TITLE

Prospective clinical and radiological evaluation of patellofemoral matrix-induced autologous chondrocyte implantation (MACI).

ABSTRACT

Background: While matrix-induced autologous chondrocyte implantation (MACI) has demonstrated encouraging outcomes in the treatment of knee chondral defects, there remains little available research specifically investigating its use in the patellofemoral joint.

Purpose: To prospectively evaluate the clinical and radiological outcome of MACI in the patellofemoral joint.

Study Design: Prospective case series.

Methods: In 47 consecutive patients undergoing patellofemoral MACI, clinical (KOOS, SF-36, VAS, six minute walk test, knee range of motion, strength assessment) and magnetic resonance imaging (MRI) assessment was undertaken pre- and post-surgery at 3, 12 and 24 months. MRI assessed graft infill and an overall MRI composite score. Results were analyzed according to the patient sample overall, and following group stratification into four sub-groups according to implant location (patella or trochlea) and the requirement of adjunct tibial tubercle transfer (TTT) for patellofemoral malalignment.

Results: The overall patient sample, as well as each the four procedural sub-groups, demonstrated clinically and statistically significant ($p < 0.05$) improvements over time for all clinical scores. Graft infill and the MRI composite score also demonstrated statistically significant ($p < 0.05$) improvements over time, with no evidence of a main effect for procedure group or interaction between procedure group and time. At 24 months post-surgery, 40.4% (n=19) of patients exhibited complete graft infill comparable to the adjacent native cartilage, with a further 6.4% (n=3) demonstrating a hypertrophic graft. A further 31.9% (n=15) of patients exhibited 50-100% tissue infill with 17% (n=8) of patients demonstrated <50% tissue infill. Two patients (4.3%) demonstrated graft failure. At 24 months post-surgery, 85% (n=40) of patients were satisfied with the results of their MACI surgery.

Conclusion: These results demonstrate that MACI provides improved clinical and radiological outcomes to 24 months in patients undergoing treatment specifically for articular cartilage defects on the patella or trochlea, both with and without concurrent realignment of the extensor mechanism if required.

Keywords: matrix-induced autologous chondrocyte implantation (MACI); patellofemoral joint; clinical outcomes; magnetic resonance imaging (MRI).

What is known about this subject: Autologous chondrocyte implantation (ACI) is now an established technique for the treatment of full thickness knee articular cartilage defects, and good clinical outcomes have been demonstrated. However, despite these encouraging outcomes, there still remains little available research 'specifically' investigating its successful use in the patellofemoral joint. In particular, evidence is particularly scarce with respect to third generation matrix-induced ACI (MACI), with very few studies specifically evaluating MACI in the patellofemoral joint. Furthermore, only four studies specifically evaluating any form of ACI (periosteal, collagen-covered or matrix-induced ACI) in the patellofemoral joint have undertaken some form of magnetic resonance imaging (MRI) based assessment of the post-operative tissue repair in these patella and/or trochlea grafts. Further clinical and radiological outcomes are required to further validate the efficacy of MACI as a suitable surgical treatment option for articular cartilage defects in the patellofemoral knee joint.

What this study adds to existing knowledge: Again, there is little available research 'specifically' investigating the use of MACI in the patellofemoral joint**.** Furthermore, only four studies evaluating any form of ACI (periosteal, collagen-covered or matrix-induced ACI) in the patellofemoral joint have undertaken some form of magnetic resonance imaging (MRI) based assessment of the post-operative tissue repair. This prospective evaluation adds to this scarce literature specifically evaluating patellofemoral MACI, by presenting a comprehensive series of patients (unpublished data) with patient-reported (KOOS, SF-36, VAS, Satisfaction), functional (six-minute walk test, knee range of motion, straight leg raise strength, isokinetic knee flexor and extensor strength) and radiological (magnetic resonance observation of cartilage repair tissue – MOCART) scores at 3, 12 and 24 months post-surgery. We have been unable to locate such an evaluation at the time of paper submission, and we feel this work will significantly benefit the current body of knowledge for MACI and cartilage repair.

INTRODUCTION

Matrix-induced autologous chondrocyte implantation (MACI) has demonstrated encouraging post-operative clinical outcomes and evidence of tissue regeneration in the treatment of knee chondral defects.[2, 8, 11] Despite this, there still remains little available research specifically investigating its successful use in the patellofemoral knee joint. Of the published work, studies specifically evaluating patellofemoral chondrocyte implantation revolve around earlier versions of the general ACI procedure, including periosteal-covered[12, 18, 21, 26, 30, 34, 39, 48] and collagen-covered[47] techniques, while two studies appear to have evaluated a combination of periosteal, collagen-covered and matrix-induced ACI methods.[29, 37] While Gobbi et al.[19, 20] demonstrated improved patient outcomes following treatment of patellofemoral cartilage lesions using autologous chondrocytes seeded into a HYAFF 11 scaffold, there are only two further studies specifically investigating patellofemoral MACI.[17, 33] Furthermore, of the aforementioned studies only four appear to undertake some form of magnetic resonance imaging (MRI) based assessment.[19, 20, 33, 47]

