A Randomized Trial Comparing Accelerated and Traditional Approaches to Postoperative Weightbearing Rehabilitation After Matrix-Induced Autologous Chondrocyte Implantation : Findings at 5 Years

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A Randomized Trial Comparing Accelerated and Traditional Approaches to Postoperative Weightbearing Rehabilitation After Matrix-Induced Autologous Chondrocyte Implantation

Findings at 5 Years

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Background: While structured postoperative rehabilitation after matrix-induced autologous chondrocyte implantation (MACI) is considered critical, very little has been made available on how best to progressively increase weightbearing and exercise after surgery.

Hypothesis: A significant improvement will exist in clinical and magnetic resonance imaging (MRI)–based scoring measures to 5 years after surgery. Furthermore, there will be no significant differences in outcomes in MACI patients at 5 years when comparing a traditional and an accelerated postoperative weightbearing regimen. Finally, patient demographics, cartilage defect parameters, and injury/surgery history will be associated with graft outcome.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: Clinical and radiological outcomes were studied in 70 patients who underwent MACI to the medial or lateral femoral condyle, in conjunction with either an ''accelerated'' or a ''traditional'' approach to postoperative weightbearing rehabilitation. Under the accelerated protocol, patients reached full weightbearing at 8 weeks after surgery, compared with 11 weeks for the traditional group. Clinical measures (Knee Injury and Osteoarthritis Outcome Score [KOOS], Short-Form Health Survey [SF-36], visual analog scale [VAS], 6-minute walk test, and knee range of motion) were assessed before surgery and at 3, 6, 12, and 24 months and 5 years after surgery. High-resolution MRI was undertaken at 3, 12, and 24 months and 5 years after surgery and assessed 8 previously defined pertinent parameters of graft repair as well as a combined MRI composite score. The association between clinical and MRI-based outcomes, patient demographics, chondral defect parameters, and injury/surgery history was investigated.

Results: Of the 70 patients recruited, 63 (31 accelerated, 32 traditional) underwent clinical follow-up at 5 years; 58 (29 accelerated, 29 traditional) also underwent radiological assessment. A significant time effect ($P < .05$) was demonstrated for all clinical and MRI-based scores over the 5-year period. While the VAS demonstrated significantly less frequent pain at 5 years in the accelerated group, there were no other significant differences between the 2 groups. Between 24 months and 5 years, a significant improvement ($P < .05$) in both groups was observed for the sport and recreation subscale of the KOOS as well as a significant decrease ($P < .05$) in active knee extension for the traditional group. There were no significant differences ($P > .05$) in the MRI-based scores between 24 months and 5 years after surgery. Patient age and defect size exhibited significant negative correlations ($P < .05$) with several MRI-based outcomes at 5 years, while there were no significant correlations ($P > .05$) between clinical and MRI-based outcomes. At 5 years after surgery, 94% and 95% were satisfied with the ability of MACI to relieve their knee pain and improve their ability to undertake daily activities, respectively.

Conclusion: The outcomes of this randomized trial demonstrate a safe and effective accelerated rehabilitation protocol as well as a regimen that provides comparable, if not superior, clinical outcomes to patients throughout the postoperative timeline.

Keywords: matrix-induced autologous chondrocyte implantation; partial weightbearing; rehabilitation; gait

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Matrix-induced autologous chondrocyte implantation (MACI) has become an established technique for the repair of full-thickness chondral defects in the knee.[2,3,14,15] It is

a 2-stage procedure with an initial arthroscopic harvest of healthy cartilage, isolation and expansion of chondrocytes ex vivo, and reimplantation of cells into the chondral defect. Over time and with an appropriate postoperative mechanical stimulus, chondrocytes can differentiate into a durable load-bearing tissue. Therefore, a successful MACI outcome should return the patient to a pain-free and normally active lifestyle.

Several factors have been proposed to influence patient outcome and quality of repair tissue following MACI: (1) successful cell culturing, (2) efficiency of the surgical procedure, (3) patient cooperation in all aspects of the preoperative and postoperative program, and (4) timely progression of weightbearing and postoperative rehabilitation. A graded program incorporating controlled exercise and progressive partial weightbearing is recommended after the general ACI procedure.[12,17] While several articles have outlined the importance of structured postoperative rehabilitation after ACI for graft protection, the facilitation of chondrocyte differentiation and development, and the return of the patient to normal physical function,[8,17,19,20,30,31] very little information has been made available on how best to progressively increase load bearing and exercise after surgery.

We presented an accelerated MACI weightbearing rehabilitation protocol[11-13] that demonstrated tolerance by both the patient and the graft to loading throughout the return to full weightbearing over a 3-month period from surgery. Until 2 years after surgery, significant improvement was reported in pain, symptoms,[13] and magnetic resonance imaging (MRI)–based outcomes[11] in patients after either a traditional or an accelerated return to full weightbearing, although significantly less severe pain and superior 6-minute walk distance were reported in the accelerated group.[13] In this article, we present 5-year clinical and radiological outcomes. First, we hypothesized that there would be a significant improvement in clinical and MRI-based scoring measures over the preoperative and postoperative timeline. Second, we hypothesized that there would be no significant differences in outcomes in MACI patients at 5 years after surgery when comparing these differing rehabilitation regimens. Finally, we hypothesized that patient demographics, cartilage defect parameters, and injury/surgery history would be associated with graft outcome, while clinical and MRI-based outcomes would also be associated at 5 years after surgery.

