TITLE

A comparison of two year outcomes in patients undergoing tibiofemoral or patellofemoral Matrix-Induced Autologous Chondrocyte Implantation (MACI)

ABSTRACT

Background: Matrix-induced autologous chondrocyte implantation (MACI) has demonstrated encouraging clinical results in the treatment of knee chondral defects. However, earlier studies suggested that chondrocyte implantation in the patellofemoral (PF) joint was less effective than the tibiofemoral (TF) joint.

Purpose: To compare the radiological and clinical outcome of those undergoing MACI to either the femoral condyles or PF joint.

Study design: Cohort study, Level of evidence, 3.

Methods: A total of 194 patients were included in this analysis, including 127 undergoing MACI to the medial (n=94) and lateral (n=33) femoral condyle, and 67 to the patella (n=35) or trochlea (n=32). All patients were evaluated clinically (KOOS, VAS, SF-36) pre-surgery and at 3, 12 and 24 months post-surgery, while magnetic resonance imaging (MRI) was undertaken at 3, 12 and 24 months, with the magnetic resonance observation of cartilage repair tissue (MOCART) scoring system employed to evaluate the quality and quantity of repair tissue, as well as an MRI composite score. Patient satisfaction was evaluated.

Results: No significant group differences ($p>0.05$) were seen in demographics, defect size, prior injury or surgical history, while the majority of clinical scores were similar pre-operatively. All clinical scores significantly improved over time ($p<0.05$), with a significant group effect observed for KOOS activities of daily living ($p=0.008$), quality of life ($p=0.008$)

and sport (p=0.017), reflecting better post-operative scores in the TF group. While the PF group had significantly lower values at baseline for the KOOS activities of daily living and quality of life sub-scales, they actually displayed a similar net improvement over time compared to the TF group. At 24 months, 93.7% (n=119) and 91.0% (n=61) of patients were satisfied with the ability of MACI to relieve their knee pain, 74.0% (n=94) and 65.7% (n=44) with their ability to participate in sport, and 90.5% (n=115) and 83.6% (n=56) were satisfied overall, in the TF and PF groups, respectively. MRI evaluation via the MOCART score revealed a significant time effect ($p<0.05$) for the MRI composite score and graft infill over the 24 month period. While subchondral lamina scored significantly better (p=0.002) in the TF group, subchondral bone scored significantly worse ($p<0.001$). At 24 months, the overall MRI composite score was classified as Good-Excellent in 98 TF patients (77%) and 54 PF patients (81%).

Conclusion: MACI in the PF joint with concurrent correction of PF maltracking if required leads to similar clinical and radiological outcomes, compared to MACI on the femoral condyles.

Key Terms: Matrix-induced autologous chondrocyte implantation, tibiofemoral, patellofemoral, chondral defect, clinical outcomes, magnetic resonance imaging.

What is known about the subject: Matrix-induced autologous chondrocyte implantation (MACI) has demonstrated encouraging clinical outcomes in the repair of full thickness articular cartilage defects in the knee.[1,6,16,24,40,48] However, much of the published research has investigated the successful use of MACI in the tibiofemoral joint, with little attention paid specifically to MACI in the patellofemoral joint. Early studies reporting poor performance of patellofemoral chondrocyte implantation may have been in part due to them not concurrently addressing patellofemoral malalignment if present,[8] or the surgery being performed in combination with first and second generation chondrocyte implantation surgical techniques.[7]

What this study adds to existing knowledge: Published literature reporting on the clinical and radiological outcomes of MACI specifically in the patellofemoral joint is scarce,[14,25,39] though some recent studies do appear encouraging and comparable to those undergoing MACI in the tibiofemoral joint, which have traditionally been superior. Furthermore, no research has attempted to investigate and compare the clinical and radiological outcome of patients undergoing MACI in the tibiofemoral or patellofemoral knee joints. This information will assist in justifing the use of this technique in treating knee chondral defects in varied locations, and allow surgeons and practitioners to better understand the post-operative time course of change of a cartilage repair method performed in two very different behaving joints of the knee.

INTRODUCTION

Matrix-induced autologous chondocyte implantation (MACI) is a well established two stage cartilage restoration procedure in the treatment of grade III and grade IV chondral defects of the knee.[1,6,16,24,40,48] The techniques of autologous chondrocyte implantation (ACI) have evolved over the years, but the principle has remained the same. In a first operation the patient's own chondrocytes are isolated from a cartilage sample arthroscopically harvested from a non-weight bearing area of the knee, and then cultured in vitro. Approximately 6-8 weeks later, a second surgery is required in which the cultured chondrocytes are reimplanted into the cartilage defect, where they may proliferate to produce a durable load-bearing tissue over time.[7] MACI is the third generation of the technique and employs a synthetic membrane that is seeded with the cultured chondrocytes, cut to the size of the chondral defect and fixed to the subchondral bone. Depending on the location of the defect, the membrane can either be implanted via a mini-arthrotomy or arthroscopically which may reduce comorbidity.[7,9]

Until more recently, much of the published research has investigated the successful use of MACI in the tibiofemoral (TF) joint, with little attention paid specifically to MACI in the patellofemoral (PF) joint.[14,25,36,39] PF chondral damage is common and has been reported in 23-45% of individuals playing sport.[2,22,33] If left untreated, these chondral lesions are likely to deteriorate causing pain, loss of function and early-onset arthritis.[11,12,51] Early studies reporting poor performance of PF chondrocyte implantation may have been in part due to them being performed in combination with first and second generation surgical techniques, whereby the implanted chondrocytes were suspended under a periosteal or collagen flap, respectively.[7,26] Another reason for these poor results was that PF malalignment was often not addressed,[8] whereas it has now become routine to realign the extensor mechanism with a

tibial tubercle transfer (TTT) and lateral retinacular release in the case of PF maltracking.[21,27,31,43]

More recently, non-comparative, prospective studies have shown encouraging clinical and graft outcomes in those undergoing PF MACI, in combination with PF realignment if requried.[14,39] These outcomes are in contrast to early reports on PF chondrocyte implantation, and appear comparable to those undergoing MACI in the TF joint which have traditionally been superior. However, research has not attempted to compare the clinical and radiological (graft development and sustainability) outcome of patients undergoing MACI in either the TF or PF knee joints. This is important to further justify the use of this technique in treating varied defect sites in the knee, and better understand the post-operative time course of clinical and radiological change after MACI performed in two different behaving joints of the knee. Therefore, we hypothesized that those undergoing PF MACI would report comparable graft outcomes evaluated via magnetic resonance imaging (MRI) (primary outcome), as well as clinical outcomes and satisfaction levels (secondary outcomes), at 24 months post-surgery, to those undergoing MACI on the femoral condyles.

MATERIALS AND METHODS

Patients

A total of 204 patients scheduled for MACI were referred into a structured research program between September 2002 and April 2014 (Figure 1). Patients were referred by six orthopaedic surgeons operating out of five hospitals (four private and one public). Pre-operatively, all patients suffered from persistent pain associated with grade III or IV unipolar chondral lesions, assessed with the International Cartilage Repair Society (ICRS) chondral defect classification system. The lesion was observed in all patients via MRI, and later confirmed at the time of first-stage arthroscopic chondral biopsy. Patients were suitable for MACI if they were 15-65 years of age and deemed able to follow a structured rehabilitation program. Patients were excluded if they had ligamentous instability, had undergone a prior extensive meniscectomy (greater than one third of the meniscus), had ongoing progressive inflammatory arthritis or had varus/valgus lower limb mal-alignment (as indicated by > 3° TF anatomic angle). The orthopaedic specialist initially evaluated the patient for joint mal-alignment and, should further investigation be warranted, the patient was sent for long leg alignment radiographs (Maquet views).

