Prospective Long-term Follow-up of Autologous Chondrocyte Implantation With Periosteum Versus Matrix-Associated Autologous Chondrocyte Implantation

A Randomized Clinical Trial

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Background: Matrix-associated autologous chondrocyte implantation (MACI) is a further development of the original autologous chondrocyte implantation periosteal flap technique (ACI-P) for the treatment of articular cartilage defects.

Purpose: We aimed to establish whether MACI or ACI-P provides superior long-term outcomes in terms of patient satisfaction, clinical assessment, and magnetic resonance imaging (MRI) evaluation.

Study Design: Randomized controlled trial; Level of evidence, 2.

Methods: A total of 21 patients with cartilage defects at the femoral condyle were randomized to MACI (n = 11) or ACI-P (n = 10) between the years 2004 and 2006. Patients were assessed for subjective International Knee Documentation Committee (IKDC) score, Lysholm and Gillquist score, Tegner Activity Score, and 36-Item Short Form Health Survey (SF-36) preoperatively (T0), at 1 and 2 years postoperatively (T1, T2), and at the final follow-up 8 to 11 years after surgery (T3). Onset of osteoarthritis was determined using the Kellgren-Lawrence score and Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score, and delayed gadolinium-enhanced MRI of cartilage was used to evaluate the cartilage. Adverse events were recorded to assess safety.

Results: There were 16 patients (MACI, n = 9; ACI-P, n = 7) who were reassessed on average 9.6 years after surgery (76% follow-up rate). The Lysholm and Gillquist score improved in both groups after surgery and remained elevated but reached statistical significance only in ACI-P at T1 and T2. IKDC scores increased significantly at all postoperative evaluation time points in ACI-P. In MACI, IKDC scores showed a significant increase at T1 and T3 when compared with T0. In the majority of the patients (10/16; MACI, 5/9; ACI-P, 5/7) a complete defect filling was present at the final follow-up as shown by the MOCART score, and 1 patient in the ACI-P group displayed hypertrophy of the repair tissue, which represents 6% of the whole study group and 14.3% of the ACI-P group. Besides higher SF-36 vitality scores in ACI-P at T3, no significant differences were seen in clinical scores and MRI scores between the 2 methods at any time point. Revision rate was 33.3% in MACI and 28.6% in ACI-P at the last follow-up.

Conclusion: Our long-term results suggest that first- and third-generation ACI methods are equally effective treatments for isolated full-thickness cartilage defects of the knee. With the number of participants available, no significant difference was noted between MACI and ACI-P at any time point. Interpretation of our data has to be performed with caution due to the small sample size, which was further limited by a loss to follow-up of 24%.

Keywords: cartilage defect; autologous chondrocyte implantation; original periosteal flap technique; matrix-associated

Full-thickness cartilage lesions present clinically with pain and significant activity impairment and may progress to degenerative osteoarthritis. The treatment of these lesions has posed a difficult challenge since the dawn of surgery.[6] To address the limited intrinsic healing potential of articular hyaline cartilage, the first procedure of autologous

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chondrocyte implantation (ACI) was introduced in 1987,[11] and its results in humans were described by Brittberg et al[4] in 1994. It was the first biological approach using cell transplantation with the aim of providing hyaline-type repair tissue to the defect area. The first generation of ACI with a periosteum cover (ACI-P) showed good midterm and long-term results over a follow-up period of more than 10 years.[23,26,33] Even though these data strongly support the use of ACI-P as an effective treatment in patients with chondral and osteochondral lesions of the knee joint, the method has been considered problematic due to the use of a periosteal flap, the increased morbidity by a separate tibial incision with resulting longer operation time, and potential graft hypertrophy.[15,32] Further concerns were the uneven distribution of chondrocytes within the defect and the potential risks of cell leakage. Thus, the original technique underwent several modifications aimed at improving clinical outcome and reducing complication rates. As a result, use of a synthetic type I/III collagen cover (second-generation ACI)[10,17] and use of 3-dimensional matrix systems (third-generation ACI or matrix-associated autologous chondrocyte implantation [MACI]) were introduced.[1,8,16] In comparison with first- and second-generation ACI, MACI simplifies the surgical treatment and reduces the number of incisions and the duration of surgery.[22]

ACI-P and MACI have been proven to be durable and effective treatment options for cartilage defects in the knee. Both techniques provide good short- and long-term results in the majority of patients.[8,16] Even though there is a trend toward applying later-generation ACI and considering this to be the superior technique over ACI-P, the scientific support for this choice is rather weak. Only a limited number of studies with high evidence levels have evaluated the clinical results of these techniques in a randomized clinical trial.[20,24,27,40]

A previously published level 1 study compared MACI versus ACI-P with a short-term follow-up of 24 months.[40] No differences were observed in the efficacy between the 2 techniques at 12 and 24 months after surgery regarding International Knee Documentation Committee (IKDC) score, Tegner Activity Score, and 36-Item Short Form Health Survey (SF-36) score; however, better efficacy was observed in the ACI-P group according to the Lysholm and Gillquist score at 12 months after surgery. Since the major interest is to determine whether later-generation ACI results in better long-term outcomes in comparison with the first-generation ACI, we decided to present an extension of this study with a comprehensive clinical and radiological follow-up of 8 to 11 years after surgery. This is, to our best knowledge, the first randomized prospective clinical trial to present long-term results of ACI-P versus MACI by evaluating the patients in terms of clinical assessment, patient satisfaction, and radiographical evaluation.

METHODS

Study Design and Data Collection

This is a follow-up study on the prospective randomized controlled trial (parallel trial design, allocation ratio 1:1) published by our group in 2010.[40] For this study, we contacted all initially included patients who had symptomatic full-thickness chondral defects of the femur and were treated with ACI with periosteum or matrix by 2 experienced surgeons at our clinic between March 2004 and June 2006; these patients were rescheduled for clinical, radiographic, and magnetic resonance imaging (MRI) examination between September 2014 and March 2016. The inclusion criteria were patients (16-50 years of age) with isolated cartilage defects (2.5-6 cm^2) localized at the medial or lateral femoral condyle detected by MRI and verified with arthroscopy. Exclusion criteria were extended cartilage erosion, restricted mobility, corresponding cartilage defects higher than grade II according to Outerbridge[30] (ie, "kissing" defects or defects on the opposing surface), extended meniscal defect (meniscal resection >1/3), untreated cruciate or collateral ligament laxity, untreated varus or valgus alignment more than 5°, obesity, inflammation, procedures in the respective knee (eg, microfracture or osteochondral autograft) less than 1 year ago, hyaluronan injection less than 6 months ago, and corticosteroid injection less than 3 months ago. Complete clinical data were available from the preoperative evaluation (T0) and at 12 months after the operation (T1), 24 months after the operation (T2), and the last follow-up (T3) from 16 patients. At these time points, patients had subjectively rated their overall condition using validated scoring systems as described below. At the final follow-up, MRI was performed on all 16 patients. Sociodemographic and occupational parameters and defect characteristics were recorded and are presented in Table 1.

