

Characteristic Complications After Autologous Chondrocyte Implantation for Cartilage Defects of the Knee Joint

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Background: Although autologous chondrocyte implantation (ACI) is a well-established therapy for the treatment of isolated cartilage defects of the knee joint, little is known about typical complications and their treatment after ACI.

Hypothesis: Unsatisfactory outcome after ACI is associated with technique-related typical complications.

Study Design: Case series; Level of evidence, 4.

Methods: A total of 309 consecutive patients with 349 ACI procedures of the knee joint were analyzed. Three different ACI techniques were used: periosteum-covered ACI in 52 cases (14.9%), Chondrogide (Geistlich Biomaterials, Wolhusen, Switzerland) membrane-covered ACI in 215 cases (61.6%), and a 3-dimensional matrix-associated ACI (BioSeed-C, Biotissue Technologies, Freiburg, Germany) in 82 cases (23.5%). In 52 patients, revision surgery was performed for persistent clinical problems. These patients were analyzed for defect size and location, technique of ACI, and intraoperative findings during revision surgery. The mean time of follow-up for patients after ACI was 4.5 years (standard deviation, ± 1.5).

Results: Four typical major complications were identified: hypertrophy of the transplant, disturbed fusion of the regenerative cartilage and the healthy surrounding cartilage, insufficient regenerative cartilage, and delamination. These diagnoses covered a total of 88.5% of the patients who underwent revision surgery. The overall complication rate was highest in the group of patients treated with periosteum-covered ACI ($P = .008$). The incidence of symptomatic hypertrophy was 5.2% for all techniques and defect locations; the highest incidence was in patients treated with periosteum-covered ACI (15.4%) ($P = .001$). The incidence of disturbed fusion was highest in the Chondrogide-covered ACI (3.7%) and the matrix-associated ACI group (4.8%). Concerning the incidence of complications by defect location, there was a tendency for increased complications in patellar defects ($P = .095$). Within the patellar defects group, no correlation was found for the occurrence of delamination, insufficient regeneration, and disturbed fusion. As a statistical trend, an increased rate of hypertrophy was found for patellar defects ($P = .091$).

Conclusion: A major proportion of complications after ACI can be summarized by 4 major diagnoses (symptomatic hypertrophy, disturbed fusion, delamination, and graft failure). Among those, the overall complication rate and incidence of hypertrophy of the transplant were higher for periosteum-covered ACI. Furthermore, an increased rate of symptomatic hypertrophy was found for patellar defects. Therapeutic concepts need to be developed to treat these typical complications of ACI.

Keywords: cartilage lesion; knee joint; autologous chondrocyte implantation; complications

Autologous chondrocyte implantation (ACI) represents a well-established surgical procedure for the treatment of

knee-joint cartilage defects. It is recommended as a treatment for isolated large cartilage defects of the knee joint by specialist colleges and orthopaedic organizations in several countries. Short- and medium-term results regarding this procedure are satisfying and reliable.^{2,16,23,26,31} Presently, one of the major points of interest focuses on the significance of ACI in comparison with other further therapeutic options (eg, transplantation of cartilaginous cylinders or microfracture).^{1,17,18,29}

Nevertheless, a small but significant number of ACI procedures lead to less than satisfactory results. Although

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some complications after ACI, such as hypertrophy of the transplant, have been acknowledged,^{13,19,26} unsuccessful and unsatisfactory clinical outcomes after ACI are rarely described in the literature available on ACI. Systematic follow-up of further complications, including their incidence, is only available in single reports with small case numbers¹³ and recommendations concerning the treatment of these complications are absent.³² Detailed descriptions of the incidence of ACI failure with relevance to defect location, patient age, defect size, and technical modification of ACI are not yet available. The follow-up of complications and adverse effects after ACI is the subject of the present study.

PATIENTS AND METHODS

Between 2001 and 2006, a total of 309 patients were treated with ACI for isolated cartilage lesions of the knee joint (total number of ACI procedures = 349) in our department. These patients were evaluated for age, defect size, defect location, and technical modification of ACI applied for the clinical outcome.

Depending on the surgeon performing ACI, the conventional technique (periosteum patch–covered ACI, 52 cases, surgeons C.E. and M.S.),² the Chondrogide (Geistlich Biomaterials, Wolhusen, Switzerland) membrane-covered ACI technique (215 cases, surgeon M.S.),^{11,29} or a matrix-associated procedure (82 cases, surgeon C.E.)^{23,25,28} were used according to individual preference (Figure 1).