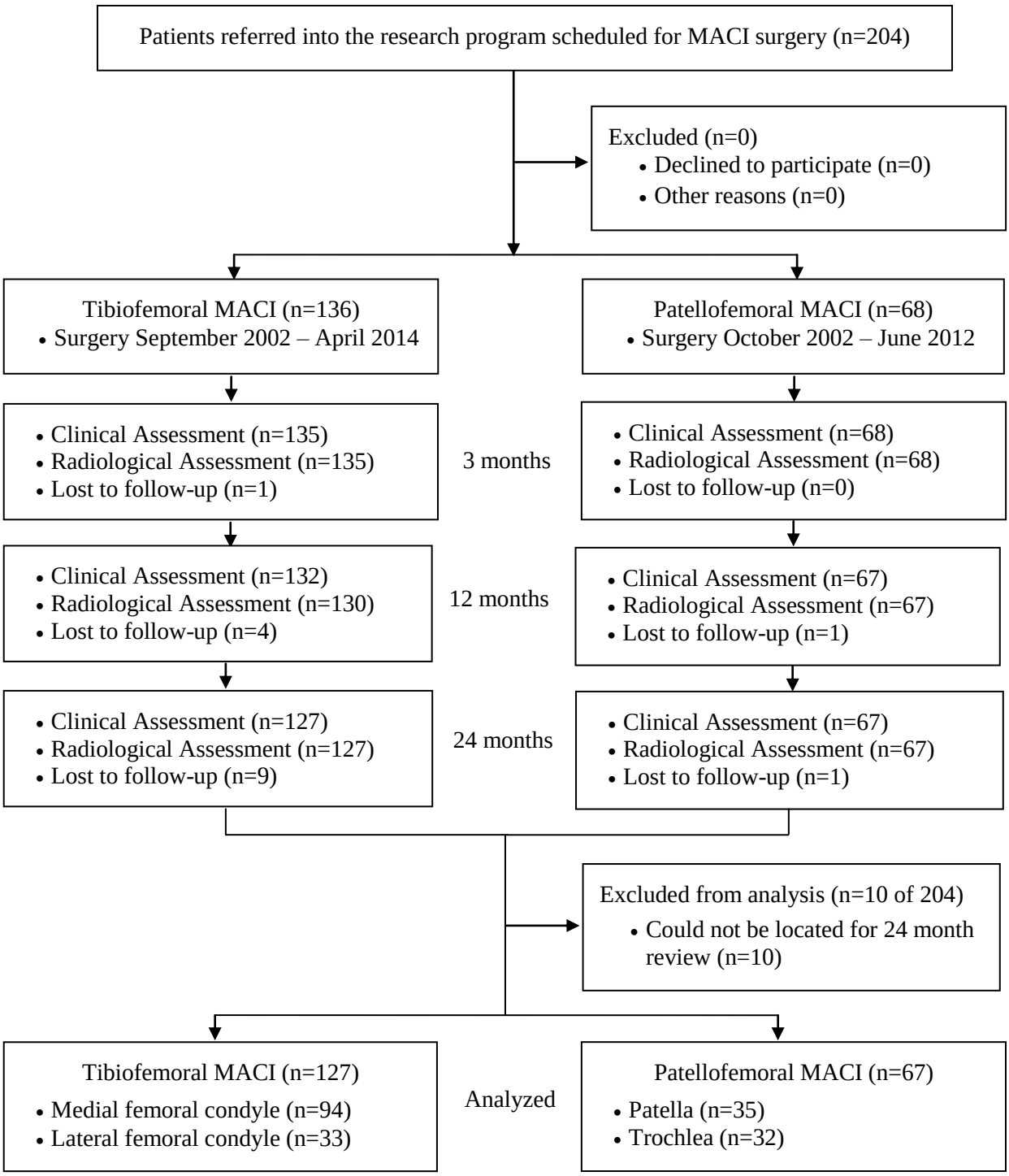

Figure 1. Flowchart demonstrating recruitment, evaluation and analysis of patients in the tibiofemoral and patellofemoral MACI groups, over the 24 month period.

This analysis included 194 MACI patients (95.1%) that could be located for 24 month review (Figure 1). This included 127 patients undergoing TF MACI to the medial (MFC) and lateral

(LFC) femoral condyles (MFC=94, LFC=33), and 67 patients that underwent MACI to the PF joint (patella=35, trochlea=32) (Table 1). Of the TF MACI group, 78 (61%) had been treated previously with one or more surgical procedures to address knee pain and/or symptoms, including: arthroscopy (n=70), microfracture (n=5), partial meniscectomy (n=68), anterior cruciate ligament (ACL) reconstruction (n=9), extensor realignment (n=2) and lateral release (n=4). Of the PF MACI group, 42 (63%) patients had been treated with one or more surgical procedures prior to their MACI procedure to address knee pain, including: arthroscopy (n=45), ACL reconstruction (n=2), extensor realignment (n=3) and lateral release (n=11).

Of the 127 TF MACI patients included in this analysis, 24 underwent concomitant surgeries at the time of MACI, including ACL reconstruction (n=7), posterior cruciate ligament (PCL) reconstruction (n=3), lateral release (n=1), partial meniscectomy (n=11) and high tibial osteotomy (n=4). Of the 67 PF MACI patients, 26 underwent concomitant patellofemoral realignment via a combined lateral PF retinacular release and anteromedial TTT, at the time of their MACI surgery.

A power calculation was performed using G-Power (Dusseldorf, Germany) for the primary outcome variable (MRI composite score), demonstrating that 38 patients were required in each group to reveal differences at the 5% significance level, with 90% power and employing an effect size of 0.76 based on previous research.[13] All patients provided their written informed consent prior to study enrolment and pre-operative clinical evaluation, and ethics approval was obtained from the relevant hospital ethics committee.

Table 1. Patient demographics, injury and surgical history, as well as patient-reported outcomes, for patients in the tibiofemoral (TF) and patellofemoral (PF) groups pre-surgery.

Variable	Measure	TF	PF	p-value
Patients	n	127	67	N/A
Defect Location	n	94 (MFC), 33 (LFC)	35 (patella), 32 (trochlea)	N/A
Gender	Males (%)	81 (63.8)	43 (64.2)	N/A
Age (y)	Mean (range)	37.7 (15-62)	37.9 (20–65)	0.972
15-20	n (%)	8 (6.3)	3 (4.5)	N/A
21-30		30 (23.6)	17 (25.3)	N/A
31-40		53 (41.7)	24 (35.8)	N/A
41-50		27 (21.3)	16 (23.9)	N/A
51-60		7 (5.5)	6 (9.0)	N/A
61-65		2 (1.6)	1 (1.5)	N/A
BMI	Mean (range)	26.4 (16.7-39.4)	26.3 (19.4–36.7)	0.896
Defect Size (cm^2)	Mean (range)	3.1 (0.7-10.0)	3.0 (0.7-12.2)	0.937
≤1.0	n (%)	9 (7.1)	9 (13.4)	N/A
1.1-2.0		34 (26.8)	14 (20.9)	N/A
2.1-3.0		18 (14.2)	11 (16.4)	N/A
3.1-4.0		19 (15.0)	6 (9.0)	N/A
4.1-5.0		11 (8.7)	12 (17.9)	N/A
≥5.1		36 (28.3)	15 (22.4)	N/A
Prior Procedures	Mean (range)	1.3 (0–4)	1.3 (0–4)	0.954
DOS (y)	Mean (range)	8.7 (1–26)	7.3 (1–21)	0.275
KOOS (Pain)	Mean (SD)	65.2 (17.6)	61.8 (15.4)	0.254
KOOS (Symptoms)	Mean (SD)	68.1 (17.5)	65.7 (16.9)	0.432
KOOS (ADLs)	Mean (SD)	76.3 (17.9)	70.2 (15.9)	0.043
KOOS (Sport)	Mean (SD)	26.0 (23.7)	26.3 (20.9)	0.955
KOOS (QOL)	Mean (SD)	31.3 (19.8)	23.4 (16.7)	0.017
SF-36 (PCS)	Mean (SD)	39.3 (9.2)	36.6 (10.9)	0.097
SF-36 (MCS)	Mean (SD)	51.4 (9.7)	52.4 (9.1)	0.534
VAS-F	Mean (SD)	5.5 (2.5)	6.0 (1.8)	0.222
VAS-S	Mean (SD)	4.8 (2.3)	5.3 (1.4)	0.366

