-up			
	Mean ± SD	81.3 ± 20.3	88.5 ± 13.0	0.19
	Range	37-95	46-100	
	n	7	100	
	Tegner activity scale			
	Preoperative			
	Median (Q1:Q3)	3 (3:4)	4 (3:5)	0.17
	Range	2-4	1-8	
	n	7	104	
	Two-year follow-up			
	Median (Q1:Q3)	5 (3:6)	6 (5-7)	0.18
	Range	3-9	2-10	
	n	7	100	
	Single-legged hop test			
	Preoperative			
	Mean ± SD	79.3 ± 8.0	80.0 ± 20.4	0.41
	Range	70-91	10-113	
	n	6	96	
	Two-year follow-up			
	Mean ± SD	83.1 ± 21.8	91.6 ± 14.9	0.30
	Range	38-105	39-122	
	n	7	100	
Long-term outcome variables	**IKDC-SKF**			
	Mean ± SD	46.9 ± 17.8	74.5 ± 18.8	0.0014**
	Range	11.5-63.0	12.6-100	
	Achievement of PASS, yes (%)	0	57 (55)	0.010**
	n	7	104	
	Lysholm score			
	Mean ± SD	58.9 ± 23.0	83.3 ± 13.4	0.0007**
	Range	8-75	32-100	
	Knee function***	Poor	Fair	
	n	7	104	
	Tegner activity scale			
	Median (Q1:Q3)	3 (1:4)	4 (3:5)	0.033**
	Range	0-5	1-10	
	n	7	104	
	Single-legged hop test			
	Mean ± SD	67.6 ± 35.7	87.5 ± 28.4	0.061
	Range	0-113	0-184	
	n	7	103	
	Osteoarthritis			
	Kellgren-Lawrence			
	Median (Q1:Q3)	1 (0:2.75)	1 (0:2)	0.54
	Range	0-4	0-4	
	n	7	104	
	Cumulative Fairbanks			
	Median (Q1:Q3)	1.5 (0:5.25)	2 (1:4)	0.65
	Range	0-6	0-6	
	n	7	104	

HT = hamstring tendon, PT = patellar tendon, SD = standard deviation, Q1 = first quartile, Q3 = third quartile, LSI = limb symmetry index, PASS = Patient Acceptable Symptom State, n = number of patients with available data for the particular analysis *Other injury includes synovitis or minor injury to the meniscus, requiring no more than meniscus shaving. **Denotes statistical significance ***Graded knee function according to Tegner et al. 262

The KT-1000 arthrometer

There were no significant correlations between the IKDC-SKF (rho = 0.04, p=0.71) and the Lysholm score (rho = 0.01, p=0.95) at the 16-year follow-up and the examination of the KT-1000 arthrometer at the two-year follow-up. No other outcome variables (Tegner activity scale, single-legged hop test, signs of OA) were associated with the KT-1000 (table availiable in Study V in the appendix).

5 Discussion

Generalized Joint Hypermobility and Specific Knee Laxity

Aspects of Influence on the Anterior Cruciate Ligament-injured Knee

DAVID SUNDEMO

This thesis has reviewed two main concepts, generalized joint hypermobility and specific knee laxity, and their influence on the ACL-reconstructed knee. Knee hyperextension, which is also evaluated in the current thesis, belong to both concepts. Specific knee laxity, as used in this thesis, includes measurements of anteroposterior and rotatory knee laxity. To simplify reading, the discussion is structured under three main headings: (1) generalized joint hypermobility, (2) knee hyperextension and (3) specific knee laxity. The discussion ends with a section on the interaction between the concepts, how to interpret the aggregated results of the current thesis and, briefly, which questions it poses for the future.

Generalized joint hypermobility

Classification of GJH and hypermobility cut-off value

As discussed in Study I, there is considerable variation in the use of methods for evaluating and defining GJH. Study I reported that six main methods were used to define GJH. The most common method for determining GJH was the Beighton score, used in 12 studies. However, even within this limited group of studies, four different cut-off values were used to determine whether GJH was present. This variability is problematic, since the comparability of results between studies is compromised. Moreover, if the methods that are used are not described in detail, the external validity, the generalizability of the results, can be questioned. In order to enable the performance of future quantitative meta-analyses of studies assessing GJH, standardized methods for determining GJH must be used.

