CLINICAL ARTICLE

Mid- to Long-Term Clinical Outcomes of Cartilage Restoration of Knee Joint with Allogenic Next-Generation Matrix-Induced Autologous Chondrocyte Implantation (MACI)

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Objective: Cartilage defect is a common pathology still lacking a unified treating option. The purpose of this retrospective study is to evaluate the safety, efficacy, and clinical and radiological outcome of cartilage restoration of knee joint with allogenic next-generation Matrix-Induced Autologous Chondrocyte Implantation (MACI) for the first time, as well as the correlation between postoperative clinical and radiological outcomes and preoperative patient history and demographics.

Methods: From July 2014 to August 2020, 15 patients who went through cartilage restoration with allogenic next-generation MACI were included in this study. Patient demographics and PROM including the International Knee Documentation Committee (IKDC) subjective knee score, Lysholm score, Tegner Activity Scale (TAS), and Knee Injury and Osteoarthritis Outcome Score (KOOS) were obtained preoperatively, at 3, 6, 12 months postoperatively and the last follow-up using an online questionnaire platform. MOCART 2.0 score was calculated at the last follow-up. Analysis of variance (ANOVA) was used to compare PROM pre- and post-operation, with two-tailed $p < 0.05$ defined as statistical significant. Pearson correlation coefficient was used to evaluate correlation between the PROM and MOCART 2.0 score at the last follow-up with patients demorgraphics.

Results: All patients were followed for an average of 66.47 $\pm$ 24.15 months (range, 21–93). All patients were satisfied with the outcome of the surgery and no complication was reported at the end of the study. No significant improvement was observed until 1 year after the implantation, except for IKDC score at 6 months. All PROM showed significant improvement 1 year post-op except for Lysholm score and TAS, which also increased significantly at the time of the last follow-up. Pearson correlation coefficient showed that the size of the defect, before or after debridement, was significantly negatively correlated with final KOOS-Pain (before debridement: $r = -0.57$, $p < 0.05$; after debridement: $r = -0.54$, $p < 0.05$) and KOOS-Symptoms score (before debridement: $r = -0.66$, $p < 0.05$; after debridement: $r = -0.67$, $p < 0.05$). The MOCART 2.0 score was found significantly and negatively correlated with BMI ($r = -0.60$, $p < 0.05$), and significantly and positively correlated with Lysholm score ($r = 0.70$, $p < 0.05$).

Conclusion: The next generation MACI with autologous chondrocyte and allogenic chondrocyte ECM scaffold could be used to treat focal articular cartilage defect in the knee joint safely and efficiently with lasting promising outcomes for more than 5 years. The size of the defects should be considered the most negatively correlated parameters influencing the postoperative clinical outcomes.

Key words: Cartilage; Chondral Defect; MACI; Matrix-Induced Autologous Chondrocyte Implantation; Tissue Engineer

Introduction

Articular cartilage is the hyaline cartilage that encapsulates the end of articular bone. It has minimal to no vascular, nervous, lymphatic, or undifferentiated stem cells, not only makes it highly resistant to load and shear force, but also limits its regenerative capacity.[1] As a result, cartilage

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defect without proper treatment could eventually develop into degenerative osteoarthritis (OA), which ultimately could lead to joint pain, joint dysfunction, and even the irreversible loss of total joint function.[2]

Conservative methods for cartilage damage, such as injections of steroid,[3] hyaluronic acid,[4] platelet-rich plasma (PRP)[5] or stem cells[6] help relieve symptoms, but no evidence indicates restoration of the damaged cartilage. When conservative treatments fail, patients often seek surgical intervention. Current surgical treatment including microfracture (MF),[7] osteochondral autograft transplantation (OAT),[8] osteochondral allograft transplantation (OCA),[9] particulated articular cartilage implantation (PACI),[10] autologous chondrocyte implantation (ACI),[11] and Matrix-induced autologous chondrocyte implantation (MACI).[12] Each treatment was applied to specific indication, which has been well-discussed and documented.[13] Among all the techniques, ACI and MACI are drawing more and more attention now as it showed promising results with broader spectrum when facing complicated cases.

At its first appearance at 1987 and first publication in 1994,[14] ACI was performed with implantation of an injection of cultured autologous chondrocyte under a flap of autologous periosteal patch.[15] Upon its release, a broad spectrum of patients with osteochondritis dissecans (OCD), patellofemoral, femoral condyle, or tibial plateau cartilage defect benefited from this technique with remission or resolve of symptoms, back to sports, postponement or even prevention from arthroplasty.

Like many first-generation technologies, certain limitations were reported as the application got widely implemented, among which hypertrophy of the repaired cartilage was the most worrying complication of all, and the periosteal patch seems to be playing a big role in the process.[16] As an ameliorate countermeasure, the second-generation technique of ACI used a bio-absorbable collagen membrane instead of autologous periosteum, known as collagen-covered ACI (CACI).[11,17] Rate of hypertrophy of the graft was reported to decrease,[11,17] with comparable clinical outcomes with ACI.

However, CACI still requires an open surgery to suture the collagen patch to the defect. In order to perform the implantation arthroscopically, more improvement led to the innovation of matrix-induced ACI (MACI), which seeded the chondrocyte on a biodegradable type I/III collagen membrane.[12,18] As there was no suspension below the membrane, fibrin glue was utilized to seal and fix the graft to the defect. However, even though the seeded patch could be delivered into the joint arthroscopically, the maneuver of the patch arthroscopically were still challenging, which greatly increased operation time. Moreover, the two-dimensional structure makes the graft unstable, and the fixation sometimes still requires extra suture.

In consideration of the imperfection mentioned above, we build the next generation three-dimensional MACI with allogenic chondrocyte extra-cellular matrix (ECM). It was composed of autologous chondrocyte and allogenic cartilage ECM scaffold. Not only did it mimic the native ECM microenvironment of chondrocytes to provide suitable physical and biochemical conditions, it also has a parallel columnar arrangement similar to that of natural articular cartilage. It meets the appropriate requirements for scaffolds used in cartilage tissue engineering and since the first animal study,[19] numerous experiments had proven its effectiveness and amelioration was made accordingly.[19–26] Here in this study we retrospectively reviewed cases of human knee joint chondral defects treated with the next generation three-dimensional MACI with allogenic chondrocyte ECM (referred as the 3-D next generation MACI below) and evaluate its safety, efficacy, and clinical and radiological outcomes for the first time. We hope (i) this could serve as clinical evidence for the utility of the 3-D next generation MACI; (ii) evaluating certain properties of the 3-D next generation MACI such as advantages, graft survivorship; (iii) finding the connection between the preoperative patient history, demographics, and postoperative clinical and radiological outcomes, therefore providing evidence for the prediction of prognosis.

Methods

This is a retrospective study. All patients that underwent cartilage restoration with the next generation MACI from July, 2014, to August, 2020, were screened for inclusion in this study. Informed consent was obtained from all participating patients. Ethical approval was granted by the Ethics Committee of PLA General Hospital (No. 2022KY061-KS001).

Patient Selection

Patients aged 18–50 who had full thickness cartilage defect detected by MRI and confirmed by arthroscopy in the knee joint were included in the study. A ligamentous stable knee joint without malalignment was required. In addition to that, the affected joint was evaluated arthroscopically at the first chondrocyte harvest surgery. Cases with more than two defects in the examined joint were excluded. The size of the defect should be bigger than 1 cm^2. Only defects of ICRS (International Cartilage Repair Society) Grade III/IV were treated with the 3-D next generation MACI. Exclusion criteria included kissing lesions, BMI >30 kg/m^2, autoimmune disease, metabolic disease (diabetes, gout, etc.), infectious disease, hematological disease, pregnancy or lactation, inflammatory arthropathy, and so forth. The specific inclusion and exclusion criteria are listed in Table 1.