MFC = medial femoral condyle; LFC = lateral femoral condyle; DOS = Duration of Symptoms; KOOS = Knee Injury and Osteoarthritis Outcome Score; ADLs = Activities of Daily Living; QOL = Quality of Life; SF-36 = 36-item Short Form Health Survey; MCS = Mental Component Score; PCS = Physical Component Score; VAS-F = Visual Analogue Scale Frequency; VAS-S = Visual Analogue Scale Severity.

Surgical technique and planning of MACI and patellofemoral realignment

During a first stage arthroscopic operation a sample of articular cartilage was harvested from a non weight bearing area of the knee. The chondrocytes from the articular cartilage

specimen were then cultured for approximately 6-8 weeks, before seeding them onto a type I/III collagen membrane (ACI-Maix Matricel GmbH, Germany) three days prior to reimplantation. During second stage reimplantation the chondral defect was prepared via open arthrotomy with debridement of all damaged cartilage down to, but not penetrating, the subchondral bone. After measuring the defect, a similar shaped and sized membrane was prepared and secured to the underlying bone using a layer of fibrin glue. Stability of the graft was checked before wound closure.

Pre-operatively, all patients underwent MRI to evaluate the location, size and severity of the chondral defect, as well as other soft tissue damage. PF patients also underwent computed tomography (CT) imaging to assess the degree (if any) of patellofemoral knee joint mal-alignment. In the 26 patellofemoral patients where Tibial Tubercle to Trochlea Groove (TT-TG) distance on CT indicated lateralization of the tibial tuberosity > 9mm, a concomitant lateral PF retinacular release and anteromedial TTT was performed using the Heatley modification[29] of the Fulkerson technique.[23] Having positioned the patella centrally in the trochlear groove at 20 degrees of knee flexion, the tibial tubercle was fixed with two 3.5mm cortical screws. Post-transfer TT-TG distance was not measured.

Post-operative Management

All patients, irrespective of graft location, underwent continuous passive motion (CPM) set at 0-30 degrees on the operated knee within 12-24 hours post-surgery, for a minimum of one hour daily; cryotherapy to control oedema; active dorsi-flexion and plantar-flexion of the ankle to encourage lower extremity circulation; isometric contraction of the quadriceps, hamstrings, and gluteal musculature to maintain muscle tone; patient education of proficient

toe-touch ambulation allowing no more than 20% of body weight through the operated limb. A knee brace was worn in all patients post-operatively for 24 hours per day.

Following hospital discharge, patients routinely participated in a standardized out-patient rehabilitation program over a 12-week period, with ongoing advice and education provided up until 12 months if required. The progression of brace restriction, weight bearing and exercises differed depending on location (TF versus PF grafts) and size of the graft, as well as patient tolerance to exercise and these rehabilitation protocols have been previously published in detail.[14,20] While it is important to note that structured, post-operative rehabilitation protocols are important in attaining optimal outcome after MACI,[20] these protocols must be individualized to accommodate the aforementioned variables, as well as concomitant surgeries (i.e. ligament reconstruction, osteotomy etc.), and the presentation of clinical signs throughout the post-operative period reflective of overload such as pain and swelling, should be continually monitored.

MRI Assessment

MRI based assessment of the repair tissue was performed at 3, 12 and 24 months after surgery, using a 1.5 T or 3 T clinical scanner (Siemens, Erlangen, Germany; Philips, Best, the Netherlands; General Electric, Milwaukee, WI, USA). Standardized proton density and T2-weighted fat-saturated images were obtained in coronal and sagittal planes (slice thickness 3 mm, field of view 14-15 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).

The magnetic resonance observation of cartilage repair tissue (MOCART) scoring system was employed to assess eight different parameters of graft repair, including graft infill, signal intensity, border integration, surface contour, tissue structure, subchondral lamina, subchondral bone and effusion.[37,38] For each of these parameters a score from 1 to 4 was used to best describe the morphologic features (1 = poor, 2 = fair, 3 = good, 4 = excellent) in comparison to the native cartilage. Infill was also permitted a fifth level (3.5, very good) corresponding with 'graft hypertrophy'. An MRI composite score was then calculated by multiplying the eight individual scores by a weighting factor and summing the weighted scores.[15,45] This composite score also ranged from 1 to 4 based on the MOCART classification system.

For consistency in MRI scoring (especially between groups), all MRI scans were scored by a single independent, experienced musculo-skeletal radiologist, with extensive experience employing the MOCART scoring tool since its inception and initial publication.[37,38] However, intra-observer reliability was assessed for the eight pertinent morphological MRI scores (kappa coefficient), as well as the continuous MRI composite score (intra-class correlation coefficient). This was achieved by re-scoring 20 randomly selected MRI images filtered through a second time to the radiologist. Evaluation of intra-observer reliability for the MRI scoring method indicated a significant correlation ($p<0.05$) between MRI-based scores within each of the eight pertinent scoring variables (signal intensity rho = 1.00; graft infill rho = 0.949; border integration rho = 0.982; surface contour rho = 1.00; structure rho = 0.840; subchondral lamina rho = 1.00; subchondral bone rho = 0.920 and; effusion rho = 0.993), and the MRI composite score (rho = 0.811), for the 20 randomly selected image pairs.

Clinical Assessment

Several patient-reported outcome (PRO) measures were used to assesss patient outcome pre-surgery and at 3, 12 and 24 months after surgery. Firstly, the Knee Injury and Osteoarthritis Outcome Score (KOOS)[47] was employed to assess knee pain, symptoms, activities of daily living (ADL), sport and recreation, and knee-related quality of life. Secondly, the 36-Item Short Form Health Survey (SF-36)[4] was used to evaluate the general health of the patient producing a mental (MCS) and physical component score (PCS). Thirdly, a visual analogue pain scale (VAS) was employed to assess the frequency (VAS-F) and severity (VAS-S) of knee pain on a scale of 0-10. Finally, at 24 months post-surgery a patient satisfaction questionnaire was employed to investigate each patient's level of satisfaction with the MACI surgery overall, as well as their satisfaction with MACI in relieving knee pain, improving their ability to perform normal daily activities, improving their ability to return to recreational activities and improving their ability to participate in sport.[16] A Likert response scale was employed with descriptors Very Satisfied, Somewhat Satisfied, Somewhat Dissatisfied and Very Dissatisfied. The clinical assessor had in excess of 10 years of clinical experience, and was independent to the treating orthopaedic surgeon(s).

Data and Statistical Analysis

Initially, given the potential differences that could be observed between patients undergoing MACI on the MFC and LFC, or between the patella and trochlea, independent t-tests were employed to investigate pre-operative patient demographics, injury and surgery history, as well as pre- and post-operative clinical scores, between these specific graft locations. In specifically comparing patella and trochlea patients, there were no significant differences ($p>0.05$) observed in pre-operative defect size, age at surgery, body mass index, the amount of prior surgical procedures and duration of symptoms. Furthermore, there were no

significant differences ($p>0.05$) observed in KOOS subscales, VAS scores or SF-36 scores pre-surgery, nor up until 24 months post-surgery. When comparing MFC and LFC patients, the aforementioned non-significant differences were also observed. Therefore, given the non-significant differences observed between MFC and LFC patients, as well as between trochlea and patella patients, together with our aim of maintaining statistical power in comparing graft outcome, we collapsed these groups accordingly.

