Different fixation methods in anterior cruciate ligament reconstruction

Extraction drilling versus compaction by serial dilation

PhD thesis

Ole Gade Sørensen

Faculty of Health Sciences
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Preface

This thesis is based on studies performed during my employment as a medical doctor and researcher at the Department of Orthopaedics, Aarhus University Hospital and the Department of Orthopaedics, Hospital Unit West during the period 2004-2009. The studies were carried out at both locations.

I am deeply indebted to a number of people who made this work possible

I would like to thank the health care personnel who attributed to the studies at Aarhus University Hospital and Hospital Unit West.

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Ole Gade Sørensen
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This thesis is based on the following papers:

I. Serial dilation versus extraction drilling in Anterior Cruciate Ligament reconstruction: a biomechanical study. Knee Surg Sports Traumatol Arthrosc. 2009 Sep 26. [Epub ahead of print]

II. The combination of radiostereometric analysis and the Telos stress Device results in poor precision for knee laxity measurements after anterior cruciate ligament reconstruction. Manuscript preparation.

III. Serial Dilation reduces Graft Slippage compared to Extraction Drilling in Anterior Cruciate Ligament Reconstruction: a Randomized Controlled Trial using Radiostereometric Analysis. Manuscript preparation.

Abbreviations

ACL: Anterior cruciate ligament

ANOVA: Analysis of variance

A-P: Anterior – posterior

BA plot: Bland-Altman plot

BMD: Bone mineral density

BPTB: Bone-patella-tendon-bone

C: Celsius

Cm: Centimetre

DFA: Distal fixation arm

Group EXDR: The extraction drilling group

Group SEDI: The serially dilated group

IKDC: International Knee Documentation Committee

Kp: Kilo pond

Mm: Millimetre

N: Newton

NSP: New standardized protocol

OFP: Original firm protocol

PFA: Proximal fixation arm

RCI: Round cannulated interference

RCT: Randomized controlled trial

RSA: Radio stereometric analysis

SA: Stress arm

SD: Standard deviation

TSD: Telos Stress Device

Contents

1. English summary

Introduction: The hamstring tendon graft has become increasingly popular in anterior cruciate ligament (ACL) reconstruction because of low donor-site morbidity. However, the tibial fixation is considered difficult, partly because of low tibial mineral bone density. Therefore, we tested whether preparation of the tibial tunnel with compaction by serial dilation provided a stronger anchorage of the graft-fixation-device complex compared with traditional extraction drilling of the tibial tunnel**.**

Prior to and during these investigations we became aware that the knee laxity measurements using the Telos Stress Device (TSD) and radio stereometric analysis (RSA) were difficult to reproduce. We therefore designed a new standardized protocol (NSP) on how to apply the TSD aimed at ensuring (1) a reliable positioning of the TSD on the patients` extremity that would result in (2) precise knee laxity measurements.

Matherials and methods

Study 1: In 20 bovine tibiae, the bone tunnels were created with either extraction drilling (group EXDR) or compaction by serial dilation (group SEDI). Twenty bovine digital extensor tendons were fixated in the bone tunnel with an Intrafix device. The graft-fixation-device complexes were mounted in a hydraulic test machine. The fixation strength was evaluated after cyclic loading.

Study 2: Part study 1: One investigator followed the official company instructions on how to apply the TSD. Another investigator followed the NSP. The TSD was applied to the knee of 30 healthy persons. Double measurements were carried out. The position of the stress arms of the TSD was marked following each measurement. The reliability of each protocol was calculated as the difference in length between the first and second markings.

Part study 2: The NSP for the TSD was then used in a clinical study. Thirty-five patients underwent ACL reconstruction. Double measurements of knee laxity by RSA were performed at a 3-month follow-up.

Study 3: Forty patients (22 males and 18 females) undergoing ACL reconstruction were randomized to either extraction drilling (group EXDR) or compaction by serial dilation (group SEDI) of the tibial tunnel. The hamstring graft was anchored with a Retrobutton® and a supplementary interference screw (Arthrex®) in the femur and a Delta interference screw (Arthrex®) in the tibia. Tantalum beads were placed in both the proximal part of the tibia and distal part of the femur. Beads were placed in the hamstring graft at the fixation sites as well. RSA was performed postoperatively and again after 6, 12, and 24 weeks. The ACL reconstructed knee was stressed with a TSD. Migration of the tantalum markers in the graft was measured in reference to the bone markers in the tibia and femur. Knee laxity was assessed at every follow-up by measuring the relation of the tibial bone markers to the femoral bone markers in both the anterior and the posterior stress positions.

Results

Study 1: The difference between group SEDI and group EXDR ranged from a mean slippage of 0 mm at 70-220 N, to a mean slippage of 0.1 mm at 70-520 N. We found no significant difference in slippage of the graft-fixation-device complex after 1600 cycles.

Study 2: Part study 1: Using the NSP for TSD positioning, the prediction interval at the marking sites ranged from ±0.4 mm - ±1.1 mm. Following the company instructions, the prediction interval ranged from ±0.8 mm - ±3.9 mm depending on marking site. Thus, the precision of positioning the stress arms of the TSD was improved at all marking sites using the NSP compared with the original company instructions. Part study 2: The double measurements of the knee laxity in the clinical study using the NSP resulted in a mean difference of 0.0 mm and a prediction interval of ±5.2 mm.

Study 3: Six patients (3 males and 3 females) were excluded during follow-up, which resulted in 17 patients in group EXDR (mean age: 32.5 years (range: 20 – 50)) and 17 patients in group SEDI (mean age: 32.0 years (range: 20 – 49)). The mean migration of the graft at the tibial fixation site after 3 months was 1.3 (SD 0.6) mm, in group EXDR and 0.8 (SD 0.5) mm in group (P = 0.02). The knee laxity after 3 months was 13.0 (SD 4.0) mm in group EXDR and 10.9 (SD 3.1) mm in group SEDI (P = 0.09).

Conclusion:

Study 1 failed to show a significant difference between group SEDI and group EXDR. In contrast in study 3 we found a significantly smaller mean migration of the hamstring graft at the tibial fixation site in group SEDI compared with group EXDR. No significant difference in stress radiographic knee laxity was found between the two groups.

Even though the NSP improved the positioning of the TSD on the patients' extremities, the combination of the TSD and RSA was not able to provide acceptable knee laxity measurements in a clinical setting compared with published results regarding other devices on the market.

2. Danish summary

Introduktion

Brugen af hamstringsener som graft ved rekonstruktion af forreste korsbånd er blevet tiltagende populært grundet få bivirkninger fra donorstedet. Det kan dog være problematisk at fiksere det nye korsbånd i skinnebenet. En af grundene til dette er den lave knogledensitet i den øvre del af skinnebenet. Når man borer knoglekanalen i skinnebenet fjerner man normalt det knoglevæv, der svarer til graftens diameter (konventionel teknik). Alternativt kan man bore op til en mindre diameter og gradvist presse den resterende del af knoglevævet ud i borekanalens væg og dermed nå den samme diameter af borekanalen men med mere knoglevæv bevaret i borekanalens periferi (seriel dilatation). Vi ville teste om seriel dilatation kunne bidrage til en stærkere fiksering af hamstringgraften i skinnebenet i forhold til den konventionelle metode.

Vi havde forinden opdaget, at det var svært at reproducere målinger af knæløsheden når man brugte en kombination af et Telos apparatur (TSD) og stereo-røntgen (RSA). Vi lavede derfor en ny standardiseret protokol (NSP) for selve påsætningen af TSD på patientens ben. Vi ønskede at undersøge (1) om en NSP kunne medføre en mere præcis påsætning af TSD på patientens ben i forhold til firmaets oprindelige protokol (OFP) og (2) om brugen af NSP ville føre til mere præcise målinger af knæløsheden ved brug af TSD og RSA.

Materialer og metoder

Studie 1: Knoglekanalen i 20 kalveskinneben blev enten tildannet med den konventionelle teknik eller ved seriel dilatation. Tyve kalvesener blev fikseret i hvert deres skinneben. Kalveknogle-senekomplekset blev herefter fastspændt i en hydraulisk test maskine. Fiksationsstyrken blev målt efter cykliske test.

Studie 2: Delstudie 1: En undersøger fulgte OFP i påsætningen af TSD. En anden undersøger fulgte NSP. TSD blev påsat 30 personer. Der blev foretaget dobbeltmålinger. Positionen af TSD`s stressarme blev markeret efter hver påsætning. Hver protokols præcision blev beregnet som forskellen i længden mellem den første og anden markering.

Delstudie 2: NSP til påsætningen af TSD blev brugt i et klinisk studie. 35 patienter fik foretaget forreste korsbåndsrekonstruktion. Præcisionen for knæløshedsmålingerne blev målt efter dobbeltmålinger ved hjælp af RSA.

Studie3: Fyrre patienter (22 mænd og 18 kvinder), som fik foretaget forreste korsbåndsrekonstruktion, blev randomiseret til udboring af knoglekanalen i skinnebenet med enten konventionel teknik eller seriel dilatation. Der blev placeret tantalumkugler i den nedre del af lårbenet og den øvre del af skinnebenet. Ligeledes blev der placeret tantalumkugler i graften svarende til fiksationsstederne. Der blev foretaget RSA efter 7-10 dage postoperativt og igen efter 6, 12 og 24 uger. Migrationen af tantalumkuglerne i hamstringgraften kunne beregnes i forhold til knoglemarkørerne i både skinneben og lårben. Løsheden af knæet kunne beregnes ved at sammenligne knoglemarkørernes position skinneben og lårben, når knæet var stresset med TSD i forreste og bagerste position.

Results:

Studie 1: Forskellen i middel migration af graften ved skinnebenfiksationen mellem den serielt dilaterede gruppe og den gruppen, hvor konventionel teknik var brugt, spændte fra 0 mm ved 70 – 220 Newton til 0.1 mm ved 70 – 520 Newton. Vi fandt ingen signifikant forskel af middel migrationen mellem de to grupper efter 1600 cycli.

Studie 2: Delstudie 1: Præcisionen ved påsætningen af TSD blev forbedret ved alle markeringspunkter, når NSP blev brugt set i forhold til OFP.

Delstudie 2: Dobbeltbestemmelserne af selve knæløsheden ved brug af NSP og RSA resulterede i en middelforskel mellem 1. og 2. måling på 0.0 mm med en præcision (prædiktionsinterval) på ±5.2 mm.

Studie 3: Seks patienter (3 mænd og 3 kvinder) blev ekskluderet i løbet af opfølgningsperioden, hvilket resulterede i 17 patienter i den serielt dilaterede gruppe (middel alder: 32.0 år (spændvidde 20 - 50)) og 17 patienter i den gruppe, hvor konventionel teknik blev brugt (middel alder: 32.5 år (spændvidde 20 - 49)). Graftens middel migration ved skinnebensfiksationen var henholdsvis 0.8 (SD 0.5) mm og 1.3 (SD 0.6) mm i de to grupper efter tre måneder (P = 0.02). Løsheden af knæet i de to

grupper efter 3 måneder måltes til henholdsvis 10.9 (SD 3.1) mm og 13.0 (SD 4.0) mm (P = 0.09).

Konklusion

I studie 1 fandt vi ikke en signifikant forskel i graftens migration mellem den serielt dilaterede gruppe og den gruppe, hvor konventionel teknik var brugt. I modsætning hertil viste studie 3, at den serielt dilaterede gruppe havde signifikant reduceret migration af graften ved fiksationen i skinnebenet efter tre måneder set i forhold til gruppen, hvor konventionel teknik var brugt. Vi fandt ingen signifikant forskel i knæløshed mellem de to grupper.