Extraction of Cartilage ECM

Cartilage ECM was extracted according to the protocol of a former study.[26] Articular cartilage was harvested from the femoral condyles of newly deceased body donor under aseptic condition. Body donor over the age of 60 or have a clear diagnosis of osteoarthritis was excluded. After rinsed with sterile PBS three times, cartilage was pulverized using a tissue disintegrator and slurry suspension of cartilage was formed. Differential centrifugation was performed under the

TABLE 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Full thickness cartilage defect	Osteoarthritis
Ligamentous stable	Extremity malalignment
Age 18–50	Previous surgery history
Normal ROM	Kissing lesions
Focal cartilage defect larger than 1 cm^2	Defect size smaller than 1 cm^2
Outerbridge Grade III/IV	BMI > 30 kg/m^2
	Autoimmune disease
	Metabolic disease (diabetes, gout, etc.)
	Infectious disease
	Hematological disease
	Inflammatory arthropathy
	Pregnancy or lactation
	Drug abuse
	Local application of steroid
	Mentally unstable

condition of constant 4°C. The suspension was first centrifuged at the speed of 1500 round per min (rpm) for 5 mins. The supernatant was collected and centrifuged at the speed of 3000 rpm for 10 mins, after which the supernatant was collected again and centrifuged at the speed of 6000 rpm for 20 mins. At last, the supernatant of the previous step was put under centrifugation again at the speed of 10,000 rpm for 30 mins and the sediment, stock solution of cartilage nanofilaments, was collected. After decellularized with 3% TritonX-100 and 0.25% trypsin (containing 0.1% EDTA, 0.1% sodium azide) for 12 h at 4°C, 50 U/ml deoxyribonuclease I and 1 U/ml ribonuclease A (both Sigma) were added to the suspension at 37°C and agitated constantly to get rid of the nucleus. After being rinsed several times with PBS and distilled water and centrifuged at the speed of 10,000 rpm for 30 mins, the deposit was collected as cartilage nanofilaments.

Fabrication of the 3-D Oriented Scaffold

A 3% (w/v) suspension of the cartilage nanofilaments with deionized water was prepared to be used for the fabrication of the oriented scaffold using the modified method of thermally induced phase separation (TIPS). Briefly speaking, the 3% (w/v) suspension of cartilage nanofilaments was loaded into a cylindrical mold with the length of 50 mm and diameter of 6 mm. Air within the liquid was discharged and the loaded mold was placed vertically on a −40°C metal plate, with the top of the mold and suspension maintained the room temperature, for 30 mins. The modified method of TIPS created a temperature gradient from the top to the bottom of the mold and suspension, which froze the water within the suspension into cylindrical crystals along the direction of the temperature gradient. Therefore, the scaffold was fabricated into oriented structure. After completely frozen, the mold was transferred into the −80°C fridge for 2 h, and freeze dried under vacuum for 48 h. The demoulded scaffolds were then cross-linked under 258 nm ultraviolet for 4 h, and then immersed into 95% (v/v) alcohol solution (containing 50 mM 1-ethyl-3-(3-dimeth-ylaminopropyl) carbodiimide hydrochloride [EDAC] and 20 mM N-hydroxysucinimide [NHS]; Sigma) for 24 h at 4°C. After rinsed by 100 mM disodium phosphate (pH = 9.1) for 2 h, PBS for 2 h, and distilled water several times, the scaffolds were lyophilized again. The scaffolds were then cut into 2 mm thick slices, sterilized by 60Co and preserved under 4°C.

Characterization of the 3-D Oriented Scaffold

The 3-D oriented scaffold was observed under scanning electron microscope (SEM) to evaluate its morphology. After dehydrated by alcohol of gradient concentration, the scaffold was dried at room temperature and sputter-coated with gold (Desk-II; Denton Vacuum Inc.), and then observed under SEM (BCPCAS-4800 Hitachi Japan). Diameter of the oriented microtubules was measured on the captured SEM micrographs. One hundred microtubules at the most central position of the micrographs were measured and the average diameter was calculated.

The porosity of the 3-D oriented scaffold was also measured. A density bottle was used according to a modified method performed previously by the senior researcher of our lab.[27] Briefly speaking, the density bottle was filled with ethanol with the density of ρ_E and weighed W_1. An OCECM scaffold with the height (H), length (L), and width (W) measured by a vernier caliper was weighed as W_s and immersed into the ethanol-filled density bottle for 30 min at room temperature and the complex of the density bottle, ethanol, and OCECM scaffold weighed W_2. The volume of the whole scaffold and the volume of the scaffold skeleton were defined respectively as V_w and V_s. The porosity of the OCECM scaffold (ε) was calculated as follow:

$$V_w = H \times L \times W.$$

$$V_s = (W_1 - W_2 + W_s)/\rho_E.$$

$$E = 1 - V_s/V_w.$$

Isolation and culture of autologous chondrocyte.

The autologous chondrocytes isolated from arthroscopic harvested cartilage was amplified in laboratory for 3–4 weeks to reach the number of 1×10^7 and seeded into the scaffold to complete the next generation MACI graft according to former established protocol.[28] It should be noted that instead of fetal bovine serum, human serum was drawn from each patient after the harvest of cartilage and was used in the process of culture and amplification of chondrocytes in the laboratory. Viability of chondrocytes were tested before incubation with the scaffold by AO-PI staining to ensure a minimal of 85%. After chondrocytes seeded in the scaffold, the 3-D next gen-MACI as incubated for 48 h and implanted back to the affected knee joint. The number of the chondrocytes seeded into the scaffold was calculated by counting the numbers of the chondrocytes lefted in the medium and six-well cell

culture plate where the construct was incubated. The seeded rate was required to be over 80%.

Surgical Technique

The procedure was done in two stages. An arthroscopic biopsy of the affected knee joint was firstly performed to evaluate the general condition of the joint, including concomitant injuries, existence of inflammation, and integrity of other structure. The location, severity, number, and size of the chondral defect was also evaluated. After that, approximately 100–200 mg of intact cartilage was harvested from the non-weight bearing part, such as the trochlear ridge or intercondylar notch, and sent to the laboratory to be cultivated and expanded (Figure 2).

The second stage should be planned as the MACI graft was completed. The implantation of the graft could be done arthroscopically (Figure 3) or through arthrotomy (Figure 4), depending on various circumstances, such as the size and location of the defect. Firstly, after explosion of the defect (Figure 3A and Figure 4A), the defect was carefully debrided with blade and curette down to the subchondral plate, with extra caution to keep the subchondral plate intact without bleeding (Figure 3B). In addition to that, the wall of the border of the defect should be trimmed vertical to the subchondral plate, as it was of great help to the integration of the fusion of the graft and the surrounding cartilage. Depending on the shape of the defect, different strategies were applied. If the shape of defect was irregular from a perfect circle, a tinfoil from the package of the surgical blade was utilized to replicate the shape and size of the defect (Figure 3C), and the graft was trimmed accordingly into the exact shape and size of the defect (Figure 3D). The graft was then fit into the defect and trimmed again if any extrusion occurs, until perfect match was achieved (Figure 3E). If the procedure was done arthroscopically and the shape of defect was close to or could be completely contained within a perfect circle without debriding too much healthy cartilage, a cylindrical metal rod of different diameter was used to debride the defect into the perfect circular shape out of the rod (Figure 4B) and carefully debrided with blade and curette down to the subchondral plate, with extra caution to keep the subchondral plate intact without bleeding (Figure 4C–E). The graft was then trimmed to fit into the same circular shape and fixed into the defect (Figure 4F). Due to the sponge-like nature of the graft, stitches could easily rip the graft into pieces so it was not considered ideal for fixation. Generally, no extra fixation was needed as the graft was built in three-dimensional form and

