# Two-Year Outcomes of a Randomized Trial Investigating a 6-Week Return to Full Weightbearing After Matrix-Induced Autologous Chondrocyte Implantation

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*Investigation performed at the University of Western Australia, Crawley, Australia*

**Background:** Matrix-induced autologous chondrocyte implantation (MACI) has demonstrated encouraging outcomes in treating patients with knee cartilage defects. Postoperatively, the time required to attain full weightbearing (WB) remains conservative.

**Hypothesis:** We hypothesized that patients would have no significant clinical or radiological differences or graft complications after an 8-week or 6-week return to full WB after MACI.

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

**Methods:** A total of 37 knees (n = 35 patients) were randomly allocated to either an 8-week return to full WB that we considered current best practice based on the existing literature (CR group; n = 19 knees) or an accelerated 6-week WB approach (AR group; n = 18 knees). Patients were evaluated preoperatively and at 1, 2, 3, 6, 12, and 24 months after surgery, using the Knee Injury and Osteoarthritis Outcome Score, 36-Item Short Form Health Survey, visual analog pain scale, 6-minute walk test, and active knee range of motion. Isokinetic dynamometry was used to assess peak knee extension and flexion strength and limb symmetry indices (LSIs) between the operated and nonoperated limbs. Magnetic resonance imaging (MRI) was undertaken to evaluate the quality and quantity of repair tissue as well as to calculate an MRI composite score.

**Results:** Significant improvements ($P < .05$) were observed in all subjective scores, active knee flexion and extension, 6-minute capacity, peak knee extensor torque in the operated limb, and knee extensor LSI, although no group differences existed. Although knee flexor LSIs were above 100% for both groups at 12 and 24 months after surgery, LSIs for knee extensor torque at 24 months were 93.7% and 87.5% for the AR and CR groups, respectively. The MRI composite score and pertinent graft parameters significantly improved over time ($P < .05$), with some superior in the AR group at 24 months. All patients in the AR group (100%) demonstrated good to excellent infill at 24 months, compared with 83% of patients in the CR group. Two cases of graft failure were observed, both in the CR group. At 24 months, 83% of patients in the CR group and 88% in the AR group were satisfied with the results of their MACI surgery.

**Conclusion:** Patients in the AR group who reduced the length of time spent ambulating on crutches produced comparable outcomes up to 24 months, without compromising graft integrity.

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

Matrix-induced autologous chondrocyte implantation (MACI) has demonstrated encouraging clinical outcomes in the repair of full-thickness knee articular cartilage defects.[4,16,21,22,30,38,47] The 2-stage surgery initially involves an arthroscopic harvest of healthy cartilage, whereby chondrocytes are cultured and subsequently seeded onto a synthetic collagen membrane for reimplantation in a second surgery. Postoperatively, a progressive weightbearing (WB) mechanical stimulus is required to permit differentiation and proliferation of chondrocytes to produce a hyaline-like tissue repair. Although early graft protection may be warranted, research supports the need for dynamic[19] and shear[52] loading to encourage cell proliferation and matrix synthesis, whereas static compression[5] and immobilization[24] appear to be detrimental, further reinforcing the role of a graded program incorporating exercises and progressive WB after MACI.

Researchers have outlined the importance of structured postoperative rehabilitation after MACI for initial graft protection, facilitation of chondrocyte differentiation and development, and return of the patient to normal physical function.[8,25,27,37,41,42] However, very little information has

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been made available on how best to progressively increase WB and exercise after surgery. As the general chondrocyte implantation technique has evolved (periosteal and collagen covered, and now matrix induced), a number of WB approaches have been proposed that have progressively become more accelerated over time.[14,36,45] Whereas Ebert et al[12-15] proposed an 8-week accelerated WB rehabilitation protocol that demonstrated tolerance by both the patient and the graft in the earlier stages and showed encouraging outcomes now out to 5 years after surgery, Edwards et al[18] compared this WB protocol with that of a 6-week return to full WB and demonstrated further benefits of this accelerated gradient to 12 months after surgery, without harm to the graft. The underlying aim of safely accelerating these WB protocols is to enhance the cell loading stimulus while accelerating the return of patients to full WB gait, normal knee joint loading, and general daily activity, which remains conservative and is a major drawback for the patient embarking on MACI.

Our study therefore presents an extension of the patient cohort reported by Edwards et al[18] with a comprehensive clinical and radiological follow-up in patients up to 24 months after surgery. We hypothesized that there would be no significant clinical or radiological differences or differences in graft complication rates between an accelerated 6-week WB approach after MACI, compared with the 8-week protocol that was considered "best practice" at that time based on the existing literature.[12-15]

## METHODS

### Patients

A randomized study design was used to allocate a total of 35 consecutive patients (n = 37 knees) to 2 different postoperative WB protocols after MACI to the medial or lateral femoral condyle: an 8-week return to full WB that we considered the current best practice based on the existing literature (CR group; n = 19 knees) or an accelerated 6-week WB approach (AR group; n = 18 knees). Patients were recruited between January 2010 and April 2014. Two of these patients underwent MACI surgery on both knees, 3 months apart; hence, a total of 37 knees were included in this study. Initially, an a priori power calculation was performed using G-Power (Heinrich-Heine University of Dusseldorf) for the primary outcome variable (the Knee Injury and Osteoarthritis Outcome Score [KOOS] pain subscale), demonstrating that 28 knees (n = 14 in each group) were required to reveal differences at the 5% significance level, with 90% power and employing a large effect size (1.1) as reported by previous research.[56] We continued recruitment beyond this to allow for attrition. All patients signed informed consent forms before study enrollment and preoperative evaluation. Ethics approval was obtained from Hollywood Private Hospital (HPH145) and the trial was undertaken according to the Declaration of Helsinki guidelines, although this study was not registered with any trial registry. A flowchart of study recruitment and assessment is demonstrated in Figure 1.

Enrolled patients were aged between 15 and 65 years and had undergone MACI to address full-thickness femoral condylar defects in the knee (<10 $cm^2$ on magnetic resonance imaging [MRI]). Multiple condylar defects and minor trochlear or patellar lesions were permitted, provided that they occurred in conjunction with a primary femoral lesion. Patients with a ligamentous or meniscal deficiency were included, provided that the deficiency was addressed at the time of MACI. Patients displaying a varus or valgus malalignment (>5° anatomic tibiofemoral angle) or those that suffered from any ongoing, progressive inflammatory arthritis, osteoarthritis, or rheumatoid arthritis were excluded. However, no patient within this study underwent multiple MACI grafting or any concomitant surgical technique in addition to MACI.

