Matrix-induced autologous chondrocyte implantation (MACI) for chondral defects in the patellofemoral joint

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Abstract

Purpose Both autologous chondrocyte implantation (ACI) and tibial tubercle transfer (TTT) have been used to treat chondral defects in the patellofemoral joint resulting in clinical improvement. Our study investigates the magnetic resonance imaging (MRI) appearance of the matrix-induced autologous chondrocyte implantation (MACI) graft at 5-year follow-up to determine if it provides a durable treatment option in patients with an average age of 42 (standard deviation 11.6).

Methods Twenty-three patients were available for followup. Nine patients required realignment of the extensor mechanism with lateral release and TTT. The MRI magnetic resonance observation of cartilage repair tissue (MOCART) scoring system was used to assess the graft status. Clinical outcomes were assessed at these time periods.

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M. Fallon Perth Radiological Clinic, Subiaco, Perth, Australia *Results* The mean weighted MOCART composite score improved from 2.87 at 3 months to 3.39 at 5 years, indicating an intact appearance in most grafts. Graft height measured >50 % of the adjacent native cartilage in 82 % of patients. Clinical improvement assessed by the Knee Injury and Osteoarthritis Outcome Score, SF-36 (PCS) and the 6-minute walk test was demonstrated between preoperative scores and final 5-year follow-up. 91 % of patients would undergo MACI again. Correlation between MOCART and clinical scores were low in MACI to the patellofemoral joint. No significant difference was found in outcome between those that required realignment surgery compared with those that did not.

Conclusion Patellofemoral MACI provides a durable graft on MRI assessment at 5 years with resultant clinical improvement. Further work is needed to determine which defect locations may benefit most from this procedure. *Level of evidence* IV.

Keywords Autologous chondrocyte implantation · MACI · ACI · Patellofemoral · Chondral defect

Introduction

Chondral damage in the patellofemoral joint has been reported in 23–45 % of individuals who play sport [1, 12, 21], with sequelae of pain and loss of function in the affected knee and early-onset arthritis [7, 35]. Autologous chondrocyte implantation (ACI) has shown success in treating articular cartilage defects in the knee [43]; however, early results of implantation in the patellofemoral joint were poor because of the failure to address patellofemoral malalignment [4]. Multiple case series have subsequently demonstrated clinical improvement in 70–90 % of patients 2–11 years after ACI with concurrent correction of patellofemoral malalignment [10, 18, 19, 24, 33, 41].

In this study, we evaluated outcomes 5 years after matrix-induced autologous chondrocyte implantation (MACI) of the patellofemoral joint. Articular cartilage and repair tissue were assessed by magnetic resonance imaging (MRI) using the magnetic resonance observation of cartilage repair tissue (MOCART) scoring system. The primary hypothesis was that MRI assessment of the MACI graft at 5 years would demonstrate an intact graft, as determined by the composite MOCART score. The secondary hypothesis was that there would be clinical improvement, as assessed by the Knee Injury and Osteoarthritis Outcome Score (KOOS), Short Form 36 Health Survey (SF-36), 6-minute walk test (6MWT), and knee range of motion (ROM). Furthermore, correlation between MRI graft status and clinical function is controversial [3], and the tertiary hypothesis was that graft status, as assessed by the composite MOCART score, would correlate with clinical outcome. This study is the largest assessing MACI in the patellofemoral joint and is important for surgeons treating chondral defects [16, 17, 25, 45].

Materials and methods

Between 2001 and 2005, we recruited patients aged 15–60 years who had symptomatic full-thickness International Cartilage Repair Society [5] grade III/IV chondral defects of the patella or trochlear and had failed nonsurgical therapy. Exclusion criteria were body mass index (BMI) >35, bipolar lesions, ongoing inflammatory arthritis, >3° of varus/valgus malalignment, and uncorrectable ligamentous deficiency.

Pre-operative assessment

All patients underwent a full medical history and examination of the knee, including KOOS, SF-36, 6MWT, and knee ROM tests. Computed tomography (CT) was performed on all patients to assess patellofemoral alignment, and MRI was performed to assess chondral defect size, location, and concomitant pathology such as meniscal or ligamentous deficiency.