Between the assessment time points, additional information had been recorded on follow-up questionnaires, including data on adverse events, treatment failures, and operations after ACI. The local ethics committee approved the study (No. 127/2004), and written informed consent forms were received from all patients. The study was performed in accordance with the German Medical Association's professional code of conduct and with the Declaration of Helsinki in the 1996 version[39] and according to the German Data Protection Act of 1990.[25]

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TABLE 1
Characteristics of the Study Population[a]

	MACI	ACI-P	*P* Value
Total patients, n (%)	9 (56)	7 (44)	
Sex, n (%)			**.017** (χ^2 test)
Male	4 (44.4)	7 (100)	
Female	5 (55.6)	0 (0)	
Age at surgery, y	30.4 ± 6.8	28.8 ± 9.1	.175 (*t* test)
	31 (17-40)	34 (16-39)	
Body mass index, kg/m^2			
Before surgery	23.32 ± 1.15	25.41 ± 2.55	**.043** (*t* test)
	23.6 (21.2-25)	25.9 (21.6-28.7)	
After surgery	24.9 ± 0.8	26.6 ± 1.2	.390 (*t* test)
	24.6 (21.2-29.3)	27.5 (22.1-30.1)	
Follow-up time, y	9.6 ± 0.9	8.6 ± 0.8	.764 (*t* test)
	10.3 (8-11)	9.3 (8-10)	
Age at final follow-up, y	40.44 ± 2.3	38.43 ± 3.4	.199 (*t* test)
	41 (27-51)	43 (26-48)	
Preinjury sports activity level, n (%)			.670 (χ^2 test)
Competitive	1 (11.1)	2 (28.6)	
Well-trained	2 (22.2)	1 (14.3)	
Occasionally	5 (55.6)	4 (57.1)	
No sports	1 (11.1)	0 (0)	
No. of previous surgeries	2.22 ± 0.4	1.86 ± 0.03	.693 (Mann-Whitney test)
	2 (1-5)	2 (1-3)	
No. of surgeries after ACI	0.33 ± 0.17	0.29 ± 0.19	.844 (Mann-Whitney test)
	0 (0-1)	0 (0-1)	

[a]Data are presented as mean ± SD with median (range) unless otherwise indicated. ACI, autologous chondrocyte implantation; ACI-P, ACI with periosteum; MACI, matrix-associated autologous chondrocyte implantation. Unpaired *t* test, χ^2 test, and Mann-Whitney *U* test were used. Boldface indicates satistical significance at $P < .05$.

Surgical Procedure and Rehabilitation

The surgical technique and clinical rehabilitation were described in detail in the initial publication.[40]

Clinical and Radiological Evaluation

Clinical outcome parameters were ascertained by means of questionnaires and clinical assessment. The postoperative changes in subjective knee function were assessed by the IKDC score[12] at 12 months, 24 months, and the last follow-up. The objective IKDC score was assessed at the final follow-up. In addition, the visual analog scale (VAS) for pain at the last follow-up was analyzed in an exploratory fashion. Postoperative changes in health-related quality of life (SF-36),[38] physical activity (Tegner Activity Score),[36] and knee functionality (Lysholm and Gillquist score)[19] were measured at the first visit and at 12 months, 24 months, and the last follow-up. All the instruments we used are valid and reliable and are widely used in medical outcome studies. All recorded data underwent further computer-assisted plausibility checks. All data sets, after necessary admissible corrections, in accordance with the instructions described by Moradi et al,[23] were subsequently prepared for statistical analysis. At the last follow-up, the radiographs were classified according to the Kellgren-Lawrence score to categorize the presence of osteoarthritis.[13]

MRI Evaluation

We performed 2 different analyses, first using morphological MRI sequences to determine the MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) score and second using the delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) technique to evaluate alterations of the T_1 relaxation time of the repair cartilage and hence the content of glycosaminoglycans.[5] Details are as follows: MRI was performed on a 70-cm, open-bore, 3.0-T whole-body scanner (Magnetom Verio; Siemens Healthineers), equipped with an 18-channel total-imaging matrix (TIM [102 × 18] configuration) in combination with a dedicated 15-channel knee coil. Standard morphological and functional MRI was performed during the same session. During the period between September 2014 and March 2016, a total of 16 patients underwent a 3.0-T MRI examination according to the study protocol, which included 4 morphological sequences: coronal proton density–weighted turbo spin-echo (with and without fat saturation), sagittal proton density, and sagittal T_1 spin-echo. To obtain the dGEMRIC images of 16 patients, we used a protocol similar to that suggested by Rehnitz et al.[34] We also used a 3D T_1-weighted VIBE sequence (repetition time/echo time, 15/2.5 ms; voxel size, 0.4 × 0.4 × 3 mm^3; acquisition time, 3.18 minutes; field of view, 159 × 159 mm; imaging matrix, 384 × 384; echo train lengths, 1) with 2 excitation flip angles (5° and 26°), which was performed before and after intravenous administration of a double dose of

gadopentetate dimeglumine (0.2 mmol/kg Gd-DTPA, Magnevist; Bayer Vital). After administration of Gd-DTPA, the participants walked for 15 minutes, and after 90 minutes the postcontrast T_1-mapping sequences were performed. The resulting T_1 values are referred to as the dGEMRIC values.