A retrospective study design has been used in several of the studies assessing GJH and the risk of ACL injury and the effect on postoperative outcome. [121, 122, 124] This means that the evaluation of whether GJH is present is conducted post injury, when the traumatic knee injury potentially affects the range of motion of the injured knee. This issue has been approached differently: by only evaluating GJH in the uninjured side of the body[140], by using an *injury allowance point*[251] and by taking historical information into account, using the 5PQ. [86] All three methods appear logical and theoretically valid, although only the 5PQ has been tested in terms of validity. [114]

Generalized joint hypermobility and ACL injury risk

Even though no original data relating to the question of GJH and ACL injury risk were reported in Studies I-V, this question is a central theme in the current thesis. Although GJH is often cited as a risk factor for ACL injury [9, 270], synthesis of the accumulated evidence on this topic has been lacking. Does GJH affect male and female ACL-injury risks in the same way? Individual studies have stratified the influence of GJH by sex [227, 270], but no comprehensive summary or synthesis has been presented.

Study I provides a detailed review of the subject. Of the five studies analyzing both males and females in the same group, they all reported associations between GJH and ACL injury. However, when summarizing the results for males and females separately, another pattern appears. Based on available evidence, it appears that there is more consistent support for GJH as a risk factor for ACL-injury risk in males than in females. In females, the results were conflicting, with one of the studies indicating that less hypermobility may be associated with ACL injury. [239] This finding was surprising, as both GJH and female sex[22, 36] are regarded as risk factors for ACL injury and since GJH is more frequently found in females.[207] It can therefore be hypothesized that the reason for the greater ACL-injury risk in females could be partly attributed to the prevalence of hypermobility. However, it is possible that other factors, including poorer neuromuscular control, [92, 106, 111, 231] hormonal factors[90] and a narrower femoral intercondylar notch, [146, 270] have a greater impact on the overall ACL-injury risk in females.

Graft failure risk

The risk of graft failure and ACL revision is an important topic. It is a dreaded complication after ACL surgery and, to better understand graft failure mechanisms, several previous studies have attempted to identify risk factors for graft failure and ACL revision [44, 140, 244, 258, 289] Study I reviews the current evidence on the subject, finding a total of four studies. In the synthesis of the evidence, no clear-cut association between GJH and graft failure risk was found. However, in two of the studies, a significant association was found [7, 141] and, in the other two, a consistently higher graft failure rate was reported, irrespective of the type of graft that was employed. [122, 124] In the two studieswhere no significant difference was found; the rate of graft failure differed by 6.9-7.2% between patients with and without GJH, with the higher rates observed for patients with GJH. Moreover, no information was provided on whether sample size analysis was performed for this specific outcome. This lack of information, in combination with the large difference in graft failure rate, generates the question of whether the studies were underpowered in terms of this specific outcome.

Knee laxity

In terms of the discussion of knee laxity, two central aspects arise: (1) the cross-sectional preoperative correlation between GJH and instrumented rotatory knee laxity/QPS and (2) the impact of GJH on postoperative knee laxity. In terms of the first aspect, appraised in Study III, the question of why it is of interest to scrutinize a potential correlation between GJH and QPS can be posed. The aim was to elucidate any potential synergistic effects between two preoperatively quantifiable variables with individual detrimental postoperative effects. The selection of QPS in particular is due to the association between rotatory knee laxity and postoperative morbidity, in terms of clinical outcome and the development of osteoarthritis. [109] In Study III, no correlation between GJH and QPS in the ACL-injured knee was found. This is the first publication to study this particular association, which means that little previous literature that could support or refute the results is available. However, one previous study reported that GJH was associated with increased preoperative laxity measured with the Lachman test, the anterior drawer test and the manual pivot-shift test. [156] This was a large study, reporting odds ratios for GJH above 2 for the anteroposterior laxity tests and above 3 for the pivot-shift test. However, the evaluation of GJH in this particular study was not clearly described. The authors used the IKDC system to define GJH, enabling the classification of ligamentous laxity into three categories: tight, normal or lax. The undetailed description allows for considerable differences in terms of evaluation methods and definitions of what should be regarded as a lax individual, leading to questionable inter-examiner variability and lower internal validity.

