One-Stage Cartilage Repair Using a Hyaluronic Acid–Based Scaffold With Activated Bone Marrow–Derived Mesenchymal Stem Cells Compared With Microfracture

Five-Year Follow-up

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Background: Articular cartilage injury is frequently encountered, yet treatment options capable of providing durable cartilage repair are limited.

Purpose: To investigate the medium-term clinical outcomes of cartilage repair using a 1-stage technique of a hyaluronic acid–based scaffold with activated bone marrow aspirate concentrate (HA-BMAC) and compare results with those of microfracture. A secondary aim of this study was to identify specific patient demographic factors and cartilage lesion characteristics that are associated with superior outcomes.

Study Design: Cohort study; Level of evidence, 2.

Methods: Fifty physically active patients (mean age, 45 years) with grade IV cartilage injury of the knee (lesion size, 1.5-24 cm^2) were treated with HA-BMAC or microfracture and were observed prospectively for 5 years. Patients were placed into the HA-BMAC group if the health insurance policy of the treating institution supported this option; otherwise, they were placed into the microfracture group. Objective and subjective clinical assessment tools were used preoperatively and at 2 and 5 years postoperatively to compare treatment outcomes.

Results: Significant improvements in outcome scores were achieved in both treatment groups at 2 years ($P < .001$). In the microfracture group, 64% were classified as normal or nearly normal according to the International Knee Documentation Committee (IKDC) objective score at 2 years, compared with 100% of those treated with HA-BMAC ($P < .001$). Normal or nearly normal objective assessments in the microfracture group declined significantly after 5 years to 28% of patients ($P = .004$). All patients treated with HA-BMAC maintained improvement at 5 years according to Lysholm, Tegner, IKDC objective, and IKDC subjective scores. Tegner, IKDC objective, and Knee injury and Osteoarthritis Outcome Score (KOOS) assessments demonstrated higher scores in the HA-BMAC treatment group compared with microfracture at 5 years. Lysholm and IKDC subjective scores were similar between treatment groups at 5 years. Poorer outcomes in the microfracture group were demonstrated in cases of lesions larger than 4 cm^2 and nonsolitary lesions. Age greater than 45 years, large size of lesion, and treatment of multiple lesions were not associated with poorer outcome in patients treated with HA-BMAC.

Conclusion: Repair of chondral injury using a hyaluronic acid–based scaffold with activated bone marrow aspirate concentrate provides better clinical outcomes and more durable cartilage repair at medium-term follow-up compared with microfracture. Positive short-term clinical outcomes can be achieved with either microfracture or HA-BMAC. Cartilage repair using HA-BMAC leads to successful medium-term outcomes independent of age or lesion size.

Keywords: cartilage repair; cartilage lesion; knee, articular cartilage; stem cell therapy; microfracture

Cartilage injury is a frequent finding in patients who undergo knee arthroscopy, yet treatment options capable of providing consistent, durable cartilage repair in symptomatic patients with functional limitation remain elusive. It is widely accepted that this type of injury may lead to

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progressive degenerative change, due to an inability of the chondral defect to heal. This progressive course often leads to a reduction in physical activity and substantial lifestyle modification. A number of treatment modalities have been used in an attempt to address this condition, with variable success. Marrow stimulation techniques, such as microfracture (MF), have been commonly used because of the simplicity of technique and low cost.[18,48,49]

Ideally, in addition to providing symptomatic relief, cartilage restoration should provide long-term benefit by reducing the incidence of degenerative cartilage wear or by slowing the progression of degenerative change. Numerous studies have demonstrated that marrow stimulation techniques lead to the preferential formation of fibrocartilaginous tissue, with variable type II collagen content and a tendency to degenerate over time.[14,37,38,46,47] To overcome these limitations, interest has increased in alternative methods of cartilage repair such as osteochondral transfer, cell-free scaffolds, and cell-based technologies.[3,8,11,16,36,39] Promising medium- and long-term clinical outcomes have been achieved with autologous chondrocyte implantation (ACI)[4,19,34,40,50,52]; however, this procedure is performed in 2 stages and is cost prohibitive. Economic impact analysis has demonstrated that 2-stage cell-based cartilage repair techniques such as ACI are several times more expensive than either 1-stage cell-based techniques or microfracture.[6]

Regarding cell-based treatment options, promising preliminary results have been obtained in 1-stage repair using a scaffold-based bone marrow aspirate concentrate (BMAC).[13,15,16] This technique relies on the presence of mesenchymal stem cells (MSCs), as well as growth factors, to stimulate differentiation into chondrocytes, potentially leading to restoration of hyaline-like cartilage.[1,45] The self-renewal capacity and multilineage differentiation potential of MSCs may lead to more reliable methods of durable cartilage reconstruction. Currently, no literature is available that examines the medium-term success of cartilage injury treated with MF compared with a hyaluronic acid–based scaffold (HA) in conjunction with clot-activated BMAC (HA-BMAC).