The process of ACI treatment involved 2 procedures. At the initial arthroscopy, cells were harvested from the intercondylar notch; the volume of the lesion was estimated to determine the appropriate cell density during culture. After *in vitro* expansion, during the second step of the cell implantation, the volume of the lesion was measured. The cells, which were originally delivered in 1 mL of medium as a centrifuged pellet, were resuspended in a volume of medium equivalent to the volume of the lesion. In all cases, the damaged area of cartilage was debrided. The debrided area was extended sideways until it was entirely surrounded by healthy cartilage. In this area, the full depth of cartilage down to the subchondral bone was removed; care was taken to avoid perforating the latter. For this stage of the operation, a curette and, in the region of the rim, a scalpel were used in a recurring sequence. This procedure was followed in all groups. In the membrane group, a Chondrogide membrane was cut to size and was sutured in a circular manner with polydioxanone suture material (6-0, Ethicon Inc, Johnson & Johnson, Nordersted, Germany); the chondrocyte suspension (1 million cells per cm² debrided defect) was then injected.^{11,30} Once the transplant had been sealed with fibrin glue (Tissucol, Baxter GmbH, Heidelberg, Germany), a Redon suction drain was placed, and the wound was closed layer by layer. The same suture technique and procedure were used in the periosteal patch group. In this group, the periosteal patch was harvested from the proximal tibia via an additional incision, as described by Brittberg et al.² In the matrix group, after *in vitro* expansion, cells were cultured on a 3-dimensional

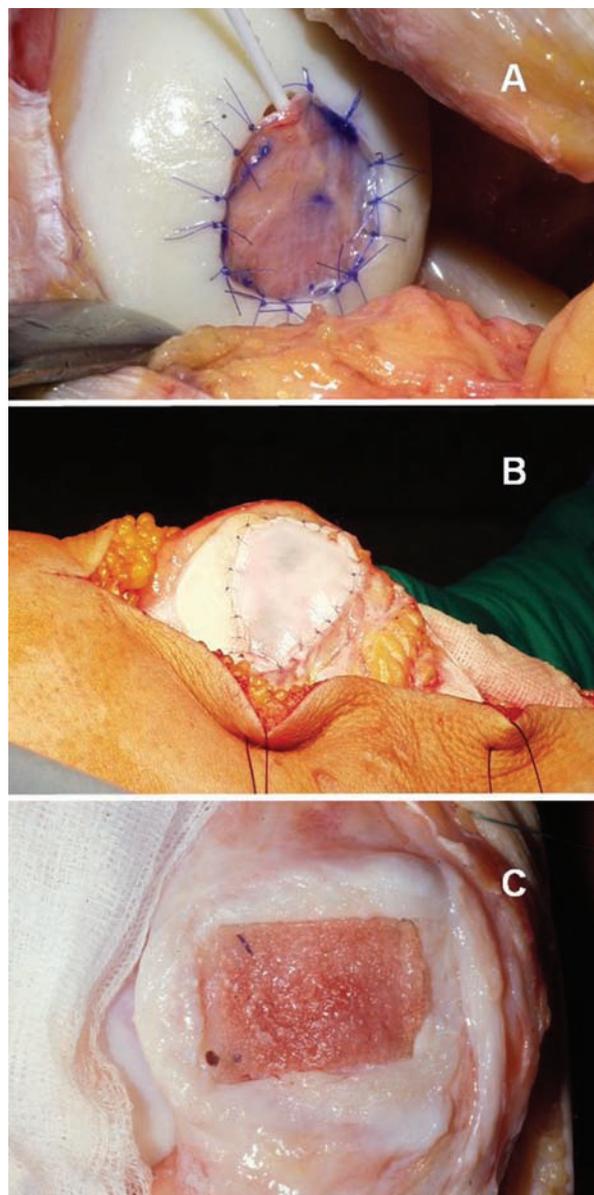


Figure 1. Different autologous chondrocyte implantation (ACI) techniques used in the present study: A, periosteum covered ACI; B, Chondrogide-covered ACI; and C, matrix-associated ACI using BioSeed-C.

poly(lactic-co-glycolic) acid fleece and afterward implanted using a transosseus fixation technique (M. Brittberg, unpublished data, 2000).^{4,25}

All patients who received revision surgery due to transplant-associated persistence of pain or loss of function in our hospital related to a complication of the ACI were participants in the present study. Arthroscopic revision surgery was indicated by 2 independent surgeons experienced in ACI. Revision surgery was performed in those cases in which patients had persistent pain and in which MRI revealed abnormal cartilage or subchondral bone signals in the area in which ACI was performed.

