Jon Olav Drogset

RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES

A clinical study

Thesis for the degree of doctor medicinae

Trondheim, October 2006

Norwegian University of
Science and Technology
Faculty of Medicine
Institute of Neuroscience

NTNU
Innovation and Creativity

NTNU
Norwegian University of Science and Technology

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ISBN 82-471-8111-8 (printed ver.)
ISBN 82-471-8109-6 (electronic ver.)
ISSN 1503-8181

Doctoral Theses at NTNU, 2006: 170

Printed by Tapir Uttrykk

RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES

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Jon Olav Drogset, M.D.

An expert is a person who has made all the mistakes that can be made in a very narrow field.
- *Niels Bohr*

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II. Drogset, JO, Grøntvedt, T. Anterior cruciate ligament reconstruction with and without a ligament augmentation device: results at 8-Year follow-up. Am J Sports Med. 2002 Nov-Dec; 30 (6):851-6.

III. Drogset, JO, Grøntvedt, T, Tegnander, A. Endoscopic reconstruction of the anterior cruciate ligament using bone-patellar tendon-bone grafts fixed with bioabsorbable or metal interference screws: a prospective randomized study of the clinical outcome. Am J Sports Med. 2005 Aug; 33(8):1160-5.

IV. Drogset, JO, Grøntvedt, T, Myhr, G. Magnetic Resonance Imaging Analysis of Bioabsorbable Interference Screws Used for Fixation of Bone-Patellar Tendon-Bone Autografts in Endoscopic Reconstruction of the Anterior Cruciate Ligament. Am J Sports Med. 2006 Feb 21; [Epub ahead of print]

V. Drogset, JO, Grøntvedt, T, Jessen, V, Tegnander, A, Mollnes, TE, Bergh, K. Comparison of in vitro and in vivo complement activation by metal and bioabsorbable screws used in anterior cruciate ligament reconstruction.
Arthroscopy. 2006 May; 22(5):489-96.

ACKNOWLEDGEMENTS

This thesis is based on studies carried out at the Department of Orthopedic Surgery, Trondheim University Hospital.
I wish to express my sincere gratitude to the following persons:
Torbjørn Grøntvedt, a good friend and mentor, for inspiring me to do this work and for valuable advice, constructive criticism and many stimulating discussions.
Professor Pål Benum, Henrik Sandbu and Eirik Rødevand, for believing in my ideas and giving me the opportunity to carry them through.
Vigleik Jessen, Grete Sofie Hortemo and Arild Aamodt for active participation in randomizing and operating some of the patients.
Ivar Rossvoll, for friendship and help with statistics.
Øystein Haave and Annja T. Viset for their great help in evaluating the radiographs.
Gunnar Myhr for his enthusiasm and support in MRI examinations and evaluation of images.
Professor Lars Engebretsen, Ullevål University Hospital and Ole Rasmus Robak, Aker University Hospital Oslo, Professor Anders Mølster, Haukeland Hospital, Torbjørn Strand, Diakonissehjemmet Hospital, Asbjørn Bøe, Hagavik Hospital, University of Bergen, Gisle Uppheim and Bjørn Ødegaard, Lovisenberg Diakonale Hospital, Oslo, Professor Kåre Bergh and Agnar Tegnander Trondheim University Hospital, Professor Tom Eirik Mollnes, Rikshospitalet University Hospital; Oslo for their support and practical work in our prospective randomized studies.
Liv Randi Sand [1], Randi Sand[2] and other nurses and technical assistants at the operating theatre[2] and outpatient clinic[1] at the Department of Orthopedics, Trondheim, for their help and patience in keeping the clinical studies going.
Professor Vilh. Finsen for help with the manuscripts.
Berit Wenaas, secretary at the Institute of Neuroscience for support and practical help with the collection of data.
Professor Are Holen and Professor Helge Rønningen at the Institute of Neuroscience for letting me keep the office during these years.
To Toril, Nikolay and Camilla for all their support and patience during some busy years, and for letting me work on my laptop at any hour of the day.
To Mona, Emilie and Aleksander.

This study was supported by grants from the Norwegian Association of Sports Medicine, Zimmer Norway and Smith & Nephew Norway.

INTRODUCTION

The motion characteristics of the articular surfaces of the tibia relative to the femur are very complex and are guided by the anterior cruciate ligament (ACL) and the other primary ligaments that span the knee. Studies performed using cadaveric models have revealed that the ACL is the primary restraint to anterior displacement of the tibia relative to the femur (Butler 1980; Fukubayashi 1982), and acts as a restraint to internal-external rotation (Markolf 1990; Fleming 2001; Kanamori 2002), varus-valgus angulation (Marder 1991) and combinations thereof (Markolf 1995; Kanamori 2002). In addition to this the ACL is an important component in the proprioceptive feedback mechanism of the joint.

The management of ACL injuries is one of the most challenging issues in the field of sports traumatology. Sporting activities in modern society are increasing and have also increased the incidence of ACL injuries. Danish studies have shown an annual incidence of 3.1 ACL injuries per 10.000 inhabitants between 0 and 50 years of age (Nielsen 1989). The reported incidence of ACL tears for female athletes ranges between 4 and 6 times greater than that of male athletes competing in similar activities. In women's professional soccer Giza et al. (Giza 2005) found an overall injury incidence rate of 1.93 injuries per 1000 player hours. The incidence of injury during practice and games was 1.17 and 12.63 per 1000 player hours, respectively. Sports activities are responsible for approximately 95% of all ACL ruptures seen in our hospital (Grontvedt 1996b). Bjordal et al (Bjordal 1997) studied 176 patients who had participated in organized soccer. Women had an incidence rate of 0.10 injuries per 1000 game hours, significantly higher than that for men (0.057). The Norwegian National ACL Registry was initiated in 2004. The numbers of ACL reconstructions recorded in Norway in 2005 was 1543 (Strand, Hafjell 2006). Hamstrings autografts were used in 57% of the cases and bone-patella-tendon-bone graft in 43%.

The material properties of the ACL vary along its length and cross section, and therefore, it may be important to match the structural properties of the graft with those of the native ACL to fully restore normal kinematics and knee function (Butler 1992). Woo et al (Woo 1991) reported that the structural properties of the ACL decrease with age and that in younger subjects the failure load and stiffness values of the ACL were 2160 ± 157 N and 242 ± 28 N/mm, respectively. These values are similar to a 10-mm-wide patellar tendon graft (the failure strength and stiffness properties are 1784 [± 580] N and 210 N/mm) and a 4-bundled hamstring tendon graft (the failure strength and stiffness values are 2422 [± 538] N and 238 N/mm) (Wilson 1999). Therefore, theoretically both graft types should provide adequate strength and normal laxity to the knee immediately after surgery.

Biological substitutes for the ACL can be prepared as either bone-tendon-bone grafts or tendon grafts. Depending on the graft material that is selected for ACL reconstruction, the bony or soft tissue portions of these constructs can be fixed either within bone tunnels or externally to cortical bone. From a biomechanical perspective, fixation represents the weakest link during the early stages of healing. The long-term goal is to obtain biological incorporation of the graft at the anatomical attachment sites of the ACL and to restore the transition from soft tissue to fibrocartilage, to calcified fibrocartilage, and to bone.
Some of these grafts and fixation methods are evaluated in the studies included in this thesis.

ANATOMY

The knee joint develops from a cleft between the mesenchymal rudiments of the femur and tibia during the 8th week of the human embryo (GRAY 1950; Gardner 1968). As the mesenchyme in the region of the future knee joint condenses to form the precartilage and the capsule of the joint, vascular mesenchyme becomes isolated within the joint. This tissue is the precursor to the cruciate ligaments and the menisci.

At 9 weeks, the cruciate ligaments are composed of numerous immature fibroblasts, the long axes of which are parallel to the course of the ligaments. At 10 weeks, the ACL and posterior cruciate ligament (PCL) are separated from each other, and over the next 4 weeks the cruciate ligaments continue to differentiate from the adjacent tissues and the insertion sites becomes more defined. By 18 weeks, the cruciate ligaments stand almost alone, and a few vascular elements are found within their substance. During the next weeks there is a continuous growth and increase in vascularity, until the ACL resembles that found in the adult. The remaining development consists of marked growth but little change in form.

The mature ACL is a band of regularly oriented, dense connective tissue which connects the femur and tibia. It is surrounded by a fold of synovium that originates from the posterior intercondylar area of the knee, and completely envelopes both the anterior and posterior cruciate ligaments. Thus, the cruciate ligaments are intraarticular and extrasynovial (Girgis 1975; Arnoczky 1983).

The ACL is attached to a fossa on the posterior aspect of the medial surface of the lateral femoral condyle. The attachment has a semilunate form, with the anterior border straight and the posterior border convex. The long axis of the femoral attachment is tilted slightly forward from the vertical, and is about 23 mm long (Kennedy 1974; Arnoczky 1983).

On the tibia, the ACL is attached to a fossa in front of and lateral to the anterior tibial spine. The anterior part of the tibial attachment lies beneath the transverse meniscal ligament, and some fascicles of the ACL may blend with the anterior attachment of the lateral meniscus. The tibial attachment of the ACL is somewhat broader than the femoral. Its length is about 30 mm. Thus, because the tibial attachment is somewhat larger than the femoral, the ACL is fan-shaped.

The ACL courses anteriorly, medially and distally across the joint as it passes from the femur to the tibia. It also has a slight outward (lateral) spiral form, as a result of its bony attachments.

The average thickness of the ACL is 11 mm, but the cross-sectional area varies along its length, being larger at its insertion sites than in the mid-region. The average length varies from 31 mm (Girgis 1975) to 38 mm (Odensten 1985a).

The geometry of the ACL is complex and not duplicated with current reconstruction techniques. The fibers on the anterior border of the ACL are longest, whereas those on the posterior edge are the shortest. The ACL has a distinct crimp pattern that straightens as the ligament is strained. Although the ACL does not have bundles that are distinct from an anatomical perspective, it has been subdivided into at least 2 functional bundles, the anteromedial (AMB) and posterolateral bundles (PLB), which work synergistically with each other to optimize its restraining function over the range of knee motion (Xerogeanes

1995).The orientation of the femoral attachment of the ACL in flexion and extension is responsible for maintaining tension in the ligament throughout the range of motion. The ACL is attached to the femur and tibia as a collection of individual fascicles that fan out over a broad, flattened area. When the knee is extended, the entire ligament is taut, with most of the load on the PLB. In flexion, the femoral attachment of the ACL assumes a more horizontal orientation, causing the AMB to tighten and the PLB to slacken (Arnoczky 1983).

An intermediate bundle is also described (Norwood 1979). This is felt to be responsible for the straight anterior stability of the knee. However, these macroscopic bundles lack a corresponding microstructure in the substance of the ACL. The functional significance of the fascicles of the ACL is that groups of fascicles work together throughout the range of joint motion (Odensten 1985a; Clark 1990)

The cells of the ACL are fibroblasts surrounded by an extracellular matrix formed by a solid, highly ordered arrangement of macromolecules, primarily type I collagen, and water. The mechanical properties of the ligament depend on the composition of the matrix, the organization of the macromolecules, and the interaction between these and the water. Small changes in this composition may lead to changes in mechanical properties, as seen with increasing age. Microscopically, the ACL is composed of 30 to 175 nm wide collagen fibrils, which are arranged in parallel (Clark 1990). These fibrils are in turn grouped into fibers that vary from 1 to 20 micrometers in diameter. They run almost parallel to the long axis of the ligament. These fiber bundles coalesce to form subfascicular units, which vary from 100 to 250 micrometers in diameter. Three to 20 subfasciculi form a collagen fasciculus which can be several millimeters in diameter. Clark and Sidles (Clark 1990) could not demonstrate an anatomical delineation of bands within the ligament. In this respect the ACL is different from other ligaments around the knee.

The ACL has a microstructure of collagen bundles of multiple types (mostly type I) and a matrix made of a network of proteins, glycoproteins, elastic systems, and glycosaminoglycans with multiple functional interactions. The complex ultrastructural organization and abundant elastic system of the ACL allow it to withstand multiaxial stresses and varying tensile strains (Duthon 2005).

The blood supply to the ACL arises from the ligamentous branches of the middle genicular artery as well as from some terminal branches of the medial and lateral inferior genicular arteries (Arnoczky 1985). These vessels reach the synovial fold that covers the ACL. In this synovium they arborize to form a web-like network of periligamentous vessels that give rise to smaller connecting branches that penetrate the ligament transversely and anastomose with a network of endoligamentous vessels. These, together with their connective tissue, are orientated in a longitudinal direction and lie parallel to the collagen bundles within the ligament.

The role of the vascular tissues in ACL repair and reconstruction has been documented both in experimental (Arnoczky 1979) and clinical (O'Donogue 1963) studies. Bray et al (Bray 2003) found the superior capacity of the medial collateral ligament (MCL) to increase its blood supply through angiogenesis and increased flow to be essential for ligament healing to occur, and may be the major difference in healing potential between the ACL and MCL.

Both the synovium and the fat pad serve as potential sources for revascularization of repaired ligaments. When no bone tunnels are used, revascularization in the dog begins at 6 weeks and is complete by 20 weeks following repair. Howell et al (Howell 1995) used MRI and an intravenous contrast agent (gadolinium diethylenetriamine pentacetic acid) to evaluate the blood supply of hamstring autografts and periligamentous tissues during the first 2 years after reconstruction. They found that the grafts acquired no discernable blood supply during the first 2 years, and the graft retained the same hypovascular appearance as the normal PCL. In contrast, the periligamentous soft tissues were richly vascularized and covered the graft by 1 month postoperatively. They concluded that the viability of the grafts may depend more on synovial diffusion than on revascularization.

The ACL receives nerve fibers from branches of the tibial nerve which penetrate the joint posteriorly. Nerve fibers and sensory receptors follow the vessels in the form of neurovascular bundles, entering the ligament from the synovium. Some nerve fibers and a variety of sensory end organs are also located in the ligament, isolated from the vessels (Kennedy 1982; Zimny 1988; Halata 1989). The nerve fibers are either unmyelinated or myelinated, and four morphologically different types of sensory endings have been described. These are two types of Ruffini end organs, Pacinian corpuscles, and free nerve endings (Schutte 1987). It has been hypothesized that these nerve endings have an important proprioceptive function in the knee (Johansson 1991; Pitman 1992). Adachi et al. (Adachi 2002) found a positive correlation between the number of mechanoreceptors and accuracy of the joint position sense, suggesting that proprioceptive function of the ACL is related to the number of mechanoreceptors.