The purpose of this study was to investigate the medium-term clinical outcomes of cartilage repair using a 1-stage technique of HA-BMAC compared with MF. A secondary aim of this study was to identify specific patient demographic factors and cartilage lesion characteristics that are associated with superior outcomes.

METHODS

Physically active patients with symptomatic chondral lesions of the knee treated with either MF or HA-BMAC between January 2005 and December 2010 were followed prospectively. Preliminary data from a subset of this cohort have been reported previously.[13,15] Inclusion criteria consisted of the following: age 30 to 60 years, body mass index (BMI) 20 to 30 kg/m^2, diagnosis of grade IV cartilage lesion (International Cartilage Repair Society classification) of at least 1 cm^2 affecting a femoral condyle or the patellofemoral articulation, participation in a sporting event at least twice per week, and availability of 2- and 5-year follow-up assessments. Exclusion criteria consisted of tricompartmental arthritis of the knee, osteonecrosis of the knee, multiple prior corticosteroid injections, general systemic illness, neurovascular disease, and inability to follow the rehabilitation protocol. Sizing and characterization of cartilage lesions were performed on preoperative magnetic resonance imaging (MRI) for each patient, and appropriate lesion shape was confirmed with arthroscopic visualization before participant inclusion. Patients were placed into the HA-BMAC group if the health insurance policy of the treating institution supported this option, and patients were placed into the MF group if HA-BMAC treatment was not available. Due to prior surgeon experiences of poor outcomes in cases of large cartilage lesions treated with MF, no patient was offered MF to treat any lesion larger than 6 cm^2. No patients younger than 30 years underwent HA-BMAC treatment. The study protocol was approved by the local institutional ethics committee.

All procedures were performed by the senior author (A.G.). Coexisting injuries were treated concurrently as needed. Study participants were evaluated preoperatively and at 2 and 5 years postoperatively. Objective knee functional assessment was performed in a nonblinded manner by the treating surgeon according to the International Knee Documentation Committee (IKDC) Knee Examination Form.[53] A final functional grade of normal, nearly normal, abnormal, or severely abnormal was given based on findings of effusion, passive motion deficit, and ligamentous stability. Patient-reported scoring tools consisted of the IKDC Subjective Knee Evaluation,[23] Knee injury and Osteoarthritis Outcome Score (KOOS),[43] Lysholm Knee Questionnaire,[31] and Tegner activity scale.[51]

Failure of procedure and postoperative complications were recorded and tracked prospectively. The operation was considered to have failed if the patient underwent reoperation to treat the primary chondral injury. In cases of failure, data obtained from the most recent clinical evaluation before reoperation were used.

Surgical Technique

Microfracture. A diagnostic arthroscopy was performed to identify and characterize all chondral lesions. The technique originally described by Steadman et al[49] was used for each case of MF. All unstable cartilaginous flaps were removed from the chondral lesions, and a well-shouldered vertical wall was created around the lesion periphery. Layers of calcified cartilage were removed by use of a curette. An arthroscopic awl was used, perpendicular to the subchondral bone, to create holes in the subchondral plate 3 to 4 mm apart, ensuring that the interposing subchondral plate between holes was left intact. Fluid pump

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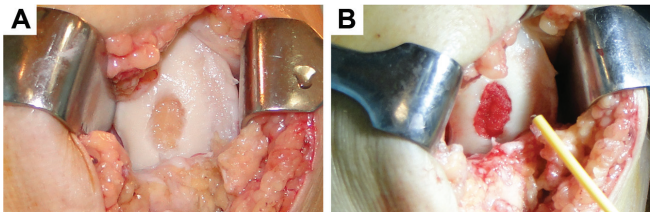

Figure 1. (A) Cartilage lesion of the medial femoral condyle. (B) Lesion treated with a hyaluronic acid–based scaffold with activated bone marrow aspirate concentrate.

pressure was briefly reduced to confirm release of marrow elements from the MF perforations.

Hyaluronic Acid–Based Scaffold With Bone Marrow Aspirate Concentrate. Arthroscopic evaluation was performed to visualize the chondral lesions and to confirm MRI findings with respect to size and location of the defect. Subsequently, 60 mL of bone marrow aspirate was harvested from the ipsilateral iliac crest by use of a dedicated aspiration kit and was centrifuged via a commercially available system (BMAC Harvest Smart PreP2 System; Harvest Technologies) to obtain a concentration of bone marrow cells approximately 6 times the baseline value.[21] Batroxobin enzyme (Plateltex Act; Plateltex SRO) was used to activate the BMAC to produce a sticky clot material. A miniarthrotomy was performed, and the chondral defects were prepared in a similar manner as described for MF. A 3-dimensional hyaluronic acid–based scaffold (Hyalofast; Anika Therapeutics Srl) was fashioned according to the defect size. The prepared clot was implanted into the cartilage defect and covered with the scaffold (Figure 1). The Hyalofast scaffold was secured to the surrounding cartilage by use of a polydioxanone suture (PDS II 6-0; Ethicon) and/or fibrin glue (Tissucol; Baxter SpA) in cases where increased stability was deemed necessary by the surgeon. The knee was cycled repeatedly from flexion to extension to confirm stability of the implanted construct.