MATERIALS AND METHODS

Patients

This trial included 70 patients (47 male, 23 female) who had undergone MACI to address localized, full-thickness medial or lateral femoral condylar defects to the knee. A block randomization procedure (gender, age <40 or >40 years) was used to allocate patients to either a traditional (n = 36) or an accelerated (n = 34) postoperative weightbearing rehabilitation protocol. Of these 70 patients, 63 (31 accelerated, 32 traditional) underwent clinical follow-up at 5 years, of which 58 (29 accelerated, 29 traditional) also underwent radiological assessment. Therefore, the results presented in this article are based on the 63 patients who had a complete clinical follow-up through to 5 years after surgery (Figure 1 and Appendix 1, available in the online version of this article at http://ajs.sagepub.com/supplemental/).

Only patients who underwent MACI to localized, full-thickness medial or lateral femoral condylar defects to the knee participated in this study. Patients were included if they were 15 to 65 years of age and deemed able to follow the rehabilitation program. Patients were excluded if they had a body mass index (BMI) >35, ligamentous instability, varus/valgus abnormalities (>5° tibiofemoral anatomic angle), had undergone a prior extensive meniscectomy, or had ongoing progressive inflammatory arthritis. 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] Preoperatively, patients were screened for clinical knee joint instability by an orthopaedic specialist, and all patients underwent MRI to approximately assess the location, size, and severity of the chondral defect (if any) as well as any other soft tissue damage incorporating the menisci or ligamentous structures.

The sample sizes used for patient recruitment were calculated based on a minimum 7-point change in the primary outcome variable, the pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS). A priori power calculation demonstrated that at least 22 participants in each of the 2 groups were required to reveal differences at the 5% significance level, with 80% power. Patients enrolled in this trial were recruited at the Hollywood Functional Rehabilitation Clinic in association with The University of Western Australia. This trial obtained approval from The University of Western Australia (RA/4/3/0464) and the Hollywood Private Hospital (HPH145) Human

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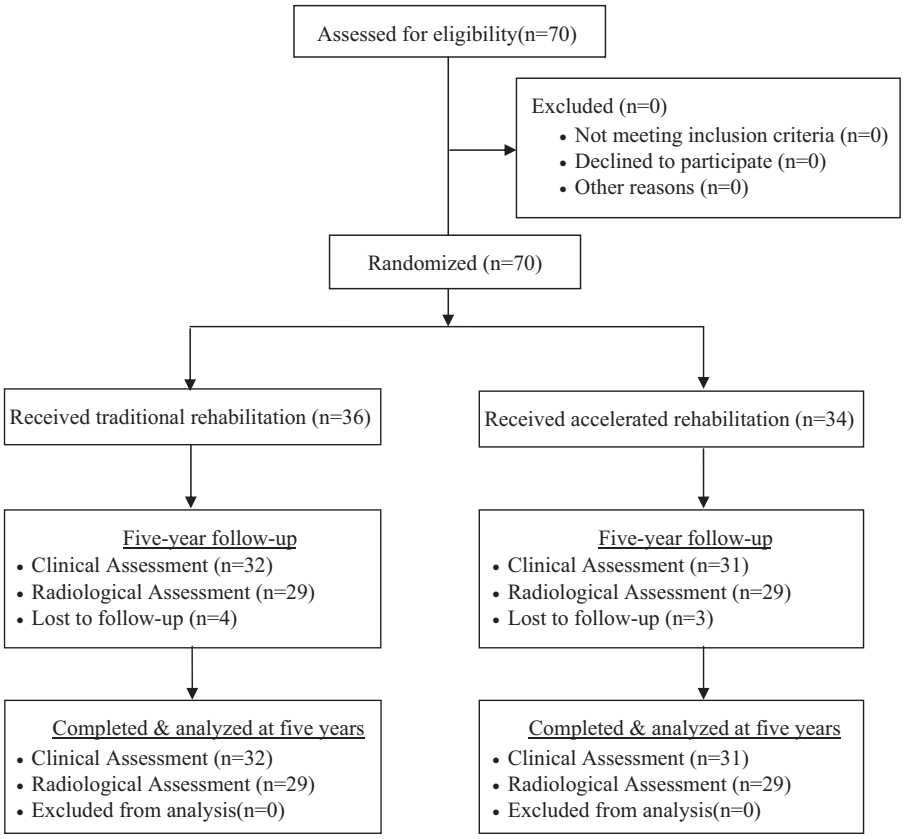

Figure 1. Patient randomization and assessment throughout the trial.

Research Ethics Committee and was undertaken according to the Declaration of Helsinki. All patients provided their written informed consent before study participation.

MACI Technique

The surgical technique has been previously described.[11-13] Briefly, MACI is a 2-stage technique, where arthroscopic surgery was performed to harvest a sample of normal articular cartilage from a nonweightbearing area of the knee. After chondral harvest, chondrocytes were isolated, cultured, and seeded onto a type I/III collagen membrane (ACI-Maix, Matricel GmbH, Herzogenrath, Germany) ex vivo over a 6- to 8-week period. At the time of second-stage implantation, the chondral defect was initially prepared by removing all damaged cartilage down to, but not through, the subchondral plate. The resultant defect was measured and used to shape the membrane, which was pressed into the defect and secured using a thin layer of fibrin glue. The wound was closed after assessment of graft stability.

Postoperative Rehabilitation

After the second-stage graft implantation, immediate postoperative inpatient rehabilitation consisted of continuous passive motion (0° to 30°) within 12 to 24 hours after surgery to reduce the chance of intra-articular adhesions; active dorsiflexion 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[4,27]; cryotherapy to control edema; and teaching of proficient toe-touch ambulation through the affected limb.