### MACI Surgery

MACI is a 2-stage surgery that involves isolating and culturing a patient's own chondrocytes in vitro and reimplanting them into the chondral defect. However, the 37 knees that underwent MACI as part this study underwent a combination of traditional miniopen[12-15] (7 in the AR group, 8 in the CR group) and arthroscopically performed[6,11] (11 in the AR group, 11 in the CR group) implantation techniques. Irrespective of the implantation method, an arthroscopic biopsy of healthy articular cartilage was initially performed, harvested from a non-WB area of the knee. Chondrocytes were then isolated, cultured, and seeded onto a type I/III collagen membrane (ACI-Maix; Matricel GmbH) ex vivo over a 6- to 8-week period. At the time of second-stage implantation, the defect site was accessed and prepared via a medial or lateral parapatellar miniarthrotomy (for the miniopen technique)[13,14,16,18] or via a standard arthroscopy routine using anteromedial and anterolateral portals (for the arthroscopic technique).[5,11]

### Postoperative WB Protocols

With respect to the 2 comparative WB gradients, a random-number generator via Microsoft Excel was used to allocate patients to an 8-week graduated return to full WB (CR

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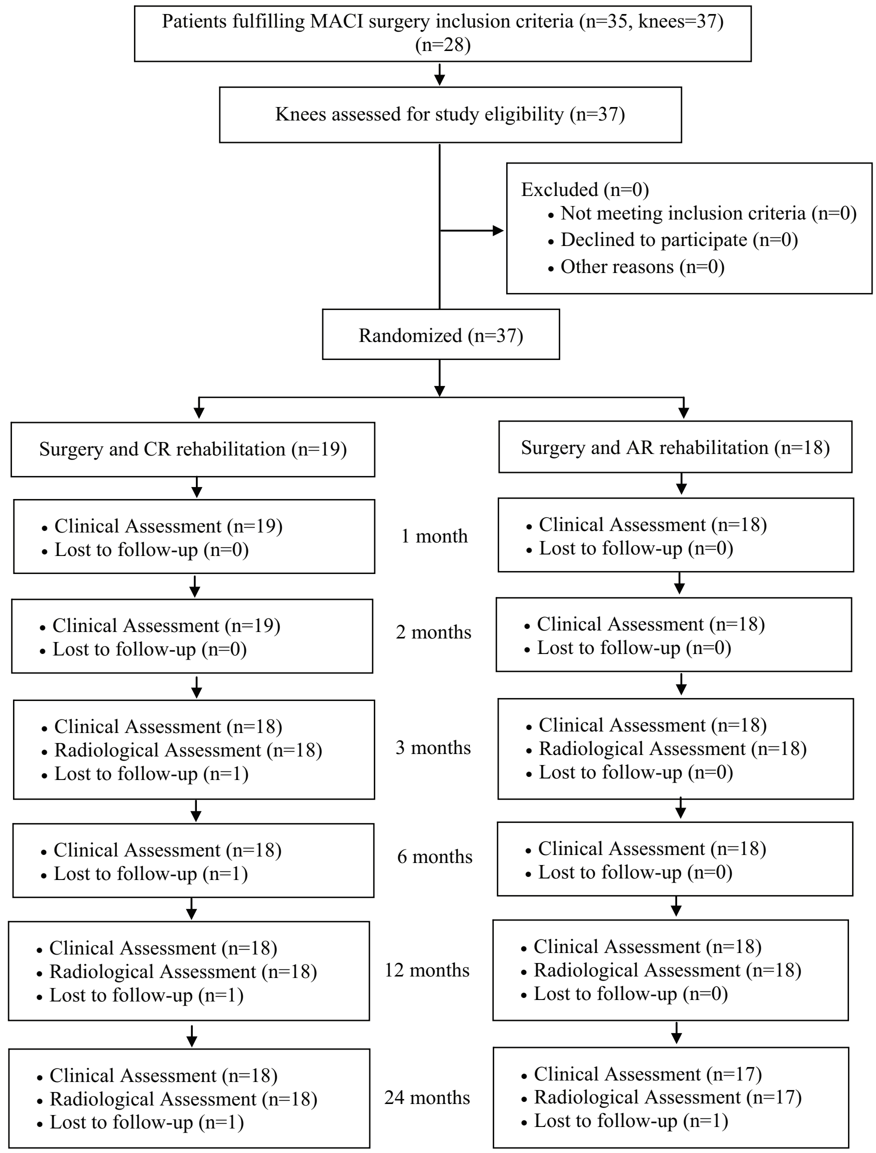


**Figure 1.** Flowchart demonstrating recruitment and evaluation over the 24-month period of patients into the accelerated (AR) and current best-practice (CR) weightbearing groups. MACI, matrix-induced autologous chondrocyte implantation.

group) based on the research of Ebert et al[12-15] or to a 6-week return to full WB (AR group). As documented by Edwards et al,[18] allocation was concealed and only the study coordinator had access to the randomization list. The study coordinator then assigned patients to the relevant intervention. The progressive WB protocols for both groups are outlined in Table 1. The 2 patients who received MACI on both knees were initially randomized into a WB protocol for their first knee and were subsequently allocated to the alternative pathway after surgery on the contralateral knee. Therefore, of the 37 knees included in this study, 18 (9 male, 9 female) were allocated to the AR group and 19 (12 male, 7 female) were allocated to the CR group (Figure 1).

The WB protocols were prescribed using the electronic bathroom scale method,[10,25] and WB replication training was an important component of each and every rehabilitation session up until the time that full WB was attained. The bathroom scale method remains the most practical and widely used modality for teaching WB restrictions.[10,25] However, although prior research has demonstrated improved accuracy with higher frequency of practice in patients specifically after MACI,[10] patients may demonstrate larger error in WB replication capacity at lower levels of WB.[10] We acknowledge that the WB levels prescribed for both groups in this study were similar (and low) in the first 3 postoperative weeks, also correlating with a time when graft protection is important, which likely resulted in significant overlap between the 2 groups at these early stages. However, we would expect WB replication error to be less after this early 3-week period once WB levels increased and more deviation in the WB protocols between the 2 rehabilitation groups existed. Furthermore, this study looked at the time to full

TABLE 1
Overview of Postoperative Weightbearing, Knee Range of Motion, Knee Bracing, and Exercise Rehabilitation Undertaken by Patients in the Study Groups[a]

Week 1
- WB: 20% BW in both the AR and CR groups
- Knee ROM: passive and active ROM from 0°-30°
- Knee bracing: 0°-30°
- Treatment/rehabilitation: isometric contractions and circulation exercises, CPM (0°-30°), and cryotherapy

Weeks 2-3
- WB: 20%-30% BW (CR group) and 20%-40% (AR group)
- Knee ROM: active ROM from 0°-30° (week 2) to 0°-60° (week 3)
- Knee bracing: 0°-30° (week 2) to 0°-90° (week 3)
- Treatment/rehabilitation: isometric and straight leg exercises, passive and active knee flexion exercises, remedial massage, soft tissue and patella mobilization, CPM (0°-90°), cryotherapy, and hydrotherapy

Weeks 4-6
- WB: 40%-60% BW (CR group) and 60%-100% (AR group)
- Knee ROM: full active ROM from week 4
- Knee bracing: 0°-90° (week 4) to full ROM (week 5)
- Treatment/rehabilitation: introduction of calf raises, weighted hip strengthening exercises, trunk strengthening, recumbent cycling

Weeks 7-12
- WB: 80%-100% BW (CR group)
- Knee ROM: full active ROM
- Knee bracing: full knee flexion permitted
- Treatment/rehabilitation: introduction of proprioceptive/balance activities, cycling, walking, resistance, and CKC activities

3-6 mo
- 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 mo
- Rehabilitation: increase difficulty of proprioceptive/balance, OKC and CKC exercises (ie, step ups/downs, squats), introduce controlled mini trampoline jogging

9-12 mo
- 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 mo

[a]AR, accelerated; BW, body weight; CKC, closed kinetic chain; CPM, continuous passive motion; CR, current best practice; OKC, open kinetic chain; ROM, range of motion; WB, weightbearing.

WB in addition to the postoperative WB gradient, whereby full WB was ensured at 8 weeks in the CR group and at 6 weeks in the AR group, once use of crutches ceased. Because of the ethical nature of this patient-informed trial, patients were aware of the 2 rehabilitation pathways and thus were able to determine their allocated WB rehabilitation group.

