ORTHOPAEDIC SURGERY

Clinical outcome and success rates of ACI for cartilage defects of the patella: a subgroup analysis from a controlled randomized clinical phase II trial (CODIS study)

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Abstract

Aim Cartilage defects of the patella are considered as a problematic entity. Purpose of the present study was to evaluate the outcome of patients treated with autologous chondrocyte implantation (ACI) for cartilage defects of the patella in comparison to patient with defects of the femoral condyles.

Patients and methods 73 patients with a follow-up of 5 years have been included in this subgroup analysis of the randomized controlled clinical trial (RCT). In dependence of defect location, patients were divided into two groups [patella defects ($n = 45$) and femoral condyle defects ($n = 28$)]. Clinical outcome was evaluated by the means of the KOOS score at baseline and 6 weeks, 3, 6, 12, 18, 24, 36, 48 and 60 months following ACI.

Results "Responder rate" at 60 months (improvement from baseline of > 7 points in the KOOS score) in patients with patella defects was 86.2%. All scores showed a significant improvement from baseline. While overall KOOS score at 60 months was 81.9 (SD 18.6) points in femoral condyle defects, a mean of 82.6 (SD 14.0) was observed in patella defects ($p = 0.2483$).

Conclusion ACI seems an appropriate surgical treatment for cartilage defects of the patella leading to a high success rate. In this study, the clinical outcome in patients with patellar defects was even better than the already excellent results in patients with defects of the femoral condyle even though the study included relatively large defect sizes for both groups (mean defect size 6.0 ± 1.7 and 5.4 ± 1.6 for femur and patella, respectively).

Keywords Autologous chondrocyte implantation · Cartilage lesion · Knee surgery · Patella · Randomized clinical trial

Introduction

In recent years, due to satisfying long-term outcome and the availability of an increasing amount of prospective randomized controlled clinical trials (RCT), autologous chondrocyte implantation (ACI) has become an established treatment option for patients with focal cartilage defects of the knee [1–3].

The incidence for patellar lesions due to cartilage injury is around one-third of all cartilage lesions [4], but because

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of the accessibility and biomechanics of the patellofemoral joint, they are very complex to treat [5]. Thus, while the best outcome has been postulated for patients with cartilage defects located on the femoral condyles in most studies with success rates between 85 and 90%, cartilage defects of the patella—compared to defects located on the femoral condyle—have always been considered more problematic and inferior clinical outcome with success rates around 60% has been reported [6–10]. Also, the durability as well as the biomechanical adjustment of patellar ACI seem limited and a significant deterioration in outcome scores has been shown after 2 years [7, 11]. Nevertheless, these considerations were based on little scientific evidence and expert opinions and some authors also report improved outcome after treatment of patellar defects [12–14] and partially even better success rates in patellar than in trochlear localization [15]. A case study of 17 patients with combined medial patellofemoral ligament construction and ACI showed promising clinical results for the treatment of patellar lesions with Spherox [14]. Thus, the authors aimed to evaluate the clinical outcome of femoral and patellar defects in comparison (in an analysis of those subgroups based on the high-quality data gained in a randomized clinical study, which can be interpreted as controlled prospective cohort study and therefore a level III evidence). We hypothesized that due to the high quality and the self-adhesive nature of the product applied, clinical outcome will be non-inferior (compared to defects of the femoral condyles) and durable in patellar defects over a long-term follow-up of 5 years.

Data of the present study represent prospective evaluated clinical data, which have been evaluated during a prospective, randomized clinical trial over a follow-up period of 5 years with the background of dose efficiency and safety. For the present study, clinical outcome of patients with patellar defects was evaluated separately and compared to outcome of patients with femoral condyle defects directly.

Patients and methods

Study design and surgical treatment

The study was conducted in full compliance with the protocol, the principles laid down in the Declaration of Helsinki, the Good Clinical Practice guidelines, and all relevant laws and regulations. The protocol and informed consent form for this study were approved by the appropriate ethics committees and federal authority (Paul–Ehrlich-Institute) before any subject was included in the study.