Rehabilitation Protocol

The rehabilitation protocol was consistent for both the MF and HA-BMAC treatment groups and was supervised by a physical therapist in each case. Early rehabilitation (0-6 weeks) focused on controlling pain, reducing effusion, maintaining range of motion, and minimizing muscle atrophy. Weightbearing was restricted for the initial 4 weeks postoperatively. On the second postoperative day, continuous passive motion was initiated at 1 cycle per minute, 6 hours per day, until the patient regained 90° of flexion. Early isometric and isotonic exercises were undertaken. Mechanical compression was used to minimize joint effusion. Touchdown weightbearing with crutches was begun in weeks 3 to 4 postoperatively, and unrestricted weightbearing typically was achieved by 6 weeks. Pool-based therapy was used to assist with return of normal gait. Active functional training was initiated at week 9 postoperatively if there was satisfactory resolution of pain and effusion. Between postoperative weeks 11 and 32, progression to running was aided by the use of proprioceptive exercises as well as strength, endurance, and aerobic training. It was expected that at 32 weeks, the patient would be able to run straight at a moderate pace and go up and down stairs without discomfort. Further rehabilitation was focused on the return to sporting activity, which typically occurs no earlier than 6 months in cases of MF and 10 months in cases of HA-BMAC.

Statistical Analysis

Data analysis was performed with Epi Info 7 and SPSS software (version 20.0; IBM Corp). Shapiro-Wilk testing and quantile-quantile plots were used to examine normality of continuous variables. All variables did not conform to a normal distribution; therefore, nonparametric testing was used. Tukey fences were calculated for continuous variables, and no contribution from outlier data was identified.[22] Continuous variables were subsequently expressed as either mean ± standard deviation or median values followed by the range or interquartile range (third quartile – first quartile). The Wilcoxon signed rank test was performed to test hypotheses about continuous data differences between preinjury, preoperative, and follow-up evaluations. The Mann-Whitney *U* test was used to test the hypotheses about continuous data differences between the 2 treatment groups. The Pearson chi-square test was performed to investigate the difference in frequency distribution between groups. IKDC objective scores are based on the grades of A (normal), B (nearly normal), C (abnormal), and D (severely abnormal). IKDC objective scores were merged into 2 categories (A and B score in category 1, and C and D in category 2). The Pearson chi-square test was used to assess the difference in the IKDC objective score between the MF and HA-BMAC treatment groups, and the McNemar test was used to assess the difference between preoperative, 2-year postoperative, and 5-year postoperative IKDC objective scores. Various subgroups were also compared by use of the Mann-Whitney *U* test for continuous variables and the Fisher exact test for IKDC objective scores. The Benjamini and Hochberg procedure was used for multiple comparisons to control the false discovery rate where appropriate.[2] An a priori power analysis determined that a total sample size of 34 (17 per group) was required to demonstrate a difference of 10 between IKDC subjective scores, with an expected standard deviation of 10,[13] based on the values of $\alpha = .05$ and $\beta = .2$. Two-tailed comparative analysis was performed, and the level of statistical significance was considered to be $P < .05$.

RESULTS

Over the study period, 50 patients with chondral injury of the knee were treated with MF and 27 were treated with HA-BMAC. Twenty-five patients who underwent MF were excluded due to younger age (<30 years), because HA-BMAC was not performed in patients under 30 years old, and 2 patients treated with HA-BMAC were lost to follow-up and excluded. Fifty patients with chondral knee

injury included in the final analysis were followed prospectively (25 MF, 25 HA-BMAC) and were available for follow-up assessment at 2 and 5 years postoperatively. The proportion of male to female patients was identical in both treatment groups. In the MF group, the mean age was 42.9 ± 7.7 years, with a median chondral lesion size of 4.5 cm^2 (range, 2.5-6 cm^2). In the HA-BMAC treatment group, the mean age was 47.0 ± 7.0 years, and the median lesion size was 6.5 cm^2 (range, 1.5-24 cm^2). The most common cause was previous trauma (56% MF, 80% HA-BMAC). The medial femoral condyle was the most frequently involved area in both treatment groups (60% of lesions), followed by the lateral femoral condyle in the MF group and the patella in the HA-BMAC group. One patient in each group participated in sports at a professional level. Mean patient age and the proportion of patients older than 45 years of age were greater in the HA-BMAC treatment group compared with the MF group (P = .035 and .048, respectively). Significant differences in cartilage lesion size (P = .003), lesion location (P = .016), and associated procedures (P = .003) were noted between treatment groups. Demographic data and lesion characteristics are summarized in Table 1. No differences in preoperative scores were found between treatment groups with respect to IKDC objective/subjective, Tegner, or Lysholm scores.