The assessment of the contralateral healthy knee, conducted in Study III, revealed an association between GJH and QPS, verified by both the Spearman correlation analysis and the multivariate analysis. In terms of confounding factors, rotatory knee laxity is influenced by the presence of meniscal injuries, age and sex. [156, 179, 260] Moreover, age and sex are factors that affect the degree of GJH. [200, 274, 286] These three factors were therefore adjusted for in the multivariate analysis. It must be said, however, that the reported correlation was weak and more studies are needed to verify these results. Also, a factor that may influence the results is that GJH is associated with skin hyperextensibility. Skin to bone motion correlation has been regarded as strong in non-hypermobile individuals for the image analysis system, [176] though it may be more of an issue in patients with GJH. Bone-anchored sensors may therefore have produced different results. Taken together, there is an indication of a possible link between GJH and QPS in the healthy knees. In ACL-injured knees, there is no clear correlation between QPS and GJH and previous conflicting data exist. As a result, future studies will shed further light on this potential association.

In terms of the second aspect, relating to GJH and postoperative knee laxity, this was reviewed in Study I. The systematic review revealed that GJH had little influence on postoperative knee laxity at two years, although there was a considerable increase in knee laxity in patients with GJH at five and eight years. The reason for this phenomenon is unknown. It is possible that the existence of GJH naturally extends the rehabilitation phase, causing fewer patients to return to their preinjury level of activity within two years. Experts on rehabilitation in patients with GJH have recommended a careful and gradual increase in rehabilitation intensity, together with a gradual return to activity, and it is possible that these recommendations have been adhered to by physical therapists. [66] When the patient returns to his/her preinjury level of activity, increased strain affects the reconstructed graft, possibly causing graft elongation, which is then observed as increased knee laxity in patients five and eight years postoperatively. Using the same argument, it has previously been reported that GJH has been associated with postoperative biological graft failure with intact but elongated grafts. [7]

Functional tests

There is a lack of knowledge in terms of functional performance in patients with GJH after ACL reconstruction and no studies assessing this were identified in Study I. However, previous studies have reported that individuals with GJH have a higher rate of torque development in knee flexion [107] and increased knee extensor rate of force [163], factors that are considered important in hop performance. [279] In line with this, a previous study has reported that children with GJH have better results in vertical counter-movement jumps. [112] These are interesting results, but they are not directly comparable to the results of Study II. Study II evaluated the relative performance between the limbs, the injured and the uninjured, to assess rehabilitation and the development of symmetrical strength. The results did not indicate any differences in the ability to regain symmetrical strength or jumping performance at one year after ACL reconstruction. Interestingly enough, a mean and median level above 90% was reached in terms of hop and strength tests, irrespective of the presence of GJH, for all the tests but one. Thus, acceptable results can be expected in the short term, in terms of hop-test and strength rehabilitation, regardless of whether or not patients have GJH.

Patient-reported outcome

Patient-reported outcome is one of the most frequently reported outcomes in assessments of ACL-injured patients with GJH, as can be observed in Study I. As summarized in Study I, there was substantial evidence demonstrating that GJH was associated with inferior postoperative patient-reported outcome. A poorer Lysholm score[122, 124], IKDC-SKF score[122, 124] and Cincinnati knee rating system[141] have previously been reported in patients with GJH, five and eight years after ACL reconstruction, with consistent findings. The evidence was more conflicting after two years. [122, 124] Revisiting the literature, inferior patient-reported outcome measures may not be entirely surprising. Even uninjured patients with self-reported GJH have increased knee joint symptoms, hindering them from performing their usual daily activities. [110] This group may therefore be particularly susceptible to post-injury disability and discomfort.

