Current Reviews in Musculoskeletal Medicine
https://doi.org/10.1007/s12178-019-09583-1

STEM CELLS IN ORTHOPAEDIC SURGERY (J DRAGOO AND K JONES, SECTION EDITORS)

Bone Marrow Mesenchymal Stem Cell Therapy and Related Bone Marrow-Derived Orthobiologic Therapeutics

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Abstract

Purpose of Review The purpose of the current article is to review the available literature related to bone marrow-derived mesenchymal stem cell therapy in the management of musculoskeletal pathologies and demonstrate the critical need for additional well-designed clinical studies.

Recent Findings In recent years, there has been a rapid increase in interest regarding the use of bone marrow-derived mesenchymal stem cells in the treatment of musculoskeletal injury and disease. The clinical use of BM-MSCs and other forms of stem cell therapy has far outpaced the basic and translational science evidence required to elucidate the potential efficacy of this orthobiologic treatment approach. Early studies have demonstrated potential clinical benefit of utilizing bone marrow-derived mesenchymal stem cell therapy in the management of knee osteoarthritis, focal chondral lesions, shoulder pathology including rotator cuff tears and glenohumeral arthritis, and degenerative disk disease in the spine. To date, most published studies are small case series often lacking a control group or a standardized method of treatment.

Summary Bone marrow-derived mesenchymal stem cell therapy is becoming an increasingly common treatment for musculoskeletal injuries and disease. Although early clinical studies have shown promising outcomes, methodological flaws and lack of standardization among trials have limited the conclusions that can be drawn from the existing literature. A better understanding of the underlying mechanism of action and more carefully designed clinical trials will help reveal the efficacy and utility of BM-MSCs as a treatment modality for various orthopedic pathologies.

Keywords Stem cell · Mesenchymal stem cell · Orthobiologics · Regenerative medicine

Introduction

In the late 1980s, Arnold Caplan and colleagues published their work on the isolation of mesenchymal stem cells (MSCs) from bone marrow and the ability of MSCs to differentiate into bone and cartilage in specific in vitro conditions [1]. Since the discovery of MSCs, there has been a rapid expansion of clinical studies investigating the potential therapeutic applications of stem cell therapy and regenerative medicine. Due in part to early in vitro studies demonstrating that bone marrow-derived MSCs (BM-MSCs) can be purified, culture-expanded, and induced to differentiate into mesodermal tissue types, there has been a particular interest in the potential clinical applications for musculoskeletal injury and disease [2–4].

However, the clinical use of BM-MSCs and other forms of stem cell therapy has far outpaced the basic and translational science required to elucidate the potential efficacy. A variety of bone marrow-derived cell and tissue preparations are

This article is part of the Topical Collection on *Stem Cells in Orthopaedic Surgery*

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Published online: 20 November 2019

frequently administered to patients with unsubstantiated claims of beneficial outcomes and curative potential [5]. As a result, the Federal Trade Commission has begun to take action against stem cell therapy clinics found to be in violation of Truth in Advertising laws [6].

Regardless of the unethical practices of clinics seizing upon the excitement of regenerative medicine, early clinical studies have shown promising results for BM-MSCs when used for osteoarthritis and focal chondral defects [7•, 8, 9•]. Yet our understanding of these cell and tissue preparations is still in its infancy. Due partly to methodological flaws in the existing literature, it is difficult to make any definitive statements regarding the efficacy of BM-MSCs for the treatment of orthopedic pathologies. The purpose of the current article, therefore, is to review the available literature related to bone marrow-derived mesenchymal stem cell therapy and demonstrate the need for additional well-designed clinical studies.

Nomenclature Inconsistencies

In 2006, the International Society for Cellular Therapy (ISCT) defined specific criteria that must be met in order for cells to be considered MSCs. The cells must be plastic-adherent in standard culture conditions, must display specific surface antigens, and must demonstrate in vitro differentiation into osteoblasts, adipocytes, and chondroblasts [10]. Yet the meaning of the term "MSC" has undergone several changes since this class of cells was originally described. As our understanding of the properties of these cells has evolved, "MSC" has been defined as mesenchymal stem cell, mesodermal stem cell, and mesenchymal stromal cell often simultaneously by different groups that disagree on the most accurate name for the cell type [11•].