In the MF group, 8% of participants were categorized as normal or nearly normal (IKDC grades A and B) preoperatively, compared with 64% at 2-year follow-up (P < .001). The proportion of those classified as normal or nearly normal at 5-year follow-up in the MF group (28%) was not significantly different from the proportion preoperatively (Table 2). Improvement was demonstrated at the 2-year follow-up assessment according to the IKDC objective, IKDC subjective, Tegner, and Lysholm scores (P < .001). A significant decline in outcome was noted for those treated with MF from the 2- to 5-year follow-up assessment according to the IKDC objective, Lysholm, and Tegner scores (Table 2). Those older than 45 years treated with MF had similar outcomes at 5 years compared with those who were 45 or younger (Table 3A). Patients treated in the MF group demonstrated poorer results in cases of large (>4 cm^2) or multiple chondral lesions at 5 years (Table 3, B and C).

One patient in the HA-BMAC group was categorized as normal or nearly normal preoperatively. At 2-year and 5-year follow-up, all patients in this treatment group were categorized as normal or nearly normal. IKDC objective, IKDC subjective, Tegner, and Lysholm scores were significantly improved in those treated with HA-BMAC at 2-year follow-up (P < .001). Improvement in IKDC objective, Tegner, and Lysholm scores was maintained at 5-year follow-up in those treated with HA-BMAC (Table 2). Patient assessment tools in the HA-BMAC treatment group at 5-year follow-up demonstrated no significant difference based on categorization by age or chondral lesion type (Table 3).

Comparing treatment groups, Lysholm and Tegner scores were similar between treatment groups at 2-year follow-up (Table 4). Tegner scores at 5-year follow-up were significantly greater in the HA-BMAC group compared with the MF group (P < .001) (Figure 2). At 2-year follow-up, 36% of patients in the MF group reached their preinjury Tegner score compared with 24% in the HA-BMAC group (P = .355). At the 5-year follow-up assessment, 16% of patients treated with MF were at the preinjury level compared with 33% of those treated with HA-BMAC (P = .185). A significantly greater proportion of patients treated with HA-BMAC, compared with MF, were classified as normal or nearly normal at 2- and 5-year follow-up according to the IKDC objective scores (Figure 3, A and B). A trend toward improved IKDC subjective score was found at the 5-year follow-up in those treated with HA-BMAC compared with MF (P = .086) (Figure 3, C and D). Tegner scores were significantly greater at 5-year follow-up in the HA-BMAC group compared with the MF group (P < .001), whereas the Lysholm scores were not significantly different (P = .178). Comparison of treatment groups by use of the KOOS assessment tool at 5-year follow-up demonstrated significantly greater scores in those patients treated with HA-BMAC, according to the KOOS–Pain (95 vs 87, P = .023) and KOOS–Sports/rec (85 vs 68, P = .013) scores (Table 5).

TABLE 1
Patient Demographics and Chondral Lesion Characteristics[a]

	Microfracture	HA-BMAC	P Value
Age, y, mean ± SD	42.9 ± 7.7	47.0 ± 7.0	.035[b]
Sport participation			>.999
Recreational	24	24	
Professional	1	1	
Lesion size, median (interquartile range), cm^2	4.5 (1.5)	6.5 (6.3)	.003[b]
Sex, male/female	16/9	16/9	>.999
Side, right/left knee	17/8	14/11	.382
Age distribution			
≤45 y	16	9	.048[b]
>45 y	9	16	
Cause of lesion			
Traumatic	14	20	.069
Nontraumatic	11	5	
Lesion size			
≤4 cm^2	8	8	>.999
>4 cm^2	17	17	
Lesion count			
Single	11	17	.087
Multiple	14	8	
Lesion location			
Medial femoral condyle	15	15	.016[b]
Lateral femoral condyle	11	1	
Patella	3	8	
Other	11	8	
Associated procedures			
High tibial osteotomy	0	9	.003[b]
Transtibial osteotomy	1	4	
Anterior cruciate ligament reconstruction	11	4	
Lateral release	4	3	

[a]Data are reported as No. unless otherwise indicated. HA-BMAC, hyaluronic acid–based scaffold with bone marrow aspirate concentrate.
[b]Statistically significant difference between groups (P < .05).

TABLE 2
Comparison of Clinical Outcome Scores Within Treatment Groups for Each Interval Assessment[a]

	Microfracture			HA-BMAC			*P* Value, Within-Time Improvement for Microfracture			*P* Value, Within-Time Improvement for HA-BMAC		
Score	Preop	2-y Follow-up	5-y Follow-up	Preop	2-y Follow-up	5-y Follow-up	Preop vs 2 y	Preop vs 5 y	2 vs 5 y	Preop vs 2 y	Preop vs 5 y	2 vs 5 y
IKDC objective (A/B/C/D), No.	0/2/8/15	4/12/9/0	2/5/13/5	0/1/12/12	16/9/0/0	19/6/0/0	<.001[b]	.063	.004[b]	<.001[b]	<.001[b]	>.999
IKDC subjective	42 (24)	80 (25)	77 (26)	40 (29)	83 (15)	86 (14)	<.001[b]	<.001[b]	.095	<.001[b]	<.001[b]	.001[b]
Tegner	3 (1)	5 (2)	4 (2)	2 (2)	5 (1)	6 (1.5)	<.001[b]	<.001[b]	<.001[b]	<.001[b]	<.001[b]	.470
Lysholm	45 (25)	90 (12)	80 (20)	45 (10)	90 (25)	90 (17)	<.001[b]	<.001[b]	<.001[b]	<.001[b]	<.001[b]	.630