After discharge from the hospital, patients attended the rehabilitation clinic on 2 occasions per week for the duration of the postoperative rehabilitation program. Patients were randomized into either a traditional (conservative) or an accelerated load-bearing rehabilitation protocol over an 8- to 12-week period (Table 1).[11-13] Weightbearing replication training was an important component of each and every session up until the time the patient returned to full weightbearing. The bathroom scale method was used to teach patients the weightbearing restrictions.[10,17] While mixed results surround the evaluation of the "bathroom scale method" as an effective tool for teaching weightbearing restrictions, with both good[23,37] and poor[6,7,16] replication abilities reported, this method still remains the most practical and widely used modality for teaching weightbearing restrictions.[10,17] In addition, our research investigating the ability of MACI patients to replicate desired weightbearing levels throughout their rehabilitation program has demonstrated improved accuracy with higher frequency of practice.[10] Furthermore, this study looked at the time to full weightbearing in addition to the weightbearing gradient, whereby full weightbearing was ensured in the traditional group at 11 weeks and at

TABLE 1
Load-Bearing Gradients Followed by Matrix-Induced Autologous Chondrocyte Implantation Patients in the Traditional and Accelerated Rehabilitation Groups[a]

	Traditional Group			Accelerated Group		
Weeks After Surgery	Weightbearing (%BW)	Crutches	Brace	Weightbearing (%BW)	Crutches	Brace
2	≤20%	2	Y	≤20%	2	Y
3	≤20%	2	Y	30%	2	Y
4	≤20%	2	Y	40%	2	Y
5	≤20%	2	Y	50%	2	Y
6	50%	1	Y	60%	1	Y
7	60%	1	Y	80%	1	Y
8	70%	1	Y	100%	1	Y
9	80%	1	Y	100%	0	N
10	90%	1	Y	100%	0	N
11	100%	1	Y	100%	0	N
12	100%	0	N	100%	0	N

[a]BW, body weight; Y, yes; N, no.

8 weeks in the accelerated group, once use of crutches was ceased. Apart from the gradient and time to attain full weightbearing, all other aspects of rehabilitation remained the same for the 2 groups, while further education and advice were provided up to the 12-month time point as required (Appendix 2, available online).

Clinical Assessment

Several clinical scores were used to evaluate patient outcome before surgery and at 3, 6, 12, and 24 months and 5 years after surgery. These included 3 subjective questionnaires: (1) the KOOS[33] to assess knee pain, symptoms, activities of daily living, sport and recreation, and knee-related quality of life; (2) the visual analog scale (VAS) to assess the frequency (VAS-F) and severity (VAS-S) of knee pain on a scale of 0 to 10; and (3) the Short-Form Health Survey (SF-36), which evaluated the general health of the patient, producing a mental and a physical component score.[1] A patient satisfaction questionnaire was also employed at 5 years after 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 and improving the ability to perform normal daily activities and their ability to participate in sport. Furthermore, the 6-minute walk test[12,32] and maximal active knee flexion and extension range were assessed. Defect size was calculated based on the dimensions of the chondral graft at the time of second-stage implantation, while the number of prior cartilage repair procedures and the duration of preoperative symptoms were obtained via a thorough patient history.

MRI Assessment

Repair tissue was assessed using high-resolution MRI at 3, 12, and 24 months as well as 5 years after surgery. All MRI scans were performed using a Siemens Symphony 1.5-T scanner (Siemens, Erlangen, Germany). 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 also obtained (slice thickness, 3-4 mm; field of view, 14-15 cm; minimum 224 matrix in at least one axis).

The MRI evaluation employed in this study has been previously outlined[11] and closely followed MRI scoring systems previously reported for ACI assessment.[32,36] The MRI parameters (signal intensity, graft infill, border integration, surface contour, structure, subchondral lamina, subchondral bone, and effusion) were selected to best describe the morphological characteristics and signal intensity of the repair tissue. These were scored individually from 1 to 4 (1 = poor, 2 = fair, 3 = good, 4 = excellent) in comparison with the adjacent native cartilage, while an additional score of 3.5 for "graft infill" was awarded for a fifth level (very good) corresponding with "graft hypertrophy," as indicated by previous work.[25,36] A combined MRI composite score was also calculated by multiplying each individual score by a weighting factor[32] and adding the scores together.[11] This composite score was also scored from 1 to 4 (1 = poor, 2 = fair, 3 = good, 4 = excellent). The MRI evaluation was performed by an independent, experienced musculoskeletal radiologist, who was blinded to the clinical details and clinical outcome assessment.

Statistical Analysis

Repeated-measures analysis of variance (ANOVA) was used to investigate the progression of the clinical and MRI scores over the 5-year postoperative timeline between the accelerated and traditional groups. Independent *t* tests were used to evaluate the difference in clinical and MRI scores between the 2 groups at 5 years as well as to investigate differences between the specific assessment time

TABLE 2
Summary of Preoperative and Postoperative Clinical Results for the Accelerated and Traditional Groups[a]

	Accelerated Group			Traditional Group			*P* Values		
Variable	Presurgery	24 Months	5 Years	Presurgery	24 Months	5 Years	Time Effect	Group Effect	Interaction Effect
KOOS									
Pain	69.81 (3.21)	86.15 (2.82)	85.49 (3.06)	67.87 (3.21)	82.5 (2.82)	86.04 (2.34)	<.0001	.243	.354
Symptoms	74.52 (3.24)	88.04 (2.59)	86.36 (13.07)	68.57 (3.24)	82.86 (2.59)	83.50 (4.23)	<.0001	.260	.585
ADL	81.94 (3.18)	92.79 (2.36)	92.34 (2.18)	76.85 (3.18)	90.32 (2.36)	93.24 (1.84)	<.0001	.256	.354
SR	29.42 (3.18)	61.17 (5.80)	71.85 (4.73)	22.75 (3.18)	55.00 (5.80)	62.14 (24.21)	<.0001	.597	.534
QOL	36.98 (3.18)	59.59 (4.33)	62.21 (4.46)	29.68 (3.18)	58.75 (4.33)	62.94 (4.44)	<.0001	.714	.564
SF-36									
PCS	41.47 (3.18)	49.79 (1.80)	48.87 (1.66)	37.11 (3.18)	47.02 (1.80)	47.74 (2.02)	<.0001	.123	.289
MCS	51.17 (3.18)	55.95 (1.07)	55.42 (1.36)	52.33 (3.18)	56.11 (1.07)	54.00 (1.64)	.001	.097	.302
VAS									
Frequency	4.77 (0.50)	2.15 (0.46)	2.16 (0.46)	5.39 (0.50)	2.86 (0.46)	3.26 (0.30)	<.0001	.016	.484
Severity	4.55 (0.45)	1.97 (0.33)	2.22 (0.40)	4.35 (0.45)	2.48 (0.33)	2.29 (0.31)	<.0001	.415	.434
6-minute walk distance, m	556.8 (20.49)	661.5 (20.1)	630.6 (20.5)	528.2 (20.49)	580.7 (20.1)	616.1 (15.1)	<.0001	.177	.481
Maximal knee flexion, deg	135.4 (2.3)	143.6 (1.58)	139.8 (1.5)	128.5 (2.4)	139.5 (1.6)	138.7 (1.3)	<.0001	.281	.131
Maximal knee extension, deg	0.4 (0.4)	–0.7 (0.2)	–0.6 (0.3)	0.7 (0.4)	0.1 (0.2)	–0.3 (0.5)	.002	.306	.884