NSP var i stand til markant at forbedre præcisionen af påsætningen af TSD på patientens ben. Det var dog ikke tilstrækkeligt til at kombinationen af TSD og RSA kunne give en acceptabel præcision af knæløshedsmålingerne, når man sammenligner med de publicerede resultater af præcisionen af andre måleinstrumenter på markedet.

3. Introduction

Approximately 2500 primary anterior cruciate ligament (ACL) reconstruction are performed every year in Denmark . Today, early postoperative motion and weight bearing after anterior cruciate ligament (ACL) reconstruction are normally accepted [2,54,62,64,74]. Therefore, stress on the graft cannot be avoided, before osteo-integration of the tendons has occurred. Forces up to 450 Newtons (N) may act upon the cruciate ligament in the rehabilitation period [30,52,65]. A strong anchorage of the graft is therefore essential to avoid slippage of the graft at the fixation sites, and thereby cause increased laxity of the knee.

Previously the bone-patella-tendon-bone (BPTB) graft was very popular in cruciate ligament reconstruction, but its use has diminished, probably due to donor-site morbidity [11,45] . On the other hand, harvest of the semitendinosus- and gracilis tendons is well accepted [69,80]. Therefore the hamstringgraft has become increasingly popular in ACL reconstruction and has been shown to be equivalent to the BPTB graft [9,18,35]. In Denmark, the hamstring graft is used in approximately 70% of all ACL reconstructions [1].

A number of different fixation devices have been used to secure the hamstringgraft at the tibial fixation site. Extra-cortical devices, such as washers, have provided a high fixation strength [7], but problems with bungee-cord effect and wind shield-wiper effect have been seen[34,68,76]. This resulted in the use of fixation devices with a juxta-articular fixation, such as interference screws. In addition Ishisbashi et al. [33] showed increased knee stability after use of joint-near fixation devices compared with extra cortical devices. Weiler et al. [77] also showed, that direct fixation of the graft in the bone tunnel, as provided by an interference screw, will minimize the micromotion of the graft in bone tunnel and probably enhance a direct tendon-to-bone healing.

Especially the tibial fixation of the semitendinosus-gracilis graft is considered problematic, partly because of the bone mineral density of the tibia is less than in the femur resulting in potentially insufficient stability of fixation implants placed in the tibial tunnel. [8]

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Compaction of the bone tunnel by serial dilation

A tunnel preparation technique that compacts the periphery of the tibia tunnel by serial dilation could provide a stronger anchorage of the graft than does traditional extraction drilling of the tibia tunnel.

The use of compaction by serial dilation in ACL reconstruction is inherited mainly from the research on hip implants. Green et al. [25] used a canine model to show that compaction could improve early fixation stiffness and strength of porous-coated implants. Histological examinations showed that compaction resulted in increased bone density at the implant surface. Kold et al. [48-50] were able to show the same benefits of compaction for implants with other surfaces. Because compaction by serial dilation tends to preserve cancellous bone material instead of removing it, as seen in conventional drilling, they suggested that the improvement of the early fixation strength is a result of both larger bone volume in the proximity of the implant and compressive forces of the compacted bone also known as the "spring-back effect" [47]. Both results minimize the gap between bone and implant surface and produce an increase in bone-implant friction.

To our knowledge, Johnson et al. [36] were the first to report the use of serial dilators. They tested the difference in fixation strength between metal interference screws and bioabsorbable interference screws in ACL reconstruction. They compacted the femoral bone tunnel by serial dilation, but did not speculate on whether the compaction could enhance the fixation strength.

Cain et al. [10] followed with a study using human cadaveric knee specimens. The tibial tunnel was serially dilated, and the graft was anchored in both tibial and femoral specimens. This entire construct was secured in a test machine that was able

to load the construct with a translatoric force. Ultimate failure load was recorded. With seven specimens in each group, Cain et al. [10] were able to show a significant difference in favour of the serial dilated group compared with the extraction drilled group.

Rittmeister et al. [63] also used a human cadaveric model. Cyclical loading tests were performed. The force applied to the graft was increased after each cycle. Loads at different permanent displacements of the grafts were recorded. A comparison between serial tunnel dilation and extraction drilling was carried out in 14 pairs of specimens (half secured with a 7 millimetre (mm) RCI screw, and half secured with a 9 mm RCI screw). The results were pooled. The serial dilated group showed higher loads at all permanent displacements, but the differences were not significant.

Nurmi et al. [56] were not able to show any positive effect of compaction by serial dilation compared with extraction drilling. In a human cadaveric set-up, 21 pairs of tibia were submitted to cyclical loading. Displacement of the graft was measured after various numbers of cycles and a single-cycle load-to-failure test was finally performed.

When we started our own studies, only findings [10,56,63] regarding serial dilation of the tibial tunnel in ACL reconstruction using hamstring grafts had been published. Dunkin et al. [17] illuminated the issue further. Their results are in line with the study of Nurmi et al. Dunkin used a porcine model. Twenty specimens underwent either serial dilation or extraction drilling. The bone volume in the periphery of the bone tunnel was measured. The serially dilated group showed significantly higher bone volumes compared with the non-dilated group, but no difference in initial fixation strength could be detected. Instead, they found a correlation between decrease in fixation strength and screw divergence.

Recently Gokce et al. [24] reported a clinical retrospective study. They investigated the influence of compaction by serial dilation on tunnel widening. In total, 44 patients were enrolled (21 in the intervention group and 23 in the control group).

Tibial tunnel enlargement was found to be significantly higher in the control group compared with the intervention group, indicating that serial dilation of the tibial tunnel could protect against tunnel widening. No significant difference in postoperative Lysholm Scores and IKDC-scores was found.

Dargel et al. [15] investigated the use of serial dilators at the femoral fixation site when a BPTB graft was used. In a porcine setup they compared three ways of preparing the femoral bone canal; (1) extraction drilling to 9 mm, (2) extraction drilling to 8 mm followed by serial dilation to 9 mm, and (3) extraction drilling to 6.5 mm followed by serial dilation to 9 mm. Surprisingly they found, that group 2 had significantly increased initial fixation strength compared with both groups 1 and 3. The springback effect was largest in group 3.

Finally, studies on compaction of the bone tunnel by stepped routers (not serial dilators) have been published [55,57]. No effect on initial fixation strength was found.

In summery, the conclusions of the studies regarding fixation strength after serial dilation of the bone tunnel in reconstruction of the ACL are contradictive, and no consensus has yet been reached. Apart from Gokce et al. [24] all studies are biomechanical studies and carried out with fresh-frozen materials. This means that it is possible to reflect on the differences in initial fixation strength, but impossible to conclude anything about long-term results of serial dilation. Keeping in mind that proper osseointegration of the hamstring graft probably has not occurred before 6 – 12 weeks after surgery, in-vivo studies are necessary to illuminate potential benefits of serial dilation in ACL reconstruction.

Knee laxity measurements

Anterior-posterior knee laxity measurements have traditionally been used to diagnose cruciate ligament rupture, and to evaluate the outcome after cruciate ligament reconstruction. In the search for an accurate and precise method, several different devices have been used.

The KT-1000 arthrometer (MEDmetric corp. San Diego, CA, USA) [13,14,51] is probably the most widely used device [3,28,29,61,72,73,79] for non-invasive knee laxity measurements. Varying results have been reported regarding the precision of the device. Steiner et al. [72] found a precision of approximately 4.2 mm (± 2 standard deviations (SD) of the mean between the first and second measurements), whereas Torzilli et al. [73] reported the precision to be approximately 2 mm. Another device for non-invasive knee laxity measurements is the Rolimeter knee-tester (Aircast Europa, Neubeuern, Germany), which has been used in several studies [4,23,27,53,59]. The reliability of the device is found to be comparable to the KT-1000 arthrometer [4,23]. The combination of a stress device and radiography (stress radiography) is another established knee laxity measurement technique. The use of the Telos Stress Device (TSD) in stress radiography is regarded by many to be the gold standard for evaluation of posterior cruciate insufficiency [42,66,71]. The intratester and intertester reliability is reported by Staubli [70]. They used one set of radiographs on each patient. To our knowledge, the precision of stress radiography in combination with the TSD following double measurements has not been reported.

Radio stereometric analysis (RSA)

RSA was originally developed by Selvik et al. [67]. Because of its high accuracy of 1 mm, RSA has mainly been used to determine the migration of arthroplasty components over time in relation to bone. RSA is an invasive method that relies on implantation of tantalum beads. The calculation of the migration is based on a set of radiographs, with the patient in relation to a calibration box. The calibration box and computer software convert the 2-dimensional radiographs into a 3-dimensional coordinate system. A set of radiographs is defined as reference, and the relation of two rigid bodies can then be calculated at each follow-up. Because of the high accuracy, RSA should have the potential to provide a precise measure of the knee laxity.

RSA and knee laxity measurements

Several studies have used the RSA in combination with a stress device [21,22,31,32,37-41,43]. Kærholm et al. [44] and Friden et al. [21] used custom-made

stress devices and reported precisions (±2 SD) of 1.6 mm and 2.2 mm, respectively. Fleming et al. [19,20] also used a custom-made pneumatic load device in combination with RSA. They tested the accuracy and repeatability in five goat knees [20], and found a good repeatability after repeated measurements. They later published a clinical study, in which they compared the knee laxity obtained by RSA, planar stress radiography, and the KT-1000 arthrometer in 15 patients. No precision after double measurements was reported in the clinical study [19]. Khan et al. [46] used TSD and RSA in six patients. They found a precision (±2 SD) of 1.9 mm. They used the original firm protocol on how to apply the TSD on the extremity of the patient. Our hypothesis was that this protocol could be improved, which potentially could result in a higher precision in knee laxity measurements.

4. Aim of the thesis

The overall aim in this thesis was to compare the fixation strength and thus the migration of the hamstring graft at the tibial fixation site after conventional extraction drilling or compaction by serial dilation of the tibial tunnel after ACL reconstruction. Prior to and during these investigations we became aware that knee laxity measurements using the TSD and RSA were difficult to reproduce. This led to further methodological considerations regarding the usefulness of the TSD combined with RSA (study II).

The individual studies in this thesis had the following aims:

Study I

To compare the initial fixation strength between extraction drilling and serial dilation of the tibial bone tunnel after cyclic loading of the hamstring graft.

Study II

Part study 1: whether a new standardized protocol would lead to a more precise positioning of the Telos Stress Device compared with the original firm protocol.

Part study 2: whether a more precise positioning of the stress arms of the Telos Stress Device would result in more precise A-P knee laxity results in a clinical study using radio stereometric analysis (part study 2).

Study III

To evaluate whether compaction by serial dilation of the tibial bone tunnel compared with extraction drilling could reduce the migration of the hamstring graft at the tibial fixation site,

5. Design

Study I

Prospective paired biomechanical randomized study using a bovine set-up.

Study II

Part study 1 and part study 2: Both part studies were performed as reliability (precision) studies after double measurements.

Study III

Prospective, randomized clinical trial using radio stereometric analysis.

6. Materials & methods

Ethical issues

Study I

The calf tibiae were obtained from a local slaughterhouse. There were no ethical considerations in this project.

Study II

In the first part of this study, we examined the precision of the application of the TSD on the patients` lower extremities. Only healthy individuals participated. No approval from the local ethics committee was needed.

The second part of the study examined the precision of knee laxity measurements. The data were retrieved from study III. For ethical considerations, please see below.

