Arthroscopic Matrix-Assisted Autologous Chondrocyte Transplantation Versus Microfracture

A 6-Year Follow-up of a Prospective Randomized Trial

Clemente Ibarra,* MD, PhD, Enrique Villalobos, MD, PhD, Antonio Madrazo-Ibarra, MD, Cristina Velasquillo, PhD, Valentin Martinez-Lopez, MSc, Aldo Izaguirre, MD, PhD, Anell Olivos-Meza, MD, PhD, Socorro Cortes-Gonzalez, MD, Francisco Javier Perez-Jimenez, MD, Alberto Vargas-Ramirez, MD, Gilberto Franco-Sanchez, MD, and Luis Guillermo Ibarra-Ibarra,† MD
Investigation performed at the Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico

Background: Few randomized controlled trials with a midterm follow-up have compared matrix-assisted autologous chondrocyte transplantation (MACT) with microfracture (MFx) for knee cartilage lesions.

Purpose: To compare the structural, clinical, and safety outcomes at midterm follow-up of MACT versus MFx for treating symptomatic knee cartilage lesions.

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

Methods: A total of 48 patients aged between 18 and 50 years, with 1- to 4-cm^2 International Cartilage Repair Society (ICRS) grade III to IV knee chondral lesions, were randomized in a 1:1 ratio to the MACT and MFx treatment groups. A sequential prospective evaluation was performed using magnetic resonance imaging (MRI) T2 mapping, the MOCART (magnetic resonance observation of cartilage repair tissue) score, second-look arthroscopic surgery, patient-reported outcome measures, the responder rate (based on achieving the minimal clinically important difference for the Knee injury and Osteoarthritis Outcome Score [KOOS] pain and KOOS Sport/Recreation), adverse events, and treatment failure (defined as a reoperation because of symptoms caused by the primary defect and the detachment or absence of >50% of the repaired tissue during revision surgery).

Results: Overall, 35 patients (18 MACT and 17 MFx) with a mean chondral lesion size of 1.8 ± 0.8 cm^2 (range, 1-4 cm^2) were followed up to a mean of 6 years postoperatively (range, 4-9 years). MACT demonstrated significantly better structural outcomes than MFx at 1 to 6 years postoperatively. At final follow-up, the MRI T2 mapping values of the repaired tissue were 37.7 ± 8.5 ms for MACT versus 46.4 ± 8.5 ms for MFx ($P = .003$), while the MOCART scores were 59.4 ± 17.3 and 42.4 ± 16.3, respectively ($P = .006$). More than 50% defect filling was seen in 95% of patients at 2 years and 82% at 6 years in the MACT group and in 67% at 2 years and 53% at 6 years in the MFx group. The second-look ICRS scores at 1 year were 10.7 ± 1.3 for MACT and 9.0 ± 1.8 for MFx ($P = .001$). Both groups showed significant clinical improvements at 6 years postoperatively compared with their preoperative status. Significant differences favoring the MACT group were observed at 2 years on the KOOS Activities of Daily Living ($P = .043$), at 4 years on all KOOS subscales (except Symptoms; $P < .05$) and the Tegner scale ($P = .008$), and at 6 years on the Tegner scale ($P = .010$). The responder rates at 6 years were 53% and 77% for MFx and MACT, respectively. There were no reported treatment failures after MACT; the failure rate was 8.3% in the MFx group. Neither group had serious adverse events related to treatment.

Conclusion: Patients who underwent MACT had better structural outcomes than those who underwent MFx at 1 to 6 years postoperatively. Both groups of patients showed significant clinical improvements at final follow-up compared with their preoperative status. MACT showed superiority at 4 years for the majority of the KOOS subscales and for the Tegner scale at 4 to 6 years. The MACT group also had a higher responder rate and lower failure rate at final follow-up.

The American Journal of Sports Medicine
2021;49(8):2165–2176
DOI: 10.1177/03635465211010487

Registration: NCT01947374 (ClinicalTrials.gov identifier).

Keywords: cartilage; articular; T2 mapping; matrix-assisted autologous chondrocyte transplantation (MACT); microfracture; randomized controlled trial

Approximately 60% of patients who undergo arthroscopic surgery of the knee have a chondral lesion.[1,36] Untreated cartilage lesions cause severe incapacitating pain and accelerate joint degenerative changes, which increase the risk of early osteoarthritis.[6,8,14] Microfracture (MFx) is a marrow-stimulating technique that involves perforating the subchondral bone to cause bone bleeding and the formation of a fibrocartilaginous tissue over the chondral lesion.[32] MFx is currently the first-line treatment method for small to medium-sized chondral lesions, given the ease and low cost of the procedure as well as good short-term outcomes.[10,12,22,26] However, 47% to 80% of patients show functional deterioration at 18 to 36 months postoperatively, which has led to the search for longer lasting alternative treatment options.[11,21] Autologous chondrocyte implantation (ACI), a restorative technique first described by Brittberg et al[3] in 1994, is currently the standard procedure for medium to large cartilage lesions of the knee as well as the second-line treatment method or salvage procedure for small lesions.[12,22,26] Newer generations of ACI, such as matrix-assisted autologous chondrocyte transplantation (MACT), have been developed to overcome several issues that negatively affect first- and second-generation ACI. In addition, these newer generations of ACI allow minimally invasive or arthroscopic implantation and, therefore, reduce the surgical time, time taken for recovery, and risk of surgical complications.[9,15,17,28,31,35]

Magnetic resonance imaging (MRI) T2 mapping provides information regarding collagen orientation and water content within the articular cartilage and has proven useful for the longitudinal evaluation of cartilage repair techniques.[27] MRI provides an essential objective outcome standard that augments the information obtained from validated, but subjective, clinical instruments. Previous randomized controlled trials (RCTs) comparing MACT with MFx have used patient-reported outcome measures (PROMs) as their primary outcomes and have not thoroughly explored postoperative structural evaluations; this may explain why no significant differences have been consistently found between these 2 techniques.[2,4,7,13,23,29] Therefore, a standardized structural evaluation with multimodal approaches and a midterm follow-up may lead to better understanding of the repair process when comparing these 2 treatment methods.

Arthroscopic matrix-encapsulated ACI (AMECI) is a 100% arthroscopic MACT technique utilizing a polyglycolic acid scaffold (Neoveil sheet; Gunze) that is seeded and encapsulated with cultured autologous chondrocytes. This technique has shown hyaline-like tissue formation in preclinical studies,[18] as well as promising structural and clinical outcomes, with an adequate safety profile.[15,24,34] The current RCT was performed based on the hypothesis that MACT leads to better structural outcomes and favorable clinical results at midterm follow-up compared with MFx as a treatment method for symptomatic cartilage lesions in the knee. Results of this study have not been previously published.

METHODS

Study Design and Patients

This single-center parallel RCT was performed at a national referral center in Mexico. Both procedures were standardized and performed by 6 fellowship-trained orthopaedic surgeons (C.I., E.V., A.I., F.J.P.J., L.S.S., A.A.). The first patient was enrolled in January 2010, and the last patient evaluation was performed in January 2019. The inclusion and exclusion criteria are presented in Table 1.

Informed consent was obtained from all participants. Chondral lesions were diagnosed by MRI and later confirmed by arthroscopic surgery. Randomization was performed once a 1- to 4-cm^2 International Cartilage Repair Society (ICRS) grade III to IV chondral lesion was confirmed. The research assistant stratified patients using the minimization method described by Taves,[33] based on the lesion location and concomitant abnormalities, to either the MFx or MACT group at a 1:1 ratio.

The study was performed according to Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by an internal ethics committee and an internal review board. The trial is registered at ClinicalTrials.gov (NCT01947374) and was conducted according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines. Grant support was awarded from the National Council of Science and Technology (SALUD 2009-01-115542). Financial sponsors and other additional

*Address correspondence to Clemente Ibarra, MD, PhD, Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Calzada México Xochimilco No. 289, Colonia Arenal de Guadalupe, Alcaldia Tlalpan, CP 14389, Mexico City, Mexico (email: clementeibarra@yahoo.com).

