Bone Marrow Aspirate Concentrate for Cartilage Defects of the Knee: From Bench to Bedside Evidence

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Abstract

Objective. To critically evaluate the current basic science, translational, and clinical data regarding bone marrow aspirate concentrate (BMAC) in the setting of focal cartilage defects of the knee and describe clinical indications and future research questions surrounding the clinical utility of BMAC for treatment of these lesions. **Design.** A literature search was performed using the PubMed and Ovid MEDLINE databases for studies in English (1980–2017) using keywords, including [“bone marrow aspirate” and “cartilage”], [“mesenchymal stem cells” and “cartilage”], and [“bone marrow aspirate” and “mesenchymal stem cells” and “orthopedics”]. A total of 1832 articles were reviewed by 2 independent authors and additional literature found through scanning references of cited articles. **Results.** BMAC has demonstrated promising results in the clinical application for repair of chondral defects as an adjuvant procedure or as an independent management technique. A subcomponent of BMAC, bone marrow derived–mesenchymal stem cells (MSCs) possess the ability to differentiate into cells important for osteogenesis and chondrogenesis. Modulation of paracrine signaling is perhaps the most important function of BM-MSCs in this setting. In an effort to increase the cellular yield, authors have shown the ability to expand BM-MSCs in culture while maintaining phenotype. **Conclusions.** Translational studies have demonstrated good clinical efficacy of BMAC both concomitant with cartilage restoration procedures, at defined time points after surgery, and as isolated injections. Early clinical data suggests BMAC may help stimulate a more robust hyaline cartilage repair tissue response. Numerous questions remain regarding BMAC usage, including cell source, cell expansion, optimal pathology, and injection timing and quantity.

Keywords

bone marrow aspirate, bone marrow aspirate concentrate, mesenchymal stem cells, articular cartilage, knee

Introduction

Articular cartilage defects are common with a reported incidence of 61% to 67% during diagnostic arthroscopy procedures with increased symptoms and disability seen as patients age.^{1,2} Because of its avascular, aneural, and alymphatic nature, articular cartilage depends on diffusion to obtain nutrients and oxygen, making intrinsic repair of focal cartilage defects *in vivo* exceedingly difficult.^{3,4} Many individuals may not develop symptoms until their chondral injury has progressed to full-thickness or near full-thickness, presenting a formidable challenge irrespective of the involved joint. Focal cartilage defects of the knee are commonly treated with marrow stimulation techniques, which have been shown to have inferior long-term clinical outcomes due in large part to the predominantly fibrocartilage repair tissue generated.^{5–7} Fibrocartilage has poor compressive stiffness under load, inferior resilience and inferior wear characteristics than hyaline cartilage.⁸ Recently, bone

marrow aspirate concentrate (BMAC) has been investigated as both a primary therapeutic as well as an augmentation to existing cartilage restoration procedures.

The properties of BMAC have been evaluated in studies ranging from animal models of cartilage damage to clinical studies.^{9,10} The purpose of this review is to critically evaluate existing literature and describe clinical indications and

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future research questions about the clinical utility of BMAC for treatment of focal cartilage defects.

Article Identification

A literature search was performed on February 20, 2017 using the PubMed and Ovid MEDLINE databases for studies in English (1980-2017) using keywords, including ["bone marrow aspirate" and "cartilage"] yielding 82 results, ["bone marrow mesenchymal stem cells" and "cartilage"] yielding 1750 results, and ["bone marrow aspirate" and "mesenchymal stem cells" and "orthopedics"] yielding 6 results. All articles were reviewed by 2 independent reviewers and additional literature found through scanning references of cited articles.