[a]Data are listed as median (interquartile range [third quartile – first quartile]) unless otherwise indicated. HA-BMAC, hyaluronic acid–based scaffold with bone marrow aspirate concentrate; IKDC, International Knee Documentation Committee; preop, preoperative.
[b]Statistically significant difference between groups compared ($P < .05$).

TABLE 3
Clinical Outcome Scores at 5-Year Follow-up Categorized by (A) Age, (B) Lesion Size, and (C) Lesion Count[a]

	Microfracture			HA-BMAC		
(A) Age	≤45 y (n = 16)	>45 y (n = 9)	*P* Value	≤45 y (n = 9)	>45 y (n = 16)	*P* Value
IKDC subjective	74.5 (28)	77 (29)	.57	86 (10)	84 (18)	.602
IKDC objective (A/B/C/D), No.	2/4/7/3	0/1/6/2	.158	8/1/0/0	11/5/0/0	>.999
KOOS–Pain	85 (36)	89 (19)	.819	95 (8)	94.5 (15)	.183
KOOS–Symptoms	76 (25)	89 (21)	.363	90 (11)	91.5 (16)	.586
KOOS–ADL	96 (31)	94 (29)	.457	95 (10)	96.5 (24)	.537
KOOS–Sports/rec	65 (40)	70 (37)	.97	90 (15)	75 (29)	.074
KOOS–QoL	78 (44)	81 (38)	.888	90 (18)	85 (24)	.585
Tegner	4.5 (3)	3 (2)	.074	6 (2)	6 (2)	.945
Lysholm	85 (19)	80 (25)	.098	90 (16)	83 (22)	.483

	Microfracture			HA-BMAC		
(B) Lesion Size	≤4 cm^2 (n = 8)	>4 cm^2 (n = 17)	*P* Value	≤4 cm^2 (n = 8)	>4 cm^2 (n = 17)	*P* Value
IKDC subjective	92 (17)	67 (21)	.004[b]	91 (8)	80 (14)	.030[b]
IKDC objective (A/B/C/D), No.	2/3/2/1	0/2/11/4	.008[b]	7/1/0/0	12/5/0/0	>.999
KOOS–Pain	99 (15)	78 (30)	.012[b]	97.5 (9)	95 (15)	.202
KOOS–Symptoms	91 (20)	77 (29)	.037[b]	95 (13)	90 (15)	.114
KOOS–ADL	98.5 (6)	87 (27)	.088	100 (12)	95 (23)	.335
KOOS–Sports/rec	80 (26)	55 (39)	.003[b]	82.5 (23)	85 (28)	.334
KOOS–QoL	97 (19)	60 (31)	.002[b]	85 (23)	81 (20)	.25
Tegner	5 (2)	3 (2)	.030[b]	5.5 (2)	6 (2)	.874
Lysholm	92.5 (10)	80 (17)	.003[b]	97 (20)	80 (19)	.128

	Microfracture			HA-BMAC		
(C) Lesion Count	Single (n = 11)	Multiple (n = 14)	*P* Value	Single (n = 17)	Multiple (n = 8)	*P* Value
IKDC subjective	90 (15)	67 (16)	.004[b]	86 (11)	77 (17)	.071
IKDC objective (A/B/C/D), No.	2/5/4/0	0/0/9/5	<.001[b]	14/3/0/0	5/3/0/0	>.999
KOOS–Pain	97 (19)	78 (32)	.004[b]	95 (8)	87.5 (18)	.068
KOOS–Symptoms	89 (21)	79 (32)	.07	95 (8)	85 (18)	.214
KOOS–ADL	97 (6)	75 (34)	.001[b]	99 (8)	80 (24)	.043[b]
KOOS–Sports/rec	75 (20)	45 (35)	<.001[b]	85 (15)	80 (46)	.41
KOOS–QoL	94 (19)	63 (40)	.002[b]	85 (18)	85 (31)	.891
Tegner	5 (2)	3 (1)	.001[b]	6 (1)	6 (2)	.51
Lysholm	90 (15)	75.5 (15)	<.001[b]	90 (16)	79 (22)	.474

[a]Data are listed as median (interquartile range [third quartile – first quartile]) unless otherwise indicated. HA-BMAC, hyaluronic acid–based scaffold with bone marrow aspirate concentrate; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QoL, quality of life.
[b]Statistically significant difference between groups ($P < .05$).