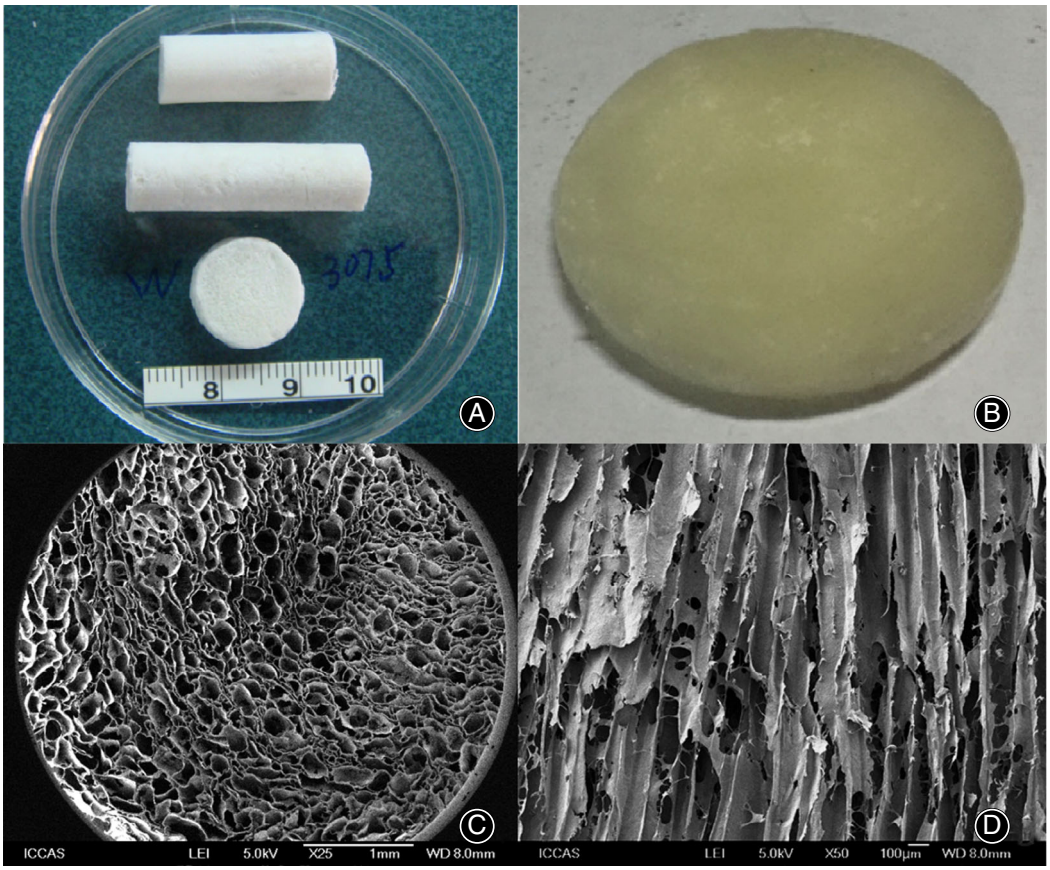

Fig. 1 Scaffold and construct of the 3-D next generation MACI. (A) Allogenic chondrocyte ECM scaffold. (B) Macroscopic view of scaffold with seeded chondrocyte. (C) Cross section and (D) vertical section view of the SEM graph of the 3-D oriented scaffold

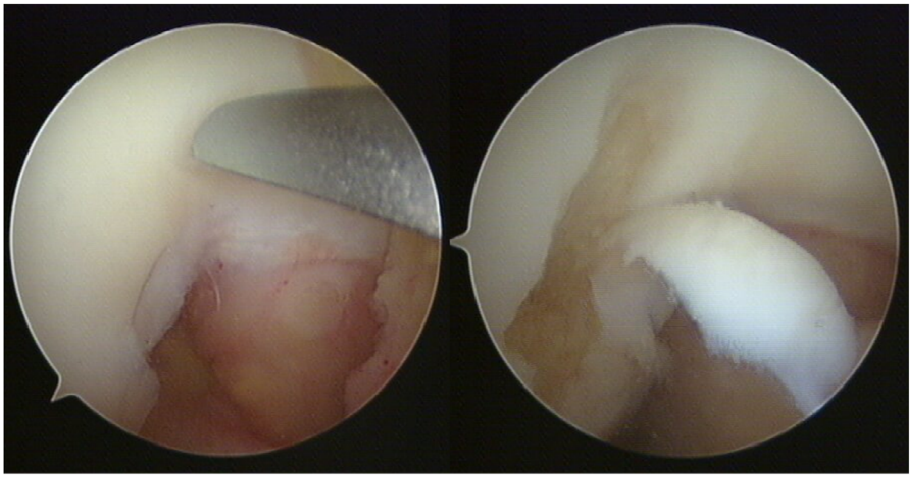

Fig. 2 Harvest of healthy cartilage from non-weight bearing area (intercondylar notch)

could be embedded into the defect if perfect match was achieved. Fibrin glue was applied on top if additional fixation was needed. Once the graft was embedded, 30 cycles of ROM were carried out on the knee joint to ensure a secure fixation of the graft. After reconfirming the position of the graft, the incision was closed, and the surgery was done (Figure 3F).

Rehabilitation Protocol

A detailed and thorough rehabilitation protocol was given to patients including brace wearing, weight-bearing, ROM (range of motion), and recommendation for physical therapy at each time point. Detailed information was listed in Tables 2 and 3.

PROM Evaluation

An online questionnaire platform was utilized to collect Patient Report Outcome Measurement (PROM) preoperatively and postoperatively at 3, 6 months, 1 year, and at the point of this study. The questionnaire was filled under professional guidance online or face to face at the follow-up

