Autologous chondrocyte implantation for the treatment of large full-thickness cartilage lesions of the knee

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ABSTRACT

Objective: To investigate the benefit, reliability, and complication rate of autologous chondrocyte implantation (ACI) in patients with large full-thickness cartilage defects of the knee.

Method: Between March 1997 and December 2001, 71 consecutive patients (24 women, 47 men) were treated with ACI at the Freiburg University Hospital, Germany, and were included in this study. Average age was 35 years (13-61). Lesions were mainly situated on the medial femoral condyle (n=46); mean defects size was 6.61 cm² (2-17.5), outerbridge grade III-IV. Number of previous surgical procedures was 2.13 (0-8). For outcome measurement, International Cartilage Repair Society (ICRS) knee examination form, Lysholm score, Cincinnati knee score, and the modified Cincinnati-knee-score were used. Correlation between treatment results, and previous surgical procedures was examined. Statistical analysis was performed using the 2-tailed paired and unpaired Wilcoxon-rang-sum-test (alpha=0.05).

Results: Mean follow-up 36 months (24-65). Modified Cincinnati score overall rating demonstrated highly significant improvements from 3.24 to 6.44 points (patients) and from 3.35 to 6.87 (physicians). Mean Cincinnati score improved from 27-72 points, ICRS score improved from grade D to grade C, and average Lysholm score from 33 points to 69 points. All but 11 patients returned to casual sports, 25 patients went in for regular sports 1-3 times a week or more. Complication rate was 11%.

Conclusion: Autologous chondrocyte implantation provides an appropriate method for the treatment of full-thickness cartilage lesions of the knee and gives good clinical short-term results.

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Cartilage lesions are common and do not heal by themselves.[1] They represent a great health care problem.[2] Several efforts to restore articular cartilage were undertaken without convincing success.[3-9] However, it is still not possible to restore hyaline cartilage using these techniques.[10-12] In 1994, autologous chondrocyte implantation (ACI) was introduced for the treatment of full thickness cartilage lesions of the knee.[13] The ability of this technique to provide hyaline-like articular cartilage in the knee joint was shown.[14-16] The ACI is now frequently performed and was recommended as the method of choice for symptomatic defects larger than 2 cm² after failed cartilage repair procedures.[17] Because few data exists about the rate of complications and revision surgeries, and because reported data vary greatly, some physicians are still hesitant to recommend ACI to their patients. Consequently, there is further demand for studies regarding benefit, safety, and reliability of ACI. Therefore, we report here on a prospective case series to investigate the benefit, reliability, and complication rate of ACI in patients with large full-thickness cartilage defects of the knee.

Methods. This is a prospective case series of 71 patients (24 women, 47 men). The inclusion criteria for this study comprised: focal full-thickness cartilage lesions of the knee on the medial or lateral femoral condyle, patella or trochlea; lesions grade III-IV in the outerbridge classification;[18] and symptoms such as pain or functional problems of the knee joint. All patients gave their oral consent following adequate information on mode of data acquisition, processing, analysis, interpretation, and publication, according to local law. Patients fulfilling at least one of the following criteria were excluded from this study: severe multifocal arthritis, diffuse