Study III

The study was approved by the Regional Committee of Biomedical Research Ethics (record number 20060158). Informed and written consent were obtained from all patients. The ethical standards of the Regional Committee of Biomedical Research Ethics were in accordance with the Helsinki Declaration of 1995. The study was registered with the Danish Data Protection Agency (record number 2006 – 41 – 7247).

Materials/patients and intervention

Study I

Ten pairs of bovine tibiae and 20 bovine digital extensor tendons were used. The bovine tendons are shown to have similar properties compared with human hamstring grafts [16] . The calves were aged 34 weeks ± 2 weeks. The fresh tibiae and tendons were stripped of soft tissue and fresh frozen at -20˚ C in sealed plastic bags. Before freezing, the diameter of the tendons was measured with a graft sizer with increments of 0.5 mm, and only tendons with a diameter of 10 mm were accepted. Twelve hours before use, the tibiae and tendons were defrosted at room temperature. This type of preservation does not affect the properties of the material[60]

Fig. 1: Two methods used to create the tibial bone tunnel. Left, 10 mm cannulated drill for extraction drilling; right, serial dilators (8-10 mm)(Smith &Nephew) with 0.5 mm increments.

A paired design was used. For each pair, one tibia was prepared with serial drilling and the other was prepared with extraction drilling. The tip of an ACL tibial drill guide was placed at the ACL footprint at the centre of the tibial plateau. Guide angle and length were set to 45˚ and 50 mm, respectively, and a guide wire was passed along, following the drill guide. In group 1, conventional extraction drilling was

performed, leaving a drill hole with a diameter of 10 mm. In group 2, both the intra-articular cortex and the antero-medial cortex were pre-drilled to 10 mm because of the thickness of the bovine cortex. Then a bone tunnel of 8 mm in diameter was created using extraction drilling. Subsequently, the tunnel diameter was compacted by stepwise serial dilation ending up with a tunnel diameter of 10 mm (Fig. 1).

The tendons were split in half in a natural cleavage. The tendons were then folded at the middle leaving a quadrupled graft. Each strand was marked, resulting in a looped intra-articular portion of 3 centimetres (cm) and a tibial portion of at least 5 cm. A running baseball suture (Ethibond Excel 2-0® Jonhson & Johnson, Langhorne, PA, USA) was applied to each leg at the tibial portion of the graft.

The tibia was then secured in a custom made fixation device on a MTS servo-hydraulic test machine (MTS Systems Corp, Eden Prairie, MN, USA) (Fig. 2). During fixation of the graft, the tibia was turned so that the anteromedial opening faced the surgeon. The prepared graft was pulled through the bone tunnel, and a 3 cm broad ruler was temporary placed in the loop, making sure that the length of the looped end was the same in all specimens. The sutures were tied together two and two and passed around an ACL Tie Tensioner (DePuy Mitek, Raynham, MA, USA). The graft was secured with a 9-11 mm Intrafix tibial fastener (DePuy Mitek). This fixation device is used in other comparative biomechanical studies, for example [12], and is shown to provide a strong fixation of the hamstring graft. During fixation of the graft, we used full tension (15.9 kg (approximately 156 N)) on the ACL Tie Tensioner (DePuy Mitek), in order to achieve the same tension in the graft during graft fixation.

Subsequently we turned the tibia-graft complex 180 degrees. A crossbar (diameter 9 mm) was passed through the looped end, mimicking the femoral fixation. The bone tunnel was aligned parallel to the loading axis in a “worst case scenario” setup (Fig. 2).

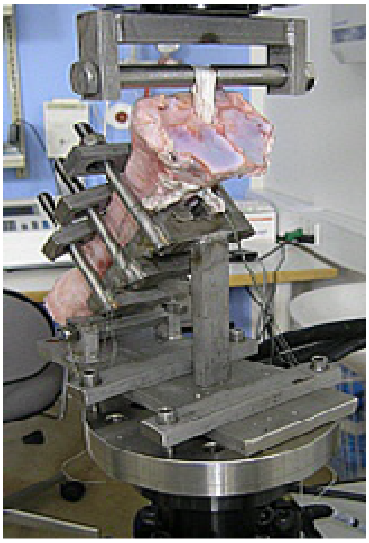

Fig. 2: Tibia-graft complex mounted in the servo-hydraulic MTS test machine.

Loading procedure

The pretension was set to 70 N [5]. The graft was cyclic preconditioned 10 times between 70 N and 120 N. Thousand cyclic loads of 70 N – 220 N were then applied at a cross-head speed of 80 cycles per minute. The load was then increased 50 N following every 100 cycles, ending with loads between 70 N and 520 N. This load protocol should reflect the forces on the ACL during walking and jogging [30,65]. Cross-bar position was recorded at the first peak load. Displacement of the graft was then measured as the displacement of the cross-bar at peak load immediately before every load increase.

Study II

Part study 1: The precision of the new standardized protocol compared with the original firm protocol for TSD positioning

The original firm protocol (OFP)

The guidelines of the OFP are as follows. For anterior stress of the tibia: (1) Positioning of the patient as shown in Fig. 3. Knee flexion angle of 10˚- 20˚, slight turning-out rotation of the lower leg through "stable lateral position". (2) The pressure device should lie approximately 7 cm below the hollow of the knee, reading of the pressure device: 15 kp. With freshly injured muscular athlete: possibly 20 kp.

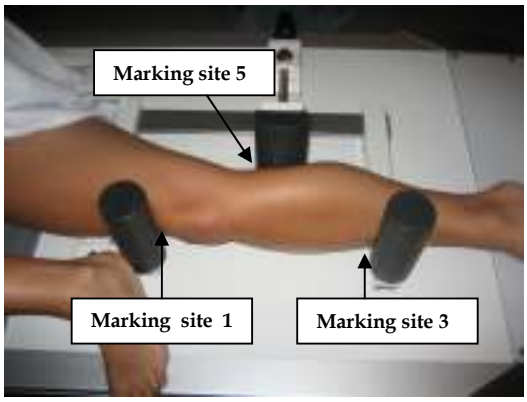

Fig 3: Anterior stress of the tibia using the TSD.

Fig 4: Posterior stress of the tibia using the TSD.

For posterior stress of the tibia: (4) Positioning of the patient as shown in Fig. 4, knee flexion angle of 10˚- 20˚. (5) The pressure device should be placed at the tuberositas tibia level. (6) Reading of the pressure device: 15 kp.

The new standardized protocol (NSP)

The TSD is assembled as shown in Fig. 5 (please note that the extension arm is not used). As seen, the TSD has a proximal fixation arm (PFA), a stress arm (SA), and a distal fixation arm (DFA).

Fig 5: The TSD, when assembled.

(1) The patient is placed in a supine position. (2) A cushion is placed under the knee. The cushion is replaced until the flexion angle of the knee is 20˚ measured with a goniometer. (3) The proximal part of the patella is marked with a transverse line. (4) Another mark is made two cm proximally and parallel to the first line. This second

mark (marking site 1) represents the position of PFA during anterior stress of the tibia. Care was taken to gently support the distal part of the patella during marking to avoid displacement of the patella (Fig 6).

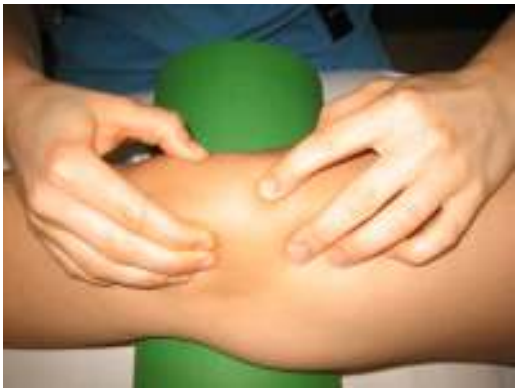

Fig 6: The patella is supported before marking to avoid displacement.

5) The proximal part of the tuberositas tibiae is palpated and marked (Fig. 7). This line represents the position of the SA during posterior stress of the tibia.

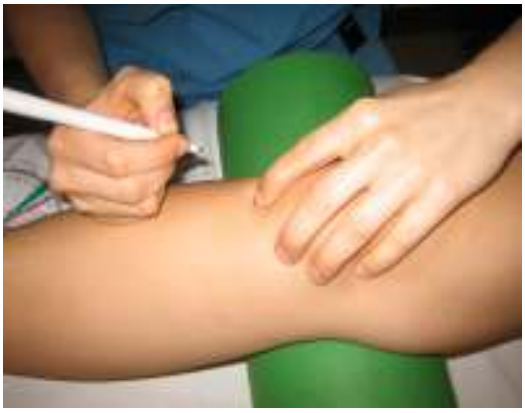

Fig 7: Palpation and marking of the tibial tuberosity.

(6) The patient is placed in an upright position with 15 cm between the medial parts of both heels. (7) The distance between marking site 1 and the floor is measured with a ruler and 2 cm are added. (8) The same distance from the floor is measured on the posterior side of the extremity and another marking line (marking site 4) is drawn. This marking represents the position of the PFA during posterior stress of the tibia. Adding 2 cm is necessary to prevent the metal in the PFA from shadowing the femoral tantalum beads during RSA. (9) The distance between marking site 2 and the floor is measured, and the same distance is marked on the posterior side of the lower leg. This marking (marking site 5) represents the position of the SA during anterior

stress of the tibia. (10) The distance between marking site 2 and the floor is multiplied by 0.70. Using this distance a transverse line is drawn on the anterior (marking site 3) and posterior (marking site 6) aspect of the lower limb (Fig 8). Marking site 3 represents the position of the DFA during anterior stress of the tibia and marking site 6 represents the position of the DFA during posterior stress of the tibia.

Fig. 8: Marking of the distal marking site on the posterior aspect of the tibia.

(11) The patient is placed in lateral position. When anterior stress is needed, the TSD is applied using the marking sites, as described above (Fig 3). The tibia is cycled 3 times with a force between 0 – 15 kp before a force of 15 kp is maintained. (12) When posterior stress is needed, the TSD is turned around (Fig. 4). The tibia is cycled 3 times with a force between 0 – 10 kp before a force of 10 kp is maintained.

Precision of the protocols

In the scientific literature reliability, precision, and reproducibility are used in different contexts. In this study, we use the term precision defined as the prediction interval (±1.96 SD) of mean difference between the first and second measurements [6].

The study took place at the Department of Orthopaedics, Hospital Unit West, Denmark from September 2006 to January 2007. One investigator used the OFP on how to apply the TSD and another investigator used the NSP. Thirty healthy individuals were included. For each investigator we defined a learning period of 30 measurements, which was followed by a test period on the same 30 individuals.

After application of the TSD, the positions of the stress arms were marked perpendicularly to the leg. To avoid mixing of the marking sites, the final marking was performed on the other side of the stress arm in relation to the marking site used for placement of the stress arms. The final markings were labelled (marking sites A-F) and were the making sites used for analysis. Double examinations were carried out during both the learning period and the test period. A pen visible only in UV light was used as a marker at the first measurement, which left the second marking unbiased by the first. The first and second measurements were separated by a break which allowed the patient to walk around in the examination room. The length in millimeters between the first and second marks at each stress position was measured. Due to practical reasons the anterior stress tests (marking site A,E,C) were performed by two investigators on 30 persons, and the posterior stress tests (marking site D,B,F) were carried out by two other investigators on 30 persons. The investigators had the same qualifications, and they had not used the TSD prior to this study.

Part study 2: Precision of the knee laxity measurements in a clinical RSA study using the NSP in the application of the TSD.

