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Reduced degenerative articular cartilage changes after meniscal allograft transplantation in sheep

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Abstract The objective of this study was to examine the gross changes after meniscal allograft transplantation with reference to the development of degenerative articular cartilage changes (DACC) and to examine the transplant behavior. The medial menisci of both knees in 32 Iceland sheep were operated on with either sham operation (C6), medial meniscectomy (M6), primary transplantation (P6), or secondary transplantation 3 months after meniscectomy (S6). These sheep were observed for 6 months. Another six sheep were observed for 3 months after meniscectomy (M3) and contralateral sham operation (C3). The DACC of the knee were visualized with an intra-articular toluidine blue injection. The dissemination area of DACC on the medial tibial plateau (MTP), the meniscal area, and the meniscus-free, exposed central area on the MTP were measured by computer image analysis based on digitized photos of the tibial plateau. These area measurements were calculated relative to the area of the MTP. The DACC in P6 knees had a mean of 4.3%, which was less than the 12.6% in M6 ($P < 0.001$) and the 16.1% in S6 ($P < 0.001$), but more pronounced than the 0.5% in C6 ($P < 0.005$). There were no detectable differences in DACC between M6, S6 and M3 (16.9%). The measurements of DACC were reproducible with correlation coefficient $r = 0.97$ on intra-tester test-retest measurements. The area of the free exposed MTP was larger in P6 and in S6 than in C6 ($P < 0.001$), demonstrating a displacement of the graft. S6 transplants showed shrinkage and were smaller than C6 menisci ($P < 0.01$). In conclusion, primary meniscal allograft transplantation reduced DACC within 6 months in sheep knees, but DACC were still present in transplanted knees. The meniscal transplants demonstrated peripheral displacement.

Key words Meniscal allograft · Transplantation · Articular cartilage · Image analysis

Introduction

Many experimental and clinical studies have documented the deleterious effect of meniscectomy on the knee joint, and it has been demonstrated that a high incidence of degenerative arthritis follows total meniscectomy [1, 13, 17, 20]. Current meniscal surgery is aimed at preserving as much meniscal tissue as possible, which includes repair in the appropriate regions of the meniscus, rather than resection [10, 15, 16, 25]. However, the surgeon may still encounter a severely injured meniscus, which is unsuitable for repair, or a previously meniscectomized knee. In these cases, the option of using a meniscal allograft seems obvious and it is becoming increasingly more common in orthopedic surgery.

Experimental studies during the past 15 years have shown that ingrowth from the adjacent capsule into the meniscal transplant does take place and that graft rejection does not seem to be a problem [2, 8, 12, 18, 23]. However, the success of meniscal allograft transplantation also depends on whether the graft can prevent articular cartilage damage. Many studies have described the articular cartilage after meniscal transplantation but, to our knowledge, only two studies have assessed cartilage degeneration systematically, and both failed to demonstrate a preventive effect of the implant [11, 18]. In addition, an articular cartilage-preserving effect of meniscal transplantation has not yet been documented in human meniscal allograft transplantation. All clinical reports have so far been short-term follow-ups without control groups. The articular cartilage has been examined with second-look arthroscopy or MRI, but results have been purely descriptive [14, 24, 28, 29, 34].

The overall aim of this study was to evaluate systematically the effect of meniscal allograft transplantation in the sheep knee joint, with special emphasis on the possible degenerative gross changes in the articular cartilage and on the transplant size and position. In addition, primary meniscal transplantation was compared with secondary transplantation.

Materials and methods

Material and study design

A total of 49 female Iceland sheep of the same breed were used in the study. The sheep were 12 to 18 months old, weighed 40 to 55 kg and were skeletally mature at the time of inclusion, which was at the time of the operation.

We tested four different treatments in the study: (1) sham-operated control knees (C), (2) meniscectomized knees (M), (3) primary allograft transplanted knees (P) in a one-step procedure, and (4) secondary allograft transplanted knees (S) in a two-step procedure with a 3-month delay from meniscectomy to transplantation. The four treatments were grouped in a balanced, incomplete block design, where both knees of the sheep were used [5]. The four treatments were tested in sets of two, matching the two sheep hind limbs, where each treatment was tested an equal number of times against the other three, also considering possible differences between right and left knees. After a pilot study, which included eight sheep, the observation time was determined to be 6 months. The experimental design for sheep observed for 6 months is shown in Table 1.

