Topical Review

AO FAS AMERICAN ORTHOPAEDIC FOOT & ANKLE SOCIETY®

Topical Review: Bone Marrow Aspirate Concentrate and Its Clinical Use in Foot and Ankle Surgery

Foot & Ankle International®
2021, Vol. 42(9) 1205–1211

DOI: 10.1177/10711007211021017
journals.sagepub.com/home/fai

Rachel Glenn, MD[1], William Johns, MD[2], Kempland Walley, MD[3], J. Benjamin Jackson III, MD, MBA[1], and Tyler Gonzalez, MD, MBA[1]

Abstract

Bone marrow aspirate concentrate (BMAC) is now commonly used in orthopedic surgery. Animal studies showed promising results for cartilage, bone, and soft tissue healing; however, many of these outcomes have yet to be translated to human models. While there has been an increase in the use of BMAC in foot and ankle procedures, the associated clinical evidence is limited. The purpose of this review is to analyze the existing literature in order to evaluate the safety and efficacy of BMAC in foot and ankle surgery.

Keywords: BMA, BMAC, foot and ankle, bone marrow aspirate, regenerative medicine, cartilage, bone, tendon, bone marrow aspirate concentrate

Biologics are becoming increasingly popular in foot and ankle surgery, with one of the most popular being bone marrow aspirate concentrate (BMAC).[4,11,25,53] Bone marrow is the primary site for storage of mesenchymal stem cells (MSCs). MSCs are multipotent cells that have the ability to differentiate into various cell types based on environmental factors, allowing the cells to aid in soft tissue and bone healing.[32,33,63] Their use in bone and soft tissue healing has shown positive results, and it is one of the few ways of intraoperatively delivering concentrated stem cells that is approved by the US Food and Drug Administration.*

Despite these encouraging findings, there is limited knowledge, conclusive evidence, and succinct organization of the results of BMAC use in foot and ankle procedures. Therefore, the purpose of this review is to critically evaluate the safety and efficacy of BMAC in foot and ankle surgery.

Methods

Search Strategy

MEDLINE, EMBASE, Google Scholar, and the Cochrane Library were searched in October 2020 without restrictions. The search strategy was developed with the assistance of a medical librarian and included the following key terms: "bone marrow aspirate," "bone marrow aspirate concentrate," "foot and ankle," and "foot and ankle surgery" combined using Boolean operators "AND" or "OR." The bibliographies of all relevant publications identified through this search strategy were searched for additional studies pertaining to BMAC use in foot and ankle surgeries.

Inclusion and/or Exclusion Criteria

The inclusion criteria were studies that report clinical outcomes following use of BMAC in any foot and ankle surgeries. The exclusion criteria were those studies that were

*References 1, 2, 8, 10, 11, 12, 18, 19, 22-24, 31, 32, 37, 39, 44, 47, 49, 58, 59.

[1]Department of Orthopaedic Surgery, Prisma Health Richland Hospital/University of South Carolina, Columbia, SC, USA
[2]Department of Orthopaedic Surgery, Rothman Orthopaedic Institute at Jefferson Health, Philadelphia, PA, USA
[3]Department of Orthopaedic Surgery, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA

Corresponding Author:
Rachel Glenn, MD, Department of Orthopaedic Surgery, Prisma Health Richland Hospital/University of South Carolina, 2 Medical Park Road, Suite 404 Columbia, SC 29203-6863, USA.
Email: rachel.glenn@prismahealth.org

not written in the English language and those that did not assess outcomes following the use of bone marrow aspirate concentration use.

Mechanism of Action

Several human tissues contain MSCs, including bone, adipose, synovium, and blood.[16,51] Bone marrow aspiration is one way to isolate MSCs for targeted delivery to a specific area during surgery. A higher concentration of MSCs may theoretically be more clinically potent and effective when using BMAC.[9] A study by Sakai et al[54] used a simple centrifuge method and evaluated the BMAC after its use. The concentrations of the colony-forming units, which represented the amount of progenitor cells, were approximately 5 times higher than in aspirate prior to concentration. In addition, the nucleated cells were 7 times higher than they were preconcentration. Similarly, Kim et al[38] reported that after centrifugation, the harvested cells may be concentrated up to 7 times the original amount. This concentration increases the content of growth factors ultimately secreted by the MSCs.[38]