Bone Marrow Aspirate Composition

Background

Bone marrow aspirate (BMA) contains a complex mixture of cellular components, including platelets, white blood cells, red blood cells, hematopoietic precursors, and nonhematopoietic precursors. BMAC is a commonly used term to describe the mixture marrow elements and mesenchymal stem cells (MSCs) isolated from bone marrow.¹¹ Various lineages of stem cells have been described that have disparate cell-differentiation potential; bone marrow-derived mesenchymal stem cells (BM-MSCs) are of particular interest given the relative ease of isolation, lack of ethical concerns, and ability to differentiate into cells critical for the treatment of osteochondral defects, including osteocytes and chondrocytes.¹¹⁻¹⁶

Four hallmark characteristics define stem cells: the abilities to reproduce, differentiate into multiple cell types, mobilize for the purposes of angiogenesis, and exert paracrine signaling functions that influence the environment in which they are present.¹⁷ Multipotent stem cells inherently have a narrow scope of cells into which they may differentiate when compared to embryonic or induced pluripotent stem cells (iPSCs).

These multipotent cells derived from BMA have been demonstrated to grow exceedingly well in culture allowing for tissue expansion for research purposes.^{13,18-20} However, cells that are extracted and expanded in *ex vivo* culture do not meet Food and Drug Administration (FDA) criteria for "minimally manipulated" and are subject to more stringent regulation for clinical use than cells that are simply separated by centrifugation.²¹ As such, current investigations within the United States regarding the clinical efficacy of BM-MSCs in orthopaedic applications use point-of-care BMAC injections or scaffold augmentation rather than culture-expanded MSCs.²² Investigators in countries outside of the United States have begun

evaluating culture-expanded BM-MSCs for treatment of cartilage defects in humans and demonstrated no significant increase in adverse events and importantly, maintenance of the MSCs phenotype.^{20,23-27}

Bone marrow MSCs only constitute 0.001% to 0.01% of mononuclear cells within BMA after the aspirate has undergone density gradient centrifugation to remove platelets, granulocytes, red blood cells, and immature myeloid precursors.^{9,28,29} Several studies have shown that BMA taken from the posterior iliac crest, yields the highest mean concentrations of BM-MSCs as compared with samples taken from the calcaneus, distal tibia, proximal tibia, distal femur, and anterior iliac crest.³⁰⁻³³ This low yield of BM-MSCs has generated significant discussion regarding whether the quantity of BM-MSCs results in significant differences in effect. This question has not been fully elucidated and remains an important area of investigation going forward.

Cytokines, Chemokines, and Growth Factors

BMAC contains a high concentration of bone marrow-derived platelets in addition to MSCs. These platelets contain a significant number of growth factors, chemokines, and cytokines identified in BMAC. They differ in their properties from the platelets found in peripheral blood used for platelet-rich plasma (PRP) preparation.³⁴ Previous reviews have characterized the effects of these cytokines and growth factors on chondrocytes, synoviocytes, and MSCs to induce chondrogenesis.^{35,36} BMAC in particular, has been shown to contain growth factors from the transforming growth factor- β (TGF- β) superfamily, which have been linked to chondrocyte proliferation and MSC differentiation.^{37,38} Another key growth factor present in BMAC is platelet-derived growth factor (PDGF), that promotes wound healing, collagen synthesis, the suppression of interleukin-1 β (a pro-inflammatory cytokine), and the enhancement of bone morphogenetic proteins-2 (BMP-2) and 7 (BMP-7) that contribute to the production of the extracellular matrix and chondrocyte proliferation.³⁸⁻⁴³ BMAC is a rich source of growth factors PDGF and TGF- β affording it great potential to induce chondrogenesis in MSCs.^{44,45} However, the full extent of the relationship between chondrocytes, synoviocytes, and BMAC (including MSCs and platelets) is likely not yet fully elucidated.

