

# Short- to Midterm Clinical and Radiological Outcomes After Matrix-Associated Autologous Chondrocyte Implantation for Chondral Defects in Knees

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**Background:** Matrix-associated autologous chondrocyte implantation (MACI) has been proven to provide favorable short-term results for chondral defects in knees. However, it remains unclear whether the clinical benefits of MACI persist in the longer term.

**Purpose:** The purpose of this prospective study was to evaluate the clinical and radiological outcomes, at short- and midterm follow-up, for patients undergoing MACI for focal chondral defects of the knee.

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

**Methods:** A total of 30 consecutive patients (31 knees) were treated using MACI between October 2010 and March 2018. There were 24 male patients and 6 female patients with an average age of 26 years (range, 12-48 years). The areas of the cartilage defect were consistently  $>2$  cm<sup>2</sup>. All patients underwent MACI for a focal chondral defect of the femoral condyles or trochlea in the knee. These patients had been evaluated for up to 5 years, with an average follow-up of 44 months (range, 6-60 months) postoperatively.

The International Knee Documentation Committee (IKDC) score, Lysholm score, and magnetic resonance imaging (MRI) with T2 mapping were used to assess the outcomes.

**Results:** No patients were lost to follow-up. Mean IKDC scores improved from 58.6 (range, 40.2-80.5) to 79.1 (range, 39.1-94.3) at 12 months and up to 88.4 (range, 83.9-100) at 5 years; mean Lysholm scores improved from 67.3 (range, 46-95) to 90.6 (range, 71-100) at 12 months and up to 95.9 (range, 85-100) at 5 years. The MRI with T2 mapping value of the transplanted area was evaluated for 21 knees, which revealed no differences compared with the normal area at 12 months postoperatively.

**Conclusion:** From the first year onward, the clinical outcome scores and MRI with T2 mapping values showed continuous and marked improvement, suggesting that MACI is a valid option for localized cartilage defects in the knee.

**Keywords:** knee; articular cartilage; biologic healing enhancement; biology of cartilage; clinical assessment/grading scales; matrix-induced autologous chondrocyte implantation

Cartilage lesions of the knee have frequently been identified during arthroscopic procedures.<sup>1,22</sup> If these lesions are left without any intervention, the articular cartilage cannot regrow and heal after injury or certain pathologies.<sup>4</sup> Among all the attempts to address this problem, autologous chondrocyte implantation (ACI) offers a biological approach.<sup>3</sup> Matrix-associated ACI (MACI), also known as the third-generation ACI, constitutes a scaffold impregnated with periosteal-free expanded chondrocytes to deliver better cell distribution over the defect and is thus capable of managing extensive osteochondral defects. In 2012, we published preliminary outcomes in a series of patients who underwent 2-stage

MACI to determine the early efficacy of this procedure in treating adolescent articular cartilage defects in the knee.<sup>6</sup> That 1-year follow-up study yielded desirable clinical results. However, it remained unclear whether the clinical benefits of MACI would persist in the longer term.

The purpose of this prospective study was to further assess the efficacy and safety of MACI up to 5 years after surgery. We hypothesized that continuous improvement in clinical and radiological outcomes observed in the first postoperative year would persist at midterm follow-up.

