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Accelerated Weightbearing Rehabilitation After Matrix-Induced Autologous Chondrocyte Implantation in the Tibiofemoral Joint

Early Clinical and Radiological Outcomes

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Background: Matrix-induced autologous chondrocyte implantation (MACI) has become an established technique for the repair of full-thickness chondral defects in the knee, although best patient outcomes appear limited by a lack of evidence-based knowledge on how to progressively increase postoperative weightbearing (WB) and rehabilitation exercises.

Hypothesis: To determine the safety and efficacy of an accelerated WB regimen after MACI in the tibiofemoral joint.

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

Methods: Clinical and radiological assessments were performed in 28 knees at 12 months after MACI to the medial or lateral femoral condyle. Both rehabilitation interventions sought to protect the implant for an initial period and then incrementally increase load bearing. Under the ''accelerated'' (AR) protocol, patients reached full WB at 6 weeks after surgery compared with 8 weeks for what was considered to be the current ''best practice'' (CR) WB regimen based on previous research. Assessments included the Knee Injury and Osteoarthritis Outcome Score (KOOS), 36-Item Short Form Health Survey (SF-36), visual analog scale, 6-minute walk test, and active knee range of motion (ROM). High-resolution magnetic resonance imaging (MRI) was used to describe the quality and quantity of repair tissue via the assessment of pertinent parameters of graft repair as well as an MRI composite score.

Results: Patients in both groups demonstrated significant improvement ($P < .05$) in all clinical measures over the preoperative and postoperative timeline from before surgery to 12 months after surgery. The AR group reported significantly better ($P < .05$) SF-36 physical component scores at 8 weeks and significantly greater ($P < .05$) KOOS quality of life scores at 6 and 12 months postoperatively. Although no differences ($P > .05$) were observed between the 2 groups for active knee ROM, the AR group did achieve full active knee extension as early as 4 weeks compared with the CR group at 12 weeks. There was no difference ($P > .05$) in graft quality as assessed by MRI (MOCART composite score: AR, 3.34; CR, 3.04), with no patients suffering any adverse effects from the implant up to 12 months, regardless of the rehabilitation protocol employed.

Conclusion: The AR approach that reduced the length of time spent ambulating on crutches resulted in improved general physical function and quality of life and an earlier attainment of full active knee extension when compared with the CR approach. There were no graft complications ascertained through MRI. This regimen appears safe and may potentially speed up the recovery of normal gait function. A larger patient cohort and follow-up are required to observe long-term graft outcomes.

Keywords: matrix-induced autologous chondrocyte implantation (MACI); partial weightbearing (PWB); rehabilitation; gait

Matrix-induced autologous chondrocyte implantation (MACI) has become an established technique for the repair of full-thickness chondral defects in the knee.[2,3,20,24] The procedure requires an initial arthroscopic harvest of healthy cartilage, whereby chondrocytes are isolated and cultured for a period of 4 to 8 weeks ex vivo and are subsequently then seeded onto a synthetic collagen membrane and reimplanted into the chondral defect, secured in place with fibrin glue. 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.

Robertson et al[42] proposed 4 main factors that influence graft and patient outcomes after MACI: (1) successful cell culturing, (2) efficiency of the surgical procedure, (3) patient cooperation in all aspects of the preoperative and

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postoperative program, and (4) timely progression of weightbearing (WB) and postoperative rehabilitation. While several works have outlined the importance of structured postoperative rehabilitation after ACI for graft protection, facilitation of chondrocyte differentiation and development, and return of the patient to normal physical function,[10,28,30,36,39,40] very little information has been made available on how best to progressively increase WB and exercise after surgery. Research supports the need for dynamic[22] and shear loading[48] similar to that experienced in normal daily activity such as walking, while static compression[5] and immobilization[26] appear detrimental to cell proliferation and matrix synthesis. Therefore, a graded program incorporating controlled exercise and progressive partial weightbearing (PWB) is recommended after the general ACI procedure[15,27]; however, the most optimal PWB gait progression remains to be determined.

With the inception of the traditional periosteal-covered ACI procedure, the proposed postoperative WB protocol consisted of what we would now consider a conservative 6-week period of toe-touch ambulation, followed by a stepwise increase over the next 6 postoperative weeks, to ultimately achieve full WB by 11 to 12 weeks postoperatively[35] (Figure 1A). With the development of second-generation collagen-covered ACI, which used a collagen membrane to contain the cultured cells as opposed to periosteum, as well as further clinical experience, Robertson et al[42] proposed a more graduated return to full WB, removing the initial 6-week period of toe-touch ambulation, implementing an initial load of 20% of the patient's body weight (BW) through the affected leg within 2 weeks of the operative procedure, and progressing to full WB again at 11 to 12 weeks postoperatively (Figure 1B).

Based on the inception of the MACI procedure, Ebert et al[19] proposed a more "aggressive" WB rehabilitation protocol in patients after MACI in the tibiofemoral joint, reducing the time to full WB from 12 to 8 weeks after surgery (Figure 1C). This proved to be a safe and effective WB regimen with no detrimental effects to the patient or integrity of the graft, demonstrating improved early clinical outcomes at 3 months[19] and maintained to 2 years[18] and, more recently, 5 years after surgery.[14] Furthermore, the return of gait normality was accelerated,[16] minimizing the effect that any ongoing, abnormal gait and knee joint loading patterns after the return to full WB may have on short- and long-term graft success.[16] We believe that this evidence-based protocol serves as a current "best practice" WB rehabilitation regimen for patients after MACI in the tibiofemoral joint.