This phase II study was set up as a single-blinded (patient blinded to applied cell dose), randomized, prospective, clinical intervention study comparing the effect of different cell doses (group A: 3–7 spheroids/cm^2; group

B: 10–30 spheroids/cm^2; group C: 40–70 spheroids/cm^2; 1 spheroid representing 200.000 cells at the time of spheroid culture). Inclusion and exclusion criteria are displayed in Table 1. In all patients, indication for study participation was determined during routine arthroscopy of the affected knee joint. Only cartilage defects grade III or IV with a size between 4 and 10 cm^2 were allowed to be included. In all cases, final eligibility was assessed by arthroscopy of the affected knee: only patients with isolated, focal symptomatic chondral and osteochondral single defects with intact adjacent cartilage were included.

After approval by the local ethics committees and federal authority following registration of the study (xxx; ClinicalTrials.gov Identifier: xxx; EudraCT Nr. xxx), patients with symptomatic full-thickness cartilage defects of the knee were included between November 2010 and September 2012 at ten German orthopedic centers.

The results of the final assessment of this study (1 year after treatment) have been published by Becher et al. (2017) [16] regarding safety outcome and by Niemeyer et al. (2016) [17] regarding MRI-assessed outcome.

Retrospectively, in dependence of defect location, patients were divided into two subgroups (patella defects ($n = 45$) and femoral condyle defects ($n = 28$)) independently from their dose group. Clinical outcome for this analysis of subgroups was evaluated by the means of the KOOS score at baseline and 6 weeks, 3, 6, 12, 18, 24, 36, 48 and 60 months following ACI. Furthermore, for the IKDC Knee Examination Score, comparative shift tables were assessed for patellar and femoral lesions.

Surgical technique, assessment and rehabilitation

In all groups, patients were treated with matrix-associated ACI with spheroid technology, which requires a two-step surgical procedure. During knee arthroscopy, chondrocytes were harvested using a standardized cartilage biopsy tool (Storz, Tuttlingen, Germany) from the intercondylar notch [18]. A total of three osteochondral cylinders were harvested in every patient for subsequent cell expansion. The chondrocyte spheroids were produced as previously described [19]. The cells were first propagated in monolayer culture before cultivation as spheroids. Spheroids were generated by seeding 2×10^5 chondrocytes in the 3D cell cultivation system and cultivation was continued.

Following cell culture period of approximately 8 weeks, in all patients, ACI was performed using a (mini-) arthrotomy or arthroscopic as standard approach. Debridement of the cartilage defect into the adjacent healthy cartilage was performed preserving the calcified layer and trying to avoid bleeding from the subchondral bone. Following debridement, the spheroids were applied at a spheroid dose corresponding to treatment group assignment (see above). The

Table 1 Principal in- and exclusion criteria

Inclusion criteria

  Age 18–50 years inclusive (male or female patient)

  Isolated symptomatic full-thickness cartilage defects (ICRS grade III or IV) on medial or lateral femoral condyle, trochlea, tibia and retropatellar defect, including OCD

  Chondral defect size ≥ 4–$10\ cm^2$ after debridement to healthy cartilage; maximum depth 6 mm

  Nearly intact chondral structure surrounding the defect as well as the corresponding joint area

  Willingness to accept restrictions on analgesis (only paracetamol and/or topical NSAIDs allowed during trial, discontinuation of pain medication required 1 week before each visit) and to follow the strict rehabilitation protocol and follow-up program

Exclusion criteria

  Defects in both knees at the same time

  Radiological signs of osteoarthritis

  Any signs of knee instability

  Valgus or varus malalignment (more than 5° over the mechanical axis)

  Clinically relevant second cartilage lesion on the same knee

  More than 50% resection of a meniscus in the affected knee or incomplete meniscal rim

  Rheumatoid arthritis, parainfectious or infectious arthritis, or condition after these diseases