## METHODS

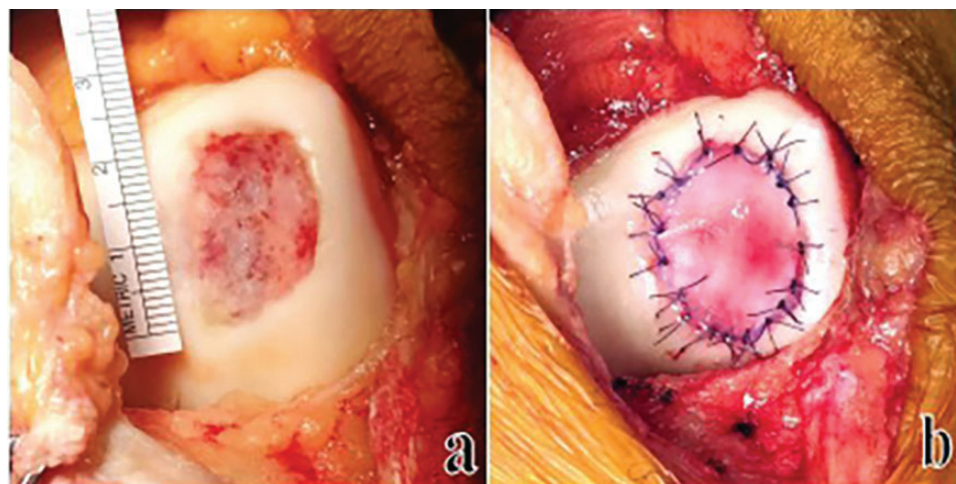
This study received approval from the ethics review committee of our institution, and informed consent was obtained from all participating patients.

The Orthopaedic Journal of Sports Medicine, 9(2), 2325967120982139

DOI: 10.1177/2325967120982139

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**Figure 1.** The second step of matrix-associated autologous chondrocyte implantation (MACI). (A) Exposed defect. (B) MACI implant secured using fibrin glue and No. 5-0 absorbable sutures.

### Patient Selection

We set the minimum age cutoff at 12 years but reconsidered the upper limit of 20 years, used in our initial study,<sup>6</sup> upon the thought that age was not an absolute contraindication for cartilage-related surgery if we were to observe outcomes for an extended period. Thus, patients were included in this study if they were more than 12 and no more than 50 years old. Other inclusion criteria were a stable joint, normal alignment of the lower extremity, cartilage defect  $>2\text{ cm}^2$ , and noninflammatory lesion. Exclusion criteria were osteoarthritis (Kellgren-Lawrence grade 3 or 4), multifocal or bilateral lesions, unstable knee or malalignment, and general medical conditions (eg, diabetes, rheumatoid arthritis).

### Manufacturing Process

The MACI technique is based on a 3-dimensional collagen type I/III scaffold seeded with cultured autologous chondrocytes, as explained in our previous study.<sup>6</sup> In brief, the harvested cartilage was expanded in serum taken from the patient's blood at the time of surgery under good manufacturing practice conditions (Guanhao Biotech Co, Ltd). After 3 weeks, a cell number of 15 to 20 million was achieved, and the cells were seeded on a biphasic collagenous scaffold. The scaffold consisted of a firm and dense membrane and a spongy area of pores arranged in columns of a set size. The chondrocyte-seeded MACI implant was

then transported back to the surgeon and was ready for implantation.

### Surgical Technique

The therapy was delivered in 2 stages. In the first stage, diagnostic arthroscopy was performed to evaluate the defect and note the number, size, and location of chondral defects. This was followed by a surgical procedure to address concurrent lesions of the meniscus or anterior cruciate ligament (ACL) (partial meniscectomy or ACL reconstruction) and to harvest a full-thickness cartilage graft from a nonweightbearing area of the trochlear ridge or intercondylar notch. After 3 to 4 weeks of preparation, the chondrocyte-seeded MACI implant was delivered to the surgeon.

The second stage entailed an arthrotomy to expose and debride the defect and to secure the MACI implant into the defect using fibrin glue and circumferential stitches using No. 5-0 absorbable sutures (Vicryl, Ethicon) (Figure 1). In 2 patients, defects were found deep in the subchondral bone. If the defect was  $>10\text{ mm}$  in depth, the subchondral bone base was no longer intact, and trabecular bone was exposed, then an impaction bone grafting was performed to ensure the defect was filled adequately before the membrane was secured onto the lesion. The same implantation procedure has been used since the beginning of our work regarding chondral treatment.<sup>6</sup>

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Final revision submitted August 5, 2020; accepted September 14, 2020.