The data are retrieved from the double measurements performed at the third follow-up in study III. The patient characteristics, insertion of the bony tantalum markers, the RSA setup, and the knee laxity calculations are given below (study III)

Study III

The study was carried out at the Institute of Sportstraumatology, Department of Orthopaedics, University Hospital of Aarhus, Denmark, and Institute of Sportstraumatology, Department of Orthopaedics, Hospital Unit West, Denmark. From March 2007 to April 2009, 40 patients with an ACL deficient knee were enrolled. All patients were between 18 and 50 years of age. Patients were operated with singlebundle hamstring graft ACL reconstruction. Patients with multiligament injuries and patients with repairable meniscal lesion, which would alter the degree of mobilization postoperatively, were excluded. Pregnancy discovered before surgery and in the follow-up period was an exclusion criterion as well. Because of the serial

dilation process, hamstring grafts with a diameter of 7 mm or less after graft preparation were excluded.

The hamstring graft was harvested through an oblique incision at the pes anserinus. The semitendinosus and gracilis tendons were folded, resulting in a four-stranded graft. With a pen the graft was divided into three portions. The femoral region measured 2.5 cm, the intraarticular region measured 3 cm, and the tibial region measured 3.5 cm (Fig 9).

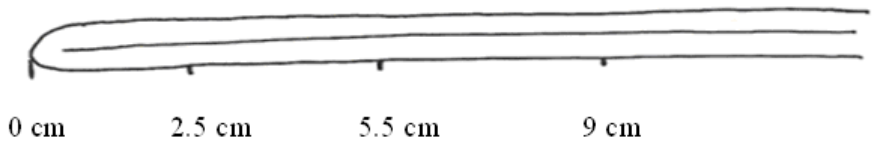

Fig. 9: Looped semitendinosus tendon divided into three regions: femoral region (0-2.5 cm), intra-articular region (2.5-5.5 cm,) and tibial region (5.5-9 cm).

A running baseball suture (Ethibond Excel 2-0® Jonhson & Johnson, Langhorne, PA, USA) was applied to each strand at the tibial portion of the graft. The diameter of the graft was measured with a graft sizer (Smith & Nephew, Andover, MA, USA).

At this point during surgery, the 40 patients were randomized to either extraction drilling (group EXDR) or compaction by serial dilation (group SEDI) of the tibial tunnel, leaving 20 patients in both groups. The randomization was performed by a nurse who was not otherwise involved in the study. Non-transparent envelopes were used. We stratified on gender by drawing a red envelope for female patients and a blue envelope for male patients.

Ligament remnants from the torn ACL were removed, and a notch plasty was performed if necessary. A tibial guide was used to place a 2.4-mm guide wire at the anterior half of the footprint of the native ACL. In group EXDR, conventional extraction drilling of the tibial tunnel was performed, leaving a drill hole with the same diameter as the graft. In group SEDI, the antero-medial cortex was predrilled to

graft diameter to prevent cortical fracture. Then a bone tunnel 2 mm smaller than the graft diameter was created by using extraction drilling. Subsequently, the tibial tunnel was compacted by stepwise serial dilation (Smith & Nephew, Andover, MA, USA) (Fig 1) producing a tunnel diameter the same size as the graft diameter.

With 90 degrees flexion of the knee and use of a femur guide, the femoral tunnel was drilled. To ensure an anatomical placement at the femoral footprint, it was optional for the surgeon to drill the femoral canal from either the antero-medial portal or through the tibial tunnel. If the tibial bone canal was used, the femoral drill was advanced through the tibial tunnel without drilling, in order not to enlarge the tibial tunnel or remove compacted bony material. A Retrobutton (Arthrex, Naples, FL, USA) was used as fixation in the femur supplemented with a 23-mm interference screw (Arthrex, Naples, FL, USA) (same diameter as the graft), to obtain a joint-near fixation. In the tibia, the graft was secured with a 35-mm Delta interference screw (Arthrex, Naples, FL, USA) with a diameter of +1 mm compared with the graft diameter. The tibial graft was fixated with a knee flexion of approximately 10 degrees and equal tension of all four graft ends.

All ACL reconstructions were performed by senior surgeons, specialized in sportstraumatology. All patients were discharged on the day of surgery. Weight bearing using crutches was allowed from day 1. A rehabilitation program was planned for every patient and physiotherapy started approximately 14 days after surgery.

Insertion of tantalum markers

In the graft, all the tantalum markers were placed in the semitendinosus tendon. In total, four beads were placed in the tibial portion of the distal part of the tendon, and three beads were placed in the femoral part of the tendon. For marker insertion, we used a spinal needle of 1.3 x 88 mm (Braun, Melsungen, Germany). The spinal needle was introduced into the tendon and advanced approximately 1 cm (Fig 10).

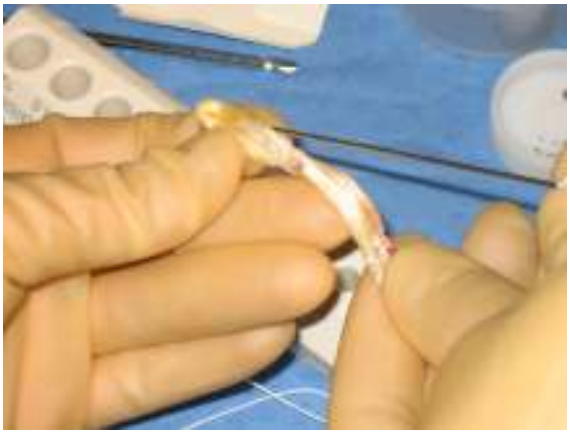

Fig 10: The spinal needle is introduced into the semitendinosus tendon.

The stent of the needle was then removed, and a 0.8-mm tantalum bead was introduced into the lumen of the needle. The stent was then reinserted and the spinal needle removed. This procedure was copied for every graft marker insertion. Because of the tapered shape of the Delta screw, we attended not to place tantalum markers within 1 cm of the joint in the tibial region of the graft in order not to place markers in non-fixated graft material.

Five tantalum markers (1.0 mm) were placed in both the femur and the tibia (three markers in medial femoral condyle, two markers in the lateral femoral condyle, three markers in the lateral tibial condyle, and two markers in the medial tibial condyle). With each condyle, the first marker was placed approximately 2 cm from the joint line and the second marker was placed a further 1.5 cm away from the joint. In the medial femoral condyle and lateral tibial condyle, we added another marker 1.5 cm behind the first marker at the same distance from the joint. The aim of this protocol was to provide an even distribution of markers in all patients. All bony markers were introduced with a 1.0-tantalum bead-insertion instrument, called a kulkanon (Wennbergs Finmek, Gunnilse, Sweden) (Fig 11).

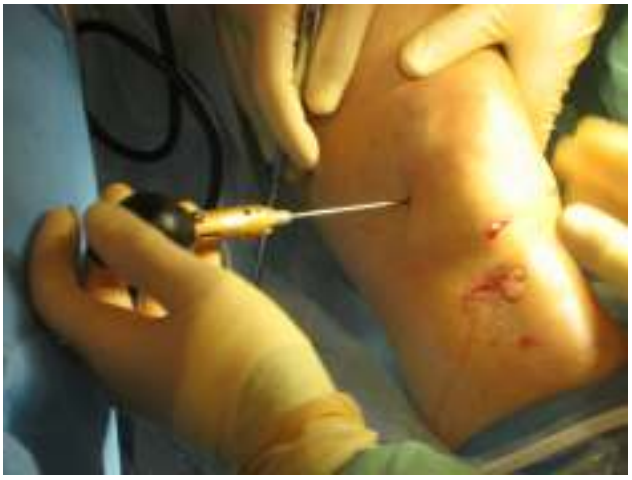

Fig 11: Insertion of 1.0- mm tantalum marker in the medial femoral condyle using a kulkanon.

The beads in the medial tibial condyle could be inserted through the oblique incision. With the three remaining condyles, 2-mm stab skin incisions were used.

RSA setup

The RSA setup described by Khan et al. [46] was used for all examinations. The patient was placed in lateral position. The TSD was applied following our own standardized protocol. The tibia of the patient was aligned in the proximal-distal direction. Beneath the patient, a calibration box (large calibration box, Medis, Leiden, the Netherlands) with two radiographic plates (uniplanar technique) was placed. Two synchronized ceiling-fixed roentgen tubes (Arco-Ceil/Medira; Santax Medico, Odense, Denmark) were used, resulting in two crossing beams of 40 degrees (Fig 12). The exposure was set to 90 kV and 10 mAs. An anterior stress of 15 kiloponds (kp) (approximately 150 N) and a posterior stress of 10 kp (approximately 100 N) were applied by use of the TSD. A set of images was taken at both anterior and posterior stress positions of the tibia. All stereo images were fully digitized (FCR Profect CS; Fujifilm (Aarhus University Hospital), and AGFA CR75.0; Agfafilm (Hospital Unit West)).

Fig. 12: RSA setup.

Analysis of all stereo images was performed twice by two different observers with the software Model Based RSA version 3.02 (Medis, Leiden, the Netherlands). A discrepancy of the results led to a third analysis performed by the two observers working together, and an outcome was agreed upon. The upper limit for mean error body fitting (stable markers used for migration analysis) was 0.5 mm.

RSA was performed 7-10 days following the ACL reconstruction and again 6, 12, and 24 weeks postoperatively. At the third follow-up, double examinations were performed in order to calculate the precision of the setup. The mean condition number (dispersion of the bone markers in the tibia) was 33.3 (SD 9.2, range 17.4 – 59.6)

Each tibial and femoral graft marker was labelled independently. The 3-dimensional position of each graft marker in relation to the bony markers in the tibia and femur (marked with red circles in Fig. 13), could be assessed at each follow-up. Only RSA images in the anterior stress position were used for migration calculations. We used the first follow-up (7-10 days) as reference and calculated the 3-dimensional x, y, z

migration values of each graft marker at 6, 12, and 24 weeks. The total migration of the graft at each follow-up was then calculated using the formula:

$$\text{Total migration} = (x^2 + y^2 + z^2)^{0.5}$$

The graft marker with the largest migration in the tibia and femur was used for analysis at each follow-up, resulting in a worst case scenario. Only tibial markers migrating with a positive y-value and femoral markers migrating with a negative y-value were considered for analysis. In the tibia, only markers inside the tibial tunnel were used for analysis.

The knee laxity at each follow-up was calculated as the 3-dimensional movement of the tibial bone markers (red circles in the tibia in Fig. 13) in relation to femoral bone markers (red circles in the femur in Fig 13) from the posterior stress position to the anterior stress position of the knee. The total knee laxity at each follow-up was calculated according to the formula:

$$\text{Total knee laxity} = (x^2 + y^2 + z^2)^{0.5}$$

The difference in knee laxity (Δ knee laxity) from the first follow-up (reference) to 6, 12 and 24 weeks was calculated as well.

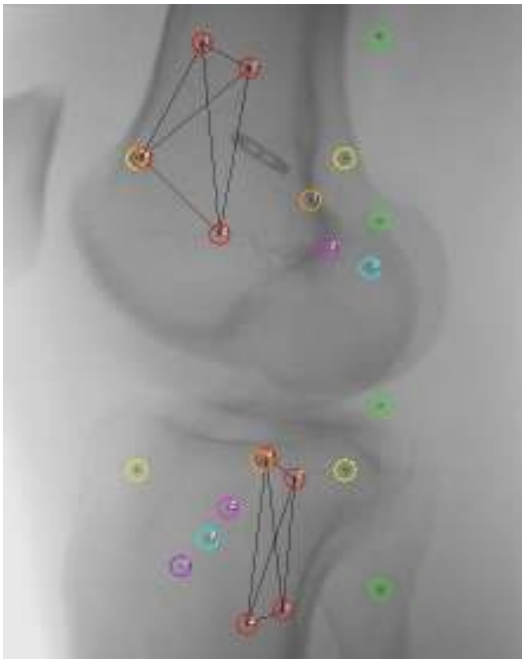

Fig. 13: Example of the marker distribution after RSA. Red circles represent the bony markers in the tibia and femur. The tibial graft markers are labelled independently (orange, pink, light blue, and purple circles (1 -4)). The femoral graft markers are labelled independently as well (orange, pink, and light blue circles (1 – 3)). The green (control markers) and yellow (fiducial markers) markers are incorporated into the calibration box beneath the patient.