## Postoperative Exercise Rehabilitation

Although the WB protocols differed between the 2 groups (AR and CR), all patients received identical postoperative education and exercise prescription (Table 1). Initially, 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; 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, hamstrings, and gluteal musculature to maintain muscle tone and minimize muscle loss; and patient education of proficient toe-touch ambulation allowing no more than 20% of body weight through the operated limb. Patients wore a knee brace postoperatively for 24 hours per day. After hospital discharge, all patients embarked on a supervised outpatient rehabilitation program consisting of 2 supervised sessions per week over a 12-week period (Table 1), with ongoing advice and education provided up until 12 months if required. All rehabilitation programs were undertaken, and clinical outcomes collected, in a single private outpatient rehabilitation clinic.

## Clinical Outcome Measures

Patients were evaluated pre- and postoperatively with the following measures: the KOOS,[46] which was our primary outcome variable to assess knee pain, symptoms, activities of daily living (ADL), sport and recreation, and knee-related quality of life (QOL); the 36-Item Short Form Health Survey (SF-36)[53] to assess the general health of the patient, producing a mental component score and a physical component score; and the visual analog scale (VAS) to assess the frequency and severity of knee pain on a scale from 0 to 10. A patient satisfaction questionnaire was also administered at 24 months after surgery to investigate patients' level of satisfaction with the MACI surgery overall, as well as their satisfaction with MACI in relieving knee pain and improving their ability to perform normal daily activities, return to recreational activities, and participate in sports. A Likert response scale was employed with the following descriptors: very satisfied, somewhat satisfied, somewhat dissatisfied, and very dissatisfied.

Postoperatively, active knee flexion and extension were measured at all time points, whereas the 6-minute walk test was administered at 3, 6, 12, and 24 months. This test measured the maximum distance the patient could walk in a 6-minute time period, and patients were instructed to walk "as far and fast as they comfortably could" for the duration of the test. The 6-minute walk test also served as a standardized warm-up before maximal isokinetic strength assessment of the quadriceps and hamstrings muscle groups, which was performed at 12 and 24 months after surgery using an isokinetic dynamometer (Isosport International). Concentric knee extension and flexion strength was measured through a range of 0° to 90° of knee flexion, at a single isokinetic angular velocity of 90° per second. Each trial consisted of 4 repetitions: 3 low-intensity repetitions of knee extension and flexion, immediately followed by 1 maximal test effort. Two trials on each lower limb were undertaken, alternating between the operated and nonoperated limbs. During each maximal effort, patients were asked to perform to their maximal muscle strength while standardized verbal encouragement was provided. For all efforts, the peak torque value (in Newton meters) and hamstring/quadriceps (H/Q) ratio were obtained, which was measured by dividing the peak concentric hamstrings torque by the peak concentric quadriceps torque. A limb symmetry index (LSI) was calculated for all strength measures by dividing the peak values on the operated limb by those recorded on the nonoperated limb. All clinical assessments were undertaken by a blinded and independent research assistant who was unaware of the WB protocol randomization.

## Radiological Evaluation

Graft repair tissue was evaluated using high-resolution MRI at 3, 12, and 24 months after surgery, using a Siemens Symphony 1.5 or a 3-T scanner (Siemens, Philips, or General Electric), at a single private radiology center. 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). 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 1 axis).

We sought to evaluate 8 pertinent parameters of graft repair (graft infill, signal intensity, border integration, surface contour, tissue structure, joint effusion, subchondral lamina, and subchondral bone),[34] following the magnetic resonance observation of cartilage repair tissue (MOCART) scoring system.[33,44,51,54] The 8 defined parameters were each scored from 1 to 4 (1, poor; 2, fair; 3, good; and 4, excellent) compared with the adjacent native cartilage, although graft infill could also be scored with a fifth level (3.5, very good) corresponding with "graft hypertrophy."[34,51] An MRI composite score was calculated by multiplying each individual score by a weighting factor[44] and adding the scores together. MRI evaluation was performed by an independent, experienced musculoskeletal radiologist who was blinded to the clinical details and clinical outcome assessment.

## Statistical Analyses

Repeated-measures analysis of variance was used to investigate the progression of clinical and radiological scores over the 24-month postoperative timeline between the AR and CR WB groups. If significant main or interaction effects occurred, independent $t$ tests were used to investigate differences in the dependent variable between the specific assessment time points. This study reports the number (percentage) of grafts evaluated as good or excellent for each of the 8 parameters of graft repair and the MRI composite score at 24 months after surgery. The kappa coefficient was used to assess intraobserver reliability for the 8 pertinent morphological MRI scores, whereas the intraclass correlation coefficient was used for the continuous MRI composite score. This was achieved by rescoring 20 randomly selected MRI images filtered through a second time to the radiologist. Statistical analysis was performed using SPSS software (version 19.0; SPSS Inc), while statistical significance was determined at $P < .05$.

# RESULTS

Table 2 provides patient, injury, and surgical information for both WB groups. No significant between-group differences ($P > .05$) were observed in these variables before surgery. Clinical and radiological evaluation was completed for all other patients (and at all time points), except for 1 patient in the CR group who did not participate in the 3-, 6-, 12-, or 24-month clinical (or radiological) evaluations and 1 patient in the AR group who could not be located at 24 months after surgery (an intention-to-treat analysis was performed using the "last value carried forward" technique) (Figure 1).

## Clinical Outcomes

Although a significant time effect ($P < .05$) existed for all patient-reported outcome scores, active knee flexion and extension, and 6-minute walk capacity demonstrating improvement from presurgery to 24 months after surgery in both groups, there were no significant group effects ($P > .05$) (Table 3). A significant time effect ($P < .05$) was observed for absolute peak knee extensor torque ($P$ = .021) and the H/Q ratio ($P$ = .034) in the operated limb, as well as the knee extensor LSI ($P$ = .041). There were no other time effects nor were there any significant group effects ($P > .05$) (Table 4). Both groups demonstrated LSIs <85% for the knee extensors at 12 months after surgery (82.1% for the AR group, 83.5% for the CR group), although these were >85% at 24 months (93.7% for the AR group,

TABLE 2
Patient, Injury, and Surgical Information for Patients in the Study Groups[a]

| Variable | AR (6-wk Return) | CR (8-wk Return) | *P* Value |
|---|---|---|---|
| No. of patients (n = 35) | 17 | 18 | |
| No. of knees (n = 37) | 18 | 19 | |
| Men/women | 9/9 | 12/7 | |
| Surgical method, open/arthroscopic | 7/11 | 8/11 | |
| Age, y | 36.4 (21.0-55.0) | 36.4 (23.0-53.0) | .977 |
| Height, m | 1.76 (1.55-2.03) | 1.77 (1.54-1.92) | .792 |
| Weight, kg | 82.3 (46.0-130.0) | 79.4 (46.0-109.3) | .627 |
| Body mass index | 26.2 (18.4-32.1) | 25.2 (19.1-33.1) | .362 |
| Defect location, MFC/LFC | 13/5 | 14/5 | |
| Defect size, $cm^2$ | 3.15 (1.00-6.25) | 2.89 (1.00-7.70) | .549 |
| Defect size group, $cm^2$ | | | |
| $\leq$1.0 | 2 | 2 | |
| 1.1-2.0 | 5 | 6 | |
| 2.1-3.0 | 4 | 5 | |
| 3.1-4.0 | 4 | 2 | |
| 4.1-5.0 | 1 | 2 | |
| $\geq$5.1 | 2 | 2 | |
| Prior procedures | 1.1 (0-4) | 1.0 (0-4) | .610 |
| Duration of symptoms, y | 7.5 (1-25) | 6.8 (1-25) | .515 |

[a]Data are reported as numbers or means (ranges) unless otherwise indicated. AR, accelerated group; CR, current best-practice group; LFC, lateral femoral condyle; MFC, medial femoral condyle.