Patellofemoral alignment was assessed clinically looking at patellar tracking, subluxation, lateral retinacular tightness, and Q-angle. Tibial tubercle–trochlear groove (TT–TG) distance and patella tilt were determined by CT. Patients with a TT–TG distance >20 mm were included in this study and underwent combined proximal lateral release and distal tibial tubercle transfer (TTT), as described by Henderson [19, 20] and performed using the Fulkerson technique [15]. Patients with isolated patellar tilt underwent lateral release without distal realignment.

MACI surgical technique

Diagnostic arthroscopy was used to assess defect size and location and any concomitant pathology. A small amount of cartilage was harvested from a lesser weight-bearing area of the knee (medial or lateral condylar ridge, or trochlear notch). The classic MACI technique was used [6, 44, 46]. Briefly, healthy chondrocytes were isolated from the cartilage tissue and cultured for 4 weeks (Genzyme, Perth, Western Australia). Up to 20 million cultured chondrocytes (approximately one million cells per cm²) were then seeded on a type I/III collagen membrane (ACI-Maix, Matricel GmbH, Herzogenrath, Germany) 4 days before implantation [46].

For graft implantation under tourniquet control, a medial or lateral parapatellar approach was used, depending on patellar alignment. The chondral defect was prepared by removing all nonviable cartilage to expose the subchondral bone. The MACI graft was shaped to fit the defect using a foil template and secured with a thin layer of fibrin glue (Tisseel, Baxter Healthcare, IL, USA). After 2 min, the knee was tested ten times through full ROM to ensure graft stability. One patella defect required interrupted 6/0 Vicryl sutures (Ethicon, NJ, USA) at 3-mm intervals [46].

In patients requiring patellofemoral realignment, the defect was approached from a lateral arthrotomy. After the MACI graft was secured, anteromedial TTT was performed using the Fulkerson technique [14, 15]. The tibial tubercle was medialised until the patella was seated in the trochlear groove at 20° of flexion. The osteotomy was secured with two 3.5-mm cortical screws. The arthrotomy was closed lateral capsule to synovium to perform a lateral release.

Post-operative rehabilitation

Patients commenced continuous passive motion set at 0° – 30° within 12–24 h of surgery to reduce the chance of intra-articular adhesions [29, 30]. Cryotherapy and elevation were used to control oedema, and patients were taught toe touch ambulation on the operated side within the first week. A hinged knee brace was worn up to 24 h a day depending on the stage of rehabilitation. An intensive structured outpatient programme was used for 12 weeks, and further activity guidelines and advice were provided until 12 months after surgery [8, 9]

MRI assessment

Follow-up MRI was conducted at 3, 12, and 24 months, and 5 years using a 1.5 Tesla scanner (Siemens, Erlangen,

Germany or General Electric, Milwaukee, WI, USA). Standard proton density and T2-weighted fat-saturated images were obtained in coronal and sagittal planes (slice thickness 3 mm, field of view 15 cm; 512 matrix in at least one axis for proton density images, with a minimum 256 matrix in one axis for T2-weighted images). Additional axial proton density fat-saturated images were obtained (slice thickness 3–4 mm; field of view 14–15 cm; minimum 224 matrix in at least one axis) [9].

The eight parameters of graft repair (signal intensity, graft infill, border integration, surface contour, structure, subchondral lamina, subchondral bone, and effusion) are closely related to variables of the MOCART scoring system [11, 26, 27, 36, 39, 45], which has a high interobserver reliability and correlates with clinical outcomes [3, 26, 27]. Some modification was required to account for discrepancies in equipment and sequence protocols. The eight parameters were scored individually relative to the adjacent native cartilage (Table 1). For the parameter "graft infill", an additional score of 3.5 was awarded for graft hypertrophy [39]. Weighted scores for each parameter were then added together to calculate the composite graft score.

Clinical assessment

Patients were evaluated in the rehabilitation clinic and assigned subjective functional scores pre-operatively and 3, 12, 24 months, and 5 years post-surgery using (1) KOOS, which scores pain, symptoms, ability to carry out activities of daily living (ADLs), sport and recreation, and kneerelated quality of life (QOL) [37]; (2) SF-36, which consists of physical and mental component summary scores, to assess general health [2]; (3) 6MWT, which is the distance the patient can comfortably walk in 6 min [2, 34]; and (4)maximal active knee ROM. At the final 5-year follow-up, a patient satisfaction survey was used to assess knee-related pain, ability to carry out ADLs, and participation in sports. This study was approved by the institutional review board of Hollywood Private Hospital (Approval number HPH145). This study was performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki. All patients provided written informed consent.