Therefore, independent t-tests were employed to investigate pre-operative patient demographics, injury and surgery history, and clinical scores between the TF and PF MACI groups, as well as between those undergoing extensor realignment (or not) specifically in the PF group. Repeated measures analysis of variance (ANOVA) was used to investigate the progression of clinical and radiological scores over the pre- and post-operative timeline up until 24 months, between the TF and PF MACI groups. Patient satisfaction rates, as well as the number and percentage of grafts evaluated as good or excellent for each of the eight parameters of graft repair and the MRI composite score, were presented at 24 months. ANOVA was also employed to evaluate any differences in clinical and/or MRI-based outcomes across the entire patient cohort at 24 months, following group stratification based on defect size ($\leq$1.0, 1.1-2.0, 2.1-3.0, 3.1-4.0, 4.1-5.0, $\geq$5.1cm^2) and defect aetiology including: A) post-traumatic (MACI surgery within 2 years of traumatic injury); B) post-traumatic (MACI surgery after 2 years of traumatic injury); C) degenerative (no specific cause of injury, duration of symptoms beyond 10 years), and; D) osteochondritis dissecans (OCD) lesion. An additional t-test analysis was performed to evaluate any between group (TF and PF) differences in MRI-based and clinical scores, within each of the aforementioned defect size and aetiology classifications. Statistical analysis was performed using SPSS software (SPSS, Version 19.0, SPSS Inc., USA), while statistical significance was

determined at $p<0.05$.

RESULTS

Of the 194 patients included, all cases were reviewed clinically and radiologically pre-operatively, as well as 3 and 24 months post-surgery (Figure 1). While all patients also underwent clinical review at 12 months post-surgery, five patients (TF = 2; PF = 3) did not undergo MRI at 12 months (an intention to treat analysis was performed using the "last value carried forward" technique for these cases).

No significant differences ($p>0.05$) were seen in demographics, defect size, prior injury or surgical history, between the TF and PF groups (Table 1). While the majority of PROs were similar between the two groups pre-surgery, the PF group did report significantly worse scores for the KOOS ADLs and QOL subscales (Table 1). Specifically in the PF group, those that did undergo extensor realignment surgery had significantly ($p=0.020$) larger chondral defects at the time of surgery (mean size = 3.4cm^2), when compared with the patients that did not require realignment (mean size = 2.7cm^2). However, there were no further differences ($p>0.05$) between patients requiring extensor mechanism realignment or not in all other variables, including pre-operative demographics, prior injury or surgical history, or clinical scores.

Clinical Outcomes

A significant time effect ($p<0.05$) existed for all PRO scores throughout the pre- and post-operative timeline (Table 2). A significant group effect existed between the TF and PF groups for KOOS ADL ($p=0.008$), QOL ($p=0.008$) and Sport ($p=0.017$). A significant interaction effect was observed for KOOS QOL ($p=0.022$) and Sport ($p=0.022$), reflecting better post-operative scores to 24 months in the TF group in these outcome measures (Table 2).

353 Additionally in the 67 PF MACI patients, there were no significant ($p>0.05$) differences
354 observed in any of the clinical scores, between those who did (n=26), or did not (n=41),
355 undergo concomitant extensor realignment surgery.
356
357 At 24 months, 93.7% (n=119) and 91.0% (n=61) of patients were satisfied with the ability of
358 MACI to relieve their knee pain, 91.3% (n=116) and 92.5% (n=62) with the improvement in
359 their ability to undertake daily activities, 87.4% (n=59) and 88.1% (n=59) with their ability to
360 return to recreational activities, and 74.0% (n=94) and 65.7% (n=44) with their ability to
361 participate in sport, for the TF and PF groups, respectively (Table 3). Overall, 90.5% (n=115)
362 of the TF group and 83.6% (n=56) of the PF group were satisfied with the results of their
363 MACI surgery (Table 3).

Table 2. ANOVA results summary for the clinical outcomes demonstrated by the tibiofemoral (TF) and patellofemoral (PF) groups. Shown are means (SD).

Time point	Group	KOOS (Pain)	KOOS (Symptoms)	KOOS (ADLs)	KOOS (Sport)	KOOS (QOL)	SF-36 (PCS)	SF-36 (MCS)	VAS-F	VAS-S
Pre-surgery	TF	65.2 (17.6)	68.1 (17.5)	76.3 (17.9)	26.0 (23.7)	31.3 (19.8)	39.3 (9.2)	51.4 (9.7)	5.5 (2.5)	4.8 (2.3)
	PF	61.8 (15.4)	65.7 (16.9)	70.2 (15.9)	26.3 (20.9)	23.4 (16.7)	36.6 (10.9)	52.4 (9.1)	6.0 (1.8)	5.3 (1.4)
3 months	TF	75.1 (14.9)	79.6 (13.2)	81.0 (12.9)	13.2 (19.0)	37.8 (19.8)	38.2 (9.5)	54.5 (10.1)	N/A	N/A
	PF	69.8 (14.1)	77.9 (13.1)	71.5 (17.5)	8.3 (12.7)	29.5 (18.3)	37.1 (8.8)	55.3 (8.8)	N/A	N/A
12 months	TF	83.1 (13.8)	83.6 (14.6)	91.8 (10.6)	47.0 (29.3)	52.5 (21.5)	46.6 (8.2)	55.1 (7.6)	N/A	N/A
	PF	79.2 (16.1)	82.9 (11.8)	85.8 (12.5)	32.6 (26.4)	45.2 (21.1)	43.9 (9.1)	55.6 (6.5)	N/A	N/A
24 months	TF	85.0 (14.1)	86.5 (12.6)	96.8 (73.9)	61.1 (29.6)	59.1 (23.0)	48.4 (8.7)	55.3 (7.0)	2.4 (2.4)	2.1 (1.7)
	PF	83.1 (12.1)	86.3 (12.1)	87.8 (11.1)	58.3 (29.9)	52.9 (23.0)	47.1 (10.2)	55.6 (6.2)	2.5 (2.4)	2.1 (1.3)
Time Effect (p-value)		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Group Effect (p-value)		0.089	0.421	0.008	0.017	0.008	0.099	0.556	0.258	0.460
Interaction Effect (p-value)		0.718	0.934	0.902	0.022	0.022	0.602	0.968	0.713	0.472

KOOS = Knee Injury and Osteoarthritis Outcome Score; ADLs = Activities of Daily Living; QOL = Quality of Life; SF-36 = 36-item Short Form Health Survey; MCS = Mental Component Score; PCS = Physical Component Score; VAS-F = Visual Analogue Scale Frequency; VAS-S = Visual Analogue Scale Severity.

Table 3. Satisfaction results at 24 months reported by the tibiofemoral (TF) and patellofemoral (PF) groups.