Outcomes

Study I

Endpoint was graft displacement at different numbers of cycles and loads.

Study II

Part study 1: Endpoint was precision at each marking site after application of the TSD using the NSP and the OFP.

Part study 2: Endpoint was precision of the knee laxity measurements at the third follow-up (study III) using the TSD and RSA.

Study III

The migration (slippage) of the graft in the tibial tunnel was the primary endpoint of this study. In preparation of the study, a difference of 1 mm between the extraction

drilling group and the serial dilated group was decided to have clinical importance. Khan et al. [46] found a SD of the slippage to be approximately 1 mm. Using a power of 0.80 and defining *P* value <0.05, we needed approximately 17 patients in each group (Stata 9.0, StataCorp LP, Texas, USA). Therefore 20 patients were randomized to each group. Laxity of the knee and slippage of the graft in the femoral tunnel were regarded as secondary endpoints

Statistical analysis

Study I

All analyses were performed using Stata 9.0 (StataCorp LP, Texas, USA). Difference in displacement of the graft was analyzed with repeated-measures analysis of variance (ANOVA). We also compared the displacement at each load with a Student *t-test* to investigate the development of displacement as a function of time and higher load cycles. Finally, we analyzed difference in standard deviation between group 1 and group 2 by using Pitmann´s test of variance. *P* values <0.05 were considered significant.

Study II

Part study 1: The mean distance and prediction interval were calculated at each marking site at the final positions of the position bars and stress bar. Prior to the study, we defined a prediction interval smaller than ±10 mm as acceptable.

Part study 2: The mean difference and prediction interval of both the knee laxity and the X, Y, Z rotation of the distal femur in relation to the tibia between the first and second measurements were calculated. The knee laxity results were visualized in a Bland-Altman plot. Given the already reported precision by Khan et al. [46] and Fleming et al. [20], we defined a prediction interval of ±1.5 mm to be acceptable prior to the study.

Study III

All analyses were performed using Stata 9.0 (StataCorp LP, Texas, USA). The significance level was set at $P < 0.05$. All data were tested for normal distribution using tests for skewness and curtosis. A Student´s *t-test* was used for normally distributed data, and a non-parametric test (Mann-Whitney) was used for non-normally distributed data. Migration of the graft inside the tibial tunnel at 12 weeks was adjusted for age, gender, and hospital, with use of an ordinal least square regression analysis.

7. Results

Patient characteristics

Study II

Part study 1: In total 60 persons were included in the study. Thirty persons (21 females, 9 males) were allocated to the anterior stress test (mean age 25 (SD 2.7, range 20 - 31)) and another 30 (14 females, 16 males) persons were allocated to the posterior stress test (mean age 24 (SD 2.5, range 20 -29)).

Part study 2: Forty patients were enrolled. In total 5 persons (2 females, 3 males) were excluded during follow-up, which left 35 persons (16 females, 19 males) (mean age 32 years) for double measurements of the knee laxity (SD 8.6 (range 20 – 50).

Study III

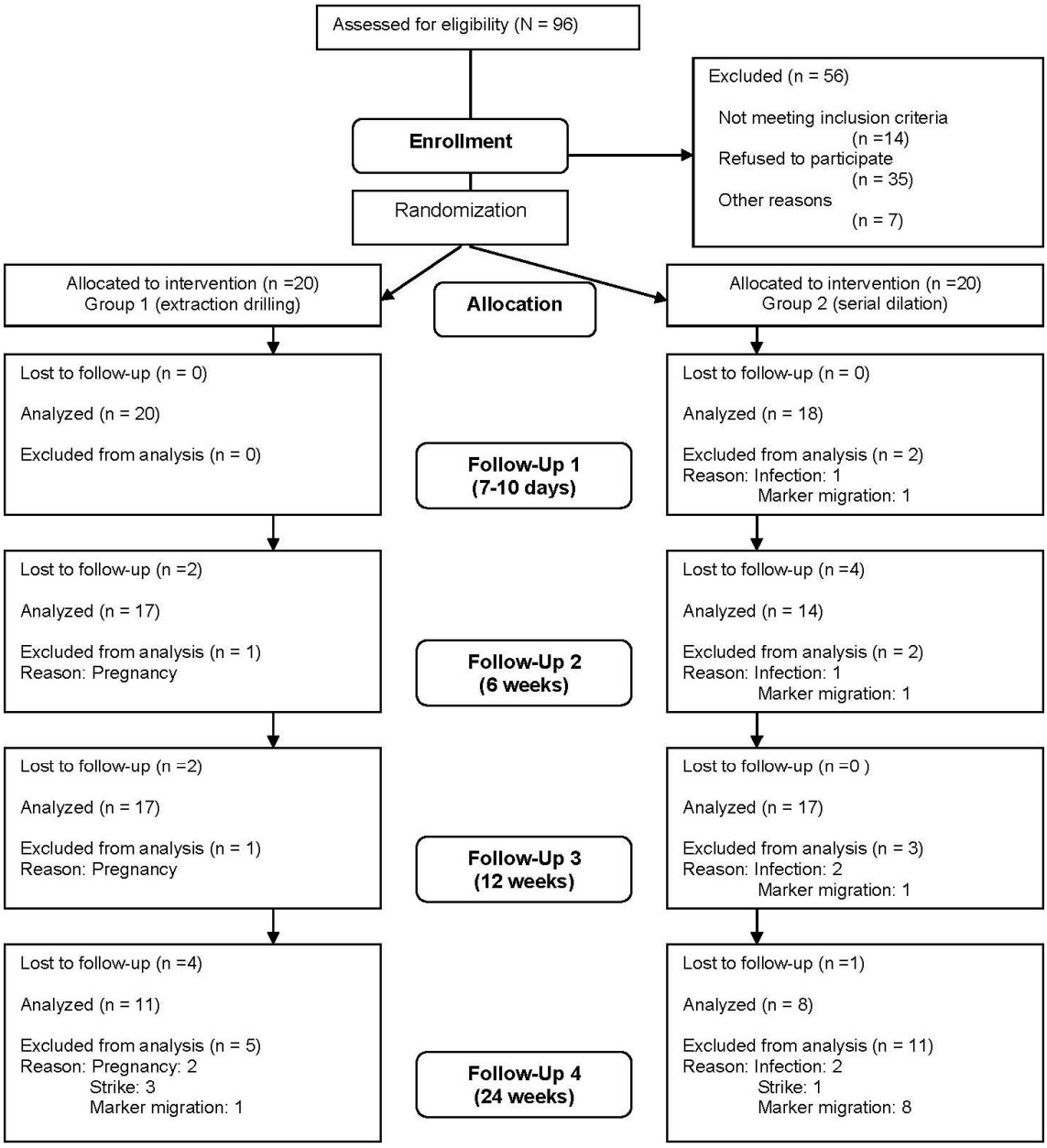

Fig. 14: Flow diagram of the patients in study III

There was no significant difference in age (P = 0.53) or gender (P = 0.40) between the patients allocated for randomization and the group of nonconsenters. There was no significant difference in gender (P = 0.28) or age (P = 0.06) between the patients allocated for randomization and the group excluded on criteria. Even though a significant P value was not reached, the group excluded on criteria tended to be younger compared with the patients allocated for randomization. This can probably be explained by the fact, that mainly younger patients with repairable meniscal injuries were excluded.

Double measurements were performed at the third follow-up. The precision of the migration measurements (defined as the prediction interval (± 1.96 SD) of mean difference between the 1st and 2nd measurement) was found to be 0.16 mm. The precision of the knee laxity measurements was 5.2 mm.

Table 1. Patient characteristics at baseline for 40 patients in two randomization groups

Group	Extraction drilling	Serial dilation
ACL reconstructions (n)	20	20
Female / male	9 / 11	9 / 11
Age, mean (SD), range	32.5 (9.43), 20 – 50	32.0 (8.13), 20 – 47
Surgery performed in University Hospital of Aarhus/ Hospital Unit West	16/4	15/5
Time from injury to surgery (SD) (months)	60.1 (97.5)	44.5 (80.1)
Time of 1st follow-up, mean (SD) (days)	8.8 (1.0)	8.6 (1.2)
Patients used for analysis at 1st follow-up (n)	20	18
Time of 2nd follow-up, mean (SD) (weeks)	6.17 (0.2)	6.1 (0.3)
Patients used for analysis at 2nd follow-up (n)	17	14
Time of 3rd follow-up, mean (SD) (weeks)	12.1 (0.4)	12.2 (0.5)
Patients used for analysis at 3rd follow-up (n)	17	17
Time of 4th follow-up, mean (SD) (weeks)	24.3 (0.5)	24.2 (0.5)
Patients used for analysis at 4th follow-up (n)	11	8
Meniscal injury (n)	5	7
Cartilage lesion >1 cm^2 (n)	3	0

(SD): standard deviation, (n): Number

Results

Study I

None of the specimens failed during the cyclic loading tests. Repeated-measures analysis of variance did not show a significant difference between the two groups. We compared the displacement in the two groups at each load (see table 2). No

statistically significant difference between the extraction drilling group and the serial dilation group was found.

Table 2: Displacement of the graft in millimetre (mm) as a result of increasing load and number of cycles

Number of cycles/load*	Extraction drilling	Serial dilation		
	Mean (SD)	Mean (SD)	P-value**	P-value***
1000/70-220 N	0.6 (0.2)	0.6 (0.1)	0.90	0.09
1100/70-270 N	0.7 (0.3)	0.7 (0.1)	0.83	0.09
1200/70-320 N	0.9 (0.3)	0.9 (0.2)	0.77	0.10
1300/70-370 N	1.0 (0.4)	1.0 (0.2)	0.70	0.12
1400/70-420 N	1.2 (0.4)	1.2 (0.2)	0.64	0.12
1500/70-470 N	1.4 (0.5)	1.3 (0.3)	0.58	0.12
1600/70-520 N	1.6 (0.6)	1.5 (0.3)	0.54	0.10

Load is given in Newton (N). ** marked P values describe the differences between extraction drilling and compaction by serial dilation (Student´s t-test). Standard deviations (SD) are shown in brackets. *** marked P values describe the differences in standard deviation between the two groups (Pittman´s test).

Study II

Part study 1

The prediction intervals ranged from ±0.4 mm to ±4.0 mm of the mean difference, depending on marking site, level of experience, and protocol (Fig. 15).