Initially, based on the ability to undergo in vitro osteogenesis and chondrogenesis [12], MSCs were thought to maintain their multipotency once injected into an injured joint. The term mesenchymal stem cell was therefore used to describe the hypothesized ability to differentiate and regenerate injured cartilage or soft tissue. However, later evidence demonstrated that MSCs are derived from pericytes, or perivascular cells surrounding capillary endothelium [13, 14]. Studies have suggested that injected MSCs do not undergo differentiation in vivo and the primary functionality is not as a stem cell [15•, 16].

Although MSCs are no longer thought to exhibit stem-like properties in vivo, these cells have been shown to influence the hematopoietic microenvironment, organize vascular networks, induce endogenous stem cell activity, and secrete bioactive factors that promote tissue healing [17–23]. The perivascular source and immunomodulatory effects make both "stem cell" and "stromal cell" inaccurate descriptions of MSCs. As a result, Dr. Caplan and colleagues have suggested that the meaning of MSC be changed from "mesenchymal stem cell" to "medicinal signaling cell" to emphasize their role as trophic mediators [11•].

Regardless of the nomenclature, the plastic-adherent, passaged cells demonstrating in vitro multipotency that were described by Caplan in the 1980s and termed "MSCs" are identified by the specific criteria defined by the ISCT [10]. When used in clinical practice, BM-MSCs are obtained by first performing a bone marrow aspiration. The bone marrow undergoes density gradient centrifugation and a heterogenous group of mononuclear cells are isolated. The mononuclear cell fraction, known as concentrated bone marrow aspirate (cBMA), is plated and the plastic-adherent populations are separated from the non-adherent populations. Immunophenotyping and staining should be performed to confirm the MSC identity. Yet the existing MSC literature contains a range of tissue processing and cell expansion techniques, and many investigators fail to meet the ISCT criteria for MSCs [24•]. This review discusses the relevant reports of bone marrow-derived, culture-expanded cells involving an effort to isolate MSCs, even if all three ISCT criteria were not explicitly satisfied.

Regulatory Considerations for Orthobiologics

The use of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), including both autologous and allogeneic bone marrow-derived tissue preparations, is regulated by the FDA's Public Health Service (PHS) Act. The PHS Act describes two broad categories of tissue preparations intended to be injected or infused into a human recipient. Section 361 of the PHS Act applies to HCT/Ps that are minimally manipulated and intended for homologous use [25]. As described by the FDA, the processing procedure for minimally manipulated cells or tissues must not "alter the original relevant characteristics relating to the tissue's utility for reconstruction, repair, and replacement" and must not "alter relevant biological characteristics of cells or tissue" [25]. Homologous use involves "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor" [25]. Additionally, Section 361 requires that the cells are not combined with any other tissue or product except for "water, crystalloids, or a sterilizing, preserving, or storage agent" [25]. Cell and tissue preparations that meet the criteria described in Section 361 can be administered to patients without obtaining premarket clearance from the FDA.

HCT/Ps that are more than minimally manipulated, are intended for non-homologous use, or are combined with another tissue-based product are regulated under Section 351 of the PHS Act. According to the FDA, homologous use for bone marrow-derived cells involves "forming and replenishing the lymphohematopoietic system." Furthermore, culture expansion of MSCs is described as more than minimal manipulation.

Allogeneic HCT/Ps, except those administered to a first- or second-degree relative of the donor, are necessarily outside the scope of PHS Act Section 361. Therefore, the majority of BM-MSC preparations that have been used in clinical trials fail to meet the criteria for Section 361 products and are regulated under Section 351. In order for Section 351 products to be marketed and administered to patients, the product must complete a Biologic License Application to demonstrate the safety and efficacy of the product to the FDA.