For management of focal cartilage defects, BMAC has shown elevated concentrations of growth factors that stimulate chondrocyte extracellular matrix synthesis, including IGF-I, FGF-18, TGF- β 1, BMP-1, and BMP-7. Furthermore, BMAC possesses elevated levels of growth factors that have been shown to decrease chondrocyte catabolic activity such as TGF- β 1 and IGF-I.³⁵ This anabolic milieu likely plays a key role in the tissue recovery and wound healing effects of BMAC.^{46,47}

Mesenchymal Stem Cells

MSCs within BMAC are characterized by their expression of CD105, CD73, and CD90 surface molecules and lack of expression of CD45, CD34, CD14 or Cd11b, CD79a or CD19 and HLA-DR.⁴⁸⁻⁵⁰ These nonhematopoietic multipotent progenitor cells are highly influenced by their surrounding cytokine and growth factor milieu, which may in turn impact proliferation and differentiation potential.^{35,47} In damaged tissues, MSCs elicit strong paracrine effects to modulate the local microenvironment that promotes anabolism.^{47,51,52}

Translational Evidence

Bone Marrow Aspirate Concentrate

Numerous studies have investigated regenerative properties of BMAC in translational models and reported predominantly positive results.⁵³⁻⁵⁶ In a goat model, Saw *et al.*⁵³ compared cartilage repair histologically following subchondral drilling alone versus augmentation with either hyaluronic acid (HA) or BMAC/HA injections. The HA group received 1 mL injections of sodium hyaluronate 1 time per week for 3 straight weeks after surgery while the BMAC group received 2 mL of BMAC in addition to HA at the same time points. After 24 weeks, the animals were sacrificed and quality of the repair tissue in the BMAC group was shown to be significantly better by Gill scoring as demonstrated by a more hyaline-like structure.⁵³

Similar investigations have been performed in equine models of cartilage defects. Fortier *et al.*⁵⁴ compared the outcomes of microfracture augmented with approximately 6 mL of autologous BMAC with those of isolated microfracture on the contralateral limb in full-thickness, 15 mm diameter, cartilage defects created along the lateral trochlear ridge. BMAC was harvested at time of microfracture surgery and injected in a 10:1 mixture with thrombin on the completion of standard microfracture of the knee. Second-look arthroscopy was conducted at 3 months and following euthanasia of the horses at 8 months, and macroscopic, histologic, and quantitative magnetic resonance imaging (MRI) were used to evaluate the quality of cartilage repair. An 8.7-fold increase in platelets within the BMAC compared with the nonmanipulated BMA was observed as well as a significantly better International Cartilage Restoration Society (ICRS) score in the BMAC group compared with isolated microfracture. In addition, the quality and quantity of the repair tissue was shown to be superior in the BMAC treated group with increased type II collagen content and improved integration.⁵⁴

Culture-Expanded Bone Marrow Derived–Mesenchymal Stem Cells

Several investigators have successfully expanded BM-MSCs from BMAC, to attain millions of cells compared to noncultured aspirates.⁵⁶⁻⁵⁹ Hui *et al.*⁵⁸ demonstrated that

higher BM-MSC concentrations (1 million cells/mL compared with 0.1 or 0.5 million cells/mL) yielded higher type II collagen and aggrecan concentrations on histology. The most recent study by Mahmoud *et al.*⁵⁹ evaluated 3 different concentrations of autologous MSCs, specifically, 0.125, 1.25, and 6.25 million MSCs/mL for treatment of osteochondral defects in rabbit knees. Significantly better histologic appearance of repair tissue was found at 4 and 12 weeks in the 1.25 and 6.25 compared with 0.125 million with an increased hyaline cartilage content. In addition, the subchondral bone, while still not normal, demonstrated evidence of restructuring in the 1.25 and 6.25 million groups compared with the lower concentration.⁵⁹ The mechanism of improved response and optimal MSC dosing is yet to be determined; however, these findings suggest that higher concentrations of MSCs allow a more robust prochondrogenic effect.