Image Analysis

The morphological image analysis was performed on our picture archiving and communication system (Centricity PACS, version 3.0.4; GE Healthcare Integrated IT Solutions). Both radiological reviewers (C.R. and his colleague) were blinded to the study groups, and evaluation was performed in consensus. The dGEMRIC (T_1) maps were analyzed by use of the workstation Leonardo (Siemens Healthineers). The morphological sequences were used to determine the MOCART score.[21] Because we did not use the entirely same sequences as in the original publication, the results are referred to as a modified or adapted 2-dimensional MOCART score, which has been presented in a similar way in another study.[18] To analyze the functional dGEMRIC images, a region of interest (ROI) analysis was applied. One ROI was placed in the repair cartilage, and another ROI was placed in the normal-appearing adjacent cartilage, with a minimum distance of 1 cm, and the resulting T_1 relaxation times were compared.

Data Management and Statistical Analysis

The IKDC score was used as the primary outcome parameter for confirmatory statistics. At the time of study initiation,[40] the sample size estimation for the main outcome parameter was based on a 2-tailed test problem for 2-sample Student t test. Power was set to 80% and the error to 5%. Using an internet-based tool for sample size estimation, we estimated a difference between the means with an SD of 5 points and 3.5 points, respectively. This resulted in a minimal sample size of 8 patients per group. The estimation was adjusted to 10 patients per group for possible preliminary dropouts.[40] Our post hoc power analysis using the G* Power 3.1 tool (introduced by Faul et al[7]) for 2-sample Wilcoxon-Mann-Whitney test showed an effect size of 0.69 and a power of 0.24. Randomization was performed through use of an internet-based computer software, assigning patients by chance to either ACI-P or MACI to ensure consistency of observation as described by Zeifang et al.[40]

A descriptive analysis of the patient data was performed to investigate whether the survey groups were homogeneous. Continuous baseline variables were presented by mean, standard deviation, median, and range. The difference between continuous baseline variables was calculated either by t test or by Mann-Whitney U test, if the variables were not normally distributed. Categorical baseline variables were summarized according to frequencies and percentages. The χ^2 test was used to analyze the proportions of categorical variables. For nonparametric time-dependent variables, we used the Friedman and Wilcoxon tests. Comparisons between subgroups of patients were performed with the Mann-Whitney U test for nonparametric data. All reported P values are 2-tailed. $P < .05$ was considered statistically significant. A Bonferroni correction was performed to prevent type I error caused by multiple testing. All statistical analyses were performed by use of SPPS software (SPSS version 23; IBM Corp).

RESULTS

Description of Study Population

In the initial study, 21 patients were treated with ACI (MACI, n = 11; ACI-P, n = 10) with a sex ratio of 6 men and 5 women in the MACI group and 10 men in the ACI-P group.[40] A total of 16 patients (MACI, n = 9; ACI-P, n = 7) were recruited for reassessment for the current study, representing a follow-up rate of 76%. The 2 groups showed a significant difference regarding sex ratio (P = .017). Body mass index before surgery showed a significant difference between groups (MACI, 23.32 ± 1.15; ACI-P, 25.41 ± 2.55; P = .043). All patients completed at least 8 years of follow-up, with a mean follow-up of 9.6 ± 0.9 years in the MACI group and 8.6 ± 0.8 years in the ACI-P group. Detailed descriptions of study population are given in Tables 1 and 2.

Clinical Evaluation

The therapy outcome was assessed by clinical scores, as shown in Tables 3 and 4. Evaluation of the clinical data in a categorical fashion is shown in Appendix Table A1 (available in the online version of this article).

The Tegner Activity Score in the ACI-P group increased continuously to the final follow-up (T0:T3; P = .017), and each increase proved to be significant when compared with the preoperative status. Categorical evaluation in the ACI-P group showed that 85.2% of patients were rated as poor to fair at T0, which improved to 72.2% being rated as good to excellent at T2. At the final follow-up, 57.4% were still rated as good to excellent. In the MACI group, no significant differences were seen over time. The MACI group started with slightly higher scores, which decreased over T_1 and T2 and improved marginally at T3. The MACI group started with 66.7% being rated as poor to fair, and this remained unchanged at all evaluation time points. One patient (11.1%) was rated as excellent in the MACI group at T0, and this category improved to 22.2% at T3. No significant difference was observed between the study groups at any time point.

The Lysholm and Gillquist score improved significantly from preoperative status to the first follow-up and remained significantly elevated at 24 months postoperatively in the ACI-P group. In the MACI group, the Lysholm and Gillquist score peaked at the first follow-up and decreased until the last follow-up, but changes were not significant. Categorical evaluation revealed that in the ACI-P group, all patients were categorized as poor to fair

TABLE 2
Defect Characteristics of the Study Population[a]

	MACI	ACI-P	*P* Value
Cause, n (%)			.949 (χ^2 test)
Osteochondritis dissecans	5 (55.6)	3 (42.6)	
Chondromalacia	4 (44.4)	4 (57.4)	
Side, n (%)			.131 (χ^2 test)
Right	6 (66.7)	2 (28.6)	
Left	3 (33.3)	5 (71.4)	
Defect localization, n (%)			.362 (χ^2 test)
Medial femoral condyle	8 (88.9)	7 (100)	
Lateral femoral condyle	1 (11.1)	0 (0)	
Additional defects, n (%)			.197 (χ^2 test)
Trochlea	1 (11.1)	0 (0)	
Retropatellar	1 (11.1)	0 (0)	
Defect size, cm^2	4.27 ± 0.2	4.08 ± 0.44	.670 (*t* test)
	4 (3-6)	4 (2.55-6)	
Kellgren-Lawrence score (at the final follow-up), n			.549 (χ^2 test)
0	1	2	
1	5	4	
2	0	0	
3	2	1	
4	1	0	

[a]Defect size is expressed as mean ± SD with median (range). ACI-P, autologous chondrocyte implantation with periosteum; MACI, matrix-associated autologous chondrocyte implantation. Unpaired *t* test and χ^2 test were used. $P < .05$ was considered significant.

at T0. Already at the 12-month follow-up (T_1), 85.2% were rated as excellent with a decrease to 71.4% at T2. At the final follow-up (T3), 72.2% were still categorized as good to excellent. In the MACI group, 66.7% were rated as poor at T0, which decreased at T_1 to 33.3% but reached preoperative levels at T3. No significant differences were seen between the study groups at any time point.

The subjective IKDC score increased significantly from baseline to the postoperative time points in the ACI-P group. In the MACI group, subjective IKDC scores showed a significant increase at T_1 and T3 when compared with preoperative status (T0:T1, $P = .011$; T0:T3, $P = .021$). Whereas the majority of patients started with poor subjective IKDC scores at T0 (ACI-P, 100%; MACI, 89.9%), the percentages of poor ratings decreased to 66.7% in MACI and 14.8% in ACI-P. No significant differences were seen in subjective IKDC scores between the 2 ACI methods at any follow-up time, as shown in Table 3.