To examine the knee conditions of the secondary transplanted knees at the time of the second-step operation, six sheep were observed for a 3-month time period. These sheep were sham-operated (C3) on one knee and meniscectomized (M3) on the other, with the two treatments equally represented on right and left knees.

Two sheep from the 6-month observation group, both having undergone M/P.operations, were excluded due to complications (see Results) and replaced by two other sheep, one treated with C/M and one with M/P. In addition, one S6 knee was inappropriate for testing after 6 months. The knees available for further investigation are listed in Table 2. Three sheep served exclusively as meniscal donors and were killed after removal of the menisci.

Table 1 Study design for sheep observed for 6 months. Planned number of sheep and knees with combination of operations on the two contralateral knees (*C* sham operation, *M* medial meniscectomy, *P* primary transplantation, *S* secondary transplantation)

Combination	Sheep			Knees				
	Right/left	Left/right	Total	C	M	P	S	Total
C/M	3	2	5	5	5			10
C/P	2	3	5	5		5		10
C/S	2	3	5	5			5	10
M/P	3	2	5		5	5		10
M/S	2	3	5		5		5	10
P/S	3	2	5			5	5	10
Total	–	–	30	15	15	15	15	60

Observation group		Knees				
		C6	M6	P6	S6	Total
Right knees		7	7	8	8	30
Left knees	8	8	7	7	30	
Total		15	15	15	15	60

Table 2 Knees in the main study and group designation (*C3* control knees with 3 months observation, C6 control knees with 6 months observation)

Observation time/Operation type	Group	*n*	Group	*n*
Control (sham)	C3	6	C6	16
Meniscectomy	M3	6	M6	15
Primary transplantation	–	–	P6	14
Secondary transplantation	–	–	S6	14

Surgical procedure

The sheep were operated on under general anesthesia by intravenous titration of ketamine and medetomidin in combination with inhalation of a mixture of nitrous oxide and oxygen. The medial menisci of both knees were operated on under one anesthetic period by use of a conventional sterile surgical technique. Sulfadoxine and trimethoprim were administered preoperatively as antibiotic prophylaxis. All operations were performed by the same surgeon.

Meniscectomy group

The knee joint was opened through a curved skin incision over the medial joint line. The joint was exposed by two medial capsulotomies: one anterior and one posterior to the medial collateral ligament. The medial meniscus was dissected sharply from the capsule, and the two horn ligaments were transected and the meniscus was removed so that the medial collateral ligament was left intact. The knees in this group (M) were sutured and closed after removal of the meniscus. The surgical wound in all four groups was closed in four layers: the capsule, the muscle facia, the subcutaneous tissues and the skin.

The harvested transplant menisci grafts were placed in a sterile, isotonic saline solution with added streptomycin to prevent bacterial contamination, and stored at 4°C. The graft was transplanted into a recipient knee within a maximum of 24 h after harvesting.

Control group

The knees in the control group (C) underwent a sham procedure, where the joint was opened with two medial capsulotomies as described above, without removal of the medial meniscus. Minor parts of the meniscal capsular fixation were detached.

Primary allograft transplanted group

Following meniscectomy the knees in the primary allograft transplanted group (P) received a fresh graft immediately during the same operative procedure. The allograft, harvested from another sheep, was prepared with nonresorbable sutures as anchors in the anterior and posterior horns. Two 1.5 mm tunnels were drilled from the medial tibial facies, distal to the medial collateral ligament, using a drill guide aimed at the anterior and posterior tibial attachments of the meniscus. To implant the allograft, the anchoring sutures were pulled through the drill holes and tied to each other in a knot on the medial tibial surface. The graft placement and mobility was tested with knee flexion and extension, and varus and valgus stress. During this procedure, it was ensured that the graft could not be displaced, peripherally or centrally. No further fixation of the graft to the capsule was used.

Secondary allograft transplanted group

The knees in the secondary allograft transplanted group (S) were subjected to delayed meniscal transplantation 3 months after meniscectomy, in a second-step operative procedure using a fresh allograft. The surgical procedure was as described above. Only the one knee in the secondarily transplanted sheep was re-operated on during the second step operative procedure.

Postoperative management

The antibiotic prophylaxis was continued with one daily dose for the first 3 postoperative days. Analgesic buprenorphine was administered three times daily in the same period. Postoperatively, the sheep were allowed full weight-bearing without restrictions. The sheep were kept in cages under more intensive observation for the first 10–14 days, and subsequently sent back to the fields for the rest of the observation period. Current ethical principles regarding animal experiments were adhered to and the sheep were kept under veterinarian supervision. The study was approved by the Danish authorities. According to the described plan, the sheep were killed 3 or 6 months after the operation with an overdose of pentobarbital.