  Pregnancy and planned pregnancy (because MRI was thus impossible)

  Obesity (body mass index $> 30\ kg/m^2$)

  Previous treatment with ACI in the affected knee

  Microfracture performed less than 1 year before screening in the affected knee

  Meniscal implant in the affected knee

  Meniscal suture (in the affected knee) 3 months before baseline

  Mosaicplasty (osteoarticular implant system) in the affected knee

  Hyaluronic acid intra-articular injections in the affected knee within the 3 months before baseline

  Specific osteoarthritis drugs—such as chondroïtin sulfate, diacerein, N-glucosamine, piascledine or capsaicin—in the 2 weeks before baseline

  Corticosteroid treatment by intra-articular route within the month before baseline or systemic (all routes) corticosteroids within the two weeks before baseline

  Chronic use of anticoagulants

  Current diagnosis of osteomyelitis, human immunodeficiency virus (1 or 2) and/or hepatitis C infection

  Complete inclusion and exclusion criteria are given in the public-access database under clinicaltrials.gov: xxx

spheroids were distributed homogenously within the defect area. After an interval of 20 min for adherence of the spheroids, the joint was closed. Using this ACI technology, no covering of the defect with either a biomaterial or a periosteum patch is needed.

Following surgery, a standardized rehabilitation protocol was applied which includes continuous passive motion from the day after surgery for 6 weeks (up to 4 h per day). Limitation on weight bearing for 6 weeks was recommended. For patients with patella defects, flexion of the affected knee was limited up to 30 degrees of flexion for weeks 1–2, 60° for weeks 3–4 and 90° for weeks 5–6 following ACI. Weight bearing was increased to full weight between 6 and 8 weeks after surgery. Individual limits of flexion were given for patients with defect of the femoral condyle, depending on the exact defect location, to avoid early exposure of the regenerative cartilage to axial compression and shear forces.

Clinical outcome was assessed by the means of KOOS score at baseline (day before arthroscopy) as well as 6 weeks, 3, 6, 12, 18, 24, 36, 48 and 60 months following ACI. Based upon this standardized questionnaire, the overall KOOS score and five subscores (Pain, Activity, Quality of Life, Symptoms, Function) each ranging from 0 (worst) to 100 (best) points were calculated [20]. For evaluation of clinical outcome, "Responders" were defined as an improvement of the overall KOOS score of more than seven points. The product name of the chondrocyte spheroids was xxx.

Furthermore, clinical outcome was assessed by clinical examination performed by a physician using the IKDC Knee Examination Score. Change in physical functioning was displayed in shift tables for both subgroups (patella and femoral condyles) and the number of patients with no change, improvement or worsening in clinical function was calculated.

Statistical evaluation

Statistical software

All analyses were performed with the software SAS 9.4 (SAS institute Inc. Cary, NY, USA) and intentionally calculated

to a full significance level of 5%. Each *p* value ≤ 0.05 represents a significant result.

Descriptive statistics

Descriptive statistics are defined as counts and percentages (frequency tables) for categorical data, and as the number of observed cases (*N*), arithmetic mean, standard deviation (SD) for continuous data.

Unadjusted analyses

Non-inferiority analyses of the patella subgroup in comparison to patients with femoral defects were performed at 12, 24, 36, 48 and 60 months, each, using a non-inferiority margin of − 8.5 points for change in the overall KOOS (as originally done in the underlying clinical trial). For testing changes to baseline, the paired *t* test was performed. For analysis of numeric parameters such as KOOS score and defect size, Spearman's correlation coefficient was performed.

Power calculation had been done for the underlying single-blinded, randomized, prospective, clinical intervention study. To ensure a power of 90% for detecting an expected change to baseline in overall KOOS of 12.5 points (STD = 15, alpha = 5%, two-sided), at least 18 patients were to be included per dosage group A, B and C. Post hoc estimation of power for the non-inferiority test of overall KOOS for the patella subgroup compared to the patients with femoral defects (margin = − 8.5, further values used from the 1-year results presented in Table 3) resulted in a power estimate of 64.9% (two-sample *t* test for mean differences with unequal variances, alpha = 2.5%, one-sided), which was sufficient to prove non-inferiority in our data.