The objective IKDC scores at the final follow-up did not show any significant differences between the 2 groups (Appendix Table A2, available online). At the final follow-up, the pain level was assessed by VAS, which showed no significant difference between the 2 groups ($P = .589$).

SF-36 and Subscales

Scores for physical health increased significantly from baseline to all postoperative time points in the ACI-P group. The MACI group showed a significant increase at T2 and T3 when compared with preoperative status (T0:T2, $P = .021$; T0:T3, $P = .008$).

Mental health scores remained unchanged in the MACI group until the 24-month follow-up and increased slightly from this value to the final follow-up. In the ACI-P group, a slight significant increase was seen when comparing T0, T_1, and T2 to the final follow-up at T3.

The differences in subscales were as follows:

Physical functioning: Both groups demonstrated significant improvements at each follow-up time in comparison with the initial scores.

Physical role functioning: All patients showed significant improvements at each follow-up time in comparison with the preoperative status except in the ACI-P group at T2.

Bodily pain: When ACI-P and MACI were evaluated together, all follow-up scores were significantly higher compared with T0. MACI showed a significant improvement only at the last follow-up in comparison with T0. In ACI-P, pain scores significantly improved from baseline to the first and last follow-up.

Vitality: Scores did not show a significant improvement from baseline to T_1 and T2. Further, scores at the last follow-up (T3) proved to be significantly higher compared with T0. At T3, ACI-P showed significantly higher scores than MACI ($P = .049$).

Social role functioning: Both groups showed a significant improvement from baseline to the last follow-up. All patients together also demonstrated significant improvements at T0:T_1 ($P = .022$), T0:T3 ($P = .022$), and T2:T3 ($P = .046$).

No significant changes were detected for the general health, emotional role functioning, and mental health subscales (Table 4).

TABLE 3
Clinical Outcome at Different Time Points[a]

	Preoperative (T0) (n = 16)	12 Months Postoperative (T1) (n = 16)	24 Months Postoperative (T2) (n = 16)	Last Follow-up (T3) (n = 16)	*P* Value (MACI)	*P* Value (ACI-P)
Tegner Activity Score					T0:T1 *P* = .236 T0:T2 *P* = .341 T0:T3 *P* = .498 T1:T2 *P* = .713 T1:T3 *P* = .234 T2:T3 *P* = .357	T0:T1 *P* = **.042** T0:T2 *P* = **.042** T0:T3 *P* = **.017**[b] T1:T2 *P* = .317 T1:T3 *P* = .581 T2:T3 *P* = .713
MACI	4.6 ± 2.7 4 (0-9)	3.9 ± 2 4 (0-7)	4.2 ± 3 3 (0-10)	4.9 ± 2.3 4 (3-9)		
ACI-P	3.2 ± 1.8 3 (2-7)	5.1 ± 2.1 6 (3-8)	5.6 ± 1.9 6 (3-8)	5.6 ± 2.1 6 (3-9)		
P value at each time point (MACI:ACI-P)	.119	.450	.255	.455		
Lysholm and Gillquist score					T0:T1 *P* = .314 T0:T2 *P* = .767 T0:T3 *P* = .374 T1:T2 *P* = .362 T1:T3 *P* ≥ .999 T2:T3 *P* = .678	T0:T1 *P* = **.018** T0:T2 *P* = **.027** T0:T3 *P* = .063 T1:T2 *P* = .343 T1:T3 *P* = .249 T2:T3 *P* = .499
MACI	65.1 ± 21.6 65 (22-92)	88 ± 29 88 (30-100)	78 ± 29 78 (28-100)	72.4 ± 16.4 66 (53-97)		
ACI-P	57.3 ± 11.9 56 (40-75)	92 ± 7.2 94 (77-98)	87 ± 19.1 94 (46-100)	82 ± 17.2 92 (50-95)		
P value at each time point (MACI:ACI-P)	.265	.185	.137	.289		
Subjective IKDC score					T0:T1 *P* = **.011**[b] T0:T2 *P* = .109 T0:T3 *P* = **.021** T1:T2 *P* = .262 T1:T3 *P* = .593 T2:T3 *P* = .511	T0:T1 *P* = **.018** T0:T2 *P* = **.028** T0:T3 *P* = **.018** T1:T2 *P* = .752 T1:T3 *P* = .917 T2:T3 *P* = .933
MACI	46.1 ± 2.5 37.4 (18.4-87.4)	69.1 ± 23.6 75.9 (29.9-100)	65.1 ± 29.4 66.7 (23-98.9)	70.4 ± 19.3 65.5 (44.8-97.7)		
ACI-P	48.9 ± 9.6 46 (37.9-64.4)	82 ± 14.1 79.3 (64.4-98.9)	82.1 ± 18.1 88.5 (52.9-100)	81.6 ± 12.2 79.3 (64.4-97.7)		
P value at each time point (MACI:ACI-P)	.396	.426	.315	.204		
SF-36 Physical Health					T0:T1 *P* = .051 T0:T2 *P* = **.021** T0:T3 *P* = **.008**[b] T1:T2 *P* = .635 T1:T3 *P* = .441 T2:T3 *P* = .594	T0:T1 *P* = **.028** T0:T2 *P* = **.043** T0:T3 *P* = **.018** T1:T2 *P* = .753 T1:T3 *P* = .866 T2:T3 *P* = .612
MACI	29.2 ± 1.3 29.2 (27.8-32.1)	30.9 ± 1.8 31.5 (28.4-32.5)	31 ± 2.3 31.5 (27.1-33.5)	31.5 ±1.2 31.3 (30.1-33.3)		
ACI-P	30.3 ± 1.2 30.6 (28.6-32.1)	31.9 ± 1 31.8 (30.4-33.1)	32 ± 1.1 32.2 (30.6-33.1)	32 ± 0.7 32.1 (30.9-32.9)		
P value at each time point (MACI:ACI-P)	.081	.340	.560	.368		
SF-36 Mental Health					T0:T1 *P* = .173 T0:T2 *P* = .066 T0:T3 *P* = .515 T1:T2 *P* = .208 T1:T3 *P* = .173 T2:T3 *P* = **.028**	T0:T1 *P* = .866 T0:T2 *P* = .310 T0:T3 *P* = **.018** T1:T2 *P* = .753 T1:T3 *P* = **.028** T2:T3 *P* = **.028**
MACI	12.1 ± 0.5 12.2 (11.4-13.2)	11.8 ± 0.3 11.8 (11.1-12.2)	11.6 ± 0.7 11.7 (10.5-12.7)	12.6 ± 1.3 12 (10.9-1.6)		
ACI-P	11.9 ± 0.6 12 (11-12.9)	11.9 ± 0.4 11.9 (11.4-12.7)	11.7 ± 0.5 11.6 (11-12.3)	13.6 ± 1 13.5 (11.9-14.8)		
P value at each time point (MACI:ACI-P)	.315	≥.999	.832	.186		

