ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION: LONG-TERM OUTCOME IN ADULTS AND ADOLESCENTS

Clinical results, health-related quality of life, radiographic findings and bone mineral assessments

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Anterior cruciate ligament reconstruction: long-term outcome in adults and adolescents
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To Linn and Petronella

Learn from yesterday, live for today, hope for tomorrow.
The important thing is not to stop questioning.

–Albert Einstein

CONTENTS

ABSTRACT

The aim of this thesis was to measure health-related quality of life (HRQoL) and assess pre-operative factors predicting a good outcome of HRQoL after anterior cruciate ligament (ACL) reconstruction. Furthermore, the aim was specifically to assess long-term radiographic findings, clinical results and bone mineral density in adolescents after ACL reconstruction. In Study I, HRQoL was evaluated using the SF-36 questionnaire two to seven years after an ACL reconstruction in 419 patients and compared with a gender- and age-matched Swedish control group (n=2,410). The patient group obtained significantly higher scores for General Health, Social Function, Role Emotional and Mental Health. The control group obtained significantly higher scores for Physical Function compared with the ACL group. After ACL reconstruction, the patients reported good health-related quality of life in comparison with a matched sample of the Swedish population. In Study II, pre-operative predictive factors for a good post-operative clinical outcome after ACL reconstruction were evaluated. Seventy-three ACL-injured patients answered the SF-36 and KOOS questionnaires, three to six years after reconstruction. Predictive factors for HRQoL were investigated using a step-wise regression analysis. Pre-operative factors, such as the pivot-shift test, the manual Lachman test, range of motion, Tegner activity level pre-injury and pre-operatively may predict a good post-operative outcome in terms of HRQoL after ACL reconstruction. In Study III, a long-term follow-up of adolescents after ACL reconstruction was performed. Twenty-nine adolescents were evaluated 10-20 years after ACL reconstruction in terms of the presence of osteoarthritis, clinical assessments and HRQoL. In the long term, patients who were adolescents at the time of ACL reconstruction revealed significantly more radiographically visible osteoarthritic changes in their operated knee compared to their non-involved contralateral knee. However, the clinical outcomes and HRQoL were comparable with those of healthy controls. In Study IV, bone mineral density (BMD) was evaluated in the same 29 adolescents, 10-20 years after ACL reconstruction. The BMD was measured in both calcanei using the DXA (Dual-energy X-ray absorptiometry) technique and compared with a control group of adult ACL-reconstructed patients, as well as a reference database with DXA measurements from healthy age-matched individuals. The BMD in patients who were adolescents at the time of ACL reconstruction differed from a control group and a reference database. In male patients, the BMD value was lower compared with both the control group and the reference database. In female patients, the BMD value was higher compared with the reference database. A decrease of one standard deviation in BMD increases the relative risk of any kind of future fracture 1.5 times. Considering the future fracture risk, it might be of clinical relevance to assess the BMD after ACL reconstruction in adolescents.

Keywords: health-related quality of life, anterior cruciate ligament, reconstruction, bone mineral density, osteoarthritic, radiography, adolescents

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SAMMANFATTNING PÅ SVENSKA

Syftet med avhandlingen var att mäta hälsorelaterad livskvalitet och att identifiera preoperativa faktorer som kan förutse en bra livskvalitet efter främre korsbandskirurgi. Ytterligare ett syfte var att utvärdera långtidsresultatet med avseende på artrosförändringar, benmineral (BMD) innehåll i hälbenet och det kliniska resultatet hos korsbandsrekonstruerade, nästan skelettmogna tonåringar. I delarbete I mättes livskvalitén 2-7 år efter rekonstruktion hos 419 korsbandsskadade patienter med SF-36 frågeformulär. Resultaten analyserades och jämfördes med en svensk ålders- och könsmatchad kontrollgrupp bestående av 2410 personer. Sammanfattningsvis uppvisade patienter efter främre korsbandsrekonstruktion en jämförbar livskvalitet med en frisk matchad kontrollgrupp. I delarbete II identifierades preoperativa faktorer med hjälp av frågeformulären SF-36 och KOOS som kan ha betydelse för det postoperativa resultatet efter 3-6 år hos 73 korsbandsrekonstruerade patienter. Bestämning av de predicerande preoperativa faktorerna gjordes med stegvis regressionsanalys. Analysen visade att pivot-shift test, Lachman test, knäts rörelseomfång, Tegners aktivitet nivå före skadan och före operation kan ha betydelse för livskvaliteten efter främre korsbandsrekonstruktion. I delarbete III utvärderades långtidsresultatet hos 29 korsbandsskadade tonåringar 10-20 år efter korsbandsrekonstruktion med avseende på förekomst av artrosförändringar, hälsorelaterad livskvalitet och det kliniska resultatet. Artrosförändringar bedömdes med röntgenundersökning, livskvalitet utvärderades med SF-36 och KOOS. Studien visade att tonåringar som nästan var skelettmogna vid korsbandsrekonstruktion har röntgenologiskt mer synliga artrosförändringar i det opererade knät jämfört med det friska ickeopererade knät. Däremot var det kliniska resultatet och livskvalitet jämförbart med friska kontroller. I delarbete IV utvärderades BMD hos samma 29 korsbandsopererade tonåringar efter 10-20 år. BMD mättes med DXA (Dual-energy X-ray absorptiometry) teknik i båda hälbenen. Resultaten jämfördes med en kontrollgrupp bestående av 34 korsbandsopererade vuxna samt med en frisk ålders- och könsmatchad grupp från DXA referens databas. Sammanfattningsvis sågs att BMD hos personer som var tonåringar vid korsbandsrekonstruktion skiljer sig från en kontrollgrupp och en referens databas. För männen var BMD-värdena lägre i jämförelse med båda grupperna och för kvinnorna högre i jämförelse med referensdatabasen. En minskning med en standard deviation i BMD ökar den framtida frakturrisken för alla typer av frakturer med 1.5 gånger. För den framtida ökade frakturrisken, är det möjligen av klinisk betydelse att mäta BMD hos korsbandsopererade tonåringar.

LIST OF PAPERS

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

I. **Health-related quality of life after anterior cruciate ligament reconstruction.**
Månsson O, Kartus J, Sernert N
Knee Surg Sports Traumatol Arthrosc. 2011;19(3):479-87

II. **Pre-operative factors predicting good outcome in terms of health-related quality of life after ACL reconstruction.**
Månsson O, Kartus J, Sernert N
Scand J Med Sci Sports. 2013; 23(1):15-22

III. **Long-term clinical and radiographic results after delayed anterior cruciate ligament reconstruction in adolescents.**
Månsson O, Sernert N, Rostgard-Christensen L, Kartus J
Am J Sports Med. 2015;43:138-145

IV. **Long-term examination of bone mineral density in the calcanei after ACL reconstruction in adolescents and matched adult controls.**
Månsson O, Sernert N, Ejerhed L, Kartus J
Arthroscopy: The Journal of Arthroscopic and Related Surgery; accepted for publication

PREFACE

Personal reflection

My first contact with an anterior cruciate ligament injury (ACL) was when I was still a medical student and had not yet started my surgical semester. One of my best friends had injured his right ACL during floorball practice and was going to be reconstructed. As I was still a medical student and my friend had many questions related to his injury and the outcome of surgery, I realised that my knowledge in the ACL field had to improve. My friend's situation enlightened me in terms of ACL injury and resulted in further interest in this small ligament. At that time, 1991, when my 25-year-old friend was injured, the national quality register for ACL injuries had not yet started. According to the 2013 Swedish National ACL Register, the mean age at ACL reconstruction for men is 27 years. It is also known that, 10-15 years after the injury, 50% of the patients have radiographically visible osteoarthritic changes (OA) regardless of whether or not reconstruction is performed. A few years later, my friend injured his left knee during soccer practice and also had this knee reconstructed. More than 20 years have passed since my friend had his first ACL reconstruction and 15 years have passed since the contralateral knee reconstruction. My friend is still very active in floorball and is able to play regularly, but he has problems with pain and sometimes effusion. At a recent follow-up, there were obvious radiographically visible OA changes in both his knees. His ACL injuries had now developed into OA. My friend is coping well with his secondary problems after his ACL injuries. He is happy still to be able to play floorball, but he is unable to run long distances.

Apparently, my friend appeared to have good health-related quality of life. But could this be true? Is it necessary to make evaluations? Yes, the evaluation of any kind of treatment is necessary in order to retrieve new knowledge and assess the patient outcome. Furthermore, refining the disease-specific outcome measurements and incorporating non-disease-specific health assessment measurements is of interest when evaluating ACL reconstructions. It is also important to evaluate the effect of treatments and to compare them with both healthy age-matched individuals and the treatment of other diagnoses in order to provide cost-effective treatment algorithms. Later in life, as a researcher, I was given the chance to answer some of my questions when I joined Professor Jüri Kartus' research group with the aim of following up ACL-reconstructed patients in terms of health-related quality of life and assessing the long-term clinical outcome.

ABBREVIATIONS

ACL	Anterior Cruciate Ligament
BMA	Bone Mineral Areal mass
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index
BMU	Basic Multicellular Unit or Bone Metabolic Unit
BPTB	Bone-Patellar Tendon-Bone
CI	Confidence Interval
CV	Coefficient of Variation
DXA	Dual-energy X-ray Absorptiometry
DXL	Dual-energy X-ray Absorptiometry and Laser technology
HT	Hamstring Tendon
HRQoL	Health-Related Quality of Life
IKDC	International Knee Documentation Committee
KOOS	Knee injury and Osteoarthritis Outcome Score
OA	Osteoarthritis
PBM	Peak Bone Mass
PROM	Patient Reported Outcome Measures
RCT	Randomised Controlled Trial
ROM	Range of Motion
SD	Standard Deviation

BRIEF DEFINITIONS

Adolescence	The period in human growth and development that occurs after childhood and before adulthood, from the age of 10 to 19 years.
BMD	The bone mineral content divided by the area of the image of a bone projected in two dimensions, which is the type of bone density that is produced by dual- and single-energy X-ray absorptiometry. BMD (Bone Mineral Density) is measured in grams/cm^2. BMA (Bone Mineral Area) is used in some literature instead of BMD and is also presented in grams/cm^2.
Closed kinetic chain exercises	Physical exercises performed where the hand or foot is fixed to the ground or base of a machine. Usually involve more than one muscle group (agonists and antagonists). Generally induce compressive forces on joints and are therefore considered safer and more functional.
DXA	Dual-energy X-ray absorptiometry machine, used for the diagnosis of osteoporosis.
EQ-5D	Euroqol, Quality of life-5 Dimensions. The EQ-5D is a generic measurement of health status. It contains five domains, mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a visual analogue scale (VAS) for overall health.
KOOS	The KOOS (Knee injury and Osteoarthritis Outcome Score) reflects the patient's opinion of symptoms and function. The KOOS comprises five dimensions, symptoms, pain, activities of daily living (ADL), sport and recreation and quality of life.
Mann-Whitney U test	A non-parametric statistical method for comparing two independent groups in relation to a continuous variable.
Non-parametric statistics	Statistical methods in which data are not required to fit a normal distribution.
Open kinetic chain exercises	Physical exercises performed where the hand or foot is free to move. Usually involve only one muscle group. Generally induce shear forces on joints but can selectively target certain muscles, which is advantageous in later stages of rehabilitation.

Osteoporosis Defined by the Working Group of the World Health Organisation as a bone density T-score at or below 2.5 standard deviations (SD) below normal peak value in grown-up young women.

PROM Patient Reported Outcome Measures is a term used specifically to refer to self-reports in a clinical trial or a clinical setting, where the responses are collected directly from the patient.

SF-36 The Short Form 36 (SF-36) is a questionnaire assessing health-related quality of life and is widely used as a generic measurement of health status. The SF-36 comprises eight subscales: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH).

Spearman's rho A non-parametric statistical test of the correlation between two groups. The strength of the correlation is expressed in rho, which can vary between 0, which indicates no correlation, and ± 1, which indicates a perfect positive or negative correlation.

T-score The difference in the number of standard deviations between the mean bone mineral density value of the individual and the mean value of a group of young healthy adults of the same gender.

Wilcoxon's signed rank test A non-parametric statistical method for comparing two related groups, such as one variable relating to the same subjects on two different occasions.

Z-score The difference in the number of standard deviations between the mean bone mineral density value of the individual and a group of people of the same gender and age.

01 INTRODUCTION

1.1 BACKGROUND

The anterior cruciate ligament (ACL) is the knee joint's primary restraint on anterior translation of the tibia in relation to the femur and a secondary restraint on the rotational stability of the knee. This ligament is well known and was first described by Galen of Greece (201-131 BC), who based his name for the ligament based on its appearance of crossing over as "ligament genu cruciate". After Galen's first description of the ACL, interest in and studies of the ACL have increased enormously. To date, more than 14,000 studies of ACL-related subjects have been published. The reason for this huge interest is that ACL ruptures are one of the most common sporting and recreational injuries. There is an ongoing debate among surgeons, physiotherapists, researchers and trainers regarding the optimal treatment, rehabilitation and preventive efforts. The two main treatment options that are discussed are non-surgical treatment and surgical reconstruction. In Sweden, the incidence is 80/100,000 inhabitants, which means that approximately 5,800 patients suffer an ACL injury every year and approximately 3,500 of them are treated surgically (www.aclregister.nu).

The result of an ACL injury is often an unstable knee joint where the combined translational and rotational instability leads to the knee joint phenomenon of "giving way". The patient experiences instability during this pivoting motion, such as a sudden change of direction during handball, walking on uneven ground or descending a staircase. Indications for surgical treatment of the ACL are repeated symptoms of knee instability and the failure of conservative treatment [39,116]. Patients can live without a functional ACL and not experience instability, but this usually requires a change in their activity level [46,62]. ACL injuries in adults are often immediately functionally disabling and predispose to subsequent injuries, chronic instability, muscle weakness and the early onset of osteoarthritis (OA) [3,13].

The overall clinical results after ACL reconstruction are good, according to the International Knee Documentation Committee (IKDC) score, in both the medium and the long term, using either bone-patellar tendon-bone (BPTB) or hamstring tendon (HT) autografts [55,69,97]. The life situation of many patients changes and this may affect their health-related quality of life in many ways. During the last decade, the patient's own evaluation, Patient Reported Outcome Measure (PROM), has become an important complement to post-operative clinical assessments [22,67,104,113,114].

ACL injuries in children were previously regarded as rare, but, in recent years, an increasing number have been reported in children who take part in competitive sports, accounting for 0.5-3% of all ACL injuries [78]. In Sweden, ACL tears in skeletally immature patients younger than 10 years of age account for 0.4% of all ACL injuries [91]. More demanding sports activities at younger ages, raised awareness of the injury, improved imaging techniques and the increase in obesity leading to increased stress on the knee ligament are possible causes of the increasing incidence [4].

ACL injuries in children treated non-surgically often lead to poor results, especially in terms of future participation in sports activity and subsequent meniscal and chondral injuries [8,44,50]. Children and adolescents are often very active and, when participating in physical activity and sports, they easily forget that they cannot/should not perform some of the activities in the same way as they did before the injury. In the management of ACL injuries in children, one of the main points of controversy is whether reconstruction should be delayed to prevent iatrogenic injury to the physes, or take place early to prevent secondary meniscal injury.

Non-surgical treatment often results in a progressive deterioration in the function of their knee [2,87]. In the event of persistent instability, the articular cartilage can be progressively damaged over time. The conservative approach protects the as yet unclosed physes, does not damage them through drilling and consequently might prevent future growth disorders. Long-term follow-ups after ACL injuries in children and adolescents are rare. Mizuta et al. reported in a study that 11 of 18 skeletally immature patients had radiographically verified degenerative changes detected 51 months after non-surgical treatment [87]. Aichroth et al. reported a high proportion of OA in children after ACL injuries and non-surgical treatment after a mean follow-up of 72 months [2].

The surgical treatment of ACL injuries in children and adolescents has been more favoured since the beginning of 2000 [126]. Skeletally immature patients treated with ACL reconstruction have a higher return to activity and functional outcomes compared with those treated non-surgically [41]. A review of the current literature supports the trend towards early surgical treatment to restore knee stability and prevent progressive meniscal and/or articular cartilage damage [30]. Henry et al. showed that ACL reconstruction in patients with an open physis resulted in fewer medial meniscus lesions after two years compared with delayed reconstruction at skeletal maturity [50]. In terms of surgical treatment, a variety of reconstructive techniques have been described. The techniques can be either extra-physeal or intra-epiphyseal (physeal-sparing) in very young children and transphyseal in adolescents or patients with an almost closed growth plate (Figures 1, 2). The transphyseal technique is the same technique as in adults using anatomical reconstruction. Physeal-sparing techniques involve a high risk of growth disturbance. The drilling injury and graft placement in the physis are important factors that can cause growth disturbance. In a study by Janarv et al., the relative size of a physeal drill injury is 7-9% in order to cause growth disturbance. Furthermore, a tendon that is transphyseally placed prevents solid bone-bridge formation in the drill hole, thereby causing growth disturbance [54]. A higher rate of growth disturbance after physeal-sparing procedures (5.9%) than after transphyseal reconstructions (1.9%) has been reported by Frosch et al. [40]. The reasons for this have not yet been clarified, but one explanation is the unfamiliar surgical technique or thermal injury to the physes from drilling. Techniques that require all-epiphyseal drilling close to the true anatomical position have a small margin of error and are challenging. Today, most surgeons recommend early surgical treatment in an attempt to prevent instability and secondary meniscal tears [58,98]. Due to the lack of high-quality studies, the ideal treatment in terms of the surgical technique, the timing of surgery and rehabilitation regimens remain controversial. Physeal-sparing and transphyseal techniques have been suggested, but these operations should be carried out at units with the appropriate experience of surgery and rehabilitation [66].