Therefore, only symptomatic complications were captured in the present study. Those patients who received arthroscopy of the affected knee joint for any other reason (such as replacement of the anterior cruciate ligament or meniscal surgery) were not included. Therefore, 52 patients were available for the present study. The mean time from initial ACI to the revision surgery was 20.4 months (standard deviation [SD] \pm 10.4).

Intraoperative diagnosis from revision surgery was taken from the surgical protocol and compared with the diagnosis that was made in our outpatient clinic at the same time the indication for a revision surgery was evident. Defect size, defect location, and ACI technique were taken from the original protocol from the ACI according to the recommendations given by the International Cartilage Repair Society (M. Brittberg, unpublished data, 2000).

Statistical Analysis

SPSS for Windows version 15.0 (SPSS Inc, Chicago, Illinois) was used for the statistical analysis designed to work up the data ascertained in this study. The χ^2 test of independence was used to reveal statistically significant differences between different surgical techniques as well as different defect localization. Multivariate regression analysis was further used to exclude other variables, such as age of the patients and defect size. *P* values $<$.1 were considered a statistical trend; those $<$.05 were considered statistically significant, and those $<$.01 were considered strongly significant.

RESULTS

Concerning the total number of patients who received ACI for cartilage lesion in our hospital, the mean age was 35.2 years (SD \pm 9.2). Periosteum-covered ACI was used in 52 cases (14.9%), while the Chondrogide-covered ACI was used in 215 patients (61.6%). Three-dimensional matrix-associated ACI (BioSeed-C, Biotissue Technologies, Freiburg, Germany) was applied in 82 cases (23.5%). As for defect location, 154 defects (43.4%) were located on the medial

femoral condyle, 29 (8.2%) on the lateral femoral condyle, 48 defects (13.5%) were located in the trochlea, and 124 patellar lesions (34.9% of the defects) were treated. Therefore, the total number of defects was 349 in 309 patients. Among the 309 patients, the ratio of men to women was 1.1:1 (165 men and 144 women). The average defect size was 4.6 cm² (SD \pm 2.2; defect sizes are given before surgical debridement of the defects was performed) (Table 1).

The mean age of the patients who received revision surgery and who participated in this study was 35.8 years (SD \pm 10.2). Fourteen (26.9%) of these patients received periosteum-covered ACI, 26 (50%) had initially been treated with Chondrogide-covered ACI, and in 12 cases (23.1%), matrix-associated ACI (BioSeed-C) was applied. Concerning the defect location, revision surgery was indicated for 26 defects located on the medial femoral condyle (50% of the defect location of the patients who needed revision surgery), 2 defects (3.8%) located on the lateral femoral condyle, 19 defects (36.5%) found on the patella, and 5 defects located in the trochlea (9.6%). In relation to the total number treated, 16.9% and 6.9% of the patients who were initially treated for defects located on the medial and lateral femoral condyle, respectively, required revision surgery. The percentage of patients who had revision surgery with initial defects of the patella and trochlea was 15.3% and 10.4%, respectively. Nevertheless, no significant difference between incidence of revision and defect localization could be demonstrated (*P* $>$.1).

Regarding the technical modification of ACI applied, the rate of patients treated with revision surgery was highest in the periosteum group (26.9%), followed by the BioSeed-C group (14.6%) and the Chondrogide-covered ACI group (12.1%) (*P* = .008).

No influence of patient age and defect size on the incidence of revision surgery was found (*P* $>$.1). The mean period of time between initial ACI and revision surgery was 20.4 months (SD \pm 14.0). The follow-up rate for clinical evaluation was 48 of 52 (92.3%); the mean duration of follow-up was 4.5 years (range, 13-86 months) from the date of revision surgery.