Specimen preparation and gross inspection

To visualize areas of the articular cartilage where incipient degenerative wear had disturbed the normally smooth and impermeable surface, a 0.1% solution of toluidine blue was injected into the joint. After the injection the knee was manually flexed and extended continuously for 1 min, and then the joint was irrigated with an isotonic saline solution. The knee joint capsule was opened leaving the menisci attached to the tibia. Localization of toluidine blue-dyed degenerative articular changes and macroscopically visible synovial changes was noted.

Capsular fibrous or synovial ingrowth into the transplant was assessed. The location of the medial meniscus and its anterior and posterior horn attachments to the tibial intercondylar area through the suture anchors were noted. Meniscal lesions were noted.

Image analysis

A photograph perpendicular to the tibial surface was taken. Following this, both menisci and the adjacent soft tissues, which block the camera survey of the tibial articular surfaces, were removed and a new photograph was taken. The gray scale photographs were scanned to produce digitized images. All photographs included a ruler to give the scale for each image.

The computer mouse was used to draw a line along the edge of the medial meniscus and along the circumference of the medial tibial plateau (MTP) (Fig. 1A). The areas of the medial meniscus and the MTP were then calculated by image analysis software [26]. The meniscal area was used as an expression of the meniscal size and was measured relative to the area of the MTP. The same procedure was used to calculate the free exposed central area on the MTP not covered by the meniscus. This area, measured relative to the area of the MTP, was used as an expression of displacement of the meniscus. The examiner was blinded to the treatment of the knee.

During the surgical procedure similar photographs of the removed menisci, including those to be used as allografts, were taken in order to recognize possible graft shrinkage and potential op-

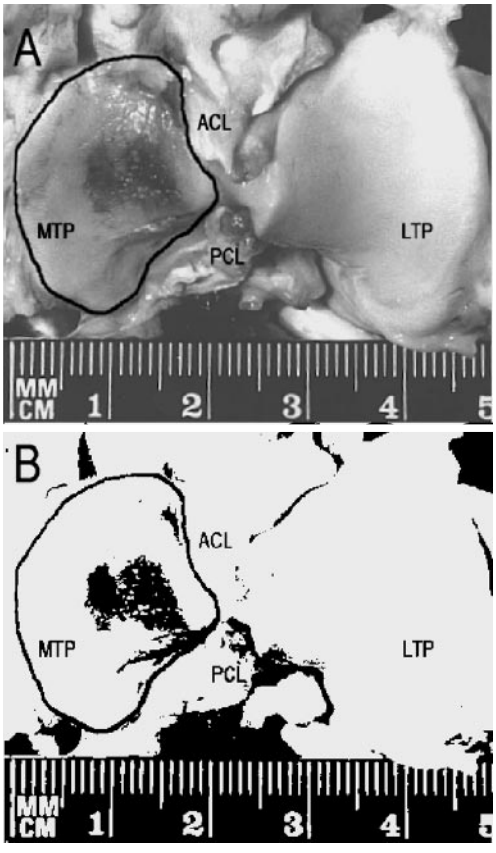

Fig. 1 **A** Medial (*MTP*) and lateral (*LTP*) tibial plateau after removal of soft tissues, 6 months after meniscectomy. The area of the MTP was manually encircled and measured by the computer. Degenerative articular cartilage changes (DACC) are dark areas stained with toluidine blue dye. **B** Same tibial plateau after computer-assisted densitometry, where all gray tones above a manually defined threshold value were converted to black. The *black areas* within the encircled MTP were measured. (*ACL* anterior cruciate ligament, *PCL* posterior cruciate ligament)

erative sizing discrepancy between the graft and the removed host meniscus.

Degenerative changes of the articular cartilage measured by the image analysis were defined as changes where the normal smooth and impermeable surface was disrupted and receptive to dye. On the gray scale images, the dark, toluidine-dyed, degenerative articular cartilage changes (DACC) were easily recognizable in contrast to the light areas where the articular cartilage was undisturbed and had an intact surface. Computer-assisted densitometry was used to filter the image according to pixel intensity, where all gray tones above a manually defined threshold value were converted to black. The black area of the articular surface corresponding to the area of the DACC was measured (Fig. 1B).