However, based on these outcomes and anecdotal experience with a more aggressive regimen, we still believe that this protocol may be conservative. With ongoing use and evolution of the MACI surgical technique, along with clinical experience and improved knowledge of histology and of the maturation process of repair tissue, we hypothesized that a more accelerated return to full WB (Figure 1D) can be tolerated without harm to the patient or compromising graft integrity.

Therefore, the aim of this study was to determine the safety and efficacy of an accelerated return to full WB after MACI in the tibiofemoral joint. We hypothesized that an accelerated WB approach (AR) would provide at least comparable, if not superior, clinical and radiological outcomes in the early postoperative stages (up to 12 months) after tibiofemoral MACI, when compared with what we consider the current "best practice" evidence-based postoperative WB rehabilitation protocol (CR) based on previously published work.[19]

MATERIALS AND METHODS

Participants

A total of 26 consecutive patients (16 male, 10 female) were recruited after MACI to the medial or lateral femoral condyle between January 2010 and February 2012 (Table 1). Two of these patients underwent MACI surgery on both knees at 3 months apart; hence, a total of 28 knees were included in this research. An a priori power calculation was performed using G-Power (Dusseldorf, Germany) for the primary outcome variable, the pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS), demonstrating that 28 knees (14 in each group) were required to reveal differences at the 5% significance level, with 90% power, using a large effect size (1.1) as reported by previous research.[50]

Patients enrolled were either male or female, were between 15 and 65 years of age, and had undergone MACI to address full-thickness femoral condylar defects in the knee (<10 cm^2 on magnetic resonance imaging [MRI]). Patients with ligamentous or meniscal deficiency were included, providing it was addressed before or at the time of MACI surgery. Multiple condylar defects and minor trochlear or patellar lesions were also permitted, providing they occurred in conjunction with a primary femoral lesion. Patients displaying varus or valgus malalignment (>5° anatomic tibiofemoral angle) or those who suffered from any ongoing, progressive inflammatory arthritis, osteoarthritis, or rheumatoid arthritis were excluded. Despite the inclusion criteria, no patient within this study underwent multiple MACI grafting or any concomitant surgical technique in addition to the MACI graft itself. A study information brochure and patient consent form were provided upon initial discussion of the study and requirements of the patient. This trial obtained approval from The University of Western

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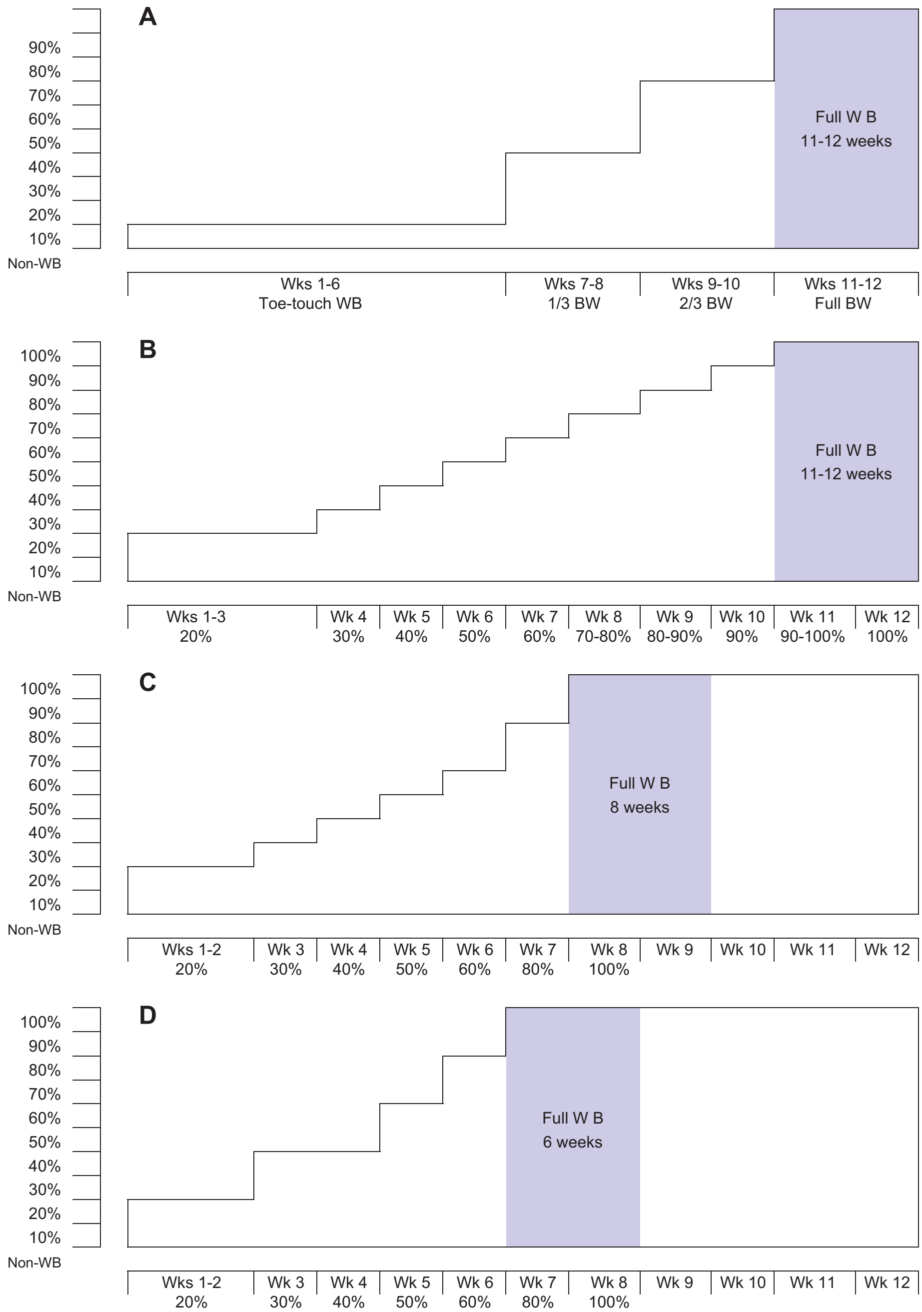