BMAC allows the transfer of a high concentration of both live cells and growth factors. Cellular elements include MSCs and hematopoietic stem cells (HSCs). Potentially transferred growth factors include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), bone morphogenic proteins (BMPs), interleukin 8, and interleukin 1 (IL-1) receptor antagonist.[2,10,15,18,19] When MSCs are in the appropriate environment in the presence of growth factors and induction proteins, either in the BMAC or at the site of injection, they have the ability to differentiate into osteogenic cells such as osteoblasts.[6,24,43]

MSCs also assist in regulating tissue regeneration by secreting cytokines and growth factors, as well as recruiting other cells and growth factors by paracrine signaling.[5,24] This can be an adjuvant to osteoinductive and/or osteoconductive biologics that need additional cells for complete function and clinically aids with healing fusion sites, fractures, and devascularized areas.[14,16,36,46,48,50,51] Furthermore, the recruitment of cells that produce TGF-β and BMPs may help with integration of the graft and host interface.[6,43] In addition, studies have shown that BMAC decreases the amount of fibrocartilage growth and promotes the growth of hyaline cartilage.[16,18,33,40]

Harvesting BMAC

As the clinical applications of BMAC have grown, the location, quality, and quantity of the aspirate have been studied. McLain et al[46] showed that the quantity of osteogenic progenitor cells decreases from the axial to appendicular skeleton, as well as proximal to distal in the appendicular skeleton, with the vertebral bodies having the highest quantity of osteoblastic progenitor cells. In foot and ankle surgery, the most frequently accessed harvest sites are the iliac crest, tibia, and calcaneus.

The concentration of progenitor cells has been found to vary by harvest location. In a study by Hyer et al,[35] there was a higher concentration of progenitor cells in the iliac crest than either the calcaneus or the distal tibia. There was no difference between the concentrations in the distal tibia or calcaneus. In a study by Marx and Tursun,[42] aspirate from the anterior and posterior iliac crest yielded the same quantity of multipotent stem cells, and this was twice as much as from the proximal tibia. Similarly, Chiodo et al[7] demonstrated that the iliac crest contained active hemopoietic cells while the proximal tibia primarily contained quiescent medullary fat.

When planning BMAC in foot and ankle surgery, the distal tibia and calcaneus may be considered more convenient harvest sites because they can easily be included in the sterile field. Although the concentration of cells is less than the iliac crest, there are still viable MSCs in these aspirates.[35] The progenitor cells and hematopoietic MSCs from calcaneal BMAC are similar to distal tibia with the same ability to undergo osteogenic differentiation and self-renew.[35,41] Li et al[41] recently published on 10 patients who had calcaneal BMAC aspirated. The aspirated cells were viable MSCs that were able to differentiate into a variety of cell lineages. Based on this literature, there are several options to harvest BMAC; however, more research is needed to better understand the ideal location that can provide the most clinical value.

To procure a usable yield of aspirate, appropriate technique must be used. In 1 study by Hernigou et al,[29] 50-mL, 10-mL, and 5-mL syringes were used to aspirate the iliac crest. A higher concentration of MSCs was obtained with smaller syringes. When using the 10-mL syringe, the yield of progenitor cell concentrations increased 300% compared to matched controls using a 50-mL syringe. The authors attributed this to the smaller syringes having a smaller diameter, which creates greater negative pressure.

Following aspiration, the collection of bone marrow aspirate is concentrated to its maximum via centrifuge machines. Three commercially available machines were compared by Hegde et al,[26] specifically the Harvest SmartPReP 2 BMAC, Biomet BioCUE, and Arteriocyte Magellan systems. The authors studied 40 patients undergoing bilateral iliac crest aspirate. Samples were analyzed before and after the centrifuge system was used, estimating the number for progenitor cells in each sample by counting the connective tissue progenitor cells (CTPs). It was concluded that the Harvest system had a greater number and concentration of CTPs after the centrifugation process.

Safety of BMAC

Overall, the evidence shows that the harvest and utilization of BMAC are safe. The complications that are reported in the literature usually are unrelated to BMAC itself and related to the primary procedure instead.[13,23,32,37] Harvesting BMAC in the lower extremity has a reported complication rate that ranges from 0% to 12%.[56,57] Roukis et al[52] performed a large retrospective, multicenter review of 530 patients who underwent bone marrow aspiration from multiple locations in the lower extremity. All aspirations were successful, and there were no reports of nerve injury, wound-healing difficulties, infection, or iatrogenic fractures. However, donor site pain can be an issue for some patients. Daigre et al[13] evaluated visual analog scale (VAS) scores from 3 different sites, specifically the distal tibia, calcaneus, and iliac crest. The authors reported significantly higher pain scores in patients who underwent calcaneal harvesting compared to those who underwent iliac crest or distal tibia harvesting.