All measurements were obtained by the same examiner in two independent, blind tests in order to analyze the test versus retest reproducibility of the image analysis method. The mean of the two measurements was used in the later analysis.

Statistics and data handling

Between-group comparisons were tested with the Mann-Whitney U test for unpaired data and by the Wilcoxon signed ranks test for paired data. The Kruskall-Wallis test was used in multiple comparisons between different groups, followed by two-by-two comparisons with Bonferroni-corrected *P*-values. The level of significance was 0.05 and *P* values were expressed relative to α-levels 0.05, 0.01, 0.005, and 0.001.

Reproducibility of the image analysis method was based on the test-retest results by analyses of systematic difference (*P*-value), strength of relation (Spearman's correlation coefficient, r_s), and variation on differences measured by 95% limits of agreement (mean difference ± 2 SD_{diff}) [4].

Results

In general, the sheep tolerated the operations well. Most were upright immediately after the anesthesia and weight-loaded their operated hind limbs. One sheep was not sufficiently mobile postoperatively and another sheep limped. These two sheep were excluded within the first postoperative month.

Gross inspection

Capsular ingrowth was demonstrated in 25 meniscal transplants in more than 75% of the transplant periphery, while the remaining three transplants showed ingrowth in 50%–75% of the periphery. There was a tendency of extrusion of the transplanted menisci peripherally towards the capsule (Fig. 2), with the suture anchor being partially pulled out through the fibrocartilaginous meniscal tissues. This phenomenon was usually most pronounced in the posterior horn. One suture was broken, and one knot on the medial tibia had loosened. None of the menisci was injured, but some of the transplanted menisci showed areas with macroscopic signs of degenerative changes, such as a change in tissue consistency, color, or shape. Furthermore, some of the grafts seemed to be reduced in height. One S6 meniscus had changed totally with conspicuous shrinkage and irregular surfaces.

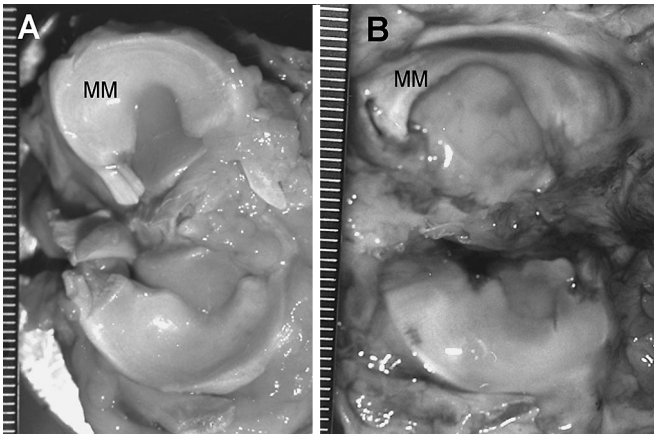

Fig. 2 A, B Tibial plateaus. **A** Control knee (C6). **B** Secondarily transplanted knee (S6). The medial meniscus allograft in S6 was considerably displaced peripherally, exposing more of the central, medial tibia cartilage than in the control knee. (*MM* medial meniscus)

DACC were present both on the femoral and tibial articular surfaces as early as 3 months after meniscectomy. The DACC were easily recognized after the intra-articular injection of toluidine dye. These changes were mostly located in the central part of the MTP, whereas the femoral DACC were observed in an anterior-posterior groove on the medial femoral condyle, corresponding to the tibiofemoral contact area. Some of the M6 and S6 knees demonstrated ridge formation of the medial femoral condyle with narrowing of the medial part of the medial joint space. One S6 knee was infected at the time of autopsy and demonstrated joint destruction. This knee could not be used in the later analyses. No loose or foreign bodies were observed in the knees.

Image analysis

Test reproducibility

No systematic differences could be demonstrated between the test and retest area measurements and all test-retest measurements showed high correlations ($r_s > 0.91$) (Fig. 3). The 95% limits of agreement were 0.3% ± 5.9% in measurements of the tibial DACC, 1.0% ± 9.5% in measurements of the meniscal size, 1.1% ± 8.9% in comparisons of the preoperative meniscal graft with the removed host meniscus, and –1.2% ± 10.8% in measurements of the free exposed MTP.