However, the summarized evidence synthesized in Study I may appear to be contradicted by the results reported in Study II. Original data, presented in Study II, did not confirm postoperative inferiority in terms of patient-reported outcome in patients with GJH. In the dichotomous analysis, comparing patients with and without GJH, no significant differences were found with regard to the KOOS subscales. The analysis of the continuous Beighton score even revealed a positive association with the KOOS sports and recreation subscale. This result suggests that a gradual increase in hypermobility is associated with less subjective impairment during a number of activities, including squatting, running, jumping and kneeling. The results of Study II may therefore appear to contradict those in previous studies. There are three main reasons that could explain the differences. First, the small number of individuals in the group with GJH results in insufficient power to draw any conclusions regarding the dichotomous analysis. Consequently, a type-II error may obscure the detection of an actual difference and no conclusions should therefore be drawn from this analysis. Second, a dichotomous analysis of GJH, performed in the studies included in Study I, cannot be directly compared with a continuous analysis of the Beighton score. Previous evidence indicates that GJH may offer athletic advantages, in certain physical activities. [71, 79] The nature of this association is unknown, although it may be reasonable to assume that the athletic advantages reside in the lower spectrum of the Beighton score scale. This may be part of the explanation. However, the group with GJH had superior results for all KOOS subscales, albeit not statistically significant. Individuals with GJH may therefore experience short-term benefits not detected in previous studies, since the follow-up time for the majority of studies has been two years or longer. This argument could be related to the previous discussion under "Knee laxity", where increasing knee laxity was observed in longer follow-up periods in ACL-reconstructed patients with GJH. Since increased knee laxity is related to inferior patient-reported outcome, patients with GJH may experience increasing impairment and symptoms when postoperative knee laxity increases. The third factor, which could partly explain the differences, is the inability to adjust for concomitant injuries to the menisci and the articular cartilage in Study II. Since Study IV reported that knee hyperextension was associated with fewer meniscal injuries, the relationship may be the same between GJH and injuries to the menisci. Injuries to the menisci are related to inferior patient-reported outcome [245]and increased anteroposterior [152, 156, 250] and rotatory knee laxity. [156, 175, 179, 246, 260] Thus, hypothetically, a potential lower rate of concomitant meniscal injuries in patients with higher Beighton scores may be a reason for superior subjective knee function.

Graft choice

The choice of graft has been discussed in patients with GJH since 2008 at the very least. [126] Generally, selecting the correct graft type for ACL reconstruction is important and perhaps particularly so in patients with GJH. As reported in Study I, increased anterior knee laxity and inferior Lysholm and IKDC scores were reported for patients receiving HT autografts, compared with patients receiving PT autografts. The same results have been found in the general population, where PT autografts have been associated with less knee laxity. [233] Moreover, as previously discussed, patients with GJH run a greater risk of developing increased knee laxity postoperatively compared with patients without GJH. Optimizing treatment to reduce the risk of postoperative knee laxity is therefore of great importance. Apart from an advantage in terms of postoperative knee laxity for the PT autograft, this graft type has also been associated with superior patient-reported outcomes, as reported in Study I. The reason for the improved results produced by PT autografts is unknown, although it may be related to the ultrastructural composition of the tissue. Hypermobility of the joints is caused by alterations in collagen and the extracellular matrix [79]. Thus, hypothetically, allografts may have theoretical advantages, since the quality of the connective tissue of the innate tendons of patients with GJH may be inferior. This argument is in contrast to the situation in the general public, where allografts are inferior in terms of both knee laxity and patient-reported outcome. [280] One study has compared the allograft failure rates of patients with and without GJH, finding increased failure in the group with GJH. [141] However, the more interesting question is to analyze whether allograft or autograft tissue is better in a population where all the patients have GJH, something that has not been done previously.

Knee hyperextension

Laxity

Hypermobility of the knees and its relationship with postoperative outcome after ACL reconstruction is an interesting subject. Study IV analyzed the ATT of the ACL-injured knee, six months after surgery, in relation to the degree of contralateral KHE. This study reported that patients with mild and moderate contralateral KHE had significantly higher ATT in the ACL-injured knee, both preoperatively and after six months. The differences were small yet significant. A study by Kim et al. investigated the influence of contralateral ATT on knee laxity and patient-reported outcome in the ACL-injured knee two years postoperatively. [127] This study reported that increased laxity in the contralateral knee was associated with increased ATT of the injured knee and with poorer IKDC and Lysholm scores. [127] The methods are not entirely comparable, since contralateral knee hyperextension may not be linearly correlated with contralateral ATT, but both studies imply that increased laxity in the contralateral knee is associated with increased laxity in the ACL-injured knee. However, Study IV reported that there was no significant increase in terms of side-to-side difference or pre- to postoperative ATT reduction. An acceptable postoperative reduction in ATT can therefore also be acquired in patients with hyperextension, at least in the short term.