The aim of this study was to prospectively evaluate pre- and post-operative clinical and radiological outcome in patients undergoing MACI to address isolated patellofemoral chondral lesions (patella or trochlea). We hypothesized that: 1) patients would significantly improve throughout the pre- and post-operative time line to 24 months in the patient-reported and functional tests employed, 2) patellofemoral chondral lesions treated with MACI in this cohort would significantly improve throughout the post-operative time line to 24 months, as assessed via MRI, and 3) significant improvements in clinical and radiological outcomes would also be observed following group stratification into patients who underwent MACI to the patella or trochlea, and did, or did not, undergo concurrent patellofemoral realignment.

MATERIALS AND METHODS

Participants

Between June 2008 and June 2012, 47 consecutive patients underwent MACI to address symptomatic cartilage defects on the trochlea (n=23) or patella (n=24) (Table 1). Pre-operatively, all patients suffered from persistent pain associated with grade III or IV chondral lesions, assessed with the International Cartilage Repair Society (ICRS) chondral defect classification system.[5] Patients were included if they were 18-65 years of age and were being treated for isolated patellofemoral chondral defects. Patients were excluded if they had a body mass index (BMI) > 35, ligamentous instability, varus/valgus abnormalities (> 3° tibiofemoral anatomic angle) or had ongoing progressive inflammatory arthritis. There were no patients excluded due to the aforementioned exclusion criteria. Patients provided their written informed consent prior to study enrollment, and ethics approval was obtained from the relevant ethics committees.

Insert Table 1.

Of the 47 patients, 27 reported a specific traumatic event (sporting or occupational) that resulted in subsequent knee pain/symptoms. While 11 patients were unable to recollect a specific traumatic event though reported an onset of pain/symptoms during a specific activity, nine were unable to recollect any reason for the onset of their pain/symptoms. A total of 28 patients had been treated previously with one or more surgical procedures to address knee pain, including: arthroscopy (n=35), anterior cruciate ligament (ACL) reconstruction (n=2), extensor realignment (n=3), lateral release (n=11) and other procedures (n=6).

Pre-operatively, all patients underwent magnetic resonance imaging (MRI) to evaluate the location, size and severity of the chondral defect, as well as any other soft tissue damage incorporating the menscii or ligamentous structures. Patients also underwent computed tomography (CT) imaging to assess the degree (if any) of patellofemoral knee joint mal-alignment. Tibial Tubercle to Trochlea Groove (TT-TG) distance was measured on CT and adjunct TTT was performed with > 0.9 cm lateralization of the tibial tuberosity. Of the 47 patients that underwent MACI, 19 underwent concurrent tibial tubercle transfer (TTT) to correct malignment as per the aforementioned criteria (Table 1). Patellofemoral alignment was also assessed clinically by the orthopaedic specialist to evaluate patella tracking, subluxation, lateral retinacular tightness and Q-angle.

The Surgical Technique

MACI is a 2-stage technique, where arthroscopic surgery was initially performed to harvest a sample of articular cartilage from a non weight bearing area of the knee. The cartilage biopsy was then sent to the laboratory (Genzyme, Perth, Western Australia), whereby chondrocytes were isolated from the cartilage tissue, cultured for approximately 6-8 weeks and seeded onto a type I/III collagen membrane (ACI-Maix Matricel GmbH, Herzogenrath, Germany) three days prior to second-stage re-implantation. At the time of second-stage implantation, the chondral defect was prepared via an open arthrotomy by removing all damaged cartilage down to, but not through, subchondral bone. The resultant defect was measured and used to shape the membrane, which was secured to the bone using a thin layer of fibrin glue. The wound was closed after assessment of graft stability.

TT-TG distance on CT indicated > 0.9 cm lateralization of the tibial tuberosity in 19 patients and, therefore, all 19 underwent concomitant patellofemoral realignment. This was undertaken via a combined lateral patellofemoral retinacular release and anteromedial TTT performed using the Heatley modification[24] of the Fulkerson technique.[14, 15] The tibial tubercle was medialised and secured with two 3.5-mm cortical screws, so that the patella was positioned centrally in the trochlear groove at 20° of knee flexion (from full knee extension). However, post-transfer TT-TG distance was not evaluated. TTT was performed concurrently with the MACI grafting.

