Variability in the Preparation, Reporting, and Use of Bone Marrow Aspirate Concentrate in Musculoskeletal Disorders

A Systematic Review of the Clinical Orthopaedic Literature

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Background: Interest in the therapeutic potential of bone marrow aspirate concentrate (BMAC) has grown exponentially. However, comparisons among studies and their processing methods are challenging because of inconsistent reporting of protocols, as well as poor characterization of the composition of the initial bone marrow aspirate and of the final products delivered. The purpose of this study was to perform a systematic review of the literature to evaluate the level of reporting related to the protocols used for BMAC preparation and the composition of BMAC utilized in the treatment of musculoskeletal diseases in published clinical studies.

Methods: A systematic review of the literature was performed by searching PubMed, MEDLINE, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials from 1980 to 2016. Inclusion criteria were human clinical trials, English language, and manuscripts that reported on the use of BMAC in musculoskeletal conditions.

Results: After a comprehensive review of the 986 identified articles, 46 articles met the inclusion criteria for analysis. No study provided comprehensive reporting that included a clear description of the preparation protocol that could be used by subsequent investigators to repeat the method. Only 14 (30%) of the studies provided quantitative metrics of the composition of the BMAC final product.

Conclusions: The reporting of BMAC preparation protocols in clinical studies was highly inconsistent and studies did not provide sufficient information to allow the protocol to be reproduced. Moreover, comparison of the efficacy and yield of BMAC products is precluded by deficiencies in the reporting of preparation methods and composition. Future studies should contain standardized and stepwise descriptions of the BMAC preparation protocol, and the composition of the BMAC delivered, to permit validating and rationally optimizing the role of BMAC in musculoskeletal care.

Bone marrow is a valuable source of stem and progenitor cells for cell-based therapies in orthopaedics[1]. Lindholm and Urist[2] first described the use of unprocessed bone marrow aspirate (BMA) with allograft bone matrix to enhance bone-healing. They were followed by Connolly and Shindell[3,4], who reported good results with injections of unprocessed BMA alone for the percutaneous treatment of tibial nonunion. Since then, BMA and material derived by the concentration of bone marrow have been utilized for the treatment of a wide variety of musculoskeletal conditions including bone defects[5-7], arthrodesis[8], chondral defects[9-12], osteoarthritis[13], tendinopathy[14], and osteonecrosis[15-18].

Concentration of the nucleated cells in BMA using a density separation centrifuge to create a bone marrow aspirate concentrate (BMAC) offers the theoretical potential to deliver a higher number of marrow-derived cells, including connective tissue progenitors (CTPs). Depending on the processing methods, the concentrations of platelets, growth factors, and cytokines may also

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Disclosure: No funding was received during the preparation or execution of this study. On the **Disclosure of Potential Conflicts of Interest** forms, *which are provided with the online version of the article,* one or more of the authors checked "yes" to indicate that the author had a relevant financial relationship in the biomedical arena outside the submitted work and "yes" to indicate that the author had a patent and/or copyright, planned, pending, or issued, broadly relevant to this work (http://links.lww.com/JBJS/E528).

be changed. In theory, variation in the cellular and chemical composition of BMAC preparations may have important anabolic and anti-inflammatory effects that may impact the local tissue response and tissue regeneration.

In recent years, interest in BMAC has grown exponentially; however, the composition of BMAC preparations that provide the optimal therapeutic effect for specific musculoskeletal pathologies remains unknown. Multiple factors affect the BMAC composition. The quality and composition of the initial BMA used to prepare BMAC are perhaps most important. These will in turn depend on the clinical and biological attributes of the patient[19] and the location and BMA technique used[20]. Multiple devices and systems are available for the harvesting and processing of BMA. Each uses slightly different methods, but all base their separation on the differences in density among red blood cells, nucleated cells, platelets, and serum proteins[21]. Separation methods may involve multiple stages, with each providing opportunities for variation. This results in vast differences in BMAC composition, between processing strategies and even between different batches prepared using the same processing methods. This makes it challenging to compare the effectiveness of BMAC preparation among individual studies and very difficult to define the optimal therapeutic composition for specific patients with specific pathologies.