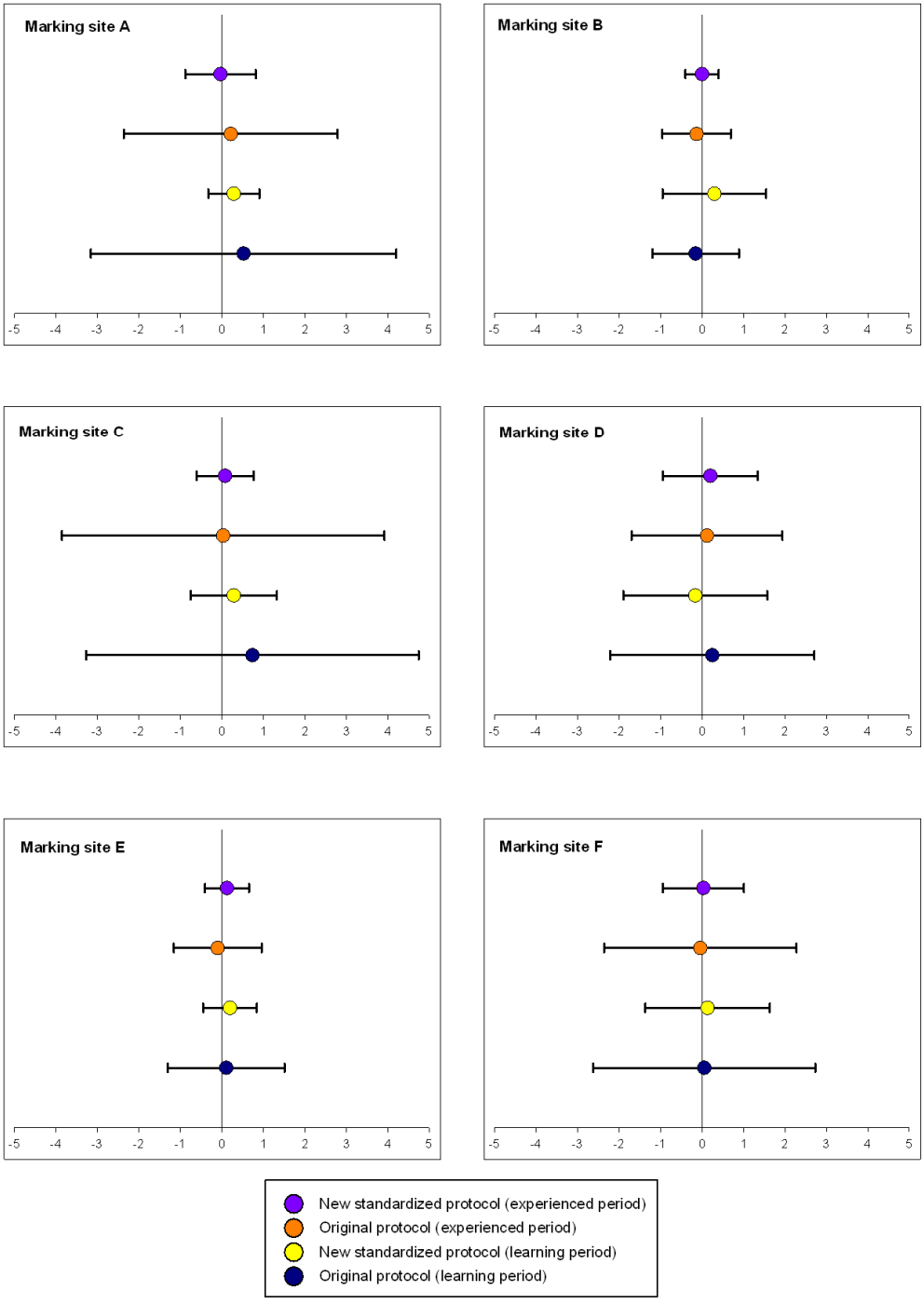

Fig. 15: Mean differences in centimetre between the first and second mark at the six marking sites are presented with coloured dots and the prediction intervals are shown with error bars.

Part study 2

We found a mean difference in knee laxity of 0.0 mm and a prediction interval of ±5.2 mm. The rotation of the femur in relation to the tibia around the X, Y, Z axes resulted in mean differences and prediction intervals of 0.6˚(±5.2˚), 0.3˚(±8.0˚), and –2.5˚(±15˚). For visualization the data is plotted in a Bland Altman plot (Fig. 16).

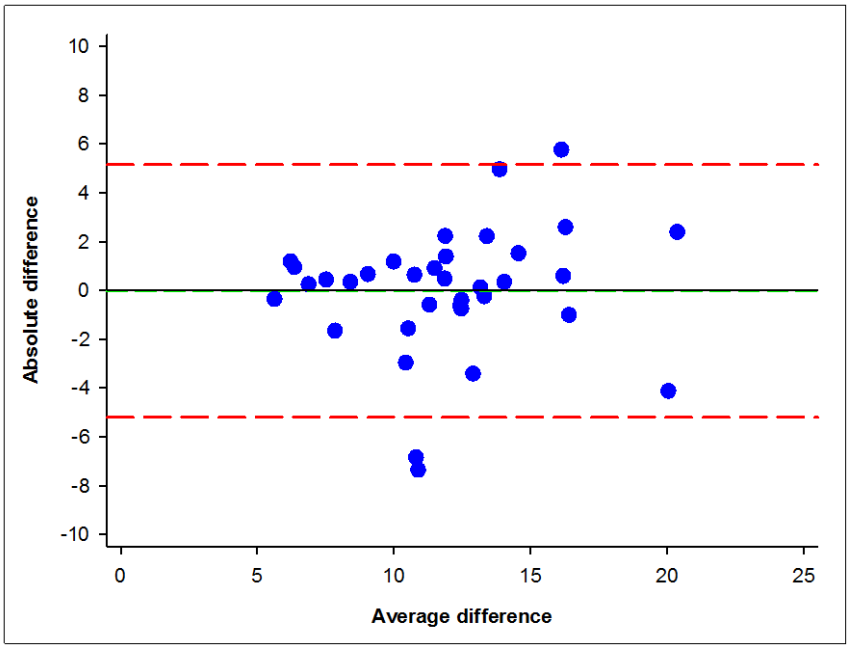

Fig. 16: Bland Altman plot. The absolute differences between the 1st and 2nd knee laxity measurements are plotted on the Y-axis against the average of the same measurements on the X-axis. The green line shows the mean differences between 35 persons. The dotted red lines show the upper and lower limits of agreement (95% prediction interval).

Study III

Fig. 17 describes the migration of the tibial graft markers inside the tibial tunnel as a function of time. At all times the migration in group EXDR was larger than in group SEDI. At 12 weeks, the difference was significant (P = 0.02). At 6 weeks no significant difference was found (P = 0.12). Borderline significance was reached at 24 weeks (P = 0.06). The results from the adjusted analysis did not differ from the results found in the univariate analysis.

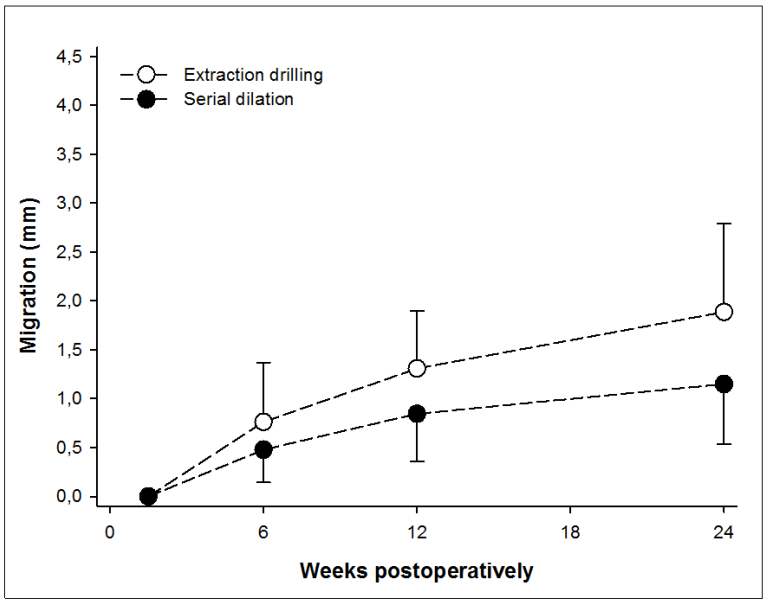

Fig. 17: Migration of the tantalum markers inside the tibial tunnel at 6, 12, and 24 weeks after surgery. Standard deviations are shown with error bars.

Fig. 18 shows the migration of the graft in the femoral tunnel. There was no statistically significant difference detected between the two groups after 6, 12, and 24 weeks ($P = 0.83$, $P = 0.69$, and $P = 0.18$, respectively).

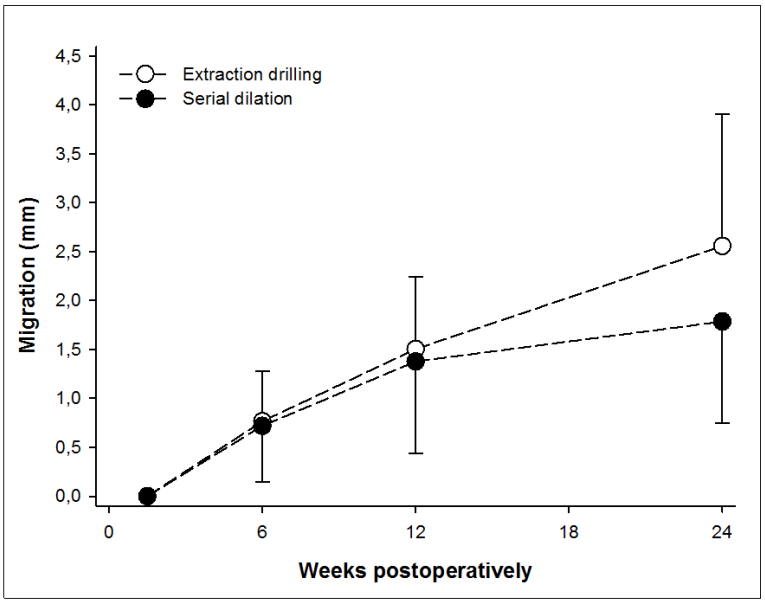

Fig. 18: Migration of the tantalum markers inside the femoral tunnel at 6, 12, and 24 weeks after surgery. Standard deviations are shown with error bars.

Fig. 19 shows the development in absolute knee laxity in the first 24 weeks after ACL-reconstruction. No significant difference was found at the first follow-up and at 6, 12, and 24 weeks (P = 0.67, P = 0.79, P = 0.09 and P = 0.34, respectively).

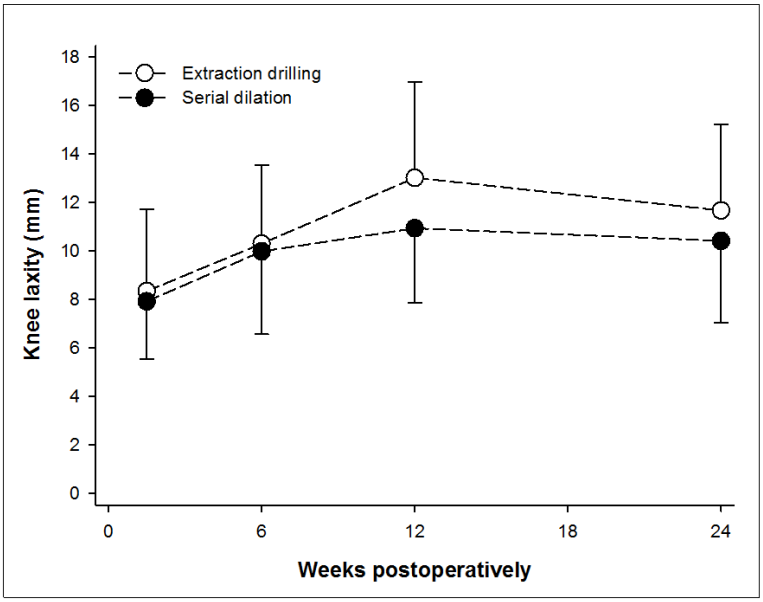

Fig. 19: Knee laxity at 7-10 days and 6, 12, and 24 weeks after surgery. Standard deviations are shown with error bars.

