



When and why should bone marrow concentrate be used to augment bone integration in osteochondral grafting?

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The use of biologics such as bone marrow concentrate (BMC) to augment musculoskeletal tissue repair is promising but simultaneously remains controversial. It is likely that not every patient treated with a biologic such as BMC truly needs it, and vice versa, that not every patient whom could have benefited from BMC receives it. This simple statement indicates that patient selection is critical for application of BMC so that the costs and any morbidity associated with harvest, generation, and application of BMC are only applied in those instances where it is necessary and might improve patient outcomes. Identifying those patients and selecting those cases for which to apply BMC is the nuanced challenge.

The manuscript “*Effects of Autogenous Bone Marrow Aspirate Concentrate on Radiographic Integration of Femoral Condylar Osteochondral Allografts*” by Oladeji from the Thompson Laboratory for Regenerative Orthopaedics and the Missouri Orthopaedic Institute provides some intriguing early results on the use of BMC in osteochondral (OC) allograft surgery that could have strong clinical implications for patients with knee osteoarthritis (OA) or focal cartilage defects.

This is the first study to report on the use of BMC for patients treated with large OC allografts in the femoral condyle specifically in a patient population where approximately 50% had concomitant procedures such as anterior cruciate ligament (ACL) reconstruction or meniscectomy. This is an important distinction compared to the recent Tirico study which reported a high success rate

in patients receiving large and smaller OC allografts for the treatment of focal cartilage defects in the femoral condyle. The majority of patients in the Tirico study were treated with OC allografts for osteochondritis dissecans (OCD) and very few had other knee pathologies. Combined, these studies would suggest that BMC augmentation of a large OC allograft of the femoral condyle might not be necessary for long-term results in patients with the single knee pathology of an OC defect. However, the Oladeji results might also suggest that BMC augmentation of large OC allografts leads to earlier graft integration which would have multiple beneficial effects for patients and the costs associated with OC allograft procedures. The use of BMC in the Oladeji patients resulted in significantly higher graft integration and less graft sclerosis as early as 6 weeks post-operatively. The effects of BMC on graft integration and sclerosis were still evident at 3 months, but not at 6 months. This suggests that the use of BMC could accelerate post-operative rehabilitation and return to function in patients.

Perhaps the most intriguing results of the manuscript is the effect of BMC on graft integration in smokers. Stratification and analysis of the data according to smoking status provides a unique insight into a potential and readily available method to mitigate the well-known negative side effects of smoking on bone healing. In patients receiving BMC, graft integration and sclerosis was not different from non-smokers at 3 weeks or 3 months post-operatively. Every physician would encourage their patients to stop smoking,

but for those patients where it is just not possible for them to overcome the addiction, a biological solution like the use of BMC might ameliorate some of the negative effects of smoking on graft integration in patients receiving large OC allografts, and render their morbidity with respect to graft integration to be no different than that present in non-smokers. This effect of BMC on smoking was not sustained to the 6 months follow-up, where non-smokers had better graft integration, which might suggest that smokers could benefit from post-operative BMC administration in an attempt to retain the positive effects of BMC on graft incorporation. Because smoking is a strong negative comorbidity, this concept of enhancing the ability of smokers to heal is worth investigating in other bone-associated pathologies such as long bone fractures, spinal fusion, dentistry, and many others.

The use of BMC in musculoskeletal applications has been reviewed by Gianikos who identified studies where BMC was reported to successfully augment repair of OC defects with scaffolds such as hyaluronic acid or collagen, treat OA, confined cartilage lesions, and bone defects (1). More recently, the authors reported on the use of bone marrow-derived biologics, including BMC in the knee (2). Readers are referred to these reviews for specifics, but the salient points that come from studies on BMC in joints, is that BMC is a combinational product that provides growth factors, bone marrow-derived mesenchymal stem cells, and the potent anti-inflammatory interleukin-1 receptor antagonist protein (IL-1ra, IRAP). No other biologic or drug can provide all three of these complimentary approaches for restoration of a normal joint environment.