Concomitant injuries

Study IV reported surprising results in terms of the relationship between contralateral knee hyperextension and concomitant meniscal injuries. The hypothesis stated that increased hyperextension would be associated with an increased risk of concomitant injuries, although the results showed the opposite. Since hypermobility is a risk factor for ACL injury, [185, 192, 203, 270] the same relationship was assumed for concomitant injuries. Study IV merely observes a difference; the study is unable to draw conclusions in terms of the cause of this difference. However, one possible explanation could be that the ACL of patients with KHE ruptures more easily. Previous studies have reported that KHE is a risk factor for ACL injury and graft rupture. [141, 185, 272] In line with this argument, less force might therefore be required to cause an injury to the ACL in these patients. Conversely, to rupture the ACL in patients without KHE, increased force and more severe traumas would be required, which could increase the risk of other concomitant injuries. This is only an hypothesis and future research is needed to better understand this association.

Specific knee laxity

Study V investigated how postoperative knee laxity affects functional performance, patient-reported outcome and the development of osteoarthritis in the long term. Differently from the other studies in the thesis, the independent variable consist of data from an ACL-injured knee. The other studies, assessing the influence of GJH and KHE, aim to isolate uninjured joints by using them as independent variables. The specific knee laxity assessed in Study V is therefore affected by much more than the anatomy and the ultrastructural quality and composition of the tissues. It may be affected by concomitant injuries, surgical technique, type of graft and quality of and adherence to rehabilitation.

Functional tests

Study V evaluated the single-legged hop test for distance. There was a 20% difference in terms of the mean single-legged hop test LSI in favor of patients with a negative pivot-shift test after two years, although the analysis was not statistically significant. As previously discussed, an LSI quotient above 90% is regarded as acceptable. [82, 265] The mean single-legged hop test LSI of the patients with a negative pivot shift after 16 years was 87%. At a mean age of 44 years (adding the mean age at operation with the mean follow-up time for the patients with a negative pivot-shift test), with a knowledge of the high risk of post-traumatic OA within 10-20 years after ACL injury, 87% must be regarded as a great result. On the other hand, a result of 67%, seen in patients with a positive pivot-shift test, implies that there may be issues of pain and disability in the previously injured knee hindering symmetrical performance.

Patient-reported outcome

One of the most interesting findings in Study V was that increased postoperative manual knee laxity generated an inferior patient-reported outcome. Increased laxity at two years, evaluated with the Lachman test, the anterior drawer test and the pivot-shift test, resulted in poorer IKDC-SKF and Lysholm scores after 16 years. The IKDC-SKF was analyzed both by analyzing the continuous variable and by using the PASS. A negative Lachman test, anterior drawer test and pivot-shift test were associated with better continuous IKDC-SKF scores and with a greater chance of achieving PASS. The majority of patients (55-61%, depending on the test) with negative laxity tests achieved PASS, while few patients with positive laxity tests did (0-38%). The PASS was originally constructed to evaluate patient satisfaction between one to five years postoperatively. With this in mind, the results showing that the majority of patients with negative knee laxity at two years have acceptable knee function after 16 years is encouraging. In contrast, two previous studies with short- to mid-term follow-ups did not report any significant

influence of anteroposterior laxity on patient-reported outcome. [109, 133] There were no associations between anteroposterior laxity and either the Lysholm score or the Tegner activity scale or with other symptoms related to ACL deficiency, in these studies. [109, 133] The difference between the results in Study V and previous studies may be attributable to the longer follow-up time and the larger cohort size of Study V, increasing the time to develop symptoms and improving study power.

The instrumented assessment of ATT, using the KT-1000, did not reveal a statistically significant correlation with patient-reported outcome. The discrepancy between the results of the instrumented ATT and the manual knee laxity tests is difficult to explain. However, since the Lachman test and the anterior drawer test were dichotomized into two separate groups, this is not completely comparable to the continuous correlation analysis which was conducted using the KT-1000. It is possible that the dichotomization of the KT-1000 ATT, using a > 5mm cut-off value, would generate a different result.