The authors declared that there are no conflicts of interest in the authorship and publication of this contribution. AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.

Ethical approval for this study was obtained from the Second Affiliated Hospital, Zhejiang University School of Medicine (study No. AF17-2017100).

## Rehabilitation

The patients underwent continuous passive motion (CPM) beginning the day after surgery, with flexion range of motion starting at 15° and increasing gradually every day. CPM was used for 6 to 8 hours daily for up to 6 weeks until the knee gained a full range of passive motion. Straight leg-raising exercise was started as tolerated, partial weightbearing with crutches was allowed after 6 weeks, and full weightbearing was allowed after 10 weeks. The rehabilitation plan was adjusted depending on whether partial meniscectomy and ACL reconstruction were performed at the time of the initial operation.

## Clinical and Magnetic Resonance Imaging Evaluation

Patient data were collected preoperatively as well as postoperatively at 1 month, 3 months, 6 months, 12 months, and then every year afterwards up to 5 years (9 time points total). The clinical outcomes for the patients were measured using the International Knee Documentation Committee (IKDC) subjective knee form and the Lysholm score. The surgery was determined to have failed if the patient required reoperation because of symptoms from the primary defects.

Magnetic resonance imaging (MRI) with T2 mapping was performed by 2 skilled musculoskeletal radiologists to evaluate the defect and the repair tissue. MRI was carried out using a 3.0-T MRI unit (Discovery MR 750 3.0-T; GE Ltd), and the following sequences were obtained using a knee coil: (1) coronal spin echoes T1 weighted image, (2) sagittal fat-saturated proton density-weighted imaging, (3) sagittal fat-suppressed 3-dimensional fast spoiled gradient echo, and (4) sagittal T2 mapping. Patients had been free from strenuous exercise and rested for 30 minutes before MRI scanning to eliminate the effect of exercise on cartilage.<sup>5,21</sup>

## Statistical Analysis

Descriptive statistics characterizing the case series and describing the clinical outcomes and MRI evaluation results are expressed as frequency and mean  $\pm$  SD. The Friedman test, with a significance level of .05, was used to analyze differences in the clinical outcome among the 9 time points. If significant differences were revealed, the Wilcoxon signed rank test was performed for a similar comparison between the 2 time points. A Bonferroni adjustment to a level was applied so that *P* values  $<.006$  ( $<.05/9$ ) were regarded as significant in the paired comparisons. Spearman rho test was used to analyze the correlation between patient age and clinical outcomes. A paired Student *t* test was used to compare baseline and postoperative MRI T2 values. Statistical analysis was performed using the SPSS software package (Version 22.0; IBM Corp).

## RESULTS

A total of 30 patients, 24 male and 6 female (31 knees), with a mean age of 26.0 years (range, 12-48 years), were

TABLE 1  
Patient Characteristics

Variable	Mean (Range) or No.
Descriptive data	
Age, y	26.0 (12-48)
Body mass index	22.2 (16-30)
Sex, male/female	24/6
Occupation	
Student	15
Worker	14
Athlete	2
Baseline characteristics	
Injured knee, left/right	15/16
Injury location, medial femoral condyle/lateral femoral condyle/trochlea	14/16/1
Defect size, cm <sup>2</sup>	4.8 (2.0-20.0)
Previous surgical procedures	3
Concomitant surgery	
Subchondral bone grafting	2
Partial meniscectomy	4
Anterior cruciate ligament reconstruction	1

included in this prospective study. The symptomatic, focal, full-thickness chondral defects among these patients reached grade 4 on the International Cartilage Repair Society (ICRS) cartilage evaluation form for the femoral condyle or trochlea. Of these patients, 17 had osteochondritis dissecans, 7 had previous trauma, and 6 had lesions of unknown origin. A total of 3 patients had undergone surgical procedures before MACI therapy including 1 partial meniscectomy, 1 microfracture of the defect, and 1 partial meniscectomy and concomitant ACL reconstruction. Patient characteristics are summarized in Table 1.