The statistical analyses were performed by StatConsult GmbH (Magdeburg, Germany). There is no potential conflict of interest for any of the authors and StatConsult GmbH.

Results

The study population comprised 73 patients aged 33.22 ± 9.2 years. The most commonly treated defect locations were patella (45/73; 62%) and femoral condyle (28/73; 38%). For this analysis, no imputation of missing values (e.g., due to patients' withdrawal from study) was done, but only observed data were assessed. Follow-up rates for the respective patient visits were 87.7% (64/73) at 12, 80.8% (59/73) at 24, 69.9% (51/73) at 36 and 64.4% (47/73) at 48 and 60 months [11% loss to follow-up, 10% ICF withdrawal, 15% other reasons (pregnancy, AEs, etc.)]. ICRS grades were mostly III C or IV A, and were evenly distributed between the treatment groups, while defects located on

the femoral condyle were slightly, but not significantly larger (femur: 6.0 cm^2 ± 1.7: patella: 5.4 cm^2 ± 1.6; $p = 0.1395$). Cell doses as well as other patient characteristics were comparable between patellar and femoral defect groups.

Defect sizes ranged from 4 to 10 cm^2 following intra-operative debridement. Demographic and baseline data are summarized in Table 2 including differences between femoral and patella subgroups.

Clinical outcome was assessed by the means of KOOS score. The overall KOOS score of all patients is summarized and compared in Table 3. A significant improvement from baseline was found within the patella subgroup at all visits already 3 months after treatment ($p < 0.001$). At final assessment (12 months after ACI), KOOS score was 73.5 ± 18.7 in the patella subgroup compared to 75.7 ± 13.9 in the subgroup of femoral defects increasing over the entire follow-up period to a maximum of 82.6 ± 14.0 in the patella subgroup at 60 months after ACI and 81.9 ± 24.2 for the femoral subgroup (Table 3). While the largest increase in knee function was observed in both groups between 6 weeks and 3 months following ACI (13.6 and 14.0 points for patella and femur group, respectively), there was no significant trend for any

Table 2 Baseline and demographic data of 75 patients included in the present trial in dependence of defect location

	Femur	Patella
n	28	45
% of cohort	38%	62%
Gender		
Male	22	29
Female	6	16
Ethnicity		
Caucasian	27	45
Asian	1	0
Black	0	0
Age		
Mean	33,82	33,45
SD	10,25	8,88
BMI		
Mean	25,3	25,13
SD	3,12	3,14
Defect size post-debridement		
Mean	6,0	5,4
SD	1,7	1,6
ICRS grade at TP		
III A	4%	7%
III B	4%	4%
III C	25%	20%
IV	0%	2%
IV A	64%	64%
IV B	4%	2%

Table 3 Functional outcome as evaluated by KOOS score in dependence of defect location at baseline and during follow-up including statistical results of non-inferiority tests per visit

	Femur			Patella			_p_ value
	Overall KOOS	Change from baseline	_n_	Overall KOOS	Change from baseline	_n_	
Baseline	60.2 ± 13.9		27	54.6 ± 15.7		44	
6 weeks	49.2 ± 16.8	-11.7 ± 18.8	25	48.7 ± 14.7	-6.8 ± 16.1	40	0.0026
3 months	63.2 ± 13.7	1.4 ± 17.5	24	62.3 ± 16.3	7.8 ± 15.7	41	0.0006
6 months	67.4 ± 15.2	6.6 ± 18.7	26	72.0 ± 15.3	17.8 ± 15.3	41	< 0.0001
1 year	75.7 ± 13.9	14.1 ± 20.6	25	73.5 ± 18.7	17.4 ± 15.2	38	0.0092
2 years	74.0 ± 19.8	9.6 ± 21.7	21	77.1 ± 15.5	21.5 ± 15.4	36	0.0003
3 years	80.1 ± 12.5	16.9 ± 17.1	20	80.9 ± 17.5	23.8 ± 14.1	29	0.0010
4 years	80.2 ± 16.4	17.1 ± 18.1	19	83.6 ± 12.5	28.2 ± 15.4	27	0.0002
5 years	81.9 ± 18.6	18.5 ± 24.2	17	82.6 ± 14.0	26.1 ± 13.7	29	0.0099