FUNCTION

Studies performed using cadaveric models have revealed that the ACL is the primary restraint to anterior displacement of the tibia relative to the femur (Butler 1980; Fukubayashi 1982) and acts as a restraint to internal-external rotation (Markolf 1990; Fleming 2001; Kanamori 2002) varus-valgus angulation (Marder 1991), and combinations thereof (Markolf 1995; Kanamori 2002). The anteromedial part is most important in flexion, whereas the posterolateral part contributes most to stability in extension (Furman 1976; Amis 1991). In addition, the ACL resists hyperextension, and is an important factor in preventing anterolateral rotatory instability of the tibia (Girgis 1975). In extension it aids medial and lateral structures in maintaining the varus-valgus stability of the knee.

The estimated loading of the ACL during daily activities vary in different studies. Morrison (Morrison 1970) estimated in vivo forces from force plate analysis, and found a peak load of 169 N in level walking, 67 N in ascending a ramp, and about 500 N in descending a ramp. Chen and Black (Chen 1980) estimated the tensile forces in the ACL to be 67 N in ascending stairs and 630 N in jogging. Downhill running seems to create the highest ACL strain (strain = change in length / initial length of the structure) among the activities tested (Henning 1985). Both cadaveric (Grood 1984) and clinical (Henning 1985; Beynnon 1995) studies have demonstrated a considerable rise in ligament stress (stress = force / area) from 30 degrees of flexion to full extension, especially if done actively against resistance placed distally on the leg.

The muscles spanning the knee apply forces and moments to the joint. As the position of the knee joint is changed, the moment arms of the different muscles and tibiofemoral joint contact position also change, which, in turn, affect ACL biomechanics. It is well documented that the ACL is strained when the quadriceps are contracted with the knee near extension (between full extension and 50° of flexion) (Markolf 1990; Fleming 2001). In contrast, contraction of the hamstring muscles produces a posterior-directed force that acts on the tibia throughout the range of knee flexion. These muscles thus protect the ACL or ACL graft (O'Connor 1993). The gastrocnemius muscle also spans the knee joint, yet its effect on the ACL has only been recently established. O'Connor (O'Connor 1993) hypothesized that contraction of the gastrocnemius could displace the tibia in an anterior direction, which, in turn, would increase the strain on the ACL. Direct measurements of ACL strain during gastrocnemius contractions have verified that the gastrocnemius is an ACL antagonist when the knee is near extension and that combined contraction of the gastrocnemius and quadriceps produces greater ACL strain values than isolated contraction of these muscles (Fleming 2001). Compressive loading of the tibiofemoral joint has been shown to increase joint stiffness and decrease anterior displacement of the tibia relative to the femur (Markolf 1981; Torzilli 1994; Beynnon 2002).Therefore, a compressive joint load, such as that produced by body weight, has been considered by some to protect a healing ACL graft. However, recent research has demonstrated that ACL strain values increase as the knee undergoes a transition from nonweightbearing to weight bearing conditions (Fleming 2001).

The ultimate strength of the ACL in a young cadaver specimen is about 1750 N. This, however, depends on several factors, of which one is the direction of the load applied. If loaded in the anatomical axis, the ligament fails at about 2200 N, and if the load is applied in the tibial axis, the failure occurs at about 1500 N. These values are similar to a 10-mm-wide patellar tendon graft (the failure strength and stiffness properties are 1784 [± 580] N and 210 N/mm, respectively) and a 4-bundled hamstring tendon graft (Woo 1991). The ultimate strength is also highly dependent on the strain rates (Noyes 1974; Kennedy 1976). At low strain rates, the failure will occur early, and at the ligament-bone junction. As the rate of load application is increased, the bony junction becomes stronger and stiffer than the ligament, due to its viscoelastic properties. In the experiment performed by Kennedy et al. (Kennedy 1976) with a fourfold increase in strain rate, the maximum load tolerated by the ACL increased by 32%.

By the use of a scanning electron microscope, Yahia et al. (Yahia 1990) found that some of the collagen fibers in the ACL start to fail between 10 - 15% of ultimate strain, and at 20% it showed ruptures of thick collagen fibers, thus indicating microscopic partial ruptures before macroscopic or total rupture occurs.

MECHANISMS OF INJURY

Rupture of the ACL was first described by J. Stark in the Edinburgh Medical and Surgical Journal in 1850. Since then, and especially during the last three decades, this injury has been the topic of many publications.

Four types of injury mechanisms have been described. The classic "unhappy triade": ACL rupture, damage to the medial collateral ligament and rupture of the medial meniscus, is caused by a forceful valgus-external rotation of the knee (Fetto 1980). This injury is often seen in skiing, when the tip of the ski is caught on an obstacle, the knee is bent into valgus, and the tibia goes into external rotation. Olsen et al. (Olsen 2004) found that the injury mechanism for anterior cruciate ligament injuries in female team handball appeared to be a forceful valgus collapse with the knee close to full extension combined with external or internal rotation of the tibia. Sell et al. (Sell 2006) concluded that the lateral jumps are the most dangerous of the stop-jumps.

A second mechanism of injury is varus-internal rotation, as seen in team handball and basketball players. Recent cadaveric research has shown that simulated contraction of the quadriceps with the knee near extension produces substantial anterior tibial translations that can create ACL injury and may explain, at least in part, one mechanism responsible for noncontact ACL injury (DeMorat 2004). In contrast, contraction of the hamstring muscles serves a protective function for the ACL or ACL graft (O'Connor 1993). Special shoes on indoor floors with high frictional surfaces are usually involved. Injury factors such as friction, angular velocity and rate of directional change seem to be important. Today's elite team handball is played at high speed. With rapid directional changes, the foot may be "locked" on the surface; the knee bent in varus and the tibia go into internal rotation. This may either cause an isolated ACL rupture, or a rupture combined with damage to the lateral meniscus, lateral capsular structures, and the lateral collateral ligament.

A third mechanism of injury is the forceful internal rotation of the tibia in knee extension, which might cause impingement of the ACL on the anterior aspect of the medial femoral condyle, and rupture of the ligament (Kennedy 1974; Fetto 1980). In support of this theory, studies have shown that a narrow intercondylar notch leads to a higher risk of ACL ruptures in athletes (Souryal 1993; Lund-Hanssen 1994). In another study however (Lombardo 2005), anterior cruciate ligament injury could not be predicted by the absolute measurement of the femoral inter-condylar notch.

In a study by Ebstrup et al (Ebstrup 2000) three video recorded incidents of knee injuries inflicted during indoor ball games were reported. Injuries and especially anterior cruciate ligament ruptures seemed to be triggered in varus loaded knees by femoral external rotation or in valgus loaded knees by femoral internal rotation with the pivot shifted to the lateral femurotibial compartment.

Finally, the fourth mechanism of injury is typically seen in the down-hill skier who is at the point of falling backwards. To prevent this, he or she powerfully contracts the quadriceps, thus pulling the tibia anteriorly. It may, however, be even more important that in this situation, the posterior part of the ski boot pushes the tibia forward. This may lead to an isolated tear of the ACL (Johnson 1982; McConkey 1986). MRI examinations of acute ACL tears have shown consistent and recurring subchondral bone lesions in the femoral and tibial condyles, with locations typical for this specific injury mechanism (Spindler 1993). These findings have led to the conclusion that the ski acts as a lever arm, producing a sudden and violent rotation of the tibia on the femur (Speer 1995). This, in combination with the pull/push mechanism, is suggested to cause the ACL rupture.

Anterior cruciate ligament injury occurs with a 4- to 6-fold greater incidence in female athletes compared with male athletes playing the same landing and cutting sports (Arendt 1995). Uhorchak et al (Uhorchak 2003) performed a comprehensive study on military academy cadets and reported that several risk factors predisposed them to noncontact ACL injury. Significant risk factors included a small femoral notch width, generalized joint laxity, and, in women, higher than normal body mass index and KT-2000 arthrometer measurements of A-P knee laxity that were 1 standard deviation or more above the mean. The mechanism underlying gender disparity in ACL injury risk is likely multifactorial in nature. Several theories have been proposed to explain those observations. These theories include related extrinsic (physical and visual differences, bracing, and shoe-surface interaction) and intrinsic (anatomical, hormonal, neuromuscular, and biomechanical differences between genders) variables. Potential factors that have not been discussed may play a role (e.g., genetics). In addition, injury data from many fields demonstrate that numerous physical and psychological parameters affect injury rates. Although there are multiple factors underlying the differences in ACL injury rates in male and female athletes, neuromuscular control may be important to injury risk and the most modifiable factor. Neuromuscular training in female athletes has been shown to increase active knee stabilization in the laboratory and to decrease the incidence of ACL injury (Hewett 1996, 1999; Myklebust 2003a).

NATURAL HISTORY OF THE ACL-INJURED KNEE

Over time, ACL-deficient patients may experience giving-way episodes and are more likely to develop further intra-articular damage, such as meniscal tears, (Noyes 1983a-b; Hawkins 1986b; Bray 1989; Buss 1995; Grontvedt 1999) and osteoarthritis of the knee (Johnson 1974; Kannus 1987). Subjects with ACL injury and posttraumatic osteoarthritis are, on average, 15 to 20 years younger than patients with primary osteoarthritis when they seek medical advice for their symptoms and when their joints show radiographic evidence of osteoarthritis (Roos 1995a).

ASSOCIATED INJURIES

Injuries of the ACL rarely occur in isolation. The effects of other injuries, including other ligament sprains, meniscal tears, articular cartilage injuries, and bone bruises, complicate the treatment and final outcome of ACL ruptures. There can be no doubt that the addition of one or more of these associated injuries adversely affects the outcomes of treatment, but it is very difficult to quantify or predict exactly how they will alter the results. Many surgeons now advocate nonsurgical management, even when grade III tears of the MCL exist in association with ACL disruptions (Noyes 1995).

Disruption of the posterolateral and lateral structures of the knee is not commonly associated with rupture of the ACL, but when they are present and not recognized, an ACL reconstruction will often fail (Jaureguito 1996; Getelman 1999; Harner 2001; Noyes 2001; Allen 2003).

Meniscal damage frequently occurs at the time of an ACL injury, and the incidence increases in patients who do not undergo reconstruction. Reports of meniscal injury associated with acute ACL disruption range from 15% to 40% and become much higher with chronic ACL deficiency (Levy 2003).The effects of chondral lesions observed at the time of ACL reconstruction are difficult to ascertain from the current literature. With the advent of MRI, it became apparent that occult osteochondral lesions (bone bruises) are commonly found in association with ACL injuries. Several investigators reported that 80% or more of ACL injuries were associated with bone bruises in the lateral compartment (Rosen 1991; Spindler 1993; Johnson 1998). Johnson et al (Johnson 1998) performed histological analysis of bone bruises in humans. They found large areas of degeneration of chondrocytes in the overlying articular cartilage and necrotic osteocytes in subchondral bone, which led them to suggest that MRI evidence of bone bruising indicates significant damage to articular cartilage homeostasis.

TREATMENT

The treatment options for ACL ruptures are either conservative or surgical. The rationale for surgical treatment includes the assumption that the ACL is vital for knee function, that ACL-deficient knees frequently degenerate, and that surgical reconstructions can succeed in restoring normal function. The rationale for nonsurgical treatment assumes that the ACL-deficient knee may function reasonably well under certain circumstances and that reconstructions do not necessarily prevent the untoward sequela of osteoarthritis. Several studies reported during the last decade, however, show that conservative treatment often leads to increasing instability of the joint, meniscal tears, cartilage injuries, pain and eventually osteoarthritic changes in patients who subject their knee to rotational loads (McDaniel Jr 1983; Noyes 1983a; Kannus 1987; Engebretsen 1990; Tandogan 2004). Patients who may be satisfactorily treated without surgical intervention, despite a totally disrupted ACL, include those who have little exposure to high-risk activities such as sports and heavy work, those who are willing to avoid high-risk activities, those who are more than 40 years of age, those who are successful in long-term coping with or adapting to an ACL insufficiency, those who have advanced arthrosis of the involved joint, and those who are unable or unwilling to comply with postreconstruction rehabilitation. Several case series reveal that a nonoperative approach to the torn ACL can be effective for the majority of patients willing to avoid high-risk activities (Bonamo 1990; Ciccotti 1994; Buss 1995; Segawa 2001). Other case series have indicated that even with return to high-risk activities, many patients do well (Roos 1995b; Casteleyn 1996). In three Swedish randomized clinical trials (RCT), superior results were achieved in patients with ACL repairs with augmentation using the iliotibial band, compared to nonoperative treatment (Odensten 1984b; Andersson 1989b, 1991).

Interest in repair techniques was low until Palmer (1937) reported success in suturing 10 cases of torn ACLs. Short term follow-up showed good results (O'DONOGHUE 1963; Liljedahl 1965). There was considerable controversy concerning the importance of the ACL until the 1970s. Thus, simply excising the disrupted ACL was common before that time. In the 1970s a trend toward primary repair of the ACL was started by surgeons who thought the ACL performed an important function (Odensten 1985b; Sandberg 1987b; Andersson 1989b, 1991). Several long term follow-up studies during recent years conclude, however, that the results of this operation deteriorate with time (Odensten 1984b; Sommerlath 1991b; Fruensgaard 1992b; Grontvedt 1996a; Strand 2005).

A nearly universally accepted indication for an ACL reconstruction is a high-risk lifestyle requiring heavy work, sports, or recreational activities (Daniel 1994). Likewise, repeated episodes of giving way (pivot shift) in spite of rehabilitation are considered a strong indication for ACL reconstruction.

In order to preserve as much as possible of the ruptured ACL with its nerve endings and possible proprioceptive function (Johansson 1991; Pitman 1992) several surgical procedures with synthetic or biologic augmentation of the repaired ACL have been published. Some of these have shown promising short term results (Clancy Jr 1988b; Schabus 1988; Sgaglione 1990). However, Grøntvedt et al (Grontvedt 1995a, 1996a) showed an unacceptable high incidence of reruptures in repairs augmented with a synthetic graft.

In recent years, arthroscopically assisted ACL reconstruction has become the procedure of choice (Arciero 1996). Initially, arthroscopic techniques required 2 incisions for outside-in drilling of bone tunnels, but there has been a trend toward using a single-incision arthroscopic approach with inside-out drilling of the femoral tunnel. This technique has also been called the 1-incision, endoscopic, or all-inside arthroscopic reconstruction of the ACL. Karlsson et al (Karlsson 1999a) found a significantly higher Lysholm score in their 1-incision group. Delay et al (Delay 2001) published a large survey among members of the American Orthopaedic Society for Sports Medicine (AOSSM) that found that 85% of surgeons use an endoscopic single-incision technique, 12% use an arthroscopic 2-incision technique, and 3% use mini-open techniques. In reviewing the additional literature concerning the outcomes of the 1-incision versus 2-incision procedures for ACL reconstruction, there is no clear evidence that one method is superior to the other.