Statistical analysis

One-way repeated measures analysis of variance was used to evaluate MRI and clinical outcomes over time. Dependent-samples t tests were used to evaluate differences in each dependent variable over time and compare MRI or clinical outcomes at 5-year follow-up between patients

 Table 1
 Post-operative magnetic resonance imaging (MRI) assessment of grafts: scoring of parameters and calculation of the MRI composite score

Scoring parameter	Score	Description	Weighting factor	
1. Signal intensity	1 = Poor	Fluid signal/ hyperintense diffuse	0.3	
2. Graft infill	2 = Fair	Hyperintense basal layer >50 %/<50 %		
	3 = Good	Hypointense		
	4 = Excellent	Isointense		
	1 = Poor	Subchondral bone exposed	0.2	
	2 = Fair	<50 % height of adjacent cartilage		
	3 = Good	>50 % height of adjacent cartilage		
	3.5 = Very Good	Hypertrophy		
	4 = Excellent	Complete infill		
3. Border integration	1 = Poor	Incomplete border, visible defect	0.15	
	2 = Fair	Incomplete border, split visible		
	3 = Good	Complete border, minor split		
 Surface Contour Structure 	4 = Excellent	Complete integration		
	1 = Poor	Ulceration, delamination, full thickness	0.1	
	2 = Fair	<50 % surface fibrillation		
	3 = Good	Focal changes only		
	4 = Excellent	Smooth surface		
	1 = Poor	Heterogenous, clefts	0.1	
	2 = Fair	Heterogenous, no clefts		
	3 = Good	>50 % Homogenous		
	4 = Excellent	>75 % Homogenous		
6. Subchondral lamina	1 = Poor	No visible lamina	0.05	
	2 = Fair	<25 % Intact		
	3 = Good	>50 % Intact		
	4 = Excellent	Fully reconstituted		

Table 1 continued

Scoring parameter	Score	Description	Weighting factor	
7. Subchondral bone	1 = Poor	Cysts, sclerosis, oedema	0.05	
	2 = Fair	oedema > 1 cm from lamina		
	3 = Good	oedema < 1 cm from lamina		
	4 = Excellent	Intact no significant oedema		
8. Effusion	1 = Poor	Severe	0.05	
	2 = Fair	Moderate		
	3 = Good	Mild		
	4 = Excellent	None		

with and without TTT. Spearman rank order correlation was used to assess intra-observer reliability for eight MRI parameters and the composite score. Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL), and significance was determined at p < 0.05.

Results

Of the 25 patients enrolled in the study, 2 were lost to follow-up. In the remaining 23 patients (13 men and 10 women), MACI grafting of the patellofemoral joint was performed in 24 knees (patella, n = 15, trochlear, n = 9); one patient underwent MACI of the patella and subsequently underwent MACI of the trochlear of the contralateral knee. Measurement accuracy was to the nearest 0.1 U for KOOS and SF-36 scores, nearest degree for knee ROM and 1 m for the 6MWT. Mean age was 42.3 years [standard deviation (SD) 11.6]; mean BMI was 25.9 (SD 4.1); mean duration of symptoms was 9.5 years (SD 6.4); and mean defect size was 3.5 cm^2 (SD 1.4). Using the Fulkerson classification [13] for patella defect location, patients were classified as type I (n = 1), type II (n = 2), type III (n = 11), or type IV (n = 1). Prior procedures included arthroscopic debridement (n = 13), microfracture (n = 1), anterior cruciate ligament reconstruction (n = 2), lateral release (n = 3), and combined lateral release/TTT (n = 2). Nine patients underwent lateral release and TTT either as a prior procedure (n = 2) or combined with MACI grafting (n = 7) and were classified as type II (n = 3), type III (n = 3), and trochlear (n = 3). Both patients who underwent previous lateral release/TTT had patella defects (one lateral type II lesion, one medial type III lesion). They were referred 19 and 26 months after realignment surgery because of pain and dysfunction.