One theoretical concern with the utilization of pluripotent stem cells is the potential for the development of a neoplastic process at the site of injection. In a large study of 1873 patients with an average 12.5-year follow-up, only 53 patients were diagnosed with cancers, and all cancers were located away from the injection site.[30] This has been corroborated by additional studies that reported no evidence of local neoplasms in their patient groups.[21,22,23,37]

Animal Studies

Animal studies have shown promising evidence for the use of BMAC to improve soft tissue healing; increase bone volume, callus formation, and woven bone formation; and improve osteocyte number.[2,3,18,20,24,45,60,61,64]

Adams et al[2] examined Achilles tendon ruptures in 108 rats. They compared treatments with regular suture, suture plus stem cell concentrate injection, or stem cell–loaded suture. In each group, the tendon was loaded at a 223-N load cell at 0.17 mm/s. Compared to regular suture, there was a higher load to failure both with suture plus stem cell concentrate and stem cell–loaded suture. The authors therefore concluded that the addition of stem cells was associated with stronger tendon repairs. Similarly, Yao et al[64] looked at the treatment of MSC-coated suture in Achilles repair in 105 rats. They demonstrated that the MSC-coated sutured created a stronger repair than standard suture repair. Urdzikova et al[61] compared 40 rat models that were treated nonoperatively without injection and 41 rat models that were treated nonoperatively but underwent MSC injection. They found an increase in collagen organization and increased vascularization in the rat models that underwent MSC injection.

BMAC has also been shown to improve bone healing in animal models. Gianakos et al[20] reviewed the literature for animal models and long bone healing for segmental defects. All articles included in the analysis reported a significant increase in radiographic bone formation compared to controls. In over 90% of the articles included in the analysis, there was significantly earlier bone healing seen histologically. In 81% of the studies, there was increased bone measured by micro–computed topography. Some of the studies also reported higher torsional stiffness when BMAC was used.

With regard to osteochondral lesions, Fortier et al[18] examined the utilization of MSCs and microfracture compared to microfracture alone in equine models. They found that there was greater healing of full-thickness defects in those lesions treated with MSC augmentation compared to those treated with microfracture alone. For those treated with BMAC, there was better repair of the defect with improved integration of repair tissue, superior collagen orientation, and increases in glycosaminoglycan and type II collagen content.[18] Similarly, McIlwraith et al[45] investigated equine models with chondral defects treated by the injection of MSCs. The authors reported improved quality of the cartilage repair with increased aggrecan content and tissue firmness in those with MSCs.

Human Evidence in the Lower Extremity

Tibia Fracture Nonunions

Early human studies examined the use of BMAC in tibial fracture nonunions. Hernigou et al[31] used BMAC to augment repair of distal tibial atrophic nonunions. Sixty patients with atrophic nonunions underwent percutaneous injection of BMAC around the nonunion gap. Fifty-three patients healed while 7 nonunions persisted. In these 7 patients, it was found that the patients were injected with lower concentrations of BMAC than the other 53, containing fewer than 1000 progenitors per cm^3 and fewer than 30000 progenitor cells in total. The authors concluded that percutaneous BMAC is effective and safe for the treatment of an atrophic tibial diaphyseal nonunion and that the BMAC must be sufficiently concentrated.[31]

In another study, Hernigou et al[27] compared patients treated with single-stage debridement with iliac crest bone graft with or without the use of BMAC for the treatment of infected tibial nonunions. Over a 7-year follow up period, 95% of patients in the BMAC group compared to 70% of the control group went on to union without recurrence of infection.

Ankle Fracture Nonunions

In the setting of ankle fracture nonunions in patients with diabetes, Hernigou et al[28] compared matched diabetic

patients who underwent either open iliac crest bone grafting or injection of the nonunion with bone marrow aspiration from the iliac crest. In the BMAC group, 82% of patients healed their nonunion compared to only 62% of patients in the iliac crest group. In addition, the authors reported a higher complication rate (11%) at the donor site in the open iliac crest group compared to the percutaneous marrow aspiration rate (2%).