The complex anatomy and the biomechanical function of the ACL have been well described by numerous authors. Several investigators, using human cadaveric knees, have reported improved ability to restore ACL function after ACL reconstructions in which 2 femoral attachment sites are used to more nearly replicate the normal ACL anatomy (Amis 1991; Radford 1994; Muneta 1999; Mae 2001; Yagi 2002). In spite of these findings, several authors conclude that 2 femoral attachment sites are not superior to a single site (Radford 1994; Hamada 2001).

In chronic ACL deficient knees the primary cause of pain and discomfort is the anterolateral rotatory instability. To prevent this, several extraarticular surgical procedures have been proposed. Benum reported a method using the lateral one third of the patellar tendon with a bone block from the patella, for stabilization. This method has shown good short term results (Benum 1982). However, the recurrence rate of symptomatic instability and the deterioration of subjective knee function are too high (Grontvedt 1995b).

There are many methods of tenodesing the lateral aspect of the tibia to the femur in order to prevent anterolateral rotation of the tibia and minimize anterior translation of the tibia relative to the femur, either as an isolated procedure or as a backup for intra-articular reconstruction. Several groups have not been satisfied with the results of these procedures and do not advise their continued routine use (Dahlstedt 1988; Larsen 1991; Vail 1992).

Despite the uncertainties of outcomes after ACL reconstructions reported in the literature, many investigators conclude that patients who desire to return to high-risk activities or who have other significant knee injuries (meniscal tears, disruptions of other ligaments, articular cartilage damage, as well as marked anterior laxity) are probably best served by an ACL reconstruction. Conversely, patients with low-risk activity levels, isolated ACL injuries, and mild pathologic laxity may be successfully treated without surgery.

GRAFTS

In the last decade, intraarticular reconstructions using autografts or allografts have become popular. Prosthetic devices have also been in use.

Many studies have compared bone–patellar tendon–bone with hamstrings tendon grafts (used as 2-strand or 4-strand constructs). Corry et al (Corry 1999) compared the outcome of anterior cruciate ligament reconstruction using hamstring tendon autograft with patellar tendon autograft. Kneeling pain after reconstruction with the hamstring tendon autograft was significantly less common than with the patellar tendon autograft. These findings are supported in a Norwegian study (Aune 2001). Eriksson et al (Eriksson 2001) concluded that patellar tendon and quadruple semitendinosus tendon grafts had similar outcomes in the medium term. Associated meniscal pathology significantly affected the final outcome and early reconstruction seemed to be beneficial. Aglietti et al (Aglietti 2004) concluded that both grafts were an equivalent option for anterior cruciate ligament reconstruction. In contrast to findings in the RCTs that compared ACL reconstruction with the 2-strand hamstrings graft to the BPTB- graft, ACL reconstruction with a 4-strand hamstrings graft appears to result in similar clinical and functional outcomes as reconstruction with a BPTB- graft during a 2-year follow-up period. Freedman et al. (Freedman 2003) found in a Meta analysis that patellar tendon autografts had a significantly lower rate of graft failure and resulted in better static knee stability and increased patient satisfaction compared with hamstring tendon autografts. However, patellar tendon autograft reconstructions resulted in an increased rate of anterior knee pain.

Allografts have been advocated as an option for ACL reconstruction and have been used a lot for many years. Decreased morbidity, preservation of the extensor or flexor mechanisms, provision of a source of graft material when the patient has none, decreased operative time, availability of larger graft sources, lower incidence of arthrofibrosis, and improved cosmetic appearance are all advantages that have been attributed to the use of allografts (Harner 1996; Victor 1997; Kleipool 1998). The possible disadvantages have been the risk of infection, slow and incomplete incorporation and remodeling of the graft, higher costs, availability, and tunnel enlargement, alteration of graft structural properties by sterilization and storage procedures, and immunologic response (Pinkowski 1989; Marks 1993; Linn 1993; Jackson 1996; Zijl 2000).

Prosthetic replacement of the ACL with synthetic material, whether for total, permanent replacement (prosthesis), a scaffold for ingrowth of host tissue, or a ligament augmentation device to protect an allograft or autograft as it heals, has not been proven to be a satisfactory solution to the ACL-deficient knee (Noyes 1992; Moyen 1994; Denti 1995; Grontvedt 1996b; Kumar 1999; Marumo 2000; Muren 2003). Although claims of acceptable results with short-term follow-ups have been published, at the present time, we are unaware of any investigation that indicates that these devices have any place in the treatment of ACL injuries (Guidoin 2000).

The position of an ACL graft is the most critical surgical variable because it has a direct effect on knee biomechanics and, ultimately, on clinical outcome. In the well-designed study by Good et al (Good 1994) subjects with an ACL graft insertion greater than 2 mm anterior to the center of the anatomical femoral insertion had significantly greater anterior-posterior (A-P) knee laxity values than subjects with centrally or posteriorly positioned femoral tunnels. Howell and Clark (Howell 1992) performed a retrospective study with a 6-month follow-up period of BPTB grafts and reported that knee stability and extension were significantly better when the center of the tibial tunnel was 2 to 3 mm posterior to the center of the normal ACL insertion on the tibia.

Most surgeons would agree that the initial tension applied to an ACL graft at the time of fixation has a direct effect on outcome. An under-tensioned graft may result in abnormal knee laxity and an unstable knee, and an over-tensioned graft may lead to graft failure, fixation failure, or restricted range of motion. The effect of preloading (application of a 39-N tensile load for 10 minutes before graft implantation) to no preloading before graft implantation showed no differences between the treatment groups with regard to activity level, clinical outcome (IKDC grade), and A-P knee laxity after two years (Ejerhed 2001).

Graft tensioning at the time of fixation involves consideration of the knee's position during the tensioning procedure (i.e., the flexion angle and internal-external rotational position of the tibia relative to the femur) and, of course, the magnitude of tension applied to the graft at the time of its fixation to bone. Both variables interact and have a direct effect on knee biomechanics. If a BPTB graft is used and the tensioning procedure is performed with the knee in extension, application of high tension (90 N) appears to produce more normal A-P knee laxity values compared to application of low tension (45 N). Similarly, if a 4-strand hamstring graft is used, application of high tension (80 N) appears to produce A-P knee laxity values similar to normal, whereas low tension (40 N and less) results in increased anterior knee laxity (Yoshiya 2002; Nicholas 2004).

Most of the studies of graft material have considered AP knee laxity as an important primary outcome measure. It is, however, essential to point out that it may be equally important to restore the rotational laxity of the reconstructed knee to within the limits of the normal knee. To accomplish this, new techniques must be developed to measure internal-external rotational laxity of the knee, or at least document displacements of the medial and lateral compartments of the tibiofemoral joint.

GRAFT FIXATION

The bony or soft tissue portions of grafts can be fixed either within bone tunnels or externally to cortical bone. The long-term goal is to obtain biological incorporation of the graft at the anatomical attachment site and to induce the transition from soft tissue to fibrocartilage, to calcified fibrocartilage, and to bone. Current rehabilitation protocols after knee ligament surgery stress immediate full range of motion, return of neuromuscular function, proprioception, and early weight bearing. Fixation methods must be rigid and stiff to allow aggressive rehabilitation principles. Current fixation techniques involve soft tissue or bone within a bone tunnel or periosteal fixation away from joint surfaces.

Stiffness is the slope of the linear region of the load-elongation curve and is usually reported in units such as Newtons per millimeter (N/mm). Present graft fixation alternatives are less stiff than the native ACL. Mechanically, the majority of tendon fixation constructs are less stiff than the interference screw against a bone plug, which has been considered the standard for fixation. Many tendon fixation devices are "indirect." They rely on linkage material to connect the tendon to the fixation device.

In the native cruciate ligament, the point of fixation is at the joint surface. However, most tendon fixation constructs are placed at a distance from the joint surface with a staple, screw and suture, or soft tissue washer. When interference fixation is placed closer to the joint surface, there is increased knee stability and also improved graft isometry.

It has been suggested that bone plug incorporation occurs before tendon incorporation in a bone tunnel, (Safran 1995) but basic science on this matter is not definite.

BONE PLUG GRAFT FIXATION

Interference Fixation

The fixation strength required for activities of daily living and an aggressive rehabilitation program appears to be met by the strength and stiffness of interference fixation. It has for this reason become the standard of graft fixation (Steiner 1994). Interference fixation was first described by Lambert (Lambert 1983) in a study using a 6.5-mm cancellous screw. In 1987, Kurosaka et al. (Kurosaka 1987) demonstrated superior strength with a larger screw diameter. Currently, a screw that is 9 mm in diameter and at least 20 mm in length is the standard used for fixation. Despite the clinical success of interference fixation, complications, usually preventable, have been reported. Screw laceration, of either the bone plug suture or the graft itself is clinical concerns. It may require another graft.

Biodegradable Interference Screws

Several different biodegradable interference screws consisting of different polymeric raw materials are currently available. Biodegradable implants consist mainly of the poly-alpha-hydroxy acids, polylactide and polyglycolide, including their copolymers, poly-D,L-lactide-co-glycolide and polyglycolide-co-trimethylencarbonate. Stereopolymers, such as poly-L-lactide, poly-L-co-D, L-lactide and poly-D, L-lactide are also used.

One polymer consists of slow degrading and highly crystalline poly-L-lactide and poly-L-co-D, L-lactide stereocopolymers with a low D, L amount. These materials are considered to have high mechanical properties compared to other poly-alpha-hydroxy acids, but their degradation can take up to several years and can be incomplete because of an accumulation of insoluble crystalline implant remnants (Claes 1992; Pistner 1993; Bergsma 1995). Another polymer is represented by amorphous poly-L-co-D, L-lactide stereocopolymers with high D, L amount and the porous poly-D, L-lactide. These materials degrade completely within 1 to 2 years, but their mechanical properties are lower (Stahelin 1997). The third polymer consists of fast-degrading copolymers such as poly-D, L-lactide-co-glycolide or polyglycolide-co-trimethylencarbonate, whose strength retention lasts for only some weeks.

For many years, biodegradable implants have been thought to offer advantages over metal. Metal implants can distort magnetic resonance imaging and release metal ions into the surrounding tissue (Shellock 1992). Further disadvantages include the need for a second surgical procedure for implant removal and revision surgeries may be complicated by the presence of a metal implant. In cruciate ligament surgery, the major advantage of biodegradable interference screws is an uncompromised revision surgery. This is especially important because the number of revisions has risen dramatically during the last few years (Noyes 1996; Uribe 1996). In case of revision after using biodegradable interference screws, surgery may be performed like a primary procedure if the material has degraded and osseous replacement has taken place with an appropriate amount of newly formed bone at the former implant site. The major disadvantage of biodegradable screws is screw breakage or drive failure during insertion.

There are still concerns about an appropriate biocompatibility of biodegradable materials because of reports on severe foreign-body reactions associated with the use of self-reinforced and highly crystalline polyglycolide implants (Bostman 1992; Hoffmann 1992;

Caborn 1997b). Today, other materials such as polylactide and its copolymers and stereocopolymers are considered to have better biocompatibility, (Bucholz 1994; Bostman 1995; Hunter 1996)found that a large proportion of patients who underwent ACL reconstruction within 3 weeks of the injury had additional surgical intervention for complications related to loss of motion, whereas none of the patients who underwent ACL reconstruction more than 3 weeks after injury required repeat operations for revision surgery or motion problems. After reviewing the literature on this subject (Cosgarea 1995; Karlsson 1999b; Mayr 2004), it appears that the time interval from ACL injury to reconstruction is not as important as the condition of the knee at the time of surgery. The knee should have a full range of motion with minimal effusion; the patient should have minimal pain and be mentally prepared for the reconstruction and rehabilitation after surgery.

AIMS OF THE STUDY

The study was designed to answer the following questions:

1. Which of the following three treatment options for acute anterior cruciate ligament tears gives the best long term results: simple repair, synthetic augmented repair (LAD), or biologic augmented repair (BPTB)? Are any of the procedures good enough to be recommended for use today?

2. What is the long term incidence of osteoarthritis of these three repair techniques?

3. Does the Kennedy Ligament Augmentation Device (LAD) have any effect on the functional and clinical outcome when using BPTB graft followed by an aggressive rehabilitation program to reconstruct chronic anterior cruciate ligament ruptures?

4. What is the medium term incidence of osteoarthritis in these two reconstruction techniques?

5. Does fixation with the poly-L-lactic acid (PLLA) interference screw improve clinical outcome after ACL reconstructions with BPTB graft compared to the metal screws?

6. Is it possible to quantify the amount of resorption of PLLA interference screws by MRI examinations two years after ACL reconstruction with BPTB graft fixed with these screws, and what is the clinical relevance of these findings?

7. How good is the short term bony integration of screws and bone blocks as measured by MRI after ACL reconstruction with BPTB grafts fixed with PLLA interference screws?