Articular cartilage

The dissemination of DACC was less in the P6 than in the M3, M6, and S6 groups ($P < 0.001$), but greater than in

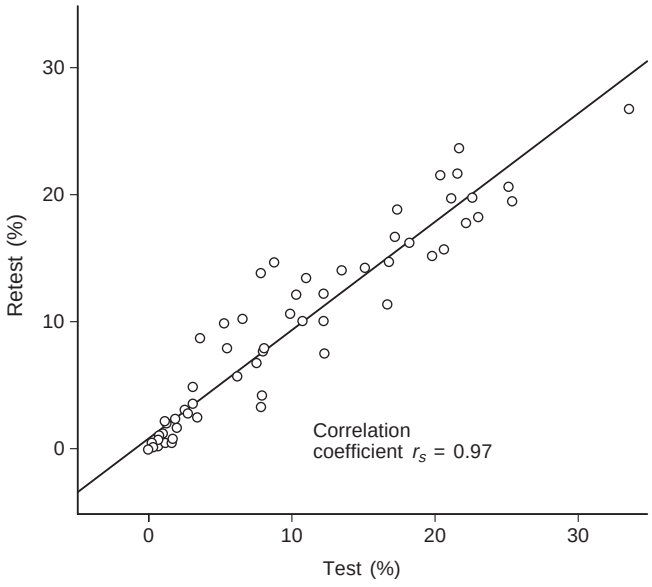

Fig. 3 Test-retest correlation of image analysis data. Percent dissemination of degenerative articular cartilage changes (DACC) on the medial tibial plateau

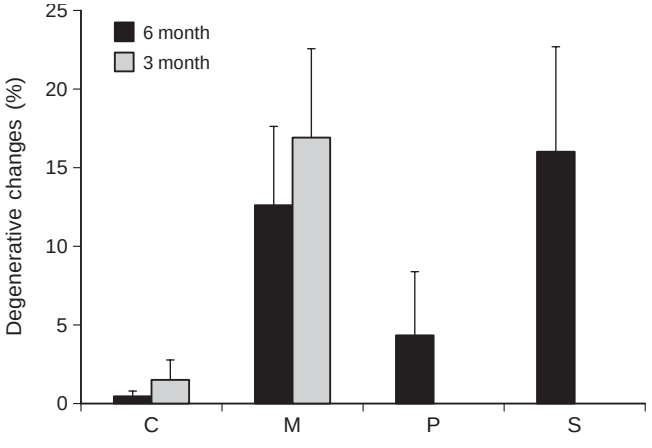

Fig. 4 Dissemination of degenerative articular cartilage changes (DACC) on the medial tibial plateau

the C3 ($P < 0.01$) and C6 groups ($P < 0.005$). There were no detectable differences between the M3, M6 and S6 groups (Fig. 4).

Meniscus

Before implantation, the P6 meniscal transplants were 3.6% undersized on average, while the S6 grafts were 9.4% oversized compared with the removed host meniscus, but the differences were not significant. The analysis of P6 transplants was based on only 11 available preoperative photos.

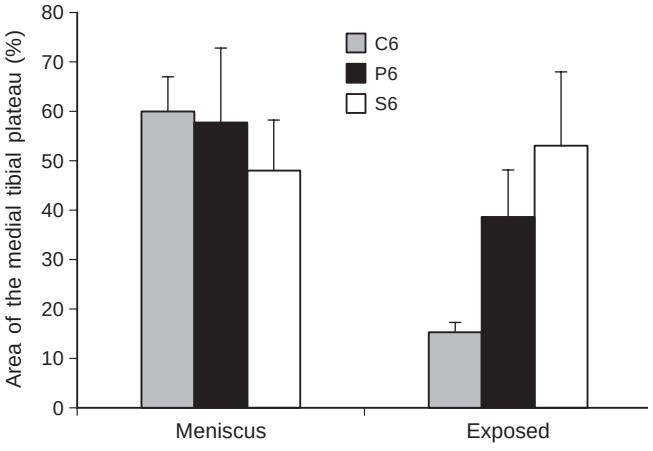

Fig. 5 Area of meniscus and free exposed articular cartilage relative to the area of the medial tibia plateau

The area of the graft before implantation compared with the same graft after autopsy, showed that mean shrinkage in P6 grafts was 2.5% (not significant) and 23.8% in S6 grafts ($P < 0.001$). The shrinkage tendency was confirmed by the measurements of the meniscal size relative to the MTP after autopsy: S6 transplants were smaller than C6 menisci ($P < 0.01$), while there was no difference between C6 and P6 menisci (Fig. 5).