The patients had been evaluated for up to 5 years, with an average follow-up of 44 months (range, 6-60 months) postoperatively. No patient was lost to follow-up. The sites of defect were as follows: medial femoral condyle (*n* = 14), lateral femoral condyle (*n* = 16), and medial femoral condyle extended to the trochlear groove (*n* = 1). The average size of the defects was 4.8 cm<sup>2</sup> (range, 2.0-20.0 cm<sup>2</sup>), classified as grade 4 according to ICRS criteria.

## Clinical Outcomes

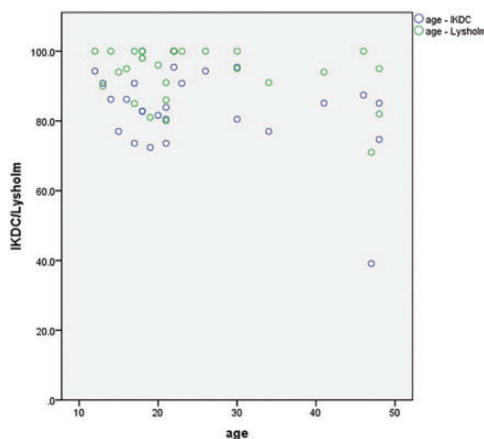
All patients had reduced knee pain and swelling as well as eliminated locking sensation at 12 months after MACI. All patients demonstrated significant improvement in both clinical scores from baseline to 12 months postoperatively, which were maintained through the 60 months of the study period.

The mean IKDC score before surgery was 58.6 (range, 40.2-80.5), with symptoms including pain and effusion, reduced knee function, and inability to perform sports activities. The mean IKDC score markedly increased to 79.1 (range, 39.1-94.3) at 12 months and to 88.4 (range, 83.9-100) at 5 years (Table 2). The mean Lysholm scores improved from 67.3 (range, 46-95) at baseline to 90.6

TABLE 2  
Clinical Scores From Baseline to 5 Years After Surgery<sup>a</sup>

	Outcome Measure, Mean (Range)	
	IKDC	Lysholm
Time point		
Preoperative	58.6 (40.2-80.5)	67.3 (46-95)
1 mo	32.2 (10.3-58.6)	40.4 (15-72)
3 mo	49.1 (20.7-78.2)	66.8 (30-100)
6 mo	66.5 (32.2-88.5)	79.1 (27-100)
12 mo	79.1 (39.1-94.3)	90.6 (71-100)
2 y	84.9 (60.9-100)	92.7 (73-100)
3 y	86.4 (70.1-100)	95.1 (85-100)
4 y	87.7 (83.9-100)	95.8 (85-100)
5 y	88.4 (83.9-100)	95.9 (85-100)
	P Value	
Friedman test	.001	.001
Wilcoxon signed rank test		
0-1 y	.002	.001
0-2 y	.001	<.001
0-3 y	<.001	<.001
0-4 y	<.001	<.001
0-5 y	.001	.001

<sup>a</sup>The Friedman nonparametric test was used to analyze the differences among all 9 time points. If significant differences were detected ( $P < .05$ ), the Wilcoxon signed rank test for paired samples was used for comparison between the results of the 2 time points, with  $P < .006$  (Bonferroni adjustment) regarded as significant. IKDC, International Knee Documentation Committee.



**Figure 2.** Spearman rho for relationship between patient age and International Knee Documentation Committee (IKDC) score ( $r_s = -0.138$ ;  $P = .492$ ) and between patient age and Lysholm score ( $r_s = -0.133$ ;  $P = .508$ ).

(range, 71-100) at 12 months and to 95.9 (range, 85-100) at 5 years postoperatively (Table 2).

The Spearman rho test, which was used to analyze the relationship between patient age and clinical scores,

showed that IKDC and Lysholm scores were both negatively correlated with age but there was no statistical significance (Figure 2).