87.5% for the CR group). LSIs for the knee flexors were >100% for both groups at 12 and 24 months, indicating a stronger operated limb.

Patient satisfaction among the CR and AR groups, respectively, was as follows at 24 months: 83% (n = 15) and 94% (n = 16) of patients were satisfied with their ability of MACI to relieve their knee pain; 94% in both groups (n = 17, n = 16) were satisfied with the improvement in their ability to undertake daily activities; 94% in both groups (n = 17, n = 16) were satisfied with their ability to return to recreational activities; and 78% and 82% (n = 14 in each) were satisfied with their ability to participate in sports. Overall, 88% of patients in the AR group and 83% in the CR group (n = 15 in each) were satisfied with the results of their MACI surgery, respectively.

## Radiological Outcomes

For the 20 randomly selected image pairs, 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 scoring variables (rho [ρ] values were as follows: signal intensity, 1.00; graft infill, 0.949; border integration, 0.982; surface contour, 1.00; tissue structure, 0.840; subchondral lamina, 1.00; subchondral bone, 0.920; and joint effusion, 0.993) and the MRI composite score (ρ = 0.811).

MRI findings revealed a significant time effect ($P < .05$) for the MRI composite score, as well as graft infill, signal intensity, subchondral lamina, subchondral bone, and joint effusion over the 24-month period (Table 5). The border integration ($P = .041$) and surface contour ($P = .022$) variables were significantly better in the AR group compared with the CR group. A significant interaction effect existed for the signal intensity variable ($P = .013$), largely owing to a decline in the CR group between 12 and 24 months (Table 5).

At 24 months after surgery, the overall MRI composite score was classified as good to excellent in 100% of patients in the AR group (n = 17) and 78% in the CR group (n = 14) (Table 6). Furthermore, the degree of graft infill was classified as good to excellent in 100% of patients in the AR group and 83% of the CR group, respectively (Table 6). Figure 2 shows the development of a MACI graft located on the medial femoral condyle of a patient in the AR group, assessed via MRI throughout the pre- and postoperative timeline.

## Complications

No early postoperative complications, such as wound infections, hematomas, or deep vein thrombosis, were observed. Of the 35 grafts that underwent MRI evaluation at 24 months after surgery, 9 (26%) were hypertrophic (n = 4 in the AR group, n = 5 in the CR group), none of which were associated with ongoing knee pain or mechanical symptoms. These were all located on the medial femoral condyle. We have now observed 2 graft failures up until 24 months after surgery, both of which presented in the CR group. Of these, 1 patient had no discernible tissue on MRI at 3 months after surgery (which continued to 12 and 24 months), whereas the second patient scored a rating of "fair" (<50% infill) for graft infill at 3 months but was devoid of any repair tissue at 12 and 24 months after surgery.

## DISCUSSION

MACI has demonstrated encouraging clinical outcomes and evidence of tissue regeneration in the treatment of

TABLE 3
Analysis of Variance Results Summary for the Clinical Outcomes[a]

| | Outcome Measure | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | KOOS | | | | | SF-36 | | VAS | | ROM | | |
| Time Point and Group | Pain | Symptoms | ADL | SR | QOL | PCS | MCS | Pain Frequency | Pain Severity | Extension | Flexion | 6-min Walk |
| Presurgery | | | | | | | | | | | | |
| AR | 63.2 ± 3.9 | 64.0 ± 4.3 | 73.8 ± 3.9 | 26.8 ± 5.8 | 31.7 ± 3.7 | 35.1 ± 1.9 | 51.1 ± 2.4 | 6.3 ± 0.6 | 5.7 ± 0.6 | — | — | — |
| CR | 66.9 ± 4.2 | 73.1 ± 4.6 | 80.6 ± 4.2 | 36.2 ± 6.2 | 35.6 ± 4.0 | 39.6 ± 2.1 | 51.5 ± 2.6 | 6.5 ± 0.7 | 5.3 ± 0.6 | — | — | — |
| 4 wk | | | | | | | | | | | | |
| AR | 70.2 ± 4.6 | 71.7 ± 4.0 | 68.2 ± 4.3 | 7.3 ± 2.9 | 36.5 ± 4.7 | 30.9 ± 1.8 | 52.7 ± 2.9 | 3.7 ± 0.6 | 2.9 ± 0.6 | 0.0 ± 0.4 | 107.8 ± 4.5 | — |
| CR | 65.5 ± 4.9 | 68.4 ± 4.3 | 62.7 ± 4.6 | 6.2 ± 3.2 | 25.7 ± 5.1 | 30.6 ± 1.9 | 51.8 ± 3.2 | 4.6 ± 0.7 | 4.5 ± 0.6 | 0.4 ± 0.4 | 110.5 ± 4.9 | — |
| 8 wk | | | | | | | | | | | | |
| AR | 77.9 ± 3.6 | 77.9 ± 2.9 | 82.1 ± 2.7 | 11.7 ± 3.5 | 41.0 ± 3.8 | 39.7 ± 2.1 | 56.8 ± 1.9 | 2.8 ± 0.6 | 2.3 ± 0.5 | –0.4 ± 0.2 | 129.2 ± 3.3 | — |
| CR | 77.3 ± 3.6 | 78.8 ± 3.1 | 77.5 ± 2.9 | 6.2 ± 3.8 | 32.2 ± 4.1 | 31.6 ± 2.2 | 58.6 ± 2.1 | 3.0 ± 0.6 | 3.4 ± 0.6 | 0.2 ± 0.2 | 129.0 ± 3.6 | — |
| 3 mo | | | | | | | | | | | | |
| AR | 80.1 ± 3.4 | 80.5 ± 2.6 | 84.3 ± 2.5 | 19.7 ± 4.0 | 45.6 ± 3.3 | 41.6 ± 2.0 | 57.5 ± 1.5 | 2.0 ± 0.4 | 1.4 ± 0.4 | –0.9 ± 0.3 | 136.7 ± 2.4 | 522 ± 21 |
| CR | 75.5 ± 3.6 | 77.5 ± 2.8 | 83.0 ± 2.6 | 11.2 ± 4.3 | 39.9 ± 3.6 | 37.2 ± 2.2 | 58.8 ± 1.6 | 2.7 ± 0.4 | 3.0 ± 0.4 | –0.2 ± 0.3 | 139.4 ± 2.6 | 509 ± 23 |
| 6 mo | | | | | | | | | | | | |
| AR | 86.2 ± 2.3 | 86.2 ± 3.2 | 91.0 ± 2.4 | 49.2 ± 5.4 | 61.6 ± 2.7 | 45.6 ± 2.1 | 57.4 ± 1.5 | 2.0 ± 0.4 | 1.9 ± 0.4 | –1.6 ± 0.5 | 142.3 ± 1.6 | 600 ± 21 |
| CR | 82.6 ± 2.5 | 82.9 ± 3.4 | 89.7 ± 2.6 | 33.5 ± 5.8 | 50.5 ± 2.9 | 44.8 ± 2.3 | 56.9 ± 1.6 | 2.5 ± 0.4 | 2.4 ± 0.4 | –1.0 ± 0.5 | 145.1 ± 1.7 | 578 ± 22 |
| 12 mo | | | | | | | | | | | | |
| AR | 86.8 ± 2.1 | 85.8 ± 2.9 | 92.5 ± 2.2 | 60.7 ± 5.9 | 70.8 ± 4.4 | 46.7 ± 1.8 | 59.3 ± 1.4 | 1.6 ± 0.3 | 2.0 ± 0.4 | –1.2 ± 0.4 | 140.9 ± 1.8 | 634 ± 20 |
| CR | 88.3 ± 2.2 | 88.7 ± 3.1 | 95.4 ± 2.3 | 64.8 ± 6.4 | 59.1 ± 4.7 | 49.6 ± 1.9 | 57.1 ± 1.5 | 1.3 ± 0.4 | 1.8 ± 0.4 | –1.6 ± 0.4 | 144.9 ± 1.9 | 626 ± 21 |
| 24 mo | | | | | | | | | | | | |
| AR | 88.0 ± 3.3 | 86.1 ± 2.5 | 92.3 ± 2.8 | 69.0 ± 7.2 | 71.5 ± 5.8 | 49.1 ± 2.5 | 54.9 ± 1.7 | 1.6 ± 0.5 | 1.7 ± 0.4 | –1.8 ± 0.4 | 143.6 ± 1.8 | 656 ± 22 |
| CR | 90.2 ± 3.6 | 88.8 ± 2.6 | 95.4 ± 3.0 | 69.4 ± 7.7 | 67.3 ± 6.3 | 50.2 ± 2.7 | 58.0 ± 1.9 | 1.4 ± 0.5 | 1.8 ± 0.4 | –2.0 ± 0.4 | 144.8 ± 2.0 | 664 ± 24 |
| *P* value | | | | | | | | | | | | |
| Time effect | <.0001 | <.0001 | <.0001 | <.0001 | <.0001 | <.0001 | .004 | <.0001 | <.0001 | <.0001 | <.0001 | <.0001 |
| Group effect | .865 | .778 | .987 | .599 | .105 | .702 | .839 | .582 | .193 | .684 | .502 | .814 |
| Interaction effect | .703 | .670 | .707 | .580 | .491 | .835 | .844 | .357 | .472 | .095 | .900 | .285 |