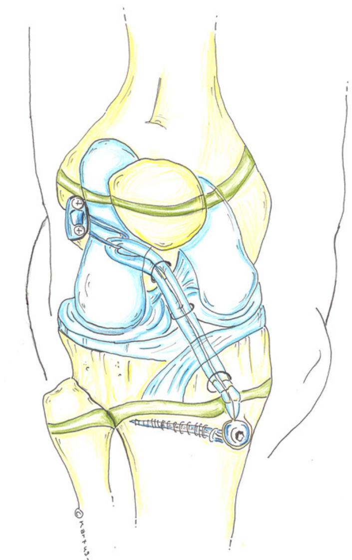

Figure 1. *Intra-epiphyseal*

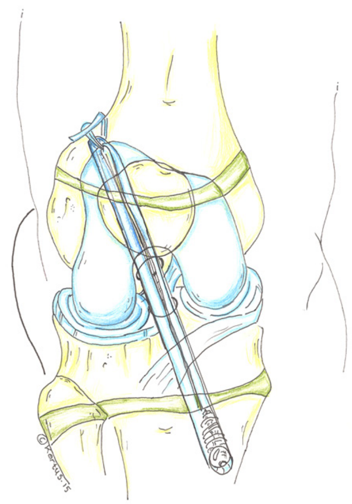

Figure 2. *Transphyseal*

1.3 PATIENT REPORTED OUTCOME MEASUREMENTS

Patient reported outcome measurements (PROM) is a term used specifically to refer to self-reports made by the patient and covers a whole range of potential types of measurement. The data may be collected via self-administered questionnaires completed by the patients themselves or via interviews. Patient reported outcomes are commonly used to assess health-related quality of life (HRQoL). ACL injuries are usually sustained by young, athletic people with a high demand to return to the same activity level as before the injury, but this is most often not the case [10,14,65]. For many patients, there is a change in life situation, which may affect their health-related quality of life in many ways. During the last decade, the patients' own evaluation has become an important complement to post-operative clinical assessments [74,104,113]. The patients' experience of their knee function is mainly assessed using questionnaires relating to function in daily life and sports. Several questionnaires and scores have been developed during the ACL research era [48,52,76,117]. The Short Form 36 (SF-36) is a questionnaire assessing health-related quality of life. It is widely used as a generic measurement (non-disease-specific) of health status and is a well-documented HRQoL questionnaire [113,114,122]. The Swedish SF-36 has been translated and the psychometric properties have been evaluated. Cross-cultural validations of patient and population groups to create norms and interpretation guidelines in Sweden have been performed [114]. The EQ-5D questionnaire is a generic instrument for measuring health-related quality of life. Sweden uses the British tariff, which has been shown to be valid for the Swedish population [21]. The EQ-5D questionnaire was developed by a group of European researchers and it has been validated and tested for reliability [19].

1.4 ACL INJURY AND OSTEOARTHRITIS

An ACL injury increases the risk of post-traumatic secondary osteoarthritis (OA) [3,123]. A prevalence ranging from 10 to 90% has been reported [75,93]. The wide variation in the prevalence of osteoarthritis is probably caused by the population heterogeneity, treatment and activity levels and associated injuries, as well as different ways of classifying OA. The single factor with the highest reported impact on the development of OA is meniscal injury and meniscectomy [57,75]. The non-surgical treatment of ACL injuries carries a more than 10 times higher risk of sustaining meniscal injury [7]. Other factors related to the development of OA are age, high BMI, chondral damage, time between injury and surgical intervention and graft choice [38]. Returning to sporting activities after ligament reconstruction might also exacerbate the development of OA [3]. The aetiology of and the mechanism for developing OA are not clearly understood. Different theories suggesting that associated injuries sustained at the time of the primary injury, secondary injuries in the ACL-deficient knee and changes in the static and dynamic bearing of the knee are all regarded as possible explanations [23]. Another theory is that inflammatory cells present at the injury remain in high concentrations in the joint and cause joint degradation in the long term, independently of whether or not the joint is stable [79]. Despite identifying risk factors and the fact that the epidemiological correlation between a traumatic knee injury and post-traumatic secondary OA is well known, the principal mechanism for post-injury OA after an ACL injury has still not been clarified.

1.5 ACL INJURY AND BONE MINERAL

In many countries, osteoporosis is a growing health problem. The peak bone mass (PBM) achieved during early adulthood will serve as "the bone bank" for the remainder of life [73]. Low bone mass is recognised as a major risk factor for osteoporotic fractures and this risk may be reduced by maximising peak bone mass in early life [47]. Physical activity during childhood and adolescence, as well as the maintenance of physical activity when ageing, are factors that may slow the physiological age-related reduction in BMD (Bone Mineral Density) [5,45]. ACL injuries treated either conservatively or surgically can lead to significant bone loss in the operated leg, as well in the non-operated leg, even though ACL reconstruction has reported higher values [99,101]. Leppala et al. reported that patients who had undergone ACL reconstruction revealed more BMD loss around the knee compared with patients treated conservatively after a follow-up of 12 months [70]. Previous studies reveal a significant decrease in BMD in both calcanei after ACL reconstruction in adults after up to five years. The surgical trauma itself, including drilling bone tunnels, accelerates the remodelling rate and consequently bone mineral loss in the post-operative period [28,112,115].

Bone remodelling starts immediately after damage or a fracture to bone structures. During the bone remodelling process, damaged bone is restored as a result of cellular and molecular events. The cytokines are released from the cytoplasm and start and accelerate the bone remodelling rate in order to restore the damaged bone. The remodelling process takes place in the bone multicellular units (BMUs) on bone surfaces, where the degradation of old bone and the formation of new bone occur [108]. The formation of new bone and the resorption of old bone maintain the balance of bone remodelling. For the formation of a marrow cavity and the fashioning of cortical and trabecular bone during growth, bone resorption is essential. In adults, damaged bone is removed during the resorptive phase of the remodelling cycle and the structure is restored during the formation phase. The remodelling rate usually decreases in young adults after growth and, after the age of 18 to 30 years, the rate is relatively slow. At the age of 20 to 30 years, the peak bone mass (PBM) is reached. After PBM, there is a small and measurable bone loss, due to a small negative balance, with more resorption and less formation in every remodelling BMU [108]. The normal loss of BMD is only approximately 0.5-1% a year after the age of 50 years. A decrease of one standard deviation in BMD increases the relative risk of any kind of future fracture 1.5 times [24,64,80]. The future hip fracture risk has been shown to be predicted by measuring a reduction in BMD in the calcaneal bone using DXL [18,85].

During childhood and adolescence, much more bone is deposited than withdrawn when the skeleton grows in both size and density [90]. During the pre-pubertal years, bone mineral content (BMC) increases at a constant rate in boys and girls until the pubertal growth spurt [32]. The four years of maximum bone gain occurs in girls at the age of 10-14 years and in boys at 12-16 years, with a higher magnitude in boys [6]. This is followed by a prolonged slow increase, for a longer period in boys than in girls, resulting in higher peak bone mass (PBM) in boys. The four peri-pubertal years are important for BMC accrual. It has been reported that up to 36% of the total bone mineral in adulthood has been gained during this period. This bone mineral gain is equal to the total loss during adulthood [11]. During the peri-pubertal BMC accrual period, bone formation may be more sensitive to disturbances caused by the traumatic ACL injury and surgery.

Approximately 86-99% of PBM in both females and males is achieved between the ages of 15 and 18 years [90]. In a study by Pettersson et al. examining 2,384 men with the DXA Calscan, the PBM in the calcaneus was reached at the age of 18.4 years [96]. The authors also concluded that physical activity was the strongest predictor of calcaneus PBM. The late pre- and early pubertal periods are said to be "a window of opportunity" to stimulate bone growth, as the skeleton is most responsive to physical activity during this period [77].

02 AIMS

The overall aim of this thesis was to evaluate the mid- and long-term results after arthroscopic ACL reconstruction surgery, in both adolescents and adults. The issues to be evaluated were the effect on health-related quality of life, the clinical results, the radiographic results and the effect on bone mineral in the calcanei.

2.1 SPECIFIC AIMS AND HYPOTHESES

Study I
The aim of the study was to evaluate the results in terms of HRQoL two to seven years after an ACL reconstruction and to compare the results with a gender- and age-matched control group. The hypothesis of the study was that patients who had an ACL reconstruction did not differ in terms of HRQoL compared with healthy controls.

Study II
The aim of the study was to identify pre-operative factors that were able to predict a good post-operative outcome, as measured by the SF-36 and KOOS three to six years after ACL reconstruction. The hypothesis of the study was that one or more pre-operative factors would be able to predict a good post-operative outcome in terms of HRQoL.

Study III
The aim of the study was to evaluate patients who were adolescents at the time of surgery in terms of clinical results, HRQoL and radiographically visible OA 10-20 years after ACL reconstruction. The hypothesis of the study was that, in the long term, patients who were adolescents at the time of ACL reconstruction would have more osteoarthritic changes in their operated knee than in their non-involved contralateral knee.

Study IV
The aims of the study were to evaluate the results 10-20 years after ACL reconstruction performed in adolescents in terms of BMD in the calcanei, activity level and health-related quality of life. Moreover, the aim was to compare the results with those of a control group of ACL-reconstructed age-matched adults by the time of follow-up and a reference database for DXA (Dual X-ray and laser technology). The hypothesis was that patients who were adolescents at the time of ACL reconstruction would have the same BMD in their calcanei as a control group of adult ACL-reconstructed patients and a reference population, 15-20 years after reconstruction.

03
PATIENTS

3.1 STUDY I

Between January 1991 and December 1999, 793 consecutive patients with an ACL injury (including primary injured patients, re-injured patients and patients with an injured contralateral knee) underwent reconstruction at two hospitals in Sweden. To evaluate the post-operative results after an ACL reconstruction, a questionnaire including the SF-36 was send by mail to these patients. Patients with incomplete questionnaires were excluded from the study. Five hundred and forty-four (69%) patients returned the questionnaires; 125 were either incomplete or could not be identified, leaving 419 to analyse and compare with healthy controls (Figure 3). One hundred and sixty-one patients were female and 258 were male. Their mean age was 27.6 years (range: 15-53). Three hundred and thirty-one had undergone reconstruction using a BPTB autograft and 78 an HT autograft.

Controls
The reference values for the Swedish population for the SF-36 are based on 8,930 individuals, of whom 2,410 were randomly selected and used as a gender- and age-matched control group. The normative database for the Swedish SF-36 does not include individuals younger than 15 years of age. For this reason, five-year age intervals were used in the comparisons and, as a result, the matching was not 1:1 in terms of age. This resulted in a male patient in one age interval being compared with a male control in the same age interval. The ratio between the patients and the controls was 1:5.9, i.e. almost six controls for every patient. The ratio was decided according to the least-ratio principle, with the smallest number of controls corresponding to one patient.

3.2 STUDY II

Between November 1996 and December 1999, 118 ACL-injured patients underwent pre-operative clinical assessments, such as range of motion (ROM), KT-1000 arthrometer knee laxity measurements, a manual Lachman test, a pivot-shift test, a one-leg-hop test, a knee-walking test, an assessment of femoro-patellar pain, the Tegner activity level and subjective evaluation score using the Lysholm knee score at two hospitals in Sweden. The SF-36 and KOOS questionnaires were sent by mail to these patients three to six years after reconstruction and 73 (62%) patients returned them (Figure 4). Patients with incomplete questionnaires were excluded from the study.

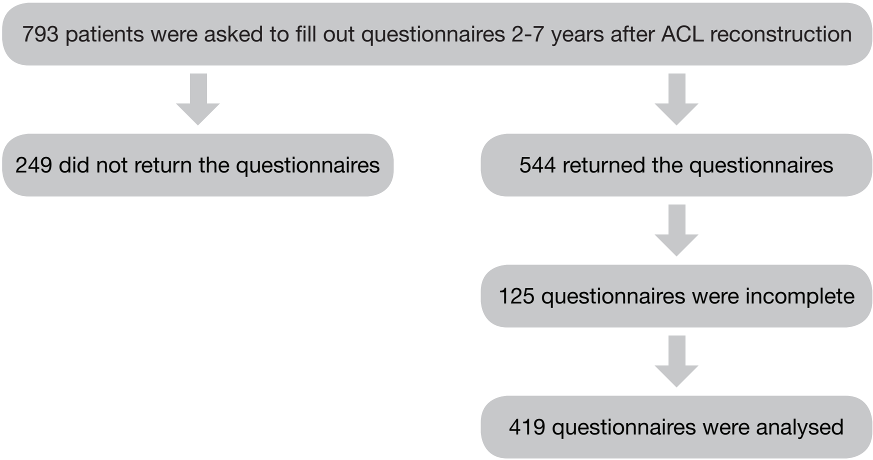

Figure 3. *Patients included in Study I.*

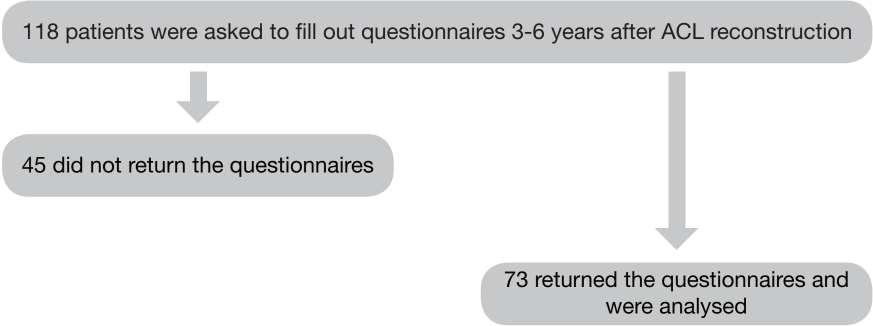

Figure 4. *Patients included in Study II.*

3.3 STUDY III

Between 1992 and 2002, 32 adolescents, aged 12-16 years (11 boys; 21 girls), with a symptomatic unilateral ACL injury, underwent reconstruction using BPTB (n=10) or hamstring tendon (HT) (n=22) autografts by one of three surgeons. The technique and graft choice was made by the surgeons. Surgery was performed at an almost skeletally mature age. Surgery was performed as soon as possible after Tanner stage 4 had been reached and an almost closed epiphyseal plate was observed on standard radiographs [81,82]. The inclusion criterion was a unilateral ACL injury. The exclusion criteria were bilateral ACL injury, contralateral ACL reconstruction, posterior cruciate ligament (PCL) injury and previous or present fractures on either lower extremity (except minor fractures to the eminence on the index side). Twenty-nine patients (91%) underwent clinical, radiographic and health-related quality of life assessments 10-20 years (median 180 months) after the reconstruction.

3.4 STUDY IV

Between 1992 and 2002, the same 32 adolescents as in Study III were included. Twenty-nine patients (91%) underwent clinical and bone mineral assessments 10-20 years (median 180 months) after the reconstruction.

Controls

The control group (Group C) was obtained from a database of ACL-reconstructed adults. Between 2004 and 2007, 34 adults (15 females and 19 males), mean age of females 26.8 years and of males 27.5 years, with a symptomatic unilateral ACL rupture underwent reconstruction using hamstring tendon autografts (HT) (n=34) by one of three surgeons. The inclusion and exclusion criteria were the same as in the study group (Group A). Sixty months post-operatively, the control group underwent follow-up assessments of BMD, Tegner activity level and EQ-5D. No one from the control group was older than 40 years at follow-up. The reference database for DXA was obtained from healthy Swedish women and men.

04
METHODS

4.1 SURGICAL TECHNIQUE

BPTB Technique

The central third of the patellar tendon was harvested and the proximal bone block was sized to 9 mm and the distal bone block to 10 mm. The bone tunnels were prepared in a standard transtibial fashion. The femoral tunnel was placed at approximately 10.30 in the right knee and 01.30 in the left knee. With an "elbow aimer" placed just in front of the posterior cruciate ligament, the centre of the tibial tunnel was situated approximately 7-8 mm anterior. A 7 mm metallic interference screw and a 9 mm Acufex (Acufex, Microsurgical Inc., Mansfield, MA, USA) metallic interference screw were used on the femoral and tibial side respectively.

HT Technique

The graft was harvested through an approximately 3-cm incision over the pes anserinus. The ST (semitendinosus) or both the ST and G (gracilis) tendons were harvested with a semi-blunt, semi-circular open tendon stripper (Acufex, Microsurgical Inc., Mansfield, MA, USA). The tendons were prepared for a triple or quadruple graft, depending on the length and thickness of the grafts. The desired diameter of the graft was a minimum of 7 to 8 mm. Both the femoral and tibial tunnels were placed at approximately the same locations as in the BPTB group. A 7 mm soft-threaded RCI (Smith and Nephew, Inc., Andover, MA 01810, USA) interference screw was used on the femoral side and a 7-9 mm screw was used on the tibial side.

In both groups, associated intra-articular injuries, such as meniscal ruptures and chondral lesions, were addressed at the time of the index operation. Due to the fact that the anatomic concept had not been established at the time the ACL reconstructions were performed, no attempt at an anatomic reconstruction was made.

4.2 REHABILITATION

All the patients were rehabilitated according to the same guidelines by their local physiotherapists, permitting immediate full weight-bearing and full ROM including full hyperextension [111]. However, no external load in open kinetic chain exercises apart from the weight of the operated leg was used during the first six post-operative weeks from 30 degrees to full (hyper) extension. Closed-chain exercises were started immediately post-operatively. Running was permitted at three months and contact sports at six months at the earliest, provided that the patient had regained full functional stability in terms of strength, co-ordination and balance as compared with the contralateral leg.