The rational development of BMAC currently lacks a system for a comprehensive and standardized reporting of BMAC preparation protocols. The purpose of this study was to perform a detailed systematic review of the literature to evaluate the current level of reporting related to the protocols of BMAC preparation and the reported composition of BMAC utilized in the treatment of musculoskeletal diseases in published clinical studies.

Materials and Methods

Article Identification and Selection

The study was conducted in accordance with the 2009 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[22]. A systematic review of the literature regarding the existing evidence for BMAC preparation in musculoskeletal studies was performed using PubMed, MEDLINE, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials (1980 to 2016). The systematic review was registered in the PROSPERO international prospective register of systematic reviews in February

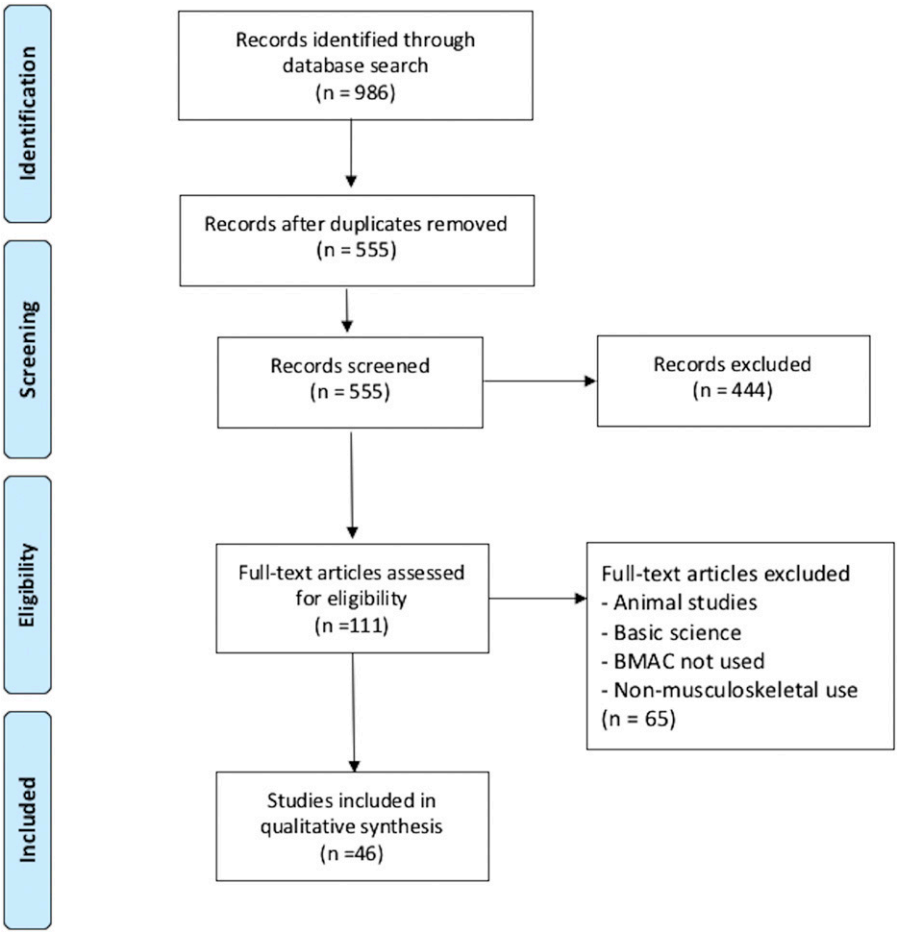

Fig. 1

PRISMA flow diagram presenting the systematic review process used in this study.