Post-operative Rehabilitation

Immediate post-operative inpatient rehabilitation consisted of: continuous passive motion (0-30 degrees) within 12-24 hours after surgery; active dorsi- and plantar-flexion of the ankle to encourage lower extremity circulation; isometric contraction of the quadriceps, hamstrings, and gluteal musculature to maintain muscle tone and minimize muscle loss;[4, 35] cryotherapy to control edema, and; teaching of proficient toe-touch ambulation through the affected limb. To protect the repaired cartilage surface, a hinged knee brace was worn post-operatively for up to 24 hours per day, depending on the stage of rehabilitation. Following these early post-operative stages, patients participated in a standardized out-patient rehabilitation program over a 12 week period, while further activity guidelines and advice were provided to patients up until 12 months post-surgery (Table 2). These protocols were individually modified for each patient dependent on the location and size of the defect, any additional surgical procedures that may have been performed and the presentation of clinical signs throughout the post-operative period reflective of overload such as pain and swelling.

Insert Table 2.

Clinical Assessment

Several patient-reported outcome (PRO) measures were employed to evaluate patient outcome pre-surgery and at 3, 12 and 24 months post-surgery, including: 1) the Knee Injury and Osteoarthritis Outcome Score (KOOS)[43] to assess knee Pain, Symptoms, Activities of Daily Living (ADL), Sport and Recreation and knee related Quality of Life (QOL), 2) the Short Form Health Survey (SF-36) which evaluated the general health of the patient, producing a mental (MCS) and physical component score (PCS),[1] and 3) the Visual Analogue Scale (VAS) to assess the frequency (VAS-F) and severity (VAS-S) of knee pain on a scale of 0-10. A patient satisfaction questionnaire was also employed at 24 months post-surgery 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 the ability to perform normal daily activities and their ability to participate in sport.

Functionally, the six minute walk test[6, 8, 11, 33, 40] was employed post-operatively to assess the maximum comfortable distance the patient could walk in a six minute period, as was maximal active knee flexion and extension range of motion (ROM). Isokinetic strength of the quadriceps and hamstrings muscle groups was assessed using an isokinetic dynamometer (Isosport International, Gepps Cross, South Australia) at 12 and 24 months post-surgery. Patients were seated in the dynamometer chair, so that the hips and knees were in a 90˚ position. The trunk and thigh were stabilized using rigid straps, and adjustments were made for thigh and leg length, in accordance with each patient's stature. Concentric knee extension and flexion strength was measured through a range of 0-90˚ of knee flexion, at a single isokinetic angular velocity of 90°/s. Each trial consisted of four repetitions: three low intensity repetitions of knee extension and flexion, immediately followed by one maximal test effort. Two trials on each lower limb were undertaken, alternating between the operated and non-operated limbs, with the first trial always undertaken on the non-operated side. Verbal encouragement was provided, standardized across all patients and trials. Patients were given adequate rest in between trials to minimize fatigue, though this was not standardized and based upon the patient's individual readiness to proceed. For all knee extension and flexion efforts, the peak torque value (Nm) was measured, while a limb symmetry index (LSI) was calculated by dividing the peak values (extension and flexion) on the operated limb by that recorded on the non-operated limb.

Magnetic Resonance Imaging (MRI) Assessment

Repair tissue was assessed using high resolution MRI at 3, 12 and 24 months post-surgery, using 1.5 T or 3 T clinical scanners (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).

For MRI-based scoring, the magnetic resonance observation of cartilage repair tissue (MOCART) scoring system[31, 32] was initially employed to evaluate eight pertinent parameters of graft repair (signal intensity, graft infill, border integration, surface contour, structure, subchondral lamina, subchondral bone and effusion). These were selected to best describe the morphology and signal intensity of the repair tissue, each scored individually from 1-4 (1=poor; 2=fair; 3=good; 4=excellent) in comparison to the native cartilage. An MRI composite score was then calculated by multiplying each of the eight individual scores by a weighting factor,[40] and summing the weighted scores.[7, 40] This composite score also ranged from 1-4 (1=poor; 2=fair; 3=good; 4=excellent). In addition to the MRI composite score, we also evaluated graft infill. MRI evaluation was performed by an independent, experienced musculo-skeletal radiologist, with almost 10 years of experience with the MOCART scoring system for cartilage repair since its initial publication in 2004.

Data and Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the sample overall and by four subgroups according to implant location (patella or trochlea) and the requirement of adjunct TTT. Fisher's exact test, one-way analysis of variance or Kruskall-Wallis test was used to evaluate differences in sample characteristics across these procedural subgroups. Repeated measures analysis of variance was used to examine changes in all outcomes over time including evaluation of both a main effect and an interaction effect with type of procedural group, with models also adjusted for sex due to imbalance across the four sub-groups. For MRI evaluation, the kappa coefficient was used to assess intra-observer reliability for graft infill, while the intra-class correlation coefficient was used for the continuous MRI composite score. This was achieved by re-scoring 20 randomly selected MRI images filtered through a second time to the radiologist. Power calculations indicated that 8 patients in each subgroup would give 80% power to detect improvements in outcome from baseline of at least one standard deviation at $\alpha=0.05$ (within each subgroup). Statistical analysis was performed with Stata/IC version 13.1 for Windows (StataCorp LP, College Station TX USA).