In Study I, rehabilitation braces were used in 248 patients during the first six post-operative weeks, while 155 patients were rehabilitated without a brace (missing values n = 16). In Study II, rehabilitation braces were used in 16 (22%) patients during the first post-operative weeks, while 57 (78%) patients were rehabilitated without a brace. In Studies III and IV, a rehabilitation brace was used in one patient during the first post-operative weeks [124].

4.3 CLINICAL EXAMINATIONS

All clinical examinations and tests of patients were assessed by three different experienced physiotherapists. The uninjured leg was always measured first.

4.3.1 MANUAL LACHMAN TEST

Studies II-IV

With the patient's knee held between full extension and 15 degrees of flexion, the femur is stabilised with one hand, while firm pressure is applied to the posterior aspect of the proximal tibia in an attempt to translate it anteriorly. A positive test indicating disruption or elongation of the ACL is one in which there is proprioceptive and/or visual anterior translation of the tibia in relation to the femur, with a characteristic mushy or soft end point. It was graded as +1 (< 5mm), +2 (5-10 mm) or +3 (> 10 mm) (Figure 5) [120].

4.3.2 INSTRUMENTED LAXITY KT-1000 ARTHROMETER

Studies II-III

The instrumented KT-1000 arthrometer examination (MEDmetric® Corp, San Diego, USA) was performed with the patient in the supine position [25]. Both legs were placed on a thigh support with the knees in 30° of flexion. A footrest and a strap around the thighs kept the legs in a neutral position. The arms were placed along the sides of the body and the patient was asked to relax. The instrument was calibrated to zero before each displacement test. The anterior displacement of the tibia in relation to the femur was registered at 89N until 2002 and, after 2002, at 134N and manual maximum test (MMT). The readings of the needle position were only accepted if the needle returned to zero ± 0.5 mm, when the tension in the handle was released. At least three measurements of each knee were made and the average value was registered. The reproducibility has been found to be good in several studies if the same experienced examiner performs the test and if the side-to-side difference between knees is presented (Figure 6) [109,125].

Figure 5. *Manual Lachman test. © Olle Månsson*

Figure 6. *Instrumented laxity KT-1000 arthrometer. © Olle Månsson*

4.3.3 THE PIVOT-SHIFT TEST

Studies II-III

The pivot-shift test is a clinical knee laxity test which evaluates a combination of translational and rotatory laxity, which represents the patient's typical giving-way phenomenon. The subjectivity, in terms of both conduct and interpretation, makes the results difficult to compare between various studies and justifies the same observer performing all the tests in a clinical study in order to increase the reliability of the test [92]. The pivot-shift test was graded from 0-III, according to IKDC guidelines [48,53].

4.3.4 RANGE OF MOTION (ROM)

Studies II-III

The ROM measurement was performed in the supine position using a hand-held goniometer graded in one-degree increments [20]. The patient first made an active full extension, followed by an active full flexion. The side-to-side difference including hyperextension was calculated. If the measurements displayed a side-to-side difference of ≥ 5° in either extension or flexion, the patient was classified as having or not having an extension or flexion deficit. The examiner always made a visual check to ensure that the measured side-to-side difference appeared reasonable (Figure 7).

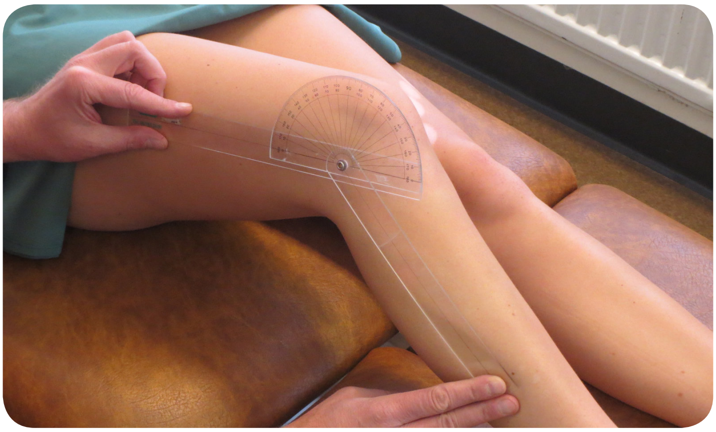

Figure 7. *Range of motion (ROM). © Olle Månsson*

4.3.5 ANTERIOR KNEE PAIN

Study II

The patient was asked to classify dichotomously whether he/she did or did not have subjective anterior knee pain if he/she registered pain while climbing stairs, sitting with the knee in 90° of flexion and during or after activity.

4.4 FUNCTIONAL TESTS

4.4.1 ONE-LEG-HOP TEST

Studies II-III
The one-leg-hop test was performed by jumping and landing on the same foot with the hands behind the back and no shoes [118]. Three attempts were made for each leg and the longest hop was registered for each leg separately. A quotient (%) between the index and uninjured leg was calculated (Figure 8).

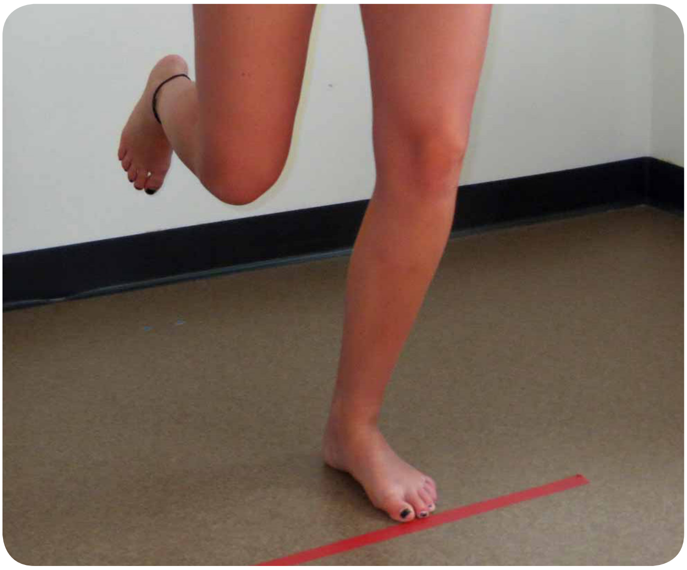

Figure 8. *One-leg-hop test. © Olle Månsson*

4.4.2 SQUARE-HOP TEST

Study III
The square-hop test was performed by standing on the leg to be tested, outside a 40x40 cm square marked with tape on the floor. For the right leg, the subjects were instructed to jump clockwise in and out of the square as many times as possible during a period of 30 s. For the left leg, the subjects performed the test in a counter-clockwise mode. The test was videotaped and both total jumps and the number of successful jumps performed, without touching the taped frame, were recorded. A quotient (%) between the index and uninjured leg was calculated. This test was modified from Östenberg et al. (Figure 9) [94].

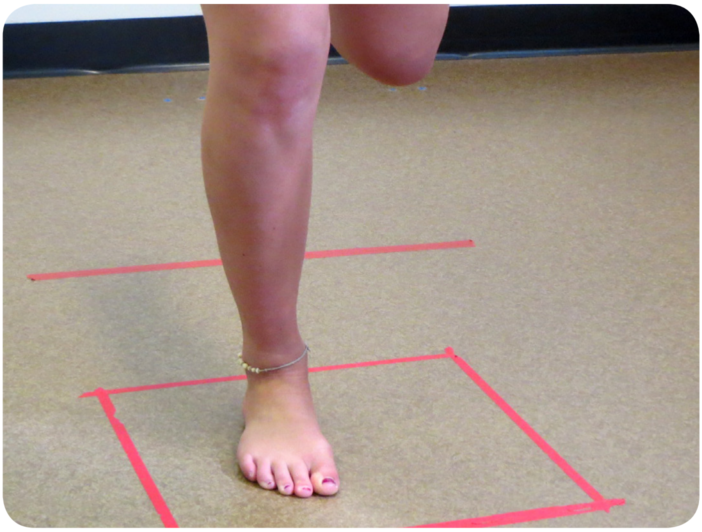

Figure 9. *Square-hop test. © Olle Månsson*

4.4.3 KNEE-WALKING TEST

Studies II-III
The classification of kneeling discomfort compared with the contralateral knee was based on the knee-walking test involving direct loading of the anterior knee region. The knee-walking test was performed on the floor of the examination room.

The patient was not allowed to use any protection or clothing during the test while walking six steps forward on his/her knees. The test was subjectively classified by the patient as OK, unpleasant, difficult, or impossible to perform, as described by Kartus et al. (Figure 10) [56].

Figure 10. *Knee-walking test. © Olle Månsson*

4.5 FUNCTIONAL SCORES

4.5.1 KNEE OSTEOARTHRITIS OUTCOME SCORE (KOOS)

Studies I-III

The KOOS (www.koos.nu) is a knee-specific, patient-administered PROM validated for both the short-term and long-term follow-up of ACL reconstructions, meniscectomies and post-traumatic OA [104,106]. The KOOS consists of five subscales; Pain, Other symptoms (Symptoms), Function in daily living (ADL), Function in sports and recreation (Sports/Rec) and Knee-related quality of life (QoL).

The patient answers nine questions to assess Pain, seven questions to assess Symptoms, 17 questions regarding ADL, five questions regarding Sports/Rec and four questions regarding QoL. All questions are graded from zero to four points. A normalised score for each subscale is then calculated, with a maximum of 100 points indicating no symptoms and zero points indicating extreme symptoms.

4.5.2 LYSHOLM KNEE SCORE

Studies II-III

The Lysholm knee score was first proposed and tested for the evaluation of knee instability (giving-way) symptoms. Since 1985, when it was presented, the revised version has also been used for patients with meniscal and chondral injuries [117]. The subscores are limp (5 points), support (5 points), locking (15 points), instability (25 points), pain (25 points), swelling (10 points), stair-climbing (10 points) and squatting (5 points). The maximum score is 100 points and the test was self-administered by the patients. The Lysholm knee-scoring scale has been validated and tested for reliability and responsiveness in the long term after ACL injuries to the knee [16]. According to Höher et al., the Lysholm knee-scoring scale was patient administered and the questionnaire did not show the scores for alternative answers [51].

4.5.3 TEGNER ACTIVITY SCALE

Studies II-IV

The Tegner activity scale was used to evaluate activity level [117]. The scale is graded numerically according to work and sports activity and is graded between 0-10, where levels 0-4 cover activities of daily living and work (level zero is sick leave because of knee problems). Levels 5-10 indicate whether the patient is able to participate in recreational or competitive sports. In most publications discussing knee surgery, the patient's return to work and sports is often documented as the Tegner activity level and it is therefore not regarded as a score [16].

4.6 HEALTH-RELATED QUALITY OF LIFE SCORES

4.6.1 EUROQOL 5-DIMENSIONS (EQ-5D)

Studies III-IV
The EQ-5D questionnaire is a generic (non-disease-specific) instrument for measuring health-related quality of life. It consists of five questions relating to five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with three different answer levels (no problems, moderate problems and severe problems). The resulting 243 possible combinations of responses are then presented as a health profile or computed to create a global health index with a weighted total value (the global health index is used in this thesis). The total index is computed using a regional tariff to adjust for cultural differences. Sweden uses the British tariff, which has been shown to be valid for the Swedish population [21]. The resulting index ranges from -0.594 (worse than death) through 0 (worst possible health status) to 1.0 (best possible health status). The EQ-5D questionnaire also includes a vertical VAS ranging from 0 (worst possible health status) to 100 (best possible health status). The response from the VAS was, however, not used in this thesis. The EQ-5D questionnaire was developed by a group of European researchers and it has been validated and tested for reliability [19]. The minimally clinical important difference has been estimated at 0.074 [121].

4.6.2 SHORT FORM 36 (SF-36)

Studies I-III
The Short Form 36 (SF-36) is a questionnaire assessing health-related quality of life and is widely used as a generic measurement of health status [113]. The Swedish SF-36 has been translated and the psychometric properties have been evaluated (http://www.promcenter.se/sv/generella-instrument/). Cross-cultural validations of patient and population groups to create norms and interpretation guidelines in Sweden have been performed [114,122]. The SF-36 comprises eight subscales: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH). Each subscale of the SF-36 is scored on a scale of 0 to 100. The higher the score, the better the health status of the patient. The SF-36 is self-explanatory and takes about 10 minutes to complete.

4.7 RADIOLOGICAL EXAMINATION

Study III
Standard weight-bearing radiographic examinations in the anterior-posterior (AP) and lateral views, with 30 degrees of flexion of the knee, were obtained and classified according to the Ahlbäck and the Fairbank rating systems [1,31]. Fairbank's classification relates primarily to mild changes, ranging from the flattening of the condyles to joint space narrowing. The Fairbank system dichotomously rates the presence of flattening, ridging and narrow-

ing of the joint in the medial and lateral compartment respectively (Figure 11). For the Fairbank system, the cumulative number of positive findings, from 0 to 6, was calculated for each patient [72]. In 1968, Ahlbäck presented his grading system for OA of the knee from mild stages with joint narrowing to severe remodelling of the bone. An independent musculoskeletal radiologist blinded to the clinical results interpreted the radiographs. In long-term follow-up studies after ACL reconstruction, most radiographic changes can be described using Fairbank's and Ahlbäck's classification systems [42].

Figure 11. *Antero-posterior view of a weight-bearing knee. According to the Fairbank classification, N is narrowing of the lateral compartment, F refers to the flattening of the femoral surface and R refers to the ridging of the lateral femoral condyle. © Olle Månsson*

4.8 BONE ABSORPTIOMETRY

Study IV

DXL Calscan

For measurements of the calcaneus, a dual-energy X-ray (DXA) and laser Calscan machine (DemeTech Co, Miami, USA) was used. The DXA Calscan device (development of the DEXA-T device) measures bone mineral area mass by fan beam dual-energy X-ray absorptiometry (DXA), but, at the same time, it measures heel thickness with a laser scan to create a three-component model (bone mineral, lean soft tissue and fat) (Figure 12). The aim is to correct for the inhomogeneous distribution of fat outside and inside the bone, which is a major source of variation in conventional DXA technology. The device automatically finds the region of interest and positioning is not critical. The short-term precision has been investigated and found to be a 0.76% coefficient of variation (CV) short term, 0.73% CV long term in vitro, 1.19% CV in vivo for mixed subjects and 1.09% CV for non-osteoporotic subjects [119]. In another study, the long-term in-vitro precision was 0.5% CV and the in-vivo precision was 1.2% CV [64]. Bone mineral measurements with the Calscan have been shown to predict future fracture risk [18].

Figure 12. *DXL Calscan machine. © Olle Månsson*

4.9 ISOKINETIC MUSCLE STRENGTH ASSESSMENT

Study III

Muscle strength was measured using the Biodex Multi-Joint System 4 Pro. The maximum isokinetic strength of both knee extension and flexion was assessed in the sitting position at an angle velocity of 60 and 180 degrees/per second. Peak torque measurements were registered on both sides. The quotient between the injured and non-injured leg is presented. The patient warmed up by riding a stationary bicycle for five minutes. The patient was tested in the sitting position with approximately 70° of hip flexion and with safety belts fastened on the trunk, pelvis and thigh to minimise extra body movements (Figure 13).

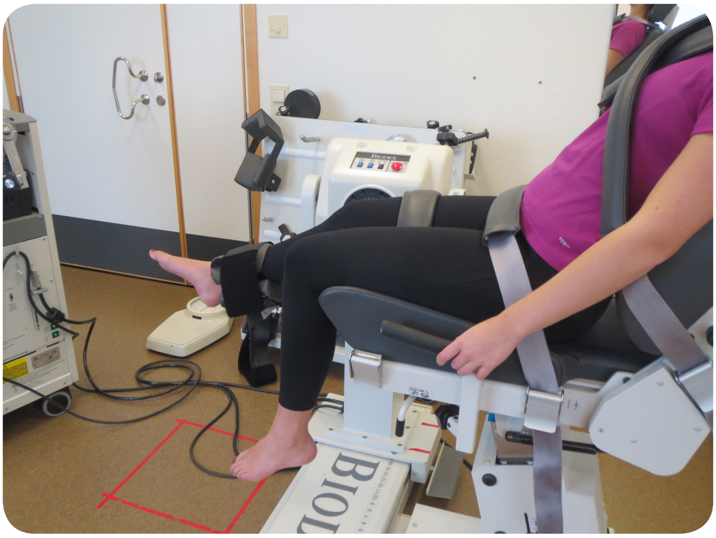

Figure 13. *Biodex Multi-Joint System 4 Pro machine. © Olle Månsson*

4.10 STATISTICAL METHODS

Study I

Median (range) values are presented unless the mean (SD) is indicated. In terms of both parametric and non-parametric variables, the Mann–Whitney U test was used for comparisons between the study groups. The chi-square test was used to compare the dichotomous variables between the two groups. The HQRL group, Sahlgrenska University Hospital, Sweden, analysed and compared the patient-related outcome with the Swedish population. A p-value of < 0.05 was considered statistically significant. All p-values are two-tailed.