Figure 1. The evolution of postoperative partial weightbearing since the inception of the general autologous chondrocyte implantation procedure, demonstrating (A) the progressive weightbearing (WB) gradient proposed by Minas and Peterson[35] involving a 6-week period of toe-touch ambulation, with a stepwise increase in load over the next 6 postoperative weeks, achieving full WB by 11 to 12 weeks postoperatively; (B) the WB gradient proposed by Robertson et al,[42] initiating WB from 20% of the patient's body weight within 2 weeks of the operative procedure, with a more graduated increase to full WB also at 11 to 12 weeks after surgery; (C) the WB protocol proposed and evaluated by Ebert et al,[19] achieving full WB at 8 weeks after surgery (CR); and (D) the accelerated WB gradient after matrix-induced autologous chondrocyte implantation proposed for this research project, designed to attain full WB at 6 weeks after surgery (AR).

Australia (Human Research Ethics Committee in 2004) and the Hollywood Private Hospital (Hollywood Private Hospital Research Ethics Committee in 2003) and was undertaken according to the Declaration of Helsinki. All patients provided their written informed consent before study participation.

TABLE 1
Descriptive Parameters for Patients[a]

Variable	AR Group	CR Group	*P* Value
No. of patients	13	13	.476
No. of knees	14	14	
Sex, male/female, n	7/7	10/4	
Age, y	34.5 (21.0-53.0)	37.1 (23.0-53.0)	
10-19	0	0	
20-29	6	3	
30-39	1	5	
40-49	5	4	
50-59	1	1	
Height, m	1.74 (1.55-2.03)	1.76 (1.55-1.87)	.729
Weight, kg	79.7 (46.0-130.0)	79.2 (46.0-109.3)	.913
BMI	25.8 (18.4-32.1)	25.3 (19.2-33.1)	.713
Defect location, MFC/LFC, n	10/4	10/4	
Defect size, cm^2	2.93 (1.00-6.00)	2.83 (1.30-7.70)	.871
$\leq$1.0	1	0	
1.1-2.0	5	5	
2.1-3.0	3	4	
3.1-4.0	4	2	
4.1-5.0	0	1	
$\geq$5.1	1	2	
Prior procedures	1.2 (0-4)	1.2 (0-4)	1.000
Duration of symptoms, y	8.2 (1-25)	7.4 (1-25)	.803

[a]Data are shown as mean (range) unless otherwise specified. AR, accelerated approach; BMI, body mass index; CR, current best practice–based approach; LFC, lateral femoral condyle; MFC, medial femoral condyle.

MACI Surgery

The general ACI procedure is a 2-stage surgical technique that involves isolating and culturing a patient's own cartilage cells (chondrocytes) in vitro and reimplanting them into the chondral defect. Of the 28 knees enrolled in this trial, 8 underwent MACI that was performed using a traditional mini-arthrotomy[14,20] (AR, n = 4; CR, n = 4), while 20 were performed via an arthroscopic MACI approach[6,12] (AR, n = 10; CR, n = 10). Regardless of the implantation technique (open or arthroscopic), an arthroscopic biopsy of healthy articular cartilage was initially required, and cartilage was harvested from a non-WB aspect of the knee. This cartilage tissue was then transported to the laboratory (Genzyme, Perth, Western Australia, Australia), where chondrocytes were isolated and cultured for 4 to 8 weeks, resulting in a 10- to 12-fold increase in viable autologous chondrocytes. These were then seeded onto a type I/III collagen membrane (ACI-Maix, Matricel GmbH, Herzogenrath, Germany) 3 days before reimplantation. At the time of second-stage implantation, the defect site was accessed and prepared via a medial or lateral parapatellar mini-arthrotomy or via a standard arthroscopic routine using anteromedial and anterolateral portals. Both MACI surgical techniques have been previously described.[6,12,14,18,19]