8. Is the biocompatibility of the PLLA interference screw any different from that of the metal screw?

REVIEW OF PAPERS

Paper I:

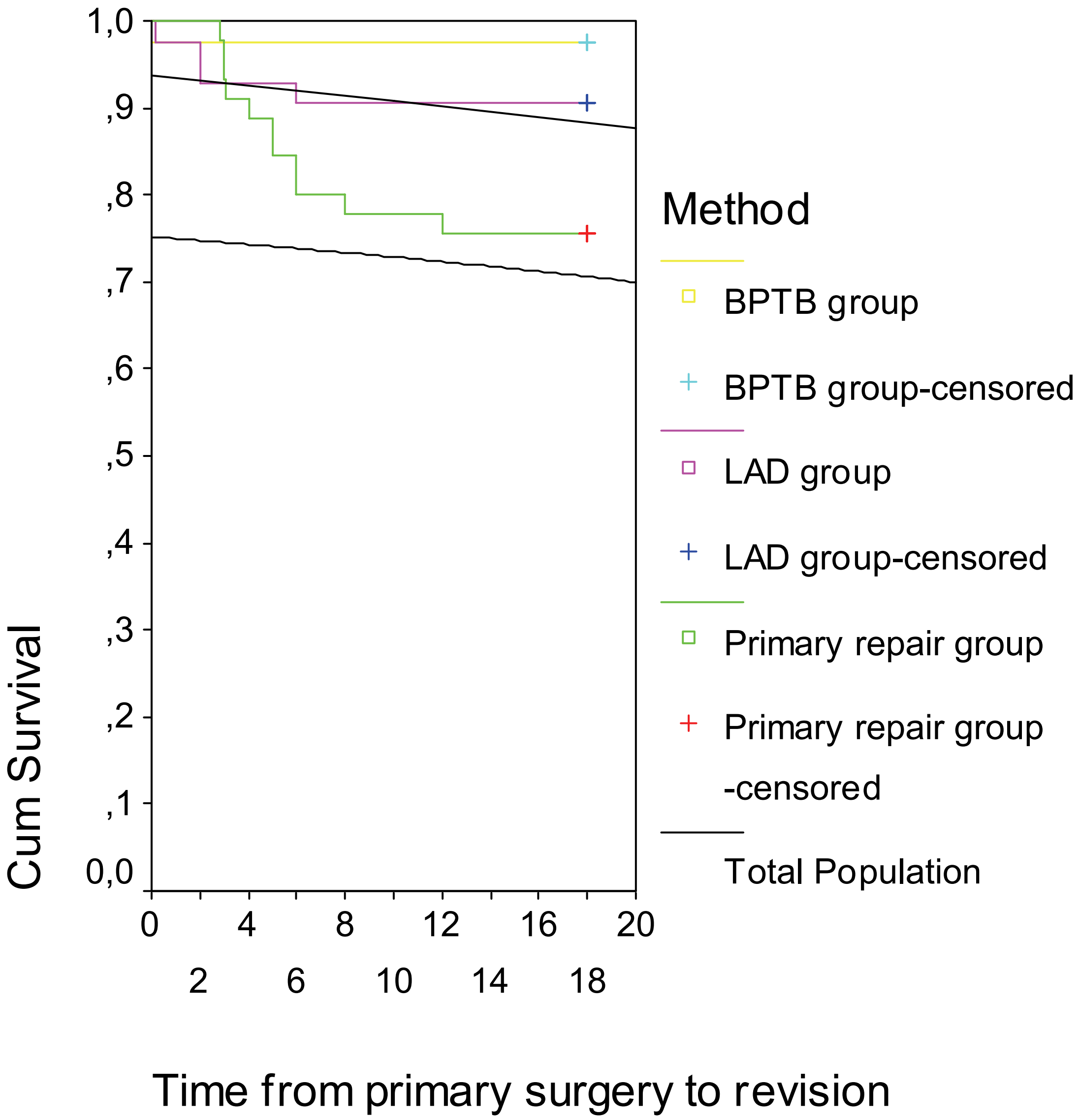
A 16-year Follow-up of Three Operative Techniques for the Treatment of Acute Ruptures of the Anterior Cruciate Ligament.

This study compares three surgical procedures used in the past to treat ruptures of the anterior cruciate ligament: acute primary repair, acute repair augmented with a synthetic ligament-augmentation device (LAD), and acute repair augmented with autologous bone-patellar tendon-bone graft (BPTB).

This is the third report on a group of patients who were randomized to the three different procedures between 1986 and 1988. There were 50 patients in each group. The patients were evaluated prospectively at one, two, five, and 16-years with use of the Tegner activity score and the Lysholm functional score. Stability of the knee was assessed with clinical examination and with use of the KT-1000 arthrometer.

A total of 129 patients (88%) completed the study. Eleven patients (24%) in the primary repair group, four patients (10%) in the LAD-group and one patient (2%) in the BPTB-group underwent anterior cruciate ligament revisions between the primary operation and the 16 years follow-up. The incidence of revisions was ten times higher in the primary repair group compared to the BPTB-group (p=0.003)

Figure 1:



In the remaining patients, the BPTB group had significantly more stable knees than the LAD-augmented group as measured by the Lachman test.

TABLE 1 LAXITY:

Laxity	Primary repair group	LAD-group	BPTB-group
Pivot Shift			
Preop.			
0	3 (6)	1 (2)	0 (0)
1+	17 (34)	14 (30)	11 (22)
2+	24 (48)	29 (62)	35 (70)
3+	6 (12)	3 (6)	4 (8)
Total	50 (100)	47 (100)	50 (100)
Five years postop.			
0	11 (27)	20 (48)	36 (75)
1+	9 (22)	7 (17)	8 (17)
2+	9 (22)	8 (19)	4 (8)
3+	12 (29)	7 (17)	0 (0)
Total	41 (100)	42 (100)	48 (100)
16 years postop.			
0	16 (57)	14 (48)	24 (68)
1+	7 (25)	10 (35)	9 (26)
2+	2 (7)	5 (17)	2 (6)
3+	3 (11)	0 (0)	0 (0)
Total	28 (100)	29 (100)	35 (100)
Lachman test			
Preop.			
0	1 (2)	0 (0)	0 (0)
1+	1 (2)	1 (2)	0 (0)
2+	40 (80)	37 (79)	39 (78)
3+	8 (16)	9 (19)	11 (22)
Total	50 (100)	47 (100)	50 (100)
Five years postop.			
0	11 (27)	16 (38)	27 (56)
1+	12 (29)	14 (33)	16 (33)
2+	15 (37)	11 (26)	4 (8)
3+	3 (7)	1 (2)	1 (2)
Total	41 (100)	42 (100)	48 (100)
16 years postop.			
0	11 (39)	6 (21)	15 (43)
1+	12 (43)	13 (45)	16 (46)
2+	4 (14)	9 (31)	4 (11)
3+	1 (4)	1 (3)	0 (0)
Total	28 (100)	29 (100)	35 (100)

KT 1000 measurements

Five years postop.			
<3 mm	14 (34)	22 (52)	38 (79)
3-5 mm	17 (41)	15 (36)	10 (21)
>5 mm	10 (24)	5 (12)	0 (0)
Total	41 (100)	42 (100)	48 (100)
16 years postop.			
<3 mm	14 (52)	18 (62)	23 (70)
3-5 mm	11 (41)	8 (28)	9 (27)
>5 mm	2 (7)	3 (10)	1 (3)
Total	27 (100)	29 (100)	33 (100)

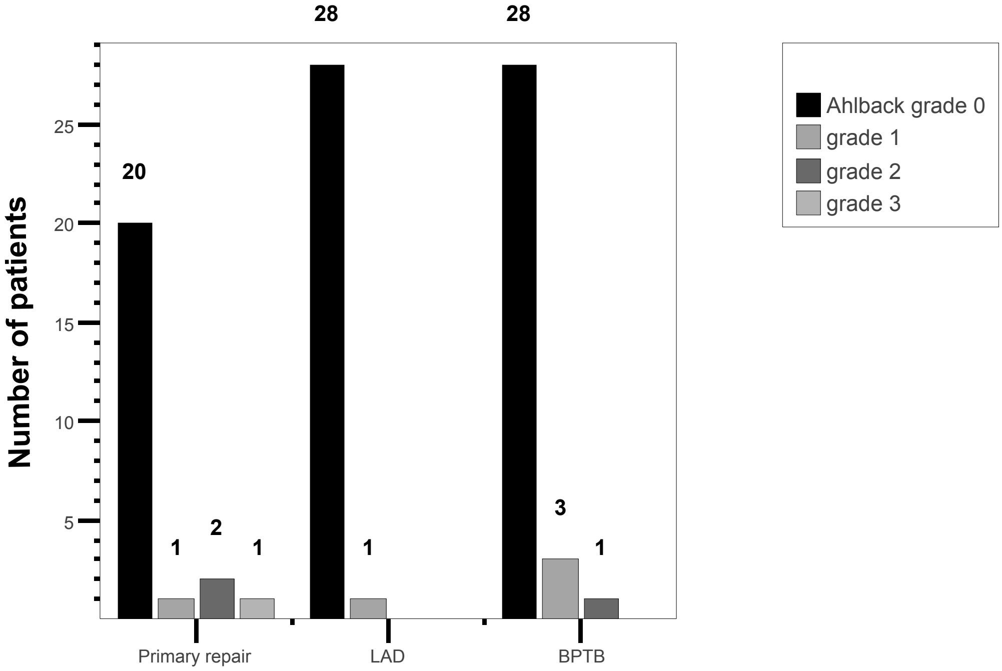
The values are given as the number of patients, with the percentage in parentheses.

Pivot shift: A grade of 0 is negative, 1+ is trace-positive, 2+ is moderate shift, and 3+ is subluxation.

The preoperative Lachman test was performed with the patient under anesthesia. A grade of 0 is negative, 1+ is slight (less than five Millimeters), 2+ is moderate (five to ten millimeters), and 3+ is severe (more than ten millimeters), compared with the normal knee.
The side-to-side difference in anterior laxity of the knee was measured with the KT-1000 arthrometer, with a load level of eighty-nine Newtons (twenty pounds) applied at 20 degrees of flexion.

Of the patients 11% had any grade of osteoarthrosis in the primarily reconstructed knee and 4% had osteoarthrosis in the other knee at 16 years (p=0.001) with no difference noted between the groups.

Figure 2:



The Lysholm activity score was 88 in the primary repair group, 85 in the LAD group and 90 in the BPTB-group at 16 years (p=0.286).

At long-term follow-up, the incidence of revision anterior cruciate ligament surgery is much higher following primary repair as compared to primary repair augmented by a bone-patellar tendon bone graft. It can be expected that approximately 11% of patients undergoing anterior cruciate ligament reconstruction acutely will develop radiologic signs of osteoarthritis in the reconstructed knee.

Paper II:

ACL-reconstruction with and without LAD-augmentation. Results after 8 years follow-up.

It has been suggested that load sharing between the Kennedy ligament augmentation device (LAD) and the biological graft would protect the latter during the early period of degeneration and weakening and that that this would allow the graft to regain mechanical strength with less risk of elongation and rupture. It was postulated that the load would gradually be transferred from the synthetic device to the autogenous graft as the biological graft remodeled and became stronger. Because of the strength of the device, a more aggressive rehabilitation would be possible.

Between 1991 and 1993 100 patients were randomized in a prospective study to ACL-reconstruction with bone-patella tendon-bone grafts with and without a LAD. A total of 51 patients were operated without augmentation (control group), and 49 patients with LAD-augmentation.

A total of 94 patients were examined in an average of eight years after surgery. Of these 15 patients were excluded because of ACL-reconstruction in the other knee in the observation period and 11 patients excluded because of reruptures in the same knee.
In the remaining 68 patients, the mean Lysholm function score was 84 in the LAD-group and 87 in the control group. There was a statistically significant relationship between peroperative detected cartilage injury and osteoarthritis after eight years ($p<0.005$). The patients assessed their clinical situation after eight years as better than before surgery. This is despite the fact that almost half of the patients had developed osteoarthritis shown on X-ray-examinations. The presence of a cartilage injury is an important predisposition for the development of osteoarthritis.

Table 2:

OA in the two groups after eight years:

		Augmented	Controls	Total
	No OA	13	21	34
Grade	1	9	9	18
	2	10	5	15
	3	1	1	2
Total		32	36	68

Table 3:

The relationship between cartilage injury detected at the time of surgery and OA after eight years ($p<0,005$)

OA	Cartilage injury		
	No	Yes	Total
No	24	10	34
Yes	12	22	34
Total	36	32	68

We observed no significant difference between the two groups concerning reruptures, Lysholm score, Lachman`s test or KT-1000 measurements. We found no positive long-term effects supporting the use of LAD-augmentations in ACL-reconstructions.

Paper III:

Endoscopic reconstruction of the anterior cruciate ligament using bone-patellar tendon-bone grafts fixed with bioabsorbable or metal interference screws.
A prospective randomized study of the clinical outcome.

Forty-one patients were randomized for the use of either metal interference screws (20 patients) or biologic absorbable PLLA-screws (21 patients). The patients were followed with clinical examinations at 6, 12 and 24 weeks, 1 and 2 years postoperatively.
The subjective knee function was better in the patients in the metal screw group.

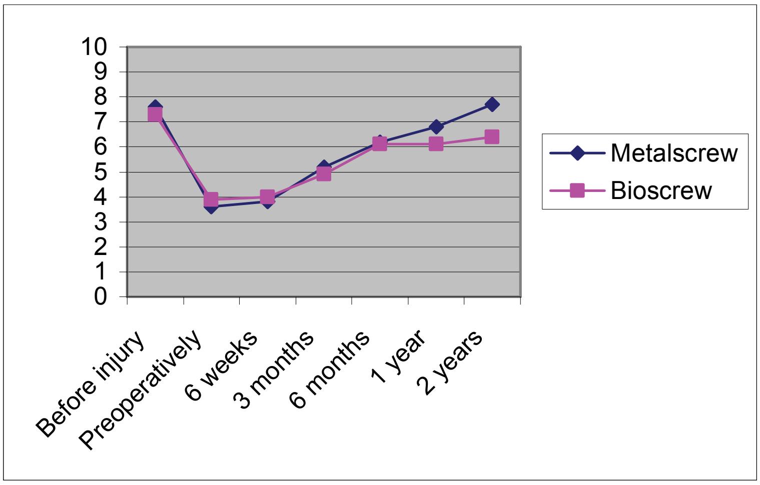
Table 4: Subjective knee function as evaluated by the patients.

Subjective knee function	Metal screws	Bioscrews	p value
Preoperatively			
Excellent	0	0	
Good	2	6	
Fair	11	9	
Poor	4	5	0.47
Six weeks postoperatively			
Excellent	0	0	
Good	15	13	
Fair	4	4	
Poor	0	0	0.86
12 weeks postoperatively			
Excellent	2	2	
Good	11	10	
Fair	2	3	
Poor	0	0	0.74
Six months postoperatively			
Excellent	5	6	
Good	9	12	
Fair	0	0	
Poor	0	0	0.89
One year postoperatively			
Excellent	10	2	
Good	7	16	
Fair	0	0	
Poor	0	0	0.03

Two years postoperatively			
Excellent	14	7	
Good	5	11	
Fair	0	0	
Poor	0	0	0.03

They had less pain at rest and a higher Tegner score.

Figure 3: Mean Tegner Activity score in the two groups.



The patients in the metal screw group also had a higher Lysholm score compared to the bioscrew group. However, there was no difference in stability between the groups. Because of the inferior results in the bioscrew group in our study, and until larger studies show other, we do not find the potential advantages of using bioscrews compared to metal screws sufficient to warrant the routine use of PLLA-screws in ACL-reconstructions.