## Radiological Outcomes

In total, 20 patients (21 knees) had consecutive MRI examinations with T2 mapping. To better compare the T2 value at different time points among the patients, we defined a Z value as the quotient of the T2 value of the transplanted area divided by that of the normal area. In the treated area, a gradual yet evident change in the internal signals for graft infill and the signal intensity, among others, was observed over the 5-year period. According to quantitative analysis, the average T2 value of the transplanted area was significantly higher than that of the normal area at baseline as well as at 3 and 6 months postoperatively ( $P < .05$ ) but gradually approached that of the normal area over time, with the Z value getting closer to 1. The difference in the average T2 values was no longer significant at 12 months postoperatively ( $P > .05$ ) and remained stable throughout the 5-year evaluation (Figures 3 and 4).

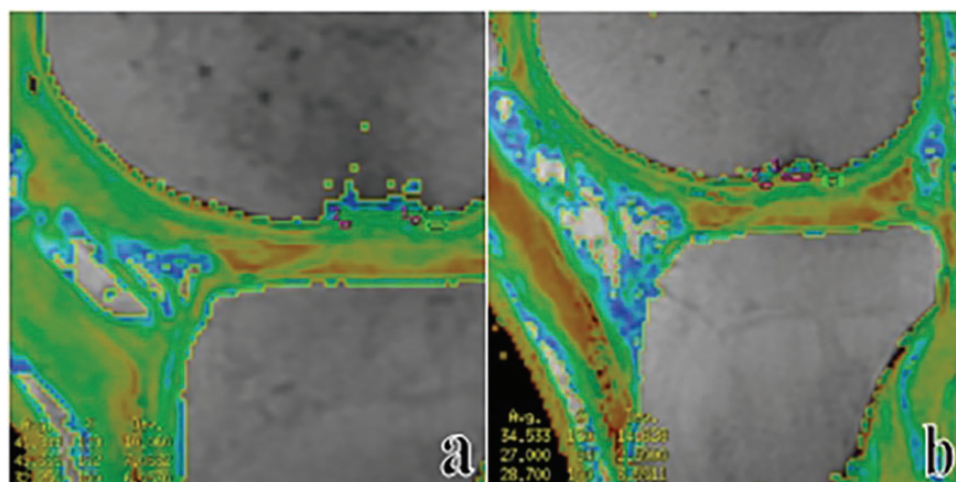
A total of 4 patients underwent second-look arthroscopic surgery. Of these, 2 surgeries were performed because of a medial meniscal tear (patients 1 and 2), and partial meniscectomy was performed. One patient (patient 3) had a painful fibrotic septum in the suprapatellar pouch, and another (patient 4) had a limited range of motion ( $0^\circ$ - $100^\circ$ ). Debridement and arthrolysis were performed. In all 4 patients, the defects were healed and showed a smooth surface (Figures 5 and 6). One of the 4 patients who received arthrolysis for stiffness had a  $22 \times 12$ -mm cartilage defect classified as ICRS grade 4 and a concomitant lateral bucket-handle meniscal tear. Because of limited range of motion (range,  $0^\circ$ - $100^\circ$ ), the patient was hospitalized again 12 months later to have his knee released arthroscopically. Under arthroscopy, the implanted area of the articular surface bulged a little and showed no difference in hardness compared with the adjacent surface (Figure 6), and the patient achieved full flexion afterward.