[a]Scores are presented as mean ± SD with median (range). ACI-P, autologous chondrocyte implantation with periosteum; IKDC, International Knee Documentation Committee; MACI, matrix-associated autologous chondrocyte implantation; SF-36, 36-Item Short Form Health Survey. Friedman, Wilcoxon matched-pairs, and Mann-Whitney *U* tests were used. Boldface indicates satistical significance at $P < .05$.

[b]Statistical assessments that remained significant after Bonferroni correction.

Subgroup Analysis

We corrected for the difference in sex distribution between MACI and ACI-P by comparing only the male patients in MACI with the ACI-P group. This did not alter the pattern of clinical scores as described above. By comparing male versus female in the MACI group, we further analyzed whether clinical scores show a sex-specific pattern. No significant differences were seen between male and female patients at any time.

TABLE 4
36-Item Short Form (SF-36) Health Survey Scale[a]

	Preoperative (T0) (n = 16)	12 Months Postoperative (T1) (n = 16)	24 Months Postoperative (T2) (n = 16)	Last Follow-up (T3) (n = 16)	*P* Value (MACI)	*P* Value (ACI-P)
Physical functioning					T0:T1 *P* = **.044**	T0:T1 *P* = **.018**
MACI	36.11 ± 24.85 35 (10-90)	67.22 ± 27.96 80 (0-7)	72.78 ± 32.70 90 (15-100)	79.44 ± 20.07 90 (45-100)	T0:T2 *P* = **.007**[b] T0:T3 *P* = **.008**[b] T1:T2 *P* = .248	T0:T2 *P* = **.028** T0:T3 *P* = **.028** T1:T2 *P* = .593
ACI-P	55 ± 21.41 55 (30-85)	86.43 ± 17.01 90 (60-100)	88.57 ± 14.92 95 (65-100)	88.57 ± 13.14 95 (70-100)	T1:T3 *P* = .106 T2:T3 *P* = .865	T1:T3 *P* = .892 T2:T3 *P* ≥ .999
P value at each time point (MACI:ACI-P)	.112	.132	.383	.361		
Physical role functioning					T0:T1 *P* = **.016**[b]	T0:T1 *P* = **.027**
MACI	19.44 ± 41.04 0 (–25 to 100)	69.44 ± 46.40 100 (0-100)	69.44 ± 46.40 100 (0-100)	80.56 ± 34.86 100 (0-100)	T0:T2 *P* = **.016**[b] T0:T3 *P* = **.018** T1:T2 *P* ≥ .999	T0:T2 *P* = .101 T0:T3 *P* = **.026** T1:T2 *P* ≥ .999
ACI-P	35.71 ± 34.93 25 (0-100)	85.71 ± 28.35 100 (25-100)	85.71 ± 28.35 100 (25-100)	92.86 ± 12.20 100 (75-100)	T1:T3 *P* = .414 T2:T3 *P* = .414	T1:T3 *P* = .655 T2:T3 *P* = .655
P value at each time point (MACI:ACI-P)	.222	.606	.606	.651		
Bodily pain					T0:T1 *P* = .069	T0:T1 *P* = **.063**
MACI	39.78 ± 28.74 31 (10-84)	68.56 ± 25.29 74 (22-100)	63.44 ± 35.39 62 (0-100)	63.67 ± 25.52 61 (32-100)	T0:T2 *P* = .107 T0:T3 *P* = **.021**	T0:T2 *P* = .051 T0:T3 *P* = **.043**
ACI-P	53 ± 14.27 51 (31-74)	76.14 ± 19.31 74 (51-100)	83 ± 21.42 84 (41-100)	76.57 ± 12.15 72 (62-100)	T1:T2 *P* = .498 T1:T3 *P* = .528 T2:T3 *P* = .866	T1:T2 *P* = .343 T1:T3 *P* ≥ .999 T2:T3 *P* = .713
P value at each time point (MACI:ACI-P)	.242	.519	.276	.183		
General health					T0:T1 *P* = .767	T0:T1 *P* = .216
MACI	69.44 ± 20.80 67 (25-92)	72.11 ± 24.96 77 (37-100)	69.67 ± 26.92 72 (30-100)	74.33 ± 19.89 87 (40-92)	T0:T2 *P* = .553 T0:T3 *P* = .345	T0:T2 *P* = .799 T0:T3 *P* = .394
ACI-P	80.57 ± 11.80 87 (67-97)	84.57 ± 13.09 77 (67-100)	81.57 ± 15.27 77 (65-100)	86 ± 15.56 90 (52-97)	T1:T2 *P* = .600 T1:T3 *P* = .722 T2:T3 *P* = .813	T1:T2 *P* = .715 T1:T3 *P* = .833 T2:T3 *P* = .674
P value at each time point (MACI:ACI-P)	.183	.309	.457	.231		
Vitality					T0:T1 *P* = .660	T0:T1 *P* = .187
MACI	23.89 ± 6.01 25 (15-30)	23.89 ± 6.01 25 (15-35)	25.56 ± 8.46 25 (15-45)	61.11 ± 19.33 60 (30-85)	T0:T2 *P* = .705 T0:T3 *P* = **.008**[b]	T0:T2 *P* = .416 T0:T3 *P* = **.018**
ACI-P	19.29 ± 8.86 20 (5-30)	22.86 ± 6.36 20 (15-35)	22.86 ± 9.51 20 (10-40)	78.57 ± 12.82 75 (65-95)	T1:T2 *P* = .334 T1:T3 *P* = **.008**[b] T2:T3 *P* = **.008**[b]	T1:T2 *P* = .891 T1:T3 *P* = **.018** T2:T3 *P* = **.018**
P value at each time point (MACI:ACI-P)	.301	.658	.380	**.049**		
Social role functioning					T0:T1 *P* = .108	T0:T1 *P* = .078
MACI	70.83 ± 34.23 75 (12.5-112.5)	97.22 ± 20.52 112.5 (62.5-112.5)	84.72 ± 31.11 100 (37.5-112.5)	106.94 ± 9.08 112.5 (87.5-112.5)	T0:T2 *P* = .416 T0:T3 *P* = **.027**	T0:T2 *P* = .206 T0:T3 *P* = **.039**
ACI-P	85.71 ± 30.13 87.5 (25-112.5)	103.57 ± 15.67 112.5 (75-112.5)	103.57 ± 15.67 112.5 (75-112.5)	107.14 ± 9.83 112.5 (87.5-112.5)	T1:T2 *P* = .109 T1:T3 *P* = .141 T2:T3 *P* = .066	T1:T2 *P* ≥ .999 T1:T3 *P* = .414 T2:T3 *P* = .655
P value at each time point (MACI:ACI-P)	.335	.464	.179	.897		
Emotional role functioning					T0:T1 *P* = .180	T0:T1 *P* = .317
MACI	77.78 ± 44.10 100 (0-100)	92.59 ± 22.23 100 (33.3-100)	81.48 ± 37.68 100 (0-100)	92.59 ± 22.22 100 (33.3-100)	T0:T2 *P* = .785 T0:T3 *P* = .276	T0:T2 *P* = .785 T0:T3 *P* = .655
ACI-P	90.47 ± 25.21 100 (33.3-100)	100 ± 0 100 (100)	85.71 ± 26.23 100 (33.3-100)	95.24 ± 12.60 100 (66.67-100)	T1:T2 *P* = .317 T1:T3 *P* ≥ .999 T2:T3 *P* = .414	T1:T2 *P* = .180 T1:T3 *P* = .317 T2:T3 *P* = .317
P value at each time point (MACI:ACI-P)	.586	.378	.944	.927		

