Outcomes After a Single-Stage Procedure for Cell-Based Cartilage Repair

A Prospective Clinical Safety Trial With 2-Year Follow-up

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Investigation performed at Rush University Medical Center, Chicago, Illinois (clinical); OrthoIndy, Indianapolis, Indiana (clinical); Robert Wood Johnson Medical School, New Brunswick, New Jersey (clinical); New England Baptist Hospital, Boston, Massachusetts (clinical); Santa Monica Orthopedic Group, Santa Monica, California (clinical); Imaging Institute and Department of Biomedical Engineering, Cleveland Clinic, Cleveland, Ohio (imaging); and Advanced Technologies and Regenerative Medicine, Raynham, Massachusetts (materials and device prototypes).

Background: There are currently several approaches being pursued to treat focal defects of articular cartilage, each having specific advantages or challenges. A single-stage procedure that uses autologous cartilage fragments, Cartilage Autograft Implantation System (CAIS), is being evaluated in patients and may offer a clinically effective option.

Purpose: To establish the safety of CAIS and to test whether CAIS improves quality of life by using standardized outcomes assessment tools.

Study Design: Randomized controlled trial; Level of evidence, 2.

Methods: Patients (n = 29) were randomized (1:2) with the intent to treat with either a control (microfracture [MFX]) or an experimental (CAIS) procedure. Patients were followed at predetermined time points for 2 years using several standardized outcomes assessment tools (SF-36, International Knee Documentation Committee [IKDC], Knee injury and Osteoarthritis Outcome Score [KOOS]). Magnetic resonance imaging was performed at baseline, 3 weeks, and 6, 12, and 24 months.

Results: Lesion size and International Cartilage Repair Society (ICRS) grade were similar in both groups. General outcome measures (eg, physical component score of the SF-36) indicated an overall improvement in both groups, and no differences in the number of adverse effects were noted in comparisons between the CAIS and MFX groups. The IKDC score of the CAIS group was significantly higher (73.9 $\pm$ 14.72 at 12 months and 82.95 $\pm$ 14.88 at 24 months) compared with the MFX group (57.78 $\pm$ 18.31 at 12 months and 59.5 $\pm$ 13.44 at 24 months). Select subdomains (4/5) in the KOOS instrument were significantly different at 12 and 18 months, and all subdomains (Symptoms and Stiffness, Pain, Activities of Daily Living, Sports and Recreation, Knee-related Quality of Life) were significantly increased in CAIS with scores of 88.47 $\pm$ 11.68, 90.64 $\pm$ 7.87, 97.29 $\pm$ 3.8, 78.16 $\pm$ 22.06, and 69 $\pm$ 23.15 compared with 75 $\pm$ 9.31, 78.94 $\pm$ 13.73, 89.46 $\pm$ 8.13, 51.67 $\pm$ 26.01, and 37.15 $\pm$ 21.67 in the MFX group. These significant improvements were maintained at 24 months in both IKDC and KOOS. Qualitative analysis of the imaging data did not note differences between the 2 groups in fill of the graft bed, tissue integration, or presence of subchondral cysts. Patients treated with MFX had a significantly higher incidence of intralesional osteophyte formation (54% and 70% of total number of lesions treated) at 6 and 12 months when compared to CAIS (8% and 25% of total number of lesions treated).

Conclusion: The first clinical experience in using CAIS for treating patients with focal chondral defects indicates that it is a safe, feasible, and effective method that may improve long-term clinical outcomes.

Keywords: cartilage; knee; arthroscopy; tissue engineering; magnetic resonance

Chondral lesions are a common cause of knee symptoms, and if left untreated, these defects may progress in size and evolve into frank osteoarthritis (OA).[10,17] Articular cartilage has limited capacity for repair after injury due to a unique tissue structure that includes a paucity of cells within lacunae, resulting in an inability to migrate to the injury site, absence of a vascular supply, complex biochemistry, and exceptional mechanical demands. Treatment of a chondral lesion by surgical intervention should ideally

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lead to the restoration of structure and function of hyaline cartilage and ultimately prevent OA. Several potential treatments are being pursued and can be organized in an intricate treatment algorithm based on the anatomy, lesion size, and functional demands of the patient.[5] While new approaches continue to be proposed and developed,[6,12,29] many of these treatments have led to inconsistent midterm results without convincing evidence that hyaline cartilage is ultimately created.

The use of bone marrow stimulation such as microfracture (MFX)[28] has clear advantages including ease of use, relatively low cost, and short-term improvement.[2,19] However, the technique may have limitations with respect to lesion size,[5] and there are mixed results as to whether MFX is able to produce long-term functional improvements.[15,20] Osteochondral autograft transplantation is appealing for the treatment of smaller defects, but mixed results have been reported.[26] Autologous chondrocyte implantation (ACI) as a treatment for larger chondral lesions has also had mixed results.[13,14,18,32] Using the ACI concept but with characterized chondrocyte implantation (CCI), there are reports of superiority when compared with MFX with respect to functional outcomes and to the quality of tissue being formed 3 years after implantation.[24,25] Fresh osteochondral allograft transplantation is another option used to treat moderate- to large-sized lesions, especially when the subchondral bone is involved. While safety and efficacy are similar to the other options, graft availability and expense continue to be limiting factors. At the heart of this debate and the reason for the diversity of approaches being explored today is whether hyaline cartilage is being produced at the repair site and whether hyaline cartilage is essential for a good and lasting outcome.[3]