[a]Data are reported as means ± SE unless otherwise indicated. ADL, activities of daily living; AR, accelerated group; CR, current best-practice group; KOOS, Knee Injury and Osteoarthritis Outcome Score; MCS, mental component score; PCS, physical component score; QOL, quality of life; ROM, range of motion; SR, sport and recreation; SF-36, 36-Item Short Form Health Survey; VAS, visual analog scale.

TABLE 4
Analysis of Variance Results Summary for Knee Strength Scores[a]

| | Operated Limb | | | Nonoperated Limb | | | Limb Symmetry Index | |
|---|---|---|---|---|---|---|---|---|
| Time Point and Group | Extension Torque, N·m | Flexion Torque, N·m | H/Q Ratio | Extension Torque, N·m | Flexion Torque, N·m | H/Q Ratio | Extensor Torque | Flexor Torque |
| 12 mo | | | | | | | | |
| AR | 183.4 ± 21.4 | 149.4 ± 11.2 | 0.87 ± 0.07 | 224.7 ± 25.9 | 140.8 ± 9.8 | 0.63 ± 0.04 | 82.1 ± 5.2 | 107.8 ± 7.9 |
| CR | 182.3 ± 25.0 | 153.2 ± 15.0 | 0.89 ± 0.08 | 224.1 ± 23.3 | 146.2 ± 8.9 | 0.69 ± 0.04 | 83.5 ± 6.3 | 108.8 ± 9.5 |
| 24 mo | | | | | | | | |
| AR | 199.5 ± 18.5 | 147.0 ± 13.5 | 0.73 ± 0.03 | 213.3 ± 20.0 | 140.0 ± 9.0 | 0.67 ± 0.03 | 93.7 ± 3.1 | 101.1 ± 4.5 |
| CR | 207.8 ± 23.2 | 155.5 ± 11.4 | 0.76 ± 0.04 | 235.8 ± 19.6 | 148.1 ± 11.3 | 0.67 ± 0.04 | 87.5 ± 3.7 | 101.2 ± 5.4 |
| *P* value | | | | | | | | |
| Time effect | .021 | .587 | .034 | .673 | .573 | .876 | .041 | .100 |
| Group effect | .867 | .673 | .740 | .713 | .575 | .581 | .816 | .800 |
| Interaction effect | .716 | .624 | .932 | .082 | .876 | .080 | .164 | .660 |

[a]Data are reported as means ± SE unless otherwise indicated. AR, accelerated group; CR, current best-practice group; H/Q, hamstring/quadriceps.

knee articular cartilage defects.[4,16,21,22,30,38,47] Although cell culture and surgical procedures continue to improve, postoperative rehabilitation and WB protocols are generally conservative and best patient outcomes may be limited by a lack of knowledge regarding how to progressively increase load bearing and exercise after surgery. This study aimed to investigate the clinical and radiological outcomes of a 6-week return to full WB after MACI performed on the tibiofemoral knee joint. This accelerated WB return provided comparable outcomes up to 24 months after surgery, without harm to the patient or the graft, compared with a protocol we deemed to be the current best practice based on the available evidence at trial onset.

Both WB groups demonstrated significant improvement over time on all subjective rating scales, although there were no between-group differences to 24 months. Although

TABLE 5
Analysis of Variance Summary of the Postoperative MRI Assessment of Grafts at 3, 12, and 24 Months After Surgery[a]

| Time Point and Group | MRI Parameter: Graft Infill | Signal Intensity | Border Integration | Surface Contour | Tissue Structure | Subchondral Lamina | Subchondral Bone | Joint Effusion | MRI Composite Score |
|---|---|---|---|---|---|---|---|---|---|
| 3 mo | | | | | | | | | |
| AR | 3.09 ± 0.16 | 2.12 ± 0.17 | 2.88 ± 0.21 | 3.41 ± 0.23 | 3.59 ± 0.21 | 3.06 ± 0.13 | 0.294 ± 0.18 | 3.65 ± 0.12 | 2.97 ± 0.11 |
| CR | 2.71 ± 0.16 | 2.16 ± 0.16 | 2.37 ± 0.19 | 2.95 ± 0.22 | 3.26 ± 0.20 | 2.84 ± 0.12 | 2.79 ± 0.17 | 3.63 ± 0.11 | 2.68 ± 0.11 |
| 12 mo | | | | | | | | | |
| AR | 3.53 ± 0.18 | 3.00 ± 0.22 | 3.24 ± 0.23 | 3.18 ± 0.27 | 3.24 ± 0.23 | 3.47 ± 0.16 | 3.41 ± 0.20 | 3.71 ± 0.11 | 3.32 ± 0.16 |
| CR | 3.18 ± 0.17 | 2.74 ± 0.21 | 2.79 ± 0.22 | 2.63 ± 0.26 | 3.16 ± 0.21 | 3.31 ± 0.15 | 3.00 ± 0.19 | 3.95 ± 0.10 | 3.01 ± 0.15 |
| 24 mo | | | | | | | | | |
| AR | 3.47 ± 0.18 | 3.30 ± 0.19 | 3.29 ± 0.25 | 3.65 ± 0.25 | 3.58 ± 0.23 | 3.59 ± 0.14 | 3.35 ± 0.22 | 3.88 ± 0.07 | 3.46 ± 0.15 |
| CR | 3.18 ± 0.17 | 2.58 ± 0.18 | 2.79 ± 0.23 | 2.79 ± 0.24 | 3.16 ± 0.21 | 3.42 ± 0.13 | 3.05 ± 0.20 | 3.95 ± 0.06 | 3.00 ± 0.15 |
| *P* value | | | | | | | | | |
| Time effect | .002 | <.0001 | .062 | .846 | .720 | <.0001 | .038 | .007 | <.0001 |
| Group effect | .117 | .136 | .041 | .022 | .192 | .227 | .208 | .305 | .052 |
| Interaction effect | .717 | .013 | .983 | .327 | .720 | .834 | .638 | .677 | .376 |

[a]Data are reported as means ± SE unless otherwise indicated. AR, accelerated group; CR, current best-practice group; MRI, magnetic resonance imaging.