TABLE I Included Studies

Study	Journal	Year	Study	Journal	Year
Bansal[38]	Indian J Orthop	2009	Singh[39]	J Nat Sci Biol Med	2014
Giannini[11]	Clin Orthop Relat Res	2009	Torres[40]	Biomed Res Int	2014
Hendrich[41]	Orthop Rev (Pavia)	2009	Ajiboye[42]	Eur Spine J	2015
Gigante[43]	Int J Immunopathol Pharmacol	2011	Centeno[44]	BMC Musculoskelet Disord	2015
Gobbi[45]	Cartilage	2011	Centeno[46]	J Pain Res	2015
Kennedy[47]	Cartilage	2011	Centeno[48]	J Pain Res	2015
Murawski[49]	Am J Sports Med	2011	Enea[50]	Knee	2015
Cavallo[51]	J Biomed Mater Res A	2013	Gobbi[52]	Cartilage	2015
Odri[53]	Eur Spine J	2012	Hernigou[78]	Int Orthop	2015
Yamada[54]	Spine	2012	Pettine[55]	Stem Cells	2015
Buda[9]	Joints	2014	Stein[56]	Int Orthop	2015
Enea[57]	Knee	2013	Tabatabaee[58]	J Arthroplasty	2015
Lee[59]	Clin Orthop Relat Res	2014	Centeno[60]	Int Orthop	2016
Martin[79]	Croat Med J	2013	Flouzat-Lachaniette[61]	Int Orthop	2016
Skowronski[62]	Ortop Traumatol Rehabil	2013	Gobbi[65]	Am J Sports Med	2016
Vulcano[64]	Eur Rev Med Pharmacol Sci	2013	Hannon[67]	Arthroscopy	2016
Centeno[66]	Biomed Res Int	2014	Krych[68]	Am J Sports Med	2016
Gobbi[12]	Am J Sports Med	2014	Mishima[70]	Eur J Orthop Surg Traumatol	2016
Hart[69]	Spine J	2014	Pepke[72]	Orthop Rev (Pavia)	2016
Hernigou[71]	Int Orthop	2014	Pettine[74]	Int Orthop	2016
Johnson[73]	Spine	2014	Sampson[75]	Regen Med	2016
Kim[13]	Eur J Orthop Surg Traumatol	2014	Shapiro[77]	Am J Sports Med	2017
Scaglione[76]	Musculoskelet Surg	2014	Gobbi[63]	Knee Surg Sports Traumatol Arthrosc	2017

2017 (registration number CRD42017058249). The following searches were performed in September 2016.

Search 1: ("bone marrow") AND (aspirate OR concentrate) AND (orthopaedic [ALL FIELDS] OR orthopedic [ALL FIELDS] OR musculoskeletal [ALL FIELDS] OR cartilage [ALL FIELDS] OR chondral [ALL FIELDS] OR osteochondral [ALL FIELDS] OR joint [ALL FIELDS] OR tendon [ALL FIELDS] OR ligament [ALL FIELDS] OR muscle [ALL FIELDS] OR meniscus [ALL FIELDS] OR knee [ALL FIELDS] OR hip [ALL FIELDS] OR shoulder [ALL FIELDS] OR ankle [ALL FIELDS] OR elbow [ALL FIELDS] OR allograft [ALL FIELDS] OR spine [ALL FIELDS] OR osteonecrosis [ALL FIELDS]).

Search 2: (BMAC OR "bone marrow aspiration concentrate" OR "bone marrow aspiration") AND (arthritis OR osteoarthritis OR chondral OR cartilage OR osteochondral) AND (treatment OR therapy).

Search 3: bone AND marrow AND aspirate AND ("orthopedics" [Mesh Terms] OR (orthopaedic [ALL FIELDS] OR

TABLE II Summary of Available Protocols for Aspiration of Bone Marrow in the 46 Identified Studies*

	Collection Site	Syringe Volume	No. of Sites	Volume per Site
No. (%) of studies reporting	43 (93%)	19 (41%)	20 (43%)	16 (35%)
Mode	Iliac crest	60 mL	2 and 6	5 mL
Median	NA	20 mL	4	5.5 mL
Minimum	NA	5 mL	1	2.5 mL
Maximum	NA	60 mL	10	12.5 mL
No. of unique entries	1	5	12	7

*NA = not applicable.