The free exposed central area of the MTP was larger in P6 than in C6 sheep ($P < 0.001$), which demonstrated graft extrusion towards the capsule (Fig. 5). The free exposed MTP in S6 was larger than in P6 sheep ($P < 0.05$).

Discussion

The results of this experimental study showed that primary meniscal allograft transplantation protected against articular cartilage degenerative changes in the medial compartment of the sheep knee, but it did not completely prevent it. To our knowledge, these results are the first to demonstrate a positive effect of meniscal allograft transplantation, and to show that a meniscal transplant may possibly delay the degenerative process. Thus, the methods used in the study should be evaluated critically, as should the results, with special attention directed to the short-term follow-up, the use of fresh allografts and the surgical fixation technique.

Other experimental meniscal transplantation studies have described changes in the articular cartilage, but these changes have either not been assessed systematically, or the studies have not included both a meniscectomy and a control group [2, 8, 12, 23]. However, one experimental sheep study, with a mean observation time of 21 months, assessed osteoarthritic changes radiographically and included both meniscectomized and control animals [11]. Both meniscectomized and transplanted knees showed

significant changes after a mean of 21 months, but there was no difference between the two groups, which is in contrast to our results. In the current study, the reported degenerative changes to the articular cartilage were based on short-term observations, and whether the transplanted knees would have developed the same degree of degenerative articular cartilage changes as the meniscectomized knees at longer term follow-up is unknown.

The results from the present experimental study cannot simply be extrapolated to human conditions. Clinical studies have demonstrated that axial alignment after meniscectomy plays a major role in the cartilage degenerative process [1], but knee alignment was not investigated in the present study and whether axial alignment may be a concurrent cause in the sheep knee is unknown. We only investigated the medial meniscus and the medial knee joint chamber in this experimental study, while human studies have demonstrated lateral meniscectomy to be more detrimental to the articular cartilage than medial meniscectomy, even though medial meniscectomy also leads to early articular cartilage degeneration [1, 20]. Though fresh allografts have been used for human meniscal transplantation, cryopreserved or frozen allografts are widely used for clinical purposes [7, 14, 19, 28, 29, 34, 38, 40]. These preservation and storage techniques have been demonstrated to cause changes, at least temporarily, in cell survival, matrix biochemical composition, and collagen architecture of the allograft [2, 3, 18, 36, 39], changes that affect the biomechanical properties of the meniscal implant and knee joint. Thus, the present results cannot be directly compared with human transplantation, and whether human meniscal transplantation can either prevent or postpone the onset of symptomatic osteoarthritis has yet to be determined.

Primary meniscal transplantation was demonstrated to be superior to secondary transplantation. Until now the indication for meniscal transplantation in humans has mostly been symptomatic degenerative joint disease, and pain relief and improved functional score have been reported after implantation, which may be regarded as a satisfactory outcome [7, 14, 34, 38]. A clinical implication of the present study may be that if the aim of meniscal transplantation is to reduce degenerative changes of articular cartilage, it has to be performed soon after meniscectomy. Ridge formation (Fairbank-changes) following total meniscectomy alter the shape of the condyles [13], and if transplantation is delayed, there may be a mechanical conflict between the transplant and the condyles. These changes may have been partly responsible for the graft extrusion in the secondarily transplanted knees. On the other hand, the results did not show whether secondary transplantation actually reduced or prevented further degenerative cartilage changes. As early as 3 months after meniscectomy, the DACC were at the same level as when measured after 6 months.

The image analysis method was introduced to obtain objective measurements. The overall interpretation of the test versus retest was that the results could be reproduced with an acceptable repeatability. The paired measurements demonstrated high correlations, and agreed acceptably on average, with low or negligible mean differences compared to the significant differences between the treatment groups. Thus, when comparing mean values, as was done in the present study, it is reasonable to assume that the method actually detected significant differences between the treatment groups without the effect of methodological bias. However, the limits of agreement accepted differences between paired observations larger than the differences found between the treatments, which implied that the variation may lead to misinterpretation of single observations. Thus, the method should be limited to comparing sample means, and small samples should be evaluated carefully. Previously presented methods have assessed the articular cartilage degeneration grossly or histologically by the use of score systems [16, 31]. It is not known if the image analysis method has a higher degree of reproducibility than these semiquantitative methods, as the repeatability of these methods has not yet been measured systematically.