[a]Data are expressed as mean (standard error). KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; SR, sport and recreation; QOL, quality of life; SF-36, Short-Form Health Survey; PCS, physical component score; MCS, mental component score; VAS, visual analog scale.

points. Correlational analysis of MRI outcomes with patient demographics (age, BMI), defect parameters (size), injury/surgery history (prior procedures, duration of symptoms), and clinical scores (KOOS, SF-36, VAS, 6-minute walk distance) was undertaken using the Spearman correlation coefficient to determine any association between graft and patient parameters at 5 years after surgery. For MRI assessment, an intraobserver reliability assessment using the Spearman rank-order correlation was undertaken for the 8 pertinent MRI scores, and the MRI composite score, using 20 randomly selected images taken throughout the postoperative timeline (3, 12, 24, or 60 months after surgery), filtered through a second time to the radiologist. Statistical analysis was performed using SPSS software (version 17.0, SPSS Inc, Chicago, Illinois), while statistical significance was determined at $P < .05$.

RESULTS

There were no significant differences in any of the patient or defect descriptive parameters between the 2 groups before surgery (Appendix 1, available online). Over the 5-year postoperative period, there was a significant time effect ($P < .05$) for all clinical scores (Table 2 and Appendix 3, available online). While a significant group effect ($P < .05$) was evident for VAS-F, there were no significant differences between the 2 groups in any of the other subjective or functional measures (Table 2). Independent t tests at 5 years demonstrated a significantly lower ($P < .05$) VAS-F in the accelerated group when compared with the traditional group (Table 3). Independent t tests also demonstrated a significant improvement ($P < .05$) in both groups for the sport and recreation subscale of the KOOS, between 24 months and 5 years, as well as a significant decrease ($P < .05$) in active knee extension for the traditional group. There were no significant changes ($P > .05$) in any of the other clinical scores between 24 months and 5 years.

Of the 63 patients who completed the satisfaction questionnaire at 5 years after surgery, 94% (n = 59) were satisfied with the ability of MACI to relieve their knee pain, 95% (n = 60) were satisfied with the improvement in their ability to undertake daily activities, and 76% (n = 48) were satisfied with the improvement in their ability to

TABLE 3
Independent *t* Tests Between the Accelerated and Traditional Groups for All Clinical and Radiological Results at 5 Years After Surgery[a]

Variable	Accelerated Group	Traditional Group	*P* Value
Graft infill	3.23 (0.17)	3.15 (0.24)	.783
Signal intensity	2.79 (0.13)	2.75 (0.20)	.861
Border integration	2.92 (0.17)	2.50 (0.22)	.138
Surface contour	2.88 (0.18)	2.45 (0.23)	.156
Structure	3.08 (0.19)	3.15 (0.22)	.819
Subchondral lamina	3.75 (0.09)	3.80 (0.09)	.702
Subchondral bone	2.54 (0.19)	2.65 (0.25)	.730
Effusion	3.75 (0.09)	3.55 (0.11)	.171
MRI composite score	3.01 (0.12)	2.91 (0.17)	.614
Clinical outcomes measure			
KOOS (pain)	85.49 (3.06)	86.04 (2.34)	.892
KOOS (symptoms)	86.36 (13.07)	83.50 (4.23)	.545
KOOS (ADL)	92.34 (2.18)	93.24 (1.84)	.762
KOOS (SR)	71.85 (4.73)	62.14 (24.21)	.179
KOOS (QOL)	62.21 (4.46)	62.94 (4.44)	.909
SF-36 (PCS)	48.87 (1.66)	47.74 (2.02)	.665
SF-36 (MCS)	55.42 (1.36)	54.00 (1.64)	.506
VAS (frequency)	2.16 (0.46)	3.26 (0.30)	.013
VAS (severity)	2.22 (0.40)	2.29 (0.31)	.905
6-minute walk test, m	630.6 (20.5)	616.1 (15.1)	.593
Knee flexion, deg	139.8 (1.5)	138.7 (1.3)	.585
Knee extension, deg	–0.6 (0.3)	–0.3 (0.3)	.590

[a]Data are expressed as mean (standard error). MRI, magnetic resonance imaging; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; SR, sport and recreation; QOL, quality of life; SF-36, Short-Form Health Survey; PCS, physical component score; MCS, mental component score; VAS, visual analog scale.

participate in sport. Overall, 94% (n = 59) of patients were satisfied with the results of their MACI surgery.