Cartilage Autograft Implantation System (CAIS) is a point-of-care surgical procedure for the primary treatment of chondral lesions in the knee. Autologous hyaline cartilage is harvested arthroscopically typically from the intercondylar notch or trochlear border. This cartilage is mechanically minced and then affixed on a synthetic, absorbable scaffold using fibrin glue. The lesion site is prepared in a manner similar to ACI. The implant, loaded with minced cartilage fragments, is placed in the lesion site with the minced cartilage facing the bone base and fixed with synthetic, absorbable staples. Preclinical studies utilizing minced chondral fragments demonstrated a robust cartilage matrix consistent with the features of hyaline-like cartilage.[8,16] We hypothesized that standard patient-reported outcome tools would detect differences between the control (MFX) and the treatment group (CAIS). In this first clinical study, we determined the safety of CAIS and evaluated initial efficacy using standardized outcomes assessment tools by comparing CAIS to MFX for the treatment of symptomatic chondral defects.

MATERIALS AND METHODS

Patient Enrollment and Baseline Characteristics

Patients were recruited for a multicenter clinical trial in 5 different clinical sites across the United States. The clinical protocol was approved by the institutional review board of each institution and executed under current Good Clinical Practice, Food and Drug Administration, and International Committee on Harmonization guidelines. Inclusion and exclusion criteria are outlined in the Appendix (available in the online version of this article at http://ajs.sagepub.com/supplemental/). Full-length long leg alignment radiographs were utilized to measure alignment. Patients were screened preoperatively and enrolled in the study. A final screen was performed intraoperatively to characterize the lesion(s). A randomization scheme (MFX:CAIS, 1:2) was developed before the start of the study for each clinical site. Patients who met the inclusion criteria were subsequently randomized to MFX or CAIS by using a blinded allocation (envelope draw) design. In this study, 29 patients were enrolled with 20 randomized to the CAIS treatment group and 9 to the MFX active control group. Patient demographics and work status are presented in Table 1. The mean duration before seeking surgical care was 2.7 $\pm$ 4.7 years for all patients (Table 2) and was not different between control and treatment groups. Injury mechanism is also presented in Table 2, and lesion characteristics are presented in Table 3. Postoperatively, patients were evaluated at predetermined time points: weeks 1 and 3 and months 2, 3, 6, 12, 18, and 24. For simplicity, we present the knee-specific outcome data (IKDC and KOOS) obtained at 6, 12, 18, and 24 months after surgery. All expected and unexpected adverse events were recorded as they occurred.

Surgical Technique

The surgical centers and staff were trained on the procedures and the proper use of CAIS. Standard arthroscopic portals were used to assess the joint for inclusion/exclusion criteria and to determine whether the lesions met the treatment criteria for the clinical study. Postdebridement measurements were taken (Table 3), and patients (who met all

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TABLE 1
Baseline Characteristics of the Patients at Time of Intervention[a]

General Demographics	MFX (n = 9)	CAIS (n = 20)
Age, y (mean ± SD)	33.0 ± 10.1	32.7 ± 8.8
Height, cm (mean ± SD)	177.0 ± 10.6	177.3 ± 10.7
Weight, kg (mean ± SD)	83.4 ± 17.8	85.0 ± 37.9
BMI, kg/m^2 (mean ± SD)	26.3 ± 3.3	27.0 ± 4.8
Gender, n (%)		
Male	5 (56)	14 (70)
Female	4 (44)	6 (30)
Ethnicity, n (%)		
White	8 (89)	17 (85)
African American	1 (11)	2 (10)
Hispanic	0	1 (5)
Work status, n (%)		
Working full-time	3 (33)	15 (75)
Working part-time	1 (11)	0
Not working due to injury	2 (22)	0
Other or students	3 (33)	5 (25)
Nicotine use, n (%)		
Current	1 (11)	5 (25)
Previous	2 (22)	1 (5)
Never	6 (67)	14 (70)

[a]MFX, microfracture; CAIS, Cartilage Autograft Implantation System; SD, standard deviation; BMI, body mass index.

screening criteria) were then randomized intraoperatively to be treated with MFX or CAIS. When 2 focal lesions were identified, both were evaluated and treated provided that all other inclusion/exclusion criteria were met.

The MFX technique was performed as described by Steadman et al.[8,28] Hyaline cartilage was arthroscopically harvested from a low load-bearing surface (eg, lateral wall of the intercondylar notch or trochlear ridge with an amount similar to that harvested for ACI, roughly 200 mg) using a unique device that minces the cartilage into 1- to 2-mm pieces. After harvest, the device (DePuy Mitek, Raynham, Massachusetts) uniformly disperses the minced cartilage onto the biodegradable scaffold. The fragments were then secured to the scaffold using a commercially available fibrin sealant (Tisseel, Baxter, Illinois). A mini-arthrotomy was performed, and the defect was identified and prepared similar to the technique utilized for ACI, whereby vertical walls were created and the damaged cartilage removed to the level of the subchondral bone using a ring curette. If bleeding was noted, hemostasis was achieved using epinephrine-soaked sponges and/or punctuated amounts of fibrin glue (Tisseel). An arthroscopic ruler was used to measure width, length, and depth of the prepared lesion. Subsequently, a template sized the area of the lesion. Sterile paper or foil was used to make a template of the cartilage defect and used to cut the implant to the appropriate size. The trimmed CAIS scaffold implant was transferred to the defect with the cartilage fragments facing the subchondral bone and affixed with 2 or more biodegradable staple anchors (prototype, Advanced Technologies and Regenerative Medicine, Raynham, Massachusetts), which consist of polydioxanone (PDO) straps and a polyglycolic acid (PGA) tip (Advanced Technologies and Regenerative Medicine).