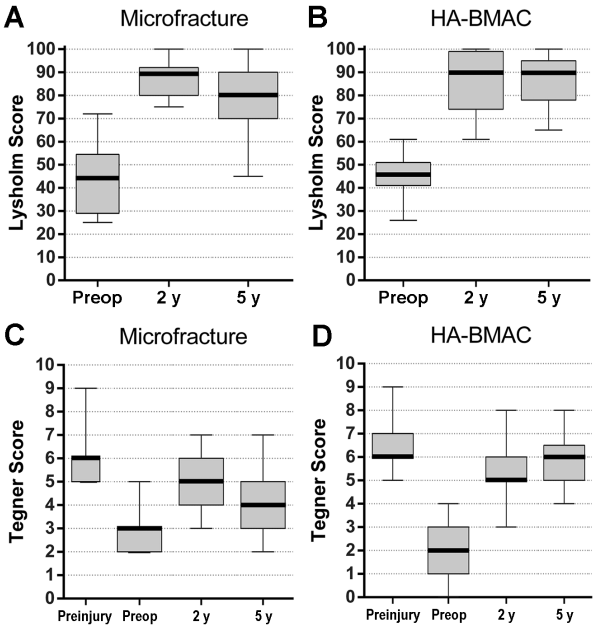

Figure 2. Box plot comparison of (A, B) Lysholm knee questionnaire and (C, D) Tegner activity scale scores at each interval assessment for treatment of cartilage lesions using either a hyaluronic acid–based scaffold with activated bone marrow aspirate concentrate (HA-BMAC) or microfracture. Whiskers depict minimum and maximum scores; shaded area indicates 25th to 75th percentile, and horizontal line represents median. Scores at 2-year and 5-year follow-up were significantly improved compared with preoperative scores in both groups ($P < .001$). Preop, preoperative.

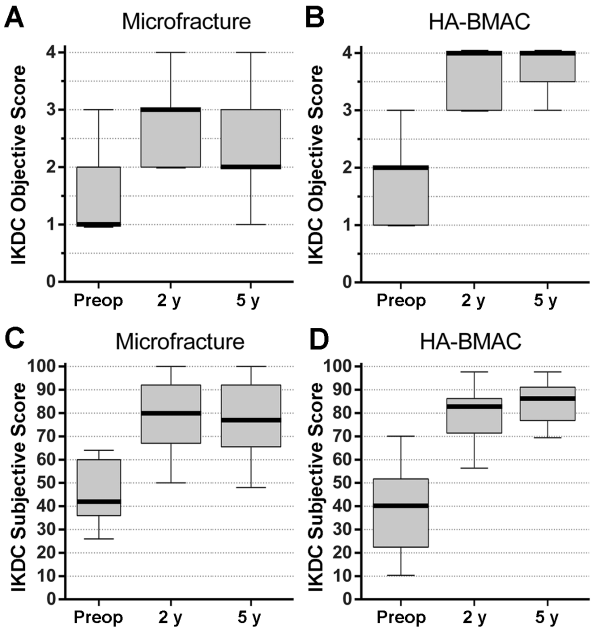

Figure 3. Box plot comparison of International Knee Documentation Committee (IKDC) (A, B) objective and (C, D) subjective scores at each interval assessment for treatment of cartilage lesions using either a hyaluronic acid–based scaffold with activated bone marrow aspirate concentrate (HA-BMAC) or microfracture. Whiskers depict minimum and maximum scores; shaded area indicates 25th to 75th percentile, and horizontal line represents median. Scores in the MF group increased significantly at 2 years ($P < .001$) but were comparable with preoperative scores at 5 years ($P = .063$). Scores in the HA-BMAC group were significantly increased at 2 years and 5 years postoperatively ($P < .001$). Preop, preoperative.

TABLE 4
Comparison of Clinical Outcome Scores Preoperatively and at 2- and 5-Year Follow-up for Chondral Defects Treated With Microfracture or HA-BMAC[a]

Score	Microfracture	HA-BMAC	*P* Value
IKDC objective (A/B/C/D), No.			
Preoperative	0/2/8/15	0/1/12/12	.552
2-y follow-up	4/12/9/0	16/9/0/0	<.001[b]
5-y follow-up	2/5/13/5	19/6/0/0	<.001[b]
IKDC subjective			
Preoperative	42 (24)	40 (29)	.143
2-y follow-up	80 (25)	83 (15)	.763
5-y follow-up	77 (26)	86 (14)	.086
Tegner			
Preoperative	3 (1)	2 (2)	.077
2-y follow-up	5 (2)	5 (1)	.115
5-y follow-up	4 (2)	6 (1.5)	<.001[b]
Lysholm			
Preoperative	45 (25)	45 (10)	.815
2-y follow-up	90 (12)	90 (25)	.845
5-y follow-up	80 (20)	90 (17)	.178

[a]Data are listed as median (interquartile range [third quartile – first quartile]) unless otherwise indicated. HA-BMAC, hyaluronic acid–based scaffold with bone marrow aspirate concentrate; IKDC, International Knee Documentation Committee.
[b]Statistically significant difference between groups ($P < .05$).