RESULTS

Of the 47 patients in this prospective follow up, all cases were reviewed clinically and radiologically pre-operatively, and at 3 and 24 months post-surgery. Two patients (patella = 1; trochlea = 1) were unavailable at 12 month follow up (an intention to treat analysis was performed using the "last value carried forward" technique for these two cases). Table 1 displays the sample characteristics, overall and by four subgroups according to implant location and TTT. The only factor which demonstrated statistically significantly imbalance was sex, with more males in groups undergoing trochlea implants.

Patient Reported Outcome (PRO) Measures

All PRO measures demonstrated clinically and statistically significant improvements over time (Table 3). There was no significant main effect for procedure (p-values ranged from 0.221 - 0.925) and no interaction between time and procedure for all outcomes (p-values ranged from 0.543 - 0.999), with the exception of pain frequency (p=0.024). For VAS-F, the group with trochlear implants and no TTT showed a more rapid improvement to three months than the other groups but had no better long-term outcome at 12 and 24 months. All procedure groups separately demonstrated clinically and statistically significant improvements in PRO measures. Figure 1 demonstrates all KOOS subscales pre- and post-operatively for patients grouped by procedure type.

Insert Table 3 and Figure 1.

At 24 months post-surgery, 85% (n=40) of patients were satisfied with the ability of MACI to relieve their knee pain, 87% (n=41) and 78% (n=37) were satisfied with the improvement in their ability to undertake daily and recreational activities, respectively, and 62% (n=29) were satisfied with the improvement in their ability to participate in sport. Overall, 85% (n=40) of patients were satisfied with the results of their MACI surgery.

Strength and Function Measures

Six minute walk test distance demonstrated statistically and clinically significant improvement over time (Table 4), with no evidence of a main effect for procedure group (p=0.936) or interaction between procedure group and time (p=0.940, see Figure 2). All procedure groups separately demonstrated clinically and statistically significant improvements in six minute walk test distance. Knee extension ROM improved significantly over time (Table 4), with no evidence of a main effect for procedure group (p=0.936). A significant time-group interaction (p=0.023) existed due to a slightly higher improvement in those patients with trochlear grafts and adjunct TTT in 12 to 24 months related to 3 to 12 months. Flexion ROM also improved significantly over time (Table 4), with no evidence of a main effect for procedure group (p=0.670) or time-group interaction (p=0.571). Both peak extension and flexion torque improved significantly from 12 to 24 months (Table 4), with no evidence of a main effect for procedure group (p=0.321 and 0.290 respectively) or time-group interaction (p=0.994 and 0.510 respectively) (Table 4). The LSI for knee extension torque indicated a post-operative strength with no significant improvement over 12 to 24 months, whereas the mean LSI for flexion torque at 24 months was 1.01 (Table 4).

Insert Table 4 and Figure 2.

MRI Results

Evaluation of intra-observer reliability indicated perfect agreement for graft infill (kappa coefficient = 1.00) and an intra-class correlation coefficient for the MRI composite score of 0.996 (95%CI: 0.991 – 0.999), for the 20 randomly selected image pairs.

The MRI composite score demonstrated a statistically significant improvement over time (Table 4), with no evidence of a main effect for procedure group (p=0.405) or interaction between procedure group and time (p=0.899, see Figure 3). Graft infill demonstrated a statistically significant improvement over time (Table 4), with no evidence of a main effect for procedure group (p=0.502) or interaction between procedure group and time (p=0.956). At 24 months post-surgery, 40.4% (n=19) of patients exhibited complete graft infill comparable to the adjacent native cartilage, with a further 6.4% (n=3) demonstrating a hypertrophic graft. A further 31.9% (n=15) of patients exhibited 50-100% tissue infill, therefore making a combined 78.7% (n=37) with infill >50% at 24 months. Therefore, 17% (n=8) of patients exhibited <50% tissue infill and, as reported below in the complications, two patients (4.3%) demonstrated graft failure (exposed subchondral bone). The magnetic resonance images (3, 12 and 24 months post-surgery) of an asymptomatic patient at 24 months are shown in Figure 4.

Insert Figure 3 and Figure 4.

Complications and Failures

The incidence of graft hypertrophy was observed on MRI in two patients (4.3%) at 3 and 12 months, and three patients (6.4%) at 24 months post-surgery. All three cases remained asymptomatic at 24 months. One patient in this group developed a deep vein thrombosis (DVT) in the early post-operative stages, was treated accordingly and recovered without sequelae. There were two graft failures (out of 47 patients), determined via graft delamination and/or exposed subchondral bone on MRI. One patient was devoid of repair tissue at 3 months which remained on MRI at 12 and 24 months. The second patient exhibited exposed subchondral bone at 24 months post-surgery, despite scores of 3.0 and 2.85 for graft infill and the MRI composite score, respectively, at 12 months post-surgery (Figure 5).