The image analysis measured the dissemination of degenerative cartilage changes and thus ignored the depth of the changes. The results should not be compared directly with histologically scored articular cartilage changes. However, the method seemed adequate in measuring the degree of DACC, at least within the range of changes presented in this study. An advantage of the image analysis method was the quantitative measurement of the DACC, but the method did not reveal detailed information about the cartilage surface, which is a well known disadvantage in almost all quantitative or semiquantitative methods. Furthermore, measuring degenerative cartilage changes by image analysis can only be used in experimental studies because photographs perpendicular to the articular surface cannot be obtained without opening the joint.

The tibial DACC were most pronounced in the central part of the meniscectomized knee, where the contact area is concentrated and the contact stress increases after meniscectomy [6, 21, 22, 27, 30]. The same central localization of the degenerative changes was noted in the transplanted knees, perhaps because of transplant extrusion in these knees with subsequent reduced congruity between the transplant and the articular cartilage. Extrusion may have led to inefficient load distribution, which resulted in increased and localized stress on the femoral-tibial contact area. However, whether the graft extrusion could be related to the degree of cartilage degeneration was not investigated.

The suspicion of horn displacement and transplant extrusion aroused by the gross inspection was confirmed by the image analysis. However, the localization of the transplant on the tibial plateau was examined in a nonweight-bearing situation, and the in vivo conditions remained unknown. The results indicated that the secondarily trans-

planted grafts were extruded more than the primary grafts, but the difference could be explained by shrinkage of the secondarily transplanted grafts.

The tendency of horn displacement has been described in other meniscal transplantation studies, where the suture-anchoring technique was also used [32, 39]. In our study, the suture anchors were placed vertically in the graft capsular edge to encircle the circumferential collagen fibers. The suture anchors were partly pulled out through the graft tissues, perhaps because of disturbance to the collagen fiber architecture. Both auto- and allograft ligamentous tissues heal in bone tunnels [33], but the ligamentous end of the horn may not have been long enough to sufficiently ensure adequate ligamentous ingrowth in the drilled bone tunnel. Insufficient horn anchoring probably aggravated graft extrusion, and proper fixation is essential to secure optimal load distribution and shock absorption [9, 27]. Techniques with donor bone plugs or bone blocks attached to the horns should be preferred in future studies [19, 38], even though insufficient horn anchoring was not necessarily the only explanation for the extrusion problem, since graft extrusion has been reported after meniscal transplantation, where the bone plug technique was used [29]. However, the effect of different horn anchoring techniques could not be determined from this study, and future experimental work stressing the anchoring technique should be encouraged.

Graft shrinkage may be time dependent, as demonstrated by the difference between the 3-month implanted secondary grafts and the 6-month implanted primary grafts, and thus it may be associated with cellular repopulation and remodeling of the collagen architecture, which has been demonstrated to occur within the first postoperative year [3, 12]. Hypothetically, the shrinkage of the secondarily transplanted grafts could also be due to the previously mentioned mechanical conflict between the graft and the condyles. The use of fresh allografts with potential donor cell survival, at least for a period of time after implantation, may possibly affect the viability, the biochemical composition, and the collagen architecture of the graft [35]. The histological appearance of the meniscal allografts presented in this study will be reported later in a prospective paper.

Preserving or restoring the collateral ligament is preferable to provide optimal stability. Temporary detachment of the collateral ligament has been used to provide a better view of the horn insertion sites [11, 18]. The experience from this study showed that, in the sheep model, the insertion sites could be located and drilled with a drill guide without sacrificing the medial collateral ligament. In human meniscal transplantation studies, there is still disagreement about whether the femoral attachment of the collateral ligament should be temporarily detached, and if open arthrotomy should be preferred to arthroscopically assisted technique to ensure the best surgical conditions [19, 36, 37, 38].

There are no long-term follow-up investigations available on meniscal transplantation to show if this would have a significant protective effect on the articular surface. There is still a great need for animal experimental studies on meniscal allograft transplantation and the methods for allograft transplantation should be refined and improved. Now, and in the future, we may critically evaluate experimental and clinical studies.

The important conclusions of this experimental study were that primary meniscal transplantation protected the articular surface against cartilage degenerative changes, although degenerative changes also occurred in the transplanted knees, and that primary transplantation was superior to secondary transplantation. Furthermore, extrusion of the meniscal transplants was a problem, particularly in the secondarily transplanted knees, which also showed shrinkage.

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