PODCAST 5-in-5

Bone Marrow Aspirate Concentrate Does Not Improve Osseous Integration of Osteochondral Allografts for the Treatment of Chondral Defects in the Knee at 6 and 12 Months

A Comparative Magnetic Resonance Imaging Analysis

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Background: Poor osseous integration after fresh osteochondral allograft transplantation (OCA) may be associated with graft subsidence and subchondral bone collapse after implantation. The augmentation of OCA with bone marrow aspirate concentrate (BMAC) has been hypothesized to improve osseous incorporation of the implanted allograft.

Purpose: To evaluate the effect of autogenous BMAC treatment on osseous integration at the graft-host bony interface after OCA.

Study Design: Cohort study; Level of evidence, 3.

Methods: A retrospective review of patients treated with OCA+BMAC or OCA alone for full-thickness chondral defects of the distal femur from March 2015 to December 2016 was conducted. Seventeen knees treated with OCA+BMAC and 16 knees treated with OCA alone underwent magnetic resonance imaging (MRI) in the early postoperative phase (mean, 6 months). Eighteen knees treated with OCA+BMAC and 16 knees treated with OCA alone underwent MRI in the late postoperative phase (mean, 12 months). Bone, cartilage, and ancillary features on MRI were graded using the Osteochondral Allograft MRI Scoring System (OCAMRISS) by a musculoskeletal radiologist blinded to the patient's history and treatment.

Results: There were no significant differences in the demographics or lesion characteristics between treatment groups in either postoperative phase. In the early postoperative phase, the mean OCAMRISS bone score was 3.0 ± 0.7 and 3.3 ± 0.7 for the OCA+BMAC group and OCA alone group, respectively ($P = .76$); 71% (OCA+BMAC) and 81% (OCA alone) of MRI scans demonstrated discernible clefts at the graft-host junction ($P = .69$), and 41% (OCA+BMAC) and 25% (OCA alone) of MRI scans demonstrated cystic changes at the graft and graft-host junction ($P = .46$). In the late postoperative phase, the mean OCAMRISS bone score was 2.7 ± 0.8 and 2.9 ± 0.8 for the OCA+BMAC group and OCA alone group, respectively ($P = .97$); 44% (OCA+BMAC) and 63% (OCA alone) of MRI scans demonstrated discernible clefts at the graft-host junction ($P = .33$), and 50% (OCA+BMAC) and 31% (OCA alone) of MRI scans demonstrated the presence of cystic changes at the graft and graft-host junction ($P = .32$). The mean OCAMRISS cartilage, ancillary, and total scores were not significantly different between groups in either postoperative phase.

Conclusion: OCA augmented with BMAC was not associated with improved osseous integration; decreased cystic changes; or other bone, cartilage, and ancillary feature changes compared with OCA alone.

Keywords: knee; articular cartilage; resurfacing; biological enhancement; bone marrow aspirate concentrate; osteochondral allograft transplantation; integration

Fresh osteochondral allograft transplantation (OCA) is an increasingly popular technique involving the single-stage transfer of mature hyaline cartilage–bone dowels into large chondral defects of the knee. Multiple studies have demonstrated good long-term results, with improvements in both pain and function postoperatively[1,15,31] and a reported 88% rate of return to sport.[20,21] The success of this procedure is dependent not only on chondrocyte viability[5,6] but largely also on osseous integration of the graft

The American Journal of Sports Medicine
2019;47(2):339–346
DOI: 10.1177/0363546518813915

bone with the host bone.[31,32] Bony incorporation of the osteochondral allograft typically occurs through a lengthy process of creeping substitution in which the host cells repopulate and remodel the subchondral bone.[12,26,27] Inadequate integration of the osseous portion of the graft before the resumption of physiological and biomechanical loading can lead to graft subsidence with subchondral bone collapse.[15,24] Therefore, methods that enhance or accelerate the graft incorporation process are of much interest.

The use of autogenous bone marrow aspirate concentrate (BMAC) has been postulated to improve osseous integration of the osteochondral allograft with the host bone. BMAC contains growth factors and osteoprogenitor cells and has been shown to improve bone consolidation and accelerate the time to union in the setting of fractures.[7,9,10] BMAC may also exert anabolic and anti-inflammatory effects that are beneficial for cartilage repair and the treatment of osteoarthritis in the knee.[4,13] The application of BMAC to a synthetic biphasic scaffold for the treatment of articular cartilage defects has been shown to improve histological scores and biological incorporation compared with scaffold treatment alone.[2,19] Recently, Oladeji et al[25] investigated whether autogenous BMAC treatment could enhance osseous integration of a femoral condylar osteochondral allograft as measured on radiographs during the initial 6 months postoperatively. The authors reported superior radiographic integration and less sclerosis for BMAC-augmented OCA compared with OCA alone; however, these characteristics were evaluated using radiographs rather than more sensitive and specific advanced imaging, such as magnetic resonance imaging (MRI). Compared with radiographs, MRI of OCA-treated knees allows for a 3-dimensional and more detailed evaluation of osseous graft integration and can additionally assess other features such as subchondral bone marrow edema and subchondral cystic changes.[22]

Therefore, the purpose of this study was to evaluate the effect of autogenous BMAC treatment on osseous integration at the graft-host bony interface after OCA of the distal femur using MRI. We hypothesized that autogenous BMAC treatment would not improve osseous integration at the graft-host interface within the first 12 months after OCA. Other osseous features, as well as cartilage and ancillary features, were also evaluated according to the Osteochondral Allograft MRI Scoring System (OCAMRISS).[22] Patients treated with BMAC+OCA were compared with patients treated with OCA alone in both early (mean, 6 months) and late (mean, 12 months) postoperative phases.