MRI results

Twenty-three patients (24 knees) were available for 5-year MRI follow-up. Intra-observer reliability was high, showing a significant correlation (p < 0.01) between radiological scores (signal intensity, r = 1.00; graft infill, r = 0.95; border integration, r = 0.98; surface contour, r = 1.00; structure, r = 0.84; subchondral lamina, r = 1.00; subchondral bone, r = 0.92; and effusion, r = 0.99) and the MRI composite score of 20 randomly selected image pairs (r = 0.81) [9]. The mean composite graft score improved at each follow-up, increasing significantly between 3 months and 5 years (p < 0.001) (Table 2; Fig. 1). For the individual parameters, scores improved or did not differ significantly between 3 months and 5 years (Table 2).

At the 5-year follow-up, 32 % of patients had complete infill of the defect, and 50 % of patients had >50 % infill. Good-to-excellent results were obtained for graft signal intensity (95 % of patients), border integration (86 %),

Table 2 MRI composite score and individual parameters at 3 months, and 1, 2 and 5-year time points

Variable	3 months	1 year	2 years	5 years	p value
MRI Composite Score	2.9	3.3	3.4	3.4	< 0.05
Signal intensity	2.0	3.0	3.2	3.3	< 0.05
Graft infill	2.9	3.1	3.2	3.4	n.s.
Border integration	3.0	3.1	3.3	3.1	n.s.
Surface contour	3.3	3.5	3.5	3.4	n.s.
Structure	3.1	3.5	3.4	3.3	n.s.
Subchondral lamina	3.3	3.9	4.0	4.0	< 0.05
Subchondral bone	3.3	3.9	3.8	3.7	< 0.05
Effusion	3.6	3.9	3.8	3.8	n.s.

p values are given for comparison between 3-month and 5-year follow-up



Fig. 1 Increase in the MRI composite score between 3-month and 5-year follow-up

surface appearance (91 %), and structure (95 %). The subchondral lamina was fully reconstituted in all patients, but one patient had a poor score for subchondral bone because of cysts, oedema, and sclerosis. Six patients continued to have a mild effusion detectable on MRI.

All nine patients who underwent MACI grafting to the trochlear had good-to-excellent graft infill at 5 years, and 88 % had a good-to-excellent score for signal intensity. One patient had evidence of graft oedema with a hyperintense basal layer and incomplete border integration with a visible split on MRI. For the patella grafts, all three patients with type I or II defects had good-to-excellent results for all MRI parameters at 5 years, with the exception of the subgroup border, where one patient demonstrated incomplete integration and a visible split. Nine of the 11 patients with a type III patella had good-to-excellent results for all eight parameters at 5 years. Two patients had poor results: one patient demonstrated heterogeneity within the graft, and the other patient demonstrated <50 % of the original graft height, with an incomplete border and split, delamination of the graft surface, bone cysts and sclerosis within the subchondral bone. Comparison of patients who underwent TTT with those that did not showed no significant differences in any of the MRI scoring parameters at 5 years.

Clinical results

Mean scores in all five KOOS subscales improved between pre-surgery and final follow-up (Fig. 2): pain score increased from 60.0 to 80.6 (p < 0.001), other symptoms score increased from 62.4 to 84.0 (p < 0.0001), ADL score increased from 69.3 to 88.3 (p < 0.001), sport and recreation score increased from 23.0 to 50.2 (p < 0.001), and knee-related QOL score increased from 19.5 to 50.8



(p < 0.001). The mean score for the SF-36 physical component summary score increased from 36.4 to 45.1 (p < 0.001) (Fig. 3); however, the increase in the mental component summary score (from 51.2 to 57.3) was not significant (Fig. 3). Results of the 6MWT improved over the study period, with the mean distance increasing from 570 to 590 m (p < 0.001). Although active knee flexion did not change significantly, knee extension improved from 1° of fixed flexion to 1° of hyperextension (p = 0.008). Survey results showed a 91 % satisfaction rate at final follow-up.

Correlation between MOCART scoring and clinical outcomes

The SF-36 mental component summary score correlated with graft infill and surface contour, and the KOOS QOL subscale correlated with subchondral bone. However, no further correlations were found between clinical scores and MRI variables or the composite MOCART score.