Study II

Descriptive data are presented as the mean (SD) and median (range), when applicable. Predictive factors for health-related quality of life were identified using a stepwise regression analysis, with the SF-36 and KOOS as the dependent variables. Wilcoxon's signed rank test was used for comparisons of the pre- and post-operative data. For comparisons of dichotomous variables, the chi-square test was used. The Spearman rank correlation test (rho) was used to test the correlation between the follow-up time and the most important clinical variables. The predictors that were used were descriptive data such as age, gender, time between injury and operation, type of graft, associated injuries and the pre-operative clinical assessments, as well as the subjective evaluation scores. The B-value represents the relationship between the dependent variable and each predictor. If the value is positive, there is a positive relationship between the predictor and the outcome, while a negative value represents a negative relationship. The B-value also shows the degree to which each predictor affects the outcome if the effects of all other predictors are kept constant. A p-value of < 0.05 was considered statistically significant. All p-values are two-tailed.

Study III

Mean (SD) and median (range) values are presented when applicable. Wilcoxon's signed rank test was used for comparisons of the pre-operative and post-operative data within the study group. All comparisons between the index side and the non-involved contralateral side were performed on 25 patients, i.e. the bilaterally reconstructed patients were excluded. A p-value of < 0.05 was considered statistically significant. All p-values are two-tailed.

Study IV

Mean (SD), 95% confidence intervals and median (range) values are presented when applicable. Wilcoxon's signed rank test was used for comparisons of the data within the study group. The Mann-Whitney U-test was used to compare the variables with the control group. Spearman's rank correlation test (rho) was used for the correlation analyses. For comparisons of dichotomous variables between the groups, the chi-square test was used. All comparisons between the index side and the non-involved contralateral side were performed on 25 patients in Group A, i.e. the bilaterally reconstructed patients were excluded. The BMD results for Group A are also reported as a percentage of increase or decrease (minus) compared with Group C and the reference database. A difference of 10% in the BMD between the study group and the control group was considered to be clinically important. In the power analyses, it was estimated that the difference between groups and the standard deviation of the measurements would have the same magnitude. To reach a power of 80%, the required sample size was 17 patients in each group. A p-value of < 0.05 was considered statistically significant. All p-values are two-tailed.

05 RESULTS

5.1 STUDY I

The results from the healthy matched controls, the total ACL group and the BPTB and HT subgroups are presented in Table 1 and Figure 14. The total ACL group and BPTB subgroup obtained significantly higher scores for GH, SF, RE and MH compared with the healthy controls. This difference was not significant for the HT subgroup. The healthy control group obtained significantly higher values for PF compared with the total ACL group and with the BPTB and HT subgroups. RP was significantly higher in the healthy control group compared with the total ACL group and the BPTB subgroup.

When analysing males separately (Table 2, Figure 15), the healthy male control group obtained higher values for PF and RP, but this difference was not significant for the HT group. The total male ACL group obtained higher values for BP, GH, VT, SF, RE and MH, but the difference was only significant for SF, RE and MH.

When analysing females separately (Table 3, Figure 16), the healthy female control group obtained higher values for PF and RP, but the difference was only significant for PF. The total female ACL group obtained higher values for BP, VT and MH. The total female ACL group and BPTB female subgroups obtained higher values for GH, SF and RE, but the difference was not statistically significant.

There were no significant differences between males and females, both when comparing the whole gender subgroups and when analysing the gender-based BPTB and HT subgroups separately.

Table 1 *The absolute values for the healthy control group, the total ACL group, the BPTB group and the HT group*

	Reference group (n=2410)	Total (n=424)	BPTB (n=331)	HT (n=78)
PF, mean (SD) Range Missing values p-value	94.1 (13.4) 0-100 55	87.1 (14.6) 5-100 3 **<0.001***	87.7 (14.0) 30-100 3 **<0.001†**	86.4(15.9) 5-100 0 **<0.001‡**
RP, mean (SD) Range Missing values p-value	89.6 (24.5) 0-100 57	85.1 (29.9) 0-100 2 **0.003***	84.6 (30.4) 0-100 2 **0.01†**	85.6 (28.6) 0-100 0 0.09
BP, mean (SD) Range Missing values p-value	79.1 (23.6) 0-100 9	81.0 (22.3) 10-100 3 0.27	81.6 (22.2) 10-100 2 0.26	80.5 (22.8) 10-100 1 0.79
GH, mean (SD) Range Missing values p-value	80.0 (20.0) 0-100 29	82.7 (17.3) 12-100 5 **0.007***	82.9 (17.3) 12-100 4 **0.009†**	82.2 (17.0) 35-100 1 n.s. (0.36)
VT, mean (SD) Range Missing values p-value	69.9 (20.5) 0-100 25	70.7 (19.7) 5-100 4 n.s. (0.99)	71.0 (19.6) 5-100 2 n.s. (0.86)	69.3 (20.6) 15-100 2 n.s. (0.74)
SF, mean (SD) Range Missing values p-value	89.9 (18.8) 0-100 4	93.4 (13.7) 0-100 3 **0.006***	93.7 (12.9) 13-100 2 **0.008†**	91.9 (17.1) 0-100 1 n.s. (0.34)
RE, mean (SD) Range Missing values p-value	88.1 (26.2) 0-100 57	90.7 (24.1) 0-100 4 **0.024***	91.1 (23.9) 0-100 3 **0.011†**	87.9(26.4) 0-100 1 n.s. (0.99)
MH, mean (SD) Range Missing values p-value	81.1 (18.0) 0-100 24	84.2 (15.3) 20-100 4 **0.002***	84.7 (14.8) 20-100 2 **0.001†**	82.2 (17.2) 24-100 2 n.s. (0.62)

* Reference group vs total
† Reference group vs BPTB (Bone-Patellar Tendon-Bone)
‡ Reference group vs HT (Hamstring Tendon)
n.s.=not significant

Table 2 *The absolute values for males in the healthy controls group, the total ACL group, the BPTB group and the HT group*

	Reference group (n=1485)	Total (n=256)	BPTB (n=199)	HT (n=49)
PF, mean (SD) Range Missing values p-value	94.8 (13.0) 0-100 33	88.7 (12.9) 5-100 1 **<0.001***	89.0 (12.1) 45-100 1 **<0.001†**	86.9 (16.5) 5-100 0 **<0.001‡**
RP, mean (SD) Range Missing values p-value	90.9 (22.9) 0-100 26	85.2 (30.3) 0-100 0 **0.005***	84.3 (31.1) 0-100 0 **0.013†**	87.8 (26.6) 0-100 0 n.s. (0.15)
BP, mean (SD) Range Missing values p-value	80.6 (23.2) 0-100 6	82.5 (22.0) 10-100 1 n.s. (0.30)	82.4 (22.7) 10-100 0 n.s. (0.23)	84.3 (20.8) 10-100 1 n.s. (0.48)
GH, mean (SD) Range Missing values p-value	80.2 (19.6) 0-100 16	82.8 (17.0) 15-100 2 n.s. (0.075)	82.5 (17.5) 15-100 2 n.s. (0.17)	84.2 (15.0) 47-100 0 n.s. (0.26)
VT, mean (SD) Range Missing values p-value	71.6 (20.1) 0-100 15	72.4 (19.2) 25-100 2 n.s. (0.84)	71.8 (20.2) 15-100 0 n.s. (0.82)	71.7 (18.0) 30-100 2 n.s. (0.98)
SF, mean (SD) Range Missing values p-value	90.4 (18.8) 0-100 0	93.9 (13.0) 12-100 1 **0.038***	93.8 (12.4) 38-100 0 n.s. (0.06)	94.3 (11.8) 50-100 1 n.s. (0.32)
RE, mean (SD) Range Missing values p-value	89.7 (24.5) 0-100 28	92.7 (21.9) 0-100 2 **0.029***	92.3 (22.2) 0-100 1 **0.049†**	91.7 (22.3) 0-100 1 n.s. (0.56)
MH, mean (SD) Range Missing values p-value	81.7 (18.3) 0-100 14	85.2 (14.9) 28-100 2 **0.004***	84.9 (15.1) 32-100 0 **0.004†**	83.7 (16.6) 28-100 2 n.s. (0.39)

* Reference group, male vs male
† Reference group, male vs BPTB (Bone-Patellar Tendon-Bone), male
‡ Reference group, male vs HT (Hamstring Tendon), male
n.s.=not significant

Table 3 *The absolute values in females for the healthy control group, the total ACL group, the BPTB group and the HT group*

	Reference group (n=922)	Total (n=161)	BPTB, (n=129)	HT (n=29)
PF, mean (SD) Range Missing values p-value	92.7 (14.0) 10-100 19	85.2 (16.1) 30-100 0 **<0.001***	85.3 (16.5) 30-100 1 **<0.001†**	86.2(14.2) 40-100 0 **<0.001‡**
RP, mean (SD) Range Missing values p-value	87.6 (26.7) 0-100 28	84.5 (29.6) 0-100 0 n.s. (0.24)	84.1 (30.3) 0-100 0 n.s. (0.30)	86.2 (28.0) 0-100 0 n.s. (0.34)
BP, mean (SD) Range Missing values p-value	76.3 (24.2) 0-100 0	78.9 (22.6) 10-100 0 n.s. (0.23)	79.3 (22.2) 10-100 0 n.s. (0.19)	78.2 (22.5) 22-100 0 n.s. (0.87)
GH, mean (SD) Range Missing values p-value	79.7 (20.4) 5-100 10	83.0 (17.4) 12-100 1 n.s. (0.11)	83.5 (17.2) 12-100 0 n.s. (0.07)	79.2 (19.5) 35-100 1 n.s. (0.83)
VT, mean (SD) Range Missing values p-value	67.3 (21.0) 0-100 7	67.9 (20.5) 5-100 0 n.s. (0.94)	69.1 (19.2) 5-100 0 n.s. (0.95)	67.4 (22.3) 25-100 0 n.s. (0.55)
SF, mean (SD) Range Missing values p-value	89.1 (18.7) 0-100 1	92.5 (14.7) 0-100 0 n.s. (0.056)	93.2 (13.8) 13-100 0 n.s. (0.060)	88.8 (23.0) 0-100 0 n.s. (0.82)
RE, mean (SD) Range Missing values p-value	85.6 (28.7) 0-100 26	87.6 (27.1) 0-100 0 n.s. (0.28)	88.6 (26.8) 0-100 0 n.s. (0.15)	83.9 (30.4) 0-100 0 n.s. (0.43)
MH, mean (SD) Range Missing values p-value	80.3 (17.5) 4-100 7	82.6 (16.0) 20-100 0 n.s. (0.12)	84.0 (14.5) 20-100 0 n.s. (0.095)	80.7 (17.9) 24-100 0 n.s. (0.76)

* Reference group, female vs female
† Reference group, female vs BPTB (Bone-Patellar Tendon-Bone), female
‡ Reference group, female vs HT (Hamstring Tendon), female
n.s.=not significant

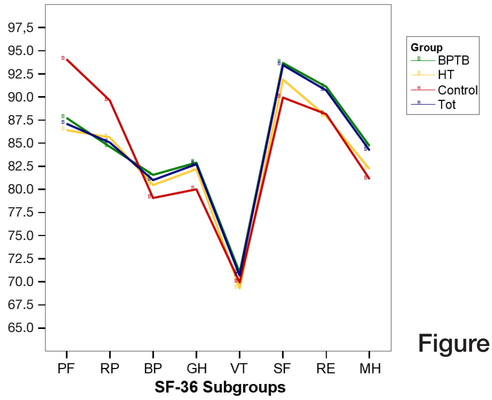

Figure 14.

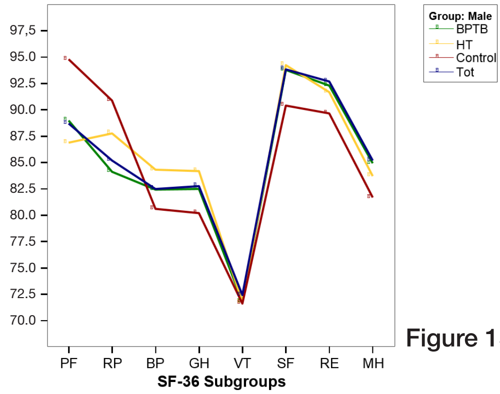

Figure 15.

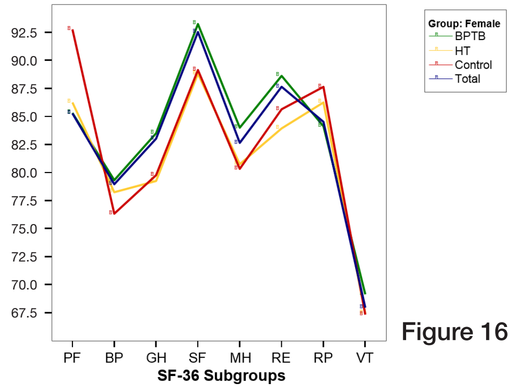

Figure 16.

Pre-operative data and post-operative data from the clinical examination at 26 months (22–36) are presented and compared in Table 4. There were no correlations between the time of follow-up and the Lysholm score, Tegner activity level and the KT-1000 side-to-side difference (Rho <0.2; p>0.34).

SF-36 (Table 5)

PF. The type of graft, pivot-shift test and manual Lachman test together explained 25% of the outcome variance in PF. The use of HT autografts at surgery was found to be a significant (p<0.05) factor for a higher score for PF at follow-up, compared with the use of a BPTB autograft. A higher score on the pre-operative pivot-shift test renders a higher post-operative PF. A higher score on the pre-operative manual Lachman test renders a lower post-operative PF.

BP. The pre-operative Lysholm knee score explained 11% of the outcome. Patients who obtained high scores on the Lysholm knee score had a higher post-operative BP.

GH. Taken together, gender, Tegner activity level pre-operatively, pre-operative flexion deficit and age explained 29% of the outcome variance in GH. Males had higher GH scores than females. The patients who had a high Tegner activity level pre-operatively had higher GH post-operatively. An increased flexion deficit pre-operatively produced higher GH post-operatively; furthermore, an older patient had higher GH post-operatively.

VT. The one-leg-hop test was found to be a significant pre-operative predictor of this variable and explained 7% of the outcome. The smaller the side-to side differences in the one-leg-hop test pre-operatively, the higher the VT post-operatively.

SF. The knee-walking test explained 11% of the outcome variance in SF. A low knee-walking test score pre-operatively produced a lower SF post-operatively.

RE. The Tegner activity level pre-injury, the one-leg-hop test and the ROM flexion deficit together explained 21% of the outcome variance in RE. The higher the Tegner activity level the patient had before injuring the ACL, the lower the RE post-operatively. The smaller the side-to-side difference in the one-leg-hop test pre-operatively, the higher the RE post-operatively. The greater the flexion deficit pre-operatively, the higher the RE post-operatively.

KOOS (Table 6)

Symptoms. The femoro-patellar pain explained 9% of the outcome variance in symptoms. The more femoro-patellar pain the patients had pre-operatively, the lower their score for symptoms post-operatively.

Pain. The Tegner activity level pre-operatively explained 8% of the outcome variance in pain. Patients with a higher Tegner activity level pre-operatively obtained higher scores for pain post-operatively.

ADL. The pivot-shift test and manual Lachman test explained 23% of the outcome variance in this variable. The higher the score on the pivot-shift test pre-operatively, the higher the ADL score post-operatively. The higher the score on the manual Lachman test pre-operatively, the lower the ADL score post-operatively.

Sport and recreation. The Tegner activity level pre-operatively explained 14% of the outcome variance in sport and recreation. The higher the Tegner activity level the patients had pre-operatively, the higher their score for sport and recreation post-operatively.

Quality of life. The Tegner activity level pre-operatively and the flexion deficit together explained 18% of the outcome variance in quality of life. Patients with a higher Tegner activity level pre-operatively obtained higher scores for quality of life. The greater the flexion deficit pre-operatively, the higher the score for quality of life-KOOS post-operatively.