tricompartmental degeneration, multiple small lesions, age >63 years, presence of active infection, injuries or afflictions of regions other than the knee, pregnancy, neoplasm's, radicular pain, paralysis, psychiatric diseases, and fibromyalgia. Between March 1997 and December 2001, 73 full-thickness cartilage defects in 71 patients were treated with ACI at the Department of Orthopedic Surgery and Traumatology, University of Freiburg, Germany. Average age was 35 years (13-61); mean follow-up 3 years (24-65 months). Mean defect size was 6.61 cm² (2-17.5), assessed intraoperatively using a centimeter-scaled gauge. Defects (n=46) most frequently involved the medial femoral condyle; grade III-IV according to the outerbridge classification.[18] The mean number of previous surgical procedures was 2.13 (0-8). In 31 patients, 34 additional surgical procedures were performed (**Table 1**). For outcome measurement, International Cartilage Repair Society (ICRS) knee examination form,[19] Lysholm score,[20] Cincinnati knee score,[21,22] and the modified Cincinnati-knee-score,[23,24] were used. The latter one was rated by patient and physician. Apart from Cincinnati score overall rating, patients were divided into 3 entities according to 1) site of the lesion, 2) type of defect, and 3) etiology: (i) Lesions on the medial (n=46), and lateral femoral condyle (n=13), patella (n=4), and trochlea (n=7); (ii) single lesions (n=47), and multiple lesions (n=24); (iii) traumatic (n=18), degenerative (n=25), and osteochondrosis dissecans lesions (n=23). Radiographic evaluation was performed using the Jaeger/Wirth osteoarthritis score:[25] 46 patients showed no radiographic signs of osteoarthritis, 4 patients had initial osteoarthritis (minute osteophytes at eminentia intercondylaris and patella pole or base, no joint base narrowing), 19 patients displayed signs of mild osteoarthritis (definite osteophytes at tibia condyles, minimal narrowing of joint space, moderate subchondral sclerosis), and 3 patients signs of moderate osteoarthritis of the knee (moderate loss of joint space to half; considerable reduction of the femoral condyle curve; moderate or small osteophytes at femur, tibia and patella; marked subchondral sclerosis). The patients were treated by 2 different surgeons in a 2-staged procedure: After preoperative evaluation, the defective knee was examined arthroscopically under general or spinal anesthesia in a tourniquet controlled bloodless field for definitive indication and biopsy: approximately 200-300 mg of articular cartilage was taken from a lesser bearing area of the knee either from the linea terminalis of the medial or lateral femoral condyle or from the intercondylar notch. This sample then was sent to a cell culturing laboratory using a transport medium provided by the company (Genzyme, Cambridge, USA) for in vitro culturing and proliferation of chondrocytes to a number of more than 10 million cells under good manufacturing practices-conditions. A second operation approximately 6-8 weeks later included medial or lateral arthrotomy in a tourniquet controlled bloodless field. Prophylactic antibiotics were given. The cartilage defect was prepared, and debrided back to healthy cartilage, building a stable rim. Strict attention was given on taking care of the subchondral bone plate to avoid subchondral bleeding. Subsequently a template was fitted to the defect size. Periosteum was harvested through a small incision from the lateral aspect of the tibia using the template. This periosteal flap then was trimmed to defect size and sutured (Vicryl 6-0) to the rim of the defect until it was completely covered except for an opening for the injection of the autologous cultured chondrocytes. After sealing with fibrin glue, the chondrocytes were injected under the periosteal flap, and the opening was sutured, too. The surgical technique and the principles of culturing the chondrocytes were described in detail elsewhere.[13,26-28] In patients with mal-alignment of the leg axis, patella, or ligament tears, these prognostically unfavorable conditions were corrected during the same operation with the ACI. High tibial osteotomy (n=9), anterior cruciate ligament reconstruction (n=8), lateral release (n=1), and Ali Crogius procedure (n=1) (**Table 1**) were performed. Additional osteochondral autograft transfers (n=12) were perfumed in patients suffering from kissing lesions or complex lesions. If required, microfracture was performed (n=3) in these lesions smaller than 1 cm² (**Table 1**). Depending on defect size and position, physiotherapy was prescribed individually. Additionally, isometric exercises were performed. Continuous passive motion (CPM) machines were used 4-6 times a day for 30 minutes starting 6-24 hours after surgery. Range of motion initially was limited to 40° of flexion and was increased in stages of 5-10° per day, limited to 90° of flexion. In patients who received an implant on the patella, flexion was limited to 60°. For 2 weeks, the operated knee was unloaded. Partial weight bearing (20 kg) was applied to patients 2 weeks postoperative. Eight weeks postoperative, the load was gradually increased to full-weight-bearing by approximately 12 weeks. Patients were allowed to return to low-impact activities such as cycling 4-6 months postoperative, and to walking 6-9 months postoperative. Contact sports and such with abrupt and rapid movements such as tennis or badminton were not recommended before 12-24 months. Data acquisition was performed by an evaluator independent from the operation team. Correlation between treatment results, and patient's previous surgical procedures was examined. Statistical analysis comprised 2-tailed paired and unpaired Wilcoxon-rank-sum-test (alpha=0.05) with SPSS for Windows© Version 11.5.

Results. Overall rating significantly improved from 3.24 (fair) to 6.44 (good) points (patient) and from 3.35 (fair) to 6.87 (good) points (physician), in the modified Cincinnati knee score rating (p<0.0001). Mean Cincinnati score improved from 27 points (poor) to 72 points (good), (p<0.0001), average ICRS score improved from grade D (3.83) to grade C (2.94), (p<0.0001), and average Lysholm score from 33 points (poor) to 69 points (fair), (p<0.0001), (**Table 2**). At follow-up, all but 11 patients returned at least to casual sports, 25 patients performed regular workouts, namely, more than 3 times a week. Good to excellent outcomes could be evaluated in up to 86% of the patients of this study analyzing the Cincinnati knee score. Investigating the results of patients with defects on the lateral femoral condyle with this score, up to 95% of the patients showed good to excellent results. Eighty-nine percent of patients with isolated lesions on the medial or lateral femoral condyle showed good to excellent results. Analyzing the different entities, the improvement in scores was greater in patients with lesions on the lateral femoral condyle than in patients with lesions on the medial femoral condyle (p=0.367), the tibia (p=0.018), or the patella (p=0.114) in the Cincinnati knee score. In this group, 6 patients showed good and excellent results, with one patient demonstrating a fair result. Lysholm score evaluation demonstrated 2 patients with excellent and one patient with good results. Modified Cincinnati knee score overall rating in both the patient and the physician assessment improved more than 100% comparing pre- and post- operative results (p<0.0001), (**Table 3**). Mean score improvement in patients displaying single lesions was greater than in patients with complex lesions (p=0.39), but not significantly. Improvements in the Cincinnati knee score were greater than in the other scores (**Table 3**. Analyzing the results of the classification according to the etiology of the defects, the patient group with osteochondrosis dissecans lesions increased more than the group with degenerative (p=0.148), and traumatic (p=0.145) lesions: (**Table 3**) 9 patients showed excellent