Paper IV:

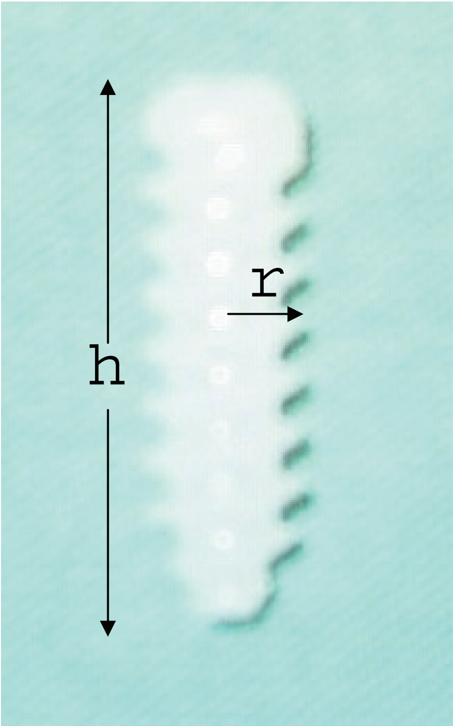
MRI analysis of bioabsorable interference screws used for fixation of bone-patellar tendon-bone autografts in endoscopic reconstruction of the anterior cruciate ligament.

The purpose of this study was to evaluate the resorption of poly-L-lactic acid (PLLA) interference screws and bony integration of the screws and bone blocks two years after endoscopic ACL reconstruction. It is useful to know whether an absorbable screw really is absorbed. The absorption of the screws is also of interest for the surgeon planning a revision. Postoperative MRI-evaluation is easier without metal artifacts.

The goal of the study was to quantify the amount of resorption of PLLA interference screws and integration of the femoral and tibial bone blocks two years after endoscopic ACL reconstruction. The hypothesis was that the screws are resorbed after two years.

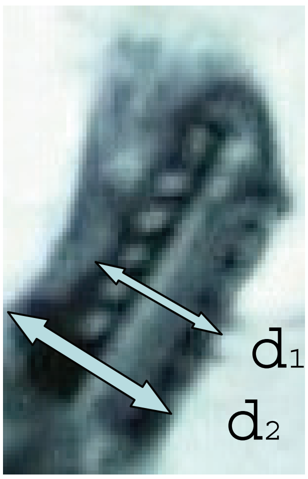
The study group consisted of 19 patients with isolated ACL ruptures reconstructed with bone-patellar tendon-bone autografts fixed with PLLA interference screws using an endoscopic technique.

Figure 4:
Measurement of the screw volume preoperatively. ($V1= \pi r^2 \times h$)
d= 2r



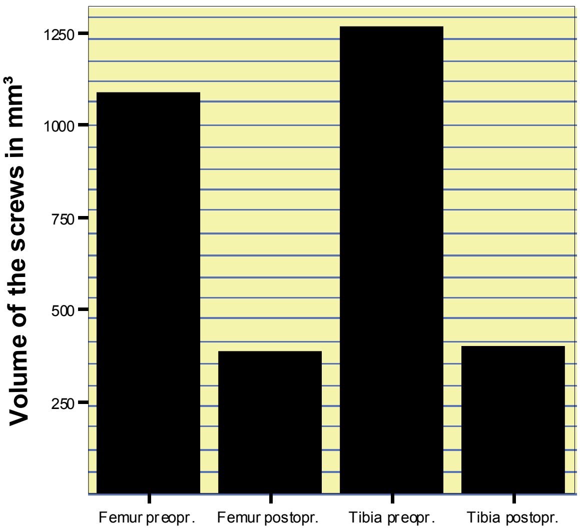
MRI was used to evaluate resorption of the screws, bony integration of the screws and integration of the bone blocks after two years.

Figure 5:
Measurement of the screw volume postoperatively. ($V2=\pi (\frac{1}{2}(r1+r2))^2 \times h$)



At two years the mean reduction in the volume of the femoral screws was 64% and 63% for the tibial screws.

Figure 6:
The mean volume of the femur and tibia screws preoperatively and at the follow up examination.



Bony integration of the femoral bone block was considered good in 17 patients and fair in two patients. Integration of the tibial bone block was considered good in 16 patients and fair in one patient who demonstrated widening of the tibial tunnel.

Figure 7:
Intermediately weighted coronal oblique image (TR/TE 2840/16) along the femur screw. Good integration of the bone block in the femur with no visible border between the bone block and the bone.

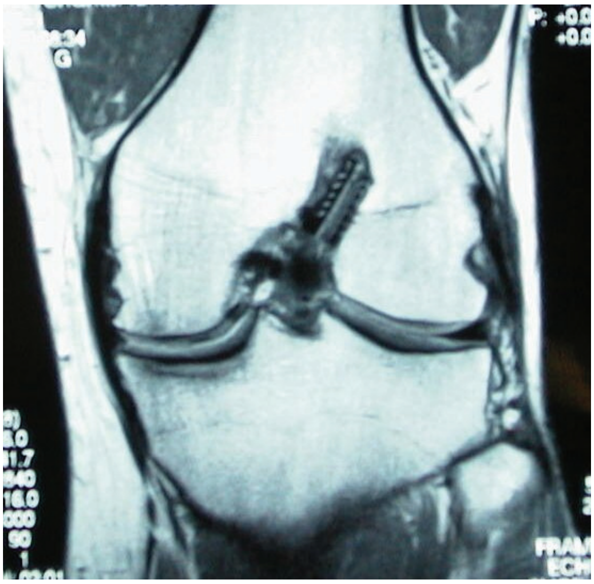
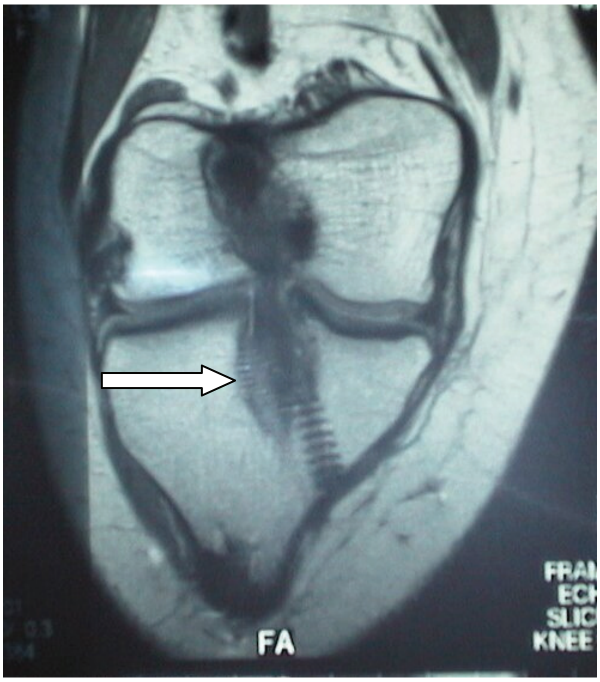
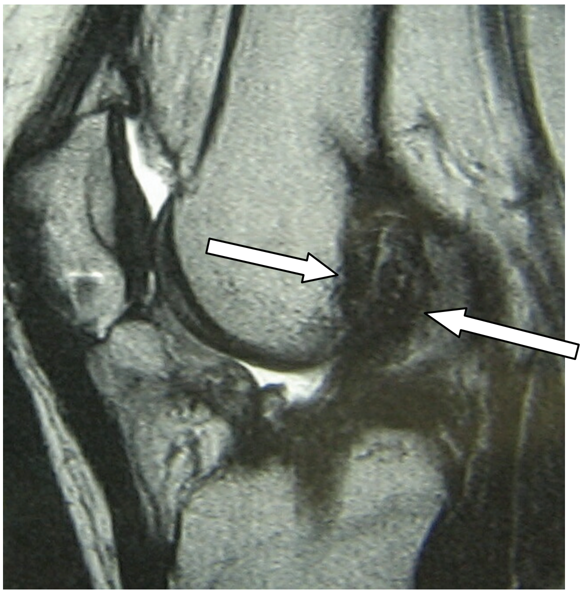


Figure 8:
Widening of the tibia tunnel.



Osteolysis around the screws was seen in three patients in the femur, and none in the tibia.

Figure 9:
Osteolysis with visible fluid around the screw in the femur on T2-weighted image.



In conclusion the mean reduction in volume of the PLLA screws as measured by MRI after two years was approximately 2/3. The integration of the bone blocks was good in 90%

of the patients. Osteolysis around the screws was visible in 16% (3/19) of the patients. Two years after ACL reconstruction using PLLA interference screws, the surgeon can thus expect to find approximately 1/3 of the volume of the screw remaining in the bone tunnels.

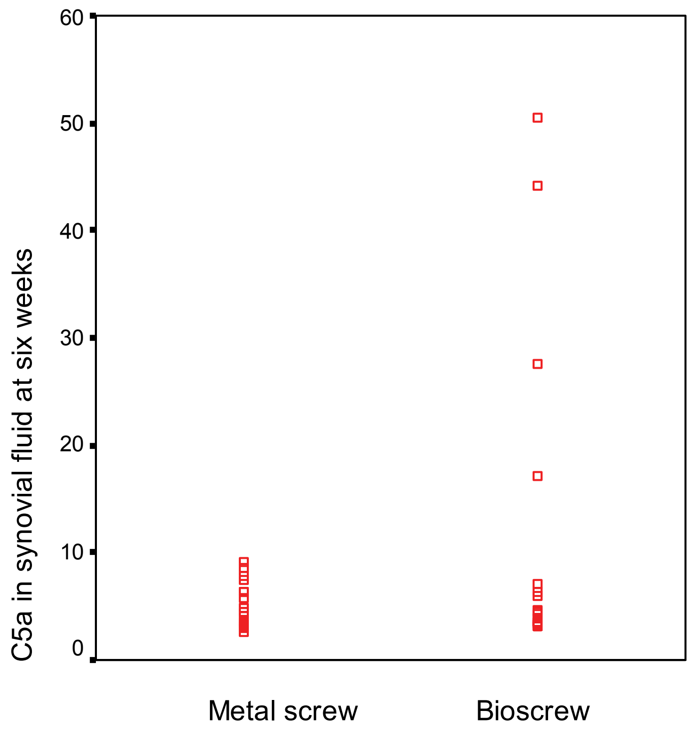
Paper V:

Comparison of in vitro and in vivo complement activation by metal and bioabsorbable screws used in ACL reconstruction.

The purpose of the study was to evaluate the biocompatibility of bioabsorbable screws (PLLA) in comparison to standard metal screws for fixation of the patellar tendon graft in human anterior cruciate ligament (ACL) reconstruction.
In this prospective randomized study we compared the biocompatibility of bioabsorbable screws with metal screws using synovial fluid complement activation (C5a and TCC), cytokine release (IL-1β, Il-8 and IL-10) and C-reactive protein (CRP) as read-outs. Furthermore, we investigated whether *in vitro* incubation of the two types of screws in serum was associated with a difference in complement activating potential.

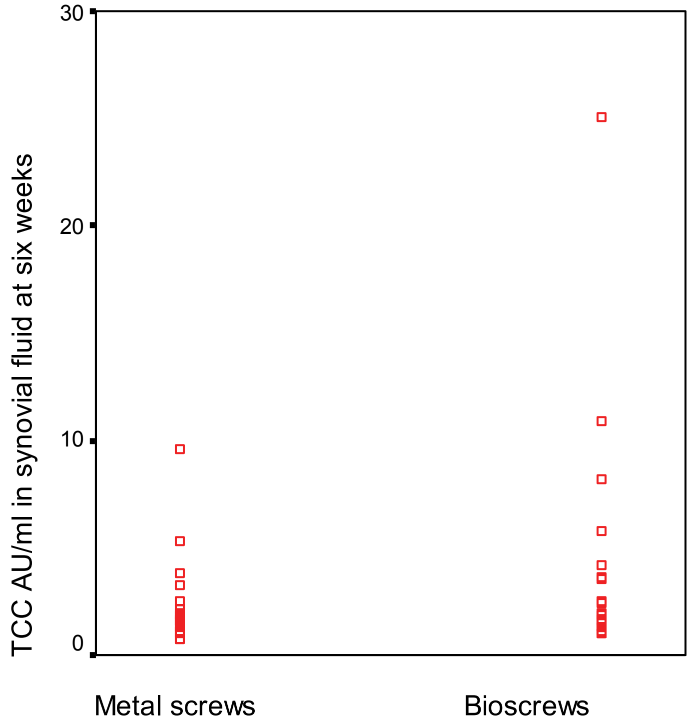
41 patients (22 women and 19 men) were prospectively randomized for the use of either metal interference screws (20 patients) or biologically resorbable PLLA-screws from Linvatec® (21 patients). Average age at the time of surgery was 26 years (15-51 years). Synovial fluid and plasma were collected preoperatively and after six weeks in both groups. Plasma was analyzed for C5a and synovial fluid in addition for TCC and IL-8. One year after surgery serum was incubated with metal, PLLA and no screws, and analyzed for C5a after one and six hours of incubation. The inflammatory mediators were measured with ELISA. Four patients in the bioscrew group samples had high C5a concentration in synovial fluid after 6 weeks, but there was no statistically significant difference between the two groups (p=0.11).

Figure 10: The increased C5a-concentration (ng/ml) in four patients in the bioscrew group in synovial fluid in the two groups after six weeks is a trend toward increased complement activation in the bioscrew group.



One patient in the bioscrew group had a high TCC value after 6 weeks, but there was no statistically significant difference between the two groups (p=0.20).

Figure 11:
The increased TCC-concentration (AU/ml) in two patients in the bioscrew group in synovial fluid in the two groups after six weeks is a trend toward increased complement activation in the bioscrew group.



In the *in vitro* study, no increased C5a generation was observed in sera incubated with a bioscrew or a metal screw compared to control.

In conclusion we did not find a statistically significant difference between the bioscrew and metal screw groups concerning C5a, TCC and IL-8 formation. However, some of the patients in the bioscrew group showed elevated values. We do not find the potential advantages of using bioscrews compared to metal screws sufficient to warrant the routine use of PLLA-screws in ACL-reconstructions.

GENERAL DISCUSSION

EVALUATION OF MATERIALS

Paper I, II, III and V are prospective, randomized studies. Paper IV is a prospective case series. The patients in paper IV were recruited from an arm of paper III comparing bioscrews with metal interference screws. In addition to this, the material in paper I was obtained from a continuation of a long-term follow-up multicenter study.

This thesis mainly deals with the surgical treatment of ACL injuries. As new surgical methods have developed over the years, we have tried to compare some of these procedures in an attempt to find the best graft and the best fixation of these grafts.