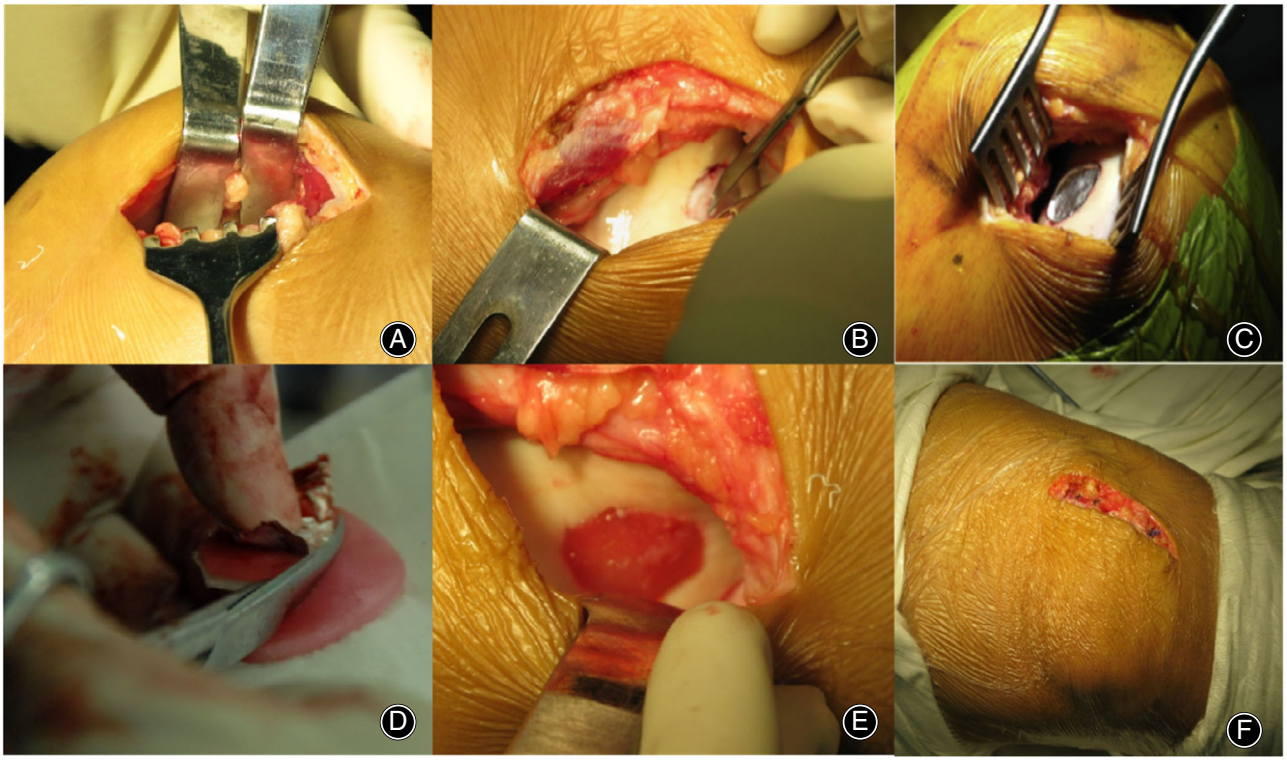

Fig. 3 Implantation of graft *via* arthrotomy. (A) Arthrotomy was performed to access the defect. (B) Defect was carefully debrided. (C) Tinfoil was used to template the defect. (D) Graft was trimmed accordingly. (E) Graft was implanted into the defect. (F) Wound was closed

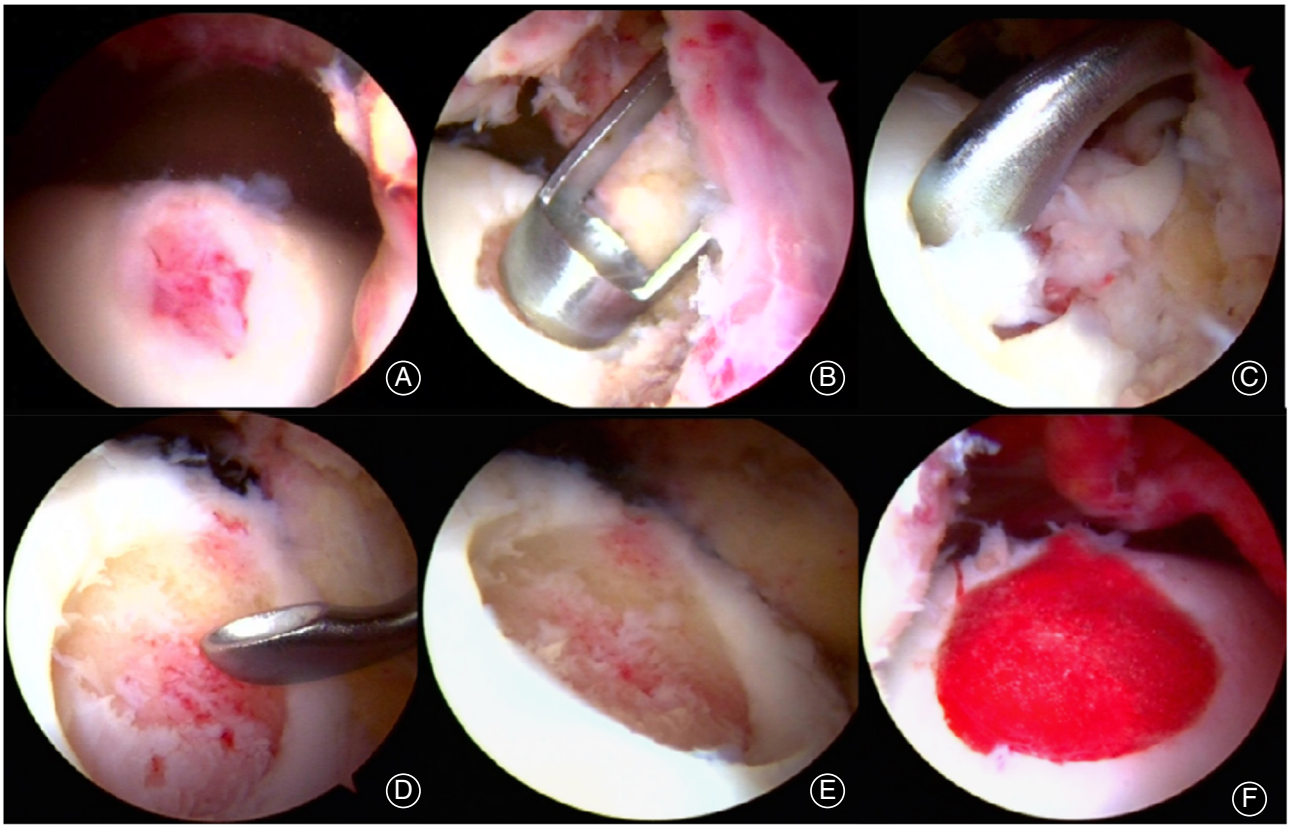

Fig. 4 Implantation of graft *via* arthroscopy. (A) Defect was spotted. (B) Cylindrical rod was used to outline the defect. (C) (D) Curette was used to debride the defect. (E) Defect after debridement. (F) Graft was implanted into the defect

visit. The International Knee Documentation Committee (IKDC) subjective knee form,[29] Lysholm score,[30] Tegner Activity Scale (TAS),[31] and Knee Injury and Osteoarthritis Outcome Score (KOOS)[32] were put together to form the final questionnaire. Failure of the treatment was defined as requirement for re-operation for persistence of the consistent symptoms without remission.

Magnetic Resonance Imaging Evaluation

Magnetic resonance imaging (MRI) was also required at the same time point. However, due to the scatter of patients all over the country, MRI was done by different radiologists at different facilities, making the result less comparable. In addition to that, the compliance of patients also differed greatly, making the collection of postoperative MRI nearly impossible. After thorough consideration, only the latest MRI results (at least 1 year postoperative) was included in the study, if it was done in the following sequences[1]: coronal spin echoes T1 weighted image,[2] sagittal fat-saturated protein density-weighted imaging,[3] sagittal fat-suppressed 3-dimensional fast spoiled gradient echo. The MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) 2.0 Knee Score was utilized to evaluate the quality of the repaired cartilage.

Statistical Analysis

Descriptive statistics for the demographic and related history of patients were presented as the mean ± standard deviation. Analysis of variance (ANOVA) was used to compare PROM at each follow-up postoperatively against preoperative stats and follow-up next to each other accordingly, with two-tailed $p < 0.05$ defined as statistical significant. In addition to that, Pearson correlation coefficient was used to measure correlation between the PROM and MOCART 2.0 score at latest time point with patients characteristic data (age, duration of symptoms, BMI, size of the defect before and after debridement), with two-tailed $p < 0.05$ defined as statistical significant. Graphpad Prism 8.0 (Graphpad Software, California, USA) was used to analyze all the data collected.