Table 1 - Characteristics of patients included in this study.

Patient's characteristics	No. of patients
Gender	
Female	24
Male	47
Age (years)	35 (range 13-61)
Height (cm)	177 (range 140-196)
Weight (kg)	74 (range 45-98)
Treated knee	41 right, 30 left
Defect size (cm^2)	6.61 (2-17.5)
Cartilage grade	3
Grade III - first lesion	68
Grade IV - first lesion	3
Grade III - second lesion	21
Grade IV - second lesion	
Localisation (1st lesion)	46
Medial femoral condyle	13
Lateral femoral condyle	4
Patella	7
Trochlea	1
Tibia	
Localisation (2nd lesion)	
Medial femoral condyle	2
Lateral femoral condyle	3
Patella	9
Trochlea	10
Etiology	
Traumatic	24
Degenerative	24
OD	23
No. of previous surgical procedures	Mean: 2.13; 6x0, 20x1, 21x2, 13x3, 7x4, 1x5, 1x7, 1x8
Additional procedures	
OATS	12
HTO	9
ACL-reconstructions	8
Microfractures	3
Ali Crogius	1
Lateral release	1
Previous surgical procedures	
Meniscectomies (25 medial, 9 lateral)	34
ACL-reconstructions,	13
Lateral releases,	7
Drillings/microfractures,	25
Abrasion arthroplasties	13
Ali Crogius	1

OD - Osteochondritis dissecans, OATS - Osteochondral autograft transfer, HTO - High tibial osteotomy, ACL - Anterior cruciate ligament

Table 2 - Overall rating as measured by the different scores.

Score	Baseline		Follow-up	
	Score	Grade	Score	Grade
International Cartilage Repair Society (range)	4 (3-4)	D (C-D)	3 (1-4)	C (A-D)
Lysholm (range)	33 (14-53)	4 (4)	69 (31-95)	3 (1-4)
Cincinnati (range)	27 (5-46)	4 (3-4)	72 (22-100)	2 (1-4)
Modified Cincinnati - patient (range)	3.24 (1-7)	-	6.44 (1-10)	-
Modified Cincinnati - physician (range)	3.37 (1-6)	-	6.87 (2-10)	-

results, 12 patients had good results, and 2 patients had fair results in the Cincinnati knee score. No correlation between number of previous surgical procedures and scoring results could be demonstrated (ICRS, r=0.33; modified Cincinnati (patient), r= -0.3; modified Cincinnati (physician), r= -0.19; Cincinnati, r= -0.37, Lysholm, r= -0.38). However, patients who underwent 2 surgical procedures or less (n=26) scored better than those who underwent more than 2 (p=0.051). Patients who were younger than 35 years (n=47) at the time of ACI scored significantly better than those who were older than 35 (p=0.005). Patients with defects smaller than 5 cm² (n=30) scored not significantly better than those with larger defects (p=0.188). At follow-up, no knee joint infection occurred. No flexion and no extension deficit as well as no effusion of clinical relevance could be observed. Revision surgery was performed in 12 patients. Eight procedures (11%) were associated with complications of ACI as follows: graft failure (n=3), hypertrophy (n=3), and delaminating (n=2) of the periosteal flap. Graft failure was treated with re-ACI. Four other surgeries were performed because of locking sensations caused by plica synovialis (n=1), and osteochondrosis dissecans (n=2). One patient's graft was removed in another hospital at the patient's request.