†L.G.I.-I. is deceased.

All authors are listed in the Authors section at the end of this article.

C. I. and E.V. are co–first authors.

Submitted June 24, 2020; accepted January 4, 2021.

One or more of the authors has declared the following potential conflict of interest or source of funding: This work received grant support from the National Council of Science and Technology (registration No. SALUD 2009-01-115542). AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.

TABLE 1
Inclusion and Exclusion Criteria[a]

Inclusion Criteria	Exclusion Criteria
• Patients willing and able to give informed consent • Age of 18-50 years • Body mass index <30 kg/m^2 • Symptomatic chondral lesions in the knee of ICRS grade III or IV diagnosed by MRI • Focal chondral lesions with an area of 1-4 cm^2, located at the femoral condyles, trochlea, or patella • Mechanical axis <10% away from the neutral line measured on a full-length weightbearing anteroposterior view • Patients medically able to undergo arthroscopic MFx or arthroscopic biopsy and subsequent MACT • Patients willing and able to follow the rehabilitation protocol	• Osteochondral lesions • Previous surgical treatment of chondral lesions • Advanced osteoarthritis in the knee of Kellgren-Lawrence grade III or IV • Meniscal resection >50% of the meniscus previously or at the time of surgery in the treated compartment • Knee ligament instability not treated previously or at the time of surgery • Patellofemoral malalignment (patellar tilt ≥10° on the Merchant view and/or a tibial tuberosity–trochlear groove distance ≥15 cm on computed tomography) not treated previously or at the time of surgery • Use of hyaluronic acid or platelet-rich plasma injections in the knee in the previous year • Chronic use of anticoagulation • Patients diagnosed with cancer or currently undergoing chemotherapy • Patients unable to undergo MRI • Patients who are pregnant or intend to become pregnant during the first year after initial enrollment • History of autoimmune disease • Evidence of HIV or chronic hepatitis B or C viral infections • Known allergy to gentamicin • Current drug or alcohol abuse • Patients deemed by the investigator as unlikely to comply with the protocol • Vascular or neurological abnormalities affecting the lower extremities • Any form of inflammatory arthritis • History of infection in the knee or diagnosis of osteomyelitis • Uncontrolled systemic disease (diabetes mellitus, hyperthyroidism, etc)

[a]ICRS, International Cartilage Repair Society; MACT, matrix-assisted autologous chondrocyte transplantation; MFx, microfracture; MRI, magnetic resonance imaging.

third parties had no role in the study design, data collection, analysis, or writing of the article.

Surgical Technique and Rehabilitation

Microfracture. For patients assigned to the MFx group, lesions were treated using the original technique described by Steadman et al.[32]

Matrix-Assisted Autologous Chondrocyte Transplantation. A 100% arthroscopic MACT technique called AMECI was performed (Figure 1). Once the chondral lesion was confirmed, a cartilage biopsy specimen was obtained from a nonweightbearing area at the intercondylar notch, and any concomitant knee abnormality was addressed during surgery. The biopsy specimen was sent to a Good Manufacturing Practice laboratory following the minimum biosecurity parameters previously described for transportation, chondrocyte isolation, expansion, and construct formation.[34] An 8 mm–diameter polyglycolic acid scaffold (Neoveil sheet) was seeded and enveloped with cultured autologous chondrocytes.

Arthroscopic implantation was performed 6 to 8 weeks later. Chondral lesions were debrided before implantation. If lesions were located on the femoral condyles or trochlea, a bioabsorbable mini-anchor (DePuy Mitek) loaded with a 0 polydioxanone suture (PDS) was embedded in the center of the defect. With use of two 16-gauge needles, the anchor sutures were passed through the matrix-encapsulated autologous chondrocyte construct. A low-profile sliding arthroscopic knot was made to introduce the polymer into the joint through a clear 10-mm cannula (Smith & Nephew) and onto the chondral lesion. If the lesion was located on the patella, a tibial guide for anterior cruciate ligament (ACL) reconstruction (ACL guide; DePuy Mitek) was placed inside the joint, with the guide pointing to the chondral lesion. A 2-mm Steinmann pin was used to drill the patella through the ACL guide (in a retrodrilling manner) until the pin was seen coming out of the chondral lesion. This was repeated to form a similar perforation approximately 4 mm away from the first but still in the chondral lesion. A suture shuttling device (Chia Percpasser; DePuy Mitek) was introduced in each perforation, recovered inside the joint, and pulled out through one of the portals. Meanwhile, a matrix-encapsulated autologous chondrocyte construct was mounted on a 0 PDS suture

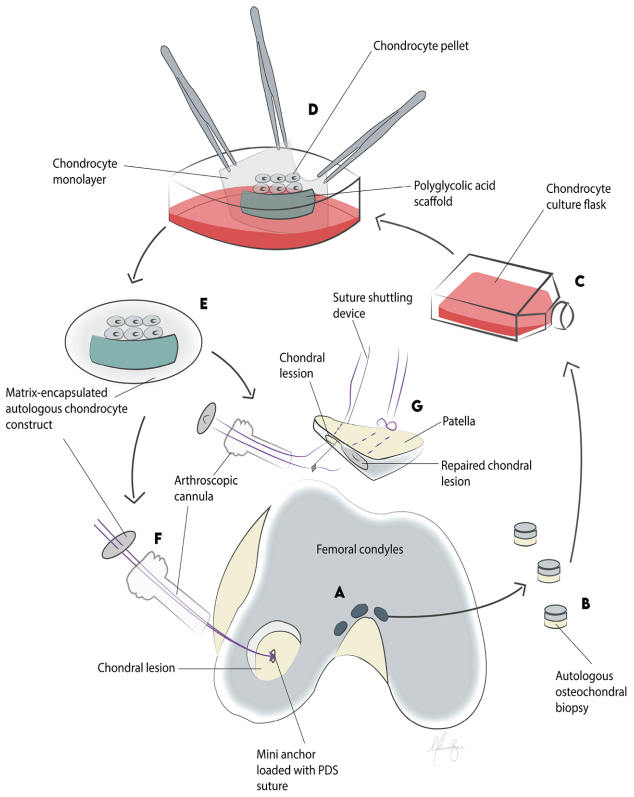

Figure 1. Arthroscopic matrix-encapsulated autologous chondrocyte implantation (AMECI). (A) Arthroscopic osteochondral biopsy specimens were obtained from a nonweightbearing area in the knee. (B) The osteochondral biopsy specimens were transported to a Good Manufacturing Practice laboratory for chondrocyte isolation. (C) The chondrocytes were expanded in culture flasks with culture medium. (D) A polyglycolic acid scaffold (8-mm diameter) was placed over a chondrocyte monolayer. A chondrocyte pellet with two-thirds of the cultured chondrocytes was placed on top of the scaffold, and these were covered and ''encapsulated'' with the chondrocyte monolayer. (E) The AMECI construct ready for implantation. (F) AMECI on the femoral condyle: the construct was implanted using a mini-anchor loaded with polydioxanone (PDS) sutures placed in the center of the chondral lesion. The sutures were passed through the construct, and a sliding knot pushed the construct into an arthroscopic cannula and onto the chondral lesion. (G) AMECI on the patella: the construct was loaded with a PDS suture. There were 2 tunnels drilled in the patella with a retrodrilling technique, and suture shuttling devices were passed through the tunnels to recover the construct sutures. The sutures were pulled, introducing the construct into the joint and onto the lesion. A knot was tied on the dorsal surface of the patella.

using two 16-gauge needles. Each end of the PDS suture was passed through a loop of the Chia Percpasser, and once both were mounted, the devices were pulled out of the joint through the perforations in the patella. The construct was firmly placed on the chondral lesion, and a surgical knot was made on the anterior cortical surface of the patella. A more detailed explanation has been provided in previous studies.[15,25,34,35]

Rehabilitation. All patients underwent rehabilitation following the same protocol.[34] During the first 6 to 8 weeks, patients underwent the following: (1) weightbearing protection, (2) continuous passive motion for 4 to 6 hours daily, (3) physical therapy focused on reducing pain and swelling, (4) range of motion progression (10° per week), and (5) muscle strengthening. Isometric strengthening of the quadriceps and knee flexors was introduced early in the rehabilitation program and was progressively advanced to exercises against resistance. The strengthening program was directed by baseline and periodic isokinetic evaluations starting at 4 months. A complete return to sports was permitted after 1 year.