After surgery and patient study consent, patients were randomized using a "random number generator" via Excel (Microsoft, Redmond, Washington), which was undertaken before study commencement. This specified whether the patient was assigned to either the postoperative WB approach that allowed a graduated return to full WB at 8 weeks after surgery, considered our current "best practice" (CR) treatment for MACI in the tibiofemoral joint as developed through prior evidence-based research,[6,12] or an accelerated WB approach (AR) that allowed full WB at 6 weeks after surgery. A concealed allocation procedure was used, whereby only the study coordinator had access to the randomization list. The CR protocol consisted of an initial 2-week period of WB at 20% BW toe-touch ambulation, followed by a progressive increase in load bearing until full WB was attained at 8 weeks after surgery.[14,18,19] The AR approach maintained the initial 2-week 20% BW toe-touch phase, with subsequent load bearing progressively increased to full WB at 6 weeks after surgery. The rehabilitation WB timelines that were followed are displayed for both the CR and AR groups in Table 2. Of the 28 knees included in this study, 14 knees (7 male, 7 female) were allocated to the AR group, while 14 knees (10 male, 4 female) were allocated to the CR group (Figure 2). The 2 patients who received MACI on both knees were initially randomized into a rehabilitation pathway for their first knee and subsequently allocated to the alternative pathway after surgery on the contralateral knee.

All patients received the same patient education and immediate postoperative inpatient rehabilitation, regardless of surgical approach or group randomization (AR or CR). This comprised continuous passive motion set at 0° to 30° on the operated knee within 12 to 24 hours after surgery, for a minimum of 1 hour daily, to reduce the chance of intra-articular adhesions; cryotherapy to control edema (20 minutes at least 3 times daily); active dorsiflexion and plantar flexion of the ankle to encourage lower extremity circulation; isometric contraction of the quadriceps,

TABLE 2
Differential WB Gradients Followed by the Study Patients[a]

	Weeks After Surgery								
	2	3	4	5	6	7	8	9	10
CR group (8 weeks to full WB)									
WB regimen (% BW)	20	30	40	50	60	80	100		
Crutches	2	2	2	2	1	1	0		
Brace	Y	Y	Y	Y	Y	Y	Y		
AR group (6 weeks to full WB)									
WB regimen (% BW)	20	40	60	80	100				
Crutches	2	2	1	1	0				
Brace	Y	Y	Y	Y	Y				

[a]AR, accelerated approach; BW, body weight; CR, current best practice–based approach; WB, weightbearing; Y, yes.

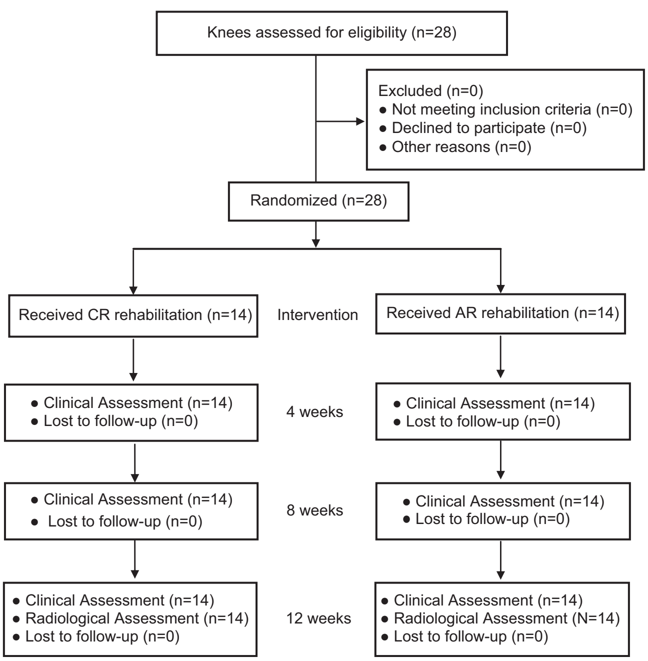

Figure 2. Patient randomization and assessment throughout the trial for our considered current ''best practice'' (CR) and accelerated (AR) approaches to postoperative weightbearing after matrix-induced autologous chondrocyte implantation to the medial or lateral femoral condyles.

hamstring, and gluteal musculature to maintain muscle tone and minimize muscle loss; and patient education of proficient toe-touch ambulation, allowing no more than 20% BW transmission through the affected limb. A range of motion control knee brace was worn postoperatively for 24 hours per day to protect the repaired cartilage surface. After hospital discharge, all patients were referred to the Hollywood Functional Rehabilitation Clinic for postoperative outpatient rehabilitation. From this time, patients attended the clinic on 2 occasions per week, for a period of 12 weeks.

Depending on the stage of rehabilitation, patients had the knee braced and used a single crutch, 2 crutches, or no walking aids (Table 2). The bathroom scale method was used to teach patients the WB restrictions.[19,27] While mixed opinions have been expressed regarding this method as an effective tool for teaching WB restrictions, with both good[32,51] and poor[7,25] replication abilities reported, it still remains the most practical and widely used modality for teaching WB restrictions.[19,27] In addition, our previous research investigating the ability of MACI patients to replicate desired WB levels throughout their rehabilitation program has demonstrated improved accuracy with a higher frequency of practice,[19] and WB replication training served as an important component of every clinic session up to the time that the patient returned to full WB. Apart from the group differences in WB gradient and time to full WB, all rehabilitation exercises and exercise modalities were similarly applied (see Appendix 1, available in the online version of this article at http://ajsm.sagepub.com/supplemental).