METHODS

Inclusion and Exclusion Criteria

Inclusion criteria included (1) symptomatic focal cartilage lesions of the knee that were classified as Outerbridge grade IV lesions at the time of arthroscopic surgery, (2) no substantial bone loss requiring additional bone grafting, and (3) treatment with fresh OCA. Exclusion criteria included (1) patellar OCA; (2) tibial OCA; (3) meniscal allograft transplantation; (4) any concomitant intra-articular ligamentous procedure, such as anterior cruciate ligament reconstruction (ACLR), because of the potential of these procedures to increase intra-articular bleeding and affect the graft-host healing process; and (5) postoperative deep infections. General contraindications that were followed for OCA were advanced osteoarthritis involving all 3 compartments, simultaneous multiligamentous reconstruction, inflammatory arthritis or autoimmune conditions, and inability to comply with the postoperative rehabilitation protocol.

Assessment of MRI Outcomes

Postoperative MRI was routinely performed at approximately 6 and 12 months for all patients who had undergone OCA in the senior author's (R.J.W.) practice to evaluate allograft contour and integration. MRI was performed on a 1.5- or 3-T system (GE Healthcare) with a standardized quadrature or 8-channel knee coil (Invivo). MRI pulse sequences included a cartilage-sensitive protocol using a moderate echo time and fast spin echo technique. All MRI scans were assessed by a fellowship-trained musculoskeletal radiologist blinded to the patient's medical history and treatment using the OCAMRISS (Table 1).[22] The OCAMRISS is a reproducible grading system specifically developed to evaluate the radiological characteristics of OCA with the inclusion of 4 features addressing the subchondral bone: subchondral bone plate congruity, subchondral bone marrow signal intensity, presence of subchondral cystic changes, and osseous integration.[22] For osseous integration, a score of 0 was given if there was any amount of crossing trabeculae, and a score of 1 was given if there was a discernible boundary along most to all of the graft-host interface, with little or no crossing trabeculae. Cartilage and ancillary features are evaluated with this grading system as well. Each transplanted dowel was graded individually. For knees with more than 1 transplanted dowel, the scores for each feature were averaged. Postoperative MRI performed at 4 to 8 months was considered to be in the

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Presented at the annual meeting of the AOSSM, San Diego, California, USA, July 2018.
One or more of the authors has declared the following potential conflict of interest or source of funding: R.J.W. has received consulting fees and education support from Arthrex and hospitality payments from Stryker. D.W. has received fellowship education support from Smith & Nephew. 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
Osteochondral Allograft MRI Scoring System (OCAMRISS)[a]

MRI Feature	MRI Score
Bone features	
1. Subchondral bone plate congruity of graft and host-graft junction	0: intact and flush; 1: disrupted or not flush by >1 subchondral thickness
2. Subchondral bone marrow signal intensity of graft relative to epiphyseal bone	0: normal; 1: abnormal (bone marrow edema pattern or hypointensity on all sequences)
3. Osseous integration at host-graft junction	0: crossing trabeculae; 1: discernible cleft
4. Presence of cystic changes at graft and host-graft junction	0: absent; 1: present
Cartilage features	
5. Cartilage signal of graft	0: normal; 1: altered intensity (either hypointense or hyperintense, but not fluid); 2: fluid signal intensity on all sequences
6. Cartilage "fill" of graft (percentage of volume)	0: 76%-100%; 1: 51%-75% or >100%; 2: ≤50%
7. Cartilage edge integration at host-graft junction	0: no discernible boundary; 1: discernible boundary; 2: discernible fissure <1 mm
8. Cartilage surface congruity of graft and host-graft junction	0: flush; 1: ≤50% offset of host cartilage; 2: >50% offset of host cartilage
9. Calcified cartilage integrity of graft	0: intact, thin, and smooth; 1: altered (disrupted, thickened, or blurred)
Ancillary features	
10. Opposing cartilage	0: normal; 1: abnormal
11. Meniscal tears	0: absent; 1: present
12. Synovitis	0: absent; 1: present
13. Fad pad scarring	0: absent; 1: present

[a]Adapted from Meric et al.[22] MRI, magnetic resonance imaging.

early postoperative phase, and postoperative MRI performed at 9 to 15 months was considered to be in the late postoperative phase.