Evaluation

The primary outcome was MRI T2 mapping, and the secondary outcomes were the MOCART (magnetic resonance observation of cartilage repair tissue) score, second-look arthroscopic surgery, PROMs, treatment responder rate, adverse events (AEs), and treatment failure.

Magnetic Resonance Imaging. MRI T2 mapping and the MOCART 2.0 score were used for the imaging evaluation (Figure 2).[30] MRI T2 mapping was performed preoperatively and at 1, 2, 4, and 6 years postoperatively. MOCART scores were evaluated at 3 months as well as at 1, 2, 4, and 6 years postoperatively. Both evaluations were performed by an independent fellowship-trained radiologist (S.C.G.) and an orthopaedic surgeon with a special interest in musculoskeletal imaging (E.V.). The intraclass correlation coefficient among the evaluators was 0.9. Blinded MRI evaluations were not possible because the anchors used for MACT were visible on imaging and identified the treatment method. MRI was performed using a 1.5-T imaging system (GE Healthcare) with an 8-channel high-definition knee array (GE Healthcare). A standard morphological MRI evaluation was performed using the fast spin echo sequence in the axial, sagittal, and coronal planes. Images were acquired with a repetition time of 1800 to 1450 ms; an echo time of 30 to 40 ms; an echo train length of 6; and a spatial resolution of 256 mm (frequency), 256 mm (phase), and 3 mm at 2 excitations. Quantitative T2 mapping was performed using a multislice multiecho pulse sequence. A total of 8 echoes were sampled: sequential multiples of the first echo time (10-11 ms) at a repetition time of 800 ms and an in-plane resolution of 384 mm (frequency), 256 mm (phase), and 3 mm at 2 excitations. The data sets were analyzed (FuncTool 4.5.9; GE Healthcare) using a color-coded map ranging from 25 to 91 ms. A total of 6 regions of interest (ROIs) were obtained: 3 from the native cartilage and 3 from the repaired tissue. ROIs 1 and 2 were 2-mm^2 rectangular areas located in the healthy native cartilage: ROI 1 was positioned in the deep layer of the cartilage, while ROI 2 was placed in the superficial layer. ROI 3 was a 4-mm^2 rectangular area that included ROIs 1 and 2 and, thus, was the average control. ROIs 4,

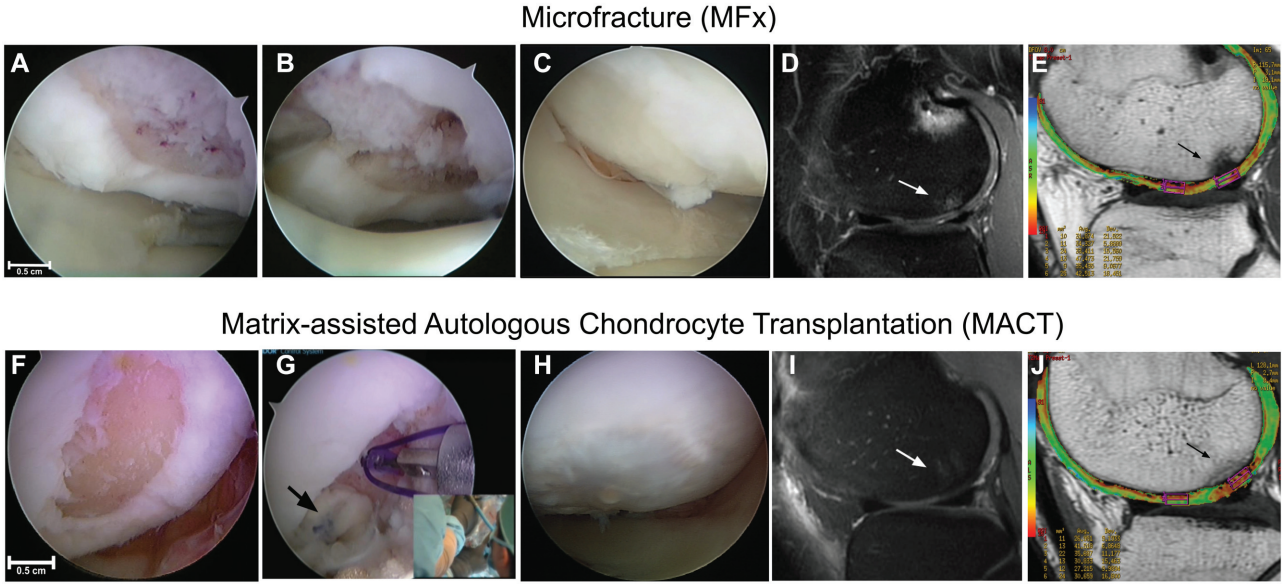

Figure 2. Arthroscopic surgical technique and structural evaluation for (A-E) microfracture (MFx) and (F-J) matrix-assisted autologous chondrocyte transplantation (MACT). The chondral lesion size was measured arthroscopically using a meniscal probe. (A) A chondral lesion located at the lateral femoral condyle (LFC). (B) MFx performed with an arthroscopic awl in the chondral lesion (the anterior horn of the lateral meniscus is seen at the bottom of the arthroscopic view). (C) Second-look arthroscopic surgery at 1 year after MFx (macroscopic International Cartilage Repair Society [ICRS] score: 9/12). (D) Magnetic resonance imaging (MRI) in the sagittal view at 9 years after MFx (MOCART [Consolidated Standards of Reporting Trials] score: 50/100), with the white arrow pointing to the repaired tissue. (E) MRI T2 mapping at 9 years after MFx (repaired tissue region of interest [ROI 6]: 42.5 ± 18.5 ms), with the black arrow pointing to the repaired tissue. (F) A chondral lesion located at the LFC. (G) Arthroscopic MACT technique: a bioabsorbable mini-anchor loaded with a 0 polydioxanone suture being placed in the previously debrided chondral lesion to introduce and fixate a construct, with the black arrow pointing at the first construct already fixed in place (picture-in-picture: ''condor view'' of the operating room). (H) Second-look arthroscopic surgery at 1 year after MACT (macroscopic ICRS score: 11/12). (I) MRI in the sagittal view at 9 years after MACT (MOCART score: 75/100), with the white arrow pointing to the repaired tissue. (J) MRI T2 mapping at 9 years after MACT (repaired tissue ROI 6: 30.7 ± 16.8 ms), with the black arrow pointing to the repaired tissue.

5, and 6 were sized, shaped, and placed in the same manner as the previous ROIs but over the repaired cartilage. ROI 3 was used as the "native ROI," and ROI 6 was used as the "repair ROI."

Second-Look Arthroscopic Surgery. Second-look arthroscopic surgery was performed at 1 year postoperatively in all patients who gave written consent (Figure 2). No biopsy specimen was obtained for a histological evaluation. There were 2 experienced arthroscopic surgeons (R.A.V., C.T.) (different from the treating surgeon), blinded to the treatment method, who conducted the ICRS cartilage repair assessment by watching the surgical video. The intraclass correlation coefficient among the evaluators was 0.7.

Clinical Evaluation. PROMs were used to evaluate the patients' symptoms and function. The Lysholm score, Tegner score, subjective International Knee Documentation Committee score, and Knee injury and Osteoarthritis Outcome Score (KOOS) were documented preoperatively and at 1, 2, 4, and 6 years postoperatively by an independent orthopaedic surgeon who was blinded to the treatment method.