Fifth Metatarsal Fractures

The use of BMAC for the treatment of fifth metatarsal fractures has recently been investigated. O'Malley et al[49] retrospectively reviewed professional basketball players with Jones fractures. The authors retrospectively reviewed the records of 10 players. Seven underwent standard percutaneous screw fixation combined with BMAC, and another 3 underwent screw fixation with "prophylactic" open bone grafting augmented with BMAC. Radiographic healing was seen at an overall average of 7.5 weeks, and average return to play was 9.8 weeks. Based on computed tomography, the authors reported no nonunions. However, 3 athletes in the percutaneous group refractured. All had high metatarsus adductus angles. The authors opined that the addition of BMAC assisted in fracture healing; however, the impact of the addition of BMAC to the rate of refracture warrants further investigation.

Murawski and Kennedy[47] investigated 26 nonprofessional athletes with fifth metatarsal fractures treated with percutaneous screw fixation and BMAC. Of the 26 fractures, 17 were Jones fractures and 9 were more distal zone 3 fractures. At an average follow-up of 5 weeks, 24 cases healed without complications. Twenty-four patients returned to their previous level of activity. One patient had a delayed union, and 1 healed but refractured at a later date. Although this was a noncontrolled study, the authors concluded the addition of BMAC to screw fixation provides "more predictable results" with regard to healing and allowing athletes to return to their previous levels of activity with few complications.[47]

Hunt and Anderson[34] retrospectively reviewed 21 elite athletes who underwent revision surgery for a refractured or nonunion of a fifth metatarsal fracture. In the revision surgery, patients were treated using intramedullary screw fixation with autologous bone graft, bone marrow aspirate (not concentrate) combined with demineralized bone matrix, or no bone graft. All of the athletes returned to their prior level of sport at 12.3 months, with only 1 patient subsequently refracturing. The authors concluded that treatment for patients in need of revision surgery for nonunion or refracture should be performed with a large solid screw and cancellous autograft. However, given that almost all patients in this series did well, further investigation is necessary to examine the role of bone marrow aspirate and demineralized bone matrix in these fractures. Furthermore, it is important to note in this study that only 1 patient was treated without bone graft or aspirate, and this patient did well.

Tendon Injuries

In vitro, BMAC has been shown to assist in healing tendon injuries by controlling inflammation, reducing fibrosis, and recruiting other cells, including tenocytes and MSCs.[12] Vascular endothelial growth factor and other cells that aid in healing are also found in BMAC and therefore have been an area of interest for use in tendon injuries as most nontraumatic tendon injuries initially begin as asymptomatic dysvascular insult.[12] Stein et al[59] reviewed 27 patients who had an Achilles rupture and underwent open repair with the addition of BMAC. At an average follow-up of 29.7 months, there were no reruptures, and 92% of the patients had returned to their sport at 5.9 months. They concluded that the addition of BMAC in treatment of Achilles tendon tears is safe, but it should be further investigated prospectively with a control group.

Osteochondral Lesions of the Talus

BMAC has also been frequently used in the treatment of osteochondral lesions of the talus (OLTs). Hannon et al[23] looked at patients with OLTs and compared BMAC combined with bone marrow stimulation (BMS) to bone marrow stimulation alone. Both groups had significantly improved foot and ankle outcome score (FAOS) and 12-item short form survey physical component score (SF-12 PCS) postoperatively. Clinical outcomes between groups were similar. However, the BMAC/BMS group had a significantly improved magnetic resonance observation of cartilage repair tissue (MOCART) scores, indicating improved cartilage repair when assessed by advanced imaging. Specifically, magnetic resonance imaging (MRI) demonstrated improved border tissue integration and repair with less fissuring in those treated in the BMAC/BMS group.

Shimozono et al[58] compared autologous osteochondral transplantation (AOT) with and without BMAC. Initially, both groups had significant improvement in FAOS and SF-12 scores, and at final follow-up, there were no statistical differences between groups with regard to FAOS, MOCART, or SF-12 scores. On imaging, the group treated with AOT and BMAC did have a significantly lower rate of cyst formation, but there were no clinically significant difference between patients who did and did not form cysts.