The relationship between specific knee laxity, knee hyperextension and GJH

Based on the results of the current thesis, it appears that patients with GJH and KHE run an increased risk of postoperative knee laxity. Moreover, as reported in Study V, increased postoperative knee laxity is associated with inferior patient-reported outcomes. GJH is therefore not just directly associated with issues related to knee pain and symptoms [110] but also with knee laxity. As knee laxity tests were associated with poorer IKDC-SKF scores and Lysholm scores and with a poorer chance of achieving PASS, it is evident that residual knee laxity is clearly burdened with considerable morbidity. So, summarizing the results of the thesis, it is obvious that patients with GJH or KHE run an increased risk of a poorer postoperative outcome and there may be negative synergistic effects between GJH, KHE and postoperative knee laxity. However, the relationship between GJH, KHE and knee laxity has barely been researched. One important question is whether GJH produces additional explanatory significance that cannot be explained by KHE alone. While GJH may indicate alterations in the ultrastructural composition of the connective tissues, such as collagen, [79] isolated KHE may instead be a manifestation of anatomic factors such as bony morphology, meniscus appearance or ligament length. One study by Kim et al. performed an interesting study on this subject. [129] The authors concluded that KHE alone was able independently to predict knee stability and function, regardless of whether patients had severe GJH. As has been reviewed, other studies have demonstrated that GJH has an effect on different aspects of the postoperative outcome. However, it is not known whether the sole explanatory variable is the existence of KHE, since only one study has addressed this specific question.

6 Limitations

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Study I

Study I is a comprehensive systematic review, including clinical studies with different study designs. The main limitations are therefore related to the quality of the studies included in the review. First, several methods were used to identify GJH in the studies and different cut-off values were used. As a result, no specific recommendations relating to different increments or intervals of hypermobility can be made. Statements relating to outcome and treatment are accordingly general. Second, sample-size calculation was missing for several of the involved studies, which increases the risk of a type-II error in these studies.

Third, quantitative analysis was not deemed appropriate because of heterogeneity, in terms of both the determination of GJH and the dispersion of confounding variables. The potential confounders sex and age were of particular interest in Study I, since females and younger individuals run a greater risk of ACL injury[13, 22] and since GJH is more common in females and in the young. [207] However, several potential confounders, including intrinsic and extrinsic risk factors and injury mechanisms, were not considered in the majority of the studies. To illustrate the importance of considering confounders in assessments of risk factors for ACL injury, the results of one of the included studies could be reviewed. This study conducted both multivariable adjusted and non-adjusted analysis and, by adjusting for known confounders, the regression coefficients changed by at least 10%. [184]

Last, one research group contributed the majority of or all the available evidence for the following topics: osteoarthritis, postoperative knee laxity, postoperative clinical outcome and the influence of graft type in patients with GJH. This research group should be commended for their impressive work, although it should also be stated that the results are possibly but not necessarily directly transferable globally. The prevalence of hypermobility is affected by ethnicity[207] and there is currently an ongoing debate about the significance of genetic alterations and their association with ACL injury. [116]

Considering the abovementioned limitations and, in some cases, the lack of studies, there was insufficient evidence to draw any conclusions on the following topics; bilateral ACL injuries, graft failure and return to physical activity.

Study II

For Study II, there are a few limitations that need mentioning. First, the most important limitation is the obviously insufficient sample size for the dichotomous analysis, not reaching the preferred 0.8 power limit. It is therefore scientifically incorrect to draw any conclusions based on this analysis. However, linear regression analysis was also performed using GJH as a continuous variable. One advantage of using linear regression analysis is that it provides the ability to adjust for known confounders.

Second, the Project ACL database contains no information on concomitant articular injuries. Meniscal and cartilage injuries are related to postoperative morbidity and could therefore potentially interfere with the results. [214, 260]

Third, good LSI measurements as a sign of a successful rehabilitation are not without their problems. Using LSI, the contralateral uninjured limb is the reference, although it should not be regarded as a reference for the preinjury strength of the injured limb. The knee function and lower limb strength of the uninjured knee often decrease after injury. Consequently, a previous study proposed that the results for the uninjured limb, acquired just a short time after injury, would be a better benchmark for successful postoperative rehabilitation, however this method was not employed in the current study. [282]

Study III

Study III has a few limitations. First, the pivot-shift examination is difficult to perform and grade and there is considerable variability between examiners. [196] However, using the standardized pivot-shift test improves the reliability of the procedure. [17] Moreover, the multicenter study design improves generalizability, though with multiple centers and examiners it is probable that the test variability increase. To mitigate this risk, pre-study investigator meetings, including all involved centers, were held to standardize examination technique. Second, there were demographic differences between the GJH and non-GJH groups in the following areas; sex, age and Marx Activity Scale. As previously reviewed, a skewing in terms of age and sex is to be expected, knowing the prevalence pattern of GJH. [200, 274, 286] To remedy the influence of variance in demographic variables, a multivariate analysis was

performed. As mentioned in the discussion, skin markers may be less accurate in patients with GJH owing the association of joint hypermobility to skin hyperextensibility. Bone-anchored sensor data was not available in this study.