TABLE 2
Knee Condition at Screening[a]

Knee Condition	MFX (n = 9)	CAIS (n = 20)
Duration since onset, y (mean ± SD)	2.31 ± 3.4	2.84 ± 5.3
Onset, n (%)		
Gradual	6 (67)	6 (30)
Acute	3 (33)	14 (70)
Cause of injury, n (%)		
Activity of daily living	2 (22)	7 (35)
Sports, contact	0	6 (30)
Sports, noncontact	6 (67)	5 (25)
Traffic	0	1 (5)
Other	1 (11)	1 (5)

[a]MFX, microfracture; CAIS, Cartilage Autograft Implantation System; SD, standard deviation.

The CAIS scaffold implant consists of an absorbable copolymer foam of 35% polycaprolactone (PCL) and 65% PGA, reinforced with a PDO mesh (Advanced Technologies and Regenerative Medicine). The polymer foam is designed to keep the tissue fragments in place and serves as a 3-dimensional scaffold for cartilage matrix generation. The reinforcing PDO mesh enables the foam to have adequate mechanical strength during implant handling.

Clinical Protocol and Rehabilitation

In general, the rehabilitation program focused initially on protection of the cartilage repair process and then progressed toward controlled loading, increased range of motion, and progressive muscle strengthening.[22] The patients received a different rehabilitation protocol depending on whether they had a lesion in the trochlea or femoral condyle but was the same for CAIS and MFX. Immediately after surgery, all patients received a hinged knee brace locked in extension. Patients with a lesion on the femoral condyle were made nonweightbearing for the first 2 weeks and were advanced to partial weightbearing with an unlocked brace from week 2 through 6. Patients with a trochlear lesion were allowed to bear weight as tolerated immediately with the brace locked in extension. Each day, the brace was removed for continuous passive motion (0°-45°) during the first 4 weeks, which was progressively increased (as tolerated) to 90° during the subsequent 3 weeks. Muscle strength was maintained using isometric quadriceps sets, straight leg raises, and isometric contraction of the hamstrings, hip abductors, and hip adductors. When tolerated, patients used a stationary bike without resistance to maintain passive range of motion. Patients returned to low load activity levels at week 6 to 8 and progressed in activity as strength and comfort permitted.

Standardized Outcomes Assessment Tools

General and knee-specific quality of life was measured at preoperative baseline and at 1 week, 3 weeks, and 2, 3, 6, 9, 12, 18, and 24 months after surgery. The primary

TABLE 3
International Cartilage Repair Society (ICRS) Grading and Lesion Size[a]

	MFX (9 patients, 13 lesions)	CAIS (20 patients, 24 lesions)
ICRS grading		
3A	6	3
3B	1	7
3C	3	7
3D	1	3
4A	2	4
4B	0	0
No. of patients with 2 lesions	4	4
Anatomic localization of lesions	Trochlea: 6 Femoral condyle: 7	Trochlea: 10 Femoral condyle: 14
Postdebridement, chondral lesion area, mm^2 (mean ± SD)	348 ± 12	275 ± 15
Postdebridement, chondral lesion depth, mm (mean ± SD)	3.1 ± 1.1	3.0 ± 1.5

[a]MFX, microfracture; CAIS, Cartilage Autograft Implantation System; SD, standard deviation.

outcome measure in this study was tolerance to the procedure (safety) and functional activity levels, measured by patient-reported outcome instruments. The following standardized outcomes assessment tools were used:

1. SF-36: The SF-36 is the most commonly used health profile[31] and has been compared with other standardized outcomes assessment instruments in the treatment of focal chondral defects.[4,7,30,31]
2. The International Knee Documentation Committee (IKDC): The IKDC Subjective Knee Evaluation Form presents 17 items related to knee symptoms, knee function, and sports activity in patients who have a variety of knee conditions, including articular cartilage injuries,[9,11] and in a healthy normal population.[1]
3. The Knee injury and Osteoarthritis Outcome Score (KOOS): The KOOS was developed for more active, younger patients with a knee injury or early-onset knee osteoarthritis.[23] This standardized outcomes assessment tool contains a total of 42 items and covers 5 subdomains: Symptoms and Stiffness, Pain, Activities of Daily Living (ADL), Sports and Recreational Activities, and Knee-related Quality of Life (QOL). Normative data of the Swedish population have been described.[21] The KOOS has been compared with other standardized outcomes assessment tools in the treatment of focal chondral defects.[4,24,25]