Insert Figure 5.

DISCUSSION

While MACI has demonstrated encouraging outcomes in the treatment of articular cartilage defects in the knee,[2, 3, 11, 16] there still remains a paucity of prospective research specifically investigating its successful use in the patellofemoral joint. We undertook a prospective clinical and radiological follow up to two years in patients following MACI to address symptomatic cartilage defects on the patella or trochlea, both with and without concurrent patellofemoral malalignment.

A significant improvement was observed over the two year period in all of PRO measures. An expected decline in the Sport and Recreation subscale of the KOOS was seen from pre-surgery to 3 months post-surgery, due to the physical limitations imposed on patients at this early post-operative time in order to minimize the risk of early graft failure.[22, 41] Of the studies specifically investigating MACI in the patellofemoral joint, only Meyerkort et al.[33] employed the KOOS and SF-36, with 24 month outcomes in this study comparable to those results. Pascual-Garrido et al.[39] reported improved post-operative KOOS scores at a mean follow-up of four years in patients following periosteal-covered ACI in the patellofemoral joint, though the results for all subscales appear better in this cohort at 24 months. Several other studies investigating a variety of ACI methods performed in the patellofemoral joint have reported improved clinical outcomes up until (and beyond) 24 months, though these have not specifically employed the KOOS and SF-36 scoring tools.[17-21, 29, 30, 36, 48]

Patients demonstrated a significant improvement over the post-operative time line for the six minute walk test, active knee flexion and extension, with the primary improvement occurring between 3 and 12 months as expected. While the six minute walk test has been reported as a foundation for functional independence and an important component of many activities of normal daily living,[40] it may be argued that it is not a validated measure in MACI patients, nor is walking on level terrain at pace is not an activity that significantly troubles patients with patellofemoral symptoms. Nevertheless, we employ this assessment routinely through our clinical practice. The six minute walk distance outcomes in this study are comparable to other research.[8, 11]

While peak knee flexor strength was not significantly different between the operated and non-operated limbs throughout the post-operative time line, and in fact higher on the operated limb at 12 and 24 months, knee extensor deficiencies were observed. While it is evident that peak knee extensor strength improved significantly over the post-operative time line in the operated limb, it still remained significantly lower than the non-operated side at 12 and 24 months. Prior research has demonstrated a reduced knee strength profile even at 4-5 years post-surgery after ACI,[9, 28, 36] with Muller et al.[36] reporting greater strength deficiencies in patients undergoing patellofemoral (versus tibiofemoral) ACI, particularly in knee extensor strength. They suggested a reason for this could be the more invasive arthrotomy required with subsequent elevation of the patella, compared to performing ACI for defects on the femoral condyles. While we did not look to compare our patellofemoral MACI cohort with a MACI group specifically undergoing MACI on the weight bearing femoral condyles, the knee extensor strength deficits in the operated limb at 12 and 24 months were clear.

Graft infill and the MRI composite score both improved significantly throughout the post-operative time line. At 24 months, 46.8% of patients exhibited complete or hypertrophic tissue infill, with a total of 78.7% of patients with infill >50%. While only few studies specifically investigating ACI in the patellofemoral joint have undertaken some form of MRI-based assessment,[19, 20, 33, 47] our results appear comparable to the limited research available. Meyerkort et al.[33] recently reported >50% tissue infill in 82% of patients at five years after MACI (32% with full infill). Gobbi et al.[20] evaluated their MRI series of patellofemoral grafts based on a scoring system developed by Henderson et al.,[25] and reported that 71.9% of cases demonstrated >50% tissue infill at 24 months, with no cases of graft hypertrophy. Vanlauwe et al.[47] evaluated a series of patients that underwent characterized chondrocyte implantation in the patellofemoral joint and, at 2-4 year follow up, 61% (19 of 31) had >50% tissue infill. However, they also reported almost 30% of patients with graft hypertrophy, with four patients requiring arthroscopic intervention for ongoing mechanical complaints. This was in comparison to the four asymptomatic patients at 24 months in this study that exhibited hypertrophic grafts at 24 months.

We observed no clinical or radiological differences up until 24 months post-surgery in patients sub-grouped according to whether MACI was performed on the patella or trochlea and with/without adjunct patellofemoral realignment. It would appear that the limited studies available specifically investigating ACI/MACI in the patellofemoral joint tend to evaluate the patient cohort overall, without any statistical analysis following group stratification based on graft location. However, in contrary to our results a recent publication demonstrated significantly better outcomes in trochlea lesions compared to the patella after matrix-assisted ACI.[13] The difference in outcomes remains unknown and more research is clearly required given that, anecdotally, we have generally found trochlea lesions to be more forgiving (compared with patella lesions), irrespective of the cartilage repair method employed. This was not reflected in our clinical results with both groups producing similar outcomes.