TABLE III Summary of BMAC Processing Characteristics*

	Initial Volume of Bone Marrow	Anticoagulant Name	Processing Machine	RPM	Time	Platelet Activator	Final Volume of BMAC
No. (%) of studies reporting	36 (78%)	26 (57%)	31 (67%)	9 (20%)	14 (30%)	5 (11%)	28 (61%)
Mode (no.)	60 mL	Heparin (14)	Harvest system (11)	3,200	15 min	Batroxobin enzyme (4)	6 mL
Median	60 mL	NA	NA	3,200	15 min	NA	6 mL
Minimum	10 mL	NA	NA	500	5 min	NA	2 mL
Maximum	300 mL	NA	NA	3,200	25 min	NA	35 mL
No. of unique entries	19	3	11	4	6	2	16

*NA = not applicable.

orthopedic [ALL FIELDS] OR musculoskeletal [ALL FIELDS] or cartilage [ALL FIELDS] OR chondral [ALL FIELDS] OR osteochondral [ALL FIELDS] OR joint [ALL FIELDS] OR tendon [ALL FIELDS] OR ligament [ALL FIELDS] OR muscle [ALL FIELDS] OR meniscus [ALL FIELDS] OR knee [ALL FIELDS] OR hip [ALL FIELDS] OR shoulder [ALL FIELDS] OR ankle [ALL FIELDS] OR elbow [ALL FIELDS] OR allograft [ALL FIELDS] OR spine [ALL FIELDS] OR osteonecrosis [ALL FIELDS])).

Human studies, presented in the English language, that reported on the clinical use of BMAC in musculoskeletal or orthopaedic conditions were included. Reviews, cadaveric studies, animal studies, basic science articles, case reports, editorial articles, special topics, letters to the editor, personal correspondence, and studies describing use for nonorthopaedic applications were excluded.

Three investigators independently reviewed the titles of all identified articles, and unrelated titles were excluded. Abstracts were subsequently reviewed, and if a study appeared to be potentially applicable, the full-text article was obtained for review to allow for further assessment of whether the article satisfied the inclusion or exclusion criteria. References from the included studies were also reviewed to reduce the risk of omission of relevant articles.

Data Collection

We collected data on the protocol used for BMAC preparation into a custom information extraction table that included the initial volume of bone marrow, anticoagulant used, collection site locations and number of sites, volume per site and syringe used, processing machine, number of spins (with rotations per minute [RPM] or gravitational forces, when reported, and time), method of platelet activation, initial and final nucleated cell count, fold increase in cell count, colony forming unit (CFU) count, qualitative characterization (on the basis of CD surface markers), final volume of BMAC, and clinical use. These factors were selected based on previously published reports on criteria that influence the composition or biological effect of BMAC[21]. For the purpose of summarizing numerical descriptors across studies, ranges were reduced to a single data point by using the midpoint of the range. Articles were defined as having "comprehensive reporting" when data on all of these metrics were reported.

Results

Article Identification and Selection (Fig. 1)

The search strategy identified 986 individual reports. After application of inclusion and exclusion criteria, 875

TABLE IV Summary of Brand and Model Information for the BMAC Processing System Used, in the 31 Studies Reporting It

Machine	No.
Harvest system (Harvest Technologies, Plymouth, MA)	11
MarrowStim Concentration System (Biomet, Warsaw, IN)	3
ART BMC system (Celling Biosciences, Austin, TX)	3
Manual serological pipetting	3
Magellan Autologous Platelet Separator System (Arteriocyte, Hopkinton, MA)	3
COBE 2991 Cell Processor (Terumo, Paris, France)	2
Biomet GPS (Biomet, Warsaw, IN)	2
BioCUE System (Biomet, Warsaw, IN)	1
Biosafe system (Biosafe, Eysins, Switzerland)	1
Kubota 9800 (Kubota, Tokyo, Japan)	1
Jouan B4i (Jouan, Saint-Herblain, France)	1
Total	31

TABLE V Quantitative Characterization of Nucleated Cells in BMAC, in the Studies Reporting It*

	Initial Nucleated Cell Count		Nucleated Cell Count After Concentration		Fold Increase of Nucleated Cells	Colony Count in BMAC
	Mean No.	Range	Mean No.	Range		
No. (%) of studies reporting	6 (13%)	4 (9%)	14 (30%)	12 (26%)	3 (6.5%)	7 (15%)
Mean	6.4×10^6 cells/mL	NA	149×10^6 cells/mL	NA	NA	1,462 CFU/mL
Median	4.7×10^6 cells/mL	18.5×10^6 cells/mL	24.9×10^6 cells/mL	30.3×10^6 cells/mL	2.6	1,134 CFU/mL
Minimum	0.07×10^6 cells/mL	4.1×10^6 cells/mL	0.06×10^6 cells/mL	0.08×10^6 cells/mL	1.37	50 CFU/mL
Maximum	18.9×10^6 cells/mL	130×10^6 cells/mL	694×10^6 cells/mL	$1,700 \times 10^6$ cells/mL	3.5	3,080 CFU/mL

*NA = not applicable.

studies were eliminated, leaving 111 articles for full-text review. After a comprehensive review of these articles, a total of 46 articles met inclusion criteria for analysis (Table I). Therefore, percentage calculations are based on a total of 46 distinct data sets.