TABLE 1
Characteristics of Patients Who Received ACI Compared With Those Who Needed Revision Surgery^a

	All Patients (N = 309)	Patients Receiving Revision Surgery (n = 52)
Age at time of ACI (y)	Mean 35.2 (SD \pm 9.2)	Mean 35.8 (SD \pm 10.2)
Sex (male:female)	165:144 (1.1:1)	22:30 (1:1.4)
Defect size (cm ²)	Mean 4.6 (SD \pm 2.2)	Mean 4.5 (SD \pm 1.7)
Defect location		
Medial femoral condyle	154 (43.3%)	26 (50.0%)
Lateral femoral condyle	29 (8.2%)	2 (3.8%)
Patella	124 (34.9%)	19 (36.5%)
Trochlea	48 (13.5%)	5 (9.6%)
Technique applied		
Periosteum-covered ACI	52 (14.9%)	14 (26.9%)
Chondrogide-covered ACI	215 (61.6%)	26 (50.0%)
Matrix-associated ACI (BioSeed-C)	82 (23.5%)	12 (23.1%)
Time from ACI to revision surgery (mo)		Mean 20.4 (SD \pm 14.0)

^aACI, autologous chondrocyte implantation; SD, standard deviation.



Figure 2. Typical MRI of a patient with transplant hypertrophy following periosteum-covered autologous chondrocyte implantation for a patellar cartilage lesion.

All patients underwent clinical examination and MRI before revision surgery. Before revision surgery, 18 cases (34.6%) had no definitive diagnosis. Revision surgery was performed for persistent complaints as early as 6.4 months and up to 34.4 months after ACI. In these cases, MRI did not reveal any specific pathologic changes.

The decision for revision surgery was based on clinical and radiologic findings. Clinical examination in this group of patients revealed exercise-related pain, subjective instability, recurrent effusions, and recurrent blockages of the joint. The revision surgeries were performed by 2 independent surgeons experienced in ACI for several years.

Magnetic resonance imaging was performed, and pathologic MRI findings in combination with persistent severe clinical findings generally led to revision surgery. Magnetic resonance imaging was able to show persistent insufficient regenerative cartilage in 21.2% of the cases. An increasing subchondral edema on MRI was found for 9.6% of the patients. Hypertrophy of the newly formed cartilage was observed in 4 cases (7.7%) (Figure 2). Osteochondral defects (necrosis of the subchondral bone) gave indication for revision surgery in 3 cases (5.8%). In 5 cases (9.6%), MRI showed an increasing subchondral edema. In the remainder of patients, various MRI diagnoses in combination with clinical findings were made that led to the need for revision surgery (delamination and heterotopic ossifications found within the regenerative tissue).

Concerning pathologic changes found intraoperatively, only 4 common major problems were observed (Figure 3). We found a hypertrophy of the regenerated cartilage in 16 cases (30.8%), insufficient fusion between the regenerated cartilage and healthy cartilage at the edge of the former defect in 12 cases (23.1%), insufficient or incomplete regenerative cartilage in 9 cases (17.3%), and delamination of

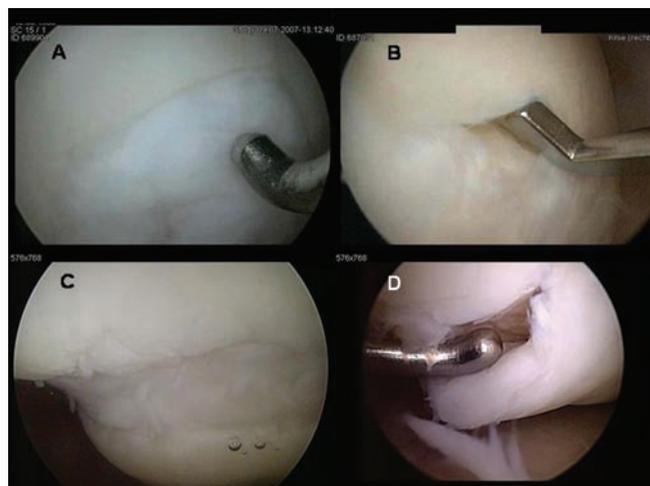


Figure 3. Arthroscopic views of characteristic patients who underwent revision surgery for hypertrophy of the transplant (A), malfusion (B), insufficient regenerative tissue (C), and delamination (D) and were participants in the present study.

intact cartilage in the range of the defect in 9 cases. In total, 88.5% of the patients who received revision surgery after ACI were affected by one of these diagnoses. Among the remaining 11.5% of the patients (6 cases), 1 patient had a traumatic cartilage lesion in the area of the ACI due to an accident. This patient was treated with a further ACI, while 3 cases of arthrofibrosis found were treated with arthroscopic arthrolysis. Two patients suffered from osteonecrosis of the subchondral bone in the defect area (treated with anterograde drilling in both cases).