Patients

In 1999, a prospective registry dedicated to the tracking of patient outcomes after articular cartilage restoration procedures was implemented at our institution. An institutional review board approved the registry, and all patients sign an informed consent form before participation. Between March 2015 and December 2016, a review of the registry identified 142 fresh OCA procedures, which were performed by the senior author. During this time interval, the decision to add BMAC was nonrandomized and corresponded with a shift in practice as part of a continuing effort to optimize the outcomes of OCA. Of the 142 knees, 33 knees were treated with patellar OCA, 1 knee underwent prior meniscal allograft transplantation and concomitant revision ACLR, 5 other knees underwent concomitant ACLR, and 1 knee developed a postoperative deep infection. These knees were therefore excluded. No knees were treated with tibial OCA. Of the remaining 102 knees, 57 knees were treated with OCA+BMAC, and 45 knees were treated with OCA alone. After screening for postoperative MRI scans, 17 knees (in 17 patients) treated with OCA+BMAC and 16 knees (in 16 patients) treated with OCA alone were in the early postoperative phase, and 18 knees (in 18 patients) treated with OCA+BMAC and 16 knees (in 16 patients) treated with OCA alone were in the late postoperative phase (Figure 1). A power analysis demonstrated that with 17 knees treated with BMAC+OCA and 16 knees treated with OCA alone, a difference in the OCAMRISS bone score (range, 0-4) of

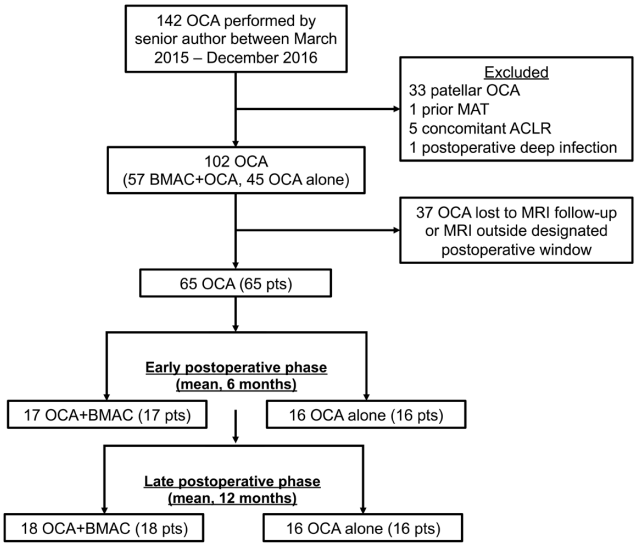

Figure 1. Patient selection flowchart. ACLR, anterior cruciate ligament reconstruction; BMAC, bone marrow aspirate concentrate; MAT, meniscus allograft transplantation; MRI; magnetic resonance imaging; OCA, osteochondral allograft transplantation.

0.85 could be detected with at least 80% power and an alpha of .05. Only 2 knees underwent postoperative MRI in both the early and the late postoperative phases, precluding the ability to perform a longitudinal analysis with the same group of knees or patients. Both patients were included in the analysis for both phases. Postoperative MRI scans of the other 23 knees were not obtained.

For all patients included in the analysis, demographic, preoperative, intraoperative, and postoperative data were collected. Demographic data included age, sex, and body mass index (BMI). Preoperative data included the number and type of previous ipsilateral knee surgical procedures. Standing lower limb alignment was assessed and recorded during the preoperative office visit. For the majority of patients, long-leg radiographs were only obtained if gross malalignment was detected and osteotomy was being considered. Intraoperative data included laterality; examination under anesthesia (range of motion, ligamentous stability); location, size, and depth of the chondral defect(s); concomitant procedures performed; and postoperative rehabilitation protocol.

Surgical Technique

Bone marrow aspirate was obtained from the ipsilateral iliac crest before OCA using a commercially available bone marrow aspiration kit (Magellan MAR0Max; Arteriocyte). Two 30-mL syringes containing 5 mL of anticoagulant citrate dextrose solution, solution A, were filled with bone marrow aspirated in a slow, controlled fashion (~50 mL total). The aspirate was then filtered and processed in the operating theater using a commercially available system (Magellan; Arteriocyte) to a final 3- to 4-mL concentrate. The harvested osteochondral dowel was then saturated with autogenous BMAC for at least 4 minutes immediately before implantation. Additionally, 1 to 2 mL of BMAC was placed in the base of all host defects immediately before graft implantation. All other aspects of the intraoperative procedure were identical for each group. The depth of the osteochondral dowels ranged from 6 to 10 mm and gently impacted into place for press-fit fixation. For a single-recipient condyle or trochlea, transplanted grafts consisted of a single dowel or 2 dowels in a stacked configuration (ie, snowman technique) depending on the lesion shape.

Postoperatively, patients remained partial (toe-touch) weightbearing in a hinged knee brace for 1 week, followed by progression to full weightbearing as tolerated. During this initial period, patients were permitted to begin active-assisted range of motion exercises, quadriceps sets, straight-leg raises, and patellar mobilization. Full range of motion was permitted immediately and encouraged with the use of a continuous passive motion device. Brace wear was required for a minimum of 2 weeks, with the total duration of bracing dependent on the restoration of quadriceps control and strength. A supervised physical therapy program was undertaken postoperatively in all cases. The duration of the postoperative physical therapy program was dependent on the restoration of normal gait, return of quadriceps function, and performance of sport-specific skills. Return to higher level activities and athletics was initiated on an individual patient basis, typically starting with a running program at 6 months. Sport-specific training and unrestricted activities were then progressed thereafter depending on the return of lower extremity strength.