Table 4 *The pre-operative and post-operative comparison of the patients who returned the questionnaire (n=73)*

	Pre-op	Fp at 26 months
Tegner activity level: median (range) Pre op vs Fp p<0.001	4 (1-8)	7 (3-10)
Lysholm knee score; points: median (range) Pre op vs Fp p<0.001	74 (25-99)	94 (60-100)
One-leg-hop test; percentage of contralateral side: mean (SD) Missing values Pre op vs Fp P< 0.001	73 (26.6) 8	89 (28.5)
Knee-walking test: OK Unpleasant Difficult Impossible Missing value Pre-op vs Fp n.s. (0.18)	34 (47%) 32 (44%) 5 (7%) 1 (1%) 1 (1%)	27 (37%) 36 (49.3%) 9 (12.3%) 1 (1.4%)
Manual Lachman (grade): 0 1 2 3 Missing value Pre-op vs Fp p<0.001	 7 (10%) 38 (52%) 27 (37%) 1 (1%)	53 (72.6%) 13 (17.8%) 5 (6.8%) 2 (2.7%)
Pivot shift (grade): 0 1 2 3 Missing values Pre-op vs Fp p<0.001	10 (14%) 15 (21%) 32 (44%) 12 (16%) 4 (5%)	63 (86.3%) 5 (6.8%) 2 (2.7%) 1 (1.4%) 2 (2.7%)
Femoro-patellar pain: yes no Missing values Pre-op vs Fp: n.s. (0.81)	22 (30%) 51 (70%)	6 (8.2%) 66 (90.4%) 1 (1.4%)
KT 1000 side-to-side difference (mm): mean (SD) Missing value Pre-op vs Fp p<0.001	4.0 (2.2) 1	0.8 (1.2)
ROM difference flexion (vs contralateral knee) (degrees): mean (SD) Missing value Pre-op vs Fp n.s.; p=0.06	6.5 (10.8) 1	4.0 (6.2) 1
ROM difference extension (vs contralateral knee) (degrees): mean (SD) Missing value Pre-op vs Fp p<0.002	-3.1 (5.7) 1	-1.0 (4.0) 1

Fp= follow-up, n.s.= not significant

Table 5 *Stepwise regression analyses for SF-36 (n=73)*			
Outcome	Predictor	R^2	B
Physical function (PF)	Graft Pivot shift Manual Lachman	0.25	9.3 7.0 -7.4
Role physical (RP)	No outcome	-	-
Body pain (BP)	Lysholm knee score	0.11	0.5
General health (GH)	Gender Tegner activity level pre-operative ROM: flexion deficit Age	0.29	-9.6 3.5 0.6 0.7
Vitality (VT)	One-leg-hop test	0.07	0.2
Social function (SF)	Knee-walking test	0.11	-7.2
Role emotional (RE)	Tegner activity level pre-injury One-leg-hop Flexion deficit	0.21	-6.0 0.3 0.6
Mental health (MH)	No outcome	-	-

B: measure the change in the dependent variable (KOOS, SF-36)
by increase/decrease in the predictor
R^2: degree of explanation as a percentage

Table 6 *Step-wise regression analyses for KOOS (n=73)*			
Outcome	Predictor	R^2	B
Symptom	Femur patellar pain	0.09	-8.9
Pain	Tegner activity level pre-operative	0.08	2.5
ADL	Pivot shift Manual Lachman	0.23	5.8 -5.9
Sport & recreation	Tegner activity level pre-operative	0.14	7.1
Quality of life	Tegner activity level pre-operative Flexion deficit	0.18	6.8 0.7

B: measure the change in the dependent variable (KOOS, SF-36)
by increase/decrease in the predictor
R^2: degree of explanation as a percentage

At the index operation, there were a total of 16 meniscal injuries, of which three were repaired, five were resected and eight were debrided. Contact sports caused 55% of the injuries (Table 7). The mean side-to-side difference as measured using the KT-1000 arthrometer pre-operatively and at follow-up is presented in Table 8. The manual Lachman test and pivot-shift test findings revealed a significant improvement at follow-up compared with those of the pre-operative assessments (p=0.005), (Table 8). The one-leg-hop test finding was significantly improved at follow-up compared with that of the pre-operative assessments (p=0.010), (Table 9). At follow-up, muscle strength measurements displayed more than 90% of the non-involved leg in both extension and flexion (Table 10). The Tegner activity level was unchanged, while the Lysholm knee score was not significantly increased at follow-up compared with the pre-operative assessments (not significant) (Table 9). The KOOS values are presented in Table 11. Compared with age-matched healthy controls, the results for the KOOS were lower in all dimensions. The SF-36 values are presented in Table 11 and showed higher scores for MH, RE, SF and GH compared with healthy controls and lower scores for PF, RP, BP and VT. The mean EQ-5D score was 0.86 and was comparable with that of healthy controls (Table 11). The reconstructed knees revealed significantly more OA changes (65%) compared with the non-involved contralateral knees (14%) (p=0.001) (Table 12). No significant difference in terms of OA changes was found between patients with meniscal/chondral injuries versus patients without meniscal/chondral injuries. There were no radiographic signs of growth disturbances at follow-up.

Table 7 *Descriptive data for the patients who took part in the follow-up*

		Total
Number of patients		29
Age, years, mean (SD)		15.2 (1.1)
Gender (male/female)		10/19
Injured side (right/left)		15/14
Tegner activity level (pre-injury) Median (range) Mean (SD)		 8.0 (4-9) 7.9 (1.3)
Graft type	BPTB (%)	10 (34)
	Hamstring (%)	19 (66)
Time between the injury and index operation (months); Median (range) Mean (SD)		 7 (2-42) 11.6 (11.3)
Follow-up period (months); Median (range) Mean (SD)		 180 (106-234) 175 (37)
Associated injuries addressed at the time of the index operation Meniscal (medial and/or lateral (%)) Meniscal and chondral (%) Other (LCL* (1), fracture** (1) (%))		 16 (55) 2 (7) 2 (7)
Contralateral reconstruction during follow-up period		4 (14)
Revision surgery during follow-up period (%): ACL ipsilateral ACL contralateral Other: meniscal injury (2), shaving of synovitis (1), chondral lesion (1), removal of tibial screw (1)		 4 (14) 1 (3) 5 (17)
Cause of injury	Contact sport (%)	16 (55)
	Non-contact sport (%)	6 (21)
	ADL (%)	7 (7)
	Other (%)	5 (17)

* Lateral collateral ligament ** Healed eminence fracture

Table 8 *Knee laxity measurements pre-operatively and at follow-up*					
		Pre-op	Follow-up*		P-value*
KT-1000 anterior side-to-side difference (mm)		89N	134N	MMT	
Median (range) Mean (SD) Missing values		2.5 (0.5-9.0) 3.4 (2.9) 6	3.5 (minus8.0-9.0) 2.8 (4.1) 0	3.5 (minus1.0-8.0) 3.3 (2.7) 0	
Manual Lachman test (%)	0	1 (3)	13 (52)		<0.001
	+1	4 (14)	12 (48)		
	+2	16 (55)			
	+3	7 (24)			
	Missing values	1 (3)	0		
Pivot shift (%)	0	4 (14)	13 (52)		0.005
	+1	20 (69)	12 (48)		
	+2	4 (14)			
	+3				
	Missing values	1 (3)	0		

*This analyses excludes patients with a bilateral ACL reconstruction (n=4)

Table 9 *The functional, objective and subjective results pre-operatively and at follow-up*			
	Pre-op	Follow-up	P-value
Tegner activity level Median (range) Mean (SD)	4.0 (8-2) 4.0 (1.4)	4.0 (1-7) 3.9 (1.9)	n.s. (0.97)
Lysholm knee score Median (range) Mean (SD)	75 (50-90) 74.8 (11.0)	84.0 (34-100) 79.3 (16.2)	n.s. (0.11)
One-leg-hop test (%) Median (range) Mean (SD) Missing values	84.0 (0-105) 78.5 (22.0) 0	92.5 (53-126) 93.2 (17.7) 1	0.01*
Square hop-test (total) (%)* Median (range) Mean (SD) Missing values		98.1 (43-190) 97.0 (30.2) 1	
Extension difference non-involved side (degrees) Median (range) Mean (SD) Missing values	0 (minus15-5) -2.5 (5.1) 7	0 (minus10-5) -2.4 (3.6) 0	n.s.* (0.80)
Flexion difference non-involved side (degrees) Median (range) Mean (SD) Missing values	0 (minus5-20) 2.5 (5.9) 7	0 (minus5-15) 3.0 (4.3) 0	n.s.* (0.50)

*This analysis excludes patients with a bilateral ACL reconstruction (n=4); n.s = not significant

Table 10 *Muscle strength measurements at follow-up (% of contralateral leg)*

Biodex			FP total*	FP male*	FP female*
Extension 60°/sec (%)	Peak torque	Median (range) Mean (SD) Missing values	86.0 (55-185) 91.3 (24.5) 1	90.3 (78-104) 90.4 (9.3) 0	82.7 (55-185) 92.0 (31.7) 1
	Total work	Median (range) Mean (SD) Missing values	92.1 (55-168) 93.4 (23.3) 1	94.5 (60-111) 91.8 (13.8) 0	88.9 (55-168) 94.4 (28.8) 1
Flexion 60°/sec (%)	Peak torque	Median (range) Mean (SD) Missing values	99.0 (79-309) 107.2 (45.0) 1	90.4 (83-115) 94.9 (11.8) 0	101.2 (79-309) 116.1 (57.3) 1
	Total work	Median (range) Mean (SD) Missing values	93.3 (64-371) 106.9 (56.8) 1	89.2 (64-118) 91.2 (18.5) 0	96.6 (72-371) 121.6 (77.0) 1
Extension 180°/sec (%)	Peak torque	Median (range) Mean (SD) Missing values	90.4 (72-111) 92.1 (11.3) 1	90.0 (77-111) 91.7 (10.8) 0	90.4 (72-111) 92.5 (12.0) 1
	Total work	Median (range) Mean (SD) Missing values	92.5 (67-111) 92.1 (10.5) 1	94.9 (78-111) 93.3 (11.0) 0	92.4 (67-103) 91.2 (10.4) 1
Flexion 180°/sec (%)	Peak torque	Median (range) Mean (SD) Missing values	98.5 (76-139) 100.3 (14.8) 1	94.6 (76-117) 97.6 (12.6) 0	100.1 (80-139) 102.4 (16.4) 1
	Total work	Median (range) Mean (SD) Missing values	96.9 (52-140) 96.4 (19.8) 1	98.9 (66-125) 97.9 (17.1) 0	94.0 (52-140) 95.3 (22.1) 1

* This analysis excludes patients with a bilateral ACL reconstruction (n=4); Fp=follow-up

Table 11 *KOOS, SF-36 and EQ 5D at follow-up*		
KOOS	Fp	Reference*
Symptom: Median (range) Mean (SD)	 89.0 (39-100) 80.8 (18.7)	 97.2 92.2
Pain: Median (range) Mean (SD)	 89.0 (44-100) 85.3 (15.5)	 92.9 88.1
ADL: Median (range) Mean (SD)	 99.0 (68-100) 93.2 (9.2)	 100.0 94.7
Sport/recreation: Median (range) Mean (SD)	 75.0 (15-100) 67.7 (28.6)	 93.7 85.6
Quality of life: Median (range) Mean (SD)	 56 (6-100) 61.3 (27.3)	 90.7 84.4
SF-36		
PF Median (range) Mean (SD)	 90.0 (60-100) 86.6 (11.7)	 93.4
RP Median (range) Mean (SD)	 100 (0-100) 87.9 (28.8)	 88.9
BP Median (range) Mean (SD)	 80 (22-100) 75.1 (22.6)	 78.5
GH Median (range) Mean (SD)	 87 (30-100) 80.7 (18.8)	 79.8
VT Median (range) Mean (SD)	 65.0 (30-95) 66.4 (17.4)	 69.4
SF Median (range) Mean (SD)	 100 (50-100) 91.8 (15.4)	 89.6
RE Median (range) Mean (SD)	 100 (0-100) 94.3 (20.1)	 88.0
MH Median(range) Mean (SD)	 88 (36-100) 82.6 (15.6)	 81.1
EQ5D		
EQ 5D Median (range) Mean (SD)	 0.80 (0.69-1.00) 0.86 (0.12)	 0.88
EQ 5D VAS Median (range) Mean (SD)	 80.0 (40-100) 79.7 (13.2)	 88

*The reference values relate to healthy, non-operated, age-matched individuals; Fp=follow-up

Table 12 *Radiographic assessment at follow-up*

Ahlbäck	Fp involved*	Fp non-involved*	
Medial: grade 0: (%) Medial: grade 1: (%)	24 (96) 1 (4)	25 (100)	
Lateral: grade 0: (%) Lateral: grade 1: (%) Lateral: grade 2: (%) Lateral: grade 3: (%)	17 (68) 6 (24) 1 (4) 1 (4)	22 (88) 3 (12)	
Fairbank			
Flattening medial (%) Narrowing medial (%) Ridging medial (%)	3 (12) 1 (4) 7 (28)	1 (4) 0 1 (4)	
Flattening lateral (%) Narrowing lateral (%) Ridging lateral (%)	10 (40) 8 (32) 15 (60)	3 (12) 3 (12) 0	
			P-value
Fairbank cumulative changes Median (range) Mean (SD)	2 (0-5) 1.8 (1.5)	0 (0-2) 0.3 (0.7)	0.001*
Any osteoarthritic changes: involved knee (%) non-involved knee (%)		19 (65) 4 (14)	

* This analysis excludes patients with a bilateral ACL reconstruction (n=4); Fp= follow-up

The groups were comparable in terms of demographics (Table 13). The BMD values for the males in the adolescent group (Group A) were lower on the injured and non-injured side, minus 15.2% (p=0.02) and minus 11.8% (p=0.05) respectively, compared with the control group (Group C). The corresponding values for the females in Group A were minus 0.8% (p=0.84) and minus 2.2% (p=0.69) respectively. Compared with the male reference database, the BMD values for the males in Group A were lower (minus 8.2% and minus 4.9% respectively). For the females in Group A, the BMD values were higher (4.1% and 4.3% respectively) compared with the female reference database. In group A four males and two females had a T-score < minus 1 both on their injured and non-injured side. The corresponding was found in Group C for two males and two females (Table 15, Figure 17). In Group C, female patients had a significantly lower value for the Tegner activity scale pre-operatively compared with the patients in Group A (p=0.006), (Table 14).

In Group A, the Tegner activity scale at follow-up revealed a significant correlation with the BMD on the injured side for men (rho=0.67, p=0.03) but not on the non-injured side (rho=0.50, p=0.14). In Group C, the Tegner activity scale at follow-up revealed a significant correlation to the BMD on the non-injured side for females (rho=0.61, p=0.03) but not on the injured side (rho=0.34, p=0.25). The EQ-5D revealed no significant difference between groups (Table 16, Figure 18). The Body Mass Index (BMI) revealed no significant difference between the groups. No other significant correlations were found between BMD, gender, activity level and the EQ-5D. At the time of follow-up, four patients in Group A had undergone bilateral reconstructions.

Table 13 *Descriptive data of the patients who took part in the follow-up*

		Group A (n=29)		Group C (n=34)		p value
		Female	Male	Female	Male	
Gender (male/female) (%)		10 (34)	19 (66)	15 (44)	19 (56)	n.s. (0.44)
Age, years at the time of reconstruction Median (range) Mean (SD)		16.0 (12-16) 15.1 (1.2)	16.0 (14-16) 15.5 (0.7)	26.0 (17-38) 26.8 (8.1)	29.0 (17-40) 27.5 (7.3)	<0.001
Age, years at follow-up Median (range) Mean (SD)		30.0 (23-35) 30.0 (3.2)	30.5 (25-34) 29.4 (3.2)	31.0 (23-43) 31.4 (7.7)	34.5 (23-45) 33.8 (6.4)	n.s. (0.07)
BMI (kg/m^2) Median (range) Mean (SD)		23.2 (20-32) 23.6 (3.3)	25.3 (20-32) 25.6 (3.6)	24.9 (19-32) 24.8 (3.9)	24.7 (19-37) 25.7 (4.1)	Female n.s. (0.24) Male n.s. (0.89)
Tegner activity level (pre-injury) Median (range) Mean (SD)		8.0 (4-9) 7.9 (1.3)		9.0 (2-10) 7.8 (2.1)		n.s. (0.71)
Graft type	BPTB (%)	10 (34)		0		<0.001
	Hamstring (%)	19 (66)		39 (100)		
Time between the injury and index operation (months): Median (range) Mean (SD)		7 (2-42) 11.6 (11.3)		7.5 (2-168) 19.6 (34.3)		n.s. (0.89)
Follow-up period (months) Median (range) Mean (SD)		180 (106-234) 175 (36.8)		62 (52-76) 62 (4.7)		<0.001
Associated injuries addressed at the time of the index operation: Meniscal (medial and/or lateral (%)) Meniscal and chondral (%) Other (LCL*, MCL**, fracture*** (%))		16 (55) 2 (7) 2 (7)		14 (41) 6 (18) 1 (3)		n.s. (0.22)
Contralateral reconstruction during follow-up period (%)		4 (14)		0		0.02
Revision surgery during follow-up period (%): ACL ipsilateral ACL contralateral Other: meniscal injury, shaving of synovitis, chondral lesion, removal of tibial screw		4 (14) 1 (3) 5 (17)		4 (12) 0 5 (15)		
Cause of injury (%)	Contact sport	16 (55)		21 (62)		n.s (0.66)
	Non-contact sport	6 (21)		8 (24)		
	Work	0		1 (3)		
	ADL	2 (7)		1 (3)		
	Other	5 (17)		3 (8)		

*Lateral collateral ligament, medial collateral ligament**, healed eminence fracture***; n.s.=not significant; A=Adolescents, C=Control group

Table 14 *The Tegner activity level pre-operatively and at follow-up*

	Group A (n=25)*			
	Pre-op		Fp	
	Female (n=15)	Male (n=10)	Female (n=15)	Male (n=10)
Tegner activity level Median (range) Mean (SD) P-value Pre-op v Fp	 **3.0 (2-8)** **3.8 (1.6)** 	 4.0 (3-7) 4.5 (1.3) 	 4.0 (1-7) 3.9 (1.9) n.s. (0.47)	 4.0 (1-6) 3.4 (2.0) n.s. (0.16)
	Group C (n=34)			
	Pre-op		Fp	
	Female (n=15)	Male (n=19)	Female (n=15)	Male (n=19)
Tegner activity level Median (range) Mean (SD) P-value Pre-op v Fp P-value Group A v C	 2.0 (0-5) 2.3 (1.5) 0.006	 3.0 (0-9) 3.6 (2.3) n.s. (0.102)	 4.0 (1-9) 4.1 (2.2) n.s. (0.08) n.s. (0.94)	 4.5 (2-9) 4.5 (1.8) n.s. (0.09) n.s. (0.26)

*The analysis excludes patients with bilateral ACL reconstruction (n=4); n.s. = not significant; A=Adolescents, C=Control group, Fp=Follow-up

Table 15 *Bone mineral assessment at follow-up*

BMD (g/cm²)	Group A (n=25)*			
	Fp injured		Fp non-injured	
	Female (n=15)	Male (n=10)	Female (n=15)	Male (n=10)
Median (range) **Mean (SD)** **95% CI** **Missing values** **P-value inj.v non-inj.**	0.497 (0.386-0.568) 0.485 (0.055) 0.454- 0.515	0.509 (0.398-0.620) 0.506 (0.081) 0.448-0.564	0.499 (0.387-0.604) 0.486 (0.058) 0.454-0.517 n.s. (0.96)	0.523 (0.432-0.627) 0.524 (0.071) 0.473-0.575 0.02
T-score **Mean (SD)** **Median (range)** **Number of patients:** **T-score < - 1 (range)**	 -0.01 (0.85) 0.20 (1.3-minus1.5) 2 (-1.3-minus1.5)	 -0.68 (1.09) -0.65 (0.9-minus2.1) 4 (-1.3-minus2.1)	 0.01 (0.88) 0.20 (1.8-minus1.5) 2 (-1.3-minus1.5)	 -0.44 (0.97) -0.45 (1.0-minus1.7) 4 (-1.1-minus1.7)
	Group C (n=34)			
	Fp injured		Fp non-injured	
	Female (n=15)	Male (n=19)	Female (n=15)	Male (n=19)
Median (range) **Mean (SD)** **95% CI** **Missing values** **P-value inj.v non-inj.** **P-value Group A v C**	0.490 (0.357-0.605) 0.489 (0.072) 0.447-0.530 n.s. (0.84)	0.593 (0.460-0.805) 0.597 (0.091) 0.552-0.642 0.02	0.496 (0.367-0.613) 0.497 (0.072) 0.455-0.538 1 n.s. (0.12) n.s. (0.69)	0.599 (0.451-0.832) 0.594 (0.095) 0.546-0.641 1 n.s. (0.83) 0.05
T-score **Mean (SD)** **Median (range)** **Number of patients:** **T-score < - 1 (range)**	 -0.29 (0.90) -0.30 (1.2-minus1.9) 2 (-1.8-minus1.9)	 0.52 (1.13) 0.50 (3.1-minus1.2) 2 (-1.1-minus1.2)	 -0.19 (0.91) -0.20 (1.3-minus1.8) 2 (-1.7-minus1.8)	 0.47 (1.21) 0.50 (3.6-minus1.3) 2 (-1.2-minus1.3)

*The analysis excludes patients with bilateral ACL reconstruction (n=4); n.s.= not significant; A=Adolescents, C=Control group, Fp=Follow-up. Reference BMD value (age: 30-39 years): female=0.466 (0.064), male=0.551 (0.084).