Paper I, II, III and V are designed according to the "golden standard" of clinical studies, as they are all prospective and randomized. The patients were included consecutively, and randomized to the special surgical procedure after the ACL rupture was verified clinically and/or arthroscopically. There were no statistically significant differences between the groups in these studies concerning preinjury activity level, concomitant ligament or meniscal injuries, sex or age.

In each of the studies in paper I, II, III and V, the patients participated in a standardized rehabilitation program designed for each study. This was managed by a team of physical therapists, who followed the patients until they were considered to be fully rehabilitated.

Paper I compares three surgical procedures we used in the past to treat ruptures of the anterior cruciate ligament: acute primary repair, acute repair augmented with a synthetic ligament-augmentation device (LAD), and acute repair augmented with autologous bone-patellar tendon-bone graft (BPTB). The material presented in paper I consists of 150 patients participating in a multicenter study, with three participating hospitals. In the different hospitals there was a possibility of dissimilar performance of the surgical procedures. However, in each hospital an experienced orthopedic surgeon was in charge of the surgery of these patients. Furthermore, prior to initiation of the study, surgery on cadaver knees were performed by these three surgeons to standardize the procedure. The follow-up protocol was similarly rehearsed with particular emphasis on the Tegner and Lysholm registrations, the Lachman and pivot shift tests, and the KT-1000 arthrometer tests. At the 16 year follow-up, all the patients were examined by one surgeon, to ensure similar evaluation of the outcome.

There were 50 patients in each group. It is difficult to interpret the outcome of repair procedures for the treatment of ACL ruptures because most published studies are retrospective, nonrandomized, and compare different surgical techniques, rehabilitation and follow-up protocols. Sandberg et al. (Sandberg 1987a) performed a prospective study comparing nonoperative cast treatment with direct repair of the ACL. They found that although there was no significant difference between the functional outcomes of the two treatments, there was a higher percentage of patients who had a positive pivot shift, in the group treated nonoperatively. Fruensgaard et al. (Fruensgaard 1992a) and Sommerlath et al. (Sommerlath 1991a) reported, in long-term retrospective follow-up studies that conservative treatment and simple suture of acutely torn ACL`s produced similar poor outcomes.

Our study was designed to see if there was a difference in the revision rate between the three procedures. Patients who had concomitant meniscal and/or medial collateral ligament injuries were included, whereas those who had posterior cruciate or lateral collateral ligament ruptures were excluded. Three patients were lost to follow-up during the first postoperative year and were excluded from the study. The two and five years results have previously been published (Grontvedt 1996a; Engebretsen 1997).

The clinical results after 16 years are presented in this paper. At this follow-up four patients were deceased, eight patients had emigrated and nine patients were lost to follow-up for other reasons. 129 patients (88%) were followed up at 16 years; 14 of these patients were interviewed by telephone only. Therefore, 78% (115 patients) had complete follow up data including an examination at 16 years. Only patients who had no ACL revisions in the operated knee and no ACL reconstructions in the contra lateral knee were included in the comparisons of the groups at the 16 year follow-up (103 patients). The reason for that is the difficulty in comparing stability without having a normal knee for comparison. Although no power analysis was performed in this study, this number of patients was considered sufficient for statistical evaluation of the results.

In paper II, which is a consequence of the results in paper I, 100 patients were randomized in a prospective study to ACL-reconstruction with bone-patella-bone grafts with and without a Kennedy ligament augmentation device (LAD, polypropylen).

Although no power analysis was performed in our study, 100 patients were considered sufficient for statistical analyses, even if the differences between the two groups should turn out to be minor. There were no statistically significant differences between the two groups concerning time from injury to surgery, preoperative meniscal injuries, preinjury activity level, preoperative functional level, age or sex. A total of 94 patients were examined an average of eight years after surgery. The patients had previously been evaluated at six months, one and two years after surgery. The evaluation after eight years was performed by one independent observer (The author, JOD). A total of 16 patients were excluded because of ACL-reconstruction in the other knee in the observation period and 10 patients, four in the control group and six in the LAD- augmented group, were excluded because of reruptures in the same knee. Of the 68 patients left, 36 were in the control group and 32 in the LAD-augmented group.

In paper III, forty one patients (22 women and 19 men) were prospectively randomized for reconstruction with either metal interference screws (20 patients) or biologic absorbable PLLA-screws (21 patients). Several other studies show no statistical difference in pullout tests using bioscrews or a metal screw (Johnson 1996; Caborn 1997a; Abate 1998; Rupp 1999; Kousa 2001). Other studies (Marti 1997; Benedetto 2000; Hackl 2000; Barber 2000; Kotani 2001; Lee 2003) show no statistical difference between the clinical results using either the bioscrew or the metal screw.

Patients with isolated ACL-ruptures or ACL-ruptures with additional minor meniscal and cartilage lesions (Outerbridge grade I and II) were included.

There were no statistically significant differences between the two groups in any measured parameter preoperatively. We wanted to observe a KT1000 max. man. difference <2mm. From previous studies the standard deviation was calculated to 1.33. From this information we calculated that we needed 10 patients in each group to be able to observe this difference. The number of patients was doubled to be able to observe differences also in other

variables.
One patient in the metal screw group suffered a rupture of the ACL in the contralateral knee six months postoperatively, and was excluded from the study. Three patients in the bioscrew group were lost to follow up at two years. The patients were followed up at 6, 12 and 24 weeks, 1 and 2 (24-35 months) years.

The study presented in paper IV was designed to quantify the amount of resorption of PLLA interference screws and integration of the femoral and tibial bone blocks two years after endoscopic ACL reconstruction on MRI. A total of 19 consecutive patients (12 women and seven men) with ACL- ruptures were included in the study. Average age at the time of surgery was 28 years (17-51 years). Mean time from surgery to MRI was 26.5 months (24-35 months). Patients with isolated ACL-ruptures or ACL-ruptures with additional minor meniscal lesions and minor cartilage lesions (Outerbridge grade I and II) were included. The patients were recruited from an arm of Paper 3.

The patients were reconstructed with a BPTB-procedure fixed with biologic resorbable poly L-lactic acid (PLLA) (Linvatec, Largo, FL, USA) screws using the endoscopic technique. It is useful to know how fast an absorbable screw is absorbed. The absorption of the screws is also of interest for the surgeon planning a revision. Postoperative MRI-evaluation is also easier without metal artifacts. Very little is found in the literature concerning quantification of the absorption and integration of the screws in humans. The absence of metal implants for fixation gives an opportunity to examine the adjacent tissue in detail and to form a time line of the tissue response in this type of surgery. As a consequence of this we wanted to quantify the integration of the femoral and tibial bone blocks and the PLLA interference screws two years after endoscopic ACL reconstruction.

In paper V, the same forty one patients as in paper III were evaluated. The aim of this study was to compare the biocompatibility of bioabsorbable screws with metal screws using synovial fluid complement activation (C5a and TCC), cytokine release (IL-1β, Il-8 and IL-10) and C-reactive protein (CRP) as read-outs. Furthermore, to investigate whether in vitro incubation of the two types of screws in serum was associated with a difference in complement activating potential. The use of bioabsorbable material for interference screws has potential benefits if the problems of inflammation are minimal and the fixation properties are sufficient. Many of these patients are young and prefer having an implant that will disappear over time. Other potential advantages for use of bioabsorbable screw fixation are a diminished need for hardware removal and that revision surgery is simplified. Postoperative MRI-diagnostics also are made easier without artifacts from metal (Macarini 2004). Blood sampling and synovial fluid aspiration were carried out prior to surgery. Serum samples were collected one year after surgery for the biocompatibility studies.

Complement analyses are being used to evaluate the biocompatibility of biomaterials (Mollnes 1991). We are not aware of previous publications studying complement activation after using biodegradable interference screws in ACL-reconstruction. Therefore we did not have a standard deviation of the results, and no sample size estimation could be performed beforehand. The weaknesses of this study were the relatively small number of patients and the fact that it was difficult to perform sample size estimation beforehand.

There is general agreement in the literature on the necessity of at least a 4 year follow-up in studies of ACL repair or reconstructions. The results in paper I and II fulfill this criterion, with a follow-up between 8 and 16 years. In paper III, IV and V, the follow-up was only 2 years. This is too short to make definitive statements about the surgical procedures used per se. Paper IV and V were, however, designed to study the biocompatibility, the integration and the resorption of the bioabsorbable interference screws and the integration of the bone blocks in the first two years postoperatively.

EVALUATION OF METHODS

All patients in the studies were examined by the author. This should ensure a standardized evaluation of the patients. However, due to the fact that in paper III, IV and V the author had performed the surgery on about half of the patients, there is a theoretical risk of bias. The use of an experienced, blinded independent observer would have provided the best chance of avoiding detection bias. Due to the fact that I did not perform any of the surgery in paper I and II, I should be considered an independent observer in these papers.

Many different methods of evaluating disability after knee ligament injury exist. Some are based on a combined evaluation of symptoms, objective knee instability, level of activity and a performance test (Noyes 1987). A comparison between a symptom-related score and a score of more complex design showed that the symptom-related score gave a more differentiated picture of the disability (Tegner 1985). As a consequence, the Lysholm score of the patients` own opinion of function was used in the clinical part of this thesis (Lysholm 1982). Risberg at al (Risberg 1999) found that the Lysholm score was not sensitive to changes over time. The Cincinnati knee score (Noyes 1984b), however, was highly sensitive to changes over time and showed significantly improved outcome between each follow-up in that study. This score has previously been found to be a sensitive outcome measurement both early and during long-term follow-up after ACL reconstruction (Risberg 1995). The Cincinnati knee score was therefore used in paper III.

The weakness of a functional score such as Lysholm is the possibility that limitations in knee function may be masked by lowering of the activity level. The functional score therefore needs to be combined with a score measuring the activity level in daily living and during recreational and competitive sports. Although terms such as "return to sports" are frequently used in similar evaluations, they do not take into consideration the vast difference in various sports in the amount of stress to the knee. Consequently, we decided to use the Tegner activity level score (Tegner 1985) which grades different activities in a standardized way on a numeric scale. The preinjury and present level of activity is readily defined with this scale. However, using these scores, we were still not able to determine whether the patient reached the same skill level in their sport. Even though the patient returned to the previous sport activity, he or she might be playing at a lower level. Furthermore, delay of surgery in chronic unstable knees may contribute significantly to a reduced level of sports activity. Thus, the Tegner score is of limited value in studies of such cases, except where various treatment methods are compared.

Grading of knee stability at clinical examination is difficult, obviously subjective, and dependent upon the skill and experience of the investigator. In the clinical studies of this thesis, the Lachman test, pivot shift tests and the KT-1000 test in paper I, II and III were all carried out by me. The Lachman test was carried out according to Torg et al (Torg 1976), and was graded as negative, slight (1+; < 5mm), moderate (2+; 5-10mm) or severe (3+; > 10mm), compared to the normal knee. The pivot shift sign (Galway 1980) is a clinical finding that confirms ACL insufficiency. In the present studies, the pivot shift sign was evaluated according to the McIntosh, Slocum and flexion-rotation-drawer (FRD) tests (Slocum 1976). The results were graded as negative, trace positive (1+), moderate (2+) or severe (3+), as compared to the normal knee. A trace positive anterolateral rotatory instability is a subtle, but definitely abnormal catching of the lateral tibial condyle felt by palpation. A 3+ anterolateral rotatory instability is a classic pivot shift phenomenon, felt like a subluxation of the lateral tibial condyle. The McIntosh, Slocum and FRD tests were used and the highest degree of instability obtained was recorded.

Instrumented testing has been introduced in an attempt to increase the precision of knee stability measurements. Several different types of arthrometers have been developed. The one used in our studies, the KT-1000 arthrometer, was designed by Daniel and coworkers (Daniel 1985). It measures anterior laxity of the tibia at constant loads of 67 and 89 N, and at maximal manual force, which is dependent on the investigator, with the knee in approximately 25 degrees of flexion. The uninjured knee serves as a control, and a side-to-side difference of more than 3 mm has been found to be indicative of ACL injury (Daniel 1985). However, it is important to consider the limitations of these types of measurements. A normal KT-1000 result does not indicate normal biomechanics of the knee. It merely reflects the position of the tibia compared to the femur and the amount of anterior-posterior translation at a certain flexion angle of the knee. The results depend firstly on finding the "neutral" position of the tibia on the femur each time the measurements are repeated, and secondly on the reproducibility of the placement of the test apparatus on the tibia. In a study by Sernert et al (Sernert 2004) the KT-1000 arthrometer testing revealed a significant increase in laxity measurements in right knees compared with left knees. This difference was found both preoperatively and postoperatively in patients undergoing ACL reconstruction. However, the KT-1000 test, done correctly, is a convenient way to check the Lachman results of the investigator (Konig 1998). In our studies the results of the two tests correlated well.

A combination with a functional knee performance test would probably have given a better indication of the rehabilitation status. One of the weaknesses of the present study is the lack of a functional test in the postoperative evaluations.

A radiographic evaluation of the knee was carried out in paper I, II and IV.
In paper I radiographs of both knees standing at 45 degrees of flexion and with a 30 degree angulation of the beam were obtained at the 16 year follow-up, and the degree of osteoarthritis was graded by an independent experienced radiologist (A.T. Viset) using the Ahlback-classification (Ahlback 1968). Also in this study the radiologist, in more than half of the patients, could tell which knee had undergone surgery.

The knees in paper II were examined with antero-posterior radiographs of both knees while standing with equal weight on both legs. The film-focus distance was standardized. The amount of osteoarthritic changes was graded according to the method reported by Ahlback (Ahlback 1968). Grade 0 indicates no degenerative changes, grade 1 minor change, grade 2 major changes, and grade 3 severe osteoarthritic changes. The radiographs were evaluated by an experienced radiologist (Ø. Haave), not involved in any other part of these studies, and blinded with respect to the other test results. However, due to the fact that the involved knee had implants, the radiologist knew which knee had undergone surgery.

Paper IV was a MRI evaluation of the knees. The MRI examinations were performed on a Marconi Edge 1.5T MR-scanner with sagittal FSE 4000/16/128, coronal fat saturated 1500/15, and coronal SE 500/10 with 4 mm slices thickness and image matrix 256x384. Two oblique coronal FSE 2840/16 imaging sequences with slice thickness 3 mm and image matrix 256x384 were added in all patients. Number of excitation was one and field of view was 16. The oblique sequences were oriented along the biological screws.