Results

Characterization of the 3-D Oriented Scaffold

Macroscopic view of the 3-D oriented scaffold was shown in Figure 1A, B. Microstructure of 3-D oriented scaffold was shown in Figure 1C, D. The vertical oriented tubular structure was clear demonsrtrated, and the porous structure was interconnected and evenly distributed. The porosity of the

TABLE 2 Rehabilitation protocol for femoral condyle defect

Primary Goal	Avoid overload of the graft; increase ROM and patella mobility; restore proprioception and muscle strength		
	Phase 1: Proliferative Phase (1–6 weeks)	Phase 2: Transitional Phase (7–12 weeks)	Phase 3: Remodeling Phase (13+ weeks)
Brace	Brace locked while ambulation and single leg raise (SLR)	Knee brace may be discontinued once independent SLR achieved	None
Weigh-bearing	Heel-toe touch down weight bearing (TDWB) with crutches	Weeks 7–8: 50% weight-bearing, weeks 9+: full weight-bearing	Full weight-bearing as tolerated
ROM	Full active ROM w/o gently assist	Full active ROM and gentle passive ROM	Progress towards full ROM equal to contralateral side
	CPM 6–8 h per day. Progress as tolerated. Goal: Minimum 90°flexion by 3 weeks, 110°by 6 weeks	Progress towards full ROM by 12 weeks	
Recommendation	Quad sets, SLR in knee immobilizer as needed, leg curl/heel slides, hip abduction	Continue quad sets, SLR in brace, leg curl and heel slides	Resisted open-chain exercise with ≤10 kg to be progressed as tolerated after 6 months
	Stationary bicycle with no resistance once 90° knee flexion obtained (>4 weeks).	Stationary bicycle with gradual increased tension per level of comfort	Cycling on level surfaces permitted with gradual increase in tension per level of comfort
	Dangle knee over side of the bed five times per day to achieve 90°.	Low weight (max 5–10 kg) open-chain leg extension and curl	Closed-chain exercise to promote knee stability and proprioception through full ROM as tolerated
		Strengthen quadriceps, hamstrings, and hip abductors/extensors using ankle weights and/or elastic band resistance through full ROM as tolerated	Treadmill walking encouraged
		Gentle closed-chain terminal knee extension 0–40°(TKE) permitted starting at 9–10 weeks as tolerated per weight-bearing restriction	

TABLE 3 Rehabilitation protocol for patellar or trochlear defect

Primary Goal	Avoid overload of the graft; increase ROM and patella mobility; restore proprioception and muscle strength		
	Phase 1: Proliferative Phase (1–6 weeks)	Phase 2: Transitional Phase (7–12 weeks)	Phase 3: Remodeling Phase (13+ weeks)
Brace	Hinge knee brace for ambulation (locked) and at night Out of brace for CPM. No brace, but towel/pillow behind heel when lying down	Hinged knee brace may be discontinued once independent SLR achieved	None
Weigh-bearing	Full weight-bearing in full extension (locked brace)	Full weight-bearing as tolerated	Full weight-bearing as tolerated
ROM	Gentle active ROM flexion as tolerated three times/day. Only passive ROM extension allowed. CPM 0–40° 6–8 h per day. Minimum 90° flexion by 3 weeks, 110° by 6 weeks	Gentle active or assisted ROM flexion and extension permitted. Progress towards full ROM by 12 weeks	Progress towards full ROM equal to contralateral side
Recommendation	Quad sets, leg curl/heel slides, hip abduction. SLR with brace locked Stationary bicycle with no resistance once 90° knee flexion obtained (>4 weeks). Dangle knee over side of the bed 5 times per day to achieve 90°.	Continue quad sets, SLR in brace, leg curl and heel slides Stationary bicycle without resistance for short intervals (5 min 2-3x/day) as tolerated No open-chain strengthening permitted until 6 months after surgery. No closed-chain leg press or squatting Strengthening of quadriceps, hamstrings, and hip abductors/extensors using elastic band isometrics and closed-chain TKE 0–40° only Backward treadmill walking with safety bars recommended for reduced patellofemoral compressive forces	Full active flexion with resistance permitted Stationary bicycling with very low resistance as tolerated Open-chain terminal extension with resistance not permitted Continue gentle closed-chain LE strengthening through functional range—TKE 0–40° and 120–70° extension from flexed positiont Treadmill forward/retro-walking, Nordic track and elliptical machine

TABLE 4 Patient demographics and history ($N = 15$ Patients)

Variables	Value
Age, y	33(18–45)
Body mass index, kg/m^2	25.19(21.02–29.97)
Defect size before debridement, cm^2	2.83(1.5–8)
Defect size after debridement, cm^2	3.53(1.5–9.24)
Duration of symptoms, m	20.06(2–79)
Follow-up time, *m*	66.47(21–93)
Sex, male/female, *n*	13/2
Knee, left/right, *n*	5/10
Defect location, MFC/LFC/PFC, *n*	5/1/9
ICRS Arthroscopic Grade, III/IV	7/8

3-D oriented scaffold was as high as 94% ± 3%. The average diameter of the pore was calculated to be 105 μm.

Patient Demographic

After careful screening process with a few lost to follow-up, a total of 15 patients, 13 male and two female, with a mean age of 33 (range, 18–45), were included in the study. All patients were followed up for a mean of 66.47 ± 24.15 months (range, 21–93). Defects were mostly located in the patellofemoral compartment (PFC) ($n = 9$), and more medial ($n = 5$) than lateral ($n = 1$) in the femoral condyle. Tibial defect was not seen in our patients, which seems reasonable as it was long considered a rarer condition.[33] The original cause of defect can be hardly proven as the onset of related symptoms in some cases was as long as 79 months, which the patient recalled vaguely, so no data on this matter was collected. Detailed patient demographic data is shown in Table 4.

Seven ICRS Grade III defects and eight ICRS Grade IV defects, respectively, were diagnosed arthroscopically at the first arthroscopic biopsy. At the second surgery to implant the graft, eight were performed with arthrotomy and seven with arthroscopy. All arthrotomy cases were outlined with tinfoil to reproduce the exact shape of the defect after debridement, as well as four cases done arthroscopically. The remaining four cases were trimmed into circular shape with the help of cylindrical rod of different diameters.

Clinical Outcomes and PROM

Relief of pain and swelling, as well as other symptoms such as effusion, limping, catching, locking, and cracking sound of the affected joint, etc., were reported by all patients in the study. There were no failed cases as no re-operation or any other end-stage surgery, for example, arthroplasty, took place during follow-up. No complications of any kind was reported. All PROM statistics were shown in Tables 5, 6.

No significant improvement was observed until 1 year after the implantation, except for IKDC score at 6 months. None the less, the mean value of all PROM except for KOOS-Sports and Reaction, which decreased at 3 months postoperatively but recovered in the short term at 6 months postoperatively, increased gradually as time passed. All RPOM showed significant improvement 1 year after the

TABLE 5 PROM results Pre- and Post-operation[a]

Outcome Measurement	Preoperative	Postoperative							
		3 mo	*p* value	6 mo	*p* value	1 year	*p* value	Final Follow-up	*p* value
IKDC score	51.67 ± 15.73	53.13 ± 11.57	0.995[†]	69.67 ± 8.67	<0.0001[***]	74.93 ± 7.15	<0.0001[***]	86 ± 5.07	<0.0001[***]
Lysholm score	58.07 ± 20.19	60.47 ± 16.51	0.9886[†]	69.13 ± 11.19	0.181[†]	74.33 ± 8.67	0.0137[*]	86.2 ± 6.59	<0.0001[***]
Tegner score	2.4 ± 0.75	2.53 ± 0.57	0.9565[†]	2.8 ± 0.43	0.2358[†]	2.93 ± 0.25	0.0516[†]	3.53 ± 0.50	<0.0001[***]
KOOS-Pain	52.78 ± 14.45	54.07 ± 12.5	0.9976[†]	66.48 ± 11.36	0.0089[**]	73.15 ± 8.52	<0.0001[***]	91.11 ± 6.22	<0.0001[***]
KOOS-Symptoms	57.38 ± 12.13	58.10 ± 9.68	0.9995[†]	68.81 ± 8.25	0.0065[**]	75.71 ± 7.24	<0.0001[***]	85.71 ± 5.71	<0.0001[***]
KOOS-ADL	65.98 ± 10.88	67.55 ± 8.98	0.9831[†]	73.24 ± 8.51	0.0160[*]	80.69 ± 5.56	<0.0001[***]	91.47 ± 4.20	<0.0001[***]
KOOS-Sports and Reaction	33.89 ± 11.11	23.33 ± 8.67	0.0088[**]	37 ± 6.8	0.8497[†]	50 ± 6.67	<0.0001[***]	67 ± 8.13	<0.0001[***]
KOOS-QOL	36.67 ± 11	37.92 ± 8.78	0.9942[†]	45.42 ± 8.44	0.0453[*]	56.67 ± 6.33	<0.0001[***]	74.17 ± 6.83	<0.0001[***]

[a]Data were expressed as mean ± SD (range) unless otherwise indicated.; [†]Statistically non-significant.; [‡]Analysis of variance (ANOVA) with two-tailed $p < 0.05$ defined as statistical significant.; * $p < 0.05$;; ** $p < 0.01$;; *** $p < 0.001$.