(continued)

TABLE 4
(continued)

	Preoperative (T0) (n = 16)	12 Months Postoperative (T1) (n = 16)	24 Months Postoperative (T2) (n = 16)	Last Follow-up (T3) (n = 16)	*P* Value (MACI)	*P* Value (ACI-P)
Mental health					T0:T1 *P* = .887 T0:T2 *P* ≥ .999 T0:T3 *P* = .725 T1:T2 *P* ≥ .999 T1:T3 *P* = .623 T2:T3 *P* = .717	T0:T1 *P* = .141 T0:T2 *P* = .932 T0:T3 *P* = .149 T1:T2 *P* = .340 T1:T3 *P* = .394 T2:T3 *P* = .206
MACI	54.67 ± 5.29 56 (48-64)	53.78 ± 6.96 52 (44-64)	54.67 ± 5.66 52 (48-64)	52.89 ± 10.73 52 (40-68)		
ACI-P	55.43 ± 5.38 56 (48-60)	59.43 ± 4.28 60 (56-68)	52.57 ± 14.86 56 (20-64)	62.86 ± 10.76 64 (44-76)		
P value at each time point (MACI:ACI-P)	.662	.103	.553	.087		

[a]Scores are presented as mean ± SD with median (range). ACI-P, autologous chondrocyte implantation with periosteum; MACI, matrix-associated autologous chondrocyte implantation. Friedman, Wilcoxon matched-pairs, and Mann-Whitney *U* tests were used. Boldface satistical significance at $P < .05$.
[b]Statistical assessments that remained significant after Bonferroni correction.

MRI Evaluation

All patients underwent MRI evaluation at the final follow-up to determine the morphological status of the cartilage as described by the MOCART score. Further, the dGEMRIC technique was used to evaluate alterations of the T_1 relaxation time of the repair cartilage and hence the content of glycosaminoglycans. Overall result and distribution in subdomains of the MOCART score are shown in Table 5.

In the majority of the patients (10/16; MACI, n = 5; ACI-P, n = 5), a complete defect filling was present. One patient in the ACI-P group displayed hypertrophy of the repair tissue, which represents 6% of the whole study group and 14.3% of the ACI-P group. Further, 4 patients (MACI, n = 3; ACI-P, n = 1) had exposed subchondral bone. The repair tissue was inhomogeneous in 10 patients (MACI, n = 6; ACI-P, n = 4). In 15 patients (MACI, n = 8; ACI-P, n = 7) alterations of the subchondral bone were present. Cystic lesions were present in 5 patients (MACI, n = 2; ACI-P, n = 3) and adhesions and synovitis in another 5 patients (MACI, n = 1; ACI-P, n = 4).

The dGEMRIC analyses revealed a mean reduction of the T_1 relaxation times after contrast of 174.6 ± 152.8 milliseconds (MACI, –237.4 ± 125.7 ms; ACI-P, –93.9 ± 154.2 ms) in the repair tissue compared with the normal cartilage (Table 6).

We found that 8 patients (MACI, n = 6; ACI-P, n = 2) had a reduction of more than 200 milliseconds, 1 patient in the MACI group had only a slight reduction (–13 ms), and 2 patients in the ACI-P group had higher T_1 values (80 and 93 ms, respectively). Figure 1 presents examples of dGEMRIC analysis in the repair tissue in 2 patients in the final follow-up after MACI and ACI-P, respectively.

Lower dGEMRIC values were present in the repair tissue compared with the normal adjacent cartilage in both techniques; however, we found similar values when comparing the 2 methods. This can be interpreted as incomplete healing with persistent reduction of the glycosaminoglycan content in the repair tissue in the long-term course. According to the MOCART score and dGEMRIC, no significant differences were found between the 2 groups.

Complications and Failures

As evaluated at the final follow-up by MRI, no patient in the MACI group and only 1 patient in the ACI-P group showed graft hypertrophy, although this patient did not receive further surgery. There were 3 patients (33.3%) in MACI and 2 patients (28.6%) in ACI-P who underwent further surgery until the last follow-up. We noted that 1 patient in the MACI group required an early arthroscopy (9 months after ACI) because of symptomatic hypertrophy. A further 2 MACI patients received arthroscopic surgery after 3 years due to pain and cartilage thinning. The 2 patients in the ACI-P group received arthroscopic synovectomy at 2 years and at 7 years after ACI. None of the patients had joint infections, postoperative fever or infection, arterial injuries, or nerve damage. None of the patients had received joint replacement surgery.