Table 4 KOOS subscales of the patella subgroup at baseline and during follow-up

	KOOS					
	Pain	Symptoms	ADL	Sport/Rec	QoL	Overall
Baseline	61.2 ± 19.0	69.9 ± 17.1	71.4 ± 19.1	43.1 ± 24.6	28.1 ± 17.1	54.6 ± 15.7
3 months	68.4 ± 18.3	76.0 ± 14.4	77.4 ± 18.1	44.9 ± 24.6	41.7 ± 22.5	62.3 ± 16.3
6 months	73.5 ± 81.1	82.7 ± 12.9	84.6 ± 15.9	60.2 ± 23.8	52.7 ± 24.2	72.0 ± 15.3
1 year	81.1 ± 15.4	83.8 ± 13.8	85.4 ± 18.3	$64.327.3$	55.2 ± 26.3	73.5 ± 18.7
2 years	82.7 ± 16.4	85.1 ± 12.7	88.2 ± 12.0	67.8 ± 25.5	61.8 ± 23.0	77.1 ± 15.5
3 years	85.6 ± 18.4	89.6 ± 12.1	88.2 ± 16.7	74.5 ± 24.5	65.3 ± 13.6	80.9 ± 17.5
4 years	85.6 ± 18.4	90.4 ± 8.4	93.2 ± 7.5	76.8 ± 20.9	69.2 ± 22.2	83.6 ± 12.5
5 years	88.3 ± 14.4	87.6 ± 13.9	91.4 ± 10.0	76.0 ± 23.0	70.6 ± 21.5	82.6 ± 14.0

deterioration of knee function as assessed by overall KOOS over time within 60 months following ACI. A slight increase in the overall KOOS even was shown in the later years following ACI (patella subgroup at 12 months: 73.5 ± 18.7, at 24 months: 77.1 ± 15.5, at 36 months: 80.9 ± 17.5, at 48 months: 83.6 ± 12.5 and at 60 months: 82.6 ± 14.0). KOOS subscores ('pain', 'symptoms', 'function in daily living', 'function in sport and recreation' and 'knee-related quality of life') of patella patients are represented in Table 4. All improvements from baseline after at least 3 months were highly significant ($p < 0.001$).

Both patella and femur groups showed a great improvement in the overall KOOS score to excellent values (Fig. 1). After 1 year, the increase was non-inferior ($p = 0.0092$) and even slightly bigger in the patella subgroup with a change from baseline of 17.4 ± 15.2 compared to 14.1 ± 20.6 in the femur subgroup. The same holds true for those remaining patients after 5 years follow-up with overall KOOS changes of 26.1 ± 13.7 in the patella subgroup compared to 18.5 ± 24.2 in the femur subgroup ($p = 0.0099$).

Only small differences could be observed in the shift tables comparing the improvement of clinical function assessed by the IKDC Knee Examination Score (Table 5): at 12 months after treatment, 44 and 54% of patients showed improvement
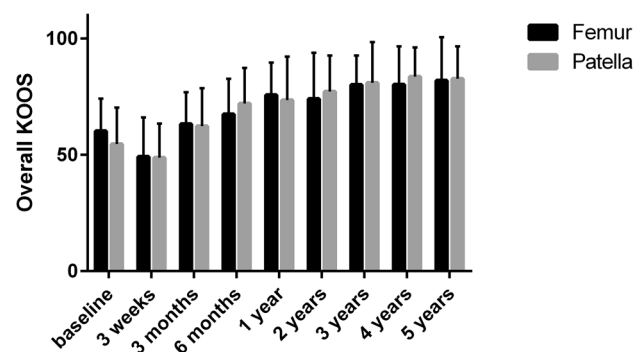
Fig. 1 Improvement from baseline of the patella and femur subgroups during follow-up by the means of overall KOOS score