Satisfaction Item	Very Satisfied		Somewhat Satisfied		Somewhat Dissatisfied		Very Dissatisfied		% TF Satisfied	% PF Satisfied
	TF	PF	TF	PF	TF	PF	TF	PF		
How satisfied are you with the results of your MACI knee surgery for relieving pain?	67 (52.8)	34 (50.7)	52 (40.9)	27 (40.3)	8 (6.3)	5 (7.5)	0 (0.0)	1 (1.5)	93.7	91.0
How satisfied are you with the results of your MACI knee surgery for improving your ability to perform daily activities at home and work?	72 (56.7)	37 (55.2)	44 (34.6)	25 (37.3)	10 (7.9)	4 (6.0)	1 (0.8)	1 (1.5)	91.3	92.5
How satisfied are you with the results of your MACI knee surgery for improving your ability to return to recreational activities (such as walking, swimming, cycling, golf, dancing etc.)	66 (52.0)	28 (41.8)	45 (35.4)	31 (46.3)	15 (11.8)	7 (10.4)	1 (0.8)	1 (1.5)	87.4	88.1
How satisfied are you with the results of your MACI knee surgery for improving your ability to participate in sports (such as football, soccer, netball, tennis, surfing etc.)	40 (31.5)	17 (25.4)	54 (42.5)	27 (40.3)	26 (20.5)	18 (26.8)	7 (5.5)	5 (7.5)	74.0	65.7
Overall how satisfied are you with the results of your MACI knee surgery?	68 (53.5)	29 (43.3)	47 (37.0)	27 (40.3)	12 (9.5)	10 (14.9)	0 (0.0)	1 (1.5)	90.5	83.6

Radiological Outcomes

MRI findings revealed a significant time effect ($p<0.05$) for the MRI composite score, as well as graft infill, signal intensity, subchondral lamina, subchondral bone and joint effusion over the 24 month period (Table 4). While subchondral lamina scored significantly better in the TF group ($p=0.002$), subchondral bone scored significantly better in the PF group ($p<0.0001$). A significant interaction effect existed for subchondral bone ($p=0.002$), largely due to a decline in the TF group between 12 and 24 months (Table 4). Specifically in the 67 PF MACI patients, there were no significant ($p>0.05$) differences observed in any of the MRI scores, between those who did, or did not, undergo concomitant extensor realignment. At 24 months, the overall MRI composite score was classified as Good-Excellent in 98 patients (77%) in the TF group and 54 patients (81%) in the PF group (Table 5). The degree of graft infill was Good-Excellent in 111 TF patients (87%) and 55 PF patients (82%) (Table 5). Figure 2 and 3 show the MRI-based progression of a MACI graft on the MFC and patella, respectively.

Table 4. ANOVA summary of the post-operative magnetic resonance imaging (MRI) assessment of grafts for the tibiofemoral (TF) and patellofemoral (PF) groups at 3, 12 and 24 months post-surgery. Shown are means (SD).

Time point	Group	Infill	Signal Intensity	Border	Surface Contour	Structure	Subchondral Lamina	Subchondral Bone	Joint Effusion	MRI Composite Score
3 months	TF	2.86 (0.76)	2.13 (0.65)	2.81 (1.00)	3.00 (0.94)	3.42 (0.98)	3.12 (0.69)	2.86 (0.75)	3.58 (0.54)	2.83 (0.49)
	PF	2.88 (0.58)	2.23 (0.57)	3.09 (0.81)	3.35 (0.81)	3.19 (0.88)	3.00 (0.62)	3.28 (0.88)	3.53 (0.50)	2.91 (0.28)
12 months	TF	3.30 (0.81)	2.86 (0.88)	2.98 (1.03)	2.95 (1.03)	3.43 (0.89)	3.67 (0.52)	2.94 (0.92)	3.72 (0.50)	3.17 (0.61)
	PF	3.21 (0.67)	2.93 (0.74)	3.11 (0.70)	3.28 (0.90)	3.26 (0.88)	3.44 (0.55)	3.69 (0.67)	3.81 (0.39)	3.21 (0.33)
24 months	TF	3.29 (0.83)	2.91 (0.74)	2.97 (1.08)	3.07 (1.09)	3.38 (0.93)	3.80 (0.42)	2.64 (1.09)	3.69 (0.51)	3.17 (0.61)
	PF	3.26 (0.83)	3.07 (0.59)	3.11 (0.95)	3.18 (1.14)	3.16 (0.95)	3.44 (0.63)	3.69 (0.80)	3.77 (0.43)	3.24 (0.56)
Time Effect (p-value)		<0.0001	<0.0001	0.417	0.797	0.643	<0.0001	0.010	<0.0001	<0.0001
Group Effect (p-value)		0.760	0.256	0.197	0.070	0.130	0.002	<0.0001	0.545	0.394
Interaction Effect (p-value)		0.692	0.831	0.069	0.367	0.942	0.121	0.001	0.342	0.854

Table 5. The number (and percentage) of grafts at 24 months post-surgery for the tibiofemoral (TF) and patellofemoral (PF) groups, rated as 'Good to Excellent' or 'Poor to Fair' for the MRI Composite Score and each of eight individual MRI parameters. Also shown are the number (and percentage) of graft failures and incidence of graft hypertrophy.

Group	Score	Infill	Signal Intensity	Border	Surface	Structure	Subchondral Lamina	Subchondral Bone	Joint Effusion	MRI Composite Score	Graft Hypertrophy	Graft Failure
TF	Good to Excellent	111 (87.4)	100 (78.7)	93 (73.2)	98 (77.2)	109 (85.8)	126 (99.2)	74 (58.3)	124 (97.6)	98 (77.2)	42 (33.1%)	11 (8.6%)
	Poor to Fair	16 (12.6)	27 (21.3)	34 (26.8)	29 (22.8)	18 (14.2)	1 (0.8)	53 (41.7)	3 (2.4)	29 (22.8)		
PF	Good to Excellent	55 (82.1)	60 (89.6)	53 (79.1)	56 (83.6)	57 (85.1)	63 (94.0)	63 (94.0)	67 (100.0)	54 (80.6)	7 (10.4%)	3 (4.5%)
	Poor to Fair	12 (17.9)	7 (10.4)	14 (20.9)	11 (16.4)	10 (14.9)	4 (6.0)	4 (6.0)	0 (0.0)	13 (19.4)		

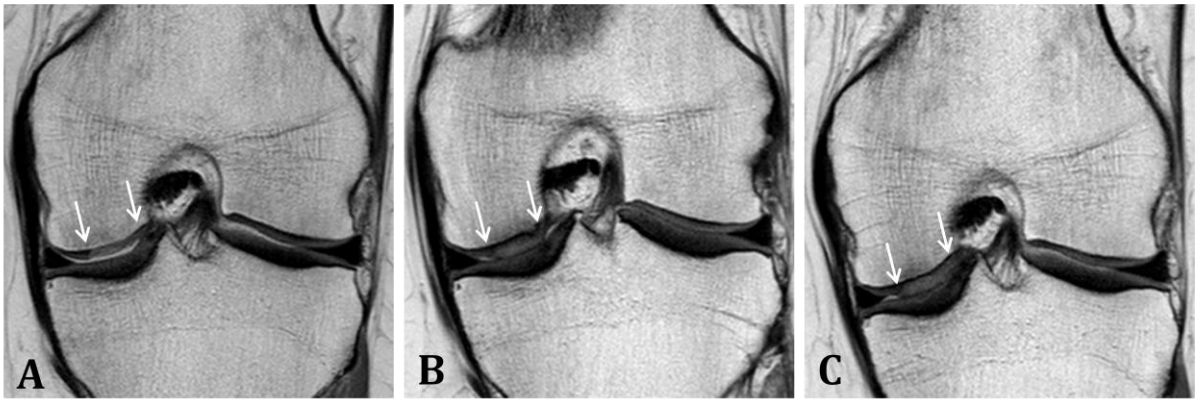

Figure 2. A MACI graft (between white arrows) on the medial femoral condyle in a patient in this study, demonstrating: (a) reduced thickness compared with the adjacent cartilage and a hyperintense signal at 3 months, (b) similar thickness to the adjacent cartilage and an isointense signal at 12 months, and (c) sustained tissue infill through to 24 months post-surgery.