Jung *et al.*⁶⁰ demonstrated increased glycosaminoglycan and type II collagen content in matrix-assisted autologous chondrocyte implantation augmented with culture-expanded BM-MSCs in a minipig model. McIlwraith *et al.*⁵⁵ sought to build on these results in an equine study, in which microfracture augmented with BM-MSCs and 22 mg of hyaluronic acid injection 1 month after surgery was compared with microfracture augmented only with only 22 mg HA for treatment of 1 cm² condylar defects of the stifle joint. After 12 months, the BM-MSCs augmented joints demonstrated significantly greater levels of aggrecan content and tissue firmness; yet, no significant clinical or histologic differences were noted.⁵⁵

Not all animal studies have reported positive results. Recently, in an equine model, Goodrich *et al.*⁵⁶ tested if the addition of BM-MSCs to an autologous platelet-enriched fibrin scaffold (APEF) would enhance chondral repair when compared to isolated APEF. Fifteen millimeter diameter full-thickness chondral defects were created along the lateral trochlear ridge and were randomly assigned one stifle joint to receive BM-MSC with AFEP while the contralateral joint received AFEP alone. At one year, no significant differences were noted on arthroscopy, MRI T2-mapping, histology, structural stiffness, or material stiffness of the repair tissue with both groups resulting in repair tissue lower in proteoglycans than normal articular cartilage. However, a thicker repair tissue and less trabecular bony edema were noted in the isolated AFEP group compared with the BM-MSCs augmented group.⁵⁶ Similar results have been reported in an equine model using culture-expanded BM-MSCs added to a fibrin matrix at an 8-month time point.⁶¹ A summary of the major translational investigations in the field can be found in **Table 1**.

In summary, many animal studies have reported improved results with the addition of BMAC and/or BM-MSCs for the treatment of focal cartilage defects. Similar to the differences in efficacy between leukocyte-rich and leukocyte-poor preparations of PRP demonstrated by Riboh *et al.*⁶² the clinical efficacy of BMAC may be influenced by the components

Table 1. Summary of Recent Translational Studies Performed Evaluating Bone Marrow Aspirate Concentrate in the Realm of Cartilage Repair/Restoration.

Study	Animal Model	Groups	Time Point	Findings
Saw <i>et al.</i> (2009) ⁵³	Goat	MFX alone vs. MFX + HA vs. MFX + HA + BMA	24 weeks postoperatively	MFX + HA + BMA showed better quality cartilage regeneration than either of the other 2 groups by histologic scoring
Fortier <i>et al.</i> (2010) ⁵⁴	Equine	MFX alone vs. BMAC + MFX	8 months postoperatively	Improved macroscopic and histologic scoring of cartilage tissue quality with improved fill on MRI in BMAC + MFX vs. MFX alone
McIlwraith <i>et al.</i> (2011) ⁵⁵	Equine	iceBMSCs + HA vs. HA alone injection a 1 month post-MFX	12 months postinjection	No significant histologic or clinical difference between groups, but BMSC group had higher levels of aggrecan in repair tissue and was firmer on gross evaluation
Goodrich <i>et al.</i> (2016) ⁵⁶	Equine	APEF alone vs. APEF + iceBMSCs injection	12 months postinjection	Similar arthroscopic, MRI T2-mapping, histological scoring, structural stiffness, and material stiffness between both groups; iceBMSCs did not enhance repair
Itokazu <i>et al.</i> (2016) ⁵⁷	Rat	hBMSCs expanded in 5% FBS, 10% FBS, and 5% FBS with FGF-2	2, 4, and 12 weeks postoperatively	FGF-2 group demonstrated increased proliferation; cell-sheets implanted on bare implants survived up to 12 weeks

MFX = microfracture; HA = hyaluronic acid; BMA = bone marrow aspirate; BMAC = bone marrow aspirate concentrate; APEF = autologous platelet-enriched fibrin; iceBMSCs = isolated culture-expanded bone marrow-derived mesenchymal stem cells; hBMSCs = human bone marrow-derived mesenchymal stem cells; FBS = fetal bovine serum; FGF-2 = fibroblast growth factor 2.

present in different preparations, and this should be investigated in future research.