Table 16 *EQ-5D at follow-up*

EQ-5D	Group A (n=25)*			
	Female (n=15)	Male (n=10)		
Median (range) **Mean (SD)**	**0.80 (0.69-1.00)** **0.82 (0.12)**	0.92 (0.69-1.00) 0.89 (0.12)		
	Group C (n=34)		Reference value	
	Female (n=15)	Male (n=19)	Female	Male
Median (range) **Mean (SD)** **P-value Group A v C**	0.80 (0.70-1.00) 0.86 (0.12) n.s. (0.43)	0.80 (0.03-1.00) 0.83 (0.22) n.s. (0.50)	0.86 (0.01)	0.90 (0.01)

* The analysis excludes patients with bilateral ACL reconstruction (n=4); n.s.=not significant; A=Adolescents, C=Control group

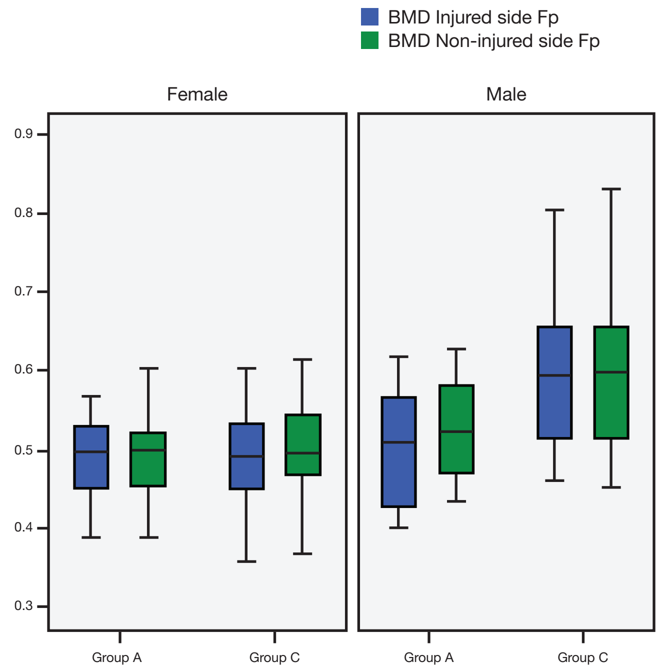

Figure 17.

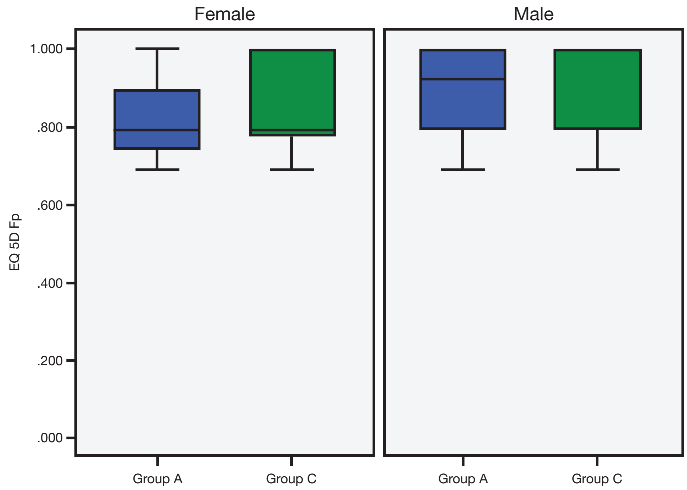

Figure 18.

06 DISCUSSION

One important finding in this thesis is that patients after ACL reconstruction reported good health-related quality of life in comparison with a matched sample of the general population. Another important finding is that pre-operative factors, such as the pivot-shift test, knee function and range of motion, Tegner activity levels pre-injury and pre-operatively may predict a good post-operative outcome in terms of HRQoL after ACL reconstruction. The third important finding is that the long-term patients who were adolescents at the time of ACL reconstruction reveal significantly more radiographically visible osteoarthritic changes in their operated knee than in their non-operated contralateral knee. Moreover, the clinical outcomes and HRQoL are comparable with those of healthy controls. Finally, the fourth important finding is that the BMD in patients who were adolescents at the time of the ACL reconstruction differs from that of a control group and a reference database. In males, the value was lower compared with both groups, while in females it was higher compared with the reference database.

6.1 PATIENT REPORTED OUTCOME MEASUREMENTS

The principal findings in Study I are that, after ACL reconstruction, the patients reported generally good health-related quality of life as measured with the SF-36 in comparison with a matched sample of the general population. The overall results after ACL reconstruction are reported as good, in both the medium and the long term using either patellar tendon or hamstring tendon autografts, according to objective, subjective and functional evaluations [14,55,69,97]. Shapiro et al. used the SF-36 and found important and significant changes with both surgical and non-surgical treatment over time [110]. However, the SF-36 was not able to identify those patients requiring ACL reconstruction. Dunn et al. reported large improvements in the physical component summary using the SF-36 (with an effect size of 1.2) at two years and these results were maintained six years after ACL reconstruction [27].

Patients with an ACL injury complain of a lack of knee stability. The main indication for performing an ACL reconstruction is therefore to give the patient a stable knee. A further indication is to improve the function of the knee in order to return to the activity level patients desire. To function without an ACL, a modification of the patient's activity level is often required [62]. In Study I, females, both controls and patients, reported poorer health than males. This is contradictory to the findings of Ferrari et al., who analysed patients five years after reconstruction and found that the female patients had significantly higher values for RP, BP and GH compared with healthy controls. However, their general results in terms of the SF-36 were in line with Study I [33]. In Study I, the healthy controls obtained higher values for PF and RF compared with the total ACL group. On the other hand, the ACL group obtained higher values for GH, SF and RE. These higher values in the ACL group could be related to a higher general health value and better mental function even before the injury. The majority of ACL injuries occur in the young athletic population and this group will probably obtain higher HRQoL scores compared with a less active aged-matched control group.

On the other hand, McAllister et al. did not find any significant differences between elite collegiate athletes who sustained an ACL injury and matched controls. Increased training time has been described as being predictive of higher RP, VT and GH [83,84]. The ACL rupture is an injury that occurs during demanding physical activities such as contact sports and skiing and most of the patients are young and physically active [100].

Briggs et al. reported that the Tegner activity level in a normal population is inversely correlated with age and the median was 5.7. In patients with an ACL injury, the pre-injury level is 8 [17,68]. As a result, the reduction in health-related quality of life after an ACL injury will not be that great compared with the control group.

In 1998, Roos et al. presented a self-administered questionnaire, the KOOS, which reflects the patient's opinion of symptoms and function [106]. The KOOS is sensitive to changes over time and a difference of ten points is regarded as a clinically significant change [102,103]. Both the SF-36 and KOOS have been shown to reliable and valid in patients with ACL ruptures and OA [105,110].

In a systematic review of HRQoL more than five years after ACL reconstruction, Filbay et al. reported that patients using the KOOS quality of life assessment were more likely to report poorer HRQoL outcomes, compared with population norms, than those assessed using the SF-36. They also concluded that revision ACL, subsequent meniscal injuries and severe radiographic OA were associated with poorer HRQoL [34]. Von Porat et al. analysed the prevalence of OA 14 years after ACL injury in male soccer players who were treated both surgically and non-surgically. They also reported that radiographic changes were found in 78% of the injured knees and no differences were seen between surgically and conservatively treated players. The results of the SF-36 were similar in terms of GH, SF, RE and MH. The result for BP was much higher in Study I than in the study by von Porat et al. [123]. The lower BP in their study could be explained by the high presence of radiographic changes (OA) due to a longer follow-up period. In Study I, the follow up time was only two to seven years. The prevalence of OA after ACL injuries at a minimum of 10 years of follow-up has been reported to be 21-48% [93]. Mohtadi et al. developed a patient-based, subjective outcome measurement instrument for chronic ACL deficiency, the ACL-QOL, which is able to distinguish patients who had surgery from those who are non-surgically treated [88]. According to Mohtadi et al., the ACL-QOL reveals that patients with an ACL injury are younger and far more active than other well-studied populations, which is in line with the findings in Study I. Mohtadi et al. emphasise the importance of a disease-specific outcome measurement to assess this unique group of patients before and after intervention [88].

Knee-related quality of life is impaired after ACL reconstruction at a minimum of five years of follow-up, compared with population-normative data for those without knee injury or pain [34]. There are previous studies reporting outcomes that were similar or better than population norms after ACL reconstruction using the generic SF-36 measurement [34]. The use of the SF-36 as a complement to traditional knee ligament evaluation tools is therefore encouraged and might demonstrate the value of treating ACL-injured patients to health-care planners.

6.2 PREDICTING HRQOL FACTORS

The principal findings in Study II are that pre-operative factors may predict good outcome in terms of HRQoL after ACL reconstruction. The pre-operative factors, pivot-shift test, manual Lachman test and type of graft, explained up to 25% of the outcome variance in physical health status in terms of HRQoL, as measured with the SF-36. In the case of the KOOS, quality of life, the Tegner activity level pre-operatively and ROM explained up to 18% of the outcome variance in quality of life.

According to Kocher et al., a pivot-shift examination may be a better measurement of "functional instability" than instrumented knee laxity or a manual Lachman examination after ACL reconstruction and the pivot-shift examination has significant associations with patient satisfaction [60]. Instability and the subjective "giving-way" phenomenon are usually the main symptoms of an ACL injury, as well as being the indication for an ACL reconstruction. Usually, if the patients do not experience the "giving-way" phenomenon during daily life and leisure time activities after reconstruction, they are satisfied with the outcome. This supports the view that a positive pre-operative pivot-shift test is an important indication for surgery [63]. Furthermore, Kocher et al. reported that the seven independent multivariate determinants of patient satisfaction were the Lysholm knee score, overall subjective knee function, IKDC ROM subscale, patellar tenderness, full giving way, flexion contracture and swelling [59]. These determinants are in line with the findings in Study II when using the SF-36 as the dependent variable. In Study II, the Lysholm knee score, Tegner activity level, pivot-shift test, manual Lachman test, flexion deficit and femoro-patellar pain were all pre-operative factors that were able to predict a good outcome in terms of HRQoL after ACL reconstruction. For this reason, limited physical activity, instability and pain are important symptoms when it comes to the patient's desire to undergo ACL reconstruction. Kostogiannis et al. reported that a positive pivot-shift test three months after injury in the non-anaesthetised patient is the strongest predictor of a future need for reconstruction, whereas a normal pivot-shift test at three months indicates a low risk of a future need for reconstruction [63]. Moreover, they found that non-surgical treatment with early activity modification and neuromuscular rehabilitation resulted in good knee function and an acceptable activity level in the majority of non-reconstructed patients, even in the long term. On the other hand, patients who were involved in contact sports at the time of injury reported poorer HRQoL when they had to reduce their activity level compared with the patients who were involved in non-contact sports [62]. The authors also reported that the patients with recurrent giving-way episodes were subsequently excluded from the long-term follow-up study because they underwent reconstruction.

It therefore appears that functional instability and a positive pivot-shift test are important factors supporting the decision to undergo ACL reconstruction. This is also in line with the findings in Study II, regarding PF and the pivot-shift test, which revealed that, the higher the grade of the positive pivot-shift test is pre-operatively, the better the outcome for PF. It is our experience that a positive pivot-shift test, rather than a positive manual Lachman test, is an important factor for the patients to take the decision to undergo ACL reconstruction, as it resembles the patients' subjective feeling of the "giving-way" phenomenon.

The use of HT autografts rendered better results in terms of PF than the use of BPTB autografts. Outcome differences between HT and BPTB autografts have been reported in many previous studies [15,35,37]. Goldblatt et al. reported that HT autografts had a reduced incidence of femoro-patellar crepitation, kneeling pain and extension loss, which may reflect the outcome in Study II for PF [43]. On the other hand, Biau et al. reported no difference in the final overall IKDC score and in the number of patients returning to full activity after the use of both HT and BPTB autografts [14]. The optimal graft choice for ACL reconstruction is unclear [12,36,107]. An ideal graft should have the characteristics of a normal ACL in terms of strength, stiffness, width and length in order to recreate the normal anatomy. In terms of individual criteria for graft choice, no clear advantage for either the HT or the BPTB technique has been demonstrated. Both techniques are reliable when it comes to improving patient performance and allowing a return to a higher level of activity than before surgery and they are therefore equally valid choices for ACL reconstructions, even in the long term [71]. In Study II, some patients underwent surgery using the ST graft and some using the ST/G graft. A previous randomised study reported no significant differences based on the use of either one or two HT tendons for ACL reconstruction [68]. In the statistical analyses, the patients were therefore classified as having undergone reconstruction using an HT graft, regardless of whether one or two tendons were harvested.

In Study II, males obtained higher GH scores and this appears to be in line with the study by Dunn et al., where female gender was significantly associated with lower activity after ACL reconstruction [26]. They found that a higher pre-operative activity level and lower baseline body mass index were associated with a higher activity level two years after ACL reconstruction. Moreover, they reported that smoking was also associated with a lower activity level. At the time of Study II, smoking habits were not registered, but they are now part of the pre-operative evaluation protocol. Regarding the KOOS, the flexion deficit and the Tegner activity level pre-operatively explained 18% of the outcome variance in quality of life. Having a flexion deficit of the knee may result in kneeling and squatting problems and increased femoro-patellar pain because of greater pressure on the patella, which might affect quality of life [86]. In Study II, the post-operative ROM including flexion was better post-operatively, which could explain the finding in terms of quality of life. For the SF-36, the greater flexion deficit pre-operatively the patients had, the higher the RE post-operatively. A flexion deficit makes daily activities difficult and, once surgery has corrected this, RE increases.

The pre-operative Tegner activity level was found to be a significant pre-operative predictor of a high post-operative score for sport and recreation. The patients who are able to continue at a high activity level despite their ACL injury may be more determined to return to the same activity level as before the injury. This is in line with the study by Biau et al. in which only 60% of the patients made a full recovery after ACL reconstruction [14].

Pain is a negative factor when assessing and predicting good quality of life. The more pain pre-operatively, the lower the post-operative score for symptoms and probably also for quality of life [49]. The pre-operative femoro-patellar pain, in Study II, predicted the outcome for symptoms according to the KOOS. The more femoro-patellar pain the patients had pre-operatively, the lower their KOOS score for symptoms post-operatively.

The knee-walking test explained the outcome in SF to a significant degree. This stresses the importance of kneeling and knee-walking for many individuals in the age group undergoing ACL reconstruction, particularly patients employed in construction or other occupations requiring kneeling, in caring for children and in religious ceremonies [29]. The finding in Study II that higher age had higher GH post-operatively might be due to the fact that older patients are less prone to return to the same activity level as before their injury. This is in line with Osti et al., who reported comparable clinical outcomes in middle-aged patients and in patients aged below 30 [95]. Furthermore, this is also supported by Arbuthnot et al. who reported that ACL reconstruction using autografts in patients above 55 years of age improves functional outcome scores and permits a return to a reasonable level of activity, although not to pre-injury levels [9]. It appears that the patients' pre-operative activity level is a strong predictor of their future activity and a positive pre-operative pivot-shift test is an important indication for surgery. This information could help to select the right patients and to offer the best treatment to each specific patient. Furthermore, using pre-operative factors that could predict a good post-operative outcome could provide cost-effective treatment algorithms.