in the clinical examination in the femur and patella group, respectively. In both groups, only 4% of patients reached lower scores in the IKDC Knee Examination Score: one patient moved from A to C in femur and two patients from A to B in patella group. The great majority of patients that showed no change were scored to group A already at baseline, so that no further improvement was possible. 60 months after treatment, 56 and 53% of patients showed improvement in the clinical examination in the femur and patella groups, respectively. In

Table 5 IKDC Knee Examination Score Shift Tables

	Femur				Patella			
	Grade at visit 4 (N=25)				Grade at visit 4 (N=41)			
Grade at baseline	A	B	C	D	A	B	C	D
A	11	0	1	0	15	2	0	0
B	6	2	0	0	17	1	1	0
C	2	2	0	0	3	1	0	0
D	1	0	0	0	0	1	0	0
	Grade at visit 9 (N=18)				Grade at visit 9 (N=30)			
Grade at baseline	A	B	C	D	A	B	C	D
A	7	1	0	0	12	1	0	0
B	6	0	0	0	13	1	0	0
C	3	0	0	0	2	0	0	0
D	1	0	0	0	1	0	0	0

Patients below the grey diagonal improved in function, patients within it showed no change and patients above it scored lower at follow-up than at baseline

each group, only one patient still scored worse than at baseline (group B instead of A). Regarding clinical outcome, "response to therapy" was defined as an improvement of the overall KOOS score from baseline of more than seven points. According to this definition, a responder rate of 86.2% (25 out of 29) was observed in the patella group after 60 months.

No correlation between improvement from baseline at 60 months (overall KOOS) and defect size was found (Spearman's correlation coefficient $r_s = 0.158$).

In the overall study period, 40 patients (89%) of the patella group reported 81 treatment-related adverse events, while in the femur group 46 events were reported by 23 patients (82%). Out of these, 58 (69%) and 30 (65%) occurred within the first 12 months after treatment. The events were mostly milder musculoskeletal injuries like joint swelling and effusion. Details are displayed in Table 6. The overall safety assessment suggests a very similar safety profile for femoral and patellar defects with slightly increased incidence for joint effusion, arthralgia and joint swelling in the patellar group.

Discussion

The data reported in the present paper represent an analysis of location subgroups of a clinical phase II prospective randomized trial of level I scientific evidence. Out of these data

and combined over all dosage groups, patients with defect of the patella have been analyzed separately and compared to outcome of patients with femoral defects.

In contrast to earlier studies, in the present study, patients with patellar defects revealed sustainably improved results regarding the clinical outcome. The overall "responder rate" (defined as > 7 points improvement from baseline in the KOOS overall score) in the patella group was 86.2% (25/29), which seems quite good. Clinical outcome was similar in both—femoral and patellar cartilage defects—even with a positive trend in favor of the subgroup of patients with patellar defects. These results have been observed in all KOOS subscores and the overall KOOS score. The highest KOOS values regarding subscores were found in the subscores 'pain', 'symptoms' and 'function in daily living' (ADL) which are in accordance to earlier cartilage repair studies using the KOOS for evaluation of clinical knee function. The values in the subscores 'function in daily sport and recreation' (Sport/Rec) and 'knee-related quality of life' (QoL) revealed improvements as well, but to a lower extent. Also the IKDC Knee Examination Score showed comparable improvement in the patella to the femur group and only a very small portion of patients scored worse after treatment than at baseline confirming the efficacy of the treatment for the great majority of femoral and patellar defects.