The incidence of these diagnoses, by defect location and technical modification of ACI applied, are shown in Figure 4 and Table 2. The incidence of hypertrophy of the transplant was highest in the periosteum-covered group (15.4%) and lowest in the Chondrogide-covered ACI group (1.9%). The incidence was 4.9% in those patients treated with matrix-associated ACI ($P = .001$). Interestingly, we did not observe any malfusion in patients treated with periosteum-covered ACI, while the ratio of patients affected by this problem was similar in both the Chondrogide-covered ACI technique (3.8%) and the matrix-associated ACI group (4.9%). The incidence of insufficient regenerative tissue in the defect area was 1.9% in the Chondrogide group, 3.8% in the periosteum group, and 3.7% in the matrix-associated ACI group. A lower incidence of insufficient regenerative tissue in the Chondrogide group was observed as statistical trend ($P = .07$). The complication of delamination was found in 3.8% of patients treated with periosteum-covered ACI, 2.8% of patients treated with Chondrogide-covered ACI, and 1.2% of the matrix-associated ACI group. No statistically significant differences were detected ($P > .1$).

Regarding defect location, the highest incidence for hypertrophy of the transplant was found in defects of the patella (8.1%), followed by the medial and lateral femoral condyle (both 3.5%); no hypertrophy was found in defects located in the trochlea

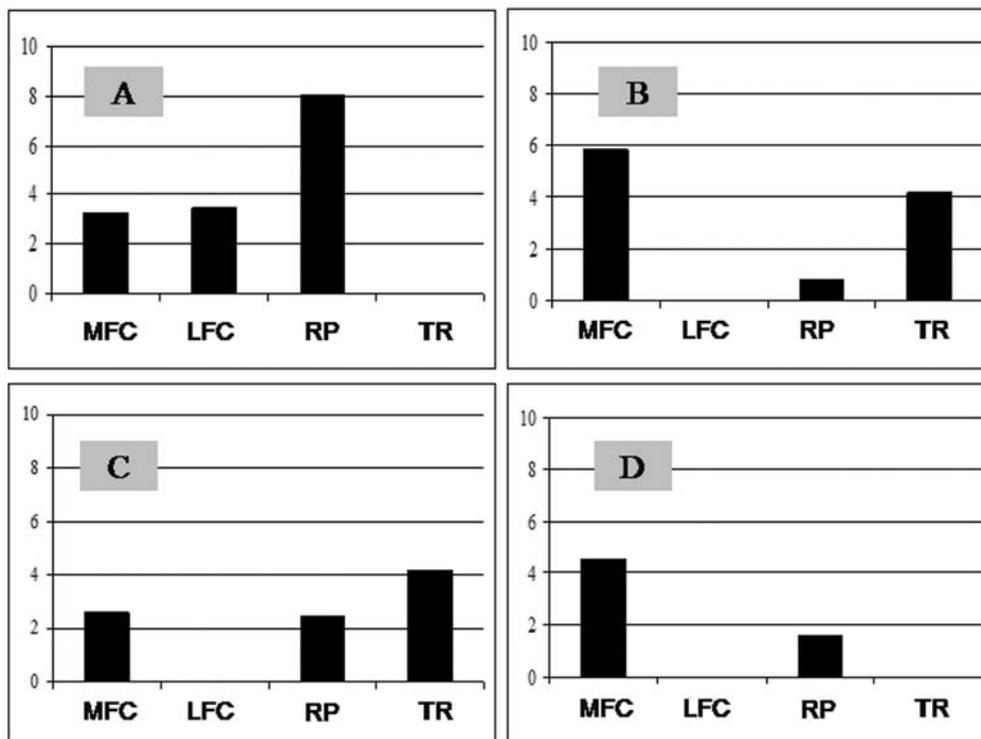


Figure 4. Incidence (in %) of hypertrophy of the transplant (A), malfusion (B), insufficient regenerative tissue (C), and delamination (D) by defect location. MFC, medial femoral condyle; LFC, lateral femoral condyle; RP, patella; and TR, trochlea.