Clinical Outcome Measures

Three patient-reported outcome measures were employed to evaluate preoperative as well as 4-week, 8-week, 12-week, 6-month, and 12-month postoperative outcomes. These included (1) the KOOS[43] to assess knee pain, symptoms, activities of daily living (ADL), sport and recreation, and knee-related quality of life (QOL); (2) the 36-Item Short Form Health Survey (SF-36)[49] to assess the general health of the patient, producing a mental (MCS) and physical component score (PCS); and (3) a visual analog scale (VAS) to assess the frequency (VAS-F) and severity (VAS-S) of knee pain on a scale of 0 to 10. Three functional capacity tests were also administered, with patients asked to perform to the best of their ability. First, active knee flexion and extension were measured at 4 weeks, 8 weeks, 12 weeks, 6 months, and 12 months after surgery, with the patient lying in a supine position. Second, a 3-repetition maximum straight-leg raise (3RM-SLR) test was administered at 12 weeks, 6 months, and 12 months after surgery to assess the strength of the quadriceps and hip flexor musculature in a supine position. While absolute strength (kg) was measured in both the operated and nonoperated limbs, we chose to present 3RM-SLR strength using the contralateral limb as a control. Therefore, strength discrepancies were presented for the patient groups, calculated as the difference between the operated and nonoperated limbs. Finally, the 6-minute walk test[23] was conducted at 12 weeks after surgery, which measured the maximum distance that the patient could walk in a 6-minute time period. Patients were instructed to walk "as far and fast as they comfortably could" for the duration of the test.

Although best attempts at patient blinding were made, because of the ethical nature of this patient-informed trial, patients were made aware of the 2 rehabilitation pathways and therefore were able to identify their allocated rehabilitation group. However, all clinical assessments were undertaken by a blinded and independent research assistant, who was unaware of the rehabilitation intervention (CR or AR).

MRI-Based Outcome Measures

Graft status was assessed at 3 months and 12 months after surgery via high-resolution MRI 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 1 axis for proton density images, with a minimum 256 matrix in 1 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 1 axis).

The MRI evaluation employed in this study assessed 8 pertinent parameters of morphological graft repair that have been previously outlined.[33] This method closely followed the magnetic resonance observation of cartilage repair tissue (MOCART) scoring system previously reported for the radiological assessment of ACI.[13,41,46] Magnetic resonance imaging 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 parameters were scored from 1 to 4 (1 = poor, 2 = fair, 3 = good, 4 = excellent) in comparison with the surrounding native cartilage. Under the scoring parameter of graft infill, an additional rating of 3.5 was included (very good), representing graft hypertrophy, which has been indicated in prior work.[33,46] In addition to individual parameter scoring, a combined MRI composite score was calculated by multiplying each individual score by a weighting factor and adding the scores together.[41] This composite score was also rated from 1 to 4 (1 = poor, 2 = fair, 3 = good, 4 = excellent). An experienced musculoskeletal radiologist blinded to the clinical details and clinical outcome assessment performed MRI evaluation.

Statistical Analyses

A series of 2-way (2 $\times$ 4) split-plot analyses of variance (ANOVA) was used, with group (AR and CR) and time (before surgery and 4 weeks, 8 weeks, 12 weeks, 6 months, and 12 months after surgery) entered as independent factors, to investigate any differences in subjective and functional outcome measures. In the occurrence of significant main or interaction effects, independent t tests were used to investigate differences in the dependent variable between the specific assessment time points. The MRI scans were taken at 12 weeks and 12 months after surgery to determine the individual and composite MRI scores. The ANOVA was again employed, with post hoc independent t tests used in the occurrence of significant main effects. Statistical analysis was performed using SPSS software (Version 19.0, SPSS Inc, Chicago, Illinois), while statistical significance was determined at $P < .05$.

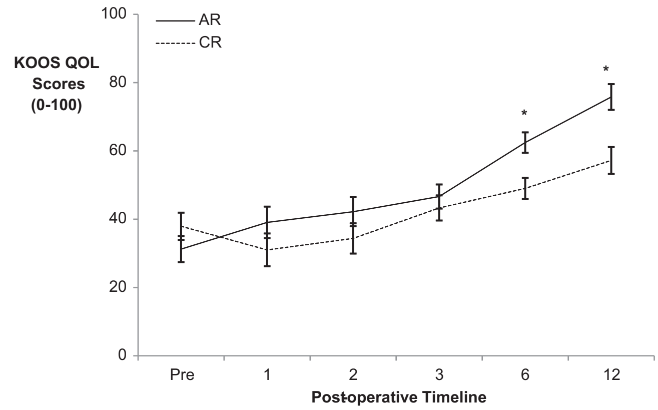

Figure 3. The Knee Injury and Osteoarthritis Outcome Score quality of life score for patients randomized to either our considered current ''best practice'' (CR) or accelerated (AR) approach to postoperative weightbearing after matrix-induced autologous chondrocyte implantation throughout the preoperative and postoperative timeline. Independent t tests revealed a significantly better score ($P < .05$) in the AR group at 6 and 12 months after surgery (*).