Treatment Responder Rate. A nonprespecified exploratory subanalysis of the responder rate was performed. Patients were considered "responders" if they achieved the minimal clinically important difference (MCID) for the KOOS Pain (KOOS-P) and KOOS Sport/Recreation (KOOS-SR). The MCID values were calculated specifically for the studied population using a distribution-based method that consisted of half the standard deviation of our change from baseline KOOS-P and KOOS-SR scores at each time point (2, 4, and 6 years).

Safety Evaluation. AEs were documented and reported at each follow-up visit. Failure was defined as the need for a reoperation because of symptoms caused by the primary defect and the detachment or absence of >50% of the repaired tissue during revision surgery.

Statistical Analysis

A sample size calculation was conducted using the anticipated MRI T2 mapping values (in ms) of the repaired tissue after MFx and MACT based on previous studies.[15] MRI T2 mapping was selected as the primary outcome, as it was considered to be the most objective noninvasive criterion to determine the quality of cartilage-like tissue formation. The parameters used were 2 independent study groups, an alpha of .05, power of 80%, an anticipated MFx mean of 50.87 ± 7.84 ms, and an anticipated MACT mean of 43.73

± 2.99 ms. A sample size of 38 (19 MFx and 19 MACT) was obtained, 5 additional patients were added to each group for probable losses, with a final sample size of 48 (24 MFx and 24 MACT).

All continuous data with a normal distribution were expressed in terms of means ± SDs and categorical data as frequencies and percentages. Intention-to-treat analysis was performed for the primary outcome. The Shapiro-Wilk test was used to assess the normality of continuous variables. All normally distributed data were compared using the Student *t* test for continuous variables and the chi-square test of independence for categorical variables. Nonparametric tests were performed for the comparison of data with a nonnormal distribution. The changes in outcomes at all time points were analyzed and compared between the MACT and MFx groups using analysis of variance. The last observation carried forward and the next observation carried backward were used for missing values, taking the next observation carried backward over the last observation carried forward. Pearson correlation analysis was performed; *P* values <.05 were considered statistically significant. Statistical analysis was performed using SPSS software Version 26 (IBM). The researchers involved in data analysis were blinded to the treatment methods.

RESULTS

Patient Characteristics

The patient characteristics were similar in both groups (Table 2); 48 patients were randomized, 46 of whom were treated (22 MACT and 24 MFx) (Figure 3). The mean lesion size was 1.8 ± 0.8 cm^2 (range, 1-4 cm^2), 1.9 ± 0.9 cm^2 for MACT and 1.7 ± 0.7 cm^2 for MFx (*P* = .41). None of the preoperative PROM scores and MRI T2 mapping values were significantly different between the groups (Tables 3 and 4). The mean final follow-up was 6 years (range, 4-9 years). The most common concomitant procedure was ACL reconstruction (45.8% MACT vs 50% MFx), followed by meniscal repair (25% vs 25%, respectively) and soft tissue patellar alignment procedures (25% vs 20.8%, respectively).

Structural Outcomes

Magnetic Resonance Imaging. MRI T2 mapping values of the repaired tissue in the MFx group showed a progressive decrease at final follow-up compared with preoperative values, without reaching statistical significance (*P* = .211) (Table 3). Repaired tissue T2 values of MACT showed a statistically significant decrease from preoperative values at 6 years (*P* = .001). Postoperative MACT T2 mapping values of the repaired tissue were significantly lower at all time points than those of MFx (*P* < .05) (Table 3 and Figure 4). Compared with those in the native cartilage, MFx had significantly higher T2 values in the repaired tissue at 1 (*P* = .015), 2 (*P* = .000), 4 (*P* = .009), and 6 (*P* = .001) years. There were no significant differences in the MACT group's repaired tissue values and native cartilage values at 1 (*P* = .119), 2 (*P* = .056), 4 (*P* = .635), and 6 (*P* = .612) years.

TABLE 2
Patient Characteristics[a]

	MACT (n = 24)	MFx (n = 24)	*P* Value
Follow-up, mo	74.0 ± 10.4	71.0 ± 15.6	.07
Sex, n (%)			.37
Female	7 (29.2)	10 (41.7)	
Male	17 (70.8)	14 (58.3)	
Age, y	33.7 ± 9.4	35.8 ± 9.1	.42
Body mass index, kg/m^2	25.5 ± 3.1	26.6 ± 3.1	.23
Defect size, cm^2	1.9 ± 0.9	1.7 ± 0.7	.41
ICRS grade IV, n (%)	24 (100.0)	24 (100.0)	
Location, n (%)			.11
Medial femoral condyle	7 (29.2)	9 (37.5)	
Lateral femoral condyle	9 (37.5)	6 (25.0)	
Trochlea	1 (4.2)	6 (25.0)	
Patella	7 (29.2)	3 (12.5)	

[a]Data are presented as mean ± SD unless otherwise specified. ICRS, International Cartilage Repair Society; MACT, matrix-assisted autologous chondrocyte transplantation; MFx, microfracture.

The baseline MOCART scores obtained at 3 months were not statistically different from those at 6 years with either technique (Table 3). The MOCART scores after MACT were significantly higher than those after MFx at all time points, with mean scores at 6 years of 59.4 ± 17.3 and 42.4 ± 16.3, respectively (*P* = .006) (Table 3 and Figure 5). Overall, 95% of patients who underwent MACT had >50% filling of the defect at 2 years and 82% at 6 years; 67% of patients who underwent MFx had >50% filling of the defect at 2 years and 53% at 6 years.

Second-Look Arthroscopic Surgery. A total of 35 patients (18 MACT and 17 MFx) underwent second-look arthroscopic surgery at 1 year postoperatively. The mean ICRS scores were 10.7 ± 1.3 in the MACT group and 9.0 ± 1.8 in the MFx group (*P* = .001) (Table 3). "Normal" cartilage-like tissue formation was found in 28% of patients after MACT and 0% of patients after MFx, while "nearly normal" cartilage-like tissue formation was found in 67% and 82%, respectively, and "abnormal" cartilage-like tissue formation was found in 5% and 18%, respectively.

Clinical Outcomes

PROM Scores. Both groups demonstrated a statistically significant improvement on all PROMs from the preoperative time point to 6 years postoperatively (*P* < .05) (Table 4). Significant differences favoring the MACT group were observed at 2 years on the KOOS Activities of Daily Living (ADL; *P* = .043), at 4 years on all KOOS subscales (except KOOS symptoms [KOOS-S]; *P* < .05) and the Tegner scale (*P* = .008), and at 6 years on the Tegner scale (*P* = .010).

Responder Rate. The MCIDs obtained for the KOOS-P were 9.8, 9.9, and 10.9 at 2, 4, and 6 years, respectively, while those obtained for the KOOS-SR were 15.4, 12.9, and 15.2, respectively. The MFx group showed a superior responder rate at 2 years, but the MACT group showed a superior responder rate at 4 and 6 years (Figure 6).