Early reported results of ACI in the patellofemoral joint were poor since patellofemoral malalignment was not addressed prior to or at the time of chondral grafting.[4] It has been demonstrated that patients undergoing ACI in the patellofemoral joint perform better after concomitant proximal and distal realignment surgery,[26, 39] even in the absence of patellofemoral malalignment,[26] and a recent review highlighted the significant clinical improvement in patients undergoing ACI with concomitant realignment.[46] This is contrary to our results, as well as others who have demonstrated equivocal outcomes in patients with normal patellofemoral alignment compared with those undergoing concurrent TTT for malalignment.[33, 48] TTT was only performed in this series if malalignment was present. Therefore, while we do not evaluate post-transfer TT-TG distance routinely, we did assume that all patients had normal alignment at the time of (and following) MACI surgery. This was the rationale for our third hypothesis, in that a similar progression of pain, symptoms and function would exist in patients who did, or did not, undergo adjunct TTT at the time of MACI surgery.

A number of limitations existed within the present study. Firstly, we employed the KOOS, SF-36 and VAS as PRO measures in this study which have been used for chondrocyte implantation[1, 10, 31, 38, 40] and we employ routinely through our institution. As outlined by Hambly and Griva,[23] there is currently no agreement on a 'gold standard' PRO measure for the evaluation of cartilage repair surgery, let alone ACI, though certainly the KOOS is recommended for use with cartilage repair patients.[42] However, we acknowledge that other PRO scores including the International Knee Documentation Committee (IKDC) Subjective Knee Form, the Cincinnati Knee Rating System, the Lysholm score and the Tegner activity scale have been used in other studies specifically reporting on ACI in the patellofemoral joint.[17-21, 29, 30, 36, 48] Furthermore, we employed the six minute walk test as a basic measure of function and, while this test has been used previously in ACI patients,[6, 8, 11, 33, 40] to the best of our knowledge it has not been validated.

Secondly, we employed the MOCART scoring system to evaluate the grafts via MRI and MRI composite score. We acknowledge the MOCART scoring tool has not been validated against arthroscopic or histological repair tissue findings, and that there are indeed other emerging imaging methods for assessing the biochemical characteristics of repair tissue, including dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) and T2 mapping.[27, 44, 45] However, it must also be acknowledged that there is currently a relative paucity of studies specifically evaluating patellofemoral MACI with any form of MRI-based assessment. We also acknowledge there was no histological analysis provided in this study, though this was unwarranted since there have been no second-look arthroscopies and associated tissue biopsies required at this time.

This study demonstrated that MACI produced improved clinical outcomes and functional tissue infill to 24 months, in patients with full thickness cartilage defects in the patella or trochlea, supporting our first two hypotheses. Our third hypothesis was also supported, whereby we observed significant improvements in all clinical and radiological outcomes for the four individual sub-groupings based on whether MACI was performed on the patella or trochlea, and with, or without, the requirement of concurrent patellofemoral realignment. Though the availability of clinical and MRI-based assessment specifically following MACI in the patellofemoral joint is limited, this research suggests MACI does provide a suitable treatment option for cartilage defects in the knee, at least up until 24 months post-surgery. Long-term follow-up (5-10 years and beyond) is essential to confirm whether the repair tissue produced has the durability required and, if so, whether a durable tissue is reflected in clinical outcome and patient quality of life.

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FIGURE LEGENDS

Figure 1. KOOS sub-scales throughout the pre- and post-operative time line for the four individual sub-groupings based on whether MACI was performed on the patella or trochlea, and with, or without, the requirement of concurrent patellofemoral realignment. Shown are means (SD).

Figure 2. Six minute walk distance throughout the post-operative time line for the four individual sub-groupings based on whether MACI was performed on the patella or trochlea, and with, or without, the requirement of concurrent patellofemoral realignment. Shown are means (SD).

Figure 3. The MRI Composite score throughout the post-operative time line for the four individual sub-groupings based on whether MACI was performed on the patella or trochlea, and with, or without, the requirement of concurrent patellofemoral realignment. Shown are means (SD).

Figure 4. Axial fat-saturated proton density magnetic resonance images of a MACI graft (between white arrows) on the patella in a single asymptomatic patient in this study, demonstrating: 50-100% infill at 3 months (a), and equivalent signal and thickness characteristics to the adjacent native cartilage at 12 (b) and 24 (c) months post-surgery.

Figure 5. Axial fat-saturated proton density magnetic resonance images of a MACI graft (between white arrows) on the patella in a single patient in this study demonstrating: a) full

tissue infill at 3 months post-surgery; b) 50-100% infill at 12 months post-surgery, and; c) graft failure at 24 months post-surgery.

TABLE 1. Descriptive parameters for the patient cohort who underwent matrix-induced autologous chondrocyte implantation in the patellofemoral joint. Shown are means (range) for the entire group, as well as the group stratified into four groups by graft location (patella or trochlea), with or without the requirement of concurrent tibial tubercle transfer.