RESULTS

There were no significant differences ($P > .05$) in any of the patient, chondral defect, or injury/surgery history parameters between the 2 rehabilitation groups (AR and CR) at the time of surgery (Table 1). Over the duration of the 12-month postoperative period, there was a significant time effect ($P < .05$) for all subjective clinical scores (see Appendix 2, available online), demonstrating improvement from before surgery to 12 months postoperatively in both groups. There was a significant group effect ($P < .05$) for the QOL subscale of the KOOS and significant interaction effects ($P < .05$) for the PCS subscale of the SF-36 as well as the symptoms and QOL subscales of the KOOS. There were no further significant group or interaction effects between the 2 groups for any of the subjective measures (see Appendix 2). Post hoc independent t tests comparing the 2 rehabilitation arms revealed significantly better ($P < .05$) scores for the PCS subscale of the SF-36 in the AR group at 8 weeks after surgery, while the AR group demonstrated significantly better ($P < .05$) KOOS QOL scores at 6 and 12 months after surgery, when compared with the more conservative CR group (Figure 3).

TABLE 3
ANOVA Summary of the Postoperative MRI Assessment of Grafts for the Rehabilitation Groups at 12 Weeks and 12 Months After Surgery[a]

	MRI Parameter[b]								
Variable	Graft Infill	Signal Intensity	Border	Surface Contour	Structure	Subchondral Lamina	Subchondral Bone	Joint Effusion	MRI Composite Score
12 weeks									
AR	3.11 (0.20)	2.14 (0.18)	2.79 (0.22)	3.43 (0.26)	3.50 (0.23)	3.00 (0.14)	2.86 (0.19)	3.57 (0.13)	2.94 (0.12)
CR	2.75 (0.21)	2.15 (0.19)	2.46 (0.23)	3.00 (0.27)	3.29 (0.24)	2.92 (0.15)	2.71 (0.20)	3.69 (0.14)	2.70 (0.12)
12 months									
AR	3.57 (0.21)	3.00 (0.23)	3.29 (0.26)	3.14 (0.30)	3.28 (0.25)	3.50 (0.18)	3.50 (0.23)	3.64 (0.13)	3.34 (0.17)
CR	3.19 (0.22)	2.69 (0.24)	2.92 (0.27)	2.85 (0.31)	3.15 (0.26)	3.46 (0.18)	2.77 (0.23)	3.92 (0.14)	3.04 (0.18)
P value									
Time effect	**.007**	**.001**	**.015**	.401	.319	**.003**	.058	.253	**.001**
Group effect	.198	.535	.261	.254	.590	.731	.073	.168	.206
Interaction effect	.783	.396	.917	.800	.869	.904	.131	.543	.622

[a]Data are shown as mean (standard error). ANOVA, analysis of variance; AR, accelerated group; CR, current best practice group; MRI, magnetic resonance imaging. Bolded *P* values indicate <.05 and hence significant.
[b]The MRI parameters were scored on a scale of 1 to 4 (1 = poor, 2 = fair, 3 = good, 4 = excellent), in comparison with the adjacent native cartilage.

Over the duration of the 12-month postoperative period, there was a significant time effect ($P < .05$) for active knee flexion and knee extension range of motion, 6-minute walk distance, and 3RM-SLR strength (see Appendix 3, available online). There was a significant group effect observed for 3RM-SLR strength, demonstrating a lower strength discrepancy between the operated and nonoperated limbs in the AR cohort compared with the CR cohort. There were no further group or interaction effects for any of the remaining functional measures.

The MRI findings evaluated by the MOCART scoring system showed a significant time effect ($P < .05$) for the MRI composite score, graft infill, signal intensity, border integration, and subchondral lamina over the postoperative period (Table 3). There were no between-group differences or interaction effects observed (Table 3). At 12 months after surgery, the degree of defect infill in the AR group was classified as very good (mean, 3.57) compared with the CR group classification of good (mean, 3.19) at 12 months (Table 3). At 12 months after surgery, 100% (n = 14) of AR patients demonstrated good to excellent infill compared with 85% (n = 11) in the CR group (see Appendix 4, available online). There was no reported graft failure up to and including 12 months after surgery across all patients, as assessed by MRI. An example of a sound MACI graft on the medial femoral condyle from this research is shown in Figure 4.

DISCUSSION

Widely employed postoperative WB protocols after MACI are generally conservative and are based on theoretical loading models and early ACI surgical techniques. Many studies show the consequences of long periods of unloading on several joint structures such as the menisci, cartilage, ligaments, and capsular structures,[8,21,34,50] which quickly adapt to this nonphysiological situation, potentially compromising the healthy environment required for tissue regeneration. Also, MACI removes a number of structural and functionally debilitating side effects associated with the surgical procedure, and therefore, we believe that current evidence-based published postoperative WB regimens can be accelerated to accommodate these developments without harm to the patient or graft. Subjective, functional, and radiological patient outcomes after the attainment of full WB need to be investigated to determine if any early detrimental effects exist as a result of an AR approach to postoperative full WB gait.

Patients in both AR and CR groups reported significant improvements in knee-related pain, symptoms, ADL, QOL, and general mental and physical well-being from before surgery to 12 months after surgery. The improvements at 12 months in KOOS-related outcomes in this study appear consistent with those reported previously by Wondrasch et al,[50] who investigated a 6-week (vs 10-week) return to full WB, as well as the 8-week (vs 12-week) return to full WB evaluated by Ebert et al.[19] Coincidently, this protocol, which has now been followed to 5 years, serves as the control protocol (CR) in this study. Although there were no significant differences in KOOS QOL scores between the 2 groups at each time point to 12 weeks, at 6 and 12 months after surgery, greater knee-related QOL scores were observed in the AR group compared with the more conservative CR group. While we would expect to see similar scores between the 2 groups at these time points, it appears that the extra 2 weeks of full WB gait had a positive effect on knee-related QOL at these time points.