Initial evaluation of intraobserver reliability for the MRI scoring method indicated a significant correlation ($P < .05$) between MRI-based scores within each of the 8 pertinent MRI scoring variables (signal intensity $\rho = 1.00$; graft infill $\rho = .949$; border integration $\rho = .982$; surface contour $\rho = 1.00$; structure $\rho = .840$; subchondral lamina $\rho = 1.00$; subchondral bone $\rho = .920$; and effusion $\rho = .993$), and the MRI composite score ($\rho = .811$), for the 20 randomly selected image pairs.

Over the 5-year postoperative period, there was a significant improvement ($P < .05$) in the MRI composite score (Figure 2) as well as individual parameters of graft infill (Figure 3), signal intensity, tissue structure, subchondral lamina, and subchondral bone (Table 4). There were no significant differences over time between the 2 groups in any of the composite or individual graft scoring measures (Table 4), while there were no differences between the 2 groups, specifically at 5 years after surgery, as demonstrated by the independent *t* tests (Table 3). Despite the deterioration in the MRI composite score (Figure 2) and graft infill (Figure 3) observed from 12 months to 5 years after surgery, independent *t* tests revealed no significant difference ($P > .05$) in these MRI-based scores between 12 and 24 months and 5 years after

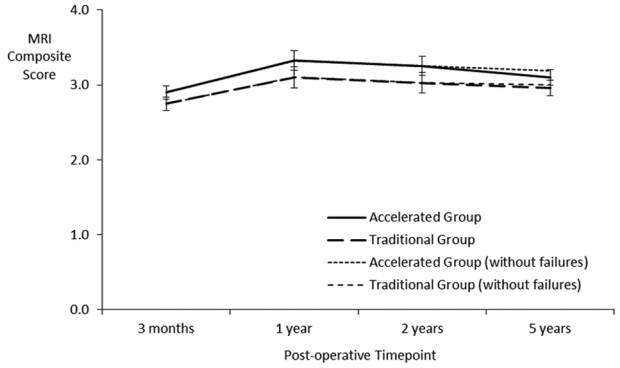

Figure 2. Change in the magnetic resonance imaging composite score over the 5-year postoperative period for the accelerated and traditional patient groups.

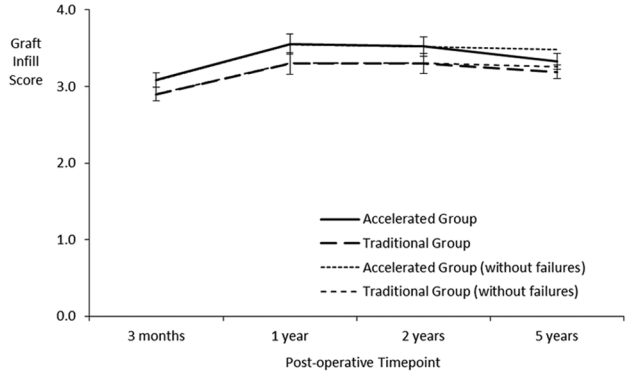

Figure 3. Change in graft infill over the 5-year postoperative period for the accelerated and traditional patient groups.

surgery, with 5-year scores still rating significantly better ($P < .05$) than at 3 months.

At 5 years after surgery, 83% (n = 24) of both rehabilitation groups demonstrated good to excellent tissue infill (Appendix 4, available online). Of the 58 grafts assessed by MRI in this cohort, further stratification by defect size demonstrated a 5-year MRI composite score mean of 3.30 for lesions ≤ 1 cm^2 (n = 7), 2.98 for lesions 1.1 to 2.0 cm^2 (n = 11), 3.17 for lesions 2.1 to 3.0 cm^2 (n = 5), 3.25 for lesions 3.1 to 4.0 cm^2 (n = 5), 2.89 for lesions 4.1 to 5.0 cm^2 (n = 6), 3.10 for lesions 5.1 to 7.5 cm^2 (n = 14), and 1.63 for lesions 7.6 to 10.0 cm^2 (n = 10). Figure 4 demonstrates the successful development of a postoperative MACI graft, as assessed via MRI, throughout the postoperative timeline to 5 years after surgery.

At 5 years after surgery, the incidence of graft hypertrophy was 24% (n = 7) and 20% (n = 6) of accelerated and traditional patients, respectively. These were nonsymptomatic and only diagnosed through the 5-year MRI evaluation. There were 5 graft failures (3 traditional, 2 accelerated) as assessed by MRI, indicated by delaminated grafts or repair sites devoid of repair tissue. While one of these was a graft delamination that occurred between 6 and 9 months after

TABLE 4
Postoperative MRI Assessment of Grafts for the Accelerated and Traditional Rehabilitation Groups[a]

	Accelerated Group				Traditional Group				*P* Values		
Variable	3 Months	12 Months	24 Months	5 Years	3 Months	12 Months	24 Months	5 Years	Time Effect	Group Effect	Interaction Effect
Graft infill	2.97 (0.16)	3.48 (0.16)	3.40 (0.17)	2.79 (0.13)	2.80 (0.16)	3.30 (0.16)	3.30 (0.16)	2.75 (0.20)	<.0001	.287	.601
Signal intensity	1.90 (0.11)	2.93 (0.17)	2.76 (0.14)	3.23 (0.17)	2.22 (0.10)	2.94 (0.17)	2.81 (0.13)	3.15 (0.24)	<.0001	.878	.272
Border integration	2.77 (0.19)	2.90 (0.19)	2.93 (0.21)	2.92 (0.17)	2.66 (0.18)	2.84 (0.19)	2.75 (0.20)	2.50 (0.22)	.329	.186	.934
Surface contour	2.90 (0.15)	2.80 (0.18)	2.97 (0.20)	2.88 (0.18)	2.81 (0.15)	2.81 (0.17)	2.72 (0.19)	2.45 (0.23)	.071	.125	.076
Structure	3.40 (0.18)	3.33 (0.19)	3.30 (0.19)	3.08 (0.19)	3.53 (0.17)	3.41 (0.18)	3.22 (0.18)	3.15 (0.22)	.008	.694	.460
Subchondral lamina	3.20 (0.14)	3.80 (0.07)	3.90 (0.05)	3.75 (0.09)	3.34 (0.14)	3.81 (0.07)	3.97 (0.05)	3.80 (0.09)	<.0001	.566	.639
Subchondral bone	2.97 (0.14)	2.97 (0.15)	2.43 (0.19)	2.54 (0.19)	2.75 (0.14)	2.91 (0.14)	2.75 (0.18)	2.65 (0.25)	.006	.715	.305
Effusion	3.73 (0.10)	3.87 (0.08)	3.67 (0.10)	3.75 (0.09)	3.50 (0.10)	3.69 (0.08)	3.56 (0.09)	3.55 (0.11)	.059	.116	.556
MRI composite score	2.81 (0.10)	3.21 (0.13)	3.14 (0.12)	3.01 (0.12)	2.80 (0.10)	3.15 (0.12)	3.07 (0.11)	2.91 (0.17)	<.0001	.303	.767