TABLE 6
Graft Ratings at 24 Months After Surgery by MRI Assessment[a]

| Group and Score | MRI Parameter: Graft Infill | Signal Intensity | Border Integration | Surface Contour | Tissue Structure | Subchondral Lamina | Subchondral Bone | Joint Effusion | MRI Composite Score |
|---|---|---|---|---|---|---|---|---|---|
| AR (n = 17) | | | | | | | | | |
| Good to excellent | 17 (100) | 16 (94) | 16 (94) | 16 (94) | 16 (94) | 17 (100) | 15 (88) | 17 (100) | 17 (100) |
| Poor to fair | 0 (0) | 1 (6) | 1 (6) | 1 (6) | 1 (6) | 0 (0) | 2 (12) | 0 (0) | 0 (0) |
| CR (n = 18) | | | | | | | | | |
| Good to excellent | 15 (83) | 16 (89) | 14 (78) | 14 (78) | 15 (83) | 17 (94) | 14 (78) | 17 (94) | 14 (78) |
| Poor to fair | 3 (17) | 2 (11) | 4 (22) | 4 (22) | 3 (17) | 1 (6) | 4 (22) | 1 (6) | 4 (22) |

[a]Data are reported as n (%). AR, accelerated group; CR, current best-practice group; MRI, magnetic resonance imaging.

comparative WB studies after MACI are scarce, the 24-month clinical outcomes in this study appear to be comparable to those previously reported by Ebert et al[15] at 24 months (KOOS and SF-36) in a trial investigating an 8-week (vs 12-week) WB approach, although with lower VAS (severity and frequency) scores in our study. More recently, Wondrasch et al[55] presented outcomes to 5 years for a 6-week (vs 10-week) return to full WB and showed no clinical group differences, although all KOOS subscales in the current study (apart from the KOOS sport and recreation subscale) appeared better at 24 months, particularly the KOOS symptoms and QOL subscales. Overall, these clinical scores appeared to be associated with patient-reported satisfaction, with high levels of satisfaction with the ability of MACI to reduce knee pain, permit ease in undertaking daily activities, and return patients to recreational and sports activities.

Active knee flexion and extension also significantly improved over the study period, although there were no group differences. Despite the lack of statistical significance, it is apparent that the AR group attained full knee extension by 4 weeks, with hyperextension from 8 weeks onward. The CR group did not attain full knee extension until 3 months after surgery. Clinically, the attainment of full active knee extension ROM in the earlier stages may permit a more normal gait pattern, which we consider important irrespective of whether the patient is partially or fully WB. As reported by Edwards et al,[18] full active knee extension is essential for normal gait and body weight acceptance through the stance phase, and a persistent fixed flexion deformity may create a functionally shorter limb, thereby promoting deleterious biomechanics of the hip, pelvis, and lower spine. Although patients in the AR group were able to walk further at 3 and 6 months in the 6-minute walk test, these differences were not statistically significant nor were they likely to be clinically relevant. Although the AR group was permitted an additional 2 weeks of ambulation without crutches, this did not appear to induce better 6-minute walk capacity. The 6-minute walk test has been reported as a key component of many ADLs and a foundation for functional

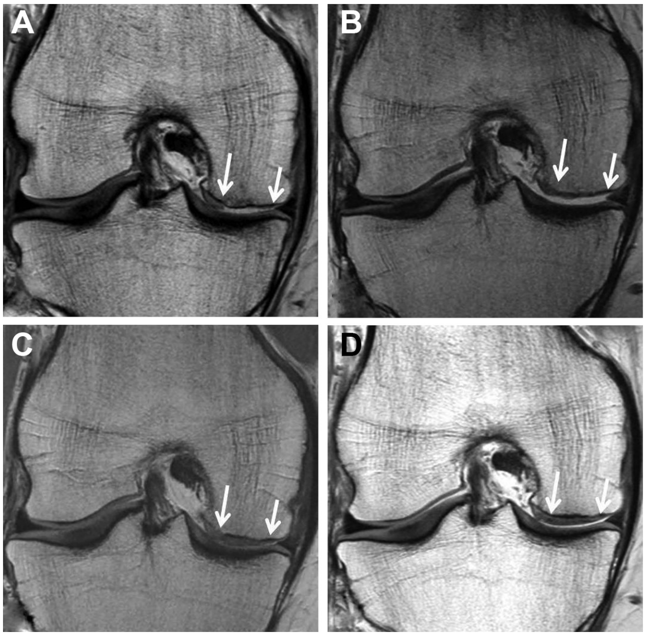


**Figure 2.** Proton-density fast spin-echo magnetic resonance images of a lesion (and subsequent graft) on the medial femoral condyle (between white arrows) in a MACI-treated patient in the accelerated weightbearing group (A) presurgery (defect between white arrows) and at (B) 3 months, (C) 12 months, and (D) 24 months after surgery. MACI, matrix-induced autologous chondrocyte implantation.

independence[20,44]; however, it could be argued that this test is not clinically relevant (nor validated) for younger, active MACI-treated patients, although it was also used as a standardized warm-up that preceded the maximal isokinetic strength testing.

There were no group differences, although significant improvement over time was observed in peak knee extensor strength and the LSI for knee extensor torque. This was expected, given that the only difference between the 2 groups was the additional 2 weeks of full WB in the AR group, and isokinetic strength assessment was not administered until 12 months after surgery. However, even at 12 months, the LSI for peak quadriceps torque was <85% for both groups; this becomes relevant when patients are considering a return to higher-level activities and sports. Postoperatively, restoration of lower limb muscle function including isokinetic knee strength is considered important for a successful return to physical activity.[1,2,28,32,48] Although these previous studies generally focused on patients who underwent anterior cruciate ligament (ACL) reconstruction, LSI cutoffs have been reported in evaluating strength and functional performance, with both <90%[29,43,48] and <85%[35,39] regarded as unsatisfactory and abnormal and suggesting that an individual is unsafe to return to sports. The results of our study suggest that although there were no group differences, the rehabilitation intervention did not restore optimal quadriceps strength by 12 months. By 24 months, the AR group was >90%, whereas the CR group remained <90%. Although this finding is not statistically significant, it may be clinically relevant because a recent study by Grindem et al[23] among patients who underwent ACL reconstruction demonstrates the important role of quadriceps strength symmetry in reducing knee reinjury rates. Although the study by Grindem et al was specific to patients with an ACL-reconstructed knee, it is interesting to note that a 3% reduced reinjury rate was permitted for every 1% increase in strength symmetry. LSIs for knee flexor strength were >100% for both WB groups at 12 and 24 months, suggesting that the rehabilitation program was adequate in restoring hamstring strength.

Our MRI findings revealed significant improvement in the MRI composite score and a range of other pertinent individual scores, including graft infill. Furthermore, the MRI composite score at 24 months was classified as good to excellent in 100% of patients in the AR group and 78% in the CR group. However, the only significant group differences were observed in graft border integration and surface contour, both of which scored better in the AR group. These findings appeared to be comparable with prior work employing this scoring tool,[13] although the poorer (yet nonsignificant) scores at 24 months for the CR group were likely attributed to the 2 graft failures observed in those patients. Of these, 1 patient lacked any repair tissue as early as 3 months after surgery, whereas the second patient was devoid of any repair tissue by 12 months. Both patients appeared to be compliant and followed the guidance provided, although graft failure may be dependent on patient-therapist communication and noncompliance, emphasizing the importance of controlled WB and exercise progression. We could not attribute these failures to the CR WB protocol. Certainly, given that there have been no graft failures in the AR group at the time of this publication, we can conclude that this accelerated 6-week WB protocol can be employed without additional concern for early graft complication and/or subsequent failure.