TABLE 5
Comparison of KOOS Results for Treatment Groups at 5-Year Follow-up[a]

	Microfracture	HA-BMAC	*P* Value
KOOS–Pain	87 (31)	95 (10)	.023[b]
KOOS–Symptoms	87 (23)	90 (12)	.060
KOOS–ADL	95 (23)	95 (20)	.217
KOOS–Sports/rec	68 (37)	85 (17)	.013[b]
KOOS–QoL	80 (39)	85 (20)	.289

[a]Data are listed as median (interquartile range [third quartile – first quartile]). HA-BMAC, hyaluronic acid–based scaffold with bone marrow aspirate concentrate; KOOS, Knee injury and Osteoarthritic Outcome Score; ADL, activities of daily living; QoL, quality of life.
[b]Statistically significant difference between groups ($P < .05$).

Associated procedures performed concurrently with cartilage repair consisted of anterior cruciate ligament (ACL) reconstruction, high tibial osteotomy, tibial tubercle osteotomy, and lateral release (Table 1). A greater number of osteotomies were performed in the patients who underwent HA-BMAC cartilage repair, and a greater number of ACL

reconstructions were performed in those treated with MF (P = .003). Subsequent within-group comparative analysis of clinical outcome in those patients who underwent HA-BMAC did not demonstrate any difference in scores between those who did or did not undergo associated osteotomy, and no within-group difference in scores were identified in those who underwent ACL reconstruction compared with those who did not. No serious adverse events were observed during the treatment or follow-up period, and no complications resulted from the procedure to harvest BMAC. One patient from the HA-BMAC group had stiffness after surgery and underwent manipulation of the knee under anesthesia at 3 months after implantation. Four patients were considered to have failed treatment in the MF group. Revision procedures were performed after the 2-year follow-up assessment in each case, at an average of 3.7 years after MF, and consisted of unicondylar knee arthroplasty, ACI, mosaicplasty, and scaffold/BMAC implantation. No failures were noted in the HA-BMAC treatment group.

DISCUSSION

Advances in cell-based cartilage therapies have enabled the treating surgeon to offer management options that may provide more durable cartilage repair. A number of methods have been developed in an attempt to address the limited long-term success of MF to relieve symptoms related to chondral lesions and to slow progressive degenerative change. The technique of cartilage repair using HA-BMAC demonstrates that good medium-term clinical outcomes, superior to those of MF treatment, may be achieved in a 1-stage procedure, at a cost significantly lower than would typically be associated with autologous chondrocyte use.

Patients treated with MF achieved substantial improvement in objective outcome assessment at short-term follow-up, with 64% of cases categorized as normal or nearly normal at 2 years postoperatively. Unfortunately, these positive outcomes significantly decreased at the 5-year follow-up, with only 28% of patients categorized as normal or nearly normal. In addition, while significant improvements were noted in subjective patient-reported outcomes after 2 years, the majority of these scores had declined after 5 years. These findings are consistent with previously published research demonstrating the short-term benefit of MF when used to treat cartilage defects[28,29] and the deterioration of these outcomes after 2 years.[14,30,47] Demographic factors and the type of cartilage lesion are important considerations for the surgeon with respect to operative planning and optimizing patient outcome. No significant difference was noted in short- or medium-term outcome in those treated with MF who were older or younger than 45 years. At 5-year follow-up, larger lesion size and the presence of multiple lesions led to poorer outcomes in those treated with MF. It is notable that many clinical outcome scores at 5-year follow-up were similar between treatment groups in those cases where cartilage lesions were smaller than 4 cm^2. After categorization by lesion size, the predominant differences in clinical outcome scores were in those cases of lesions larger than 4 cm^2, where the HA-BMAC treatment group outcomes were superior. Furthermore, those cases of MF treatment in larger lesions were limited to 6 cm^2 in area, whereas lesion size in the HA-BMAC treatment arm was often much greater.

Although a single patient in the HA-BMAC treatment group was objectively graded as normal or nearly normal preoperatively, all patients in this group were classified as normal or nearly normal at the 2-year follow-up. This improvement showed no deterioration at the 5-year assessment. The maintenance of objective and subjective outcomes at medium-term follow-up is comparable with more expensive, 2-stage procedures using autologous chondrocytes.[10,17,30] Published literature has been inconsistent concerning the effect of patient age and lesion characteristics in cases of cell-based cartilage treatment; a number of studies have reported poorer outcomes in older patients or large lesion size,[15,33] whereas other studies have reported no such effect on prognosis.[32,44] Data from the current study have demonstrated that clinical improvement in those who undergo cartilage repair with HA-BMAC may be achieved irrespective of older age, large lesion size, or the treatment of multiple chondral lesions.