## DISCUSSION

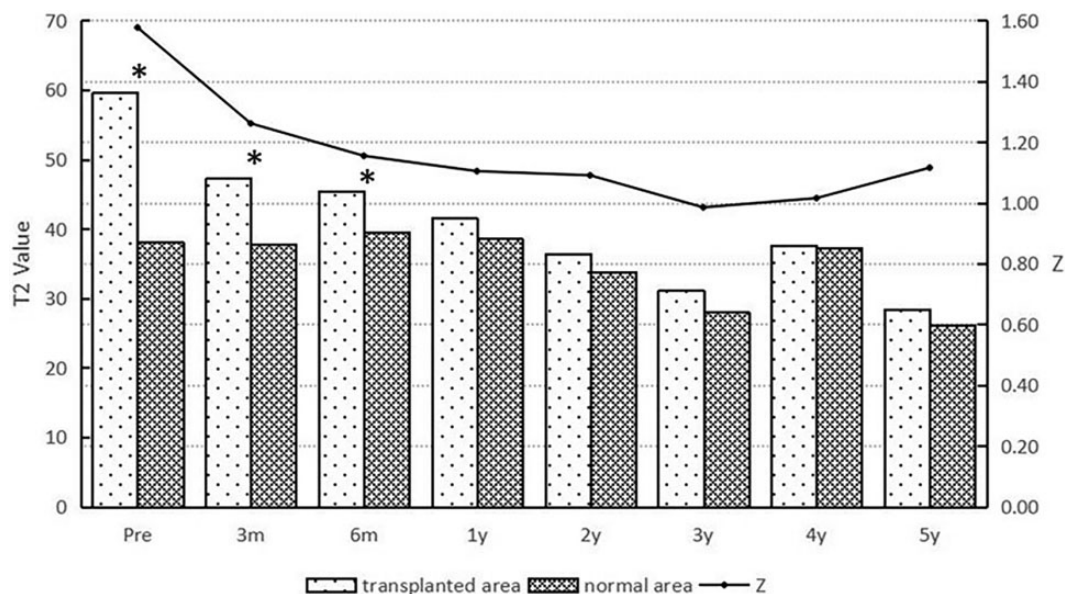
The most important finding of this study was that the MACI procedure is a promising and effective cell-based therapy for an extended follow-up period of up to 5 years. Our previous report focused on the treatment of focal chondral defects in adolescent patients (age range, 14-20 years) with the same MACI technique.<sup>6</sup> Overall, subjective and objective improvements were achieved in all patients. After 1 year, on average, the 2 validated scores used in that previous study continued to demonstrate a statistically significant improvement ( $P < .05$ ). At a follow-up of 1 to 3 years, the results of MACI for full-thickness cartilage defects have been encouraging, consistent with other reports.<sup>11,12,15,18</sup>

Microfracture has been the gold standard for full-thickness chondral defects because it recruits mesenchymal stem cells into the chondral defect. However, the





**Figure 3.** Magnetic resonance imaging scans with T2 mapping of the knee joint: (A) 3 months postoperatively and (B) 12 months postoperatively.



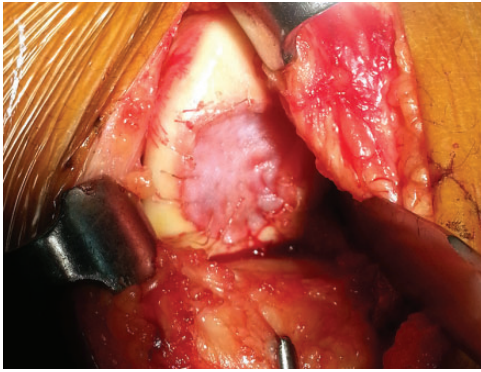
**Figure 4.** Magnetic resonance imaging with T2 value at all 9 time points. The paired Student *t* test was used to compare the T2 values of the transplanted area and normal area preoperatively ( $P = .004$ ) as well as at postoperative 3 months ( $P = .006$ ), 6 months ( $P = .001$ ), 12 months ( $P = .262$ ), 2 years ( $P = .180$ ), 3 years ( $P = .160$ ), 4 years ( $P = .772$ ), and 5 years ( $P = .403$ ). Significant differences were present at the preoperative, 3-month postoperative, and 6-month postoperative time points. \* $P < .05$ .