We acknowledge a range of limitations in the present study. First, we employed a number of patient-reported outcome scores (KOOS, SF-36, and VAS) that are used routinely for autologous chondrocyte implantation,[3,14,33,40,44] although we lack a specific cartilage repair outcome measure at this stage.[26] Other clinical scoring tools exist and have been used in other research, which may make the comparison of outcomes among these studies difficult. Furthermore, MACI aims to return patients to a pain-free and normally active lifestyle,[17] and patients generally expect a return to their preinjury activity level.[7] An activity-based questionnaire that evaluates the frequency and intensity of physical activity/sport may have provided some further insight into individual patient outcomes up until 24 months. It is also acknowledged that patients were aware of their WB randomization and, although they were asked to answer all scores truthfully, the degree of potential bias resulting from patients' knowledge of their treatment protocol was unknown. Finally, we employed the MOCART morphological tool to score graft status, and evolving MRI evaluation methods investigating the biochemical characteristics of the repair tissue are emerging, including dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) and

T2 mapping.[31,49,50] These may provide more information on the "ultrastructure" of the repair tissue.[9]

In conclusion, our hypothesis that there would be no significant clinical or radiological differences was generally supported and, although differences existed in some of the MRI-based measures, the 2 WB groups (AR and CR) were similar in all other clinical measures. Two graft failures were observed in the CR group, although we could not attribute this to the more conservative pathway. The AR group reduced the length of time spent ambulating on crutches and produced comparable outcomes up to 24 months, without compromising graft integrity.

## REFERENCES


1. Ageberg E, Thomee R, Neeter C, Silbernagel KG, Roos EM. Muscle strength and functional performance in patients with anterior cruciate ligament injury treated with training and surgical reconstruction or training only: a two to five-year followup. *Arthritis Rheum*. 2008;59:1773-1779.
2. Augustsson J, Thomee R, Karlsson J. Ability of a new hop test to determine functional deficits after anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc*. 2004;12:350-356.
3. Bartlett W, Gooding CR, Carrington RW, Briggs TW, Skinner JA, Bentley G. The role of the Short Form 36 Health Survey in autologous chondrocyte implantation. *Knee*. 2005;12:281-285.
4. Behrens P, Bitter T, Kurz B, Russlies M. Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI) - 5-year follow-up. *Knee*. 2006;13:194-202.
5. Buschmann MD, Gluzband YA, Grodzinsky AJ, Hunziker EB. Mechanical compression modulates matrix biosynthesis in chondrocyte/agarose culture. *J Cell Sci*. 1995;108:1497-1508.
6. Carey Smith R, Ebert JR, Davies H., Garrett S, Wood DJ, Janes GC. Arthroscopic matrix-induced autologous chondrocyte implantation: A simple surgical technique. *Techn Knee Surg*. 2010;9:170-175.
7. Della Villa S, Kon E, Filardo G, et al. Does intensive rehabilitation permit early return to sport without compromising the clinical outcome after arthroscopic autologous chondrocyte implantation in highly competitive athletes? *Am J Sports Med*. 2010;38:68-77.
8. Deszczynski J, Slynarski K. Rehabilitation after cell transplantation for cartilage defects. *Transplantation proceedings*. 2006;38:314-315.
9. Domayer SE, Welsch GH, Dorotka R, et al. MRI monitoring of cartilage repair in the knee: a review. *Semin Musculoskelet Radiol*. 2008;12:302-317.
10. Ebert JR, Ackland TR, Lloyd DG, Wood DJ. Accuracy of partial weight bearing after autologous chondrocyte implantation. *Arch Phys Med Rehabil*. 2008;89:1528-1534.
11. Ebert JR, Fallon M, Ackland TR, Wood DJ, Janes GC. Arthroscopic matrix-induced autologous chondrocyte implantation: 2-year outcomes. *Arthroscopy*. 2012;28:952-964 e952.
12. Ebert JR, Fallon M, Robertson WB, et al. Radiological assessment of accelerated versus traditional approaches to post-operative rehabilitation following matrix-induced autologous chondrocyte implantation (MACI). *Cartilage*. 2011;2:60-72.
13. Ebert JR, Fallon M, Zheng MH, Wood DJ, Ackland TR. A randomized trial comparing accelerated and traditional approaches to postoperative weightbearing rehabilitation after matrix-induced autologous chondrocyte implantation: findings at 5 years. *Am J Sports Med*. 2012;40:1527-1537.
14. Ebert JR, Robertson WB, Lloyd DG, Zheng MH, Wood DJ, Ackland T. Traditional vs accelerated approaches to post-operative rehabilitation following matrix-induced autologous chondrocyte implantation (MACI): comparison of clinical, biomechanical and radiographic outcomes. *Osteoarthritis Cartilage*. 2008;16:1131-1140.
15. Ebert JR, Robertson WB, Lloyd DG, Zheng MH, Wood DJ, Ackland T. A prospective, randomized comparison of traditional and accelerated approaches to postoperative rehabilitation following autologous chondrocyte implantation: 2-year clinical outcomes. *Cartilage*. 2010;1:180-187.
16. Ebert JR, Robertson WB, Woodhouse J, et al. Clinical and magnetic resonance imaging-based outcomes to 5 years after matrix-induced autologous chondrocyte implantation to address articular cartilage defects in the knee. *Am J Sports Med*. 2011;39:753-763.
17. Ebert JR, Smith A, Edwards PK, Ackland TR. The progression of isokinetic knee strength after matrix-induced autologous chondrocyte implantation: implications for rehabilitation and return to activity. *J Sport Rehabil*. 2014;23:244-258.
18. Edwards PK, Ackland TR, Ebert JR. Accelerated weightbearing rehabilitation after matrix-induced autologous chondrocyte implantation in the tibiofemoral joint: early clinical and radiological outcomes. *Am J Sports Med*. 2013;41:2314-2324.
19. Elder SH, Goldstein SA, Kimura JH, Soslowsky LJ, Spengler DM. Chondrocyte differentiation is modulated by frequency and duration of cyclic compressive loading. *Ann Biomed Eng*. 2001;29:476-482.
20. Enright PL. The six-minute walk test. *Respiratory Care*. 2003;48:783-785.
21. Genovese E, Ronga M, Angeretti MG, et al. Matrix-induced autologous chondrocyte implantation of the knee: mid-term and long-term follow-up by MR arthrography. *Skeletal Radiol*. 2010;40:47-56.
22. Gobbi A, Kon E, Berruto M, et al. Patellofemoral full-thickness chondral defects treated with second-generation autologous chondrocyte implantation: results at 5 years' follow-up. *Am J Sports Med*. 2009;37:1083-1092.
23. Grindem H, Snyder-Mackler L, Moksnes H, Engebretsen L, Risberg MA. Simple decision rules can reduce reinjury risk by 84% after ACL reconstruction: the Delaware-Oslo ACL cohort study. *Br J Sports Med*. 2016;50:804-808.
24. Grumbles RM, Howell DS, Howard GA, et al. Cartilage metalloproteases in disuse atrophy. *J Rheumatol Suppl*. 1995;43:146-148.
25. Hambly K, Bobic V, Wondrasch B, Van Assche D, Marlovits S. Autologous chondrocyte implantation postoperative care and rehabilitation: science and practice. *Am J Sports Med*. 2006;34:1020-1038.
26. Hambly K, Griva K. IKDC or KOOS? Which measures symptoms and disabilities most important to postoperative articular cartilage repair patients? *Am J Sports Med*. 2008;36:1695-1704.
27. Hirschmuller A, Baur H, Braun S, Kreuz PC, Sudkamp NP, Niemeyer P. Rehabilitation after autologous chondrocyte implantation for isolated cartilage defects of the knee. *Am J Sports Med*. 2011;39:2686-2696.
28. Itoh H, Kurosaka M, Yoshiya S, Ichihashi N, Mizuno K. Evaluation of functional deficits determined by four different hop tests in patients with anterior cruciate ligament deficiency. *Knee Surg Sports Traumatol Arthrosc*. 1998;6:241-245.
29. Juris PM, Phillips EM, Dalpe C, Edwards C, Gotlin RS, Kane DJ. A dynamic test of lower extremity function following anterior cruciate ligament reconstruction and rehabilitation. *J Orthop Sports Phys Ther*. 1997;26:184-191.
30. Kon E, Di Martino A, Filardo G, et al. Second-generation autologous chondrocyte transplantation: MRI findings and clinical correlations at a minimum 5-year follow-up. *Eur J Radiol*. 2011;79:382-388.
31. Kurkijarvi JE, Nissi MJ, Kiviranta I, Jurvelin JS, Nieminen MT. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and T2 characteristics of human knee articular cartilage: topographical variation and relationships to mechanical properties. *Magn Reson Med*. 2004;52:41-46.
32. Lee DY, Karim SA, Chang HC. Return to sports after anterior cruciate ligament reconstruction - a review of patients with minimum 5-year follow-up. *Ann Acad Med Singapore*. 2008;37:273-278.
33. Marlovits S, Singer P, Zeller P, Mandl I, Haller J, Trattnig S. Magnetic resonance observation of cartilage repair tissue (MOCART) for the evaluation of autologous chondrocyte transplantation: determination of interobserver variability and correlation to clinical outcome after 2 years. *Eur J Radiol*. 2006;57:16-23.
34. Marlovits S, Striessnig G, Resinger CT, et al. Definition of pertinent parameters for the evaluation of articular cartilage repair tissue with high-resolution magnetic resonance imaging. *Eur J Radiol*. 2004;52:310-319.