No statistical difference in Δ knee laxity between the extraction drilling group and the serial dilation group was found (P = 0.67, P = 0.14, P = 0.17 after 6, 12, and 24 weeks, respectively) (Fig.20).

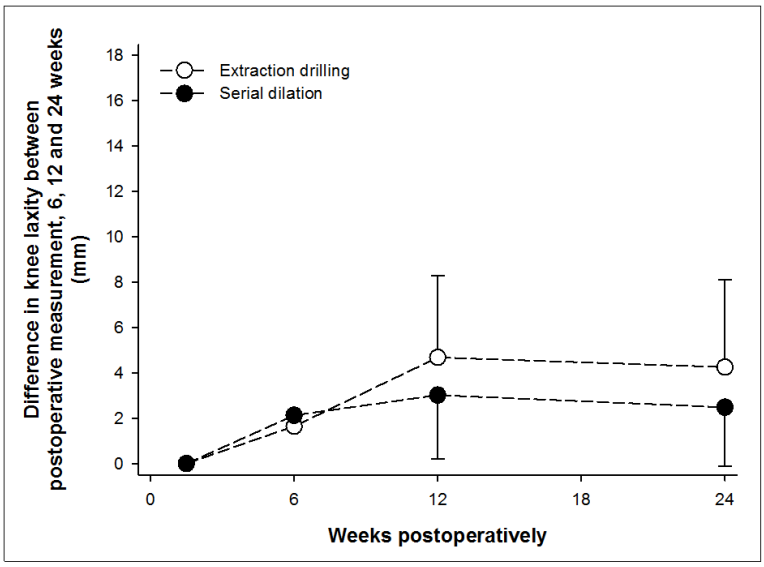

Fig. 20: Δ knee laxity at 6, 12 and 24 weeks. Standard deviations are shown with error bars. Error bars at 6 weeks are removed because of overlap.

Complications

We experienced two patients with deep infections in the operated knee in group SEDI.

8. Discussion

Key findings

Study I

In this study we found no significant difference between compaction by serial dilation and extraction drilling. In addition we investigated the development in difference between the two groups as a result of increasing loads and cycles. Again no significant difference between the two groups could be detected (Table 2).
Looking at Table 2, the standard deviations seem to be smaller in the dilated group than in the extraction drilling group, which could indicate that compaction by serial dilation produces a more uniform fixation than does extraction drilling. No significant difference between the standard deviations in the two groups was found (Table 2).

Study II

The results of this study show that it is possible to increase the precision of the TSD positioning by an optimized protocol (aim 1). Regarding marking site B (the tibial tuberosity), both protocols had an acceptable precision during the "experienced" period (Fig. 15). At all marking sites the NSP had a superior precision compared with the OFP. At all marking sites except one (marking site D), the NSP produced an acceptable precision. In contrast, the original protocol was only able to produce an acceptable precision at a single marking site (marking site B). At almost all marking sites, some practice before using the TSD is beneficial.

Looking at the manufactures directions in the original protocol, there is absolutely no guidance on how to position the proximal and distal stress arms. As a result, the precision is very poor at marking sites A, C, D, and F. At marking sites A and C, the prediction interval ranges by approximately ±4 cm. This means that the distance between the position arms can differ up to 8 cm from one investigation to another, which subsequently must result in a potential difference in the measured knee laxity.

Even though the TSD was precisely applied on the patients' extremities, the precision of the A-P knee translation measurements using RSA in our study was very disappointing, with a precision of more than ±5 mm (aim 2). Khan et al. [46] reported a precision of ±1.9 mm on six patients with a setup similar to ours. Fleming et al. [20] reported a higher precision. They published the translation data obtained in five goats. Using Fleming et al.'s data, we tried to calculate the precision, defined as ±2 SD. This resulted in a precision of ±1.77 mm, which is far more precise compared with our data.

The results indicate that we were not able to control the rotation of the tibia in relation to the femur. The rotation around the Z-axis (flexion/extension of the knee) is especially problematic, with a precision of ±15˚. We inspected the data for the persons with the largest differences in knee laxity measurements (the outliers in Fig. 16). We found that all persons had a substantial difference in Z-rotation of the knee. When we apply the TSD, we measure the flexion degree of the knee before force was applied. The knee tended to extend and flex, when posterior and anterior force, respectively, were applied to the knee. For some reason, we could not control the magnitude of this extension/flexion movement, even though we started out with the same degree of flexion. In future studies, we recommend measuring knee flexion after force appliance.

Study III

To our knowledge, we are the first to evaluate potential benefits of compaction by serial dilation after ACL reconstruction in a prospective clinical randomized trial. At the 3 months follow-up, we found a significantly reduced graft migration at the tibial fixation site (P = 0.02) in group SEDI compared with group EXDR. At the 6 months follow-up, we recorded a marginally significant difference (P = 0.06). Since several patients were excluded from the last follow-up a substantial risk of a type II error exists for this result. The value of the 6 month follow-up data is thus questionable. In the power calculation, we defined a difference of 1 mm between the two groups to be clinically relevant. The mean difference between the two groups was 0.5 mm in favour of group SEDI (Fig. 17). The graft is introduced to the knee joint at an angle of

approximately 50 – 60 degrees in relation to the tibial plateau, which must mean, that a migration at the tibial fixation site of 0.5 mm results in an increased knee laxity of less than 0.5 mm. Thus, even though we found a significant difference in graft migration between the two groups, the clinical relevance is debatable.

In Fig. 17 and Fig. 18 the mean migration of the hamstring graft at the femoral fixation site is approximately the same as seen at the tibial fixation site. This finding is surprising, since we theorized that tibial fixation of the hamstring graft is more demanding than femoral fixation. In addition, we have used a hybrid femoral fixation, which has been shown to be superior to cortical button fixation or interference screw fixation alone [58]. Migration at the femoral fixation site is related to knee laxity [26] and if compaction of the bone tunnel by serial dilators is able to produce the same effect on the femoral migration as that seen at the tibial fixation site, a clinically relevant reduction of total migration might be obtained. Further studies are needed to elucidate this question.

Knee laxity measurements revealed no differences between group SEDI and group EXDR. Knee laxity increased in both groups from the postoperative measurement to 3 months follow-up. From 3 to 6 months the knee laxity was unchanged or slightly decreased. The fluctuation of the knee laxity cannot be explained merely by migration at the fixation site. Other factors could have influenced the results. Despite a 7- 10 days wait before the first measurement, the patients may still have been affected by the surgery, and therefore not able to fully relax due to postoperative pain. This would result in increased muscle tension and an underestimation of the knee laxity. The slight decrease in knee laxity we observed from the third to the fourth follow-up could be a result of the knee stabilizing exercises provided by the rehabilitation. Looking at the standard deviations of the knee translation measurements, the fluctuation seen in Figs. 19 and 20 could merely be coincidental.

Comparison with relevant findings from other studies

As mentioned in the introduction, we are not the first to investigate a possible beneficial effect of serial dilation in ACL reconstructions using hamstring grafts. The results of Cain et al. [10] were in line with the findings in our RCT (study 3). In contrast, other biomechanical studies could not show a significant difference by using serial dilation at the fixation sites of the hamstring graft [17,56,63]. Looking at the results from Rittmeister et al. [63], it seems as if the difference between the serial dilated specimens and their non-dilated controls is highest in the two sub-groups secured with 7-mm RCI screws. The standard deviations of the sub-groups were not published, which makes it impossible for us to calculate whether the mean difference in load at a given permanent displacement is significantly different in the dilated versus the non- dilated sub-group. The study of Nurmi et al. [56] had one major limitation. Nine specimens failed during the cyclical loading test. These specimens were excluded from the data analysis. Six of these failures were in the extraction drilling group and only three were in the serial dilated group. A different outcome of the study might have resulted if the failures had been included in the analysis. To our knowledge, only Gokce et al. [24] have studied the use of compaction by serial dilators in a clinical study. Forty-four patients were enrolled in a retrospective study. They found a protective effect of serial dilation on tunnel enlargement. No significant difference in postoperative Lysholm scores and IKDC scores was found. If that had been the aim of the study, one could suspect that the study was underpowered.

Limitations/Generalizability

Study I

A bovine set-up was used in this study. Weiler et al.[78] described the BMD in the proximal part of the bovine tibia. They stated that a calf tibia of approximately 24 weeks of age has the same BMD as that of tibiae in young adults. In Denmark, we do

not slaughter calves this young. Our animals were between 32 and 36 weeks of age. This means that our animals weighed more, and consequently had a higher BMD in the proximal tibia. Brand et al. [8] showed that BMD is related to fixation strength. The dislocation in both our groups might be underestimated because of the high BMD, and from a clinical point of view, we might expect a greater migration of the tendon in the tibial tunnel in patients undergoing ACL reconstruction.

Amis et al. [12] performed a creep test of the tendons in a study with a bovine set-up quite similar to that used in this study. They tested five tendons to quantify the creep (irreversible stretch) and calculated the average creep of these tendons. The average creep was then subtracted from the measured displacement of the graft, giving the slippage of the graft. When a constant is subtracted from the displacement in both groups, one ends up with a smaller mean slippage in both groups. However, the mean difference, the *P* value, and the standard deviation of the test will be the same. Because of that, we did not perform creep tests in this study.

We assume that it takes 6-12 weeks before a proper in-growth of the tendon to the bone at the tunnel entrance has occurred. A strong fixation is necessary during this period to prevent slippage of the graft at the fixation site. We tested our fixation-device complexes with 1600 cycles with varying loads. The number of cycles and loads approximate the degree of mobilization within the first 7-14 days after surgery. In addition, we used cadaveric animal material, which means that we tested the initial fixation strength of serial dilation versus extraction drilling. Therefore, based on this study and other studies with comparable designs, we are not able to predict how compaction by serial dilation will perform on a long-term basis. To answer that question, we need prospective clinical randomized trials with at least 3 months of follow-up (study III).

In Table 2, there is a steady decrease in *P* values with an increase in load and number of cycles. A significant difference was not reached at any time, but the development is very interesting from a clinical perspective, because the patients perform much more than 1600 steps during the part of the postoperative period in which the in-

healing of the tendon to the bone has not been completed, and migration of the tendon at the fixation sites is still a possibility. Again, study III should provide the answer to this question.

Study II

We could have chosen to examine the persons in a random order, minimizing the risk that the examiner could recognize patient details when performing double measurements. In this study, there were only a few minutes between the first and second measurements for the same person, which gives the investigator the opportunity to remember some of the details of the patient's knee, resulting in better reliability. We wanted to correlate the results found in this study with the precision of knee laxity measurements found in the clinical TSD-RSA study, in which we only made one or two examinations per day, which necessitated a short time interval between the first and second measurements. Therefore the same time interval was used in the TSD study.

One major problem with the TSD is that people feel uncomfortable when it is applied. They are not able to fully relax. Especially the position of the "healthy" leg is difficult. Some patients actually experience the TSD application as a painful experience [42]. This potentially results in a higher degree of muscles tension during the measurements, which could result in underestimated knee laxity measurements. In a pilot study, we discovered that use of the extension arm (Fig. 3) contributed to the aching. In the NSP, we did not use the extension arm. No patient complained of pain, but we were not able to fully remove the feeling of discomfort.

Another problem is the plasticity of the skin. The stress applied with the TSD allows the skin to move several cm in relation to the underlying bone. Even though we can place the stress arms in approximately the same position on the skin, we cannot be sure that the relation of the stress arms to the femoral and tibial bone can be repeated. This could result in a different anterior-posterior translation potential of the knee from measurement to measurement and a reduced knee laxity measurement precision.