DISCUSSION

The highest but yet unreached goal in the treatment of articular cartilage lesions is to generate substitute cartilage with the same biomechanical and biochemical properties of hyaline cartilage. Even though third-generation ACI is considered to present the highest treatment standard, the superiority of this advancement is not well-supported by clinical studies, and few studies have addressed whether higher generation ACI results in superior clinical outcome.[2,3,10,20,24,27,40]

To the best of our knowledge, this is the first randomized controlled trial with a follow-up of almost 10 years comparing the original technique (ACI-P) with the third-generation technique (MACI). Interpretation of our data has to be

TABLE 5
Magnetic Resonance Observation of Cartilage Repair (MOCART) Score at the Last Follow-up[a]

	MACI (n = 9)	ACI-P (n = 7)	*P* Value
Defect repair filling			.425 (Wilcoxon matched-pairs and Mann-Whitney *U* tests)
Complete (on a level with adjacent cartilage)	5 (55.5)	5 (71.4)	
Hypertrophy (over the level of the adjacent cartilage)	0 (0)	1 (14.3)	
Incomplete >50% of the adjacent cartilage	0 (0)	0 (0)	
Incomplete <50% of the adjacent cartilage	1 (11.1)	0 (0)	
Subchondral bone exposed	3 (33.4)	1 (14.3)	
Integration			.206 (Wilcoxon matched-pairs and Mann-Whitney *U* tests)
Complete integration with adjacent cartilage	2 (22.2)	3 (42.8)	
Incomplete integration (demarcating border visible)	2 (22.2)	2 (28.6)	
Defect visible <50% of the length of the repair tissue	3 (33.4)	2 (28.6)	
Defect visible >50% of the length of the repair tissue	2 (22.2)	0 (0)	
Structure			.696 (χ^2 test)
Homogeneous	3 (33.4)	3 (42.8)	
Inhomogeneous or cleft formation	6 (66.6)	4 (57.2)	
Surface			.217 (Wilcoxon matched-pairs and Mann-Whitney *U* tests)
Surface intact (lamina splendens intact)	2 (22.2)	3 (42.8)	
Surface damaged <50% of repair tissue depth	3 (33.4)	3 (42.8)	
Surface damaged >50% of repair tissue depth	4 (44.4)	1 (14.3)	
Signal proton density weighted mode			.193 (Wilcoxon matched-pairs and Mann-Whitney *U* tests)
Isointense	5 (55.5)	6 (85.7)	
Moderately hyperintense	3 (33.4)	1 (14.3)	
Markedly hyperintense	1 (11.1)	0 (0)	
Subchondral lamina			.849 (χ^2 test)
Intact	8 (88.9)	6 (85.7)	
Not intact	1 (11.1)	1 (14.3)	
Subchondral bone			.362 (χ^2 test)
Intact	1 (11.1)	0 (0)	
Not intact (edema, cyst)	8 (88.9)	7 (100)	
Signal T1			≥.999 (Mann-Whitney *U* test)
Isointense	9 (100)	7 (100)	
Moderately hyperintense	0 (0)	0 (0)	
Markedly hyperintense	0 (0)	0 (0)	
Adhesions			.146 (χ^2 test)
No	8 (88.9)	4 (57.2)	
Yes	1 (11.1)	3 (42.8)	
Effusion			.771 (χ^2 test)
No	7 (77.7)	5 (71.4)	
Yes	2 (22.2)	2 (28.6)	
Mean MOCART score	58.9 ± 18.3	71.4 ± 19.3	.206 (*t* test)

[a]Absolute numbers (percentages) are presented for categorical data of the MOCART subscores at the last follow-up (T3). A lower MOCART score corresponds to more normal magnetic resonance imaging diagnostic findings. MACI, matrix-associated autologous chondrocyte implantation; ACI-P, autologous chondrocyte implantation with periosteum. Unpaired *t* test, Wilcoxon matched-pairs test, Mann-Whitney *U* test, and χ^2 test were used. $P < .05$ was considered significant.

performed with caution due to the small sample size, which was further limited by a loss to follow-up of 24%.

Our data confirm that early improvement after ACI is sustained for a long period, as shown by the significant improvement in almost all outcome parameters, which persisted until the final follow-up. Considering the ACI-P group, our results are in accordance with previous publications with long-term follow-up.[23,26,29,33] Ogura et al[29] provided a sufficient survival rate for the treatment of large cartilage lesions up to 20 years after ACI-P. Those investigators showed that the greatest improvement in clinical scores occurred during the first 2 years. Peterson et al[33] reported that 92% of 224 patients had a satisfactory result in a study evaluating ACI-P after a mean follow-up of 12.8 years. In another study by our group, we evaluated 23 patients after first-generation ACI-P with a mean follow-up of almost 10 years, showing substantial improvement in all clinical outcome parameters, although a small deterioration was found between the intermediate and final evaluations.[23] Interestingly, no deterioration was

TABLE 6
Delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage Data at the Last Follow-up[a]

	Post T1 Repair Site	Post T1 Normal Cartilage	Post T1 Difference
MACI (n = 9)	557.7 ± 123.2	795.1 ± 57	–237.4 ± 125.7
	532 (421.3 to 741.4)	823.6 (693 to 849.1)	–293 (–380.4 to –13.2)
ACI-P (n = 7)	709.6 ± 165.6	803.5 ± 46.8	–93.9 ± 154.2
	732 (419.9 to 894.4)	802.3 (737.2 to 874.3)	–83 (–338 to 93.2)
P value	.563	.344	.857

[a]Values are presented in milliseconds as mean ± SD with median (range). Unpaired *t* test was used. $P < .05$ was considered significant. ACI-P, autologous chondrocyte implantation with periosteum; MACI, matrix-associated autologous chondrocyte implantation; T1, T1 relaxation time.