BM-MSCs for Osteoarthritis (Table 1)

In an early case report of a single patient with osteoarthritis from 2008, Centeno et al. harvested autologous iliac crest BM-MSCs, culture-expanded the cells, and injected 22.4 × 10^6 cells into the intra-articular space. At the 3-month follow-up, the patient reported decreased pain and MRI analysis demonstrated an increase in both meniscus and cartilage volume [26]. However, as the cartilage was not later biopsied, it is uncertain whether the increase in cartilage volume is due to fibrocartilage formation or true hyaline cartilage.

Davatchi et al. published a case series of 4 patients with moderate to severe OA who were treated with a mean of 8–9 × 10^6 autologous, culture-expanded MSCs injected into the knee [27]. The authors reported meaningful improvement in pain at 6-month follow-up, with marginal improvement in time to onset of pain with walking and stairs. They did not note significant changes on physical exam or on radiographs [27]. Subsequently, Davatchi et al. published a 5-year follow-up study on 3 of the 4 patients and demonstrated an improvement in pain compared with baseline and 6 months with no difference in physical or radiographic outcomes [28].

Emadedin et al. presented a series of 6 female patients with radiographic evidence of knee OA treated with 20–24 × 10^6 autologous culture-expanded iliac crest BM-MSCs [29]. They observed a significant improvement in pain, functional outcomes, and maximum walking distance over the first 12 months with peak improvement at 6 months and marginal to minimal improvement in physical exam findings such as patellar crepitus and knee range of motion. Additionally, there was an increase in cartilage thickness with simultaneous decrease in subchondral edema on post-treatment MRI. In the follow-up study in 2015, Emadedin et al. expanded their treatment to the ankle and hip OA and presented data on 17 patients (6 ankle, 6 knee, 5 hip). Patients were treated with varying amounts of MSCs based on location (ankle 57 ± 47 × 10^6, hip 24 ± 4 × 10^6, knee 55 ± 8 × 10^6) [30]. The authors noted significant improvement in walking distance, total WOMAC score, and WOMAC subscores throughout the 30-month follow-up period.

A pilot study by Orozco et al. presented 12 patients with chronic knee pain and radiographic evidence of OA who were treated with 40 ± 1 × 10^6 autologous BM-MSCs. They showed a statistically significant, meaningful improvement in pain score for 12 months after injection [31]. Additionally, they observed improvement in the mean poor cartilage index (from 19.5 to 15.4%) as measured by T2 MRI mapping over the same time period after initial treatment, indicating cartilage healing potential. In the subsequent 24-month follow-up study of the same cohort, Orozco et al. reported that the pain score stabilized at their 12-month level while the radiographic improvement as measured by poor cartilage index on T2 MRI mapping continued [32].

The same group subsequently published a randomized controlled trial of 30 patients comparing allogeneic BM-MSCs with intra-articular hyaluronic acid [33]. Patients were either injected with 40 × 10^6 allogeneic BM-MSCs or an equal volume of hyaluronic acid. They observed significant improvement in pain and function over the 12-month follow-up period which was also significantly better than the active control treated with hyaluronic acid. Radiographically, there was a significant improvement in the mean poor cartilage index among the allogeneic MSC-treated group.

BM-MSCs for Focal Cartilage Defects (Table 1)

In an early study of BM-MSCs used to treat focal cartilage defects, Wakitani et al. transplanted autologous culture-expanded BM-MSCs (1.3 × 10^7 cells per patient on average) in collagen gel into the articular cartilage defects of patients undergoing high tibial osteotomies [34]. Compared with the control group who received cell-free collagen gel, there was no difference in patient-reported clinical outcomes, although arthroscopic and histologic analysis revealed neocartilage formation and improved grading in the experimental group. In a smaller follow-up study looking at articular cartilage defects in the patellofemoral joint, Wakitani et al. implanted autologous, culture-expanded BM-MSCs under either periosteal or synovial scaffolds in 3 patients and showed IKDC score improvement in all patients with second look arthroscopy and MRI showing evidence of neocartilage formation [35].