In 2009, Giannini et al[22] performed a prospective study looking at 48 patients who were treated with BMAC for talar osteochondral lesions. They obtained 60 mL of aspirate from the posterior iliac crest, which was concentrated. Arthroscopy was then performed. The lesion was prepared by removing

the unstable cartilage and subchondral plate until healthy bone was reached. The BMAC composite was then placed on top of the lesion. At a minimum follow-up of 24 months, the mean American Orthopaedic Foot & Ankle Society (AOFAS) score improved from 64.4 to 91.4 points. In addition, histologic evaluation demonstrated new cartilaginous tissue formation in different stages of remodeling, similar to what would be seen after autologous chondrocyte implantation. Furthermore, 94% of patients returned to low-impact activity at a mean of 4.4 months, and 77% returned to high-impact activity at a mean of 11.3 months. Two patients underwent arthroscopy for continued pain, which demonstrated full-cartilage integrate but chondral hypertrophy.

As a follow-up study in 2013, Giannini et al[21] collected 4-year follow-up results. At 48 months on average, the overall AOFAS score improved significantly from 63.73 preoperatively to 82.19, and 73% of patients returned to sports. There was a peak time at 24-month follow-up where patients had the most improved AOFAS score. In addition, on examination of the lesions on T2 MRI, 78% of patients had regenerated tissue in the lesion area that was similar to hyaline cartilage. They concluded that there were good clinical results and regeneration of hyaline cartilage when using BMAC for treatment of OCL of talus.

With regard to advanced imaging, Hannon et al[23] and Giannini et al[22] both used MRI at a minimum 24 months postoperatively to evaluate cartilage healing. They both found that there was filling of the defect, integration of the borders, and repair of the surface tissue with decreased fissuring and fibrillation.

Kennedy et al[37] reviewed 72 patients with OCL of the talus who were treated with autologous osteochondral transplantation and BMAC. There was improvement of the mean FAOS scores in these patients from 52.67 to 86.19 pre- to postoperatively. The mean SF-12 scores also improved from 59.4 to 88.63 pre- to postoperatively. At an average of 23 weeks, 95% of patients had returned to their preinjury pain level.

Similarly, Clanton et al[8] reported short-term follow-up for 32 patients with 38 OCLs of the talus who underwent microfracture plus augmentation with cartilage extracellular matrix and BMAC. At a median follow-up time of 36.7 months, they showed improvements in all FAOS domains; 83% of patients returned to playing sports, and 9 patients required a second surgery. However, it is important to note that this was a case series, and there was no control/comparison group.

Osteoarthritis of the Ankle and Lower Extremity

The anti-inflammatory effect of BMAC has also been studied for its potential use in osteoarthritis.[5,17,55,62] The interleukin receptor antagonist proteins in BMAC may possibly decrease the catabolic effects of IL-1 and other inflammatory cytokines.[5,17] This may potentially result in decreased inflammation, assist in cartilage repair, and facilitate chondrogenesis.[55,62] Further clinic research is needed to determine if BMAC will play any future clinical role in the treatment of foot and ankle arthritis.

Conclusion

BMAC is used with increasing frequency in foot and ankle surgery. In addition to animal studies, there are now early clinical series that describe its use in various pathologies. Further high-level, prospective, and comparative investigations will be necessary to fully assess BMAC's clinical utility in foot and ankle surgery.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. ICMJE forms for all authors are available online.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Rachel Glenn, MD, https://orcid.org/0000-0003-4239-4688
William Johns, MD, https://orcid.org/0000-0001-9939-7447
Kempland Walley, MD, https://orcid.org/0000-0003-4488-0663
J. Benjamin Jackson III, MD, MBA, https://orcid.org/0000-0002-9444-087X
Tyler Gonzalez, MD, MBA, https://orcid.org/0000-0002-3210-8097

References

1. Adams SB Jr, Thorpe MA, Parks BG, et al. Stem cell-bearing suture improves Achilles tendon healing in a rat model. *Foot Ankle Int*. 2014;35(3):293-299.
2. Adams SB, Lewis JS Jr, Gupta AK, et al. Cannulated screw delivery of bone marrow aspirate concentrate to a stress fracture nonunion: technique tip. *Foot Ankle Int*. 2013;34(5):740-744.
3. Ai J, Ebrahimi S, Khoshzaban A, et al. Tissue engineering using human mineralized bone xenograft and bone marrow mesenchymal stem cells allograft in healing of tibial fracture of experimental rabbit model. *Iran Red Crescent Med J*. 2012;14:96-103.
4. Barnett MDJ, Pomeroy GC. Use of platelet-rich plasma and bone marrow-derived mesenchymal stem cells in foot and ankle surgery. *Tech Foot Ankle Surg*. 2007;6:89-94.
5. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. *J Cell Biochem*. 2006;98:1076-1084.
6. Cassano JM, Kennedy JG, Ross KA, Fraser EJ, Goodale MB, Fortier LA. Bone marrow concentrate and platelet-rich plasma differ in cell distribution and interleukin 1 receptor antagonist