Adverse Events and Treatment Failure. In both groups, 79.1% (38/48) of patients presented a minor AE, 62.5% (30/

TABLE 3
Magnetic Resonance Imaging T2 Mapping and MOCART Values, and ICRS Scores[a]

	Preoperative	3 mo	1 y	2 y	4 y	6 y	*P* Value[b]
T2 value for native ROI, ms							
MFx	37.4 ± 5.1		39.8 ± 7.8	35.4 ± 6.7	38.5 ± 4.9	37.8 ± 4.3	.743
MACT	36.9 ± 3.9		37.5 ± 6.8	35.6 ± 3.7	37.6 ± 4.9	36.5 ± 4.9	.730
P value	.525		.321	.904	.873	.474	
T2 value for repair ROI, ms							
MFx	54.1 ± 13.9		46.6 ± 8.2	46.4 ± 9.2	45.6 ± 10.2	46.4 ± 8.5	.211
MACT	61.2 ± 18.5		40.3 ± 4.5	38.6 ± 5.7	36.9 ± 5.6	37.7 ± 8.5	.001
P value	.210		.005	.003	.005	.003	
MOCART score							
MFx		42.8 ± 19.8	47.6 ± 17.2	56.1 ± 14.5	49.1 ± 16.9	42.4 ± 16.3	.872
MACT		62.6 ± 8.1	69.6 ± 8.4	66.0 ± 14.0	63.8 ± 17.8	59.4 ± 17.3	.989
P value		.004	<.001	.040	.022	.006	
Second-look arthroscopic ICRS score							
MFx			9.0 ± 1.8				
MACT			10.7 ± 1.3				
P value			.001				

[a]Data are presented as mean ± SD. ICRS, International Cartilage Repair Society; MACT, matrix-assisted autologous chondrocyte transplantation; MFx, microfracture; MOCART, magnetic resonance observation of cartilage repair tissue; ROI, region of interest.
[b]Preoperative versus 6 years (final follow-up), except for the MOCART score, which was 3 months versus 6 years.

TABLE 4
Patient-Reported Outcome Measure Scores[a]

	Preoperative	1 y	2 y	4 y	6 y	*P* Value[b]
Lysholm						
MFx	51.1 ± 25.8	81.5 ± 16.5	84.2 ± 16.7	74.9 ± 23.5	78.8 ± 21.5	.002
MACT	55.1 ± 23.3	84.1 ± 21.7	89.4 ± 16.1	87.9 ± 13.1	85.9 ± 19.8	<.001
P value	.531	.289	.175	.077	.152	
Tegner						
MFx	2.3 ± 1.5	4.1 ± 2.2	4.9 ± 2.5	3.7 ± 1.9	4.4 ± 2.3	.032
MACT	2.6 ± 1.9	4.5 ± 2.1	5.3 ± 2.6	6.0 ± 2.6	6.5 ± 2.0	.001
P value	.945	.583	.678	.008	.010	
IKDC						
MFx	45.7 ± 22.8	67.7 ± 22.4	77.3 ± 18.4	64.6 ± 21.6	66.6 ± 21.1	.001
MACT	43.7 ± 15.3	73.9 ± 18.6	81.9 ± 16.4	77.7 ± 17.8	75.8 ± 19.2	<.001
P value	.741	.342	.424	.055	.186	
KOOS-S						
MFx	51.5 ± 24.5	83.1 ± 16.4	83.7 ± 15.0	78.2 ± 19.9	81.8 ± 18.0	<.001
MACT	58.7 ± 18.9	84.9 ± 14.2	85.9 ± 15.1	82.5 ± 23.4	82.7 ± 19.8	.001
P value	.320	.820	.565	.192	.753	
KOOS-P						
MFx	51.2 ± 21.6	82.0 ± 14.3	87.6 ± 11.7	76.5 ± 19.9	77.9 ± 21.3	<.001
MACT	54.2 ± 19.3	84.6 ± 16.4	90.8 ± 15.0	90.3 ± 12.1	86.4 ± 20.4	<.001
P value	.650	.698	.102	.020	.214	
KOOS-ADL						
MFx	55.9 ± 24.8	87.7 ± 11.3	90.2 ± 9.9	80.5 ± 17.7	81.7 ± 20.1	<.001
MACT	59.5 ± 23.4	90.2 ± 13.5	93.9 ± 9.8	89.9 ± 17.1	89.9 ± 15.9	.001
P value	.666	.341	.043	.031	.136	
KOOS-SR						
MFx	22.7 ± 31.8	64.4 ± 27.2	73.5 ± 26.9	58.9 ± 32.2	60.0 ± 34.6	.002
MACT	27.3 ± 21.9	67.2 ± 31.3	74.0 ± 26.8	81.9 ± 17.8	73.9 ± 27.8	<.001
P value	.133	.620	.904	.034	.265	
KOOS-QoL						
MFx	25.7 ± 28.0	55.1 ± 28.0	67.2 ± 26.5	51.7 ± 28.5	55.5 ± 30.3	.006
MACT	26.9 ± 17.0	53.3 ± 22.9	67.7 ± 25.1	70.1 ± 25.0	69.8 ± 23.2	<.001
P value	.490	.827	.989	.031	.197	

[a]Data are presented as mean ± SD. ADL, Activities of Daily Living; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; MACT, matrix-assisted autologous chondrocyte transplantation; MFx, microfracture; P, Pain; QoL, Quality of Life; S, Symptoms; SR, Sport/Recreation.
[b]Preoperative versus 6 years (final follow-up).

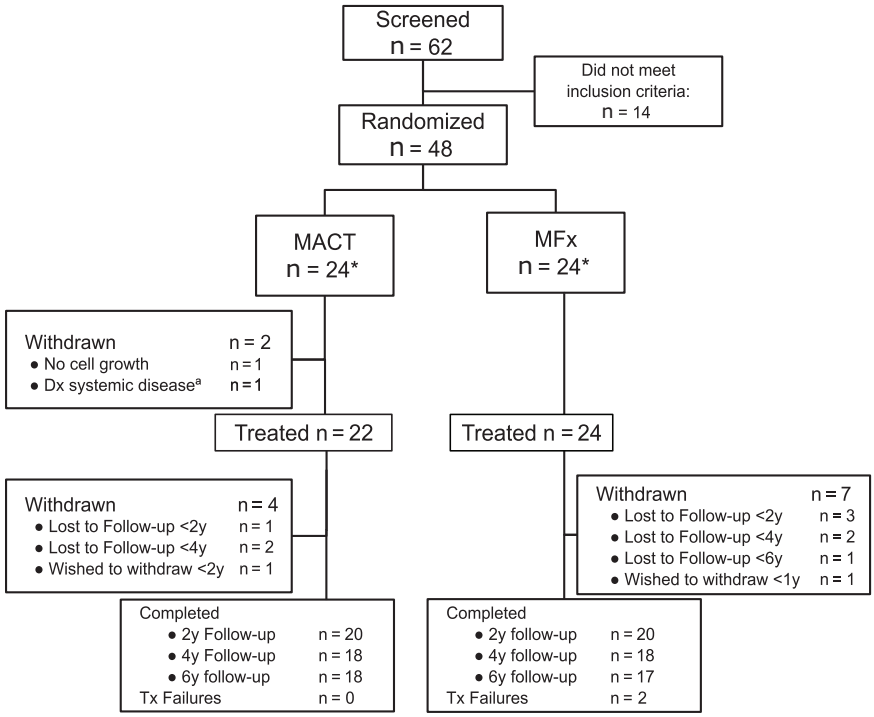

Figure 3. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. *The study was powered to find differences on magnetic resonance imaging T2 mapping, resulting in 19 patients per group; 5 additional patients were added to each group to compensate for probable losses. [a]During cell culture, the patient was diagnosed with hyperthyroidism. Dx, diagnosed; MACT, matrix-assisted autologous chondrocyte transplantation; MFx, microfracture; Tx, treatment.

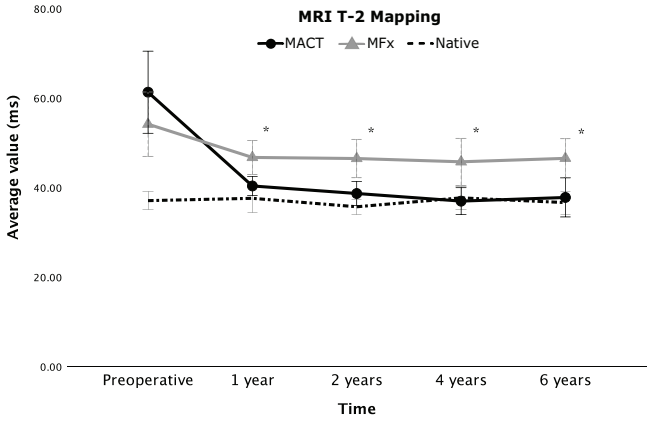

Figure 4. Mean (95% CI) magnetic resonance imaging (MRI) T2 mapping values of patients treated with matrix-assisted autologous chondrocyte transplantation (MACT) and microfracture (MFx). *$P < .05$ for MACT versus MFx. Native, average T2 values of the native cartilage in the MACT and MFx groups.