We used a ruler to measure the distance from the floor to the marking sites. Use of a laser pointer could, perhaps, improve the positioning of the TSD and thereby lower the prediction interval of the knee laxity.

Study III

Only ten patients in group EXDR and eight patients in group SEDI could be analyzed at the last follow up for different reasons (Fig 14). In group EXDR only one patient had a negative tibial marker migration on the Y-axis, whereas eight patients in group SEDI had the same problem and had to be excluded from further analysis. The question is why did we see this difference? A negative marker migration must result from loose markers. One explanation for the negative migration could be that the osseointegration of the graft has ended, and the transformation of tendon to bone provides a random movement of the graft markers. If this is right, one could speculate that the difference between the two groups must mean that serial dilation of the tibial tunnel results in a faster in-healing of the tendon to bone compared with extraction drilling. Another explanation could be that the migration of the graft markers could be reversibly influenced by the stress provided by the TSD. The position of the graft markers at the postoperative measurements would then be registered too close to the knee joint. As the influence of the TSD diminish over time as a result of the ongoing osseointegration, the migration of the markers at later follow-ups could be detected as negative on the Y-axis of the coordinate system, merely because of a "false" measurement of marker position at baseline. This could explain some of the negative marker migration seen, but it cannot explain the difference between the serially dilated group and the extraction drilling group at the fourth follow-up. To detect whether or not the stress from the TSD cause marker migration, comparative studies with stressed and unstressed knees are necessary.

From 16 April to 15 July 2008 Danish hospital personnel were on strike. As a result, we were not able to perform elective procedures during this period. Therefore four patients (three patients in group EXDR and one patient in group SEDI) had their

fourth follow-up postponed. Given the RSA guidelines in Valstar et al. [75], these four patients were excluded from analysis (Fig 14).

As explained above, RSA measurements were not performed until 7-10 days after surgery because of pain and swelling of the knee, which could result in increased muscle tonus during the stress test. Therefore we cannot say anything about the migration at the fixation site during the first week after surgery. The TSD is not able to provide precise knee laxity measurements, and our opinion is that it can be left out in future studies. Thus the first follow-up (not stressed) could then be made very shortly after surgery, and would therefore also include migration during the first week.

Another limitation of the study is the interpretation of marker migration in patients with only one or two markers available for analysis. We placed four markers at the tibial fixation site and three markers at the femoral fixation site. Markers that migrated in the wrong direction, indicating that they were loose, were excluded from analysis. One marker could be placed in the graft, but outside the tibial tunnel, in which case the marker was excluded from analysis as well. Only one or two tibia markers would then be available for analysis, which makes it impossible to test for loose markers, as described by Khan et al. [46]. In these cases, we cannot be certain whether the marker migration is representative for the actual graft migration or a result of a random movement of a loose marker. In future studies we recommend that at least five or six markers be inserted at each fixation site to insure that testing for loose graft markers is possible.

I a short time period we experienced three patients with deep infections in the operated knee after arthroscopic knee surgery at the same hospital. Two of the infections was seen after ACL reconstruction and were both enrolled in this study and randomized to group SEDI. The last infection resulted after a knee arthroscopy. Two infections in 40 patients is a high incidence, but we believe it was coincidental and not a result of the use of tantalum beads or the serial dilation procedure. Of course this problem calls for awareness in future studies.

9. Conclusion

Studies I and III

The biomechanical test in this thesis failed to show a significant difference in initial fixation strength between serial dilation and extraction drilling of the tibia bone tunnel in ACL reconstruction. The number of cycles and loads used in study I resembled the degree of mobilization within the first 7-14 days after surgery. Based on study I alone, we cannot say anything about long term results after serial dilation. To overcome that problem we carried out study III. This study showed that compaction by serial dilation of the tibial tunnel significantly reduced the migration of the hamstring graft at the tibial fixation site compared with conventional extraction drilling. The mean difference between the two groups at 3-month follow-up was 0.5 mm, which must be interpreted as a difference with limited clinical impact. The mean migration of the hamstring graft at the femoral fixation site was larger than expected. If serial dilation at the femoral fixation site could produce the same reduction in graft migration as seen at the tibial fixation site, the use of serial dilation of the bone tunnels in ACL reconstruction could be clinically beneficial for the patient. We were not able to show any significant difference in knee laxity between the serially dilated group and the extraction drilling group. The use of tantalum markers inserted into the hamstring graft and evaluation of fixation site graft migration using RSA in clinical studies is still new and some methodological considerations are still needed.

Study II

This study showed that even though we were able to position the TSD with a good precision, the combination of the TSD and RSA failed to provide knee laxity measurements with a acceptable precision. A fast and non invasive method, such as the KT-1000 arthrometer, is a more precise device for knee laxity measurements and it provides results almost comparable to most RSA results. RSA is very resource demanding and invasive, and its role in clinical A-P translation measurements seems to be limited at the present time. RSA has a high potential due to a high accuracy, but a stress device that can produce reliable joint translation results is needed.

10. Perspectives and future research

There are some methodological questions remaining that still need attention.
(1) It is extremely important to investigate whether the measured migration of the graft markers at the fixation sites truly reflects the migration of the graft or just a random migration because of loose markers. This could be done by placing five or six markers at each fixation site, and then measure the distance between the graft markers at each follow-up. A marker with a migration pattern different from the other graft markers should be considered loose and excluded from the analysis.
(2) Does the stress provided by the TSD cause reversible marker migration? A comparative study with stressed and unstressed knees is necessary.
(3) What is the magnitude of the migration of the graft at the fixation sites during the first 7-10 days?
These questions call for further studies.

The use of tantalum markers inserted into the hamstring graft that allow evaluation of fixation site-graft migration using RSA in clinical studies has a great potential. In fact every fixation method introduced on the market could be tested using this method, including a potential benefit of serial dilation of the femoral bone tunnel. As mentioned above, some methodological challenges have to be overcome first.

We still believe that RSA can play a part in future knee laxity measurements. At the moment we do not have a stress device which can provide a precise load application to the knee. The search for a better stress device is ongoing. A device that could provide precise anterior-posterior knee translation measurements and precise rotational instability measurements would be preferable.

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Appendices

THESES FROM THE ORTHOPAEDIC RESEARCH GROUP

PhD and Doctoral Theses from the Orthopaedic Research Group,
www.OrthoResearch.dk,
University Hospital of Aarhus, Denmark

PhD Theses

1. In vivo and vitro stimulation of bone formation with local growth factors
   Martin Lind, January 1996
   www.OrthoResearch.dk

2. Gene delivery to articular cartilage
   Michael Ulrich-Vinther, September 2002
   www.OrthoResearch.dk

3. The influence of hydroxyapatite coating on the peri-implant migration of polyethylene particles
   Ole Rahbek, October 2002
   www.OrthoResearch.dk

4. Surgical technique's influence on femoral fracture risk and implant fixation. Compaction versus conventional bone removing techniques
   Søren Kold, January 2003
   www.OrthoResearch.dk

5. Stimulation and substitution of bone allograft around non-cemented implants
   Thomas Bo Jensen, October 2003
   www.OrthoResearch.dk

6. The influence of RGD peptide surface modification on the fixation of orthopaedic implants
   Brian Elmengaard, December 2004
   www.OrthoResearch.dk

7. Biological response to wear debris after total hip arthroplasty using different bearing materials
   Marianne Nygaard, June 2005
   www.OrthoResearch.dk

8. DEXA-scanning in description of bone remodeling and osteolysis around

cementless acetabular cups
Mogens Berg Laursen, November 2005
www.OrthoResearch.dk

9. Studies based on the Danish Hip Arthroplasty Registry
   Alma B. Pedersen, 2006
   www.OrthoResearch.dk

10. Reaming procedure and migration of the uncemented acetabular component in total hip replacement
    Thomas Baad-Hansen, February 2007
    www.OrthoResearch.dk

11. On the longevity of cemented hip prosthesis and the influence on implant design
    Mette Ørskov Sjøland, April 2007
    www.OrthoResearch.dk

12. Combination of TGF-β1 and IGF-1 in a biodegradable coating. The effect on implant fixation and osseointegration and designing a new in vivo model for testing the osteogenic effect of micro-structures in vivo
    Anders Lamberg, June 2007
    www.OrthoResearch.dk

13. Evaluation of Bernese periacetabular osteotomy; Prospective studies examining projected load-bearing area, bone density, cartilage thickness and migration
    Inger Mechlenburg, August 2007
    Acta Orthopaedica (Suppl 329) 2008;79

14. Rehabilitation of patients aged over 65 years after total hip replacement - based on patients' health status
    Britta Hørdam, February 2008
    www.OrthoResearch.dk

15. Efficacy, effectiveness, and efficiency of accelerated perioperative care and rehabilitation intervention after hip and knee arthroplasty
    Kristian Larsen, May 2008
    www.OrthoResearch.dk

16. Rehabilitation outcome after total hip replacement; prospective randomized studies evaluating two different postoperative regimes and two different types of implants
    Mette Krintel Petersen, June 2008
    www.OrthoResearch.dk

17. CoCrMo alloy, *in vitro* and *in vivo* studies
    Stig Storgaard Jakobsen, June 2008
    www.OrthoResearch.dk

18. Adjuvant therapies of bone graft around non-cemented experimental orthopaedic implants. Stereological methods and experiments in dogs
    Jørgen Baas, July 2008
    Acta Orthopaedica (Suppl 330) 2008;79

19. The Influence of Local Bisphosphonate Treatment on Implant Fixation
    Thomas Vestergaard Jakobsen, December 2008
    www.OrthoResearch.dk

20. Surgical Advances in Periacetabular Osteotomy for Treatment of Hip Dysplasia in Adults
    Anders Troelsen, March 2009
    Acta Orthopaedica (Suppl 332) 2009;80

21. Polyethylene Wear Analysis. Experimental and Clinical Studies in Total Hip Arthroplasty.
    Maiken Stilling, June 2009
    www.OrthoResearch.dk

22. Step-by-step development of a novel orthopaedic biomaterial: A nanotechnological approach.
    Thomas H.L. Jensen, September 2009
    www.OrthoResearch.dk

23. Osteoclastic bone resorption in chronic osteomyelitis
    Kirill Gromov, November 2009
    www.OrthoResearch.dk

24. Use of medications and the risk of revision after primary total hip arthroplasty
    Theis Thillemann, December 2009
    www.OrthoResearch.dk

Doctoral Theses

1. Hydroxyapatite ceramic coating for bone implant fixation. Mechanical and histological studies in dogs
    Kjeld Søballe, 1993
    Acta Orthop Scand (Suppl 255) 1993;54

2. Growth factor stimulation of bone healing. Effects on osteoblasts, osteomies, and implants fixation
   Martin Lind, October 1998
   Acta Orthop Scand (Suppl 283) 1998;69

3. Calcium phosphate coatings for fixation of bone implants. Evaluated mechanically and histologically by stereological methods
   Søren Overgaard, 2000
   Acta Orthop Scand (Suppl 297) 2000;71

4. Adult hip dysplasia and osteoarthritis. Studies in radiology and clinical epidemiology
   Steffen Jacobsen, December 2006
   Acta Orthopaedica (Suppl 324) 2006;77

5. Gene therapy methods in bone and joint disorders. Evaluation of the adeno-associated virus vector in experimental models of articular cartilage disorders, periprosthetic osteolysis and bone healing
   Michael Ulrich-Vinther, March 2007
   Acta Orthopaedica (Suppl 325) 2007;78