Statistical Analysis

Comparisons between groups were performed using the independent-samples t test for continuous characteristics and the chi-square test or Fisher exact test for discrete variables. Significance was set at $P < .05$.

RESULTS

For the early postoperative phase, the mean patient age was 32.0 years (range, 18-48 years) for the OCA+BMAC group and 31.8 years (range, 14-49 years) for the OCA alone group. The mean duration of MRI follow-up was 5.5 months (range, 5-8 months) for the OCA+BMAC group and 5.4 months (range, 4-8 months) for the OCA alone group. The mean chondral defect area was 6.1 cm^2 (range, 2.3-16.5 cm^2) for the OCA+BMAC group and 4.7 cm^2 (range, 2.0-7.5 cm^2) for the OCA alone group ($P = .14$). Two or more dowels were placed at a single condylar or trochlear location in 3 (18%) knees in the OCA+BMAC group and 3 (19%) knees in the OCA alone group ($P > .99$). There were no statistically significant differences in the demographics and lesion characteristics between groups (Table 2). Twelve of 17 (71%) MRI scans from the OCA+BMAC group and 13 of 16 (81%) MRI scans from the OCA alone group demonstrated discernible clefts along most to all of the graft-host junction ($P = .69$). Seven of 17 (41%) MRI scans from the OCA+BMAC group and 4 of 16 (25%) MRI scans from the OCA alone group demonstrated the presence of cystic changes at the graft and graft-host junction ($P = .46$) (Table 3). There were no significant differences in the mean OCAMRISS bone, cartilage, ancillary, or total scores between groups in the early postoperative phase (Table 2).

For the late postoperative phase, the mean patient age was 35.9 years (range, 16-56 years) for the OCA+BMAC group and 37.0 years (range, 20-64 years) for the OCA alone group. The mean duration of MRI follow-up was 12.3 months (range, 9-15 months) for the OCA+BMAC group and 11.4 months (range, 9-15 months) for the OCA alone group. The mean chondral defect area was 3.9 cm^2 (range, 1.0-7.5 cm^2) for the OCA+BMAC group and 4.5 cm^2 (range, 1.5-7.5 cm^2) for the OCA alone group. Two or more dowels were placed at a single condylar or trochlear location in 4 (22%) knees in the OCA+BMAC group and 5 (31%) knees in the OCA alone group ($P = .70$). There were no statistically significant differences in the demographics and lesion characteristics between groups (Table 4). Eight of 18 (44%) MRI scans from the OCA+BMAC group and 10 of 16 (63%) MRI scans from the OCA alone group demonstrated discernible clefts along most to all of the graft-host junction ($P = .33$) (Figure 2). Nine of 18 (50%) MRI scans from the OCA+BMAC group and 5 of 16 (31%) MRI scans from the OCA alone group demonstrated the presence of cystic changes at the graft and graft-host junction ($P = .32$) (Table 3). There were no significant differences in the mean OCAMRISS bone, cartilage, ancillary, or total scores between groups in the late postoperative phase (Table 4).

A comparison of OCAMRISS scores between phases (involving different groups of patients) demonstrated lower mean osseous integration scores in the late postoperative phase compared with the early postoperative phase for

TABLE 2
Patient Characteristics, Intraoperative Data, and OCAMRISS Scores in the Early Postoperative Phase[a]

	OCA+BMAC (n = 17)	OCA Alone (n = 16)	*P* Value
Patient characteristics			
Age, y	32.0 ± 9.4	31.8 ± 12.5	.96
Sex, male/female, n	11/6	13/3	.44
Body mass index, kg/m^2	25.8 ± 3.5	26.5 ± 5.2	.63
No. of prior ipsilateral knee surgeries	1.4 ± 0.9	1.1 ± 1.0	.39
MRI follow-up, mo	5.5 ± 0.9	5.4 ± 0.7	.69
Lesion characteristics			
OCA location, n (%)			
Medial femoral condyle	5 (29)	10 (63)	.08
Lateral femoral condyle	8 (47)	3 (19)	.14
Trochlea	5 (29)	4 (25)	>.99
Total condyle defect area, cm^2	6.1 ± 3.5	4.7 ± 1.4	.14
OCAMRISS score			
Bone features	3.0 ± 0.7	3.3 ± 0.7	.76
Cartilage features	3.4 ± 1.0	3.1 ± 1.2	.83
Ancillary features	2.5 ± 0.9	2.6 ± 0.8	.60
Total	8.9 ± 1.6	9.0 ± 2.2	.90

[a]Data are reported as mean ± SD unless otherwise indicated. BMAC, bone marrow aspirate concentrate; MRI, magnetic resonance imaging; OCA, osteochondral allograft transplantation; OCAMRISS, Osteochondral Allograft MRI Scoring System.