Imaging

Magnetic resonance imaging (MRI) was performed using a standardized protocol at postoperative time points of 3 weeks and 6, 12, and 24 months. All postoperative images were performed on 1.5-T whole-body imaging systems using an extremity coil with standardized image acquisition parameters. The magnetic resonance protocol consisted of coronal, sagittal, and axial images using fast spin echo (FSE) techniques with and without fat suppression and a sagittal fat-suppressed 3-dimensional spoiled gradient-recalled echo sequence. Five qualitative measurements were assessed for each repair site (37 in total) in each patient. Volume (fill) of the graft bed repair tissue was assessed by evaluating the volume of the repair tissue within the repair site relative to the volume of the entire postdebridement defect. Repairs were graded by percentage (in quartile increments) of fill total volume. Volume (fill) of the graft bed repair tissue excluded any hypertrophic repair tissue. The integration of the repair tissue into the adjacent, "native" articular cartilage was judged by the magnetic resonance signal intensity at the repair tissue-cartilage interface. The presence of any fluid-like signal intensity at the repair-cartilage interface was used as a criterion to classify the integration as incomplete. The presence or absence of any cysts beneath the repair site was recorded, but the size of the cysts was not measured. The presence or absence of intralesional osteophytes on magnetic resonance images was recorded. Intralesional osteophytes were judged to be present if any portion of the subchondral bone plate within the repair site was higher than expected compared with the adjacent, untreated articular surface. Presence of scar tissue at the infrapatellar fat pad was assessed by the presence or absence of linear, low signal structures within the articular space or synovial thickening of connecting structures.

Statistical Analysis

Comparisons of the standardized outcomes assessment data between the control group (MFX) and the experimental group (CAIS) at the different time points were made using a Student *t* test. The MRI data were analyzed by a Fisher exact test. The *P* value for determining statistical significance was set at $\leq .05$, and statistical power was calculated post hoc; no pre hoc power study was performed.

RESULTS

Patient Enrollment

Patients (a total of 582) were either referred to or screened by the clinical sites between March 2006 and December

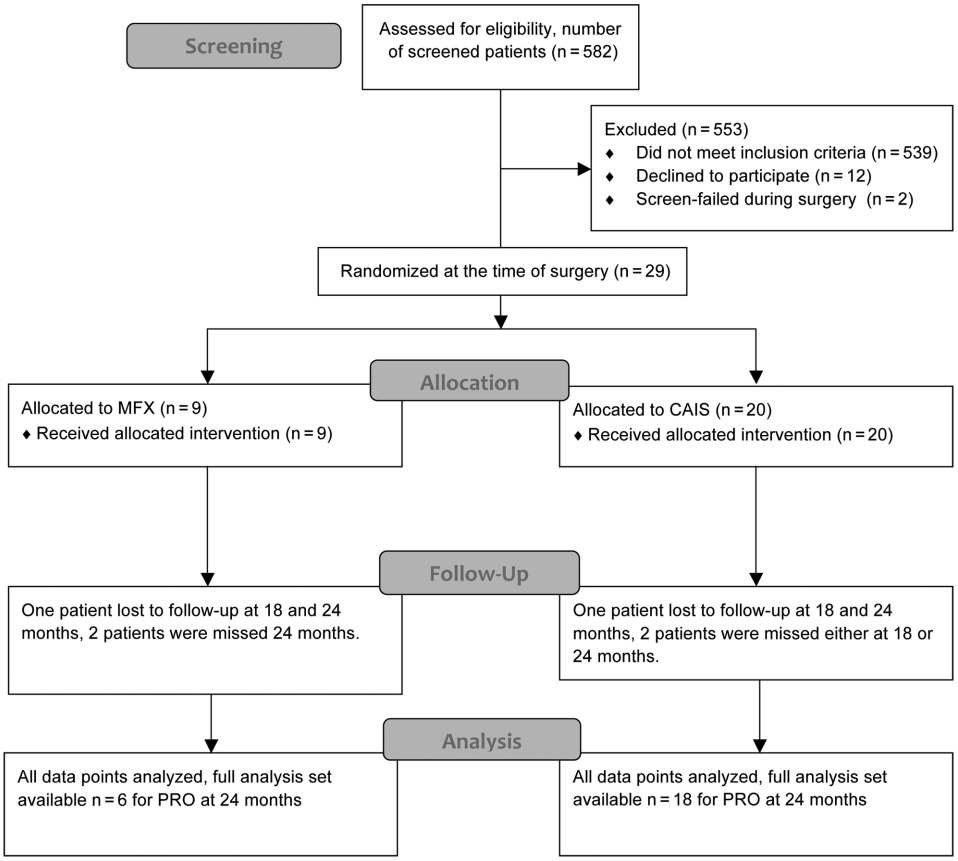

Figure 1. Flow chart illustrating the number of patients who were screened, met inclusion criteria, and were subsequently enrolled in the pilot study.

2007. In this pilot study, 31 patients met inclusion/exclusion criteria and consented, 2 patients failed screening intraoperatively, and a total of 29 patients were randomized and entered the trial (Figure 1). Patients who were placed in the CAIS treatment group received a mini-open procedure, while the MFX group was treated arthroscopically; total blinding was not possible. We noted a difference in gender distribution with more men than women and in activity level with more full-time workers being enrolled in the CAIS group (Table 1), which is attributed to randomization in a small sample size. With respect to duration of symptoms (Table 2), ICRS grade, and area and depth of the chondral defect, no differences were noted, indicating that despite differences in patient demographics, lesion features were similar (Table 3). Throughout the duration of the pilot study, all postsurgical events and complications (expected and unexpected adverse events) were recorded, and there were no differences between the 2 groups (Table 4). In the CAIS group, the number and nature of the events were consistent with what has traditionally been reported with MFX.[22,30] Two patients were lost to follow-up (1 MFX, 1 CAIS) at 18 and 24 months, respectively, and 4 patients (2 MFX, 2 CAIS) missed one time point (either at 18 months or 24 months). One patient in the CAIS group required a diagnostic arthroscopic procedure at 18 months, at which time 2 additional, new lesions were identified, which were deemed not related to the study protocol and treated with MFX.