TABLE 6 PROM results between each follow-up[a]

Outcome Measurement	3 mo	6 mo	1 year	Final Follow-up	*p* value (3–6 months)	*p* value (6 months–1 year)	*p* value (1 year–Final Follow-up)
IKDC score	53.13 ± 11.57	69.67 ± 8.67	74.93 ± 7.15	86 ± 5.07	0.0004***	0.6319[†]	0.0354*
Lysholm score	60.47 ± 16.51	69.13 ± 11.19	74.33 ± 8.67	86.2 ± 6.59	0.4130[†]	0.8321[†]	0.1299[†]
Tegner score	2.53 ± 0.57	2.8 ± 0.43	2.93 ± 0.25	3.53 ± 0.50	0.6337[†]	0.9565[†]	0.0205*
KOOS-Pain	54.07 ± 12.5	66.48 ± 11.36	73.15 ± 8.52	91.11 ± 6.22	0.0227*	0.4621[†]	0.0003***
KOOS-Symptoms	58.10 ± 9.68	68.81 ± 8.25	75.71 ± 7.24	85.71 ± 5.71	0.0126*	0.2191[†]	0.0236*
KOOS-ADL	67.55 ± 8.98	73.24 ± 8.51	80.69 ± 5.56	91.47 ± 4.20	0.3027[†]	0.0910[†]	0.0039**
KOOS-Sports and Reaction	23.33 ± 8.67	37 ± 6.8	50 ± 6.67	67 ± 8.13	0.0003***	0.0007***	<0.0001***
KOOS-QOL	37.92 ± 8.78	45.42 ± 8.44	56.67 ± 6.33	74.17 ± 6.83	0.1185[†]	0.0044**	<0.0001***

[a] Data were expressed as mean ± SD (range) unless otherwise indicated.; [†] Statistically non-significant.; [‡] Analysis of variance (ANOVA) with two-tailed $p < 0.05$ defined as statistical significant.; * $p < 0.05$;; ** $p < 0.01$;; *** $p < 0.001$.

surgery except for Lysholm score and TAS, which also increased significantly at the time of the last follow-up.

Pearson correlation coefficient showed the size of the defect, before or after debridement, was significantly negatively correlated with final KOOS-Pain (before debridement: $r = -0.57$, $p < 0.05$; after debridement: $r = -0.54$, $p < 0.05$) and KOOS-Symptoms score (before debridement: $r = -0.66$, $p < 0.05$; after debridement: $r = -0.67$, $p < 0.05$) (Figure 5). No significant correlation was found otherwise.

MRI Results

All MRI results collected were done more than 1 year after the implantation (Figure 6). The total of MOCART 2.0 score at the last follow-up was 74 ± 8.70, ranging from 60–85. Detailed statistics of different index was shown in Table 7. Pearson correlation coefficient was calculated between the total MOCART 2.0 score and indexes of patients demographic as well as PROM scores. The MOCART 2.0 score was found significantly and negatively correlated with BMI

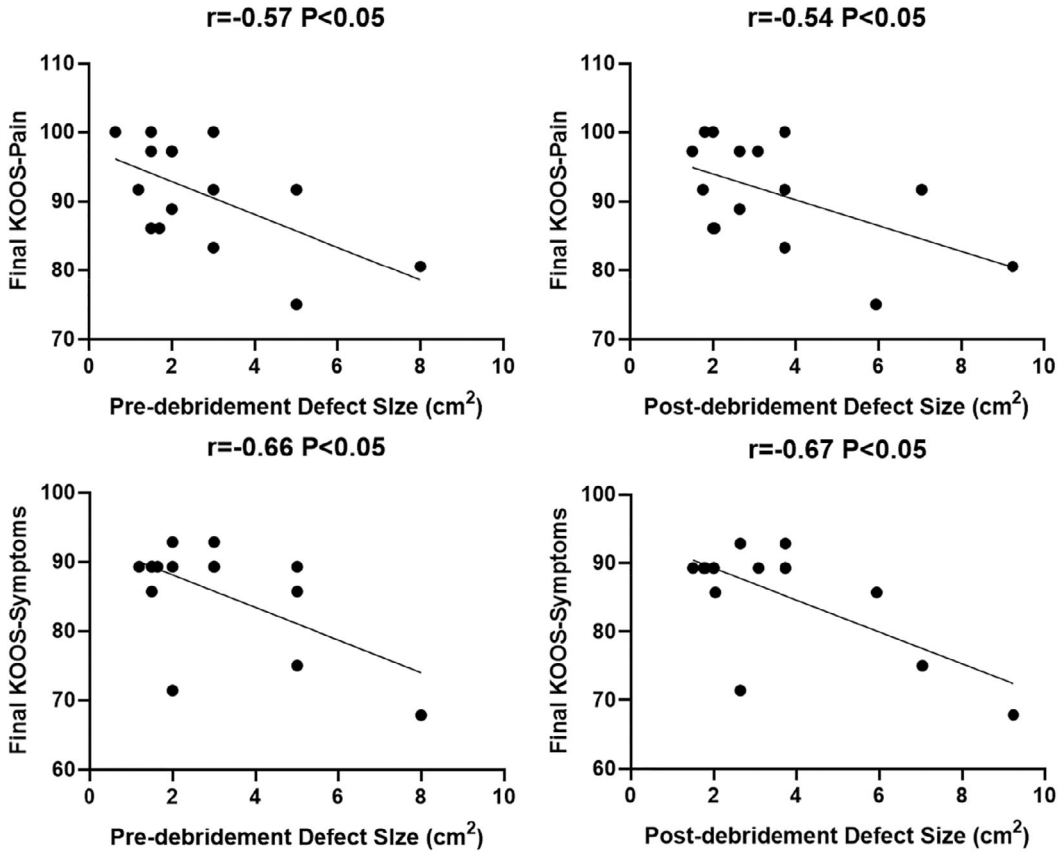

Fig. 5 Pearson correlation coefficient test of pre-/post-debridement defect size and the final KOOS-Pain and KOOS-Symptoms score