Figure 3. A MACI graft (between white arrows) on the patella in a patient in this study, demonstrating: (a) 50-100% infill at 3 months, (b) equivalent signal and thickness characteristics to the adjacent cartilage at 12 months, and (c) sustained tissue infill through to 24 months post-surgery.

Complications and Failures

A number of early post-operative complications were reported, including wound site opening with or without an associated local infection (TF n=3; PF n=2), deep vein thrombosis (TF n=2; PF n=1) and the development of a post-operative hematoma (TF n=1; PF n=1). These early complications were treated accordingly without further issue. At 24 months post-surgery, a significantly greater ($p<0.001$) percentage of TF patients (n=42, 32.1%) displayed hypertrophic grafts on MRI, compared with PF patients (n=7, 10.4%). At 24 month follow-up, all hypertrophic cases remained asymptomatic clinically, without patient-reported mechanical symptoms or associated pain.

At 24 months, 11 TF grafts (8.6%) had failed, including 7 on the MFC and 4 on the LFC, as indicated by no discernible tissue on MRI (Table 5). Only 3 PF grafts (4.5%) had failed, including 2 on the patella and 1 in the trochlea (Table 5). Regardless, all cases that demonstrated graft failure on MRI at 24 months, were clinically symptomatic at 24 month clinical review. The mean patient age at the time of MACI surgery in patients demonstrating graft failure at 24 months was: MFC 48.7 years (range 42-62, n=7); LFC 35.8 years (range 29-39, n=4); patella 31.5 years (range 26-37, n=2), and; trochlea 39.0 years (n=1). Figure 4 shows 4 MRI-based failures in this cohort, one in each defect location.

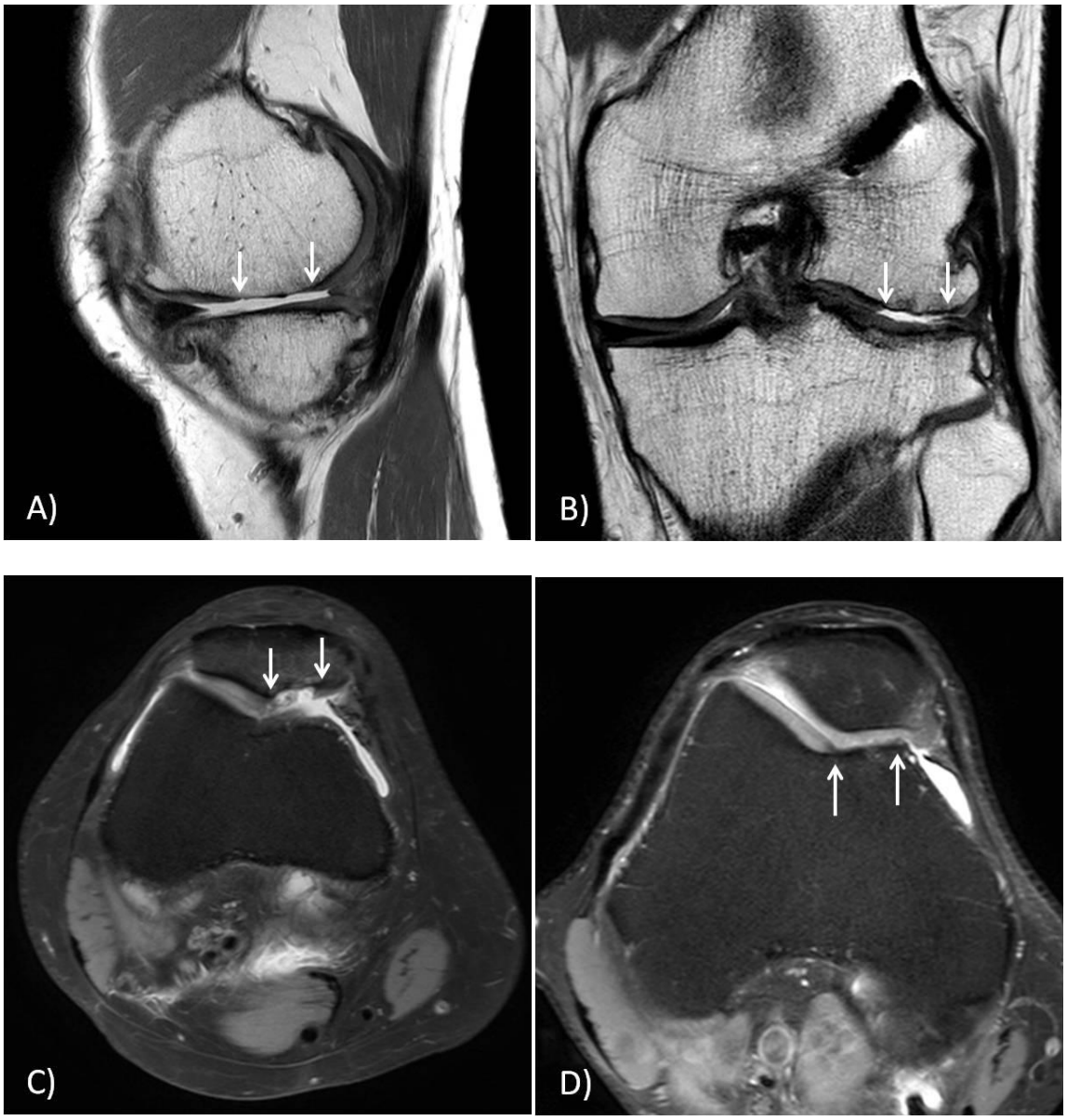

Figure 4. Four individual graft failures (between white arrows) on magnetic resonance imaging (MRI) at 24 months post-surgery, including: A) a sagittal proton density fast spin echo image of a failed MACI graft on the medial femoral condyle; B) a coronal proton density fast spin echo image of a failed MACI graft on the lateral femoral condyle; C) an axial fat-saturated proton density image of a MACI graft on the patellar medial facet, and D) an axial fat-saturated proton density image of a MACI graft on the medial side of the trochlea.

Sub-group Analysis based on Defect Size and Aetiology

Comparison of mean clinical (KOOS Pain, Symptoms and Sport) and MRI-based (graft infill and MRI composite score) outcomes at 24 months for the TF and PF groups, when sub-grouped via defect size, is shown in Table 6. There were no differences ($p<0.05$) between groups at any specified defect size in KOOS Pain or Symptoms at 24 months. This was also the case for KOOS Sport, apart from significantly better Sport scores in the 3.1-4.0cm^2 defect size in the TF group (Table 6). There were no group differences ($p<0.05$) at any specified defect size in graft infill or the MRI composite score at 24 months, apart from significantly better composite scores in the PF group in those undergoing MACI for defects ≥5.1cm^2 (Table 6).

Comparison of mean clinical (KOOS Pain, Symptoms and Sport) and MRI-based (graft infill and MRI composite score) outcomes at 24 months for the TF and PF groups, when sub-grouped via defect aetiology, is shown in Table 7. In evaluating the overall MACI cohort, inclusive of all TF and PF patients, KOOS Pain was significantly better ($p<0.05$) at 24 months post-surgery in patients undergoing MACI within 2 years of their traumatic injury, compared with those undergoing MACI outside of 2 years of their traumatic injury, as well as degenerative lesions without a specific injury (Table 7). Furthermore, KOOS Pain was significantly better ($p<0.05$) in those undergoing MACI outside of 2 years of their traumatic injury, compared with degenerative lesions (Table 7). For KOOS Symptoms, patients with post-traumatic chondral lesions (undergoing MACI either within or after 2 years of their traumatic injury) were significantly better ($p<0.05$) at 24 months than those undergoing MACI for degenerative lesions (Table 7). There were no differences ($p>0.05$) in the KOOS Sport subscale based on defect aeitology for the overall patient cohort. Furthermore, there

were no differences ($p>0.05$) observed between groups (TF and PF) in the KOOS Pain, Symptoms or Sport subscales, within each aetiology sub grouping (Table 7).