TABLE 3
Scores of OCAMRISS Bone Features[a]

	Early Postoperative Phase			Late Postoperative Phase		
MRI Feature (Score)	OCA+BMAC	OCA Alone	*P* Value	OCA+BMAC	OCA Alone	*P* Value
1. Subchondral bone plate congruity of graft and host-graft junction (0: intact and flush; 1: disrupted or not flush by >1 subchondral thickness)	1.00 ± 0.00	1.00 ± 0.00	>.99	1.00 ± 0.00	1.00 ± 0.00	>.99
2. Subchondral bone marrow signal intensity of graft relative to epiphyseal bone (0: normal; 1: abnormal [bone marrow edema pattern or hypointensity on all sequences])	0.91 ± 0.26	0.94 ± 0.25	.78	0.86 ± 0.33	0.98 ± 0.08	.18
3. Osseous integration at host-graft junction (0: crossing trabeculae; 1: discernible cleft)	0.68 ± 0.47	0.83 ± 0.37	.29	0.39 ± 0.47	0.57 ± 0.48	.27
4. Presence of cystic changes at graft and host-graft junction (0: absent; 1: present)	0.41 ± 0.51	0.28 ± 0.45	.44	0.44 ± 0.48	0.35 ± 0.46	.58

[a]Data are reported as mean ± SD. BMAC, bone marrow aspirate concentrate; MRI, magnetic resonance imaging; OCA, osteochondral allograft transplantation; OCAMRISS, Osteochondral Allograft MRI Scoring System.

both the OCA+BMAC (0.39 vs 0.68, respectively) and the OCA alone (0.57 vs 0.83, respectively) groups, indicating evidence of more crossing trabeculae at the bony interface (Table 3); however, this did not reach statistical significance ($P = .08$ and $P = .09$, respectively). There were no significant differences in the mean OCAMRISS bone, cartilage, ancillary, or total scores between the early and late postoperative phases for either group.

DISCUSSION

In this study, OCA augmented with BMAC was not associated with improved osseous integration or decreased cystic changes at the graft-host bony interface compared with OCA alone at approximately 6 and 12 months after graft implantation. Additionally, BMAC treatment did not improve OCAMRISS bone, cartilage, ancillary, and total scores at approximately 6 and 12 months after graft implantation.

BMAC saturation of synthetic biphasic scaffolds for the treatment of osteochondral defects has been reported to improve cartilage maturation but not bony remodeling.[2,19] Betsch et al[2] created osteochondral defects in the medial femoral condyles of mini-pigs and compared treatment with a BMAC-saturated biphasic scaffold with a biphasic scaffold alone. At 26 weeks, fibrous tissue and remnants of the implanted scaffolds were consistently present in the osseous space of the defects in both groups. Additionally, subchondral cysts were present in 36% of defects from both experimental groups. In human patients, Krych

TABLE 4
Patient Characteristics, Intraoperative Data, and OCAMRISS Scores in the Late Postoperative Phase[a]

	OCA+BMAC (n = 18)	OCA Alone (n = 16)	*P* Value
Patient characteristics			
Age, y	35.9 ± 12.4	37.0 ± 11.1	.80
Sex, male/female, n	9/9	12/4	.17
Body mass index, kg/m^2	27.5 ± 3.5	26.1 ± 4.4	.54
No. of prior ipsilateral knee surgeries	0.7 ± 0.7	0.7 ± 1.1	.95
MRI follow-up, mo	12.3 ± 1.9	11.4 ± 1.6	.15
Lesion characteristics			
OCA location, n (%)			
Medial femoral condyle	6 (33)	8 (50)	.49
Lateral femoral condyle	8 (44)	4 (25)	.27
Trochlea	5 (28)	4 (25)	>.99
Total condyle defect area, cm^2	3.9 ± 1.9	4.5 ± 1.8	.35
OCAMRISS score			
Bone features	2.7 ± 0.8	2.9 ± 0.8	.97
Cartilage features	3.1 ± 1.2	3.1 ± 1.7	.44
Ancillary features	2.5 ± 1.2	2.4 ± 1.1	.83
Total	8.3 ± 2.6	8.4 ± 2.5	.90

[a]Data are reported as mean ± SD unless otherwise indicated. BMAC, bone marrow aspirate concentrate; MRI, magnetic resonance imaging; OCA, osteochondral allograft transplantation; OCAMRISS, Osteochondral Allograft MRI Scoring System.

et al[19] compared the use of a synthetic biphasic scaffold with BMAC with a scaffold alone for the treatment of cartilage defects of the knee. At 12 months, the BMAC group demonstrated superior cartilage fill to the scaffold alone group on quantitative T2 MRI; however, there were no differences in integration of the bone phase portion of the scaffold between groups. These results, along with those of the current study, contradict the findings of Oladeji et al,[25] which reported enhanced osseous integration of femoral condylar allografts with the use of BMAC compared with controls on radiographs during the initial 6-month postoperative period after OCA.