Complications and failures

One patient developed deep vein thrombosis while in hospital and was treated according to the usual protocol. Graft hypertrophy was detected by MRI in three patients. One patient underwent arthroscopic debridement at 26 months with subsequent improvement in symptoms. The other two patients were not sufficiently symptomatic to warrant debridement; at the 5-year follow-up, they remained hypertrophic on MRI. Two of the nine patients who underwent TTT required removal of their screws for symptoms related to pain around the tibial tubercle.



Fig. 3 SF-36 physical component summary (PCS), mental component summary (MCS) scores before and after matrix-induced autologous chondrocyte implantation of the patellofemoral joint. Data are expressed as mean $(\pm SD)$

Discussion

The most important finding of the present study was that MACI grafting to the patellofemoral joint can result in a durable graft and a marked improvement in symptoms. Few studies have described outcomes after MACI in the patellofemoral joint. Gigante et al. [17] reported that 11 of 12 patients who underwent patella MACI in conjunction with Fulkerson TTT were satisfied at 3-year follow-up. Genovese et al. [16] described the intact appearance of three patella MACI grafts by MR arthrography at 5-year follow-up. Our results are consistent with these previous studies.

Limited data exists in the literature regarding the MRI appearance of the patellofemoral joint following ACI. Gobbi et al. [18] evaluated 27 patients treated with second-generation ACI using a hyaluronan-based scaffold and reported >50 % infill of the defect in 70 % of patients and a normal or nearly normal signal in 75 % of patients after 5 years. Vanlauwe et al. [41] evaluated ACI of the patellofemoral joint using characterised chondrocytes covered by a type I collagen membrane and showed that 19 of 34 patients had >50 % filling on MRI (follow-up, 2–4 years). These studies are consistent with our results demonstrating >50 % filling of the defect on MRI in 82 % of patients, and good-to-excellent signal intensity in 95 % of patients.

Magnetic resonance imaging data provides an assessment of the MACI graft that is not confounded by the effect of realignment surgery, which alone can result in clinical improvement of pain and function. In a series of 98 patients treated with proximal and distal realignment for patellofemoral pain, Henderson and Francisco [20] reported that 81 % had good or excellent results, as assessed using a modified Trillate grading scale. Pidoriano et al. [34] reported good-to-excellent outcomes from TTT alone for 87 % of patients with Fulkerson type I or II defects (mean follow-up, 46.8 months); however, only 55 % of patients with type III lesions (medial facet) and 20 % with type IV lesions (diffuse) had good-to-excellent outcomes. Of the 11 patients with a type III lesion in our study, 73 % had goodto-excellent outcomes according to the MRI composite score, and 82 % had KOOS scores >70 in the categories of pain, other symptoms, and ADLs at the 5-year follow-up. Furthermore, 91 % of these patients were satisfied with their surgery and would undergo the MACI procedure again.

Correlation between clinical and radiological outcomes is controversial in cartilage restoration. Success or failure of a graft must be evaluated using a non-invasive method. A meta-analysis by Blackman et al. [3] showed that the overall MOCART score correlated with multiple clinical outcomes (International Knee Documentation Committee Subjective Knee Evaluation Form, KOOS, Tegner Activity Score, 6MWT, SF-36, and the Lysholm and Cincinnati scoring systems) in the short to mid term but not at longterm follow-up. Marlovits et al. [26] found that the MO-CART variable "filling of the defect" correlated with all KOOS variables, and the MOCART variables "subchondral bone" and "structure of repair tissue" correlated with all KOOS variables except "symptoms". In our study, correlations were observed between the SF-36 mental component summary score and graft infill and surface contour, and between the KOOS QOL subscale and subchondral bone, but not between any of the descriptive MRI variables and clinical scores. Correlation between graft status and clinical outcomes may be lower in the patellofemoral joint because of the duel effects of ACI and patellofemoral realignment surgery on clinical outcome. However, we believe that MRI assessment is still useful to assess graft status in the patellofemoral joint because it provides a non-invasive method to evaluate cartilage. The MOCART scoring system shows that MRI characteristics of the repair tissue are similar to those of healthy adjacent cartilage [26, 27], which is a good indication of graft success. We believe that both MRI, which may predict long-term success, and clinical scores, which assess pain and function, are necessary. However, improved MRI or clinical scoring systems may be required, which would ideally be validated against arthroscopy and histological findings. This may need to be a scoring system specific for the patellofemoral joint because of the confounding effect of realignment surgery.