Although both patient groups experienced a significant deterioration in the sport and recreation subscale of the KOOS from before surgery to 12 weeks after surgery, given the strict physical limitations imposed on patients

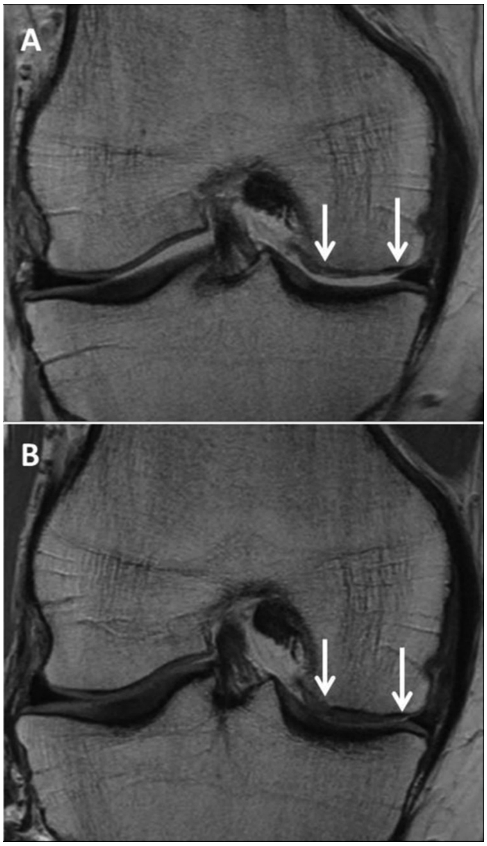

Figure 4. An example of a postoperative matrix-induced autologous chondrocyte implantation graft from this research is shown on the medial femoral condyle between the white arrows. Images are of the same patient and representative of (A) 12 weeks after surgery with a hyperintense signal and reduced thickness compared with the adjacent native cartilage (arrows) and (B) 12 months after surgery with similar thickness to the adjacent native cartilage (arrows).

postoperatively, with most sports and recreational activities contraindicated well into the postoperative timeline,[9,27,37,39,40] the AR group demonstrated significantly better scores at 6 months after surgery, with both groups reporting significantly better scores at 12 months after surgery.

The restriction in permitted physical activity was also reflected in the acute decline in the PCS subscale of the SF-36 from preoperative to 4-week postoperative scores. Interestingly, by 8 weeks after surgery, not only did the AR group report significantly higher PCS values than the CR group, but they also reported significantly higher scores when compared with their preoperative status. Because patients in the AR group are full WB and ambulating unaided well before this time, as opposed to the CR group, which is essentially full WB and walking unaided for the first time at this 8-week mark, the improved sense of physical well-being and function in the AR group was not surprising. Furthermore, the AR group actually reported a better PCS value at the 8-week time point compared with their presurgery scores, unlike the CR group, which suggests that despite the identical activity restrictions (apart from time to full WB) for the 2 groups, the AR patients' sense of physical well-being and function was greater than before surgery. By 3, 6, and 12 months after surgery, the 2 rehabilitation pathways were similar in their sense of physical well-being, with no differences existing between the 2 groups. There were no other significant group or interaction effects reported in the remaining patient-reported measures; however, observed power for these nonsignificant findings was below 0.5, indicating that the sample size may not have been sufficient enough to detect meaningful effects.

The 6-minute walk test has been reported as a key component of many activities of normal daily living and a foundation for functional independence,[23,41] while the 3RM-SLR has proven to be a low-risk method to assess the strength of hip flexor and quadriceps musculature without overloading the implant site.[18,19] Because of the fragile nature of the graft in its early developmental stages, these functional tests were not conducted until 12 weeks after surgery. Although the strengthening and range of motion exercise protocols undertaken by both groups were identical, we anticipated that given the AR group was allowed a 2-week reduction in time to full WB, the associated extra time permitted for ambulation without a functional aid may induce superior 6-minute walk times as has been reported in previous studies.[19] This was not the case, and while no significant improvements were observed in the 6-minute walk distance, the results do demonstrate comparability between the AR and CR groups.

In addition to the significant improvement over time from 12 weeks to 12 months in both groups, there was a significant group effect in favor of the AR cohort observed for 3RM-SLR strength scores. This was demonstrated by a lower discrepancy in operated and nonoperated limbs for the AR group at 12 weeks and 6 and 12 months, essentially demonstrating a stronger hip flexor complex in the AR group. While this may suggest that the AR protocol and associated extra 2 weeks of ambulation did provide an additional strength benefit, we did not document such postoperative information as limb dominance and activity type/duration after the initial 12-week period. Little research has been reported on the recovery of strength in MACI patients and long-term graft outcomes; however, a recent study by Ebert et al[17] demonstrated that at 5 years after surgery, there were no significant differences between the operated and nonoperated limbs in the 3RM-SLR, irrespective of an 8-week accelerated protocol or a 12-week "conservative" protocol. Additionally, the study also investigated knee flexor and extensor strength between the operated and nonoperated limbs using isokinetic dynamometry, which found no differences in hamstring muscle strength but significantly reduced quadriceps muscle strength in the operated side, indicating that perhaps the early postsurgical rehabilitation may not be adequate for long-term knee strength.[17] Unfortunately, we have yet to assess postoperative maximal knee extension and flexion strength, given the relatively early timeline and fear of adverse effects on the graft; however, these will be investigated at a later date.