Standardized Outcomes Assessment Tools

The SF-36 instruments did not detect significant differences between the active control group (MFX) and the treatment group (CAIS). Figure 2 shows the unadjusted scores for the Physical Component Score from the SF-36 and indicates that after the immediate postoperative period, progressive improvements were seen in both groups but the differences between groups were not statistically significant. We chose to report the standardized assessment data for selected time points for the following reasons: (1) data from early time points would not represent changes that potentially might be associated with cartilage repair, and (2) data at the earlier time points were not significantly different between the groups. The complete data set (IKDC and KOOS) is available in the Appendix (available online). Knee-specific outcomes were obtained by using IKDC (subjective knee evaluation) and KOOS (Table 5). Unadjusted scores for IKDC and 4 of the 5 KOOS (Symptoms and Stiffness, Pain, ADL, Sports and Recreation) were greater in the CAIS group than in the MFX group at the 12-month time point. At 12 months, the *P*

TABLE 4
Recorded Postsurgical Events or Complications[a]

Category, Occurrence (% of Total)	MFX	CAIS
Local postsurgical events		
Joint effusion	9 (100)	18 (90)
Decreased range of motion	8 (89)	18 (90)
Joint swelling	8 (89)	17 (85)
Arthralgia	7 (78)	18 (90)
Joint crepitation	4 (44)	6 (30)
Muscle weakness	2 (22)	1 (5)
Sensory loss	1 (11)	6 (30)
Contusion	1 (11)	3 (15)
Hemarthrosis	1 (11)	3 (15)
Arthritis	1 (11)	2 (10)
General postsurgical events		
Nausea	3 (33)	9 (45)
Gastroenteritis (viral)	2 (22)	0 (0)
Impingement syndrome	2 (22)	2 (10)
Pruritus (generalized)	1 (11)	3 (15)
Anxiety	1 (11)	1 (5)
Constipation	0	2 (10)
Hypoesthesia	0	2 (10)
Pyrexia	0	2 (10)

[a]Any time point throughout the study. MFX, microfracture; CAIS, Cartilage Autograft Implantation System.

value (post hoc power) for the IKDC instrument was .02 (.61), and for the KOOS subdomains Symptoms and Stiffness, Pain, ADL, and Sports and Recreation, *P* values were .02 (.59), .004 (.84), .02 (.57), and .004 (.84), respectively (Table 5). These differences persisted at 18 months, and the *P* value (post hoc power) for total IKDC score was .03 (.51); similarly, differences in the KOOS subdomains Pain, ADL, Sports and Recreation, and Quality of Life were .007 (.78), .002 (.92), .003 (.85), and .014 (.66), respectively. At 24 months after surgery, the scores in the IKDC and all subdomains of KOOS for CAIS were statistically higher when compared with MFX. The *P* value (post hoc power) for the IKDC instrument at 24 months was .02 (.90). Similar values were obtained when analyzing KOOS data at 24 months with *P* values (post hoc power): .02 (.62), .02 (.65), .03 (.87), .02 (.57), and .01 (.78) for Symptoms and Stiffness, Pain, ADL, Sports and Recreation, and Knee-related Quality of Life, respectively.

Magnetic Resonance Imaging

All patients were evaluated with MRI at predetermined time points, and repairs were assessed as described above. A qualitative analysis of each series of images was performed by an experienced radiologist (C.S.W.), who was blinded with respect to the treatment that the patients received; however, the presence of the staples in the CAIS group made total blinding difficult. A longitudinal image series of 2 representative patients (MFX, right knee; CAIS, left knee) are shown in Figure 3A (sagittal views) and 3B (coronal views). The CAIS device was easily identifiable by its low signal at early time points (Figure 3B, CAIS, 3 weeks). At 3 weeks, defects in the CAIS group were completely covered with "tissue" that was generally

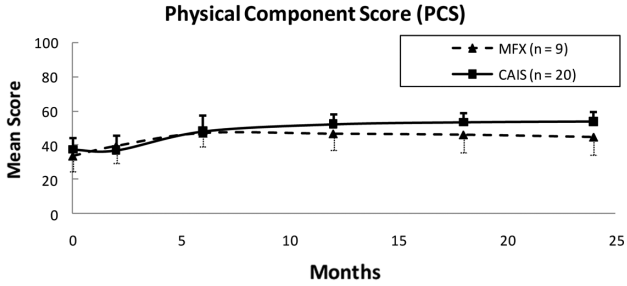

Figure 2. Physical Component Score of the SF-36 in patients treated with microfracture (MFX) or Cartilage Autograft Implantation System (CAIS) over a 24-month period after surgical intervention. The data show the overall well-being in both groups and indicate that CAIS is safe. A trend of a gradual, consistent, and progressive improvement may be present after 12 months in patients treated with CAIS.