ACI has been introduced by Lars Peterson and Mats Brittberg in 1994. In this first case series clinical outcome,

Table 6 Treatment-related adverse events per SOC and PT

	Femur		Patella		Total	
	n_E	N_P	n_E	N_P	n_E	N_P
Total numbers	46	23 (82%)	81	40 (89%)	127	63 (84%)
Musculoskeletal and connective tissue disorders	41	23 (82%)	72	40 (89%)	113	63 (84%)
Joint effusion	25	20 (71%)	46	38 (84%)	71	58 (77%)
Arthralgia	5	4 (14%)	9	9 (20%)	14	13 (17%)
Joint swelling	3	2 (7%)	6	6 (13%)	9	8 (11%)
Joint crepitation	2	2 (7%)	3	3 (7%)	5	5 (7%)
Tendonitis	1	1 (4%)	2	1 (2%)	3	2 (3%)
Joint lock	1	1 (4%)	1	1 (2%)	2	2 (3%)
Patellofemoral pain syndrome	1	1 (4%)	1	1 (2%)	2	2 (3%)
Muscular weakness	–	–	2	1 (2%)	2	1 (1%)
Cartilage hypertrophy	–	–	1	1 (2%)	1	1 (1%)
Extraskeletal ossification	1	1 (4%)	–	–	1	1 (1%)
Muscle atrophy	–	–	1	1 (2%)	1	1 (1%)
Osteochondrosis	1	1 (4%)	–	–	1	1 (1%)
Osteonecrosis	1	1 (4%)	–	–	1	1 (1%)
Injury, poisoning and procedural complications	2	2 (7%)	5	5 (9%)	7	7 (9%)
Ligament sprain	1	1 (4%)	3	3 (7%)	4	4 (5%)
Fall	1	1 (4%)	1	1 (2%)	2	2 (3%)
Wound dehiscence	–	–	1	1 (2%)	1	1 (1%)
General disorders and administration site conditions	2	2 (7%)	2	2 (4%)	4	4 (5%)
Pain	2	2 (7%)	1	1 (2%)	3	3 (4%)
Oedema peripheral	–	–	1	1 (2%)	1	1 (1)
Vascular disorders	–	–	2	2 (4%)	2	2 (3%)
Deep vein thrombosis	–	–	1	1 (2%)	1	1 (1%)
Lymphoedema	–	–	1	1 (2%)	1	1 (1%)
Skin and subcutaneous tissue disorders	1	1 (4%)	–	–	1	1 (1%)
Scar pain	1	1 (4%)	–	–	1	1 (1%)

N_E number of events, N_P number of patients

there was a high failure rate reported for the subgroups of patients with cartilage defects of the patella compared to patients with defects of the femoral condyles [21].

Ever since, cartilage defects of the patella were considered as a problematic entity with unsatisfying outcome. This has been confirmed by several subsequent studies showing moderate results and the inferiority in direct comparison to defects in the medial femoral condyle [6, 7, 11, 22]. Nevertheless, the majority of these studies are either retrospective or non-controlled and therefore of lower quality. Such inferior study layouts represent either level III or IV scientific evidence. In contrast, there are some recently published papers on treatment of patella cartilage defects with (M) ACI, who also report efficiency and reliable results. As stated earlier, Siebold et al. showed an increase in clinical outcome scores from baseline to up to 4 years for patients treated for chondral defects of the patella with a concomitant patellofemoral ligament reconstruction [14]. Due to the small study group, differences were not significant, but a trend was shown. The present study clearly confirms this trend.

Ebert et al. compared the effect of matrix-assisted ACI (MACI) in patients with tibiofemoral (TF) and patellofemoral (PF) lesions [15] showing significant group differences between the TF and PF groups for KOOS 'ADL', 'QoL', and 'Sport/Rec'. These differences were not confirmed by the present study.