Nejadnik et al. compared a non-randomized cohort of 72 patients with full thickness cartilage defects implanted with either autologous chondrocytes or autologous BM-MSCs (9.2 × 10^6 cells per knee on average) and observed improved outcomes in both groups with no significant differences between the two cohorts with respect to functional outcomes [36]. Similarly, Haleem et al. in a smaller case series used platelet-rich fibrin glue to deliver autologous BM-MSCs (mean 15 × 10^6 cells per knee) covered with a periosteal flap to treat full thickness cartilage defects in the femoral condyles [37]. They observed significant improvement in Lysholm and revised Hospital for Special Surgery knee score with 3 of the 5 patients showing radiographic improvement, including

Table 1 BM-MSC and cBMA studies targeting orthopedic pathologies. International Society for Cellular Therapy minimum criteria for MSCs: adherence to plastic in standard culture conditions, specific surface antigen expression (≥ 95% positive for CD105, CD73, CD90; ≤ 2% positive for CD45, CD34, CD14 or CD11b, CD79α or CD19, HLA-DR), and in vitro differentiation to osteoblasts, adipocytes, and chondroblasts demonstrated by staining of in vitro cell culture

Study	N	Indication	MSCs	Co-injected/implanted materials	No. of MSCs injected	Control group	Met ISCT criteria
Centeno 2008	1	Osteoarthritis	Yes	Nucleated cells, platelet lysate, PBS	22.4×10^6	No control group	No
Davatchi 2011	4	Osteoarthritis	Yes	Trypsin suspension	$8–9 \times 10^6$	No control group	No
Davatchi 2016	3	Osteoarthritis	Yes	Trypsin suspension	$8–9 \times 10^6$	No control group	No
Emadedin 2012	6	Osteoarthritis	Yes	Physiological serum (Gibco, Germany)	$20–24 \times 10^6$	No control group	No
Emadedin 2015	17	Osteoarthritis	Yes	Normal saline	Ankle $57 \pm 47 \times 10^6$ Knee $55 \pm 8 \times 10^6$ Hip $24 \pm 4 \times 10^6$	No control group	No
Orozco 2013	12	Osteoarthritis	Yes	Ringer-lactate	40×10^6	No control group	No
Orozco 2014	12	Osteoarthritis	Yes	Ringer-lactate	40×10^6	No control group	No
Vega 2015	30	Osteoarthritis	Yes	Ringer-lactate	40×10^6	Control group received intra-articular hyaluronic acid	No
Wakitani 2002	24	Focal cartilage defect	Yes	Collagen gel	13×10^6	Cell-free control group received spongialization, collagen gel-sheet implantations, periosteal cover	No
Wakitani 2007	3	Focal cartilage defect	Yes	Soluble bovine collagen, porcine collagen, gel	-	No control group	No
Nejadnik 2010	72	Focal cartilage defect	Yes	Ascorbic acid	9.2×10^6	Control group received cartilage repair with autologous chondrocytes	No
Haleem 2010	5	Focal cartilage defect	Yes	PBS, platelet-rich fibrin glue	15×10^6	No control group	No
Wong 2013	56	Focal cartilage defect	Yes	Autologous serum, hyaluronic acid	14.6×10^6	Control group received hyaluronic acid injections	No
Gessmann 2012	8	Bony defect	No	Autologous thrombin	-	No control group	-
Petri 2013	5	Bony defect	No	Bovine xenogenous scaffold	-	Control group received revascularized fibular transplants	-
Pascual-Garrido 2012	8	Patellar tendinopathy	No	Balanced solution	-	No control group	-
Centeno 2015	10	ACL tear	No	PRP, platelet lysate	-	No control group	-
Stein 2015	28	Achilles tear	No	-	-	No control group	-
Gangji 2011	24	Osteonecrosis of femoral head	No	-	-	Control group received core decompression without cBMA injection	-
Tabatabaee 2015	28	Osteonecrosis of femoral head	No	-	-	Control group received core decompression without cBMA injection	-
Pepke 2016	24	Osteonecrosis of femoral head	No	-	-	Control group received core decompression without cBMA injection	-
Singh 2014	30	Lateral Epicondylitis	No	Lignocaine solution	-	No control group	-
Centeno 2015	115		No	PRP, platelet lysate	-	No control group	-