higher in signal than the native cartilage, indicating the implants remained affixed in all patients. Table 6 provides a summary of the findings and represents the analysis for all lesions (1 and 2 lesions combined). Volume fill of the graft bed was satisfactory in most patients with progressive improvement over time, and by 24 months, nearly all lesions in both groups had a 76% to 100% fill of the repair site. The assessment of tissue integration showed a similar trend with progressive improvement over time, and while differences between MFX and CAIS were observed, they were not significantly different. Subchondral cysts were absent at 3 weeks but were present in about a quarter of the patients in both treatment groups at 12 and 24 months. Intralesional osteophytes, superficial to the original subchondral bone, were not seen at 3 weeks but were significantly more common at 6 and 12 months in MFX patients. We did not detect significant differences at 24 months, possibly because we lost these patients to follow-up. Scarring of the synovial membrane around the infrapatellar fat pad was seen more frequently and was more pronounced at 12 and 24 months in patients who received CAIS, most likely as a result of the mini-open procedure. In all cases, the scar tissue appeared as very thin bands of tissue.

DISCUSSION

Within the context of tissue engineering, it is generally agreed upon that a successful tissue repair strategy needs to include a bioactive component (cells or growth factors) that drives the biological process and a matrix (a biomaterial serving as a carrier or scaffold) that provides architectural support and facilitates the integration of the repaired tissue with the contiguous tissue. Osteochondral autografting, which theoretically contains both a bioactive component and a matrix, has limited use in light of the recommended lesion size, which is between 1 and 2.5 cm^2.[5] Autologous chondrocyte implantation (ACI), while promising, has not led to consistent long-term benefits when compared with microfracture[13,14]; on the other hand, it may be recommended when seeking a second-line treatment for patients with larger chondral defects.[18,32] More elaborate

TABLE 5
Unadjusted PRO Data[a]

Parameter	Baseline	Month 6	Month 12	Month 18	Month 24
IKDC (total score)					
MFX	34.56 ± 18.71 (n = 9)	57.44 ± 14.20 (n = 9)	57.78 ± 18.31 (n = 9)	62.57 ± 11.43 (n = 7)	59.50 ± 13.44 (n = 6)
CAIS	39.10 ± 15.10 (n = 20)	61.00 ± 15.98 (n = 20)	73.90 ± 14.72[b] (n = 20)	77.12 ± 14.79[b] (n = 17)	82.95 ± 14.88[b] (n = 19)
KOOS (Symptoms and Stiffness)					
MFX	45.63 ± 23.81 (n = 9)	74.60 ± 11.63 (n = 9)	75.79 ± 14.15 (n = 9)	75.89 ± 13.60 (n = 8)	75.00 ± 9.31 (n = 6)
CAIS	63.93 ± 24.69 (n = 20)	82.50 ± 16.14 (n = 20)	87.32 ± 10.33[b] (n = 20)	85.29 ± 14.22 (n = 17)	88.47 ± 11.68[b] (n = 19)
KOOS (Pain)					
MFX	45.99 ± 20.23 (n = 9)	79.63 ± 9.92 (n = 9)	76.54 ± 14.77 (n = 9)	78.13 ± 13.40 (n = 8)	78.94 ± 13.73 (n = 6)
CAIS	57.85 ± 21.22 (n = 20)	84.31 ± 11.12 (n = 20)	90.28 ± 8.71[b] (n = 20)	91.18 ± 8.46[b] (n = 17)	90.64 ± 7.87[b] (n = 19)
KOOS (Activities of Daily Living)					
MFX	54.90 ± 18.83 (n = 9)	88.73 ± 8.12 (n = 9)	86.44 ± 13.39 (n = 9)	86.21 ± 10.86 (n = 8)	89.46 ± 8.13 (n = 6)
CAIS	68.44 ± 19.73 (n = 20)	92.43 ± 6.02 (n = 20)	95.36 ± 6.56[b] (n = 20)	96.80 ± 4.20[b] (n = 17)	97.29 ± 3.80[b] (n = 19)
KOOS (Sports and Recreation)					
MFX	26.11 ± 25.83 (n = 9)	43.33 ± 27.95 (n = 9)	42.22 ± 31.63 (n = 9)	41.88 ± 26.31 (n = 8)	51.67 ± 26.01 (n = 6)
CAIS	29.25 ± 21.90 (n = 20)	45.50 ± 31.70 (n = 20)	72.63 ± 19.93[b] (n = 20)	74.71 ± 21.03[b] (n = 17)	78.16 ± 22.06[b] (n = 18)
KOOS (Knee-related Quality of Life)					
MFX	20.83 ± 22.53 (n = 9)	50.00 ± 21.19 (n = 9)	47.22 ± 22.34 (n = 9)	42.19 ± 22.35 (n = 8)	37.15 ± 21.67 (n = 6)
CAIS	24.69 ± 16.41 (n = 20)	50.94 ± 23.32 (n = 20)	62.19 ± 23.07 (n = 20)	65.81 ± 19.90[b] (n = 17)	69.08 ± 23.15[b] (n = 18)

[a]Values are means ± standard deviations. MFX, microfracture; CAIS, Cartilage Autograft Implantation System; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score.
[b]Mean from CAIS statistically significant from mean from MFX at the same time point: $P \leq .05$.