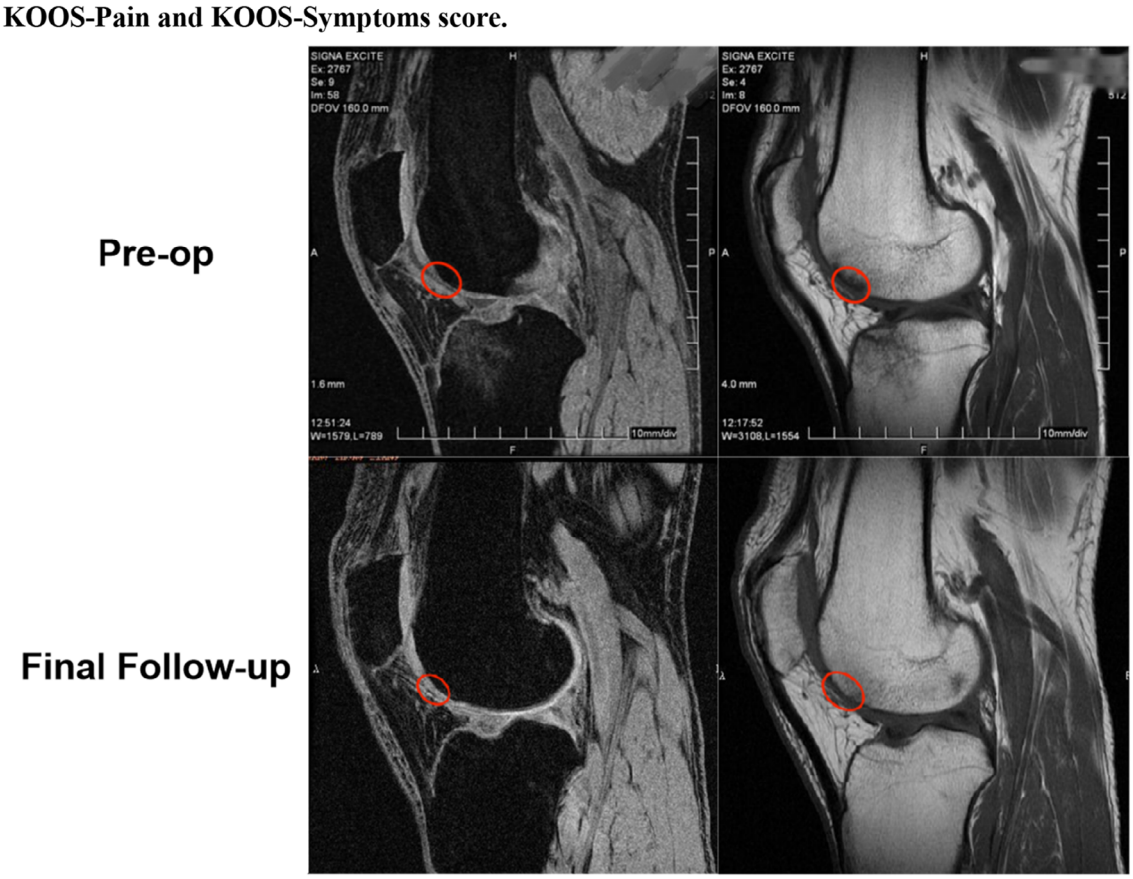

Fig. 6 MRI of affected knee joint preoperatively and at the final follow-up (84 months). Red circle indicates the cartilage defect and the graft after implantation

($r = -0.60$, $p < 0.05$), and significantly and positively correlated with Lysholm score ($r = 0.70$, $p < 0.05$) (Figure 7).

Discussion

This study retrospectively reviewed the clinical and radiological outcomes of 15 patients of focal articular cartilage defect in the knee joint for an average of 66.47 ± 24.15 months.

TABLE 7 MOCART 2.0 score at the final follow-up*

	Score
Volume fill of cartilage defect	16.33 ± 2.97
Integration into adjacent cartilage	13.33 ± 2.44
Surface of the repair tissue	8 ± 2.54
Structure of the repair tissue	0.67 ± 2.58
Signal intensity of the repair tissue	11.33 ± 2.29
Bony defect or bony overgrowth	9 ± 2.07
Subchondral changes	15.33 ± 2.29
Total	74 ± 8.70

* Data were expressed as mean ± SD (range) unless otherwise indicated.

The results of this study provides evidence for the efficacy and safety of the next generation MACI treatment for focal articular cartilage defect. Significant improvement was observed 1 year after the surgery, and lasted until the final follow-up. Both PROM and radiological evidence demonstrated promising outcomes after the surgery with no documented complication or failure, comparable to numerous reports utilizing MACI for similar situation.[34–36] Pearson correlation coefficient showed the size of the defect, before or after debridement, was significantly negatively correlated with final KOOS-Pain (Before debridement: $r = -0.57$, $p < 0.05$; after debridement: $r = -0.54$, $p < 0.05$) and KOOS-Symptoms score (Before debridement: $r = -0.66$, $p < 0.05$; after debridement: $r = -0.67$, $p < 0.05$). The MOCART 2.0 score was found significantly and negatively correlated with BMI ($r = -0.60$, $p < 0.05$), and significantly and positively correlated with Lysholm score ($r = 0.70$, $p < 0.05$).

Advantages of the Scaffold

In tissue-engineering construct like MACI, scaffolds serve as temporary supporting structures not only providing 3D support of tissue growth and formation but also establishing the

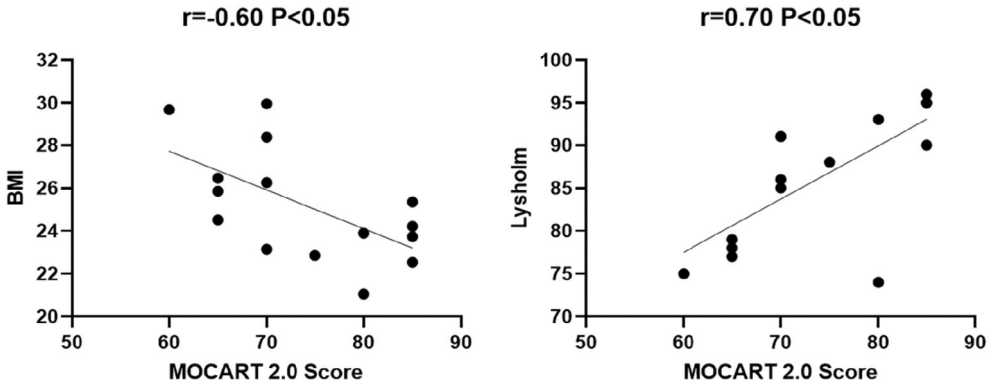

Fig. 7 Pearson correlation coefficient test of BMI/Lysholm score with MOCART 2.0 score

biological environment necessary for cellular growth, differentiation, and tissue formation.[37] Decellularized cartilage scaffolds are thought to be chondro-inductive because they can establish the native microenvironment where chondrocytes are developed. Many studies have proved the fact that the adhesion sites present the biochemical signals and aid the recruitment and the differentiation of progenitor cells.[21,38,39] In that case, allogenic chondrocyte ECM serves as the best component for MACI scaffold theoretically.

The ECM of cartilage is composed of fibers and non-collagenous elements of the ECM ground substance, including glycosaminoglycans (GAGs), proteoglycans, and glycoproteins. A compressive resistance is generated through negative electrostatic repulsion forces between proteoglycan aggregates and interstitial fluid26. GAGs are negatively charged, repelling each other while attracting ions (e.g., Ca^{2+} and Na^{+}) and water,[40] ensuring maintenance of the mechanical properties and hydration of the ECM. The amount of GAGs in articular cartilage largely determines the biochemical and biomechanical properties of the cartilage. The GAG content in the scaffold we used in this study, as well as the repaired tissue after implantation was similar to native cartilage, mirroring the function of water absorption and mechanical properties of original cartilage.[20,21,24,25]

Survivorship of the Graft

It is worth noting that no sign of deterioration was observed through 5 years of follow-up. Though long-term follow-up of several reports showed satisfactory results,[41–43] deterioration was reported 5 years after the surgery in most reports,[35,44] presented as significant decrease in some PROM scores. With that being said, the survivorship of the graft was reported to be more than 10 years, and patients were satisfied overall with outcomes. Postoperative deterioration was documented in reports with various treatment, including microfracture,[7] OAT,[8] OCA,[9] and so forth, and was considered one of the main cause of failure of the treatment. Especially in highly active professional athletes or patient younger than 30, failure of the graft might lead to revision surgery, which could be devastating, both for daily and sports life, and should be avoided as much as possible. In this study, all PROM scores demonstrated slow but steady postoperative growth up to 93 months at most, with no relapse of previous symptoms, normal joint function, and QoL (quality of life), except for KOOS- Sports and Reaction, which decrease in the first several months could be understandable as recovery in the first several months could be relatively slow.

Different Approach: Arthrotomy or Arthroscopy?