[a]Data are expressed as mean (standard error). Scoring of the 8 individual magnetic resonance imaging (MRI) parameters and calculation of the MRI composite score (1 = poor, 2 = fair, 3 = good, 4 = excellent) in comparison to the adjacent native cartilage.

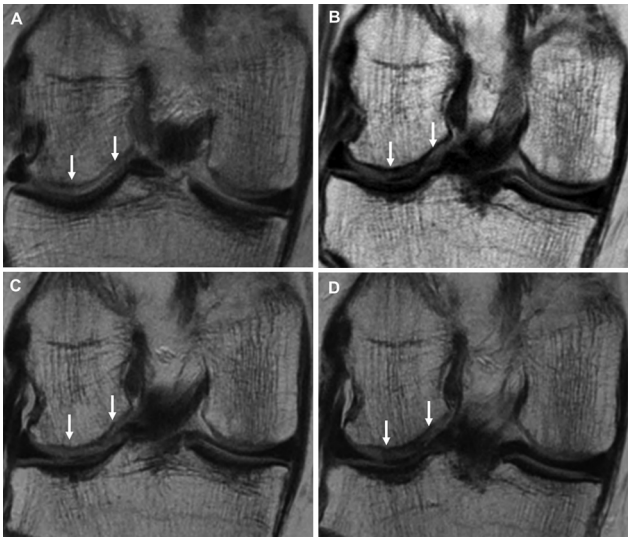

Figure 4. Proton density fast spin echo magnetic resonance images of a matrix-induced autologous chondrocyte implantation (MACI) graft (between white arrows) to the lateral femoral condyle. Images are of the same patient and representative of (A) 3 months after surgery with a hyperintense signal and reduced thickness compared with the adjacent native cartilage, (B) 12 months after surgery with similar thickness to the adjacent native cartilage, (C) 24 months after surgery with equivalent signal and infill characteristics as well as good integration with the adjacent native cartilage and underlying bone, and (D) 5 years after surgery with maintenance of the MACI graft.

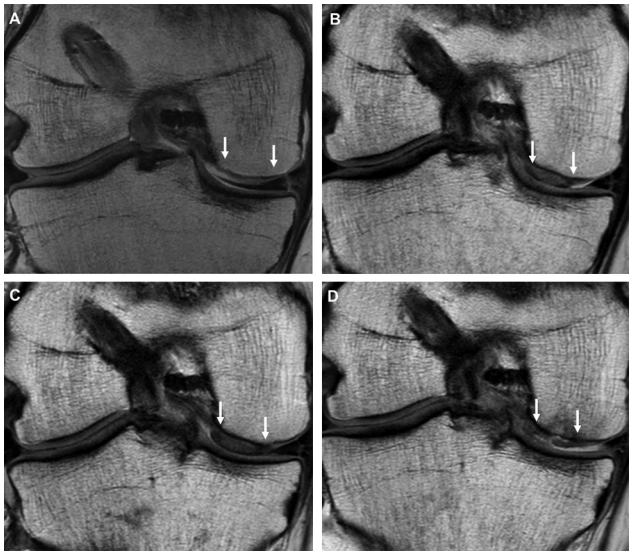

Figure 5. Proton density fast spin echo magnetic resonance images of a failed matrix-induced autologous chondrocyte implantation (MACI) graft (between white arrows) to the medial femoral condyle. Images are of the same patient and representative of (A) 3 months after surgery with reduced thickness compared with the adjacent native cartilage, (B) 12 months after surgery with hypertrophic growth compared with the adjacent native cartilage, (C) 24 months after surgery with continued graft hypertrophy, and (D) 5 years after surgery with progressive graft delamination.

surgery, the 2 others had no discernible tissue infill as early as 3 months, which was further highlighted at 12 and 24 months as well as 5 years after surgery. These 3 cases have been previously documented.[11,13] The other 2 cases have occurred between 2 and 5 years, diagnosed at 5-year MRI evaluation. Clinical and radiological scores for these 5 patients were retained in the analysis. Figure 5 demonstrates a delaminated graft at 5 years as indicated by MRI, despite favorable scans at 3, 12, and 24 months after surgery.