Clinical Indications

Many authors have begun investigating the clinical indications and efficacy of biologic adjuvants including BMAC especially for larger chondral lesions of the knee.^{10,63,64} Similar to the trajectory of PRP, BMAC usage will require appropriate clinical and academic scrutiny to determine the best method to harvest, prepare, and administer this treatment.

Current usage has included intra-articular administration in patients with focal chondral defects and degenerative changes along the spectrum of osteoarthritis. Since these 2 pathologies are typically age dependent, it is important to understand how this might affect the characteristics of autogenous treatments. Much like the clinical efficacy of cartilage repair and restoration procedures decrease with age, the utility, or what Stolzing *et al.*⁶⁵ refer to as the “fitness” of BMAC, may exhibit similar age-related decline. Specifically, authors have reported a reduction in the absolute number of MSCs within BMA and a decreased proliferative capacity.^{65,66} These are important variables to consider when thinking about which patients may receive significant benefit from BMAC injections.

While specific age groups have not been clearly defined in the literature, a recent systematic review by Chahla *et al.*⁹ reported the age range for which BMAC has been investigated thus far for treatment of chondral lesions and/or knee

osteoarthritis. Eleven studies were identified for inclusion, 8 of which specifically focused on the treatment of focal chondral defects. It was reported that all 8 studies evaluated BMAC in combination with or without microfracture or as isolated treatment compared to another injection medium, matrix assisted autologous chondrocyte implantation (MACI) or control group. The patient age ranged in these 8 studies between 17 and 58 years of age.⁶⁷⁻⁷³

Several investigators have reported the clinical application of scaffolds augmented with BMAC for both condylar and patellofemoral cartilage lesions.^{7,68,70,71,74} While applications of BM-MSCs that use *ex vivo* expansion face additional regulatory hurdles in the United States, these techniques may be used in the future in a manner similar to current applications of autologous chondrocyte implantation (ACI) and MACI.

Overall, the clinical indication for BMAC and ideal method of processing and delivery still requires further evaluation. Current studies include many different methods that are yet to reveal a single ideal use at this stage.

Clinical Outcomes

Numerous clinical reports have described the clinical efficacy of scaffolds augmented with BMAC in the treatment of chondral lesions of the knee (**Table 2**).^{68,70,71,74-76} In 2011, Gobbi *et al.*⁷⁰ demonstrated predominantly hyaline-like fill and positive clinical outcomes at 2-years in patients treated with BMAC embedded in collagen type I/III scaffolds for

Table 2. Summary of Recent Clinical Investigations Performed Evaluating Bone Marrow Aspirate Concentrate in the Realm of Cartilage Repair/Restoration.