Some articles claimed that third-generation MACI was upgraded to perform the procedure arthroscopically,[45] yet the official guide provided by the manufacturer of MACI® (Vericel®, Cambridge, MA, US) suggest arthrotomy as standard approach for the implantation procedure. Maneuver of the membrane with arthroscopic instrument is still highly in demand for surgical skill, but the really challenging part is perfect template match of the defect with tinfoil arthroscopically. Even if it was done arthroscopically, the increased incidence of complication due to extension of operation time might offset the benefit of a less invasive approach. It remains controversial as to the best approach for implantation, and some lesions are impossible to accesses arthroscopically due to their size or location. Seven cases were done arthroscopically in this study, with one defect on the trochlear and others on the medial or lateral femoral condyle. Defects of all eight cases performed with arthrotomy all located on the patella make it nearly impossible to template or access with cylindrical rod. Based on clinical experience, we found the most challenging part was to template the defect arthroscopically. So debriding the defect into a perfect round shape was recommended if the implantation was done arthroscopically. The next generation MACI graft used in this study was built in 3-D construct and was thicker than the membrane used in third-generation MACI, facilitating the maneuver and embedment of the graft into the defect. A set of self-developed surgical instrument was used for debridement of defect and deliver of the graft (Figure 8), greatly simplifying the procedure and shortened operation time.

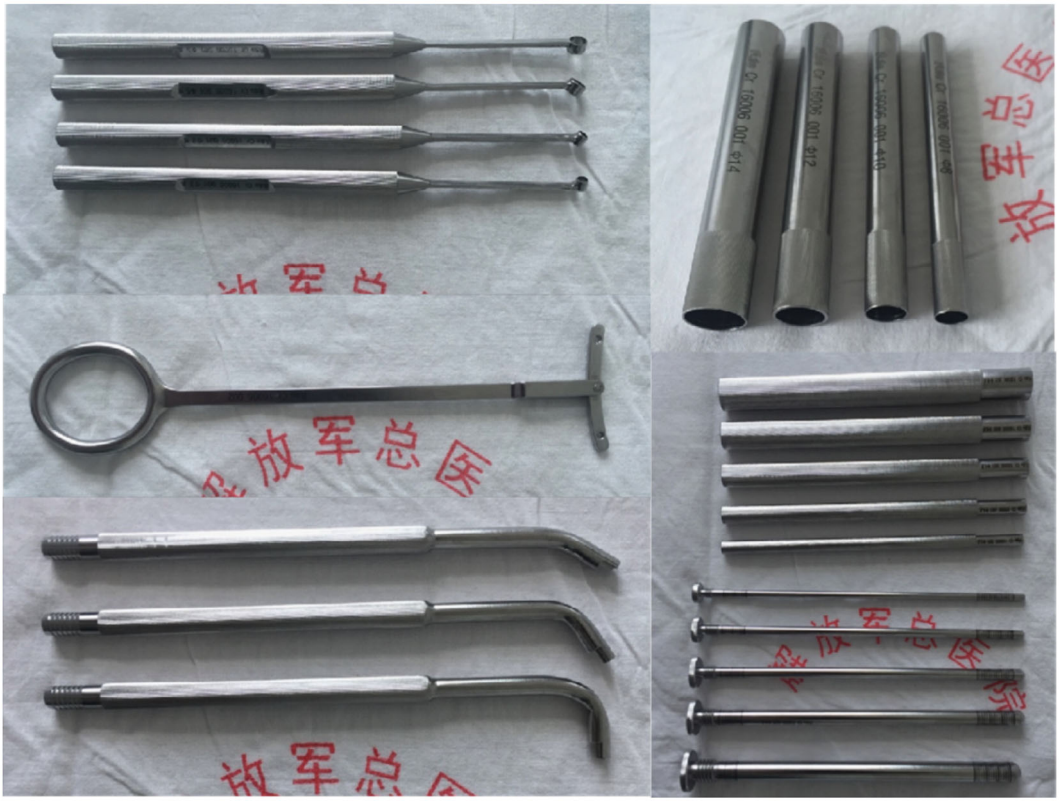

Fig. 8 Self-developed surgical instrument for debridement of defect and deliver of the graft

Clinical, Radiological Outcomes, and Correlation

All postoperative PROM scores recovered slowly, with only IKDC score increased significantly at 6 months. Based on the information we gathered through online or face-to-face interview, though thorough rehab protocol was given to all patients, the compliance to stick to the protocol were still poor. Only one patient claimed that the protocol was strictly carried out and every recommendation was followed. No professional physical therapist was consulted though the process of rehab. The negligence of rehab may be one of the biggest sources for slow recovery. It was worth noticing that Lysholm score was not significantly increased even 1 year after the implantation. It could be due to the fact the sample size was not big enough, and considering the standard deviation was relatively big before the surgery, the scatter of data could also be another confounding factor.

KOOS-Pain and KOOS-Symptoms score were found significantly negatively correlated with the size of the defect, before or after debridement. Without any doubt, the size of the defect after debridement was relevant with the size of the defect before debridement, but how to debride the defect also plays an important part. Tinfoil template is indeed challenging and time-consuming, but would no doubt preserve more healthy cartilage comparing with debridement with custom cutter. On the other hand, custom cutter indeed provides close-to-perfect vertical wall around the defect, hence there is a better match and integration between the graft and healthy cartilage. It's the surgeon's judgment call at the time of surgery, as there is no solid evidence demonstrating the benefits of each method. Anyhow, our study demonstrated that of all the parameters that might concern the final outcome of the procedure, defect size should be considered one of the most important preconditions to take into consideration.

The MOCART 2.0 score was found significantly and negatively correlated with BMI, and positively with Lysholm score. The correlation between patient's symptoms, complaints, and radiological outcome were not always significant, as reported by many doctors.[46,47] Doctors deal with inconsistent results between symptoms and radiological outcomes almost every day. With that being said, abnormalities spotted on imaging should still be treated as a sign for underlying conditions. Being overweight was an acknowledged detrimental factor in terms of joint health and many other diseases, and BMI >30 was one of the exclusion criteria in this and many other study. Overload of the graft is certainly a contradiction in any cartilage restoration operation, but BMI might be an out-of-date parameter to represent this situation, especially for cartilage defect patients. A relatively larger section of the patient population is highly active and athletic, many of which have BMI >30 with low percentage of body fat and high percentage of muscle. Muscle is also a well-acknowledged protecting factor in terms of joint health,

supporting the joint with dynamic control. In that case, preoperative TAS should be taken into consideration to evaluate the real component behind high BMI. In this study, most patients were of medium build, and BMI could well reflect the load on the joint.

Strengths and Limitations

The strengths of this study includes (i) the first study to report the clinical application of an innovated, allogenic, three-dimensional scaffold MACI to treat chondral defect in human; (ii) several correlations were found between different parameters pre- and postoperatively, providing predicable factors for the prognosis of this remedy. The main limitation of this study was the small sample size. As an innovated product, the screening was kept relatively strict, narrowing appropriate patient population. The follow-up time was not strictly screened due to the same reason. With solid evidence proving its safety and efficacy, inclusion criteria will be broadened to recruit more patients with similar problems. The incompletion of data is another limitation, hopefully be resolved also with expansion of patient population. Finally, the lack of second-look arthroscopy and histology result made it hard to evaluate the outcome more directly. Certain improvements will be made in the coming consecutive reports accordingly.

Conclusion

The next generation MACI with autologous chondrocyte and allogenic chondrocyte ECM scaffold could be used to treat focal articular cartilage defect in the knee joint safely and efficiently, with lasting promising outcomes for more than 5 years. The size of the defects should be considered the most negatively correlated parameters influencing the postoperative clinical outcomes. Further investigation with larger sample size and a control group with microfracture would be more ideal for further evaluation.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Yufeng Liu and Ning Ma. The first draft of the manuscript was written by Yufeng Liu, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Conceptualization, editing, and supervision were carried out by Zhe Zhao and Quanyi Guo.

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Conflict of Interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Ethics Statement

Ethical approval was granted by the Ethics Committee of PLA General Hospital (No. 2022KY061-KS001).

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