The whole purpose of performing an OC allograft is to preserve the joint, but more specific to bone, and how BMC might have elicited its effect on increased graft bone integration and decreased graft bone sclerosis, is its recently identified osteogenic protein content (3). Also from the Department of Orthopaedic Surgery and the Thompson Laboratory for Regenerative Orthopaedics, the authors compared the osteogenic capacity of platelet rich plasma (PRP) compared to BMC and no-treatment controls in an *ex vivo* study using OC allografts cultured for 7 or 14 days. In allografts saturated with BMC, viable cells were adhered to the osseous portion of the allograft bone at both 7 and 14 days. In the culture media of OC allografts treated with BMC, there was significantly more bone morphogenetic protein-2 (BMP-2) osteoprotegerin (OPG) than PRP or untreated control groups at day 7. The presence of

these osteoinductive proteins provides some insight into a potential mechanism of action for the effects of BMC on enhancing early OC allograft bone integration.

The use of bone marrow aspirate concentrate was first reported in the ankle by Kennedy and Murawski when used in conjunction with OC cylinder grafts (4). The study reported excellent bone and cartilage integration of the graft to the host in 72 patients. In particular, the study examined T2 mapping magnetic resonance imaging (MRI) of the cartilage host-graft interface, indicating excellent stratification in both deep and superficial zones. In a level 3 comparative study between OC lesions of the talus (OLTs) treated with BMC and microfracture compared to patients treated with microfracture alone, both groups had similar clinical scores at 2 years follow-up (5). The group treated with BMC however showed better radiological MOCART scores and had improved superficial zone stratification on T2 mapping MRI. The study reported significantly improved defect filling, border repair integration and surface tissue repair along with less fissuring and fibrillation in OLTs treated with BMC compared to those without.

When BMC is used in combination with a collagen scaffold to treat OLTs the results have been equally promising. Giannini *et al.* reported that all 48 patients at minimum 2-year follow-up had excellent MRI incorporation that correlated with excellent patient based outcome scores (6). Of the 3 patients in whom a second look arthroscopy and a biopsy was taken, both histological and immunohistochemical analysis demonstrated various degrees of hyaline cartilage formation. More recently, BMC has been investigated as a potential adjunct to reduce postoperative cyst formation following osteochondral autograft transfer system (OATS) in the talus. Shimozono *et al.* demonstrated that the number and size of these cysts was significantly reduced when BMC was used by comparison to when an OATS plug was used alone (7). In a systematic review on the use of BMC in OLT the investigators concluded that there was promising data to supports its continued use but cautioned that high level studies were not yet available to substantiate its widespread application at that time (8). Despite this, BMC continues to be used as a biologic adjunct in the treatment of OLT in many centers and this use is based on solid preclinical data.

In many of the studies investigating BMC, increased patient population sample sizes would provide more compelling evidence, but these studies indicate that there is at least one additional way future data could significantly

improve patient outcomes. If a more sophisticated statistical analysis were completed with an increased patient population, the author would likely be able to provide insight into patient selection and a defined time-point for increased risk of failure. For example, if a general linear model, as opposed to the presently used multiple *t*-test, were used and included numerical as opposed to categorical data for independent variables such as day of post-op radiograph, actual body weight, number of cigarettes/cigars smoked per week, age, etc., then patient selection and post-operative monitoring might be better defined. Regardless of the shortcomings of these early data, the manuscript provides compelling data for continued use of BMC to improve outcomes for patients presenting with challenging clinical knee pathology, and suggests that large OC allograft success is improved by soaking the graft in BMC, even in patients with the significant comorbidity of smoking.

Finally, like all studies where the use of biologics such as BMC or PRP are used, investigators should strive to define what is delivered to each patient and to incorporate those laboratory values such as platelet and leukocyte counts in the BMC or PRP products as well as the total number delivered to the patient so that dosing of biologics can be related to outcome potential (9). Several position statements from individual groups and societies have made recommendations for reporting when using biologics. Including these data into a larger data set in patients receiving large OC allografts soaked in BMC might further enhance bone integration/repair if a threshold of some measure for BMC were identified.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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