fibrous cartilage generated by microfracture tends to deteriorate over time.<sup>7,13,14</sup> Osteochondral mosaicplasty provides the advantages of transplanting hyaline cartilage.<sup>8</sup> However, limitations of graft availability and donor-site morbidity remain to be resolved.<sup>2</sup>

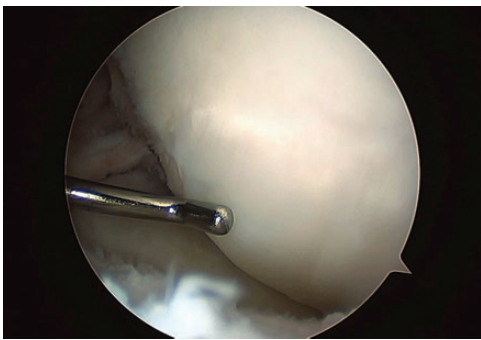
A common complication of periosteal hypertrophy has been reported for ACI using periosteum.<sup>10</sup> To avoid this problem, we used cell-seeded scaffolds for implantation, known as MACI. This technique not only obviates periosteal harvesting, but also provides a chondrocyte-scaffold construct to be sutured directly to the base of prepared chondral defects.

We have used this technique from the beginning of our practice for the treatment of medium to large full-thickness focal defects of the articular cartilage. Defects that extend deeply into the subchondral bone are treated using concomitant bone grafting. The 2 patients who underwent this additional procedure did not have inferior scores in clinical evaluations, although the subchondral plate was not restored to the normal structure at 5 years postoperatively.

After obtaining our initial results, we continued our investigation efforts with additional MRI with T2 values applied. The collected data showed steady and sustainable



**Figure 5.** The implantation procedure of a patient during his second surgery.



**Figure 6.** Intraoperative macroscopic observation during a patient's second-look surgery.

improvement during this longer follow-up period. Quantitative T2 mapping is a proven technique to delineate the interaction of water molecules and collagen fiber orientation within the articular cartilage. Alterations in T2 values are closely associated with changes in water content, collagen structure, and organization of hyaline cartilage.<sup>16,20</sup> However, the values are subject to the magic angle effect and volume effect<sup>9,17</sup> as well as variation among time points of measurement even in healthy cartilage for the same individual. To better compare the T2 values at different time points among these patients, we defined a Z value, which is the quotient of the T2 value of the transplanted area divided by that of the unaffected area at the posterior margin of the femoral condyle, to minimize the effect of a patient's activity status. To eliminate the confounder of exercise on the T2 value of cartilage, an MRI investigation was carried out when a patient had been free from exercise and seated for 30 minutes.<sup>6</sup> This current study found that the T2 value of the transplanted area in the early stage after MACI was much higher than the value for the healthy area, and it gradually decreased with time, leading the Z value to become closer to 1 over time. The results showing that the collagen and water content of the repaired tissue gradually became the same as that of healthy cartilage and that the repaired tissue formed a hyaline cartilage-like repair were consistent with those of the previous report.<sup>19</sup>

The main limitation of the current study is that it was not a controlled trial; that is, MACI was not compared with the microfracture procedure at any time point during follow-up. We cannot definitively conclude that MACI is superior to other techniques. However, the outcome of microfracture has been reported as unsustainable in the long run, and joint function tends to deteriorate.<sup>7,14</sup> Furthermore, not all patients in this study had MRI results with T2 mapping. Finally, we had minimal second-look information to further investigate the newly implanted cartilage on the molecular biological level.

## CONCLUSION

The MACI procedure is a promising and effective cell-based therapy for osteochondral defects and represents a viable alternative for properly selected young and middle-aged patients. Moreover, 3.0-T MRI with T2 mapping provides a noninvasive and dynamic tool to evaluate the repair process of cartilage in the graft area after MACI. A prospective, randomized clinical trial is warranted to determine the exact value as well as the cost-benefit ratio of this relatively expensive procedure.

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