In paper IV the measurement of the screw volume preoperatively (V1) was calculated from the formula $V1 = \pi r^2 \times h$

where

r = radius of the screw

h = length of the screw

The measurement of the screw volume postoperatively (V2) was calculated from the formula $V2 = \pi (\frac{1}{2}(r1+r2))^2 \times h$

where

r1 = largest radius of the screw

r2 = smallest radius of the screw

The resorption of the screw ΔV was

$\Delta V = V1 - V2$

The resorption of the screw in percent was

$\% = 100\% \times \Delta V/V1$

The integration of the bone block was considered good if no visible border between the bone block and the bone was visible on MRI; fair with <1mm visible border and poor with >1mm visible border between the bone block and the bone. Osteolysis around the screws was defined as visible fluid around the screws. To choose the appropriate imaging sequences and avoid distortions, MRI measurements were compared to an in vitro MRI measurement of a sample screw.

The volume of the screws in this study is calculated as the volume of a cylinder. The fact that the screws are conical at one end, and therefore do not have the shape of a cylinder, is a systematic error and should not influence the results. The surface of the screw is threaded. The MRI measurements were done at the outer part of the thread. The screws are also resorbed from the inside through the screw hole, and this factor is not measured in our study. The MRI evaluation was performed by a radiologist (G. Myhr), experienced in musculoskeletal MRI.

In paper V blood sampling and synovial fluid aspiration were carried out prior to surgery. Plasma samples were analyzed for CRP and C5a. The preoperative synovial fluid and the synovial fluid after six weeks were analyzed with measurements of C5a, TCC, IL-1β, IL-8- and IL-10. Serum samples were collected one year after surgery for the biocompatibility studies. C5a was quantified by a sandwich ELISA technique using neoepitope-specific monoclonal antibodies as described elsewhere by Bergh et al (Bergh 1992). TCC (soluble SC5b-9), the final activation product generated when complement is activated was detected by ELISA principally as described for C5a. The assay is based on a monoclonal antibody (aE11) specific for a neoepitope exposed in C9 when incorporated into the TCC complex, as previously described by Mollnes et al (Mollnes 1985). For the quantification of cytokines the following commercial ELISA kits were used and the procedures performed according to the instructions of the manufacturer (CLB, Amsterdam, The Netherlands): IL-1β, IL-8 and IL-10.

We are not aware of previous publications studying complement activation after using biodegradable interference screws in ACL-reconstruction. Complement analyses are used to evaluate the biocompatibility of biomaterials (Mollnes 1991). In this study we measured C5a, biologically the most potent of the anaphylatoxins generated during complement activation, and the terminal SC5b-9 complex (TCC) as a sensitive indicator of complement activation and bioincompatibility (Bergh 1992; Mollnes 1995, 1997). These studies have demonstrated widely varying complement activation properties of different materials. Reference levels of C5a in normal or inflamed synovial fluid have not been established. However, it is important to bear in mind that the true levels of C5a generated are not directly reflected by measurements of C5a in the fluid phase as C5a binds rapidly and strongly to cellular C5a receptors, particularly on leucocytes. The true extent of complement activation when measured in the fluid phase may thus be underestimated (Bergh 1991).

The weaknesses of this study were the relatively small number of patients and the fact that it was difficult to perform a power analysis beforehand.

STATISTICAL METHODS

All data in the clinical studies were processed with the Statistical Package for Social Studies (SPSS Inc, Chicago, Illinois).

In paper I the Statistical Package for the Social Sciences (SPSS) 11.0 was used for the statistical analyses. A nonparametric analysis of variance (Kruskal-Wallis test) was used to determine the significance of the overall difference in the outcome measures between the three repair groups at a particular follow-up time point. Paired comparisons between the three groups at each evaluation time point were made using the Mann-Whitney test. The Wilcoxon test for paired data was used to test for the significance of the changes in the outcome measures for a particular repair group between any two follow-up time points. Comparisons were considered significant at a p level of less than 0.05.

In paper II the Mann-Whitney, Pearson chi-squared and the unpaired t-tests were used for comparisons of the two groups. A p-value of <0.05 was considered as significant.

In paper III the Mann-Whitney, Pearson chi-squared and the independent samples t-tests were used for statistical analysis. The significance level was set to $p<0.05$. A power of 0.9 was selected for sample size estimation. We wanted to observe a KT1000 max. man. difference <2mm. From previous studies the standard deviation was calculated to 1.33. From this information we calculated that we needed 10 patients in each group to be able to observe this difference. The number of patients was doubled to be able to observe differences also in other variables (Karlsson 2003).

In paper IV the Fisher Exact Test was used to calculate the correlation between resorption and osteolysis of the screws and the KT 1000 measurements.

In paper V the level of significance was also set at $p < 0.05$. The Mann-Whitney, Wilcoxon Rank Test and the Pearson chi-squared were used. For the correlation analysis the Spearman Test was used. For the comparison of the three groups in the *in vitro* test, the Kruskal Wallis

Test was used.

DISCUSSION

Paper I:
A 16-year Follow-up of Three Operative Techniques for the Treatment of Acute Ruptures of the Anterior Cruciate Ligament.

Several follow-up studies have reported that results of the acute repair of anterior cruciate ligament (ACL) ruptures deteriorate with time. (Feagin Jr 1976; Odensten 1984a; Sommerlath 1991a; Fruensgaard 1992a). Short-term results of ACL repair plus augmentation were encouraging (Clancy Jr 1988a; Schabus 1988; Andersson 1989a). However, there are no long-term studies.

Eleven patients (24%) in the primary repair group, four patients (10%) in the LAD-group and one patient (2%) in the BPTB-group underwent ACL-revision surgery between the primary operation and the 16 years follow-up. The incidence of revisions was thus ten times higher in the primary repair group than in the BPTB-group (p=0.003). With the numbers available the incidence of revisions was not statistically significant different between the primary repair group and the LAD-group (p= 0.066) nor between the BPTB-group and the LAD-group (p=0.167). We found that the patients who had a primary repair of a ruptured anterior cruciate ligament had an unacceptably high revision rate.

At 16 years there was no significant difference between the groups as measured with the Tegners activity level score. Concerning the Lysholm functional score, 30% of the patients in the primary repair group had functional scores within the poor and fair categories (0 to 83 points). A total of 35.5% of the LAD-group and 14% of the BPTB-group had functional scores within the poor and fair categories.

The subjective knee function as graded by the patients was fair/poor in five patients in the primary repair group, six patients in the LAD-group and one patient in the BPTB-group. We did not find any difference between the groups concerning subjective knee function. However, the patients who had the most lax knees and the greatest functional problems in each group had been revised and excluded from further comparison.

In the present study, the patients in the BPTB-group had a higher activity and functional level at 16 years than the two other repair groups. The Tegner activity score was higher in the BPTB-group at all time intervals. In this group five patients underwent ACL-reconstruction in the contralateral knee as compared to only one patient in the primary repair group. This may indicate that the patients who had stable knees performed more risky activities and thereby more often injured their opposite knee and.

At 16 years one patient in the primary repair group, one in the LAD-group and none in the BPTB-group had an extension deficit greater than 10 degrees. In general, the patients in all three repair groups showed an improvement in their ability to attain full flexion over the one to 16 year follow-up period. However, one patient in the primary repair group and one in the BPTB-group still demonstrated a flexion deficit of more than 30 degrees at 16 years. At that time, there was no significant difference in range of motion among the three groups. Arthrofibrosis following patellar tendon reconstructions, when ACL surgery is done acutely, has been reported previously (Paulos 1987; Mohtadi 1991; Shelbourne 1991). The early limited range of motion problems in the BPTB-group in the present study is probably related to the acute, open surgical procedure and the conservative rehabilitation protocol that was used.

The knees in the BPTB-group were more stable than those in the LAD-group at 16 years (p=0.026). There was no difference in anterior laxity as measured with KT 1000 between the knees in the primary repair group and those in the LAD group (p=0.55) nor those in the BPTB group (p=0.50) at 16 years. There was also no difference between the knees in the LAD group or the BPTB group (p=0.13). The percentage of patients with a side-to-side difference in anterior laxity of three millimeters or more were 48% (13 of 27) in the primary repair group, 38% (11 of 29) in the LAD- group and 30% (10 of 33) in the BPTB group. At the five-year follow-up, the rate of instability failures in the LAD group had increased significantly, probably due to ruptures of the LAD itself. However, the stability outcome of the LAD group was still significantly better than that of the primary repair group. In paper II, no positive long-term effects supporting the use of LAD augmentation in anterior cruciate ligament reconstruction were found. In the present study 21% of the BPTB-patients at five years and 30% at 16 years had side-to-side differences of three millimeters or more as measured by the KT-1000 at follow-up (p=0.114). This indicates that the BPTB-graft did not stretch during the 16 years of this study.

Nine out of 85 patients (11%) had osteoarthrosis in the operated knee compared to 4% (3 of 85) in the other knee 16 years after surgery (p=0.001). A total of 11% osteoarthrosis is surprisingly low, especially when the long postoperative immobilization and slow rehabilitation are taken into account. Four patients in the primary repair group, one patient in the LAD-group and four patients in the BPTB-group had osteoarthrosis of the knee at 16 years. In paper II, half developed osteoarthrosis at eight years as verified by radiographic examination using the Ahlback classification. The only differences between these two studies were that this study of 100 patients involved an aggressive rehabilitation protocol and arthroscopic surgery and that the patients were allowed to return to sports early. Myklebust et al. (Myklebust 2003b) found in a study of handball players with a reconstructed ACL that 42% of the group had developed gonarthrosis after eight years. The high percentage of osteoarthrosis in their study may be explained by a high sports activity level. We found a surprisingly low incidence of osteoarthrosis in our patients after 16 years, but patients in our study had a lower activity level, compared to the handball players in Myklebust`s study.

In summary we obtained the best results when the ACL repair was augmented with a BPTB-graft. In all outcome measures other than for early limited range of motion, the BPTB-augmentation technique was superior to primary repair and repair augmented with the LAD. Based on these data, we conclude that open primary repair has an unacceptably high revision rate and should not be performed. It can be expected that approximately 10% of patients undergoing anterior cruciate ligament reconstruction acutely will develop radiological evidenced osteoarthritis in the reconstructed knee. We no longer perform any of these open surgical techniques.

Paper II:
Anterior Cruciate Ligament Reconstruction with and without a Ligament Augmentation Device. Results at 8-Year Follow-up.

The treatment of chronic ACL deficient knees has been a problem for several decades. ACL-reconstruction with the use of the bone-patellar tendon-bone autologous graft has been one of the most frequently used methods with overall good results (Noyes 1984a). However, it has been well documented in animal studies that these grafts undergo an initial necrosis, followed by revascularization and remodeling (Clancy Jr 1981; Butler 1989). During this period, the mechanical resistance of the graft is reduced, and theoretically it can stretch or rupture if submitted to strong forces before it has regained normal strength. The length of this reduced strength period is not known in humans, but the majority of surgeons recommend not returning to twisting sports until 6 to 12 months after surgery. Since Kennedy and his colleagues (Kennedy 1980) in 1980 introduced the LAD made of a polypropylene braid to protect the autologous transplant during the initial repair phase, several reports have been published on the short term effects of the use of the augmentation of various biological grafts both in animals and in humans. They claimed that the load-shearing between the LAD and the biological graft would protect the graft during the period of degeneration and weakening sufficiently to allow the transplant to regain mechanical strength without risk of elongation or rupture.

Grøntvedt et al (Grontvedt 1996b) compared 100 patients randomized to ACL-reconstruction with and without augmentation of the bone-patellar tendon-bone graft with the Kennedy ligament augmentation device, and observed no significant functional or clinical difference between the two groups after two years.

The aim of our study was to observe any differences concerning these parameters in the same patients after eight years. A total of 15 patients were excluded because of reconstruction of the anterior cruciate ligament in the other knee in the observation period. Eleven patients suffered reruptures of the reconstructed anterior cruciate ligament in the same knee and were excluded from the study; four in the non-augmented and six in the augmented group. There was no statistically significant difference in the Tegner activity level between the two groups at either the preinjury or follow-up examinations. For both groups together, the Tegner score decreased from a mean preinjury level of 7.5 to 5.3 after eight years. This decrease is highly significant ($p<0,001$) and can at least partly be explained by the fact that these patients have become older, and for that reason have decreased their level of activity.

There was no statistically significant difference in the Lysholm score between the two groups at either the preinjury or follow-up examinations. The Lysholm score was statistically highly significantly improved after 8 years compared to the preinjury level ($p<0,001$). There was no statistically significant difference in the range of motion between the two groups at either the preinjury or follow-up examinations.

At eight years three patients had a Lachman 2+ in the augmented group and six in the non-augmented group. One patient in each group had a Lachman 3+. In addition four patients (7.8% of all the patients in the non-augmented group) and six patients in the augmented group (12.3%) were revised.

There was no statistically significant difference in the Lachman test between the two groups at either the preinjury or follow-up examinations. Eight years of follow-up should have shown the putative benefit of the LAD in the remodeling process. Several other studies also show no significant benefit with respect to residual laxity after augmentation (Noyes 1984a, 1992; Roth 1985; Jonsson 1992; Moyen 1992).

There was a significant relationship between peroperative detected cartilage injury and osteoarthritis after eight years ($p<0,005$). There was no significant relationship between meniscal injuries and osteoarthritis after eight years. This indicates that concomitant cartilage injuries may play an important role in the development of osteoarthritis in ACL- injured patients. There was a significant correlation between decrease in subjective function and the development of osteoarthritis (p=0,001). 50% of the patients had developed radiological osteoarthritis after eight years. There was no significant difference between the groups concerning osteoarthritis (p=0,145). Several other studies also show a similar incidence of osteoarthritis (Sommerlath 1992; Roos 1995a; Otto 2002; Myklebust 2003b).

In summary, our results show no benefit of the LAD, as we found a complete equivalence both in functional and clinical tests between the augmented and the non-augmented groups. Half of the patients had developed osteoarthritis. The presence of a cartilage injury is an important predisposition for the development of osteoarthritis.

Paper III:
Endoscopic reconstruction of the anterior cruciate ligament using bone-patellar tendon-bone grafts fixed with bioabsorbable or metal interference screws. A prospective randomized study of the clinical outcome.

The great majority of patients with non operated ACL injuries experience that giving way is a problem (Hawkins 1986a). ACL reconstruction using bone-patella-tendon-bone-grafts (BPTB) has been the gold standard. Metal screws have been used for graft fixation. Because these screws will remain in the femur and tibia, and may cause problems if revision is required, different bioabsorbable screws have been developed.
Several studies show no statistical difference in pullout tests using bioscrews or metal screws (Johnson 1996; Caborn 1997a; Abate 1998; Rupp 1999; Kousa 2001). The bioabsorbable screws in the present study are made from poly L-lactic acid (PLLA) and are fully resorbed. Many of these patients are young and prefer having an implant that disappears over time. The aim of this study was to compare the clinical outcome using bioabsorbable interference screws or metal screws for ACL-reconstruction.