approaches preselect chondrocytes before implantation (ChondroCelect, TiGenix, Leuven, Belgium, or CCI) and have midterm data that are promising,[24,25] but this technique also requires 2 surgeries. Microfracture is easier to use but may have limitations with regard to lesion size[5] and long-term sustained clinical gains.[15] In the present study, the chondral lesion in both groups was a moderate-sized defect and appropriate for treatment with MFX, our active control group. In addition to the morphological similarities, the defects in both groups had equivalent ICRS grades. This study demonstrated that CAIS is safe to use with risks comparable with those of MFX. The use of standard outcomes assessment tools demonstrated consistent and progressive improvements during the second year after surgery in CAIS when compared with MFX. Moreover, the use of established standard outcome instruments in this study will allow the investigators to determine the minimally important difference (MID). The MID sets the threshold to compare differences of the mean and is used to show noninferiority, but the MID can also be used to predict the sample size in a larger trial.

The current study is limited by the fact that it has a small sample size, and as a result, random variation in patient demographics, activity level, and onset of symptoms may not have been fully controlled. The screening data indicated that there were more patients with acute onset of symptoms in the CAIS group than in the control group, and as a result, the patients treated with CAIS may have been predisposed to achieve better outcomes. On the other hand, chondral lesion characteristics (ICRS grade and morphometrics) were not different between the 2 groups. Baseline values for both groups using either IKDC or KOOS instruments were similar, and no significant differences were noted. The baseline values were consistent with the data reported in the MFX literature[27] and other cartilage repair studies,[24,25,32] indicating that the sample was representative. Using the normative data of the IKDC instrument, both the MFX and CAIS patients had equivalent baseline values, and our sample could be placed in the 5th to 10th deciles when compared with a normal, healthy age-matched population.[1] In the current study, there were more men and more full-time workers in CAIS compared with MFX. In a normal healthy population, gender differences have been documented in the KOOS instrument in the 55- to 74-year-old age group but not in patients between the years of 18 and 55 years, the