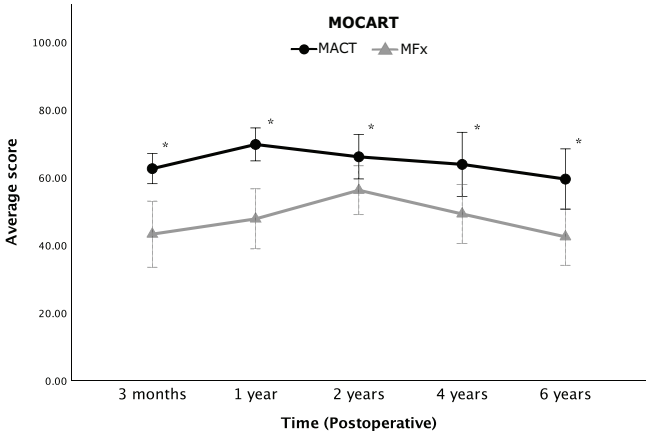

Figure 5. Mean (95% CI) MOCART (magnetic resonance observation of cartilage repair tissue) scores of patients treated with matrix-assisted autologous chondrocyte transplantation (MACT) and microfracture (MFx). *$P < .05$ for MACT versus MFx.

48) of which were 1-episode AEs, and 66.6% (32/48) occurred during the first 18 months postoperatively. The most frequently reported AEs were joint pain in 70.8% (17/24) of patients after MFx and 54.1% (13/24) of patients after MACT, muscle atrophy in 50% (12/24) and 58.3% (14/24), respectively, and joint crepitation in 16.6% (4/24) and 25% (6/24), respectively. There were 2 serious AEs reported: 1 patient with synovitis after MACT and 1 patient with septic arthritis after MFx. Neither case was considered to be directly related to the treatment method. There were no treatment failures reported after MACT at these time points, in contrast to 2 (8.3%) treatment failures after MFx. One of these patients underwent MFx again after he had symptoms, and >50% of the repair tissue

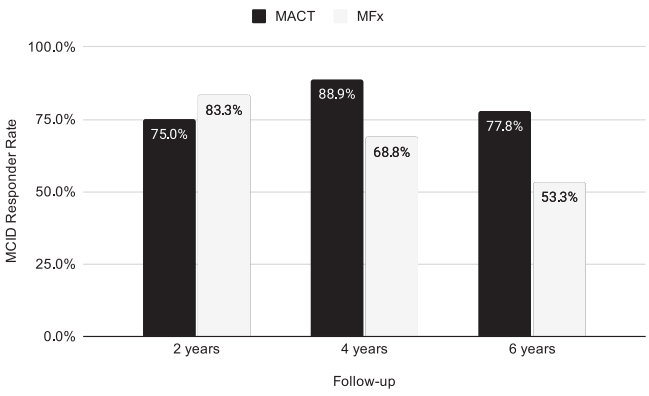

Figure 6. Treatment responder rate based on the minimal clinically important difference (MCID). Patients were considered ''responders'' if they achieved the MCID for the Knee injury and Osteoarthritis Outcome Score (KOOS) pain and KOOS Sport/Recreation. MACT, matrix-assisted autologous chondrocyte transplantation; MFx, microfracture.

was found to be detached at approximately 1 year postoperatively. The other patient had knee locking symptoms, which required surgery at approximately 4 years postoperatively, at which point >50% of the repaired tissue was found to be detached. Neither patient required knee arthroplasty.

Correlations

The 2 groups were analyzed together (n = 46). All structural outcomes had a strong to moderate significant correlation with each other; however, only trends were found without significant correlations between structural and clinical outcomes.

DISCUSSION

The most important finding in this RCT was that MACT showed statistical superiority in all structural variables: MRI T2 mapping and the MOCART score at all time points and second-look arthroscopic surgery at 1 year, confirming our hypothesis. Both treatment arms showed a significant clinical improvement from the preoperative time point to 6 years postoperatively. Patients in both groups had similar clinical outcomes during the first 2 years postoperatively; however, significant differences were observed at 4 and 6 years. The MFx group had a greater percentage of patients considered "responders" at 2 years than the MACT group; however, the MACT group had a greater percentage of "responders" at 4 and 6 years. In addition, no treatment failures were reported after MACT, in contrast to 2 treatment failures after MFx.

Despite the enriching information that MRI T2 mapping provides about cartilage, to the best of our knowledge, no RCT has used this evaluation method to compare MACT with MFx. MRI T2 mapping was selected as the primary outcome measure because an objective evaluation of the repaired tissue was needed (without damaging the repaired tissue) to prevent clinical bias generated by other treated concomitant joint abnormalities, which is a common scenario in cartilage repair surgery. When comparing T2 mapping values of the repaired tissue with the native cartilage values in both groups independently, our results were similar to those of Welsch et al.[37] The MFx group's values were significantly higher than the native cartilage values at all time points (1, 2, 4, and 6 years), but the MACT group's values showed no significant differences to the native cartilage values from 1 to 6 years postoperatively. This finding may indicate that MACT forms a repair tissue with intrinsic characteristics similar to the native cartilage but different from the repair tissue formed after MFx. In contrast to the findings reported by Welsch et al, we obtained significantly lower T2 mapping values after MACT at all time points than after MFx. This may be explained in part by differences in the hardware and software used to analyze T2 mapping. However, to reduce potential bias by technology, comparisons were made by considering the native cartilage values. Values that resemble the healthy native cartilage indicate a healthier repair tissue.

No previous studies have found statistically significant differences in the MOCART score between MACT and MFx at 2 and 3 years postoperatively.[13,23,37] In this study, we found significant differences between groups from our first evaluation, performed at 3 months postoperatively, until our last evaluation, with significantly higher scores in the MACT group. We consider that this could be explained by the implementation of MOCART Version 2.0, recently published by Schreiner et al,[30] which addressed major advancements in MRI as well as novel cartilage treatment approaches. Furthermore, the new variable "bony defect or bony overgrowth" possibly lowered the MFx group's score because it is well-known that one of the main disadvantages of MFx is the resulting subchondral bone overgrowth.[21] A greater percentage of patients had >50% filling of the defect after MACT than after MFx, which was in agreement with the results of a previous study.[29] As mentioned earlier, MRI provides an essential objective outcome standard that augments the information obtained from validated subjective clinical instruments. To the best of our knowledge, this is the first RCT to compare MFx with MACT using a prospective sequential MRI evaluation. This allowed better understanding of the morphological changes of the repaired tissue (in both techniques) over time.

Moreover, 2 previous RCTs reported a greater percentage of "normal" or "nearly normal" tissue formation after MACT than after MFx in second-look arthroscopic surgery; however, no significant differences in the mean ICRS score were found.[13,29] Our study is one of the few studies in which more than three-quarters of the patients (18 after MACT and 17 after MFx) underwent second-look arthroscopic surgery for a macroscopic tissue evaluation. Similarly, we found that a greater percentage of patients who underwent MACT had "normal" or "nearly normal" tissue formation after treatment than that of patients who underwent MFx as well as a significantly higher mean ICRS score. These findings suggest that MACT achieves a higher quality repair tissue than MFx.