At the one and two year follow-up the patients' assessments of the subjective knee function showed that there was a statistically significant difference between the two groups in favor of the metal screw group ($p<0.05$). At the one year control mean pain score at rest on the modified Cincinnati score from 0 (no pain) to 10 (unbearable pain) was 0.27 in the metal screw group and 0.84 in the bioscrew group ($p<0.05$). At the two year control the mean values were 0.04 in the metal screw group and 0.81 in the bioscrewgroup ($p<0.005$). There was a statistically significant difference between the two groups concerning Tegner activity score in favor of the metal screws at the 2-year control ($p<0.005$). The knee function at two years compared to before injury was evaluated on a scale from 0 (same function as before the injury) to 10 (very bad knee function compared to before injury). The mean values were 0.93 in the metal screw group and 2.19 in the bioscrew group ($p<0.05$). This may be due to dissolving of the screws and activation of the complement system with an inflammatory reaction and pain (Paper IV). The mean Lysholm score was 84 in the metal screw group and 78 in the bioscrew group at six weeks ($p<0.05$) and respectively 97 and 94 at two years ($p<0.05$). Six patients in the bioscrew group had an extension deficit between 5-10° after three months to only one patient in the metal screw group ($p<0.05$). Several other studies (Marti 1997; Benedetto 2000; Hackl 2000; Barber 2000; Kotani 2001; Lee 2003) show no statistical difference between the clinical results when using either the bioscrew or the metal screw.

We found no statistically significant difference between the groups in stability measured by pivot shift, the Lachman test or the KT-1000 at any time. In our study the measurements of increased pain and decreased subjective knee function may be explained by an increase in inflammatory parameters in some patients in the bioscrew group (Paper V), although we could not detect any difference in intraarticular swelling between the groups. The differences in the parameters found in this study are numerically small but statistically significantly different. The clinical significance of these findings is uncertain.

Because of the inferior results in the bioscrew group in our study, and until larger studies show other, we do not find the potential advantages of using bioscrews compared to metal screws sufficient to warrant the routine use of PLLA-screws in ACL-reconstructions.

Paper IV:
MRI analysis of bioabsorable interference screws used for fixation of bone-patellar tendon-bone autografts in endoscopic reconstruction of the anterior cruciate ligament.

Metal screws have been used for many years for interference fixation of ACL reconstructions performed using bone-patellar tendon bone grafts with good clinical results reported (Clancy Jr 1988a; Grontvedt 1996a; Shelbourne 1997; Drogset 2002). Metal screws usually will be left in place both on the femoral and tibial side with difficulties in revising a reconstruction. The screws interfere with MRI imaging following surgery. Many of these patients are young and prefer having an implant that disappears over time. For the above reasons, bioabsorbable screws have been developed. It is interesting to know whether an absorbable screw really is absorbed. The absorption of the screws is also of interest for the surgeon planning a revision. Very little is found in the literature concerning quantification of the absorption and integration of the screws in humans. The use of MRI (Lajtai 1999) provides observations not available by other imaging methods. The absence of metal implants for fixation gives an opportunity to examine the adjacent tissue in detail and to form a time line of the tissue response in this type of surgery.

The bioabsorbable screws used in this study were made from poly L-lactic acid (PLLA). The mean reduction in volume was 64% (26.0- 86.1) of the femur screw and 63% (24.0-76.7) of the tibia screw. Pistner et al (Pistner 1993) used three poly L-lactides with different molecular weights and implanted them as small rods into the dorsal muscle of rats. The samples degraded very fast, reaching the same molecular weight level after 20 weeks, and then degraded simultaneously. Morgan et al (Morgan 2002) reported 75% decrease in the molecular weight of the PLLA-screws after 30 months in vivo after ACL-reconstruction in one patient. In another study Fink (Fink 2000) included 20 patients who had the femoral bone block fixed with a polyglyconate bioabsorbable interference screw. Computed tomography scans showed complete degradation of the bioabsorbable screws at 12 months. The reason for the big differences in the results between these studies is probably because of the different polymers used in the different implants.

The integration of the bone blocks in the femur in our study was good in 17 patients (90%) and fair in two patients (10%). The integration of the bone blocks in the tibia was good in 16 patients (94%) and fair in one patient (6%) who had widening of the tibia tunnel. None of the patients had a poor integration of the bone blocks in the femur or tibia. In Warden's study (Warden 1999) two patients developed an abnormal signal in the tibial tunnel; one with fluid anterior to the graft and the other with fluid/edema within the graft. The abnormal signal resolved with time in both patients. Martinek (Martinek 1999) reported a case of an osteolytic tibial tunnel enlargement in association with a pretibial cyst formation 8 months after successful ACL reconstruction with autologous BPTB graft and tibial graft fixation with a bioabsorbable interference screw.

In our study osteolysis around the screws in the femur was visible in 3 patients (16%). In a retrospective study Marti (Marti 1997) compared the clinical outcome and the radiographic incorporation of the bone blocks between two groups of patients undergoing ACL reconstruction using either metallic or bioabsorbable interference screws for fixation of the BPTB autograft. All patients showed osseous incorporation of the bone block autografts within the femoral and tibial bone tunnels with no osteolytic changes. In a prospective, randomized study comparing the safety and efficacy of the PLLA screw with that of the metal cannulated interference screw for ACL- reconstruction, McGuire (McGuire 1999) found no radiographic evidence of osteolytic change or bone resorption around the bioscrews. In our study there was no statistically significant correlation between the patients having osteolysis around the screws in the femur and the patients having poor subjective knee function ($p=1.00$), low Lysholm score ($p=0.34$) or intraarticular effusions ($p=1.00$) at two years. None of the patients had osteolysis with fluid around the screw in the tibia.

There was no significant correlation between the absorption of the screws in the femur and the KT 1000 measurements ($p=1.000$) or the screws in the tibia and the KT 1000 measurements ($p=1.000$). There was no significant correlation between the osteolysis around the screws in the femur and the KT 1000 measurements ($p=0.817$). Macarini et al (Macarini 2004) found that in only 4 out of 35 cases was the process of osteointegration of the PDLLA bioabsorbable screw and bone plug complete 3 years after the operation, with consequent restoration of bone morphology. In another study by Barber (Barber 1995), six of 85 bioscrews (7%) broke on insertion. No lytic bone changes or tunnel widening were found in any patient where bioscrews were used. In our study none of the screws broke during insertion. Overall the integration of the bioabsorbable screws is satisfactory in most studies, and the rate of osteolysis is low.

Paper V:
Comparison of in vitro and in vivo complement activation by metal- and bioabsorbable screws used in ACL reconstruction.

Metal screws have been used for graft fixation of ACL reconstructions with bone-patella-tendo-bone-grafts (BPTB) for several years. Due to the fact that the screws will be left in the bone, and difficulties in revising a reconstruction with metal interference screws, a bioabsorbable screw has been developed. The use of this material for interference screws has potential benefits if the problems of inflammation are minimal and the fixation properties are sufficient. Many of these patients are young and prefer having an implant that will disappear over time. Other potential advantages for use of bioabsorbable screw fixation are a diminished need for hardware removal and that revision surgery is simplified. Postoperative MRI-diagnostics also are made easier without artifacts from metal (Macarini 2004). Friden and Rydholm (Friden 1992) reported a case of severe synovial reaction to biodegradable rods used for fixation of osteochondritis dissecans of the knee, and Smith et al reported fractures of the screws on insertion (Smith 2003). Tegnander et al (Tegnander 1994) showed that the C5a-concentration in plasma incubated in the presence of polylactic acid was found to be higher than in plasma incubated in the absence of PLLA. Activation of the alternative pathway of the complement system may occur when blood or other bodily fluids are exposed to foreign substances. It is highly important that biodegradable materials are biocompatible.

In this study there were no statistically significant differences between the groups in any measured parameter preoperatively. The C5a concentration in synovial fluid after 6 weeks was 5.0 ng/mL (3-9) in the metal screw group and 10.3 ng/mL (3-51) in the bioscrew group (p=0.11). Four out of 21 patients in the bioscrew group, but no patients in the metal screw group had a substantially higher C5a value in the 6-week sample and correspondingly a greater increase during the 6 weeks after surgery. The clinical results in these patients (Paper III) showed that the subjective knee function was better in the patients with metal screws than those with bioscrews; the metal screw patients had less pain at rest, a higher Tegner score, a higher Lysholm score and a better subjective knee function at two years compared to the bioscrew group. However, there was no difference in stability between the groups.

After six weeks the mean TCC concentration in synovial fluid was 2.3 AU/mL (range: 0.7-9.6) in the metal screw group and 4.1 AU/mL (1.0-25.1) in the bioscrew group (p=0.20).

Selected samples were initially tested for the cytokines IL1-β, IL-8 and IL-10. Only IL-8 was detectable in the synovial fluid and thus the whole material was measured only for IL-8. The IL-8 concentration in synovial fluid after 6 weeks was 187.4 pg/mL (13.3-472.0) in the metal screw group and 180.4 pg/mL (13.7-480.0) in the bioscrew group (p=0.89). The increase in IL-8 concentration in synovial fluid from preoperatively to six weeks was statistically significant in both the metal screw group (p=<0.0001) and in the bioscrew group (p=<0.0001). There was a statistically significant correlation between the increase in C5a concentration and the increase in TCC concentration (r=0.52; p=0.001), between the increase in C5a concentration and the increase in IL-8 concentration (r=0.49; p=0.005) and between the increase in TCC concentration and the increase in IL-8 concentration (r=0.44; P=0.011) in synovial fluid from preoperatively to six weeks after operation.

No overall difference was observed when sera were incubated for 1 h with a metal screw or a bioscrew (p=0.22). Similar results were obtained after six hours incubation.

In our study no patients had clinically detectable synovial reactions, however, some patients in the bioscrew group showed a trend toward increased complement activation. We are not aware of previous publications studying complement activation after using biodegradable interference screws in ACL-reconstruction. Complement analyses are used to evaluate the biocompatibility of biomaterials (Mollnes 1991). In this study we measured C5a, biologically the most potent of the anaphylatoxins generated during complement activation, and the terminal SC5b-9 complex (TCC) as a sensitive indicator of complement activation and bioincompatibility (Bergh 1992; Mollnes 1995, 1997). The results from those studies have demonstrated widely varying complement activation properties of different materials.

We found significant increases of C5a, TCC and IL-8 in synovial fluid from preoperative values compared to six weeks postoperatively. At 6 weeks postoperatively a trend towards higher levels in the bioscrew group compared to the metal screw group was observed regarding C5a. The same trend is reflected by the finding that 3 of 21 patients receiving a bioscrew but none receiving a metal screw, responded with a more pronounced increase of C5a (i.e.> 10 ng/mL) from baseline to the 6 weeks control. Concerning TCC, this trend was somewhat less pronounced.

However, it is important to bear in mind that the true levels of C5a generated are not directly reflected by measurements of C5a in the fluid phase as C5a binds rapidly and strongly to cellular C5a receptors, particularly on leucocytes. The true extent of complement activation when measured in the fluid phase may thus be underestimated (Bergh 1991).

The weaknesses of this study were the relatively small number of patients and the fact that it was difficult to perform sample size estimation beforehand.

In summary no statistically significant difference was observed between the bioscrew and metal screw groups concerning C5a, TCC and IL-8 formation. We have therefore in this study not been able to demonstrate a general bioincompatibility of the materials used. However, some of the patients in the bioscrew group showed elevated values of C5a.

GENERAL CONCLUSIONS

1. In paper I we obtain the best results when the ACL repair is augmented with a BPTB-graft. In all outcome measures other than for early limited range of motion, the BPTB-augmentation technique is superior to primary repair and repair augmented with the LAD. Based on these data, we conclude that open primary repair has an unacceptable high revision rate and should not be performed.

2. It can be expected that approximately 11% of patients undergoing acute anterior cruciate ligament reconstruction with these three repair techniques will develop osteoarthritis in the reconstructed knee.

3. In paper II the patients assess their clinical situation after eight years as better than before surgery. We observe no significant difference between the two groups concerning reruptures, Lysholm score, Lachman`s test or KT-1000 measurements. We find no positive short or long-term effects supporting the use of LAD-augmentations in ACL-reconstructions.

4. Almost half of the patients in the two groups in paper II have developed osteoarthritis. The presence of a cartilage injury is an important predisposition for the development of osteoarthritis.

5. In paper III the subjective knee function is better in the patients in the metal screw group; they have less pain at rest, a higher Tegner score, a higher Lysholm score and a better subjective knee function. However, there is no difference in stability between the groups. Because of the inferior results in the bioscrew group in our study, and until larger studies show other, we do not find the potential advantages of using bioscrews compared to metal screws sufficient to warrant the routine use of PLLA-screws in ACL-reconstructions.

6. In paper IV we find that the mean reduction in volume of the PLLA screws after two years is approximately 2/3. The clinical relevance is that the surgeon can expect to find approximately 1/3 of the volume of the screw remaining in the bone tunnels at two years.

7. When using PLLA interference screws for graft fixation, MRI analyses shows that the integration of the bone blocks is good in 90% of the patients. Osteolysis around the screws is visible in 16% of the patients. None of the patients had a poor integration of the bone blocks in the femur or tibia.

8. In paper V no statistically significant difference was observed between the bioscrew and metal screw groups concerning C5a, TCC and IL-8 formation. We have therefore in this study not been able to demonstrate a general bioincompatibility of the materials used. However, some of the patients in the bioscrew group showed elevated values.

Papers are not included due to copyright.

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Abbreviations:

ACL	anterior cruciate ligament
AMB	anteromedial bundle
BPTB graft	bone patella tendon bone graft
C5a	complement 5a
CRP	C-reactive protein
ELISA	enzyme-linked immunosorbent assays
IL	interleukin
KT 1000 max. man.	KT 1000 maximum manual force
MCL	medial collateral ligament
MRI	magnetic resonance imaging
N	Newton
N/mm	Newtons per millimeter
OA	osteoarthrosis
LAD	Kennedy ligament augmentation device
PCL	posterior cruciate ligament
PLLA	poly-L-lactic acid
PLB	posterolateral bundle
RCT	randomized clinical trials
SPSS	Statistical Package for Social Studies
TCC	terminal complement complex

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