There are multiple differences between the aforementioned study and ours that may have confounded or contributed to this discrepancy in results. First, orthogonal view radiographs likely are not able to assess osseous integration topographically throughout the graft-host junction as well as MRI. With a radiographic assessment, the authors reported averages of 84% and 74% allograft integration for the BMAC and no BMAC groups at 6 months, respectively.[25] In contrast, with an MRI assessment, we found that the majority of grafts (71% and 81%, respectively) had discernible clefts along most to all of the graft-host interface at 6 months. Second, biological incorporation of the allograft may be affected by the BMAC harvest and preparation techniques, which differed between the 2 studies. Bone marrow harvested from the metaphysis of the distal femur has been shown to consist of a lower concentration of mononucleated progenitor cells compared with marrow harvested from the iliac crest.[23] Additionally, the total and progenitor cell concentrations in BMAC have been shown to differ among commercial preparation systems.[17,30] Third, patient- and procedure-specific differences between the 2 studies may have had effects on the rates of graft healing and remodeling. In the former study, a substantial percentage of patients in each group (40% and 33% of no BMAC and BMAC, respectively) were smokers, whereas all patients in our study were nonsmokers. It is well known that smoking adversely affects bony remodeling and the incorporation of allograft bone.[11,16,25,33] If BMAC-augmented OCA is able to offset the deleterious effects of smoking, any augmentative effect of BMAC treatment in a group of smokers may be more readily detected. This same phenomenon may also apply for patient BMI and obesity; the average BMI of all patients in the former study was over 30 kg/m^2, whereas the mean BMI of patients in our study was 26 kg/m^2. A significant limitation of both studies is that neither specifically quantified the osteoprogenitor cell concentration and differentiation potential or growth factor concentrations in BMAC used for each patient, which have been shown to vary substantially among donors depending on multiple factors, such as age[8,18] and cigarette use.[14] Last, any concomitant intra-articular procedure involving the drilling of bone (ie, meniscal transplantation or cruciate ligament reconstruction) may increase the amount of intra-articular bleeding in the postoperative period and augment graft-host integration. At least 36% of patients in each group in the former study underwent a concomitant intra-articular procedure, whereas all patients who underwent a concomitant intra-articular procedure in our study were excluded because of the risk for confounding.

An augmentative agent that enhances the rate of allograft bone integration would help prevent subsidence of the osteochondral graft in response to joint loading. However, soaking the osteochondral graft in BMAC before implantation may be too simplistic of a solution to be effective, given the abundant bleeding from the host cancellous bone bed and lack of measures that prevent BMAC from eluting out from the graft-host interface. Delivery systems (eg, hydrogels) that help maintain the biological augments at the graft-host junction after implantation may more

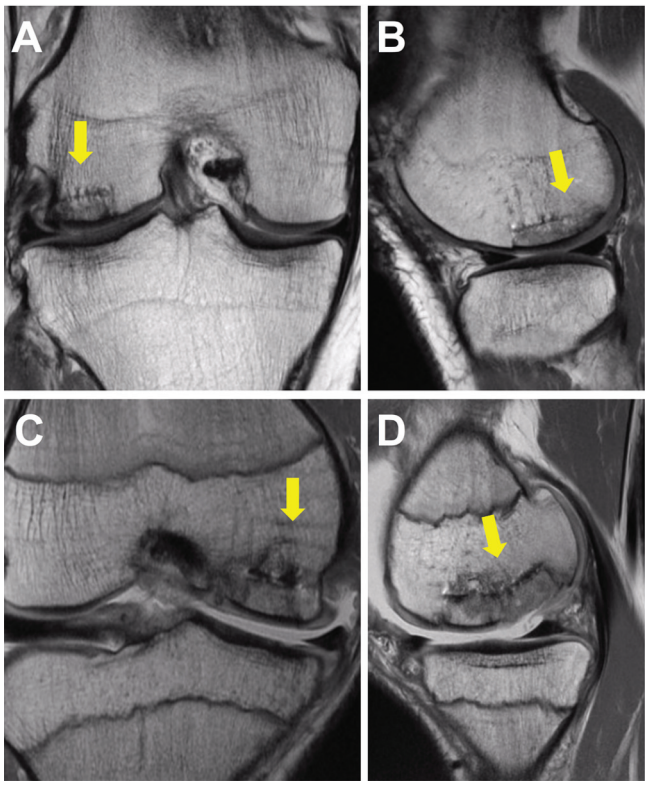

Figure 2. Representative 12-month coronal and sagittal magnetic resonance imaging sections in (A, B) a 20-year-old male patient, demonstrating crossing trabeculae and minimal subchondral bone marrow edema, and (C, D) a 16-year-old male patient, demonstrating discernible clefts at the host-graft junction and significant subchondral bone marrow edema. Both were treated with osteochondral allograft transplantation augmented with bone marrow aspirate concentrate. Arrows indicate host-graft junction.

effectively produce an enhanced bony remodeling response. Furthermore, the percentage of mesenchymal stem cells in autogenous BMAC from human patients has been shown to be less than 5%.[29] These stem cells, when taken from their native environment, may develop vastly different phenotypes and functions when placed into different tissues.[3,28] Further research is needed to identify the specific cells and growth factors within BMAC that can augment the creeping substitution process and the mechanisms by which they exert their effects in the setting of OCA.