When evaluating MRI-based outcomes at 24 months post-surgery based on defect aetiology across the overall MACI cohort, inclusive of all TF and PF patients, graft infill was significantly better ($p<0.05$) in patients undergoing MACI within 2 years of their traumatic injury, compared with those undergoing MACI outside of 2 years of their traumatic injury, as well as degenerative lesions (Table 7). Furthermore, graft infill was significantly better ($p<0.05$) in those undergoing MACI outside of 2 years of their traumatic injury, compared with degenerative lesions (Table 7). There were no differences ($p>0.05$) in the MRI composite score based on defect aeitology for the overall patient cohort. Furthermore, there were no differences ($p>0.05$) observed between groups (TF and PF) in either graft infill or the MRI composite score, within each aetiology sub grouping (Table 7).

Table 6. Clinical (KOOS Pain, Symptoms and Sport) and MRI-based (graft infill and MRI composite score) outcomes at 24 months post-surgery in the tibiofemoral (TF) and patellofemoral (PF) groups, following sub-group analysis by defect size (cm^2). Shown are means (SD).

Outcome Measure	Defect Size (cm^2)											
	≤1.0		1.1-2.0		2.1-3.0		3.1-4.0		4.1-5.0		≥5.1	
	TF	PF	TF	PF	TF	PF	TF	PF	TF	PF	TF	PF
Mean Size cm^2 (SD)	0.9 (0.1)	1.0 (0.1)	1.7 (0.3)	1.6 (0.3)	2.7 (0.3)	2.6 (0.4)	3.7 (0.3)	3.9 (0.2)	4.8 (0.3)	4.8 (0.3)	7.7 (1.3)	7.7 (1.3)
KOOS (Pain)	86.9 (12.4)	85.2 (13.1)	83.7 (14.9)	84.6 (10.7)	82.2 (13.8)	80.6 (14.5)	86.0 (14.6)	82.6 (15.1)	90.5 (6.2)	87.3 (6.4)	84.6 (12.5)	87.6 (11.5)
KOOS (Symptoms)	91.2 (6.7)	90.3 (6.6)	86.0 (12.6)	86.6 (12.4)	82.3 (17.2)	83.3 (11.4)	86.2 (11.1)	83.6 (8.8)	91.1 (6.3)	88.3 (6.1)	88.3 (10.1)	91.5 (6.2)
KOOS (Sport)	49.0 (37.4)	47.7 (36.8)	59.2 (32.5)	56.0 (29.8)	65.0 (33.1)	63.2 (29.6)	56.4 (27.7)	48.6 (24.0)	64.0 (18.5)	61.0 (32.3)	60.1 (20.0)	58.8 (24.1)
Infill	3.2 (0.7)	3.1 (0.8)	3.4 (0.7)	3.2 (1.0)	3.2 (1.0)	3.4 (0.6)	3.3 (0.5)	3.1 (0.9)	3.4 (0.9)	3.5 (0.5)	3.1 (1.2)	3.3 (0.5)
MRI Composite Score	3.3 (0.4)	3.3 (0.5)	3.3 (0.5)	3.0 (0.7)	3.0 (0.8)	3.3 (0.2)	3.3 (0.3)	3.1 (0.8)	3.2 (0.8)	3.4 (0.2)	2.8 (0.9)	3.3 (0.4)

KOOS = Knee Injury and Osteoarthritis Outcome Score; MRI = magnetic resonance imaging.

Table 7. Clinical (KOOS Pain, Symptoms and Sport) and MRI-based (graft infill and MRI composite score) outcomes at 24 months in the tibiofemoral (TF) and patellofemoral (PF) groups, following sub-group analysis by defect aetiology. Shown are means (SD).

Outcome Measure	Defect Aetiology							
	Post-traumatic (MACI surgery within 2 years of traumatic injury)		Post-traumatic (MACI surgery after 2 years of traumatic injury)		Degenerative (no specific cause of injury, duration of symptoms beyond 10 years)		Osteochondritis Dissecans Lesion	
	TF	PF	TF	PF	TF	PF	TF	PF
N (%)	31 (24.4)	11 (16.4)	64 (50.4)	34 (50.8)	25 (19.7)	22 (32.8)	7 (5.5)	0 (0)
KOOS (Pain)	89.8 (9.9)	90.2 (8.4)	84.9 (13.3)	82.3 (11.9)	75.9 (18.6)	78.6 (11.6)	92.6 (4.7)	N/A
KOOS (Symptoms)	90.6 (9.7)	89.1 (8.3)	86.0 (11.6)	87.1 (10.1)	79.8 (16.3)	81.6 (10.2)	92.9 (5.8)	N/A
KOOS (Sport)	59.3 (29.1)	58.3 (31.3)	64.3 (29.4)	60.7 (27.4)	45.2 (27.7)	43.8 (32.4)	70.3 (21.0)	N/A
Infill	3.6 (0.4)	3.4 (1.1)	3.3 (0.7)	3.2 (0.7)	2.9 (1.0)	3.1 (0.7)	2.5 (1.4)	N/A
MRI Composite Score	3.4 (0.4)	3.2 (0.9)	3.2 (0.6)	3.3 (0.5)	2.9 (0.6)	3.2 (0.4)	2.4 (1.0)	N/A

KOOS = Knee Injury and Osteoarthritis Outcome Score; MRI = magnetic resonance imaging.

DISCUSSION

Despite third generation ACI techniques, it is generally believed that MACI performed in the PF knee joint is less effective than the TF knee joint. Much of this non-favourable reputation has been attained when early ACI techniques were employed, often without appropriately addressing adjunct PF malalignment.[8] However, published data specifically investigating the outcomes of third generation ACI (MACI), with simultanious PF re-alignment if indicated, is limited.[14,25,39] The purpose of this study was to clinically and radiologically compare MACI in a large cohort of patients who had undergone MACI to the TF or PF knee joint, with concomitant extensor mechanism relalignment if required. As hypothesized, the most important finding of the present study was that both groups had significant improvement in all clinical scores over the 24 month period with only minor discrepancies. Both MACI grafting of the TF and PF joint, for symptomatic focal articular cartilage lesions, results in good clinical outcome, high levels of patient satisfaction and regeneration of tissue, sustained to 24 months post-surgery.

When comparing the TF and PF groups pre-surgery, similar demographic data were observed. However, KOOS ADL and QOL sub-scales were significantly inferior at baseline in the PF group, which may be partly explained by specific KOOS ADL items more relevant to sympromatic PF patients, such as descending and ascending stairs, and rising from sitting.[46,47] The high and comparable duration of symptoms between the TF and PF groups (8.7 and 7.3 years, respectively), is likely reflective of most patients embarking on a range of alternative first-line treatments, before deciding upon MACI when conservative (or non-regenerative surgcial) methods had failed.