Active knee extension and flexion were undertaken in all patients at all postoperative time points. While not significant, full active knee hyperextension was attained as early as 4 weeks in the AR group; a persistent fixed flexion deformity (FFD) existed in the CR group, with full knee extension not regained until 12 weeks postoperatively. The significance of greater active knee range of motion in patients may relate to a more "normal" gait pattern and the avoidance of abnormal and potentially detrimental knee loading patterns encountered during gait. A full active knee extension is essential for normal gait and acceptance of BW throughout the stance phase, while a lack of full extension essentially presents with a functionally shorter limb, further promoting deleterious biomechanics in the hip, pelvis, and lower spine moving proximally in the WB kinetic chain. Furthermore, a FFD and the associated increase in knee flexion at heel strike and during weight acceptance may act to produce greater knee flexion moments, which have been associated with more frequent and severe postoperative anterior knee pain.[44] In doing so, an increased external knee flexion moment during the stance phase of gait requires and forces the relative activation of the quadriceps to increase, thereby placing greater loads on the patellofemoral joint. No significant differences were observed between the AR and CR groups for active knee flexion at each postoperative time point. Overall, these findings suggest that the AR protocol employed was well tolerated by patients undergoing MACI in this study, without concerns over any decline in early clinical and/or functional outcome.

The MRI findings evaluated by the MOCART scoring system showed a significant time effect for the MRI composite score, graft infill, signal intensity, border integration, and subchondral lamina from 12 weeks to 12 months after surgery, whereby graft quality continued to progress and mature into a suitable load-bearing tissue. There were no between-group differences or interaction effects observed in any of the scores, indicating that early WB activities had no detrimental effect on the graft in terms of tissue characteristics and signal intensity, which is consistent with prior research.[50] Despite the lack of significance in MRI scoring measures, the AR group still appeared to score better than the CR group in 7 of 8 individual scores, as well as the MRI composite score, at 12 months. Both bone edema (subchondral bone) and joint effusion may be seen as signs of graft overloading and, subsequently, an inability of the early regenerative tissue to appropriately transmit forces acting across the tissue.[50] The MRI scans at 12 weeks demonstrated no differences in bone edema between the 2 groups, while all patients scored only mild to no joint effusion. Furthermore, joint effusion scores at 12 months were comparable, while subchondral bone was bordering significance in favor of the AR group, at least suggesting that the AR pathway did not present any detriment or overloading of the graft.

Determination of graft failure in this study was defined as complete delamination of the implanted graft and, therefore, its inability to withstand the dynamic forces (compressive and shear) placed upon it during either WB regimen. Other researchers have demonstrated that delamination generally presents within the first 6 months in approximately 5% of patients.[35] There was no graft delamination observed in this study at 12 months from either WB group. Furthermore, graft failure may be heavily dependent on patient noncompliance, emphasizing the importance of controlled WB and exercise progression, as well as patient compliance through comprehensive education and patient-therapist communication in the early postoperative stages. Nevertheless, given these comparable results and the absence of any graft delamination at 12 weeks (and 12 months) after surgery, these findings do suggest that the AR protocol can be employed without great concern for early graft complication or failure. Our hypothesis was supported, whereby there were no adverse effects on graft outcome, irrespective of the rehabilitation protocol.

Several limitations are recognized in the present study. First, we acknowledge that this is an early follow-up for a surgical procedure that produces repair tissue that continues to develop over a 2- to 3-year period.[4,27] However, the aim of this study was to investigate the early safety and efficacy of this accelerated WB regimen. Second, while we employed a number of self-reported questionnaires (KOOS, SF-36, VAS) used routinely for ACI,[1,19,33,38,41] 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.[29] Furthermore, 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. Third, the MRI scoring system employed evaluates morphological graft outcome. New methods of assessing the biochemical characteristics of repair tissue have emerged,[31,45,47] which may assist in evaluating the "ultrastructure" of the repair tissue.[11] These should be employed in the long-term follow-up of these patients.

This study has demonstrated comparable, if not superior, early subjective, functional, and radiological outcomes in patients following an accelerated approach to postoperative WB rehabilitation after MACI in the tibiofemoral joint compared with an evidence-based WB protocol that we considered to be current "best practice." Our hypotheses were generally supported, whereby both the patient and the graft tolerated the accelerated return to full WB without detriment, while superiority in some of the patient-reported subjective and functional scores was observed up to 12 months after surgery, and with superior outcomes demonstrated as early as 2 months. This regimen may also reduce the time and expense associated with the rehabilitation process, accelerate the time of return to a normal gait pattern, and enable the patient to return sooner to regular activities of daily living. The MACI tissues continue to develop and remodel through to 24 months after surgery,[4,27] and despite demonstrating that this "accelerated" WB protocol did not compromise graft adherence and patient outcomes in the early postoperative stages, a longer term postoperative follow-up is required to determine if there are any detrimental effects that may emerge as a result of the accelerated regimen.

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