TABLE 2
Overall Incidence of Hypertrophy of the Transplant, Malfusion, Insufficient Regenerative Tissue, and Delamination Based on Technique of Autologous Chondrocyte Implantation (ACI) Applied^a

Technique of ACI Applied	Revision Surgeries Performed (% of All Patients Treated With This Specific Technique)	Diagnosis Found During Revision Surgery (% of All Patients Treated With This Specific Technique)
Periosteum-covered ACI	14 of 52 (26.9)	Hypertrophy: 8 (15.4) Malfusion: 0 Insufficient regenerative tissue: 2 (3.8) Delamination: 2 (3.8) Others: 2 (3.8)
Chondrograde-covered ACI	26 of 215 (12.1)	Hypertrophy: 4 (1.9) Malfusion: 8 (3.8) Insufficient regenerative tissue: 4 (1.9) Delamination: 6 (2.8) Others: 4 (1.9)
Matrix-associated ACI (BioSeed-C)	12 of 82 (14.6)	Hypertrophy: 4 (4.9) Malfusion: 4 (4.9) Insufficient regenerative tissue: 3 (3.7) Delamination: 1 (1.2) Others: 0

^aFor the overall revision rate after ACI, an increased incidence was found for periosteum-covered ACI ($P = .008$).

($P = .09$). Malfusion was found most frequently in defects of the medial femoral condyle (5.8%) and the trochlea (4.2%). No malfusion was found in the lateral femoral condyle and only 1 case

of malfusion was found in patella defects (0.8%). Detailed results, including incidences of insufficient regenerative tissue and delamination, are provided in Figure 4.

DISCUSSION

Autologous chondrocyte implantation represents a well-established and acknowledged therapy for the treatment of isolated cartilage defects of the knee joint. As in most procedures, however, unsatisfactory results for patients and surgeons can be observed. These might include complications or a complete failure of the procedure. The incidence of such unsatisfactory results varies from 10% to 30%, depending on studies and location of the transplant.^{3,12,15,17,26,27,29} Although detailed short- and medium-term results after ACI are available, few studies deal with complications after this procedure.^{13,32} Even less information can be found concerning the therapeutic options for ACI failure or complications after ACI. The systematic analysis of such complications depending on surgical modification of ACI and defect location is the focus of this study.

During the time of this study, a total of 349 ACIs on 309 patients were evaluated. All revision procedures were performed at our hospital. We cannot exclude the fact that further treatment after ACI for a small number of patients was undertaken at other hospitals. Still, we assume to have acquired the great majority of complications. The total number of patients who needed further intervention after ACI was 52 (16.8% of all transplanted patients); this is comparable to the percentage of patients with unsatisfactory results after ACI found in other similar studies.^{12,14,27}

Attracting attention in this group of patients is the high heterogeneity of nonspecific preoperative diagnoses. It is most likely that this result is a reflection of the still rather limited clinical experiences available with this procedure. This applies to the assessment of the clinical follow-up, and also to the evaluation of the clinical outcome by means of MRI. It depends on the sensitivity and specificity of certain adjustments and has a high potential for improvement.^{6,24} Evidence suggests clinical follow-up after ACI can be very difficult.²¹ In 18 cases of persistent discomfort, the indication for revision surgery was noted to be unclear, and in the remaining cases, 9 indefinite diagnoses were made. Surprisingly, an intraoperative confirmation of such high heterogeneity of diagnoses could not be made. Therefore, based on intraoperative findings, 4 diagnosis groups were formed in which 88.5% of the revision patients could be included. Some of these diagnoses have previously been described.^{13,19,32} The four major complications are (1) hypertrophy of the regenerated cartilage, which can be suggested if within the debrided defect area, a mechanically stable regenerate has formed that extends to the level of the native surrounding cartilage; (2) insufficient fusion of the regenerated cartilage and healthy cartilage at the edge of the former defect, which can be diagnosed if after ACI an intact and functionally stable regenerative tissue has formed but is not integrated entirely into the surrounding cartilage (Rarely, this situation can be found in a circular manner, but in most cases only small sections are not integrated.); (3) graft failure or formation of an insufficient regenerative cartilage (We believe that this condition can be diagnosed if only parts of the regenerative tissue are insufficient. It is usually present as soft, mechanically less-enduring

replacement tissue. If only solitary parts of the regenerative cartilage contain such tissue, a partial graft failure can be diagnosed.); and (4) delamination, which describes a shearing of the regenerative cartilage from the subchondral lamella in regularly formed cartilage tissue. Further observed diagnoses in this work leading to revision surgery were not always associated with an unsatisfactory outcome in the area of the ACI but with general surgical complications after arthrotomy, such as arthrofibrosis in 3 cases.