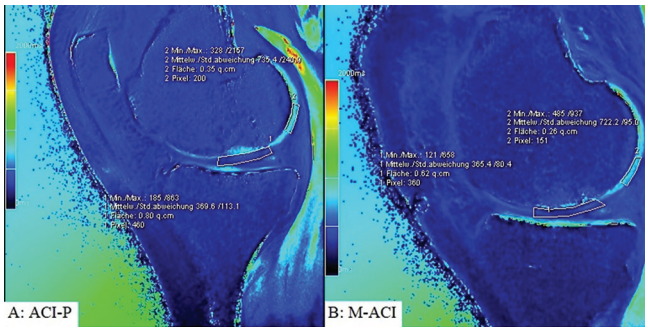

Figure 1. Representative examples of dGEMRIC analysis in the repair tissue are shown for (A) autologous chondrocyte implantation with a periosteum cover (ACI-P) and (B) matrix-associated autologous chondrocyte implantation (MACI). dGEMRIC, delayed gadolinium-enhanced magnetic resonance imaging of cartilage.

found in the ACI-P group of this study between the intermediate and final evaluation time point.

Compared with the well-documented clinical improvement after ACI-P,[23,26,29,33] substantial knowledge about the long-term progression of MACI is still rare.[1,8,16] Aldrian et al[1] evaluated 16 patients treated with MACI with a 10-year follow-up, showing significant improvement in all clinical scores. Kreuz et al[16] described 21 patients who had received MACI and experienced significant improvement of IKDC and Lysholm scores 12 years postoperatively. In 2016, Gille et al[8] evaluated 14 patients with a mean follow-up of 15 years, reporting significant improvement in all assessed scores after MACI. All 3 of these studies lacked any comparative cohort or control group.

In our clinical evaluation, the MACI group showed no significant improvement in daily knee functionality (Lysholm score) and sports activity (Tegner Activity Score), which is different from the results for the ACI-P group and could be due to higher baseline scores in this group. However, MACI showed significant long-lasting improvements in subjective IKDC and SF-36 physical health scores. The comparison between both groups revealed that only the vitality subscale of SF-36 at the final evaluation time point showed significantly higher scores for ACI-P. Our findings are consistent with the limited number of studies published on the comparison between different generations of ACI[2,3,20,24] or comparison of ACI with other techniques such as microfracture.[14] The largest retrospective study was published by Nawaz et al,[24] who evaluated the functional outcome of 827 patients who received either ACI with Chondron and periosteum (ACI-C/ACI-P) or MACI. No differences were found between the survival rates of the ACI-C/ACI-P and MACI techniques after 10 years of follow-up.

The only study showing better results for higher generation ACI was published by Niemeyer et al.[27] In a matched-pair analysis in 46 patients with 10 years of follow-up, those investigators found significantly better functional outcomes in the patients who underwent second-generation ACI compared with ACI-P.

Even though clinical results are the primary outcome criterion, it is of utmost interest to analyze the biological features of the cartilage repair tissue after ACI.[31] Because histological evaluation is not conducted in routine follow-up, MRI assessment is considered the most effective noninvasive tool to evaluate the internal structures of the knee. We conducted MRI assessment by applying a morphological graft scoring system (MOCART) and dGEMRIC, which provides information regarding the histological quality of the repair tissue. MRI evaluation at the final follow-up showed a complete defect filling in 55.6% and 71.4% of MACI and ACI-P patients, respectively. This is in line with the study by Kreuz et al,[16] who reported complete defect filling of 57.1% of patients who underwent MACI. In the study by Aldrian et al,[1] the majority of patients who underwent MACI developed good-quality repair tissue on imaging, showing complete integration of the graft at the early follow-up, which was maintained until 5 years after surgery and followed by a gradual degradation. After 10 years of follow-up, the mean MOCART score of their patients was 70.4 ± 16.1. Their results are comparable with our patients who received ACI-P (71.4 ± 19.3). Manfredini et al[20] did not find any significant differences between patients who underwent ACI-P (Carticel technique) and patients who had arthroscopic MACI based on a hyaluronan scaffold (Hyalograft C).

In this study, we further provide data on the composition of the cartilage assessed by dGEMRIC. Our data indicate higher quality of the transplant and cartilage in ACI-P patients. Reports on dGEMRIC for the postoperative evaluation of cartilage repair are scarce and have provided controversial results.[8,37] Vasiliadis et al[37] found no correlation between dGEMRIC and clinical scores in a study evaluating 31 patients who underwent ACI-P surgery with 9 years of follow-up. Those investigators reported that the

cartilage defect area was restored in most of the cases, and the quality of the repair tissue was identical to the surrounding cartilage.

The clinical data presented in the current prospective randomized trial seem to indicate that ACI-P provides equal if not better results than MACI. When critically reviewed, this finding is in accordance with the available literature. The MRI evaluation looking at morphological features and quality of the repair tissue did not show significant differences between ACI-P and MACI; any differences found favored the ACI-P group. This raises the question why higher generation ACI is considered the method of choice and thought to present a higher treatment standard. This might be due to practical advantages of MACI, such as shorter operation time and no need for an additional incision. Further, MACI is more appliable to difficult locations in the joint than is ACI-P, and cells are thought to remain in place and more equally distributed.[35] Some studies have reported high revision rates due to graft hypertrophy or adhesions after ACI-P.[26,27] In our study, graft hypertrophy was found in only 1 patient in ACI-P group at the last follow-up by MRI. This presents a hypertrophy rate of 6% for the total sample and 14.3% in the ACI-P group. It remains unknown at this stage why the modifications of ACI do not result in superior morphological repair tissue. One explanation might be the chondrogenic potential of periosteum, by providing either growth factors or mesenchymal stem cells.[28,32] Collagen fleece or matrices lack this additional effect, and their presence in the cartilage defect might even be suppressive for cartilage growth.

The main weakness of this randomized clinical trial is that it is underpowered, which limits the detection of confounding factors, correlation, and subgroup analysis. Further, the randomization method was not stratified by sex and left the ACI-P group with only male patients. The results of this investigation should be tested by performing a randomized clinical trial stratified by sex and age with a larger sample size.

CONCLUSION

The long-term results of this randomized clinical trial confirm that first- and third-generation ACIs are equally effective for the treatment of cartilage defects in the femoral condyle. Even though superiority of one method over the other was not evident, a tendency toward more reliable clinical and radiological improvements was found in ACI-P versus MACI. Taken together, there is still no sufficient evidence to show any superiority of one ACI generation over the other, and further trials, particularly studies aiming to evaluate the long-term follow-up of different generations of ACI, are necessary.

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