Study	Population	Groups	End Point	Findings
Gobbi et al. (2011) ⁷⁰	<ul style="list-style-type: none"> 15 patients ICRS grade IV lesions Mean age 48 years 	BMAC embedded with a collagen I/III matrix	24-month follow-up	<ul style="list-style-type: none"> Significant improvement in KOOS, IKDC, Lysholm, Marx, SF-36 and Tegner scores at 6, 12, and 24 months MRI at 1 and 2-years complete defect fill in 80% of defects 3 specimens were histologically analyzed and demonstrated hyaline-like tissue
Gobbi et al. (2014) ⁷¹	<ul style="list-style-type: none"> 25 patients ICRS grade IV lesions mean age 46.5 years 	BMAC embedded with a collagen I/III matrix	Minimum 3-year follow-up; mean 41.3 months	<ul style="list-style-type: none"> Average number of colony forming units 4041 (range 2500-5700) Significant improvement in KOOS, IKDC, Lysholm, Marx, and Tegner scores at final follow-up All patients returned to previous daily and specific sporting activities (32% at preinjury level, however) Complete defect filling on MRI at final follow-up in 80% Patients younger than 45 years and with smaller or single defects had better outcomes
Enea et al. (2015) ⁶⁷	<ul style="list-style-type: none"> 9 patients Outerbridge grade III or IV lesions 	Treated with arthroscopic MFJ covered with a collagen membrane immersed in BMAC	Mean 29-month follow-up	<ul style="list-style-type: none"> Significant improvement in IKDC, Lysholm, and mean VAS at final follow-up One failure—underwent successive surgery On second-look arthroscopy, all but 1 patients were asymptomatic and 4 were classified as nearly normal ICRS grade Mostly hyaline-like cartilage was only seen histologically in 1 of the 4 patients with ICRS grade II repair tissue
Gobbi et al. (2017) ⁷⁴	<ul style="list-style-type: none"> 40 total patients Prospectively evaluated for 4 years ICRS grade IV lesions 	<ul style="list-style-type: none"> Group 1: 20 patients older than 45 years (mean 50) Group 2: 20 patients younger than 45 years (mean 36.6) BMAC embedded in a hyaluronan-based scaffold— younger group 	4-years	<ul style="list-style-type: none"> At final follow-up, significant improvement in all KOOS score categories, Tegner, IKDC in both age groups Lesions <8 cm² had significantly better IKDC scores as did patients with single lesions MRI at final follow-up demonstrated completed defect filling in 80% of those >45 years and 71% in those <45 years. 3 patients from older group and 2 from younger group had repair tissue histologically analyzed—demonstrated mix of hyaline-fibrocartilage mainly greater in the HA-BMAC group Tegner, KOOS-pain, and KOOS-sport scores at 5 years were significantly greater in the HA-BMAC group Significantly greater proportion of patients treated with HA-BMAC were classified as normal or near normal at 2- and 5-year follow-up on IKDC score
Gobbi and Whyte (2016) ⁷⁷	<ul style="list-style-type: none"> 50 patients ICRS grade IV lesions Prospective cohort study minimum 5-year follow-up 	<ul style="list-style-type: none"> Group 1: 25 patients—treated with hyaluronic acid-based scaffold with BMAC Group 2: 25 patients treated with BMAC 	5-years	<ul style="list-style-type: none"> Age >45 years, larger lesion size, and treatment of multiple lesions were not associated with inferior outcomes in HA-BMAC group but were seen in the microfracture group PRP (78%) and BMAC (75%) groups had superior cartilage fill (67%-100% fill) compared to control group (18%) On MRI at 12 months, PRP group had a similar mean T2 value to that of control group while BMAC had a mean T2 value closer to that of superficial hyaline cartilage
Krych et al. (2016) ⁷⁶	<ul style="list-style-type: none"> 46 patients Outerbridge grades III or IV lesions Only patients treated with TruFit scaffold (Smith & Nephew, Andover, MD, USA) 	<ul style="list-style-type: none"> Group 1: scaffold only (n = 1) Group 2: scaffold with PRP (n = 23) Group 3: scaffold with BMAC (n = 12) 	12-months	

MFJ = microfracture; HA = hyaluronic acid; BMAC = bone marrow aspirate concentrate; PRP = platelet-rich plasma; ICRS = International Cartilage Repair Society; KOOS = Knee Injury and Osteoarthritis Outcome Score; IKDC = International Knee Documentation Committee; VAS = visual analog scale; MRI = magnetic resonance imaging.

large (9.2 cm²) defects. This work was furthered in a cohort study of 25 patients (mean age 46.5 years) with large (mean 8.3 cm²) full-thickness chondral defects of the knee.⁷¹ Patients treated with BMAC and a collagen type I/III matrix reported significantly improved outcomes, including Lysholm, visual analog scale-pain (VAS), Knee Injury and Osteoarthritis Outcome Scores (KOOS), Marx and Tegner scores at minimum 3-year follow-up. In addition, patients younger than 45 years and those with single and smaller lesions had better outcomes. Overall, MRI demonstrated complete filling of the defect in more than 80% of patients and a mainly hyaline-like cartilage repair tissue on histological analysis.⁷¹ More recently, Gobbi *et al.*⁷⁴ reported significant improvement in patients older than 45 years with focal ICRS grade IV articular cartilage lesions of the knee treated with an HA scaffold (Hyalofast) soaked in BMAC compared to the scaffold alone. Complete defect filling was observed in 80% of the BMAC group compared to 71% in the control group.⁷⁴