At 5 years after surgery, patient age exhibited a significant negative correlation ($P < .05$) with the MRI composite score, graft infill, border integration, and surface contour, while defect size was also negatively correlated ($P < .05$) with the MRI composite score, graft infill, signal intensity, border integration, surface contour, and tissue structure (Table 5). The BMI and preoperative injury/surgery history

TABLE 5
Spearman Correlation Coefficients of the MRI Composite Score and 8 Pertinent Parameters of Tissue Repair With Patient Demographics, Chondral Defect Parameters, Injury/Surgery History, and Clinical Outcomes Scores at 5 Years After Surgery[a]

Variable	MRI Composite Score	Graft Infill	Signal Intensity	Border Integration	Surface Contour	Structure	Subchondral Lamina	Subchondral Bone	Effusion
Patient demographics									
Age	–.36[b]	–.35[b]	–.19	–.53[b]	–.36[b]	–.21	–.07	–.12	–.25
Body mass index	–.15	–.22	–.29	–.16	–.06	.11	.07	.07	.10
Chondral defect parameter									
Defect Size	–.48[b]	–.49[b]	–.43[b]	–.50[b]	–.47[b]	–.44[b]	–.26	–.09	–.17
Injury/surgery history									
Prior procedures	–.16	–.28	–.18	–.16	–.04	–.05	–.14	.01	–.11
Duration of symptoms	–.19	–.14	–.02	–.21	–.20	–.12	.06	–.19	–.27
Clinical outcomes score									
KOOS (pain)	.05	.08	.17	.09	–.16	–.04	–.05	–.10	–.02
KOOS (symptoms)	.05	.14	.04	–.01	–.09	–.02	–.19	.07	.04
KOOS (ADL)	–.13	–.06	–.01	.02	–.30	–.14	–.16	–.06	–.03
KOOS (SR)	.06	.16	.08	.18	–.14	–.23	–.04	–.09	.10
KOOS (QOL)	.02	.06	.05	.02	–.29	–.10	–.09	–.05	.03
SF-36 (MCS)	.01	.06	.01	–.06	–.17	–.14	–.02	.04	–.09
SF-36 (PCS)	–.06	.05	.07	.00	–.26	–.27	–.26	–.06	.11
VAS (frequency)	.01	–.04	–.14	.06	.24	.14	.07	.09	.01
VAS (severity)	–.14	–.16	–.18	–.06	.07	–.06	.01	–.07	.06
6-minute walk test, m	.11	.18	.10	.30	.10	.17	.05	–.19	–.03

[a]MRI, magnetic resonance imaging; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; SR, sport and recreation; QOL, quality of life; SF-36, Short-Form Health Survey; MCS, mental component score; PCS, physical component score; VAS, visual analog scale.
[b]$P < .01$.

exhibited no correlation with MRI parameters, while there were no correlations between clinical and MRI scores (Table 5).

DISCUSSION

While MACI has demonstrated good clinical efficacy for the repair of full-thickness articular cartilage defects in the knee,[2,3,14,15] there remains a lack of evidence-based research on the optimal postoperative rehabilitation protocols to facilitate further improvement in patient and graft outcomes. This is despite the general consensus that good rehabilitation after MACI is critical in early graft protection, followed by the facilitation of chondrocyte differentiation and development and the return of the patient to normal physical function.[8,17,19,20,30,31] We presented an accelerated, although structured, MACI weightbearing rehabilitation protocol that was not only safe but also demonstrated reduced pain and symptoms and a faster return to normal function at 2 years after surgery compared with a traditionally conservative weightbearing regimen.[11-13] This article presents the 5-year outcomes of this trial.

A significant improvement in all clinical scores was demonstrated over the 5-year period. While a significant group effect was evident for VAS-F even at 5 years, there were no other differences in clinical scores between the 2 groups. Interestingly, both groups significantly improved further between 24 months and 5 years in the sport and recreation subscale of the KOOS, indicating that, at least with regard to physical function, patients still improve from 24 months on. However, all other subjective scores between 24 months and 5 years were not significantly altered. The use of the KOOS, SF-36, and VAS has been limited with regard to the clinical evaluation of MACI, and little comparable data exist. Patients in both groups reported better scores for all KOOS subscales when compared with those reported previously for both collagen-covered ACI[32] and MACI[24] patients at only 24 months after surgery. While pain and symptoms in this trial were comparable with those from a recent 5-year MACI KOOS evaluation in a different patient cohort,[14] performing activities of daily living, sport and recreation, and knee-related quality of life all rated slightly better in both groups within this study. While cell culturing and surgical methods remained relatively unchanged throughout patient recruitment of these different trials, the improved outcomes in the current trial may be related to the particular attention paid to postoperative rehabilitation. Furthermore, the other prospective study investigated MACI grafts in varying locations, including the patellofemoral joint.[14]

Performance in the 6-minute walk test and active knee flexion and extension were all significantly better in the accelerated group up until 24 months after surgery.[13] However, while these functional outcomes remained better in

the accelerated group at 5 years, these differences were now not significant. Furthermore, a significant decrease in active knee extension was observed for the traditional group from 24 months to 5 years after surgery, although no other significant changes in any of the other functional scores were seen between 24 months and 5 years. It was thought that the early return to full weightbearing and knee mobilization may have provided these early superior outcomes in the accelerated group, although these early benefits appear to have diminished to nonsignificant values at 5 years after surgery.

The MRI composite score (Table 4 and Figure 2) and graft infill (Table 4 and Figure 3) significantly improved over time for both rehabilitation groups. For both measures, it was observed that the score decreased marginally from 1 to 2 years and again from 2 to 5 years (Figures 3 and 4). Despite this deterioration, no significant differences in these MRI-based scores between 12 and 24 months and 5 years after surgery were observed, with 5-year scores still rating significantly better than 3 months. Signal intensity, tissue structure, subchondral bone, and subchondral lamina all significantly improved over time (Table 4), although there were no differences in any of the other MRI scoring parameters between the 2 rehabilitation groups. It is difficult to compare these measures with different MRI scoring systems and assessors. However, recent research using an identical scoring method and the same independent radiologist[14] documented marginally better MRI composite scores and graft infill at 5 years. Again, it should be noted that this other prospective study investigated MACI grafts in varying locations, including the patellofemoral joint.[14]

One incident of graft failure in this patient cohort was previously reported between 6 and 9 months after surgery for a patient within the accelerated group, while 2 others (1 traditional, 1 accelerated) had no tissue infill as early as 3 months.[11,13] Since this time (between 2-5 years), 2 further graft failures were noted (both in the traditional group), as observed through the 5-year MRI evaluation. The initial graft delamination (6-9 months) was of unknown origin, although the patient's BMI at the time of failure was 33.1, indicative of an "obese" score. However, the 2 recent failures occurred in patients with 5-year BMI scores of 24.2 and 26.1. While it has generally been reported that graft delamination presents within the first 6 months,[26] the lack of 5- to 10-year published MACI research has not allowed this later postoperative period to be adequately assessed. Of the 58 grafts that could be assessed via MRI at 5 years after surgery, a graft failure rate of 8.6% remains for the entire cohort.