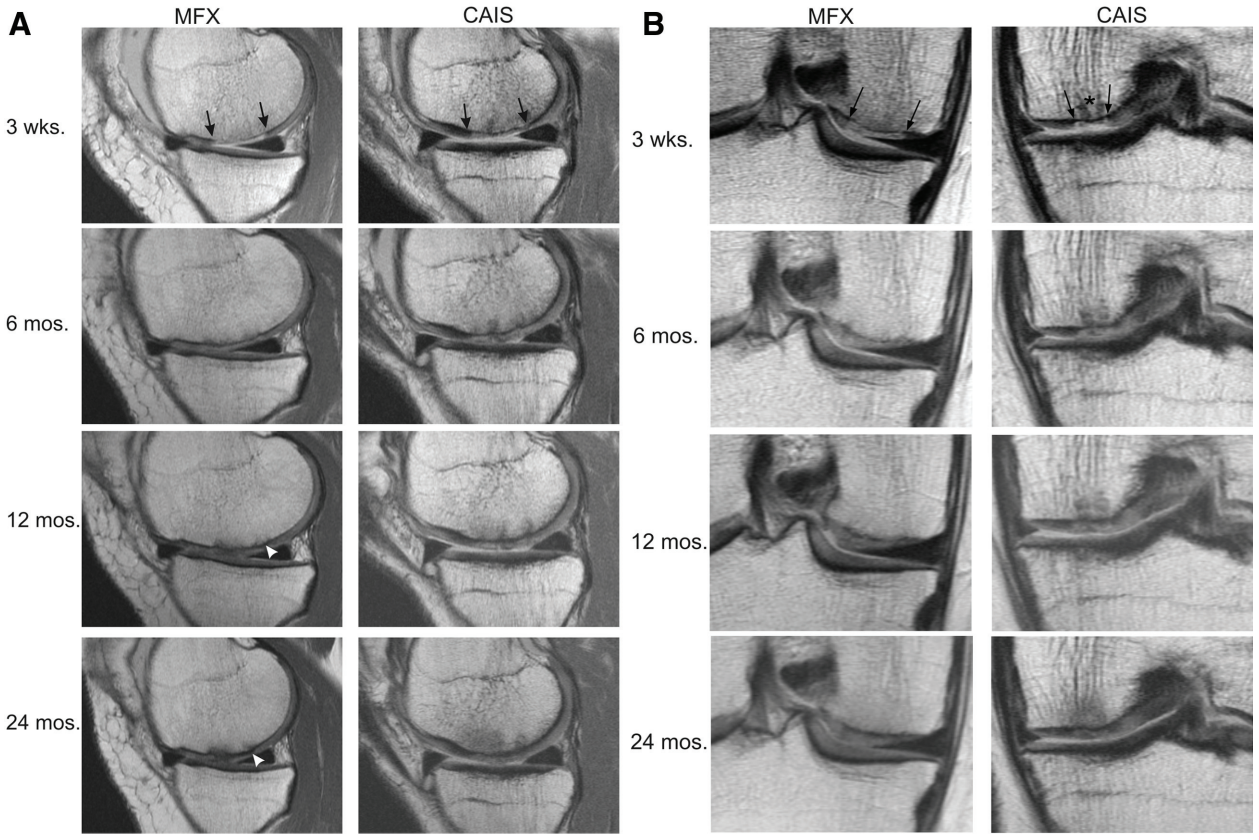

Figure 3. Magnetic resonance images (intermediate-weighted fast spin echo) of 2 representative patients (patient #1001, MFX; patient #2002, CAIS) treated with microfracture (MFX) (A) or Cartilage Autograft Implantation System (CAIS) (B). Repair sites were equivalent in size and located on the medial femoral condyle (between arrows, 3 weeks). At 3 weeks, the repair site in the medial femoral condyle is clearly visible as a high intensity region representative of the early biological processes for MFX and CAIS. The patient treated with CAIS has 2 low intensity structures (medial and lateral to ''*'' on 3-week image), which diminished on subsequent time points representing the gradually absorbed staples. At 12 and 24 months, an intralesional osteophyte (white arrowheads, A) develops in the patient treated with MFX.

age group that matched our sample. One KOOS subdomain (Sports and Recreation) has been reported to be particularly age dependent, with differences found between healthy younger (18-34 years old) and healthy older individuals (75-84 years old).[21] The mean age of patients in both treatment groups was the same, implying that significant improvements in the CAIS group are unlikely to be age dependent. The literature suggests that in a normal healthy population under 35 years, the use of IKDC or KOOS would lead to similar conclusions. The data in the current study indicate that knee-specific self-reported quality of life as measured by IKDC or KOOS led to similar inferences, namely, that patients who were treated with MFX improved compared with baseline but that patients who were treated with CAIS scored higher when compared with patients treated with MFX. Both assessment instruments were able to detect improvement in the patients treated with CAIS in selected subdomains starting at 12 months and 18 months and in the complete instruments at 24 months.

The patients in this study tolerated both procedures very well as indicated by the SF-36 data. It is possible that patients who were recruited into this trial were ideal candidates for MFX or CAIS alike because of the size of the lesion and age and activity level of the patients. Patient recruitment and lesion characterization are important factors in clinical trial design, especially in a pilot trial such as this study. For instance, the use of MFX as a control for ACI demonstrated the limitation of MFX in the treatment of a large chondral lesion (5 cm^2).[13] The demonstration of robust cartilage formation may require sophisticated imaging studies or second-look arthroscopy with histological analysis of a biopsy, studies that have been performed in other trials[14,24,25] and should be included in a larger study for CAIS. The evolution of the MRI appearances of the 2 treatments supports the concept that MFX and CAIS may have different repair or biological processes. The correlation of structural changes using quantitative MRI techniques or established morphological methods with clinical outcomes whether they be clinician-based evaluation scales or patient-reported outcomes assessment tools may be an important future endeavor for advancing the field of cartilage repair.

This clinical study reports the initial outcomes of a single-stage autologous tissue repair strategy (CAIS) in

TABLE 6
Summary of Qualitative Magnetic Resonance Imaging Findings[a]

Variable	Time Point	Criterion	MFX (n = 13)	CAIS (n = 24)	*P* Value (Fisher exact test)
Fill of the graft bed	Week 3	0%-25%	1	8	.283
		26%-50%	6	6	
		51%-75%	4	5	
		76%-100%	2	5	
	Month 6	0%-25%	0	1	.374
		26%-50%	3	2	
		51%-75%	3	3	
		76%-100%	7	18	
	Month 12	0%-25%	0	2	.750
		26%-50%	0	1	
		51%-75%	4	5	
		76%-100%	9	16	
	Month 24[b]	0%-25%	0	1	.802
		26%-50%	0	2	
		51%-75%	1	1	
		76%-100%	7	19	
Integration into adjacent cartilage	Week 3	Yes	4	6	.716
		No	9	18	
	Month 6	Yes	5	13	.495
		No	8	11	
	Month 12	Yes	8	11	.495
		No	5	13	
	Month 24[b]	Yes	7	14	.222
		No	1	9	
Presence of subchondral cysts	Week 3	Yes	0	0	—
		No	13	24	
	Month 6	Yes	2	3	1.0
		No	11	21	
	Month 12	Yes	5	5	.275
		No	8	19	
	Month 24[b]	Yes	3	4	.372
		No	5	16	
Presence of intralesional osteophytes	Week 3	Yes	0	1	1.0
		No	13	23	
	Month 6	Yes	7	2	.004[c]
		No	6	22	
	Month 12	Yes	9	6	.015[c]
		No	4	18	
	Month 24[b]	Yes	6	10	.401
		No	2	10	
Presence of scar tissue	Week 3	Yes	5	15	.396
		No	4	5	
	Month 6	Yes	5	17	.158
		No	4	3	
	Month 12	Yes	4	18	.016[c]
		No	5	2	
	Month 24[b]	Yes	2	16	.032[c]
		No	4	3	

[a]Total number of lesions evaluated. MFX, microfracture; CAIS, Cartilage Autograft Implantation System.
[b]Two patients were lost to follow-up (1 MFX, 1 CAIS) at both 18 and 24 months, and 4 patients (2 MFX, 2 CAIS) missed one time point (either at 18 months or 24 months).
[c]Significantly different: $P \leq .05$.

patients who have focal chondral defects. The standardized outcomes assessment tools and MRI data on CAIS indicate that an approach using small cartilage fragments dispersed onto a biodegradable scaffold (CAIS) is a safe and feasible treatment.

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