With regard to patellofemoral maltracking, Henderson and Lavigne [19] reported that patellofemoral ACI patients perform better after concomitant proximal and distal realignment surgery, even in the absence of patellofemoral malalignment. The benefits of TTT in this group are probably related to anteriorisation of the patella, with a resultant decrease in joint reaction force in the patellofemoral joint, creating an environment conducive for cartilage repair. Pascual-Garrido et al. [33] suggested that anteromedialisation may improve clinical outcomes. Vasiliadis et al. [42] reported equivocal outcomes at 13-year follow-up for patients with normal patellofemoral alignment compared with those who required TTT for malalignment. When performing a TTT on a patient with a type III lesion, care must be taken to avoid over-medialisation of the patella, leading to high contact pressure on the medial facet. Our results did not show any significant difference in MRI outcomes between patients who underwent TTT and those who did not. In our study, patients who had distal realignment with TTT also had proximal realignment with a lateral release, as described by previous studies [19, 20]. It is standard practice in our institution to perform lateral release in patients requiring TTT.

The mean age of our patients was 42.3 years, which is older than that of patients in previously reported studies of ACI in the patellofemoral joint (30.9–35 years) [17, 19, 23, 33, 41, 42]. Of studies looking at ACI in older patients with a mixture of tibiofemoral and patellofemoral lesions, a case series by Rosenberger et al. [38] evaluating patients older than 45 years found good clinical improvement at 2-year follow-up, similar to reported outcomes in younger patients. In a matched pair analysis Niemeyer et al. [32] observed sustained clinical improvement, with no significant difference between older patients (>40 years) and vounger patients. In contrast, Kon et al. [22] found that older patients (>40 years) treated with tibiofemoral ACI had inferior results compared with younger patients, although both groups showed clinical improvement. Our results indicate that outcomes for older patients who undergo patellofemoral MACI are similar to those of younger patients [17, 19, 23, 33, 41, 42], with a mean KOOS pain score of 80.6 at 5-year follow-up, and 91 % satisfaction rate.

The difficulty remains in choosing between ACI, patella realignment surgery, or combined procedures according to the defect location. Patients with type III and IV patella defects have poor clinical results when treated with TTT alone, with success rates of 55 and 20 %, respectively [34]. However, patellofemoral ACI results reported by Minas and Bryant [28], which included 91 % type III and IV lesions, indicated a clinical success of 70 %. Henderson and Lavigne [19] showed that 86 % of patients (including 66 % type III and IV lesions) had good-to-excellent results when combined lateral release, and TTT was performed for patellofemoral maltracking. In the group with normal patellofemoral alignment, ACI was the sole procedure, and good-to-excellent results decreased to 55 %. A review by Trinh et al. [40] noted improved results in patients who underwent realignment. In our study, type III lesions treated with MACI and patellofemoral realignment if indicated had good results, with 82 % showing good-toexcellent MRI appearance of the graft at 5-year follow-up and KOOS score >70 for pain, other symptoms, and ADLs.

The clinical relevance of the study is MACI grafting to the patellofemoral joint, which is a viable treatment option for chondral defects in patients aged between 15 and 60 years of age. Patients with trochlear or patella Type III and IV chondral defects should be considered for MACI grafting. Patients with Type I and II patella chondral defects also benefit from MACI grafting; however, the benefit over TTT alone is unclear.

Limitations of the study include study design (Level 4 case series) [31]. As has been reported in previous studies, the clinical results are confounded by proximal and distal realignment surgery in the patellofemoral joint. In addition, the MRI MOCART score has not been validated against

arthroscopic findings or histological repair tissue. However, the MOCART score compares repair tissue to the healthy native adjacent cartilage, demonstrating that ACI can produce a repair tissue with MRI characteristics similar to native articular cartilage [26, 27]. In our opinion, it would be unethical to subject patients who are functioning well to arthroscopic assessment and histological biopsy of the graft.

Conclusions

The study shows that MACI grafting can provide a durable graft in the patellofemoral joint as assessed by the MO-CART scoring system at 5-year follow-up in patients with an average age of 42.3 years old. These patients demonstrated sustained clinical improvement at final follow-up. Correlation between the MOCART scoring system and clinical outcome is low in patellofemoral MACI.

Conflict of interest No author had conflict of interest to declare. No funding was provided for this study.

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