BMAC Aspiration Characteristics

There was heterogeneity among studies in the reported BMAC aspiration protocols (Table II). The collection site from which BMA was aspirated was reported in 43 (93%) of the studies, and it was the iliac crest in each of these. The volume of the collection syringe was reported in 19 (41%) of the studies; the median volume was 20 mL. The number of BMA sites was reported in 20 (43%); the median number was 4 sites. The volume of BMA extracted per site was reported in 16 (35%); the median aspiration volume was 5.5 mL (range, 2.5 mL to 12.5 mL) per site.

BMAC Processing Characteristics

There was also heterogeneity among studies in the BMAC processing protocols (Table III). The total volume of bone marrow aspirated was reported in 36 (78%) of the studies; the median volume was 60 mL (range, 10 to 300 mL). The specific anticoagulant that was used was reported in 26 (57%) of the studies (heparin in 14, acid-citrate-dextrose [ACD-A] in 12). Use of an automated processing machine, rather than a manual centrifuge, for BMAC preparation was reported in 31 (67%) of the studies. Eleven different processing machines were reported (Table IV).

In describing the centrifugation process, 9 (20%) of the studies reported the spin rate and 14 (30%) reported the spin time. The median spin rate was 3,200 RPM (range, 500 to 3,200 RPM), and the median spin time was 15 minutes (range, 5 to 25 minutes). Five (11%) of the studies reported on the use of platelet activation (batroxobin enzyme in 4, $CaCl_2$ in 1). The final volume of BMAC that was prepared and injected was reported in 28 (61%) of the studies; the median was 6 mL, with 16 unique volumes.

BMAC Quantitative Characteristics

The mean number of nucleated cells in the BMA before processing was reported in 6 (13%) of the studies, and a range was reported in 4 (9%) (Table V). The starting nucleated cell concentration varied extensively among studies. In the studies that reported a mean concentration, the mean averaged 6.4×10^6 cells/mL. In the studies that reported a range, the lowest concentration was 7×10^4 cells/mL and the highest was 18.9×10^6 cells/mL, with a median difference of 18.5×10^6 cells/mL between the least and most concentrated samples within individual studies.

The mean number of nucleated cells after processing was reported in 14 (30%) of the studies, and a range was reported in 12 (26%). The mean number of nucleated cells after concentration was 1.49×10^8 (range, 6×10^4 to 6.94×10^8). The fold increase of nucleated cells after concentration was reported in only 3 (6.5%) of the studies; the median increase was 2.6-fold. A CFU assay was reported in 7 (15%) of the studies, with a mean CFU of 1,462/mL (range, 50 to 3,080 CFU/mL).

BMAC Qualitative Characteristics

Flow cytometry analysis of cell surface markers of the processed cell population was reported in 7 (15%) of the studies. This

TABLE VI Clinical Indications for Which BMAC Was Used

Clinical Indication	Frequency
Osteochondral defect and osteochondral lesions (knee, talus)	16
Lumbar arthrodesis	6
Osteonecrosis of femoral head	5
Osteoarthritis	5
Fracture repair	5
Rotator cuff pathology	2
Discogenic pain	2
Anterior cruciate ligament tear	1
Acetabular bone defect	1
Tibial bone defect	1
Tennis elbow	1
Achilles tendon rupture	1
Total	46

reporting was highly heterogeneous. All 7 of these studies reported on CD34, 4 reported on CD90 and CD105, 2 reported on CD73 and CD45, and 1 reported on CD19, CD14, CD11b, and HLA-DR.