Previous RCTs that have compared MACT with MFx used clinical evaluations as their primary outcome, showing significant improvements from preoperative values to those at final follow-up for both techniques independently.[2,4,7,13,23,29] However, clinical outcomes comparing both techniques have been controversial during the first 3 years postoperatively, with some studies reporting no differences between MACT and MFx and others reporting MACT to be statistically superior on some PROMs.[2,7,13,23,29] Brittberg et al[4] confirmed that MACT was statistically superior to MFx at 5 years postoperatively on the co-primary endpoints of the KOOS-P and KOOS-SR as well as on the secondary endpoint of the KOOS-ADL. We found no major statistical differences between MACT and MFx during the first 2 years postoperatively; however, we observed the statistical superiority of MACT on all KOOS subscales (except KOOS-S) at 4 years and on the Tegner scale at 4 and 6 years. In addition to the clinical outcomes, we found that the failure rate after MACT was 0%, while that after MFx was 8.3%; these results were similar to those of Hoburg et al[13] and Brittberg et al.[4] These findings suggest that both treatment methods are excellent options for clinical improvement in the short term (first 2 years) but that MACT is superior to MFx at midterm (4-6 years) follow-up. This RCT is one of the only trials to include 1- to 4-cm^2 chondral lesions, while all others have included lesions >4 cm^2, which puts MFx at a great disadvantage.[2,7,13,23,29] A recent study confirmed that 56% of orthopaedic surgeons limit the use of MFx to lesions <2 cm^2 because bigger lesions show less favorable outcomes.[19] Our inclusion of this lesion size allowed a more realistic clinical outcome comparison and introduced arthroscopic MACT as a treatment option for small chondral lesions.

Responder analysis is used to determine which patients demonstrate a clinical improvement that is sufficiently large for the patients to consider that they feel better than before surgery. Originally, thresholds to determine whether a patient was a responder were arbitrarily determined by specialists; however, novel factors, such as the MCID, are objectively calculated specifically for each population and time point.[16] We calculated the MCID for our cohort using the KOOS-P and KOOS-SR as indicators for pain and function as recommended by regulatory agencies.[5] Previous RCTs that have used "responder" analysis to compare MACT with MFx showed MACT to have a higher responder rate than MFx at 2 and 3 years.[7,13,29] We observed better responder rates during the first 2 years postoperatively in patients who underwent MFx than in those who underwent MACT (83% vs 75%, respectively); however, MFx showed a progressive decrease at 4 and 6 years (Figure 6). The responder rate of patients who underwent MACT increased from 2 to 4 years and was maintained at >75% at 6 years. This finding relates to the natural history of MFx, which deteriorates over time,[11,21] as well as the time that it takes for MACT tissue to mature.

No correlation was found between the clinical and structural outcomes, which could be explained by the small cohort size and the study design. Indeed, a positive correlation between clinical and structural outcomes has not been consistently obtained in previous studies.[4,13,23,29,37] We consider that both clinical and structural outcomes are complementary and time dependent, so they might not correlate when evaluated at the same time points. Further studies with larger and more homogeneous populations, as well as with a longer follow-up, are needed to study their correlation in depth.

Our study has several limitations. First, there was a significant loss of patients over time, which could have affected the power of the study. Indeed, only 18 patients for MACT and 17 for MFx were available at final follow-up; however, significant differences and power were still found in the primary outcome comparison (T2 mapping: $P = .003$). Second, up to 50% of patients had "major" concomitant abnormalities, which are expected in the daily practice of cartilage repair procedures. The stratification process used in randomization and the objective structural evaluation used as the primary outcome helped to reduce the risk of confounding bias by concomitant abnormalities. Third, the 2 surgical procedures required for MACT make this treatment more expensive, with more complicated logistics, and it is impossible for the patients to be blinded; this increased the risk of procedure bias for the clinical evaluation but not for the structural evaluation. Fourth, no biopsy specimens were obtained for a histological evaluation during second-look arthroscopic surgery because we treated small chondral lesions and this would have involved removing approximately 10% to 20% of the repair tissue. Finally, suture anchors in MACT violate the subchondral bone, as well as make blinding of the MRI evaluation impossible, because the anchors are easily identified by evaluators. This could have potentially caused measurement bias in the subjective MOCART evaluation but not in objective measurements such as T2 mapping.

Our study also has several strengths as follows: (1) this is the first transarthroscopic RCT comparing MACT with MFx; (2) the mean follow-up of patients in both groups was 6 years, making this an RCT (comparing MACT with MFx) with the longest follow-up to date; (3) the study comprised a broad outcome assessment system with constant periodic and sequential MRI evaluations; (4) approximately three-quarters of patients in the study underwent second-look arthroscopic surgery; and (5) the study was performed in a single center–controlled scenario with no commercial funding, which minimized external bias.

ACI and MACT have been described as salvage treatment options after MFx, showing less favorable and predictable outcomes than when used as first-line treatment methods. This raises the idea that MFx "burns the bridges" for future cartilage repair procedures.[20] After comparing MACT with MFx in similar 100% arthroscopic approaches for relatively small chondral lesions (1-4 cm^2) and with a multimodal evaluation system, we found that MACT was structurally and clinically superior at 4 and 6 years postoperatively. Our findings suggest that this arthroscopic MACT technique (AMECI) could be considered as a first-line treatment method for relatively small chondral lesions (1-4 cm^2) based on the treatment-response expectations of patients.

AUTHORS

Clemente Ibarra, MD, PhD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Enrique Villalobos, MD, PhD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Antonio Madrazo-Ibarra, MD (School of Medicine, Universidad Panamericana, Mexico City, Mexico); Cristina Velasquillo, PhD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Valentin Martinez-Lopez, MSc (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Aldo Izaguirre, MD, PhD (Facultad de Medicina de Tampico "Dr. Alberto Romo Caballero," Universidad Autonoma de Tamaulipas, Victoria, Mexico); Anell Olivos-Meza, MD, PhD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Socorro Cortes-Gonzalez, MD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Francisco Javier Perez-Jimenez, MD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Alberto Vargas-Ramirez, MD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Gilberto Franco-Sanchez, MD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Luis Guillermo Ibarra-Ibarra, MD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Luis Sierra-Suarez, MD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Arturo Almazan, MD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Carmina Ortega-Sanchez, MSc (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Cesareo Trueba, MD (Hospital Español, Mexico City, Mexico); Fernando Barbosa Martin, MD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico); Reynaldo Arredondo-Valdes, MD (Hospital Regional "1 de Octubre," Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico); Daniel Chavez- Arias, MD (Instituto Nacional de Rehabilitacion Luis Guillermo Ibarra Ibarra, Mexico City, Mexico).

ACKNOWLEDGMENT

The authors thank Carmen Parra, MSc, for her contribution in the cell culture process for this project; Victor Guevara, MD, Fernando Hernandez-Perez, MD, and Fernando Gomez-Verdejo, MD, for contributing in the clinical evaluation; Vania Gasca-Saucedo, MD, for contributing in the structural evaluation; Jaime Guadarrama-Becerril, MD for contributing in the isokinetic evaluation; and Francisco Cruz, MD, for participating in the recruitment and surgical procedure of the patients.