Table 1 (continued)

Study	N	Indication	MSCs	Co-injected/implanted materials	No. of MSCs injected	Control group	Met ISCT criteria
		Shoulder rotator cuff tear or shoulder osteoarthritis					
Hernigou 2014	45	Shoulder rotator cuff tear	No	-	-	Matched control group underwent rotator cuff repair without cBMA injection	-
Giannini 2009	48	Talar osteochondral lesion	No	Platelet-poor plasma, collagen powder or hyaluronic acid, platelet gel	-	No control group	-
Buda 2013	48	Talar osteochondral lesion	No	Platelet-poor plasma, collagen powder or hyaluronic acid, platelet gel	-	No control group	-
Pettine 2015	26	Degenerative disk disease	No	-	-	No control group	-
Pettine 2016	26	Degenerative disk disease	No	-	-	No control group	-
Hart 2014	40	Spondylodesis bone grafting	No	Spongious bone chips	-	Control group received posterolateral fusion with spongious allograft chips alone	-

complete defect fill and restoration of femoral condyle congruity at 12 months of follow-up.

In a randomized control trial of patients with cartilage defects undergoing high tibial osteotomy for medial compartment varus OA, Wong et al. randomized patients to receive either intra-articular injection of autologous cultured BM-MSCs with hyaluronic acid (mean 14.6×10^6 cells) or intra-articular injection of hyaluronic acid alone 3 weeks after the procedure [38]. There was improvement in patient-reported outcome measures in both arms of the study with the experimental group demonstrating superior functional outcomes.

cBMA Is Not Equivalent to BM-MSC Therapy (Table 1)

While BM-MSC therapy requires a BLA as mandated by the FDA, cBMA can be used as a therapeutic intervention without undergoing a lengthy regulatory process. As such, there has been a surge in the number of providers offering cBMA injections. Because cBMA does not involve isolation of specific phenotypic markers and expansion of the desired cell types, it contains a heterogenous mixture of bone marrow cells including hematopoietic cells. In both direct-to-consumer advertising and the existing literature, cBMA is often falsely equated to MSC therapy. Studies often report utilizing cBMA as a source of MSCs [39–41], despite evidence that only 0.01 to 0.001% of the cells contained in cBMA are MSCs [3]. Although cBMA is not equivalent to BM-MSC therapy, it may still provide therapeutic benefits for orthopedic pathologies.

Gessmann et al. performed a feasibility study with 8 patients undergoing distraction osteogenesis in which they harvested autologous BM aspirate, centrifuged the aspirate to produce a BM concentrate, and injected it in combination with thrombin into the site of regeneration [42]. The study reported its mean healing rate as being "short in comparison with the [previously] named studies concerning post-traumatic bone defects" that did not utilize BM augmentation. However, given the small sample size and lack of a control group, this comparison should be cautiously considered. A similar methodology was used by Petri et al., who then seeded their BM concentrates onto bovine xenogenous scaffolds for 5 patients with long bone defects ranging from 3 to 14 cm [43]. When compared with a group of 11 patients who received revascularized fibular transplants for similar indications, the group treated with cBMA had higher rates of fluoride influx on PET scan (indicating a higher perfusion rate), were able to bear weight without pain within an average of 11.3 weeks after surgery, and achieved a bone density of 75% of that of the contralateral healthy bone within the study period.

Pascual-Garrido et al. reported on 8 patients with clinical and radiological evidence of chronic patellar tendinopathy refractory to conservative management [44]. BM-derived mononuclear cells were harvested, concentrated by centrifuge,

and injected into patellar tendon lesions (mean 30×10^3 cells per injection). Using long-term follow-up consisting of periodic standardized clinical outcomes surveys, the study showed statistically significant improvement in the majority of its reported scores.