Clinical Indications

BMAC was used across a wide range of clinical indications. These included knee and talar osteochondral defects and osteochondral lesions (n = 16), lumbar arthrodesis (n = 6), osteonecrosis of the femoral head (n = 5), osteoarthritis (n = 5), fracture repair (n = 5), rotator cuff pathology (n = 2), discogenic pain (n = 2), anterior cruciate ligament tear (n = 1), acetabular bone defect (n = 1), tibial bone defect (n = 1), tennis elbow (n = 1), and Achilles tendon rupture (n = 1) (Table VI).

Discussion

The principal finding of this systematic review was that the reporting in the orthopaedic clinical literature regarding the use of BMAC was highly heterogeneous and inconsistent. Of the 46 BMAC clinical studies identified in this review, none provided a comprehensive reporting of a preparation protocol that would allow the preparation method to be accurately reproduced. The iliac crest was the source and a centrifuge device was used for processing in all studies that reported this information. However, the method of aspiration was not well documented, and it varied widely among the studies in which it was documented. The studies demonstrated no consensus regarding a standardized reporting method for describing the composition of the starting material (BMA), the composition of the processed BMAC product that was used therapeutically, or the efficacy of the processing methods (yield of cells and CFUs, fold change in the concentration of cells and CFUs). Overall, only 30% of the studies provided quantitative metrics on the concentration of cells and CFUs in the final BMAC product. It might have been possible to estimate the characterization of the delivered product in some studies in which the average initial composition of the BMA was reported but the average composition of processed BMAC was not, if the machine efficacy was known to a precise level. However, we advocate characterizing the composition after processing for each sample, so that one can accurately correlate the composition of the therapy delivered with the outcome.

While use of BMAC is promising as a therapeutic modality, the success of BMAC procedures varies from patient to patient. It is generally assumed that the composition of BMAC will be related to its clinical efficacy. However, the critical quality attributes that are associated with success or failure of BMAC use are not yet known. Association of the quality attributes of BMAC with clinical outcome will require systematic quantitative analysis and reporting of both composition and outcomes. The uncertainty regarding BMAC composition, combined with the heterogeneity and inconsistency in BMAC preparation protocols, represents a critical gap in current clinical practice and the systematic optimization and validation of BMAC as an effective therapeutic tool. Closing this gap will require standardization of reporting of BMA composition, BMAC composition, BMA aspiration methods, BMAC processing methods, and BMAC processing efficacy.

A minimum data set for reporting of each of these attributes is offered below, and need not be overly complex to substantially advance the field. A minimum data set for BMA or BMAC composition can be defined by the total volume and the concentrations of nucleated cells, platelets, red blood cells, and CFUs.

A minimum data set for the description of a BMA aspiration technique should include the site of aspiration, gauge of the needle, make and model of the needle, volume of aspirate harvested at each site, anticoagulation method, syringe size, aspiration speed or force, method of needle repositioning between aspiration sites (to minimize contamination with peripheral blood), and total aspiration volume.

A minimum data set for BMAC processing efficacy can be defined by calculations of cell and CFU yields and the fold change achieved in the concentrations of nucleated cells, CFUs, platelets, and red blood cells when the processed sample is compared with the starting sample.

A minimum data set for the description of BMAC processing technique should also be included, as it greatly affects the viability and concentration of cells and growth factors remaining in the end product[21,23,24]. Therefore, studies should report on the make and model of the centrifuge device, device settings or protocol, methods for separation of red blood cells from nucleated cells and platelets (e.g., density shelf or optical sensor), duration of each spin and the g-force generated in each spin, and composition and volume of any diluents that are added to change the viscosity of the cell suspension or induce Rouleau formation among red blood cells.

Characterization of cells on the basis of surface markers has been proposed and performed extensively. The classic MSC (mesenchymal stromal cell, or mesenchymal stem cell) surface markers (expression of CD73, CD90, and CD105, with the absence of CD34, CD45, CD14, CD19, and HLA-DR) are consistent features of culture-expanded cell populations[25]. However, these surface markers have been reported to be unpredictable for determining performance and subsequent biological potential[26]. Further research is required to identify alternative or complementary surface markers, including proposed markers for stemness such as CD146, STRO-1, and CD271[27-30]. Of all of the analyzed studies that reported on BMAC use for orthopaedic conditions, only 15% performed some form of surface marker analysis. The application of these markers in the development of quantifiable consensus-based standards in BMA and BMAC preparations is still to be defined and optimized.