As BMAC has been discussed as a potential single-stage alternative to ACI or MACI, Gobbi *et al.*⁷⁵ directly compared these 2 treatment options for patellofemoral chondral lesions in a nonrandomized prospective trial. The only significant difference in patient reported outcome measures was a higher IKDC subjective score in the BMAC group. In addition, 81% of patients in the BMAC group had complete filling of the chondral lesion compared with 76% in the MACI group on MRI with integration to surrounding cartilage also higher in the BMAC group (93.7% vs. 88.2%, respectively). More recently, Gobbi and Whyte⁷⁷ reported 5-year outcomes of 50 patients with grade IV cartilage injuries in the knee treated with HA-based scaffold treated with BMAC compared with those treated with microfracture noting significant improvement in outcomes scores at 2-years for both groups. However, after 5-years the normal or near normal objective assessments of the microfracture repair declined significantly while the HA-BMAC cohort maintained improvement in Lysholm, IKDC scores, Tegner, and KOOS scores.

Krych *et al.*⁷⁶ recently published a prospective study of full-thickness cartilage defects treated with either a scaffold ($n = 11$), scaffold plus PRP ($n = 23$), or scaffold plus BMAC ($n = 12$). The PRP and BMAC groups had superior cartilage fill compared with control groups on quantitative MRI T2-mapping at 12-months. There were no significant differences in bony overgrowth, subchondral edema, or gross appearance of the repair tissue between the 3 groups.⁷⁶ These results, while not in a randomized design and at just 1-year follow-up, demonstrate the utility of BMAC augmented scaffolds to possibly improve biological incorporation potentially leading to a more native cartilage repair.

Others have corroborated these positive clinical results. Enea *et al.*^{67,68} conducted 2 separate studies in which a

resorbable polyglycolic acid/hyaluronan matrix augmented with BMAC was used in combination with microfracture for treatment of predominantly condylar lesions that were Outerbridge type 3 or 4 and ≥ 1.5 cm². In their earlier study,⁶⁸ significant improvements in IKDC subjective, Lysholm, VAS, and Tegner scores from baseline at an average 22-month follow-up have been reported. In addition, MRI performed between 8 and 12 months demonstrated complete defect filling. However, this study only included 9 patients with just 2 of them consenting to biopsy harvest on second look arthroscopy making meaningful interpretation of histologic analysis difficult. More recently, Enea *et al.*⁶⁷ conducted a separate study of 9 patients, 4 of who consented to second look arthroscopy and biopsy after collagen-covered microfracture augmented with BMAC. Histologically, hyaline-like tissue was predominant in only 1 of 4 defects with a mixture of hyaline-like cartilage and fibrocartilage noted in 2 other lesions. Eight of 9 patients reported improved IKDC, Lysholm, and VAS pain scores at 29-month follow-up.

BMAC has been investigated for clinical use of very large chondral defects. Skowronski *et al.*⁷³ demonstrated good clinical results in 54 patients with ICRS grade III or IV large lesions (4-12 cm²) in the knee treated with BMAC and a collagen membrane. Specifically, there were 35- and 25-point improvements in the Lysholm and KOOS functional scales, respectively, at 1-year. Although this was a short-term follow-up study, the authors present what may become a viable alternative to 2-stage ACI. In a separate study, the same group compared clinical outcomes of 46 patients with osteochondral lesions of the knee treated with either BMAC ($n = 21$) or MSCs obtained from peripheral blood ($n = 25$) sandwiched within a collagen membrane at 1- and 5-years postoperatively. Eighty-six percent of patients reported overall significant improvement with superior outcomes observed in patients treated with peripherally derived MSCs. MRI analysis demonstrated satisfactory reconstruction of the cartilaginous surfaces and good integration with the surrounding tissue in both treatment groups.⁷²