Study IV

First, one of the more significant limitations of Study IV is the short follow-up period, with postoperative assessments taking place at six months. At six months after surgery, postoperative rehabilitation is still ongoing and many patients have not returned to sport, meaning that the strength of the graft will not have been tested to the limit of its ability. The results of the study should therefore not be regarded as representative of patients who have returned to sport but merely as short-term results showing the state of the graft during the later stage of ACL rehabilitation. Second, the differences in ATT are very small in absolute numbers. The different group means are within the interval of the margin of error for the KT-1000 for individual patients. [237] However, the group mean, with each mean containing data on hundreds or thousands of patients, is something entirely different from a mean from an individual patient, where three or more examinations are analyzed to create an individual examination mean. Thus, even though the differences are small and are probably not clinically significant, they indicate a progressive increase in ATT with an increasing degree of contralateral KHE.

Study V

Study V has a few limitations that need to be considered. First, there is a risk of attrition bias. Of all the patients originally recruited to the cohort, 76% attended the 16-year follow-up. Moreover, patients with a graft rupture and contralateral ACL injury had to be excluded in order to realize the aim of the study, the way patients with intact grafts but increased knee laxity at two years coped in the long term.

Second, as previously mentioned as a limitation for Study III, the pivot-shift test is difficult to perform and interpret. [97] A fairly small number of patients were considered to have positive tests. This may affect the power of the analyses involving the pivot-shift test.

Third, the manual knee laxity tests were dichotomized for the purpose of analysis. This generates a simplification of the outcome. However, very few patients were considered to have grade 2 laxity and no patients had grade 3 laxity, which explains why dichotomization was considered to be a good alternative.

Fourth, radiographs assessing the baseline degree of OA were not available. A skewing in the baseline degree of OA may therefore have been present.

Fifth, the study is based on two randomized controlled trials. Randomized controlled trials is the gold standard to evaluate and compare treatment regimens. However, in the present study the randomization process was not related to the aim of the study and did therefore not contribute in terms of improved study quality. Instead, the randomization process may have introduced unknown factors, possibly affecting the outcome which may bias the results.

Last, the surgical technique used to perform the ACL reconstructions in Study V was non-anatomic. It was isometric and mainly used a transtibial approach. Consequently, the results of the Study V may not be entirely representative of modern anatomic surgical techniques.

7 Future perspectives

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DAVID SUNDEMO

The scientific efforts that are being made to understand the different aspects of ACL injury mechanics and ACL treatment are substantial. This is a field that has been relevant for many decades, but, following the increase in human knowledge in general, it has recently seen rapid progress, to the benefit of our patients. In 2012, there were 11,000 studies on the topic of ACL. In 2019, more than 20,000 studies are available after searching through the PubMed database and this database is not even totally exhaustive. Consequently, there has been almost a doubling of the number of studies in seven years. This is truly remarkable. Even so, research on the influence of GJH and KHE on ACL-injury risk and outcome is surprisingly scarce and the quality of the available studies varies. To exemplify, there is no randomized, controlled trial that compares treatments or outcomes in patients with GJH. This is unexpected, since GJH has been regarded as a risk factor for ACL injury since 2004 at the very least and the publication of Uhorchak's four-year prospective study. [270] In terms of future perspectives and recommendations, many different factors could be discussed. However, to keep it concise, this section will focus on five main areas that need to improve within the research covered by the current thesis.