There are several limitations of this study other than those already mentioned. As with any retrospective cohort study, there was no process for randomization in BMAC treatment, which was instead determined by a recent shift in practice. Only a portion (64%) of all patients treated with OCA during the study period underwent postoperative MRI within the defined windows of the early or late postoperative phase. A considerable number of these patients from the senior author's practice were collegiate or professional athletes and were more likely to have MRI follow-up. Furthermore, only 2 knees underwent postoperative MRI in both the early and the late postoperative phases, precluding the ability to perform a longitudinal analysis with the same group of knees. These factors introduce the potential for selection bias. The majority of patients did not have preoperative long-leg standing radiographs (ordered based on the surgeon's discretion), which precluded a more accurate quantification of lower leg alignment in this study. Additionally, at least 3 knees in each group received multiple osteochondral dowels, some of which were 2 dowels transplanted into the same condyle using a stacked technique. These may have a prolonged bone integration process compared with that of a single transplanted dowel because of the increased graft-host contact area. Despite the power analysis performed for this study, more patients may have been needed in each group to detect a difference in osseous integration and the presence of cystic changes specifically. Finally, this study analyzed bony incorporation of osteochondral allografts at 6 and 12 months; it is possible that the incorporation times of these grafts occur over a longer period than was analyzed in this study. Additionally, it is the senior author's experience that the subchondral bone features on MRI in the early postoperative period do not always correlate with clinical outcomes, which is consistent with other reports.[22] Therefore, clinical decisions on rehabilitation and return to play are typically made independently from the MRI findings.

In conclusion, OCA augmented with BMAC was not associated with improved osseous integration; decreased cystic changes; or other bone, cartilage, and ancillary feature changes at the graft-host junction compared with OCA alone in the early (~6 months) and late (~12 months) postoperative phases. Multiple factors can influence the creeping substitution process, including patient age, smoking history, and BMAC harvest and preparation techniques. Further research into the specific cells and growth factors within BMAC that can enhance osseous integration of osteochondral allografts is warranted.

REFERENCES

1. Assenmacher AT, Pareek A, Reardon PJ, Macalena JA, Stuart MJ, Krych AJ. Long-term outcomes after osteochondral allograft: a systematic review at long-term follow-up of 12.3 years. *Arthroscopy*. 2016;32(10):2160-2168.
2. Betsch M, Schneppendahl J, Thuns S, et al. Bone marrow aspiration concentrate and platelet rich plasma for osteochondral repair in a porcine osteochondral defect model. *PLoS One*. 2013;8(8):e71602.
3. Caplan AI, Correa D. The MSC: an injury drugstore. *Cell Stem Cell*. 2011;9(1):11-15.
4. Chahla J, Dean CS, Moatshe G, Pascual-Garrido C, Serra Cruz R, LaPrade RF. Concentrated bone marrow aspirate for the treatment of chondral injuries and osteoarthritis of the knee: a systematic review of outcomes. *Orthop J Sports Med*. 2016;4(1):2325967115625481.
5. Cook JL, Stannard JP, Stoker AM, et al. Importance of donor chondrocyte viability for osteochondral allografts. *Am J Sports Med*. 2016;44(5):1260-1268.
6. Czitrom AA, Keating S, Gross AE. The viability of articular cartilage in fresh osteochondral allografts after clinical transplantation. *J Bone Joint Surg Am*. 1990;72(4):574-581.
7. Desai P, Hasan SM, Zambrana L, et al. Bone mesenchymal stem cells with growth factors successfully treat nonunions and delayed unions. *HSS J*. 2015;11(2):104-111.