BMAC preparations also contain platelets and degranulations of platelets that can increase the concentration of some growth factors in the final BMAC product (e.g., transforming growth factor-beta [TGF-β1], platelet-derived growth factor [PDGF], vascular endothelial growth factor [VEGF], bone morphogenetic proteins [BMPs]), as well as the concentrations of some other factors that antagonize the

desired effect, such as noggin or sclerostin (BMP antagonists)[31-33]. It is possible to add information regarding the concentration of potential bioactive growth factors and cytokines in a BMA or BMAC sample as a metric of composition. Other candidate molecules with modulatory effects on CFUs, local angiogenesis, and inflammation include basic fibroblast growth factor (bFGF), TGF-β1, epidermal growth factor, interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α). However, while these may be clinically relevant, and worthy of study until the range of potential candidate targets is narrowed, the systematic analysis and reporting of the myriad of potentially bioactive molecules in BMA and BMAC preparations should not be considered essential to clinical reporting.

An assay of CFUs provides a measurement of the number of colony-founding cells (stem and progenitor cells) capable of generating progeny that proliferate and generate at least 1 connective tissue phenotype. This could be bone, cartilage, fibrous tissue, muscle, fat, or stroma. This heterogeneous mixture of colony-founding cells in native tissues is referred to as connective tissue progenitors, CTPs. A CFU assay involves placing a defined number of starting cells into tissue culture under established conditions, and assessing the number of colonies that form[20,23,34,35]. This assay provides the prevalence of CTPs (abbreviated P_{CTP}) in that population, which is usually expressed as the number of CTPs per million nucleated cells. This assessment can be performed using manual methods of counting, as reported by 7 of these 46 BMAC studies. Use of automated systems for image analysis to extract quantitative CFU data using this nomenclature has been formalized by ASTM International in the *Standard Test Method for Automated Colony Forming Unit (CFU) Assays—Image Acquisition and Analysis Method for Enumerating and Characterizing Cells and Colonies in Culture*[35,36]. The field of cellular therapy will benefit substantially from the expanded use of standardized quantitative CFU assay methods to assess CTPs and other stem and progenitor populations (e.g., hematopoietic or endothelial progenitors) in the initial BMA and the final BMAC preparation, and from reporting on their enrichment. Automated analysis eliminates the large variation between observers using subjective manual methods[35,37]. At present, however, merely the consistent use of manual CFU assays to measure CTPs would advance the field.

BMAC, like many other biological agents, offers a promising approach for the treatment of musculoskeletal conditions[9,11-13,16,38-77]. To uncover its potential, however, it is essential to focus efforts on defining a system of communication that includes effective nomenclature, standardized methodology, and unambiguous quantitative and qualitative metrics for BMAC characterization. Without standardization, assessments of BMAC treatments risk being prematurely dismissed as being inconsistent or ineffective, simply as a result of poor measurement and reporting, because effective and ineffective preparations have been inappropriately clustered together under the single umbrella term of "BMAC."

This systematic review is not without limitations. We did not attempt to correlate the limited data on BMAC composition with clinical reports of outcomes in these studies. Such an assessment is currently precluded by the small data set and the wide variation in clinical indications, outcome measures, and follow-up periods among these studies. Moreover, given the existing variation in methodology and the lack of correlation with clinical outcome, we are unable to suggest a standardized protocol or nomenclature for BMAC preparations for the treatment of musculoskeletal disorders. As with all systematic reviews, there is a chance that some eligible studies have been disregarded; however, we took several steps to minimize the potential for sampling bias.

In conclusion, the composition of BMAC is highly variable. The reporting of BMAC preparation protocols in clinical studies is incomplete and inconsistent. Studies did not provide sufficient information to allow the protocol to be reproduced. Comparisons among BMAC products with respect to processing efficiency and clinical efficacy are currently precluded by the absence of standardized reporting. Future studies should contain standardized and stepwise descriptions of the BMAC preparation protocol and the composition of BMAC delivered, to permit validating and rationally optimizing the role of BMAC in musculoskeletal care. ■

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