While there were no significant differences between the 2 groups, the high rate of graft hypertrophy (27% of grafts) previously reported at 24 months[11] was also evident at 5 years (accelerated 24%, n = 7; traditional 20%, n = 6). This hypertrophic incidence is higher than that from other published MACI research,[14,36] and while patients in this trial were nonsymptomatic, the reason for this high rate is unknown. It should be noted that one of the delaminated grafts that occurred between 2 and 5 years (Figure 5) did occur in a hypertrophic graft, and therefore, these need to be closely monitored from this time to ascertain whether symptoms do emerge or whether a correlation between graft hypertrophy and tissue breakdown appears.

Patient age and chondral defect size exhibited a number of significant negative correlations with the MRI scoring parameters at 5 years, including the MRI composite score and graft infill. Age restrictions are generally indicated for chondrocyte implantation surgery[21,29] because, as one ages, there is an associated reduction in tissue regenerative capacity. With regard to defect size, small chondral lesions (<2 cm^2) may be amenable to other cartilage repair methods such as osteoarticular transplantation systems (OATS) and microfracture. However, in addition to the "hyaline-like" articular cartilage repair produced (as opposed to the fibrocartilage, which is generally the result of microfracture), MACI is also recommended for larger defects. However, these data would suggest there may be an upper limit whereby a poorer graft outcome may be observed. After stratification by defect size, grafts between 1.0 and 5.0 cm^2 demonstrated a mean 5-year MRI composite score between 2.89 to 3.30. While grafts between 5.1 and 7.5 cm^2 still provided a mean composite score of 3.10, those above 7.6 cm^2 provided a mean of only 1.63, which were clearly below the group averages.

In contrast to 24-month outcomes,[11] BMI exhibited no association with any of the MRI scores. On the basis of these data, it would appear that excessive body weight does not affect outcomes at this point in the postoperative timeline, although patients with above-average BMI need to be closely monitored to evaluate whether long-term graft outcome is affected by a prolonged history of tibiofemoral (and graft) overload during normal ambulation. There were also no correlations between clinical and MRI outcomes at 5 years. Whether this is a result of the relatively small sample size, or clinical assessment tools not specific enough to accurately reflect patient outcomes following cartilage repair, it does again highlight the need for both MRI-based assessment and clinically patient-reported outcomes in assessing MACI surgery.

The level of satisfaction with the MACI surgery reported by patients at 5 years in this study was high, even given the 8.6% graft failure rate (as assessed via 5-year MRI), further highlighting the poor correlation between clinical and MRI-based outcomes. Of the 63 patients, 94% and 95% were satisfied with the ability of MACI to relieve their knee pain and improve their ability to undertake daily activities, respectively. Patient satisfaction and perceived improvement may be as important to the patient as a measurable improvement in clinical outcome.

Several limitations are acknowledged in the present study. First, a number of self-reported questionnaires were employed to assess patient outcome. While patients were asked to answer all questionnaires truthfully and to the best of their ability, the degree of potential bias resulting from patient knowledge of their own treatment protocol remains unknown, even at 5 years. Furthermore, while the subjective tools used (KOOS, SF-36, VAS) have been used routinely for chondrocyte implantation,[1,12,24,28,32] it has been recently stated that further development of these

questionnaires is required and that, at present, there are no specific cartilage repair outcome measures.[18] Unfortunately, while ongoing education and advice were provided to patients up until 12 months after surgery, following their supervised postoperative rehabilitation program, patients essentially progressed toward unrestricted activities from that time on. Therefore, the introduction of an activity-based questionnaire, evaluating the frequency and intensity of physical activity/sport, may have provided some further insight into individual patient outcome up until, and including, 5 years after surgery. Second, the MRI scoring system employed evaluates morphological graft outcome. New methods of assessing the biochemical characteristics of repair tissue have emerged,[22,34,35] which may assist in evaluating the "ultrastructure" of the repair tissue.[9] Finally, no follow-up arthroscopy or histological analysis was undertaken in this cohort. While this may provide information on repair tissue structure, postoperative arthroscopic biopsy provides several ethical barriers, particularly when patients are satisfied with their postoperative outcome.

Our first hypothesis was supported, whereby there was a significant improvement in all clinical measures as well as several MRI-based measures throughout the preoperative and postoperative timeline. Our second hypothesis was also generally supported. While the accelerated group still reported less frequent pain (VAS-F) at 5 years, in comparison with the traditional group, all other clinical and MRI-based measures were not different between the 2 groups. Our third hypothesis was only partially supported. Patient age and chondral defect size were significantly correlated with MRI scoring parameters at 5 years, although no other correlations existed. Furthermore, there was no correlation between clinical and MRI scores.

Despite the general consensus that structured postoperative rehabilitation after MACI is crucial to optimizing patient and graft outcome,[8,17,19,20,30,31] this area has not been paid the same attention as the development of surgical and cell culturing methods. The outcomes of this randomized trial demonstrate a safe and effective accelerated rehabilitation protocol as well as a regimen that provides several superior clinical outcomes to patients throughout the postoperative timeline.

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