Besides the categorization of transplant-associated complications after ACI, this study describes incidence and dependency on defect localization, patient age, defect size, and the technical modification. In our patient cohort, the incidence of hypertrophy of the regenerated cartilage was 5.2% and therefore in a range that has previously been described.^{10,12,13,32} The overall incidence of malunion was 3.9%; the incidence of (partial) graft failure and delamination were each 2.9%. These complication rates do not seem to differ from data previously presented.^{13,32} No correlation between the frequency of revision surgery and patient age and defect size could be observed. This coincides with other studies that observed correlations of these 2 parameters with functional results. Nevertheless, in our study, the only parameter assessed was complications requiring revision surgery.

When examining the incidence of complication based on defect location, it is striking that in the current study a large number of defects were located on the patella. Although the treatment of patellar lesions seems uncommon in some countries such as the United States, using ACI for the treatment of patellar lesions has become more and more accepted. This is represented by some studies exclusively dealing with the issue of ACI for patellar defects.^{5,7,20,22} Nevertheless, clinical results still seem inferior to those of defects located on the femoral condyles.^{19,22,27} Concerning the defect locations, we observed different allocations of incidences for the individual diagnosis groups that might help to further explain inferior clinical results described for patellar lesions. The incidence of hypertrophy of the regenerated cartilage was 8.1% for the patella, which is higher than for the medial and lateral femoral condyles (each 3.5%, $P = .09$). Interestingly, no hypertrophy was observed for the trochlea. The higher incidence of hypertrophy of the patella, compared with other locations of the knee joint, correlated with MRI findings performed earlier by our group.¹⁹ In contrast to these findings, malunion was more frequent for the medial femoral condyle (5.8%) than for the patella (0.8%). One possible explanation for these findings could be that higher patellar shear forces provide stimuli for hypertrophy.^{8,9} Data to compare these findings with earlier studies are not available, as studies dealing with the topic of hypertrophy do not contain detailed information about hypertrophy locations.^{10,13} Interestingly, patients in whom hypertrophy occurred in the further clinical course after ACI were younger, while those in which insufficient regeneration was observed were, on average, older than the entire study population (Table 3).

The fact that during the time of assessments different ACI techniques were performed allows evaluation of complication rates based on ACI technique. When analyzing

TABLE 3
Detailed Characteristics of Patients Who Received Revision Surgery by Intraoperative Finding^a

Diagnosis of Revision Surgery	Age at Time of Revision Surgery (y)	Defect Location	Defect Size (cm ²)	Technique of ACI Applied	Follow-up (mo)
Hypertrophy (16 cases)	Mean 32.4 (SD ± 10.2)	MFC: 5 (31.3%) LFC: 1 (6.3%) RP: 10 (62.5%) TR: 0 (0%)	Mean 3.8 (SD ± 1.2)	P: 8 (50%) C: 4 (25%) M: 4 (25%)	Mean 56.7 (SD ± 17.2)
Malfusion (12 cases)	Mean 39.4 (SD ± 9.7)	MFC: 9 (75.0%) LFC: 0 (0%) RP: 1 (8.3%) TR: 2 (16.7%)	Mean 4.1 (SD ± 1.5)	P: 0 (0%) C: 8 (66.7%) M: 4 (33.3%)	Mean 46.4 (SD ± 14.8)
Insufficient regenerative tissue (9 cases)	Mean 41.0 (SD ± 8.0)	MFC: 4 (44.4%) LFC: 0 (0%) RP: 3 (33.3%) TR: 2 (22.2%)	Mean 5.0 (SD ± 1.3)	P: 2 (22.2%) C: 4 (44.4%) M: 3 (33.3%)	Mean 52.1 (SD ± 20.4)
Delamination (9 cases)	Mean 35.0 (SD ± 7.9)	MFC: 7 (77.8%) LFC: 0 (0%) RP: 2 (22.2%) TR: 0 (0%)	Mean 5.6 (SD ± 2.4)	P: 2 (22.2%) C: 6 (66.7%) M: 1 (11.1%)	Mean 63.0 (SD ± 12.6)
Others (6 cases)	Mean 31.2 (SD ± 13.7)	MFC: 1 (16.7%) LFC: 1 (16.7%) RP: 3 (50%) TR: 1 (16.7%)	Mean 4.7 (SD ± 1.6)	P: 2 (33.3%) C: 4 (66.7%) M: 0 (0%)	Mean 48.8 (SD ± 22.9)
Overall 52 (cases)	Mean 35.8 (SD ± 10.2)	MFC: 26 (50.0%) LFC: 2 (3.8%) RP: 19 (36.5%) TR: 5 (9.6%)	Mean 4.5 (SD ± 1.7)	P: 14 (26.9%) C: 26 (50.0%) M: 12 (23.1%)	Mean 54.0 (SD ± 17.1)