Nevertheless, all clinical scores significantly improved over the pre- and post-operative timeline up until 24 months. However, while many of the PROs employed were comparable between groups, a significant group effect did exist for the KOOS sub-scales of ADLs, Sport and QOL in favour of the TF group. However, as previously stated patients in the PF group had significantly lower values at baseline for the KOOS ADLs and QOL sub-scales and overall, actually displayed a similar net improvement over time compared to the TF group (17.6 versus 20.5 points for ADLs; 32.0 versus 35.5 for Sport). Furthermore, despite the significantly worse scores for the KOOS QOL sub-scale in the PF group, compared with the TF group, the largest net improvement over the pre- and post-operative timeline was still noted in the PF group. Therefore, these data suggest that MACI is similarly effective in the PF group for those KOOS sub-scales, despite the lower values at 24 months. In a 24-month follow-up of a Level 1 randomized controlled trial (RCT) comparing MACI and microfracture,[48] KOOS sub-scale results reported were similar to the results of these PF and TF groups, and better than the results for microfracture. Compared to pre-existing studies which specifically evaluated the performance of early generation ACI in the PF joint in combination with correction of a PF maltracking, the results of the present study with MACI appear consistently superior.[27,43]

Overall, the improvement in clinical scores appeared associated with high levels of patient-reported satisfaction, including that with the ability of MACI to reduce knee pain, permit ease in undertaking daily activities, and returning the patient to recreational activities. However, TF patients appeared more satisfied in the ability of MACI to improve sports participation, as well as with their surgical outcome overall. Satisfaction is multi-factorial, and requires the patient to recollect their pre-operative state, the surgical procedure and the early, mid and later post-operative phases. The reliability of patients' estimates of previous health status has

been questioned, whereby the events intervening between the anchor points may influence the recall of their original status.[32] Furthermore, satisfaction with sport can be influenced by much more than just the surgical outcome itself, including ongoing pain, swelling, lack of confidence, fear of re-injury and/or persisting neuromuscular deficits. Many of these factors were not evalauted as part of this study. Previous research[17] has outlined factors such as duration of symptoms and graft size that contribute to post-operative satisfaction after MACI, which were similar between groups in this study, as well as variables such as pre-operative scores on the 36-item Short Form Health Survey and post-operative course of rehabilitation, which were not documented. Regardless, reported satisfaction after MACI in both the TF and PF groups was high at 24 months.

Interestingly, patients who did, or did not, require concommitant realignment, were comparable in both demographics and clinical scores at baseline, despite those requiring realignment presenting with significantly larger chondral defects. Furthermore, there were no differences between these patients post-surgery in clinical scores and MRI-based outcomes. According to our protocols, extensor realignment was performed as an adjunct to MACI grafting if TT-TG measurement on pre-operative CT imaging exceeded 9 mm. TT-TG measurement was performed as described by Schoettle et al.[49] The 9 mm threshold employed to perform concommitant TTT is arbitrary and may be considered low, considering that in the setting of PF instability then corrections are generally performed if TT-TG exceeds 20 mm[10] or 15 mm.[3,28,34] Furthermore, Gigante et al.[25] employed a threshhold of 20 mm to perform a realignment procedure in their study evaluating the efficacy of MACI in the PF joint. Our low threshold for extensor mechanism realignment may have contributed to the similar pre-operative clinical characteristics though, regardless, post-operative outcomes were also comparable. We acknowledge that this relatively low threshold for performing TTT may

contribute to an increased incidence of over-medialization. Given that post-operative CT imaging was not routinely employed, especially in patients that do not present with associated post-operative symptoms as was the case in this PF MACI group, we are unable to say whether this occurred within this cohort.

Radiological assessment in this study was performed using the MOCART score, which has been shown to be a reliable, reproducible, and accurate in assessing cartilage repair tissue.[37,38] The majority of individual scoring parameters, including the overal composite score and graft infill, showed no differences between groups up until 24 months. However, the TF group scored significantly better for subchondral lamina, and significantly worse for subchondral bone. The reason for this is not clear. It has been previously suggested that bone edema may be seen as a sign of overloading and, subsequently, an inability of the early regenerative tissue to appropriately transmit forces acting across the tissue[52] Therefore, it may be related to the increased weight bearing on a TF graft, but further research would be needed to confirm this. Furthermore, a non-significant tendency towards a higher percentage of failures was observed in the TF group (8.6%), compared with the PF group (4.5%), which may also be partly explained by the higher weight bearing loads on a TF graft. Compared with two previous studies using the same MRI-based outcome scores for the assessment of MACI repair tissue in the PF joint, these results appear similar.[14,39]

It may be suggested that MRI-based outcome is not as important as patient-reported outcome and satisfaction. This study primarily sought to evaluate how graft development (and tissue sustainability) in a PF lesion via MACI compared to that of a TF lesion, up until 24 months post-surgery. This remains important given the underlying rationale of MACI is the regeneration of a sustainable hyaline-like tissue repair, capable of withstanding the demands

of daily activity. Furthermore, early reports suggested that graft outcome was poorer in a PF graft (particularly if patella tracking was not well addressed in maligned cases)[8] and, even if patients are relatively asymptomatic in the short-term with poor graft development or failed grafts, research suggests that these persistent chondral lesions are likely to deteriorate with time causing pain, loss of function and early-onset arthritis.[11,12,51] In this study, it is worthy to note that of the 14 MRI-based failures at 24 months, all 14 were clinically symptomatic. Of these, 8 had already sought orthopaedic consultation due to increasing pain/symptoms prior to their 24 month clinical review, and the other 6 reported higher levels of pain and symptoms at their 24 month clinical review, before being sent for their 24 month MRI.

Graft hypertrophy, which has been reported to be a common post-operative complication after ACI,[5,18,30,35,42,44] was observed in only 10.4% of PF grafts, whereas 33.1% of TF grafts were considered hypertrophic. Given the excessive compressive and shear loads experienced over the femoral condyles this is a rather unexpected finding and contradictory to previous reports, which showed an increased rate of hypertrophy for patellar grafts.[41] Hypothetically, instead of removing overgrown graft tissue, additional loading created in the TF joint during WB activities may provide an increased chondrocyte stimulus in TF grafts. Regardless, none of the hypertrophic grafts were symptomatic at 24 month review, with no patient reporting mechanical symptoms or associated pain. Graft hypertrophy did not appear to influence PROs or patient satisfaction. Furthermore, no graft that demonstrated tissue hypertrophy within the 24 month period, failed before 24 months in this study, nor had to be surgically reduced.

We acknowledge some limitations in this study. Firstly, as a primary method of clinical assessment we used the KOOS score, which has been shown to be very responsive to

improvement after MACI surgery.[19] However, there are a number of other PRO measures that have been used to assess ACI[50] which may be able to better differentitate differences in patients undergoing TF and PF joint surgery. Furthermore, despite the differences observed in sport satisfaction, we did not employ any functional (i.e. single limb hop tests, isokinetic knee strength assesment) or activity based outcome measures (i.e. Tegner, Noyes or Marx Activty Scales), which would have given us additional information on group performance. Secondly, in the 26 patients where PF MACI was combined with a proximal (lateral release) or distal (TTT) realignment procedure, the clinical result was the sum of these combined interventions. Therefore, the specific effect of each individual procedure could not be assessed. However, we believe that the encouraging results for PF MACI in this study are largely attributed to the fact that PF maltracking was corrected at the same time and that assessment of each component is irrelevant. Furthermore, it is likely that a realignment procedure on its own would have not provided the regenerated tissue observed on MRI, as a result of the MACI procedure. Finally, the MOCART score that was used compares repair tissue to the native adjacent cartilage.[37,38] It shows that ACI often results in a repair tissue with similar MRI appearance to the surrounding native cartilage. However, the MRI MOCART score has not been validated against arthroscopic findings or histological repair tissue, which would involve another invasive procedure and is largely unethical in otherwise pain-free and well functioning patients.

Despite some clinical differencies between the TF and PF groups, our hypothesis was largely supported in that PF MACI provided comparable clinical outcomes, satisfaction levels and MRI-based graft outcomes to that of TF MACI, up until 24 months post-surgery. We conclude from this study that MACI in the PF joint with simultaneous correction of patellofemoral maltracking if required, leads to similarly good clinical and radiological

outcome compared to MACI of the TF joint. These results could help to guide orthopaedic surgeons in the often complex and demanding management of patients with symptomatic cartilage defects of the knee.

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