35. Mattacola CG, Perrin DH, Gansneder BM, Gieck JH, Saliba EN, McCue FC 3rd. Strength, functional outcome, and postural stability after anterior cruciate ligament reconstruction. *J Athl Train*. 2002;37:262-268.
36. Minas T, Peterson L. Advanced techniques in autologous chondrocyte transplantation. *Clin Sports Med*. 1999;18:13-44, v-vi.
37. Mithoefer K, Hambly K, Logerstedt D, Ricci M, Silvers H, Della Villa S. Current concepts for rehabilitation and return to sport after knee articular cartilage repair in the athlete. *J Orthop Sports Phys Ther*. 2012;42:254-273.
38. Nehrer S, Dorotka R, Domayer S, Stelzeneder D, Kotz R. Treatment of full-thickness chondral defects with Hyalograft C in the knee: a prospective clinical case series with 2 to 7 years' follow-up. *Am J Sports Med*. 2009;37(suppl 1):81S-87S.
39. Noyes FR, Barber SD, Mangine RE. Abnormal lower limb symmetry determined by function hop tests after anterior cruciate ligament rupture. *Am J Sports Med*. 1991;19:513-518.
40. Ossendorf C, Kaps C, Kreuz PC, Burmester GR, Sittinger M, Erggelet C. Treatment of posttraumatic and focal osteoarthritic cartilage defects of the knee with autologous polymer-based three-dimensional chondrocyte grafts: 2-year clinical results. *Arthritis Res Ther*. 2007;9:R41.
41. Reinold MM, Wilk KE, Macrina LC, Dugas JR, Cain EL. Current concepts in the rehabilitation following articular cartilage repair procedures in the knee. *J Orthop Sports Phys Ther*. 2006;36:774-794.
42. Riegger-Krugh CL, McCarty EC, Robinson MS, Wegzyn DA. Autologous chondrocyte implantation: current surgery and rehabilitation. *Med Sci Sports Exerc*. 2008;40:206-214.
43. Risberg MA, Holm I, Ekeland A. Reliability of functional knee tests in normal athletes. *Scand J Med Sci Sports*. 1995;5:24-28.
44. Robertson WB, Fick D, Wood DJ, Linklater JM, Zheng MH, Ackland TR. MRI and clinical evaluation of collagen-covered autologous chondrocyte implantation (CACI) at two years. *Knee*. 2007;14:117-127.
45. Robertson WB, Gilbey H, Ackland T. *Standard Practice Exercise Rehabilitation Protocols for Matrix-Induced Autologous Chondrocyte Implantation Femoral Condyles*. Perth, Western Australia: Hollywood Functional Rehabilitation Clinic; 2004.
46. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)-development of a self-administered outcome measure. *J Orthop Sports Phys Ther*. 1998;28:88-96.
47. Saris DB, Vanlauwe J, Victor J, et al. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. *Am J Sports Med*. 2009;37(suppl 1):10S-19S.
48. Thomee R, Kaplan Y, Kvist J, et al. Muscle strength and hop performance criteria prior to return to sports after ACL reconstruction. *Knee Surg Sports Traumatol Arthrosc*. 2011;19:1798-1805.
49. Tiderius CJ, Tjornstrand J, Akeson P, Sodersten K, Dahlberg L, Leander P. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC): intra- and interobserver variability in standardized drawing of regions of interest. *Acta Radiol*. 2004;45:628-634.
50. Trattnig S, Millington SA, Szomolanyi P, Marlovits S. MR imaging of osteochondral grafts and autologous chondrocyte implantation. *Eur Radiol*. 2007;17:103-118.
51. Trattnig S, Pinker K, Krestan C, Plank C, Millington S, Marlovits S. Matrix-based autologous chondrocyte implantation for cartilage repair with Hyalograft((R))C: two-year follow-up by magnetic resonance imaging. *Eur J Radiol*. 2006;57:9-15.
52. Vunjak-Novakovic G, Martin I, Obradovic B, et al. Bioreactor cultivation conditions modulate the composition and mechanical properties of tissue-engineered cartilage. *J Orthop Res*. 1999;17:130-138.
53. Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol*. 1998;51:903-912.
54. Welsch GH, Mamisch TC, Zak L, et al. Evaluation of cartilage repair tissue after matrix-associated autologous chondrocyte transplantation using a hyaluronic-based or a collagen-based scaffold with morphological MOCART scoring and biochemical T2 mapping: preliminary results. *Am J Sports Med*. 2010;38:934-942.
55. Wondrasch B, Risberg MA, Zak L, Marlovits S, Aldrian S. Effect of accelerated weightbearing after matrix-associated autologous chondrocyte implantation on the femoral condyle: a prospective, randomized controlled study presenting MRI-based and clinical outcomes after 5 years. *Am J Sports Med*. 2015;43:146-153.
56. Wondrasch B, Zak L, Welsch GH, Marlovits S. Effect of accelerated weightbearing after matrix-associated autologous chondrocyte implantation on the femoral condyle on radiographic and clinical outcome after 2 years: a prospective, randomized controlled pilot study. *Am J Sports Med*. 2009;37(suppl 1):88S-96S.