Similarly, Centeno et al. studied cell-based therapeutics for ACL tears. The authors presented a 10 patient series involving injection of a cocktail of BM-derived cells from the iliac crest concentrated via centrifuge, platelet lysate, and platelet-rich plasma (PRP) into ACL tears ranging from grades 1 to 3 [45]. Using standardized questionnaires and MRI analysis, the authors demonstrated significant improvements in ligament integrity over time. However, this study's findings are significantly limited given the lack of a control group and the current understanding that patients with partial ACL tears may achieve similar outcomes with conservative management.

Use of cBMA for tendon injuries is also being studied as an augment to surgical treatment. Stein et al. presented a retrospective study on the effects of cBMA on primary Achilles tendon repairs [39]. While the study lacked a control group, it cited randomized control trials from literature as a historical control. At a mean follow-up of 30 months, there were no re-ruptures and Achilles tendon Total Rupture Scores (ATRS) were higher in the MSC-treated group compared with the historical control.

Gangji et al., Tabatabaee et al., and Pepke et al. each performed prospective randomized clinical trials ($N = 24$–28 hips per study) comparing surgical decompression alone versus decompression augmented by autologous cBMA injections for femoral head osteonecrosis [46–48]. These studies utilized similar methodologies in which BM aspirate from patients' iliac crests was harvested, concentrated by centrifuge, and implanted at the site of decompression. Cumulatively, patients who received these injections showed significant improvement in pain scores, improved radiologic findings (i.e., lower progression of disease based on Association Research Circulation Osseous staging), and improved standardized outcome scores.

In search of effective conservative therapies to treat symptomatic lateral epicondylitis, Singh et al. presented a series of 30 patients with clinically diagnosed tennis elbow who were treated with cBMA injected at the patient's point of maximal tenderness [40]. Using the Patient-rated Tennis Elbow Evaluation score, significant improvement was seen when comparing pre-injections scores with post-injections scores, suggesting viability of this intervention. However, limited conclusions can be drawn from this study given its lack of a control group.

Cell-based therapies are currently being investigated as an alternative to surgery for shoulder pathology including rotator cuff tears and glenohumeral osteoarthritis. Centeno et al. presented a series of 115 shoulders diagnosed with either of these diagnoses that were treated with injections of cBMA combined with autologous platelet lysate and PRP [41]. Although the study lacked a control group, pre-injection and post-injection pain and functional outcomes were compared and showed significant improvement in both. Hernigou et al. presented a study that investigated the benefits of injecting cBMA intra-operatively during shoulder arthroscopy for rotator cuff tears [8]. Compared with a matched control group of 45 patients, cBMA-treated patients healed significantly faster and had a significantly lower rate of re-tear at 10 years of follow-up.

Talar osteochondral lesions are often painful and non-responsive to non-surgical management. Implantation of autologous chondrocytes has been shown to be efficacious, but requires two surgical procedures. In an effort to minimize surgical risk and cost, Giannini et al. devised a one-step procedure that involved intra-operative harvesting of iliac crest BM aspirate, concentrating the aspirate via centrifuge, and implanting it with a collagen matrix at the site of the defect in conjunction with various growth factors via ankle arthroscopy [49]. At mean evaluation time of 29 months, patients showed significant clinical improvement based on the American Orthopaedic Foot and Ankle Society score, while MRI and histologic evaluation suggested the presence of regenerated tissue at the site of implantation. The authors of this study went on to publish mid-term results at a mean follow-up of 53 months, which were consistent with their initial findings [50].