Discussion. The present study demonstrated that patients with large full-thickness cartilage lesions of the knee benefit from ACI. Comparing pre- and post-operative state, they significantly improved activities of daily living, performance in their jobs and in sports. Shortcomings of this study are non-randomization, the number of <100 patients and the follow-up of 3 years. However, patient status at 2 years follow-up after ACI was reported as an important indicator for future outcome.[14] We could confirm these findings as most complications and improvements occurred within this 2-year-period. Yet, ACI will not be recommended unrestricted for widespread clinical use. Good to excellent outcomes could be evaluated in up to 86% of the patients. The Cincinnati knee score demonstrated good to excellent results in up to 95% of the patients with defects on the lateral femoral condyle. Eighty-nine percent of patients with isolated lesions on the medial or lateral femoral condyle showed good to excellent results. This is less than in other series.[15] However, these favorable results could not be measured in all scores as 21 patients did not improve in ICRS score. An explanation of this fact may be the ICRS knee examination form being the strictest knee score currently used: The lowest grade of any section (for example, ligament status, function) of an evaluation will be taken as the final grade and therefore overrule the better grades of other sections. In this

Table 3 - Rating broken down by localization, number, and etiology of the cartilage defects.

Localization/ number/etiology	ICRS		Lysholm		Cincinnati		Modified Cincinnati patient		Modified Cincinnati physician	
	Baseline	F/U	Baseline	F/U	Baseline	F/U	Baseline	F/U	Baseline	F/U
MFC (n=46)	D (3.83)	C (2.93)	33	70	27	72	3.2	6.36	3.33	6.89
range	C-D (3-4)	A-D (1-4)	14-53	31-95	5-46	22-100	1-7	1-10	1-6	2-10
LFC (n=13)	D (3.85)	C (2.69)	35	75	30	80	3.77	7.23	3.85	7.23
range	C-D (3-4)	A-D (1-4)	24-44	51-95	16-40	40-100	3-5	2-9	2-5	4-10
Patella (n=4)	D (3.75)	C (3.25)	31	64	22	67	2.75	5.5	3.5	6.0
range	C-D (3-4)	C-D (3-4)	24-39	55-75	14-30	46-97	2-4	5-7	3-4	5-8
Trochlea (n=7)	D (3.85)	C (3.29)	33	65	24	65	2.86	6.0	2.71	7.14
range	C-D (3-4)	C-D (3-4)	16-44	55-81	12-40	46-81	2-4	5-7	1-5	5-9
Single (n=47)	D (3.85)	C (2.98)	33	72	27	75	3.21	6.52	3.34	7.11
range	C-D (3-4)	B-D (2-4)	24-44	49-95	14-45	46-100	1-5	4-9	1-5	3-10
Multiple (n=24)	D	C (2.86)	33	66	26.58	66	3.29	6.29	3.41	6.42
range	C-D (3-4)	A-D (1-4)	14-53	31-95	5-46	22-100	2-7	1-10	1-6	2-10
Traumatic (n=18)	D (3.83)	C (2.96)	35	65	29	69	3.26	6.39	3.18	6.35
range	C-D (3-4)	A-D (1-4)	24-44	31-95	5-45	22-100	2-5	1-10	1-5	2-9
Degenerative (n=25)	D (3.8)	C (3.0)	32	69	25	70	3.2	6.32	3.52	7.2
range	C-D (3-4)	B-D (2-4)	16-49	40-85	12-46	25-88	2-5	3-10	2-5	3-10
OD (n=23)	D (3.87)	3 (2.86)	34	74	26	77	3.27	6.64	3.39	7.05
range	C-D (3-4)	A-D (1-4)	14-53	49-95	12-43	40-100	1-7	2-10	1-6	3-10

ICRS - International Cartilage Repair Society, MFC - Medial femoral condyle, LFC - Lateral femoral condyle, OD - Osteochondritis dissecans, F/U - Follow-up

study, the treatment of patella lesions was less successful than the treatment of defects of femoral condyle lesions (p=0.114). However, this finding might be due to statistical effects linked to the small number of patellar cases. Nevertheless, it corresponds to earlier reported findings.[13,14,22] Features indicating worse prognosis could be identified: multiple surgical procedures, higher age, and large defects. This corresponds to findings of other groups.[29] Rate of complications of the present study was 11%. From these, 7% were due to hypertrophy of the periosteal flap. No patients were suffering from adhesions limiting range of motion. Peterson et al[14] reported that 26% of 101 patients developed graft or periosteal hypertrophy, and 10% were suffering from intra-articular adhesions. Other authors reported rates of revision surgery between 0%[23] and 25%.[28] Three patients (4%) of the present study showed graft failure, corresponding to rates ranging from 5%[14] to 13%.[30] Reoperations were mainly caused by problems associated with the periosteal flap.[15,23,28] As this is a major drawback of the original ACI-technique, methods substituting the periosteum by a biodegradable scaffold were developed.[31-33] Nevertheless, long-term data has not been published yet.

Most of the patients included in the present study suffered from pain or dysfunction of the knee joint prior to ACI. They underwent several failed cartilage repair procedures and had to endure massive restrictions. This entails quality of life, ability to work, and sportsmanship. Thus, we consider the outcome of this study as an acceptable result for the treatment of large full-thickness cartilage lesions of the knee in this difficult cartilage condition and highly demanding surgery.

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Statistics

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