Together, these studies demonstrate the promising, but inconsistent clinical results of BMAC for single-stage management of chondral defects in the knee. Furthermore, as bony injury is not uncommon when full-thickness cartilage lesions are present in the knee, others have reported good early clinical results of BMAC for improving the time needed to heal bony defects as well.^{24,25}

BMAC has recently been investigated as augmentation to osteochondral allograft transplantation (OCA) to try and enhance osseous integration of the allograft.⁷⁸ Stoker *et al.*⁷⁸ demonstrated that OCA treated with autogenous BMAC had viable cells located specifically on the osseous portion of the allografts at 7 and 14 days of culture and significantly higher colony forming units per milliliter than

leukocyte reduced PRP. Osteogenic proteins were also significantly higher in the OCA group cultured with BMAC. While in a dog model, these early results suggest autogenous BMAC may be able to deliver both MSCs and osteogenic proteins that can have a potential role in improving osseous integration of OCA. Others have evaluated these principles in humans treated with OCA. Oladeji *et al.*⁷⁹ conducted a prospective, nonrandomized trial of patients who were scheduled to undergo large condylar OCA (>2.5 cm²) who either received BMAC concomitantly or did not receive BMAC. The group that received BMAC had significant higher graft integration scores radiographically at 6-weeks, 3-months, and 6-months after surgery as determined by a blinded musculoskeletal radiologist. There was significantly less graft sclerosis in the BMAC at 6-weeks and 3-months, as well.⁷⁹ While in a small, nonrandomized cohort, these results lay the foundation for future investigation into the utility of BMAC to enhance osseous integration of OCA.

It is worth noting that authors are also investigating BMAC for treatment of meniscal injury in the knee giving the poor intrinsic ability of meniscal tears to heal in adults similar to chondral defects. Early *in vitro* work in this field have shown BMAC have potential to promote macroscopic and microscopic healing of meniscal defects.^{80,81} This remains an active area of research as several authors have reported beneficial and nonbeneficial outcomes following treatment of meniscal injuries with BMAC.⁸⁰

Future Research Questions

A greater understanding of the molecular biology of BMAC is necessary to improve methods of harvest, isolation, expansion, selective differentiation and ultimately, of administration in the clinical setting. Improvements in the ability to accurately quantify the number of stem cells in a BMAC sample and the effects of patient age at time of autologous BMA harvest will be critical in determining if stem cell quantity and fitness influence the quality of repair tissue. This has practical clinical implications for determining the amount of BMA desired to obtain a quantity of BMAC sufficient for patients to have clinical benefit. Further investigation into the timing of injection whether as augmentation of a cartilage repair or restoration procedure or as a postoperative injection at a defined time point requires further clarification. The effect of cryopreservation, including duration of cryopreservation, on the efficacy of BMAC should also be investigated. Large, multicenter prospective studies with defined inclusion criteria, outcome measures, and adequate control groups are needed going forward to gain a better understanding of the clinical efficacy and ideal clinical indications for BMAC.

Conclusion

BMAC had demonstrated promising results in the clinical application for repair of chondral defects of the knee either as an adjuvant procedure or as an independent management technique. A subcomponent of BMAC, BM-MSCs, possess the power to differentiate into cells important for osteogenesis and chondrogenesis. It was reported that modulation of paracrine signaling is perhaps the most important proregenerative function of BM-MSCs. The majority of animal studies have demonstrated good clinical efficacy of BMAC both concomitant with cartilage restoration procedures, at defined time points after surgery, and as isolated injections. Early clinical data suggests BMAC may help stimulate a more robust hyaline cartilage repair tissue response through both chondrocyte differentiation of MSCs and paracrine signaling. Numerous questions remain regarding BMAC, including optimal concentration of cells, which patients may benefit the most from injection, and the timing of injections.

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