Variable		Total Group	Patella (with TTT)	Patella (no TTT)	Trochlea (with TTT)	Trochlea (no TTT)	*P* value
Number of Patients		47	9	15	10	13	-
Gender (males/females)		30/17	3/6	7/8	8/2	12/1	0.009[a]
Body Weight (kg)		79.7 (56.0 – 117.0)	76.2 (60.0-104.4)	76.8 (58.2-117.0)	84.8 (60.3-101.6)	81.6 (56.0-99.5)	0.312[b]
Body Mass Index		25.4 (19.5-33.8)	25.1 (20.4-33.0)	25.3 (21.1-33.8)	25.8 (19.5-31.1)	25.6 (19.6-30.7)	0.973[b]
Age (y)		37.6 (20-61)	37.4 (25-49)	37.7 (25-61)	36.2 (23-45)	38.5 (20-54)	0.959[b]
	20-29	11	2	5	2	2	-
	30-39	17	2	4	5	6	-
	40-49	13	5	3	3	2	-
	50-62	6	0	3	0	3	-
Defect Size (cm^2)		3.3 (1.0-7.2)	3.4 (1.0-5.0)	3.1 (2.3-6.0)	3.2 (1.0-6.0)	3.6 (1.0-7.2)	0.994[c]
	≤1.0	4	1	0	1	2	-
	1.1-2.0	7	2	0	2	3	-
	2.1-3.0	16	1	11	2	2	-
	3.1-4.0	5	1	2	2	0	-
	4.1-5.0	10	4	1	2	3	-
	≥5.1	5	0	1	1	3	-
Prior Procedures		1.2 (0-3)	1.0 (0-3)	1.4 (0-3)	1.1 (0-2)	1.1 (0-3)	0.760[c]
Duration of Symptoms (y)		7.3 (1-20)	7.6 (2-20)	8.4 (1-18)	6.8 (1-18)	6.2 (1-20)	0.752[c]

[a] Fisher's exact test; [b] analysis of variance; [c] Kruskall-Wallis test.

TABLE 2. Progression of post-operative weight-bearing, knee range of motion and exercise rehabilitation following matrix-induced autologous chondrocyte implantation (MACI) in the patellofemoral joint.

Post-operative Timeline	Rehabilitation Guidelines
Week 1-3	• Weight-bearing Status: ≤ 20% BW (week 1-2) to 30% BW (week 3) • Ambulatory Aids: 2 crutches used at all times • Knee ROM: active ROM from 0-30° (week 1) to 0-60° (week 3) • Knee Bracing: 0-30° (week 1-2) to 0-45° (week 3) • Treatment/Rehabilitation: circulation, isometric and straight leg exercises, passive and active knee flexion exercises, remedial massage, soft tissue & patella mobilisation, CPM, cryotherapy and hydrotherapy
Week 4-5	• Weight-bearing Status: 40% BW (week 4) to 80% BW (week 5) • Ambulatory Aids: 1-2 crutches used at all times • Knee ROM: active ROM from 0-90° (week 4) to 0-110° (week 5) • Knee Bracing: 0-60° (week 4) to 0-90° (week 5) • Treatment/Rehabilitation: introduction of calf raises, weighted hip adduction and abduction, trunk strengthening, recumbent cycling
Week 6-12	• Weight-bearing Status: Progress to full weight bearing (week 6-12) • Ambulatory Aids: as required • Knee ROM: active ROM from 0-125° (week 6) to full range (week 7) • Knee Bracing: Full knee flexion • Treatment/Rehabilitation: introduction of proprioceptive/balance activities, cycling, walking, resistance and CKC activities
3-6 months	• Treatment/Rehabilitation: introduction of more demanding OKC (terminal leg extension) and CKC (inner range quadriceps and modified leg press), upright cycling, rowing ergometry and elliptical trainers
6-9 months	• Treatment/Rehabilitation: increase difficulty of proprioceptive/balance, OKC & CKC exercises (ie. step ups/downs, modified squats), introduction of controlled mini trampoline jogging
9-12 months	• Treatment/Rehabilitation: increase difficulty of CKC exercises (ie. lunge and squat activities on unstable surfaces), introduction of agility drills relevant to patient's sport, return to competitive activity after 12 months

ROM = range of motion; BW = body weight; CPM = continuous passive motion; CKC = closed kinetic chain; OKC = open kinetic chain

TABLE 3. Patient-reported outcome measures pre- and post-surgery (mean(SD)), with estimated mean differences (95% CI, p-value) from pre-surgery.