^aACI, autologous chondrocyte implantation; SD, standard deviation; MFC, medial femoral condyle; LFC, lateral femoral condyle; RP, retropatellar; TR, trochlea; P, periosteum-covered ACI; C, Chondrograde-covered ACI; M, matrix-associated ACI/BioSeed-C.

the overall complication rates, a higher incidence in the group of patients who were treated with cell suspension and periosteum-covered ACI (26.9%) can be detected in comparison with the other 2 techniques ($P = .008$). Here, the incidence of complications requiring revision amounted to 12.1% for patients who had been treated with cell suspension and Chondrograde membrane and 14.6% of patients who received BioSeed-C. When assessing the individual diagnoses, it becomes apparent that, similar to previous studies,¹⁰ the incidence of hypertrophy of the regenerated cartilage is closely correlated with the use of periosteum-covered ACI (15.8% vs 1.9% in the Chondrograde group and 4.9% in the BioSeed-C group; $P = .001$). An admittedly novel and, from our point of view, interesting observation is that the clinical problem of malfusion was not present in patients from the periosteum group, whereas the incidence of malfusion in the Chondrograde group and the BioSeed-C group was almost identically high (3.9% and 3.7%, respectively). A possible explanation for these findings could be that in contrast to avital biomaterials, vital periosteum tissue leads to a better fusion with native surrounding cartilage. On the other hand, in the patient group treated with BioSeed-C, the technique allows treatment of poorly contained defects such as defects located on the edge of the condyle. Such indications have been included in the BioSeed-C group of patients and might cause at least part of the malfusions observed in the BioSeed-C group.

Concerning the incidence of graft failure and delamination, no obvious differences were observed. The ratio of insufficient regenerative cartilage in the group of patients treated with Chondrograde membranes was the lowest (1.9%), whereas the lowest rate of delamination was observed in the BioSeed-C group (1.2%). Still, the idea that the 3-dimensional structure of collagen could provide a better adherence onto the subchondral lamella remains hypothetical.

A very important issue arising from this study is the need to establish standardized therapeutic approaches to address these complications. According to our understanding of the repair process after ACI, patients with transplant hypertrophy are usually treated with shaving or partial resection of the transplant. On the basis of previous experience, we are convinced that bipolar electrocounters give the best results because conventional shavers often carry the risk of an aggressive debridement. This observation correlates with the treatment techniques other groups performed.^{10,13} In case of disturbed fusion of the regenerative cartilage and the surrounding cartilage, local bone-marrow stimulative therapy (such as microfracture or anterograde drilling) is commonly performed locally in the area of the lesion. This can possibly contribute to the formation of a sufficient connection between the newly built cartilage and the native cartilage, in our opinion. In the group of patients with incomplete or insufficient cartilage in the defect area, the therapy depended on the size of the area of insufficient tissue. In smaller defects ($\leq 2 \text{ cm}^2$),

microfracture or the transplantation of osteochondral cylinders was performed (1 case). In larger defects, we performed repeat ACI. The same principle is usually applied in cases of partial delamination. In these cases, the delaminated tissue was removed and therapy applied depending on the defect size observed after complete resection of the delaminated cartilage. Although treatment results after revision surgery are not presented in this article and no complete data are available on our patients, an improvement of function can be achieved in the majority of the cases using these therapeutic concepts.

In summary, despite satisfactory results in the treatment of patients who undergo ACI, some patients will experience ACI technique-dependent complications. Knowledge of these complications and treatment possibilities seems to be an essential responsibility in the support of patients who undergo ACI. The majority of these complications can be summarized as hypertrophy of the transplanted cartilage, malunion, (partial) graft failure, and delamination. From our experience, the sensitivity of MRI and clinical findings do not seem to be adequate to make a certain preoperative diagnosis. In the case of persistence of discomfort, the indication for revision arthroscopy should be made generously. Diagnoses of transplant hypertrophy observed in our patient cohort seem to be associated with the use of periosteum, while we suspect that hypertrophy and malunion are related to specific locations with a higher proportion of hypertrophies found on the patella. In contrast, disturbed unions were found more frequently on the femoral condyles. Greater case numbers in multicenter analyses will most likely clarify this observation. No consistent concept can be found concerning the performed therapies for the detected complications. Further studies need to be conducted to establish concepts and therapeutic strategies to address these complications.

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