6.3 ASPECTS OF OSTEOARTHRITIS

In Study III, the principal findings are that patients who were adolescents at the time of ACL reconstruction reveal significantly more radiographically visible OA in their operated knee than in their non-involved contralateral knee. There is no consensus in the literature in terms of clinical treatment decision criteria to determine whether a skeletally immature child should undergo transphyseal ACL reconstruction, physeal-sparing ACL reconstruction, or non-surgical treatment [89]. Kohl et al. reported satisfactory mid-term (mean, 4.1 years) results and no signs of OA after transphyseal ACL reconstruction in children [61]. However, at mid-term follow-up, it is probably too early to detect radiographic signs of OA. Using the same evaluation system as in Study III, Aichroth et al. reported a high proportion (43%) of OA changes in children after ACL injuries treated non-surgically at a mean follow-up of six years [2]. Similar results were found in adults in a study by von Porat et al., who reported radiographic changes in 78% of the injured knees 14 years after an ACL injury and no differences between surgically and non-surgically treated knees [123]. Mizuta et al. reported radiographically verified degenerative changes detected in 11 of 18 patients, treated non-surgically, after a follow-up of 51 months. The diagnosis was confirmed by arthroscopy and meniscal injuries were detected in 13 of the 18 skeletally immature patients [87]. Modern physeal-sparing early reconstruction is probably better in terms of the incidence of meniscal tears and chondral injuries, compared with delaying surgery until skeletal maturity [41]. Study III involves a long-term follow-up and reveals that patients who were adolescents at the time of ACL reconstruction have significantly more radiographically visible OA changes in their operated knee than in their non-involved contralateral knee after a follow-up of 175 months. These patients were almost at a skeletally mature age at surgery and no further growth in the knee was expected. Considering the age of maturity in Study III, there appears to be no difference in the long term between adults and adolescents when it comes to the development of post-traumatic secondary OA after ACL injury.

6.4 ASPECTS OF BONE MINERAL DENSITY

The principal findings in Study IV are that BMD in patients who were adolescents at the time of ACL reconstruction differed from that in an adult control group and a reference database. The results from Study IV reveal that the BMD in the calcanei of males was lower compared with the control group and the reference database. The females had a higher BMD than the reference database. In Study IV, at the time of injury and ACL reconstruction in the adolescent group (Group A), at the age of 15 years, the females had completed the rapid period of bone gain. This is in contrast to the males in Group A, where an interruption occurred in the middle of the rapid BMD gain period. The low BMD found in the males in Group A might be due to a disturbance in BMC accrual at pubertal age caused by the traumatic ACL injury and surgery. Furthermore, the findings in the present study might also be due to the fact that bone formation in males, at the age when ACL injury and surgery occur, is more sensitive to disturbances, compared with the more mature female bone at the same age. The bone formation during adolescence, which occurs earlier in females, together with a high pre-injury activity level, might explain the relatively higher BMD values for the females in Group A compared with a reference population. The mean Tegner activity level pre-injury for Group A was 7.9. The corresponding value pre-operatively was 4.1 and was unchanged at follow-up. In contrast, Lidén et al. reported a significant improvement in the Tegner activity scale at the seven-year follow-up after ACL reconstruction compared with the pre-operative values [71]. Furthermore, Stener et al. reported a decrease in BMD in the calcanei on both the operated and the non-operated sides, despite an increased activity level compared with the pre-operative level [112]. In Study IV, the pre-injury Tegner activity scale had decreased for both females and males at follow-up in Group A. If the activity level pre-injury had been maintained at follow-up, a higher BMD might have been measured. Another factor when it comes to the low activity level could be the relatively long follow-up period in Group A and the natural decrease in activity followed by ageing. In previous studies, ACL-reconstructed adult patients, both female and male, have revealed a higher BMD in the calcanei pre-operatively compared with a gender- and age-matched group [28,112]. This might be due to the fact that they are mostly athletes with a higher degree of activity. In Study IV, where the majority of the patients were injured during sporting activities, this was not, however, able to compensate for low BMD in adulthood. The surgery itself, the ACL reconstruction, could also reduce BMD in the calcanei, as seen in the adults in Group C in Study IV and other studies [28,112]. The surgical trauma accelerates the remodelling rate and also the bone mineral loss in the post-operative period. Consequently, the period of late pre- and early pubertal age which is said to be “a window of opportunity" to stimulate bone growth, as the skeleton is most responsive to physical activity during this period, might also be a period sensitive to the disturbance of bone growth [77]. In Study IV a reduction in the T-score with more than 1 unit was seen mostly in males in Group A, but also in females in Group A as well as both males and females in the control group. This indicated that a not negligible part of young patients undergoing ACL reconstruction run an increased future fracture risk. Considering the future fracture risk, it might be of clinical relevance to assess the BMD after ACL reconstruction in adolescents. Study IV indicates that at least boys with an ACL injury and subsequent ACL reconstruction run a subsequent risk of a significantly lower BMD in their calcanei as adults and it might be necessary to consider bone health when planning for the treatment of an ACL injury during adolescence.

07 STRENGTHS & LIMITATIONS

7.1 STUDY I

The strength of Study I is the large unselected group of patients in the study. The limitations are that the patients underwent surgery more than 20 years ago and the lack of pre-operative data that could have given valuable information about the change over time.

7.2 STUDY II

The strengths of Study II are the number of pre-operative clinical assessments and subjective evaluation scores. One limitation is that the BPTB group was small. Other limitations are the clinical follow-up examination and questionnaire answers ranging over a long period, as well as the relatively low return rate of the questionnaires. However, the patients who chose not to return their questionnaires had a similar age and gender distribution as those who did. Unfortunately, the data in the present study do not allow us to further analyse these patients because of too many missing values.

7.3 STUDY III

The strengths of Study III include its high follow-up rate and its long follow-up period. Limitations of the study are the small size of the study group, the fact that no physical control group was used and the lack of an interim follow-up with specific assessments. Furthermore, no subgroup analyses of BPTB versus HT grafts were conducted because of small subgroups and because patients with BPTB grafts had a longer follow-up.

7.3 STUDY IV

The strengths of Study IV are the long follow-up period and the high follow-up rate. The limitations of the study include the limited size of the cohort, the lack of pre-operative BMD data and the lack of an interim follow-up with specific assessments. Moreover, the fact that no statistical comparisons were possible to perform between the study groups and the reference database is another limitation. Finally in Group A both the BPTB and HT were used.

08 CONCLUSIONS

After ACL reconstruction, the patients reported a good HRQoL measured with the SF-36 in comparison with a matched sample of the general population.

Pre-operative factors, such as pivot shift, knee function and ROM, and Tegner activity levels pre-injury and pre-operatively may predict a good post-operative outcome in terms of HRQoL after ACL reconstruction.

In the long term, adolescents at the time of ACL reconstruction reveal significantly more radiographically visible osteoarthritic changes in their operated knee. However, the clinical outcomes and HRQoL are comparable with those of healthy controls.

The BMD in patients who were adolescents at the time of the ACL reconstruction differed from a control group and a reference database. In males, the value was lower compared with both groups, while it was higher in females compared with the reference database. The reduction in the T-score indicates that at least males with an ACL injury and subsequent ACL reconstruction run a subsequent risk of a significantly lower BMD in their calcanei as adults and consequently an increased future fracture risk.

09
FUTURE PERSPECTIVES

Further refining the disease-specific outcome measurements and also incorporating non-disease-specific health assessment measurements, are of interest when evaluating ACL reconstructions. ACL injuries are usually sustained by young, athletic people and this thesis suggests that, in the long term, their HRQoL does not differ from that of a normative population. The cost of the health-care system is substantial in most societies. It is therefore important to evaluate the effect of the treatments and to compare them with both healthy age-matched individuals and the treatment of other diagnoses in order to provide cost-effective treatment algorithms.

Pre-operative factors that are able to predict a good outcome in terms of HRQoL after ACL reconstruction could help to select the right patients and to offer the best treatment to each specific patient. Furthermore, using pre-operative factors that could predict a good post-operative outcome could provide cost-effective treatment algorithms. It is therefore important to further assess and refine possible pre-operative factors in the future.

For skeletally immature children, the recommendations are physeal-sparing and transphyseal techniques. To our knowledge, there are no long-term follow-ups of OA changes among skeletally immature children. Considering the results of Study III and the age of maturity, there appears to be no difference in the long term between adults and adolescents when it comes to the development of post-traumatic secondary OA after ACL injury. It would be interesting, by way of comparison, in a future study to assess OA changes in the long term among skeletally immature ACL-injured children.

Study IV indicates that at least boys with an ACL injury and subsequent ACL reconstruction run a subsequent risk of a significantly lower BMD in their calcanei as adults and consequently an increased future fracture risk. Due to the limited size of the study group and the lack of pre-operative BMD data, it would be interesting to perform a study comparing surgically and conservatively treated adolescents, involving pre-operative BMD data, and thoroughly examine the difference in BMD between males and females found in Study IV.

10
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11 REFERENCES

1. Ahlback S. Osteoarthrosis of the knee. A radiographic investigation. Acta Radiol Diagn (Stockh). 1968:Suppl 277:277-272.

2. Aichroth PM, Patel DV, Zorrilla P. The natural history and treatment of rupture of the anterior cruciate ligament in children and adolescents. A prospective review. J Bone Joint Surg Br. 2002;84(1):38-41.

3. Ajuied A, Wong F, Smith C, et al. Anterior cruciate ligament injury and radiologic progression of knee osteoarthritis: a systematic review and meta-analysis. Am J Sports Med. 2014;42(9):2242-2252.

4. Al-Hadithy N, Dodds AL, Akhtar KS, Gupte CM. Current concepts of the management of anterior cruciate ligament injuries in children. Bone Joint J. 2013;95-B(11):1562-1569.

5. Alwis G, Linden C, Ahlborg HG, Dencker M, Gardsell P, Karlsson MK. A 2-year school-based exercise programme in pre-pubertal boys induces skeletal benefits in lumbar spine. Acta Paediatr. 2008;97(11):1564-1571.

6. Alwis G, Rosengren B, Stenevi-Lundgren S, Duppe H, Sernbo I, Karlsson MK. Normative dual energy X-ray absorptiometry data in Swedish children and adolescents. Acta Paediatr. 2010;99(7):1091-1099.

7. Andernord D, Karlsson J, Musahl V, Bhandari M, Fu FH, Samuelsson K. Timing of surgery of the anterior cruciate ligament. Arthroscopy. 2013;29(11):1863-1871.

8. Arbes S, Resinger C, Vecsei V, Nau T. The functional outcome of total tears of the anterior cruciate ligament (ACL) in the skeletally immature patient. Int Orthop. 2007;31(4):471-475.

9. Arbuthnot JE, Brink RB. The role of anterior cruciate ligament reconstruction in the older patients, 55 years or above. Knee Surg Sports Traumatol Arthrosc. 2010;18(1):73-78.

10. Ardern CL, Taylor NF, Feller JA, Webster KE. Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. Br J Sports Med. 2014;48(21):1543-1552.

11. Bailey DA. The Saskatchewan Pediatric Bone Mineral Accrual Study: bone mineral acquisition during the growing years. Int J Sports Med. 1997;18 Suppl 3:S191-194.

12. Barenius B, Nordlander M, Ponzer S, Tidermark J, Eriksson K. Quality of life and clinical outcome after anterior cruciate ligament reconstruction using patellar tendon graft or quadrupled semitendinosus graft: an 8-year follow-up of a randomized controlled trial. Am J Sports Med. 2010;38(8):1533-1541.

13. Beynnon BD, Johnson RJ, Abate JA, Fleming BC, Nichols CE. Treatment of anterior cruciate ligament injuries, part I. Am J Sports Med. 2005;33(10):1579-1602.

14. Biau DJ, Tournoux C, Katsahian S, Schranz P, Nizard R. ACL Reconstruction: A Meta-analysis of Functional Scores. Clin Orthop Relat Res. 2007;458:180-7.

15. Biau DJ, Tournoux C, Katsahian S, Schranz PJ, Nizard RS. Bone-patellar tendon-bone autografts versus hamstring autografts for reconstruction of anterior cruciate ligament: meta-analysis. BMJ. 2006;29(332):995-1001.

16. Briggs KK, Lysholm J, Tegner Y, Rodkey WG, Kocher MS, Steadman JR. The reliability, validity, and responsiveness of the Lysholm score and Tegner activity scale for anterior cruciate ligament injuries of the knee: 25 years later. Am J Sports Med. 2009;37(5):890-897.

17. Briggs KK, Steadman JR, Hay CJ, Hines SL. Lysholm score and Tegner activity level in individuals with normal knees. Am J Sports Med. 2009;37(5):898-901.

18. Brismar TB, Janszky I, Toft LI. Calcaneal BMD Obtained by Dual X-Ray and Laser Predicts Future Hip Fractures-A Prospective Study on 4 398 Swedish Women. J Osteoporos. 2010;2010:875647.

19. Brooks R. EuroQol: the current state of play. Health Policy. 1996;37(1):53-72.

20. Brosseau L, Balmer S, Tousignant M, et al. Intra- and intertester reliability and criterion validity of the parallelogram and universal goniometers for measuring maximum active knee flexion and extension of patients with knee restrictions. Arch Phys Med Rehabil. 2001;82(3):396-402.

21. Burstrom K, Johannesson M, Diderichsen F. Swedish population health-related quality of life results using the EQ-5D. Qual Life Res. 2001;10(7):621-635.

22. Calvisi V, De Vincentiis B, Palumbo P, Padua R, Lupparelli S. Health-related quality of life in patients with anterior cruciate ligament insufficiency undergoing arthroscopic reconstruction: a practice-based Italian normative group in comorbid-free patients. J Orthop Traumatol. 2008;9(4):233-238.

23. Chaudhari AM, Briant PL, Bevill SL, Koo S, Andriacchi TP. Knee kinematics, cartilage morphology, and osteoarthritis after ACL injury. Med Sci Sports Exerc. 2008;40(2):215-222.

24. Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet. 1993;341(8837):72-75.

25. Daniel DM, Stone ML, Sachs R, Malcom L. Instrumented measurement of anterior knee laxity in patients with acute anterior cruciate ligament disruption. Am J Sports Med. 1985;13(6):401-407.

26. Dunn WR, Spindler KP. Predictors of activity level 2 years after anterior cruciate ligament reconstruction (ACLR): a Multicenter Orthopaedic Outcomes Network (MOON) ACLR cohort study. Am J Sports Med. 2010;38(10):2040-2050.

27. Dunn WR, Wolf BR, Harrell FE, Jr., et al. Baseline predictors of health-related quality of life after anterior cruciate ligament reconstruction: a longitudinal analysis of a multicenter cohort at two and six years. J Bone Joint Surg Am. 2015;97(7):551-557.

28. Ejerhed L, Kartus J, Nilsén R, Nilsson U, Kullenberg R, Karlsson J. The effect of anterior cruciate ligament surgery on bone mineral in the calcaneus: a prospective study with a 2-year follow-up evaluation. Arthroscopy. 2004;20(4):352-359.

29. Ejerhed L, Kartus J, Sernert N, Köhler K, Karlsson J. Patellar tendon or semitendinosus tendon autografts for anterior cruciate ligament reconstruction? A prospective randomized study with a two-year follow-up. Am J Sports Med. 2003;31(1):19-25.

30. Fabricant PD, Jones KJ, Delos D, et al. Reconstruction of the anterior cruciate ligament in the skeletally immature athlete: a review of current concepts: AAOS exhibit selection. J Bone Joint Surg Am. 2013;95(5):e28.

31. Fairbank TJ. Knee joint changes after meniscectomy. J Bone Joint Surg Br. 1948;30B(4):664-670.

32. Faulkner RA, Bailey DA, Drinkwater DT, McKay HA, Arnold C, Wilkinson AA. Bone densitometry in Canadian children 8-17 years of Age. Calcif Tissue Int. 1996;59(5):344-351.

33. Ferrari JD, Bach BR, Jr., Bush-Joseph CA, Wang T, Bojchuk J. Anterior cruciate ligament reconstruction in men and women: An outcome analysis comparing gender. Arthroscopy. 2001;17(6):588-596.

34. Filbay SR, Ackerman IN, Russell TG, Macri EM, Crossley KM. Health-related quality of life after anterior cruciate ligament reconstruction: a systematic review. Am J Sports Med. 2014;42(5):1247-1255.

35. Forster MC, Forster IW. Patellar tendon or four-strand hamstring? A systematic review of autografts for anterior cruciate ligament reconstruction. Knee. 2005;12(3):225-230.

36. Frank CB, Jackson DW. The science of reconstruction of the anterior cruciate ligament. J Bone Joint Surg Am. 1997;79(10):1556-1576.

37. Freedman KB, D'Amato MJ, Nedeff DD, Kaz A, Bach BR, Jr. Arthroscopic anterior cruciate ligament reconstruction: a metaanalysis comparing patellar tendon and hamstring tendon autografts. Am J Sports Med. 2003;31(1):2-11.

38. Friel NA, Chu CR. The role of ACL injury in the development of posttraumatic knee osteoarthritis. Clin Sports Med. 2013;32(1):1-12.

39. Frobell RB, Roos EM, Roos HP, Ranstam J, Lohmander LS. A randomized trial of treatment for acute anterior cruciate ligament tears. N Engl J Med. 2010;363(4):331-342.

40. Frosch KH, Stengel D, Brodhun T, et al. Outcomes and risks of operative treatment of rupture of the anterior cruciate ligament in children and adolescents. Arthroscopy. 2010;26(11):1539-1550.

41. Gausden EB, Calcei JG, Fabricant PD, Green DW. Surgical options for anterior cruciate ligament reconstruction in the young child. Curr Opin Pediatr. 2015;27(1):82-91.