A deterioration in knee function in terms of the implant of a prosthesis or cartilage repair revision surgery as shown by von Keudell (starting after 4 years) [12] or by Gobbi et al. (starting after 2 years) [7] and Biant (starting before year 5) [13] could not be reproduced by the present study. A GLM comparable to the one described by Kon et al. was used as the multivariate analysis to assess the influence of patient or lesion characteristics on the score at final follow-up and showed no significant effect of the sex on the IKDC at 5-year follow-up ($p = 0.494$) even though the comparability is restricted due to the shorter follow-up [6]. Even though

the incidence rate of treatment-related adverse events was slightly increased in the patella group, no significant differences in the portion of patients suffering from a graft-related adverse event and/or a re-operation could be detected as has been shown by Angele et al. [23].

Concerning the better clinical outcome of ACI for patella defects in the present compared to previous studies, there are various potential explanations. Since the present study is an analysis of location subgroups of the prospective randomized clinical trial on different doses of ACI, the inclusion and exclusion criteria have been defined very strictly and thus the patient selection represents—especially in comparison to non-controlled cohort studies and daily life—an ideal population that is not representative of the daily life [24]. For example, only isolated cartilage defects were included in accordance to the study protocol, while almost all concomitant pathologies such as instability or malalignment of the joint were excluded. A second potential explanation is the use of a modern pure autologous cell product in the present study, which allows minimal invasive arthroscopic application. Furthermore, in most cases, detachment of the vastus medialis obliquus (VMO) muscle is not necessary, which might have a further positive effect on clinical outcome, especially within the timespan shortly after ACI treatment. Most other ACI products (based on the use of biomaterials) require, especially for the application at the patella, an obligatory arthrotomy including detachment of the VMO. A third potential explanation is also associated with the high-level evidence study: In this study, there was a uniform and monitored strict rehabilitation protocol the ACI patients must have followed. The need and usefulness of such rehabilitation programs and its effect on clinical outcome is well known [25–27]. In contrast to uncontrolled studies, this also might affect the clinical outcome positively. A fourth explanation could be a better understanding of the underlying pathologies: Since the introduction of ACI in 1994, there has been an important learning curve on the understanding of the etiology of cartilage defects and underlying pathologies. Recent studies demonstrate a correlation between abnormal PF joint geometry and the incidence of cartilage defects [28] and the concept to address both—cartilage defect and underlying pathology—became more popular in recent years. This might also contribute to the fact, that the number of studies increased, which report good and satisfying clinical outcome of patients who underwent cartilage repair procedures of the patella.

The present study shows some limitations: since the study represents an analysis of location subgroups from a randomized trial, it can be interpreted as a controlled prospective cohort study and therefore a level III evidence. Nevertheless, since parameters such as defect location cannot be randomized, it represents the highest achievable evidence for this approach. All parameters that potentially influence clinical outcome were distributed equally between defect locations except for defect size, which has been slightly larger in defect of the femoral condyle (see Table 3). Since correlation of defect size was not shown with the change from baseline in the KOOS score at 24 months (Table 2), it seems unlikely that this factor compromises the results of the present study. Nevertheless, it remains as a potential limitation.

Taken together, the present study underlines and confirms the value of ACI (and especially matrix-associated ACI with spheroid technology) for treatment of cartilage defects of the patella in a well-defined subgroup of selected patients. ACI seems an appropriate surgical treatment for cartilage defects of the patella leading to an excellent success rate. In this study, the clinical outcome in patients with patellar defects was even better than the already excellent results in patients with defects of the femoral condyle, even though the study included relatively large defect sizes for both groups (mean defect size 6.0 ± 1.7 and 5.4 ± 1.6, respectively).

No conclusion on a potential superiority over any other treatments or even conservative treatment can be drawn. This was not part of the present study.

Conclusion

The present study underlines and confirms the value of ACI (and especially matrix-associated ACI with spheroid technology) for treatment of cartilage defects of the patella in a well-defined subgroup of selected patients. In addition to the already proven benefits of ACI for defects on the femoral condyle, ACI seems an appropriate surgical treatment for cartilage defects of the patella leading to an excellent success rate.

Compliance with ethical standards

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