8. Ganguly P, El-Jawhari JJ, Giannoudis PV, Burska AN, Ponchel F, Jones EA. Age-related changes in bone marrow mesenchymal stromal cells: a potential impact on osteoporosis and osteoarthritis development. *Cell Transplant*. 2017;26(9):1520-1529.
9. Gianakos A, Ni A, Zambrana L, Kennedy JG, Lane JM. Bone marrow aspirate concentrate in animal long bone healing: an analysis of basic science evidence. *J Orthop Trauma*. 2016;30(1):1-9.
10. Gianakos AL, Sun L, Patel JN, Adams DM, Liporace FA. Clinical application of concentrated bone marrow aspirate in orthopaedics: a systematic review. *World J Orthop*. 2017;8(6):491-506.
11. Glassman SD, Anagnost SC, Parker A, Burke D, Johnson JR, Dimar JR. The effect of cigarette smoking and smoking cessation on spinal fusion. *Spine (Phila Pa 1976)*. 2000;25(20):2608-2615.
12. Glenn RE Jr, McCarty EC, Potter HG, Juliao SF, Gordon JD, Spindler KP. Comparison of fresh osteochondral autografts and allografts: a canine model. *Am J Sports Med*. 2006;34(7):1084-1093.
13. Gobbi A, Karnatzikos G, Scotti C, Mahajan V, Mazzucco L, Grigolo B. One-step cartilage repair with bone marrow aspirate concentrated cells and collagen matrix in full-thickness knee cartilage lesions: results at 2-year follow-up. *Cartilage*. 2011;2(3):286-299.
14. Greenberg JM, Carballosa CM, Cheung HS. Concise review: the deleterious effects of cigarette smoking and nicotine usage and mesenchymal stem cell function and implications for cell-based therapies. *Stem Cells Transl Med*. 2017;6(9):1815-1821.
15. Gross AE, Shasha N, Aubin P. Long-term followup of the use of fresh osteochondral allografts for posttraumatic knee defects. *Clin Orthop Rel Res*. 2005;435:79-87.
16. Haverstock BD, Mandracchia VJ. Cigarette smoking and bone healing: implications in foot and ankle surgery. *J Foot Ankle Surg*. 1998;37(1):69-74, discussion 78.
17. Hegde V, Shonuga O, Ellis S, et al. A prospective comparison of 3 approved systems for autologous bone marrow concentration demonstrated nonequivalency in progenitor cell number and concentration. *J Orthop Trauma*. 2014;28(10):591-598.
18. Kretlow JD, Jin YQ, Liu W, et al. Donor age and cell passage affects differentiation potential of murine bone marrow-derived stem cells. *BMC Cell Biol*. 2008;9:60.
19. Krych AJ, Nawabi DH, Farshad-Amacker NA, et al. Bone marrow concentrate improves early cartilage phase maturation of a scaffold plug in the knee: a comparative magnetic resonance imaging analysis to platelet-rich plasma and control. *Am J Sports Med*. 2016;44(1):91-98.
20. Krych AJ, Pareek A, King AH, Johnson NR, Stuart MJ, Williams RJ 3rd. Return to sport after the surgical management of articular cartilage lesions in the knee: a meta-analysis. *Knee Surg Sports Traumatol Arthrosc*. 2017;25(10):3186-3196.
21. Krych AJ, Robertson CM, Williams RJ 3rd. Return to athletic activity after osteochondral allograft transplantation in the knee. *Am J Sports Med*. 2012;40(5):1053-1059.
22. Meric G, Gracitelli GC, McCauley JC, et al. Osteochondral Allograft MRI Scoring System (OCAMRISS) in the knee: interobserver agreement and clinical application. *Cartilage*. 2015;6(3):142-149.
23. Narbona-Carceles J, Vaquero J, Suarez-Sancho S, Forriol F, Fernandez-Santos ME. Bone marrow mesenchymal stem cell aspirates from alternative sources: is the knee as good as the iliac crest? *Injury*. 2014;45(Suppl 4):S42-S47.
24. Oakeshott RD, Farine I, Pritzker KP, Langer F, Gross AE. A clinical and histologic analysis of failed fresh osteochondral allografts. *Clin Orthop Relat Res*. 1988;233:283-294.
25. Oladeji LO, Stannard JP, Cook CR, et al. Effects of autogenous bone marrow aspirate concentrate on radiographic integration of femoral condylar osteochondral allografts. *Am J Sports Med*. 2017;45(12):2797-2803.
26. Pallante AL, Gortz S, Chen AC, et al. Treatment of articular cartilage defects in the goat with frozen versus fresh osteochondral allografts: effects on cartilage stiffness, zonal composition, and structure at six months. *J Bone Joint Surg Am*. 2012;94(21):1984-1995.
27. Ranawat AS, Vidal AF, Chen CT, Zelken JA, Turner AS, Williams RJ 3rd. Material properties of fresh cold-stored allografts for osteochondral defects at 1 year. *Clin Orthop Relat Res*. 2008;466(8):1826-1836.
28. Rohban R, Pieber TR. Mesenchymal stem and progenitor cells in regeneration: tissue specificity and regenerative potential. *Stem Cells Int*. 2017;2017:5173732.
29. Shapiro SA, Kazmerchak SE, Heckman MG, Zubair AC, O'Connor MI. A prospective, single-blind, placebo-controlled trial of bone marrow aspirate concentrate for knee osteoarthritis. *Am J Sports Med*. 2017;45(1):82-90.
30. Tucker MS, Bernard JA, Degen RM, Moran G, Dines JS. Differences in the cellular content and mesenchymal stem cell in vitro expansion of different bone marrow concentration systems. *Trans Orthop Res Soc*. 2016;62:0719.
31. Williams RJ 3rd, Ranawat AS, Potter HG, Carter T, Warren RF. Fresh stored allografts for the treatment of osteochondral defects of the knee. *J Bone Joint Surg Am*. 2007;89(4):718-726.
32. Williams SK, Amiel D, Ball ST, et al. Analysis of cartilage tissue on a cellular level in fresh osteochondral allograft retrievals. *Am J Sports Med*. 2007;35(12):2022-2032.
33. Ziran BH, Hendi P, Smith WR, Westerheide K, Agudelo JF. Osseous healing with a composite of allograft and demineralized bone matrix: adverse effects of smoking. *Am J Orthop (Belle Mead NJ)*. 2007;36(4):207-209.