42. Gillquist J, Messner K. Anterior cruciate ligament reconstruction and the long-term incidence of gonarthrosis. Sports Med. 1999;27(3):143-156.

43. Goldblatt JP, Fitzsimmons SE, Balk E, Richmond JC. Reconstruction of the anterior cruciate ligament: meta-analysis of patellar tendon versus hamstring tendon autograft. Arthroscopy. 2005;21(7):791-803.

44. Graf BK, Lange RH, Fujisaki CK, Landry GL, Saluja RK. Anterior cruciate ligament tears in skeletally immature patients: meniscal pathology at presentation and after attempted conservative treatment. Arthroscopy. 1992;8(2):229-233.

45. Guadalupe-Grau A, Fuentes T, Guerra B, Calbet JA. Exercise and bone mass in adults. Sports Med. 2009;39(6):439-468.

46. Hartigan EH, Lynch AD, Logerstedt DS, Chmielewski TL, Snyder-Mackler L. Kinesiophobia after anterior cruciate ligament rupture and reconstruction: noncopers versus potential copers. J Orthop Sports Phys Ther. 2013;43(11):821-832.

47. Heaney RP, Abrams S, Dawson-Hughes B, et al. Peak bone mass. Osteoporos Int. 2000;11(12):985-1009.

48. Hefti F, Müller W, Jakob RP, Stäubli HU. Evaluation of knee ligament injuries with the IKDC form. Knee Surg Sports Traumatol Arthrosc. 1993;1(3-4):226-234.

49. Heijne A, Ang BO, Werner S. Predictive factors for 12-month outcome after anterior cruciate ligament reconstruction. Scand J Med Sci Sports. 2008;19(6):842-9.

50. Henry J, Chotel F, Chouteau J, Fessy MH, Berard J, Moyen B. Rupture of the anterior cruciate ligament in children: early reconstruction with open physes or delayed reconstruction to skeletal maturity? Knee Surg Sports Traumatol Arthrosc. 2009;17(7):748-755.

51. Hoher J, Bach T, Munster A, Bouillon B, Tiling T. Does the mode of data collection change results in a subjective knee score? Self-administration versus interview. Am J Sports Med. 1997;25(5):642-647.

52. Irrgang JJ, Anderson AF, Boland AL, et al. Development and validation of the international knee documentation committee subjective knee form. Am J Sports Med. 2001;29(5):600-613.

53. Irrgang JJ, Ho H, Harner CD, Fu FH. Use of the International Knee Documentation Committee guidelines to assess outcome following anterior cruciate ligament re-

construction. Knee Surg Sports Traumatol Arthrosc. 1998;6(2):107-114.

54. Janarv PM, Wikstrom B, Hirsch G. The influence of transphyseal drilling and tendon grafting on bone growth: an experimental study in the rabbit. J Pediatr Orthop. 1998;18(2):149-154.

55. Jennings S, Rasquinha V, Dowd GS. Medium term follow up of endoscopically assisted BPTB ACL reconstruction using a two-incision technique--return to sporting activity. Knee. 2003;10(4):329-333.

56. Kartus J, Stener S, Lindahl S, Engström B, Eriksson BI, Karlsson J. Factors affecting donor-site morbidity after anterior cruciate ligament reconstruction using bone-patellar tendon-bone autografts. Knee Surg Sports Traumatol Arthrosc. 1997;5(4):222-228.

57. Keays SL, Newcombe PA, Bullock-Saxton JE, Bullock MI, Keays AC. Factors involved in the development of osteoarthritis after anterior cruciate ligament surgery. Am J Sports Med. 2010;38(3):455-463.

58. Kocher MS, Smith JT, Zoric BJ, Lee B, Micheli LJ. Transphyseal anterior cruciate ligament reconstruction in skeletally immature pubescent adolescents. J Bone Joint Surg Am. 2007;89(12):2632-2639.

59. Kocher MS, Steadman JR, Briggs K, Zurakowski D, Sterett WI, Hawkins RJ. Determinants of patient satisfaction with outcome after anterior cruciate ligament reconstruction. J Bone Joint Surg Am. 2002;84-A(9):1560-1572.

60. Kocher MS, Steadman JR, Briggs KK, Sterett WI, Hawkins RJ. Relationships between objective assessment of ligament stability and subjective assessment of symptoms and function after anterior cruciate ligament reconstruction. Am J Sports Med. 2004;32(3):629-634.

61. Kohl S, Stutz C, Decker S, et al. Mid-term results of transphyseal anterior cruciate ligament reconstruction in children and adolescents. Knee. 2014;21(1):80-5.

62. Kostogiannis I, Ageberg E, Neuman P, Dahlberg L, Friden T, Roos H. Activity Level and Subjective Knee Function 15 Years After Anterior Cruciate Ligament Injury: A Prospective, Longitudinal Study of Nonreconstructed Patients. Am J Sports Med. 2007;35(7):1135-43.

63. Kostogiannis I, Ageberg E, Neuman P, Dahlberg LE, Friden T, Roos H. Clinically assessed knee joint laxity as a predictor for reconstruction after an anterior cruciate ligament injury: a prospective study of 100 patients treated with activity modification and rehabilitation. Am J Sports Med. 2008;36(8):1528-1533.

64. Kullenberg R. Reference database for dual X-ray and laser Calscan bone densitometer. J Clin Densitom. 2003;6(4):367-372.

65. Kvist J. Sagittal tibial translation during exercises in the anterior cruciate ligament-deficient knee. Scand J Med Sci Sports. 2005;15(3):148-158.

66. LaBella CR, Hennrikus W, Hewett TE, Council on Sports M, Fitness, Section on O. Anterior cruciate ligament injuries: diagnosis, treatment, and prevention. Pediatrics. 2014;133(5):e1437-1450.

67. Lavoie P, Fletcher J, Duval N. Correlation between patients' satisfaction and objective measurement of knee stability after ACL reconstruction using a patellar tendon autograft. Knee. 2001;8(1):19-24.

68. Laxdal G, Kartus J, Ejerhed L, et al. Outcome and risk factors after anterior cruciate ligament reconstruction: a follow-up study of 948 patients. Arthroscopy. 2005;21(8):958-964.

69. Leiter JR, Gourlay R, McRae S, de Korompay N, MacDonald PB. Long-term follow-up of ACL reconstruction with hamstring autograft. Knee Surg Sports Traumatol Arthrosc. 2014;22(5):1061-1069.

70. Leppala J, Kannus P, Natri A, et al. Effect of anterior cruciate ligament injury of the knee on bone mineral density of the spine and affected lower extremity: a prospective one-year follow-Up study. Calcif Tissue Int. 1999;64(4):357-363.

71. Lidén M, Ejerhed L, Sernert N, Laxdal G, Kartus J. Patellar Tendon or Semitendinosus Tendon Autografts for Anterior Cruciate Ligament Reconstruction: A Prospective, Randomized Study With a 7-Year Follow-up. Am J Sports Med. 2007;35(5):740-8.

72. Liden M, Sernert N, Rostgard-Christensen L, Kartus C, Ejerhed L. Osteoarthritic changes after anterior cruciate ligament reconstruction using bone-patellar tendon-bone or hamstring tendon autografts: a retrospective, 7-year radiographic and clinical follow-up study. Arthroscopy. 2008;24(8):899-908.

73. Lin YC, Lyle RM, Weaver CM, et al. Peak spine and femoral neck bone mass in young women. Bone. 2003;32(5):546-553.

74. Logerstedt D, Di Stasi S, Grindem H, et al. Self-reported knee function can identify athletes who fail return-to-activity criteria up to 1 year after anterior cruciate ligament reconstruction: a delaware-oslo ACL cohort study. J Orthop Sports Phys Ther. 2014;44(12):914-923.

75. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am J Sports Med. 2007;35(10):1756-1769.

76. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. Am J Sports Med. 1982;10(3):150-154.

77. MacKelvie KJ, Khan KM, McKay HA. Is there a critical period for bone response to weight-bearing exercise in children and adolescents? a systematic review. Br J Sports Med. 2002;36(4):250-257.

78. Maffulli N, Del Buono A. Anterior cruciate ligament tears in children. Surgeon. 2012;11(2):59-62.

79. Marks PH, Donaldson ML. Inflammatory cytokine profiles associated with chondral damage in the anterior cruciate ligament-deficient knee. Arthroscopy. 2005;21(11):1342-1347.

80. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996;312(7041):1254-1259.

81. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Archives of disease in childhood. 1969;44(235):291.

82. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Archives of disease in childhood. 1970;45(239):13-23.

83. McAllister DR, Motamedi AR, Hame SL, Shapiro MS, Dorey FJ. Quality of life assessment in elite collegiate athletes. Am J Sports Med. 2001;29(6):806-810.

84. McAllister DR, Tsai AM, Dragoo JL, et al. Knee function after anterior cruciate ligament injury in elite collegiate athletes. Am J Sports Med. 2003;31(4):560-563.

85. Miller PD, Siris ES, Barrett-Connor E, et al. Prediction of fracture risk in postmenopausal white women with peripheral bone densitometry: evidence from the National Osteoporosis Risk Assessment. J Bone Miner Res. 2002;17(12):2222-2230.

86. Millett PJ, Wickiewicz TL, Warren RF. Motion loss after ligament injuries to the knee. Part I: causes. Am J Sports Med. 2001;29(5):664-675.

87. Mizuta H, Kubota K, Shiraishi M, Otsuka Y, Nagamoto N, Takagi K. The conservative treatment of complete tears of the anterior cruciate ligament in skeletally immature patients. J Bone Joint Surg Br. 1995;77(6):890-894.

88. Mohtadi N. Development and validation of the quality of life outcome measure (questionnaire) for chronic anterior cruciate ligament deficiency. Am J Sports Med. 1998;26(3):350-359.

89. Moksnes H, Engebretsen L, Risberg MA. The current evidence for treatment of ACL injuries in children is low: a systematic review. J Bone Joint Surg Am. 2012;94(12):1112-1119.

90. Nguyen TV, Maynard LM, Towne B, et al. Sex differences in bone mass acquisition during growth: the Fels Longitudinal Study. J Clin Densitom. 2001;4(2):147-157.

91. Nordenvall R, Bahmanyar S, Adami J, Stenros C, Wredmark T, Fellander-Tsai L. A population-based nationwide study of cruciate ligament injury in Sweden, 2001-2009: incidence, treatment, and sex differences. Am J Sports Med. 2012;40(8):1808-1813.

92. Noyes FR, Grood ES, Cummings JF, Wroble RR. An analysis of the pivot shift phenomenon. The knee motions and subluxations induced by different examiners. Am J Sports Med. 1991;19(2):148-155.

93. Oiestad BE, Engebretsen L, Storheim K, Risberg MA. Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. Am J Sports Med. 2009;37(7):1434-1443.

94. Ostenberg A, Roos E, Ekdahl C, Roos H. Isokinetic knee extensor strength and functional performance in healthy female soccer players. Scand J Med Sci Sports. 1998;8(5 Pt 1):257-264.

95. Osti L, Papalia R, Del Buono A, Leonardi F, Denaro V, Maffulli N. Surgery for ACL deficiency in patients over 50. Knee Surg Sports Traumatol Arthrosc. 2011;19(3):412-417.

96. Pettersson U, Nilsson M, Sundh V, Mellstrom D, Lorentzon M. Physical activity is the strongest predictor of calcaneal peak bone mass in young Swedish men. Osteoporos Int. 2010;21(3):447-455.

97. Pinczewski LA, Lyman J, Salmon LJ, Russell VJ, Roe J, Linklater J. A 10-Year Comparison of Anterior Cruciate Ligament Reconstructions With Hamstring Tendon and Patellar Tendon Autograft: A Controlled, Prospective Trial. Am J Sports Med. 2007;35(4):564-74.

98. Ramski DE, Kanj WW, Franklin CC, Baldwin KD, Ganley TJ. Anterior cruciate ligament tears in children and adolescents: a meta-analysis of nonoperative versus operative treatment. Am J Sports Med. 2014;42(11):2769-2776.

99. Reiman MP, Rogers ME, Manske RC. Interlimb differences in lower extremity bone mineral density following anterior cruciate ligament reconstruction. J Orthop Sports Phys Ther. 2006;36(11):837-844.

100. Renstrom P, Ljungqvist A, Arendt E, et al. Non-contact ACL injuries in female athletes: an International Olympic Committee current concepts statement. Br J Sports Med. 2008;42(6):394-412.

101. Rittweger J, Reeves ND, Narici MV, Belavy DL, Maganaris CN, Maffulli N. Persisting side-to-side differences in bone mineral content, but not in muscle strength and tendon stiffness after anterior cruciate ligament reconstruction. Clin Physiol Funct Imaging. 2011;31(1):73-79.

102. Roos EM, Bremander AB, Englund M, Lohmander LS. Change in self-reported outcomes and objective physical function over 7 years in middle-aged subjects with or at high risk of knee osteoarthritis. Ann Rheum Dis. 2008;67(4):505-510.

103. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes. 2003;1:64.

104. Roos EM, Roos HP, Ekdahl C, Lohmander LS. Knee injury and Osteoarthritis Outcome Score (KOOS)--validation of a Swedish version. Scand J Med Sci Sports. 1998;8(6):439-448.

105. Roos EM, Roos HP, Lohmander LS. WOMAC Osteoarthritis Index--additional dimensions for use in subjects with post-traumatic osteoarthritis of the knee. Western Ontario and MacMaster Universities. Osteoarthritis Cartilage. 1999;7(2):216-221.

106. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J Orthop Sports Phys Ther. 1998;28(2):88-96.

107. Samuelsson K, Andersson D, Karlsson J.

Treatment of anterior cruciate ligament injuries with special reference to graft type and surgical technique: an assessment of randomized controlled trials. Arthroscopy. 2009;25(10):1139-1174.

108. Seeman E, Delmas PD. Bone quality--the material and structural basis of bone strength and fragility. N Engl J Med. 2006;354(21):2250-2261.

109. Sernert N, Kartus J, Kohler K, Ejerhed L, Karlsson J. Evaluation of the reproducibility of the KT-1000 arthrometer. Scand J Med Sci Sports. 2001;11(2):120-125.

110. Shapiro ET, Richmond JC, Rockett SE, McGrath MM, Donaldson WR. The use of a generic, patient-based health assessment (SF-36) for evaluation of patients with anterior cruciate ligament injuries. Am J Sports Med. 1996;24(2):196-200.

111. Shelbourne KD, Nitz P. Accelerated rehabilitation after anterior cruciate ligament reconstruction. Am J Sports Med. 1990;18(3):292-299.

112. Stener S, Kartus J, Ejerhed L. Anterior cruciate ligament reconstruction reduces bone mineral areal mass. Arthroscopy. 2013;29(11):1788-1795.

113. Sullivan M, Karlsson J. The Swedish SF-36 Health Survey III. Evaluation of criterion-based validity: results from normative population. J Clin Epidemiol. 1998;51(11):1105-1113.

114. Sullivan M, Karlsson J, Ware JE, Jr. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. Soc Sci Med. 1995;41(10):1349-1358.

115. Takata S, Abbaspour A, Kashihara M, Nakao S, Yasui N. Unilateral chronic insufficiency of anterior cruciate ligament decreases bone mineral content and lean mass of the injured lower extremity. J Med Invest. 2007;54(3-4):316-321.

116. Tashman S, Kopf S, Fu FH. The Kinematic Basis of ACL Reconstruction. Oper Tech Sports Med. 2008;16(3):116-118.

117. Tegner Y, Lysholm J, Lysholm M, Gillquist J. Rating systems in evaluation of knee ligament injuries. Clin Orthop. 1985;198:43-49.

118. Tegner Y, Lysholm J, Lysholm M, Gillquist J. A performance test to monitor rehabilitation and evaluate anterior cruciate ligament injuries. Am J Sports Med. 1986;14(2):156-159.

119. Thorpe JA, Steel SA. The DXL Calscan heel densitometer: evaluation and diagnostic thresholds. Br J Radiol. 2006;79(940):336-341.

120. Torg JS, Conrad W, Kalen V. Clinical diagnosis of anterior cruciate ligament instability in the athlete. Am J Sports Med. 1976;4(2):84-93.

121. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005;14(6):1523-1532.

122. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-483.

123. von Porat A, Roos EM, Roos H. High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: a study of radiographic and patient relevant outcomes. Ann Rheum Dis. 2004;63(3):269-273.

124. Wright RW, Fetzer GB. Bracing after ACL reconstruction: a systematic review. Clin Orthop Relat Res. 2007;455:162-168.

125. Wroble RR, Van Ginkel LA, Grood ES, Noyes FR, Shaffer BL. Repeatability of the KT-1000 arthrometer in a normal population. Am J Sports Med. 1990;18(4):396-399.

126. Ziebarth K, Kolp D, Kohl S, Slongo T. Anterior cruciate ligament injuries in children and adolescents: a review of the recent literature. Eur J Pediatr Surg. 2013;23(6):464-469.

I

Health-related quality of life after anterior cruciate ligament reconstruction.

Månsson O, Kartus J, Sernert N

Knee Surg Sports Traumatol Arthrosc. 2011;19(3):479-87

II

Pre-operative factors predicting good outcome in terms of health-related quality of life after ACL reconstruction.

Månsson O, Kartus J, Sernert N

Scand J Med Sci Sports. 2013; 23(1):15-22

III

Long-term clinical and radiographic results after delayed anterior cruciate ligament reconstruction in adolescents.

Månsson O, Sernert N,
Rostgard-Christensen L, Kartus J

Am J Sports Med. 2015;43:138-145

IV

Long-term examination of bone mineral density in the calcanei after ACL reconstruction in adolescents and matched adult controls.

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