ORCID iD

Enrique Villalobos https://orcid.org/0000-0002-7702-1630

REFERENCES

1. Arøen A, Løken S, Heir S, et al. Articular cartilage lesions in 993 consecutive knee arthroscopies. *Am J Sports Med*. 2004;32(1):211-215.
2. Basad E, Ishaque B, Bachmann G, Stürz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomized study. *Knee Surg Sports Traumatol Arthrosc*. 2010;18(4):519-527.
3. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med*. 1994;331(14):889-895.
4. Brittberg M, Recker D, Ilgenfritz J, Saris DBF; SUMMIT Extension Study Group. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: five-year follow-up of a prospective randomized trial. *Am J Sports Med*. 2018;46(6):1343-1351.
5. Center for Biologics Evaluation and Research. Preparation of IDEs and INDs for products intended to repair or replace knee cartilage. United States Food and Drug Administration. Published August 23, 2019. Accessed May 20, 2020 https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents/preparation-ides-and-inds-products-intendedrepair-or-replace-knee-cartilage
6. Cicuttini F, Ding C, Wluka A, Davis S, Ebeling PR, Jones G. Association of cartilage defects with loss of knee cartilage in healthy, middle-age adults: a prospective study. *Arthritis Rheum*. 2005;52(7):2033-2039.
7. Crawford DC, DeBerardino TM, Williams RJ 3rd. NeoCart, an autologous cartilage tissue implant, compared with microfracture for treatment of distal femoral cartilage lesions: an FDA phase-II prospective, randomized clinical trial after two years. *J Bone Joint Surg Am*. 2012;94(11):979-989.
8. Davies-Tuck ML, Wluka AE, Wang Y, et al. The natural history of cartilage defects in people with knee osteoarthritis. *Osteoarthritis Cartilage*. 2008;16(3):337-342.
9. Erggelet C, Sittinger M, Lahm A. The arthroscopic implantation of autologous chondrocytes for the treatment of full-thickness cartilage defects of the knee joint. *Arthroscopy*. 2003;19(1):108-110.
10. Everhart JS, Campbell AB, Abouljoud MM, Kirven JC, Flanigan DC. Cost-efficacy of knee cartilage defect treatments in the United States. *Am J Sports Med*. 2020;48(1):242-251.
11. Gobbi A, Karnatzikos G, Kumar A. Long-term results after microfracture treatment for full-thickness knee chondral lesions in athletes. *Knee Surg Sports Traumatol Arthrosc*. 2014;22(9):1986-1996.
12. Gou GH, Tseng FJ, Wang SH, et al. Autologous chondrocyte implantation versus microfracture in the knee: a meta-analysis and systematic review. *Arthroscopy*. 2020;36(1):289-303.
13. Hoburg A, Niemeyer P, Laute V, et al. Matrix-associated autologous chondrocyte implantation with spheroid technology is superior to arthroscopic microfracture at 36 months regarding activities of daily living and sporting activities after treatment. *Cartilage*. Published online January 1, 2020. doi: 10.1177/1947603519897290
14. Houck DA, Kraeutler MJ, Belk JW, Frank RM, McCarty EC, Bravman JT. Do focal chondral defects of the knee increase the risk for progression to osteoarthritis? A review of the literature. *Orthop J Sports Med*. 2018;6(10):2325967118801931.
15. Ibarra C, Izaguirre A, Villalobos E, et al. Follow-up of a new arthroscopic technique for implantation of matrix-encapsulated autologous chondrocytes in the knee. *Arthroscopy*. 2014;30(6):715-723.
16. Katz NP, Paillard FC, Ekman E. Determining the clinical importance of treatment benefits for interventions for painful orthopedic conditions. *J Orthop Surg Res*. 2015;10:24.
17. Kon E, Filardo G, Di Matteo B, Perdisa F, Marcacci M. Matrix assisted autologous chondrocyte transplantation for cartilage treatment: a systematic review. *Bone Joint Res*. 2013;2(2):18-25.
18. Masri M, Lombardero G, Velasquillo C, et al. Matrix-encapsulation cell-seeding technique to prevent cell detachment during arthroscopic implantation of matrix-induced autologous chondrocytes. *Arthroscopy*. 2007;23(8):877-883.
19. Medina J, Garcia-Mansilla I, Fabricant PD, et al. Microfracture for the treatment of symptomatic cartilage lesions of the knee: a survey of the International Cartilage Regeneration and Joint Preservation Society. *Cartilage*. Published online September 10, 2020. doi: 10.1177/1947603520954503
20. Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. *Am J Sports Med*. 2009;37(5):902-908.
21. Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR. Clinical efficacy of the microfracture technique for articular cartilage

repair in the knee: an evidence-based systematic analysis. *Am J Sports Med*. 2009;37(10):2053-2063.
22. Niemeyer P, Albrecht D, Andereya S, et al. Autologous chondrocyte implantation (ACI) for cartilage defects of the knee: a guideline by the working group ''Clinical Tissue Regeneration'' of the German Society of Orthopaedics and Trauma (DGOU). *Knee*. 2016;23(3):426-435.
23. Niemeyer P, Laute V, Zinser W, et al. A prospective, randomized, open-label, multicenter, phase III noninferiority trial to compare the clinical efficacy of matrix-associated autologous chondrocyte implantation with spheroid technology versus arthroscopic microfracture for cartilage defects of the knee. *Orthop J Sports Med*. 2019;7(7):2325967119854442.
24. Olivos Meza A, Cortés González S, Ferniza Garza JJ, Pérez Jiménez FJ, Enrique VC, Ibarra C. Arthroscopic treatment of patellar and trochlear cartilage lesions with matrix encapsulated chondrocyte implantation versus microfracture: quantitative assessment with MRI T2-mapping and MOCART at 4-year follow-up. *Cartilage*. Published online April 3, 2019. doi: 10.1177/1947603519835909
25. Olivos-Meza A, Madrazo-Ibarra A, Ibarra Ponce de León C. Arthroscopic technique to treat articular cartilage lesions in the patellofemoral joint. In: Amarasekera HW, ed. *Recent Advances in Arthroscopic Surgery*. London: IntechOpen; 2018:67-76.
26. Oussedik S, Tsitskaris K, Parker D. Treatment of articular cartilage lesions of the knee by microfracture or autologous chondrocyte implantation: a systematic review. *Arthroscopy*. 2015;31(4):732-744.
27. Potter HG, Black BR, Chong LR. New techniques in articular cartilage imaging. *Clin Sports Med*. 2009;28(1):77-94.
28. Riboh JC, Cvetanovich GL, Cole BJ, Yanke AB. Comparative efficacy of cartilage repair procedures in the knee: a network meta-analysis. *Knee Surg Sports Traumatol Arthrosc*. 2017;25(12):3786-3799.
29. Saris D, Price A, Widuchowski W, et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: two-year follow-up of a prospective randomized trial. *Am J Sports Med*. 2014;42(6):1384-1394.
30. Schreiner MM, Raudner M, Marlovits S, et al. The MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) 2.0 knee score and atlas. *Cartilage*. Published online August 17, 2019. doi: 10.1177/1947603519865308
31. Schuette HB, Kraeutler MJ, McCarty EC. Matrix-assisted autologous chondrocyte transplantation in the knee: a systematic review of mid- to long-term clinical outcomes. *Orthop J Sports Med*. 2017;5(6):2325967117709250.
32. Steadman JR, Rodkey WG, Rodrigo JJ. Microfracture: surgical technique and rehabilitation to treat chondral defects. *Clin Orthop Relat Res*. 2001;391(suppl):S362-S369.
33. Taves DR. Minimization: a new method of assigning patients to treatment and control groups. *Clin Pharmacol Ther*. 1974;15(5):443-453.
34. Villalobos E, Madrazo-Ibarra A, Martínez V, et al. Arthroscopic matrix-encapsulated autologous chondrocyte implantation: a pilot multicenter investigation in Latin America. *Cartilage*. Published online May 14, 2020. doi: 10.1177/1947603520918630
35. Villalobos E, Olivos-Meza A, Izaguirre A, Ibarra C. Arthroscopic approaches for cartilage repair in the knee joint. In: Emans PJ, Peterson L, eds. *Developing Insights in Cartilage Repair*. Springer; 2014:227-239.
36. Villalobos FE, Izaguirre A, Almazan A, Cruz F, Pérez F, Ibarra JC. P57 articular cartilage injuries in 1309 knee arthroscopies: a public health problem in a developing country? *Osteoarthritis Cartilage*. 2007;15:B102.
37. Welsch GH, Trattnig S, Domayer S, Marlovits S, White LM, Mamisch TC. Multimodal approach in the use of clinical scoring, morphological MRI and biochemical T2-mapping and diffusion-weighted imaging in their ability to assess differences between cartilage repair tissue after microfracture therapy and matrix-associated autologous chondrocyte transplantation: a pilot study. *Osteoarthritis Cartilage*. 2009;17(9):1219-1227.