	Mean (SD)	Difference	95% CI	p-value
KOOS Pain				
Pre-surgery	61.4(15.6)			
3 months	68.5 (14.0)	7.1	1.4 - 12.8	0.015
1 year	79.2 (15.7)	17.8	13.1 - 22.5	<0.001
2 years	83.3 (11.4)	22.0	16.4 - 27.5	<0.001
KOOS Symptoms				
Pre-surgery	64.7 (17.2)			
3 months	77.7 (13.1)	13.0	8.3 - 17.6	<0.001
1 year	82.9 (11.7)	18.2	13.4 - 23.0	<0.001
2 years	86.4 (9.8)	21.7	16.9 - 26.5	<0.001
KOOS ADL				
Pre-surgery	69.0 (16.1)			
3 months	71.1 (17.5)	2.2	-3.8 - 8.2	0.481
1 year	86.0 (12.4)	17.0	11.7 - 22.3	<0.001
2 years	87.5 (11.0)	18.6	13.8 - 23.3	<0.001
KOOS Sport				
Pre-surgery	24.6 (21.0)			
3 months	8.1 (12.6)	-16.5	-25.3 - -7.8	<0.001
1 year	32.6 (26.2)	7.9	-0.5 - 16.3	0.064
2 years	50.1 (29.4)	25.5	17.8 - 33.1	<0.001
KOOS QOL				
Pre-surgery	22.9 (16.0)			
3 months	29.4 (18.1)	6.5	0.3 - 12.6	0.039
1 year	45.4 (20.9)	22.5	15.8 - 29.2	<0.001
2 years	53.3 (23.0)	30.4	23.6 - 37.3	<0.001
SF-36 PCS				
Pre-surgery	34.9 (9.7)			
3 months	36.8 (8.9)	1.9	-1.2 - 5.1	0.225
1 year	44.2 (8.8)	9.3	6.3 - 12.3	<0.001
2 years	47.1 (10.20	12.2	9.3 - 15.0	<0.001
SF-36 MCS				
Pre-surgery	51.3 (8.8)			
3 months	55.6 (8.8)	4.2	2.7 - 5.8	<0.001
1 year	55.6 (6.5)	4.3	1.8 - 6.8	0.001
2 years	55.7 (6.1)	4.4	1.7 - 7.0	0.002
Pain Frequency (VAS)				
Pre-surgery	6.4 (1.6)			
3 months	3.9 (2.1)	-2.5	-3.1 - -2.0	<0.001
1 year	2.3 (1.6)	-4.1	-4.7 - -3.5	<0.001
2 years	2.1 (1.4)	-4.3	-5.0 - -3.7	<0.001
Pain Severity (VAS)				
Pre-surgery	5.4 (1.4)			
3 months	2.4 (0.9)	-2.9	-3.4 - -2.4	<0.001
1 year	2.0 (1.4)	-3.4	-3.8 - -2.9	<0.001
2 years	1.8 (1.1)	-3.6	-4.1 - -3.1	<0.001

ADL – Activities of Daily Living; QOL – Quality of Life; SF-36 – 36 item Short Form Health Survey; PCS – Physical Component Score; MCS – Mental Component Score; VAS – Visual Analogue Pain Scale.

TABLE 4. Six minute walk test, strength and magnetic resonance imaging (MRI) measures pre- and post-operatively (mean (SD)), with estimated mean differences (95% CI, p-value) from pre-surgery.

	Mean (SD)	Difference	95% CI	p-value
Six minute Walk test (m)				
3 months	490 (104)			
1 year	607 (80)	117	98-137	<0.001
2 years	618 (77)	129	110-148	<0.001
Knee Extension (deg)				
3 months	-0.2 (0.9)			
1 year	-0.8 (1.4)	-0.6	-1.0 - -0.2	0.004
2 years	-0.7 (1.3)	-0.5	-0.9 - -0.1	0.010
Knee Flexion (deg)				
3 months	132.1(13.9)			
1 year	141.0 (7.4)	8.9	5.8-12.1	<0.001
2 years	140.9 (6.9)	8.8	5.7-11.9	<0.001
Peak Extension Torque (Nm)				
1 year	124.9 (60.0)			
2 years	138.3 (58.2)	13.4	4.6-22.1	0.003
Limb Symmetry Index (Extension)				
1 year	0.83 (0.20)			
2 years	0.86 (0.20)	0.03	-0.04 – 0.10	0.372
Peak Flexion Torque (Nm)				
1 year	106.7 (39.3)			
2 years	119.8 (39.0)	13.1	5.1-21.1	0.001
Limb Symmetry Index (Flexion)				
1 year	0.95 (0.20)			
2 years	1.01 (0.16)	0.06	0.00 – 0.12	0.070
MRI Composite Score				
3 months	2.9 (0.5)			
1 year	3.2 (0.4)	0.3	0.1-0.4	<0.001
2 years	3.2 (0.6)	0.3	0.2-0.5	<0.001
MRI Infill				
3 months	2.9 (0.6)			
1 year	3.2 (0.7)	0.3	0.1-0.5	0.001
2 years	3.3 (0.8)	0.3	0.2-0.6	0.001