Our findings demonstrated that an important advantage of HA-BMAC treatment, compared with MF treatment, is the continued benefit at 5-year follow-up. Although we are awaiting the long-term outcomes of this procedure, these results are encouraging, particularly given the reasonable cost of the procedure and the 1-stage nature of the technique. The comparatively greater clinical benefits observed after HA-BMAC treatment may be partially explained by previously demonstrated disadvantages of MF treatment, such as the fibrocartilaginous nature of the repair tissue or the development of intralesional osteophytes after violation of the subchondral plate.[20]

MSC therapy to treat cartilage injury depends on a variety of growth factors to optimize differentiation toward chondrocyte lineage and chondrogenesis.[7,25,26] MSCs have an inherent potential to differentiate into mesenchymal tissue such as cartilage,[9,24,41,54] and the successful outcomes in patients treated with HA-BMAC suggest that this technique may better provide the necessary environment for the formation of healthy cartilage tissue. Although many surgeons prefer to use cartilage repair interventions in a younger population, some evidence suggests that the chondrogenic potential of MSCs is independent of age.[35,45] The benefits that were demonstrated in those patients over 45 years of age in the HA-BMAC treatment arm suggest that with the appropriate cartilage lesion, successful outcomes are not limited to a younger patient demographic.

In 2014, Gobbi et al[15] evaluated the outcomes of a 1-stage BMAC procedure using a type I/III collagen scaffold to treat large chondral defects. At a minimum of 3 years of follow-up, although good clinical outcomes were achieved, greater improvement was reported in younger patients and in those with smaller or solitary lesions. In contrast to these findings, our 5-year outcomes demonstrated similar positive outcomes in patients over 45 years of age and those with large or multiple lesions treated with BMAC and a hyaluronic acid–based scaffold. While there is evidence that scaffold composition may affect cell-seeding,[12,42] it remains unclear whether

a scaffold matrix based on hyaluronic acid would consistently be associated with different clinical outcomes compared with a type I/III collagen scaffold. The primary role of the scaffold is to contain and secure the clot-activated BMAC within the chondral defect, in close contact with the exposed subchondral bone. We do not expect the differentiation and proliferation of mesenchymal stem cells to be substantially altered when a hyaluronic acid–based scaffold is used as opposed to a collagen matrix. One notable benefit to the hyaluronic acid–based scaffold is the pliable and adhesive nature of the graft when combined with BMAC, making the HA-BMAC more suitable for arthroscopic use in select cases.

Considering the routine use of MF in cartilage repair, it is important to highlight the comparative superiority of HA-BMAC with respect to more durable clinical outcomes and the similar results obtained with respect to the more cost-prohibitive autologous chondrocyte implantation procedure. Kon et al[30] reported superior clinical outcomes at 5 years using an arthroscopic matrix-assisted chondrocyte implantation procedure compared with MF treatment. Using a 1-stage procedure, the current findings demonstrate similar durability of cartilage repair at 5 years.

The present study has several limitations. The HA-BMAC group contained a greater proportion of patients older than 45 years, and this group had a median lesion size of 6.5 cm^2, compared with 4.5 cm^2 in the MF group. The difference in median lesion size can be largely explained by the upper limit of 6 cm^2 used for lesions treated with MF. The increased proportion of those over 45 years of age treated with HA-BMAC may be partially explained by the preferential treatment of larger lesions (>6 cm^2) in this group. While this demonstrates discrepancies between the treatment arms, these differences may also add strength to the findings, given the improved outcomes observed in those treated with HA-BMAC. Although the medial femoral condyle was the primary repair site in both groups, the second most frequently involved area of the knee was not consistent between treatments. While short- and medium-term patient-reported outcomes are not necessarily expected to be inferior in those who have a cartilage lesion located within the lateral compartment,[5,27] it is notable that the MF treatment group in our study had an increased proportion of lateral femoral condyle lesions. In addition, the types of associated surgeries that were performed were not identical between groups. Although outcome scores between those who did or did not undergo associated osteotomy or ACL reconstruction were similar, a greater proportion of associated osteotomies were performed in the HA-BMAC group and a greater proportion of ACL reconstructions were performed in the MF group. Regarding subjective patient-reported outcomes, the KOOS assessment was only available after 5 years of follow-up because of the recent validation of this tool for the Italian language.

Given the higher costs of some cell-based cartilage repair treatments, it is unlikely that such therapy will be used regularly for the typical chondral lesion commonly identified during knee arthroscopy, unless this technology becomes more affordable. Treatment consisting of a 1-stage procedure using a clot-activated BMAC-associated scaffold has the potential for routine use as a method to provide durable cartilage repair at a reasonable cost.

CONCLUSION

Repair of chondral injury using a hyaluronic acid–based scaffold with activated bone marrow aspirate concentrate provides good clinical outcomes and durable cartilage repair at medium-term follow-up that is superior to that achieved with microfracture. Positive short-term clinical outcomes can be achieved with either MF or HA-BMAC. Cartilage repair using HA-BMAC leads to successful medium-term outcomes independent of age or lesion size.

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