First, the assessment and determination of GJH has to be standardized. This is important. To enable comparisons between studies and to be able to perform quantitative meta-analyses, the determination of GJH needs to be standardized. Both standardized evaluation methods and cut-off values should be used. The recommendation would be to use the definition of GJH presented in the consensus document by Malfait et al. in 2017, with variable cut-off values depending on age and maturity. [158] Moreover, to consider any potential post-injury alterations in the range of motion of the ACL-injured knee, either the five-point questionnaire[86, 158] or an injury allowance point should be used. [251]

Second, the reason why patients with GJH run an increased risk of ACL injury and inferior postoperative outcomes needs to be more thoroughly investigated. This topic is not directly covered by the current thesis, but it is a central aspect of future research to deepen our understanding of GJH and its detrimental effects on ACL-injured athletes. Associated impaired neuromuscular function has been mentioned. [185] The reason for GJH has been related to the constitution and ratio of the connective tissues, including collagen and fibrillin. [79] Studies assessing the ultrastructural composition of the tendons and ligaments of athletes with GJH would increase our understanding of whether the connective tissues of individuals with GJH are of inferior quality.

Third, additional high-quality, preferably prospective studies, are needed to better understand whether GJH affects ACL-injury risk differently in males and females. There is also a need for randomized, controlled trials in the assessment of treatment options for patients with GJH. The current evidence suggests that PT autografts are the best alternative, although this is based completely on retrospective observational studies. [122, 124] To make scientifically sound recommendations in terms of type of graft and surgical technique, randomized, controlled trials are crucial.

Fourth, two of the studies raised the question of potential athletic advantages for patients with GJH. Study II reported better patient-reported outcomes with a gradually increasing Beighton score, while Study III observed a higher level of preoperative physical activity in patients with GJH. There are few studies assessing this subject and there is some conflicting evidence. Patients with GJH have been reported to prefer stable activities [228], potentially generating a lower level of physical activity. However, increased jumping ability has been observed in children with GJH. [112] The association between GJH and physical activity is puzzling and future studies have many blanks to fill. One important aspect in assessments of GJH and physical activity is not to forget the prevalence of GJH. This prevalence is clearly related to age, and younger populations have a higher prevalence of GJH but also tend to be more physically active.

Fifth, with the foundation in the data emanating from the current thesis, one study in particular provides new and original data that may be of direct clinical relevance in the future; increased knee laxity two years after ACL reconstruction generates inferior patient-reported outcome in the long term. One interesting fact is that there was no difference between the laxity-based groups at two years, but, after 16 years, significant differences had emerged. This creates a window of opportunity where it is possible to improve the situation for patients with increased laxity at two years, in order to mitigate the risk of long-term detrimental effects. Surgeons should mainly consider optimizing the treatment by reducing knee laxity caused by meniscal root tears, symptomatic collateral ligament injuries or pathology to the anterolateral structures. Moreover, routine-based follow-up visits to the orthopedic surgeon could be considered to evaluate knee function and laxity and, if appropriate, offer additional treatments including individualized physical therapy or revision surgery in the event of graft rupture.

8 Conclusions

Generalized Joint Hypermobility and Specific Knee Laxity

Aspects of Influence on the Anterior Cruciate Ligament-injured Knee

DAVID SUNDEMO

Study I

Generalized joint hypermobility was associated with increased risk of ACL injury in males. Moreover, GJH was associated with increased knee laxity and inferior patient-reported outcomes postoperatively. Based on the limited evidence available, a patellar-tendon autograft appears to be superior to hamstring-tendon autograft in patients with GJH. However, the studies included in the review were heterogeneous and there is a need for consensus in the evaluation and definition of GJH in sports medicine literature.

Study II

One year after ACL reconstruction, a linear increase in the BS was associated with an improved sport-specific patient-reported outcome. No association between GJH and return to sport, hop tests and muscular strength was identified, however. Acceptable limb symmetry results are expected in terms of hop tests and muscular strength one year after ACL reconstruction, irrespective of the presence of GJH.

Study III

A weak correlation between GJH and QPS of the contralateral healthy knee was identified, indicating increased rotatory knee laxity in these patients. Generalized joint hypermobility does not appear to correlate with QPS in ACL-injured knees.

Study IV

Contralateral knee hyperextension was associated with greater pre- and postoperative ATT in the ACL-injured knee. In patients with contralateral knee hyperextension, concomitant injuries to the menisci were less frequent.

Study V

Increased manual anteroposterior and rotatory knee laxity two years after ACL reconstruction was associated with inferior patient-reported outcome after a mean of 16 years.

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10 References

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