Degenerative disk disease (DDD) is associated with significant morbidity that is often not amenable to conservative therapies. Pettine et al. studied the use of intra-discal injections of cBMA for DDD [51]. The authors injected 26 symptomatic patients and evaluated their post-injection outcomes using disability scores, pain scores, and MRIs. At 1-year follow-up, patients experienced significant improvements in disability and pain scores, and also showed a significant dose-dependent response with patients receiving greater amounts of cells experiencing a faster and greater reduction in pain scores. These findings were later strengthened with a follow-up study at 24 months, which showed similar outcomes [52]. In the operative setting, Hart et al. performed a blinded, prospective, randomized clinical trial to assess whether adding cBMA to bone allografts during spondylodesis increases fusion rate [53]. In the 80 patient study, 40 patients were given cBMA intra-operatively and assessed post-operatively using spinal X-rays and CT scans. When compared with the control group, patients whose procedure included BM-MSCs achieved significantly faster fusion rates at 1- and 2-year follow-up.

Methodological Concerns

Many of the studies evaluating the efficacy of BM-MSC treatment for musculoskeletal pathologies demonstrated statistically significant within-group improvements from baseline pain levels and functional status. While this is encouraging, studies

consisting of multiple groups that directly compared BM-MSC with other forms of therapy have demonstrated mixed results. As highlighted by Jones et al., studies that found no significant differences in outcome measures between the stem cell therapy group and the comparator group often emphasized within-group differences or between-group subscore differences [24]. This may be misleading to readers as it is possible to misinterpret the highlighted differences as more clinically important than the true effect.

Existing studies involving bone marrow-derived cell therapies consist of a heterogenous collection of various cell processing techniques, protocols for culture expansion, number of injected cells, concomitant surgical procedures, and combined orthobiologic therapies. While some studies fail to specify the number of cells administered, the studies that did report doses utilized a wide range of number of cells administered. A recent review of bone marrow aspirate concentrate as a treatment for orthopedic pathologies concluded that the heterogeneity of the cell preparation protocols and the inconsistency of adequate protocol reporting were too great to draw conclusions regarding efficacy [54].

Consensus recommendations from the 2018 American Academy of Orthopaedic Surgeons and National Institutes of Health U-13 Conference emphasized the importance of improved standards for studies evaluating stem cell therapies [55]. Among the recommendations for future studies are a focus on strong study design and standardized reporting of cell processing techniques. The true efficacy of BM-MSCs and other orthobiologic therapies will only be understood when these recommendations are incorporated into future clinical trials.

Conclusion

Bone marrow-derived mesenchymal stem cell therapy is becoming an increasingly common treatment for musculoskeletal injuries and disease. Although early clinical studies have shown promising outcomes, methodological flaws and lack of standardization among trials have limited the conclusions that can be drawn from the existing literature. A better understanding of the underlying mechanism of action and more carefully designed clinical trials will help reveal the efficacy and utility of BM-MSCs as a treatment modality for various orthopedic pathologies.

Acknowledgments The authors would like to thank Joanne Halbrecht, MD for providing her expertise on mesenchymal stem cell therapies.

Compliance with Ethical Standards

Conflict of Interest Matthew Kingery, Amit Manjunath, and Utkarsh Anil declare that they have no conflicts of interest. Eric Strauss serves as a paid consultant to Arthrex and Organogenesis.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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stem cells could lead to an improvement in pain management and quality of life in patients with knee OA. They found their hypothesis supported by 6-month follow-up data, in which the experimental arm reported significant improvement in knee pain and quality of life.

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11.• Caplan AI. Mesenchymal stem cells: time to change the name! Stem Cells Transl Med. 2017;6(6):1445–51. https://doi.org/10.1002/sctm.17-0051 **The author, a researcher at Case Western Reserve University, reviewed the transformation of the term "mesenchymal stem cell" from its discovery to current day. He acknowledged that the initial definition of the phrase referred to bone marrow and periosteum that could be isolated and expanded in culture while maintaining their in vitro capacity to be induced to form a variety of mesodermal phenotypes and tissues; however, he then argued that the definition has been contorted in modern day literature to infer clinically beneficial properties despite lacking a strong scientific backing. This was validated by several studies, cited below, that interchange terms including (but not limited to) "stem cells," "bone marrow aspirate concentrate," and "bone marrow cells"**.
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