protein concentration. *Knee Surg Sports Traumatol Arthrosc*. 2018;26:333-342.
7. Chiodo CP, Hahne J, Wilson MG, Glowacki J. Histological differences in iliac and tibial bone graft. *Foot Ankle Int*. 2010;31(5):418-422.
8. Clanton TO, Johnson NS, Matheny LM. Use of cartilage extracellular matrix and bone marrow aspirate concentrate in treatment of osteochondral lesions of the talus. *Tech Foot Ankle Surg*. 2014;13(4):212-220.
9. Connolly J, Guse R, Lippiello L, et al. Development of an osteogenic bone-marrow preparation. *J Bone Joint Surg Am*. 1989;71(5):684-691.
10. Connolly J, Guse R, Tiedeman J, et al. Autologous marrow injection as a substitute for operative grafting of tibial nonunions. *Clin Orthop Relat Res*. 1991;266:259-270.
11. Cottom JM, Plemmons BS. Bone marrow aspirate concentrate and its uses in the foot and ankle. *Clin Podiatr Med Surg*. 2018;35(1):19-26.
12. Courneya JP, Luzina IG, Zeller CB, et al. Interleukins 4 and 13 modulate gene expression and promote proliferation of primary human tenocytes. *Fibrogenesis Tissue Repair*. 2010;3:9.
13. Daigre JL, DeMill SL, Hyer CF. Assessment of bone marrow aspiration site pain in foot and ankle surgery. *Foot Ankle Spec*. 2016;9(3):215-217.
14. Dallari D, Savarino L, Stagni C, et al. Enhanced tibial osteotomy healing with use of bone grafts supplemented with platelet gel or platelet gel and bone marrow stromal cells. *J Bone Joint Surg Am*. 2007;89(11):2413-2420.
15. DiGiovanni CW, Lin SS, Baumhauer JF, et al. Recombinant human platelet derived growth factor-BB and beta-tricalcium phosphate (rhPDGF-BB/beta-TCP): an alternative to autogenous bone graft. *J Bone Joint Surg Am*. 2013;95(13):1184-1192.
16. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells: the International Society for Cellular Therapy position statement. *Cytotherapy*. 2006;8:315-317.
17. Fortier LA, Barker JU, Strauss EJ, McCarrel TM, Cole BJ. The role of growth factors in cartilage repair [review]. *Clin Orthop Relat Res*. 2011;469(10):2706-2715.
18. Fortier LA, Potter HG, Rickey EJ, et al. Concentrated bone marrow aspirate improves full-thickness cartilage repair compared with microfracture in the equine model. *J Bone Joint Surg Am*. 2010;92(10):1927-1937.
19. Gangji V, De Maertelaer V, Hauzeur JP. Autologous bone marrow cell implantation in the treatment of non-traumatic osteonecrosis of the femoral head: five year follow-up of a prospective controlled study. *Bone*. 2011;49(5):1005-1009.
20. Gianakos A, Ni A, Zambrana L, Kennedy JG, Lane JM. Bone marrow aspirate concentrate in animal long bone healing: an analysis of basic science evidence. *J Orthop Trauma*. 2016;30(1):1-9.
21. Giannini S, Buda R, Battaglia M, et al. One-step repair in talar osteochondral lesions: 4-year clinical results and t2-mapping capability in outcome prediction. *Am J Sports Med*. 2013;41(3):511-518.
22. Giannini S, Buda R, Vannini F, Cavallo M, Grigolo B. One-step bone marrow-derived cell transplantation in talar osteochondral lesions. *Clin Orthop Relat Res*. 2009;467(12):3307-3320.
23. Hannon CP, Ross KA, Murawski CD, et al. Arthroscopic bone marrow stimulation and concentrated bone marrow aspirate for osteochondral lesions of the talus: a case-control study of functional and magnetic resonance observation of cartilage repair tissue outcomes. *Arthroscopy*. 2016;32(2):339-347.
24. Harford JS, Dekker TJ, Adams SB. Bone marrow aspirate concentrate for bone healing in foot and ankle surgery. *Foot Ankle Clin*. 2016;21(4):839-845.
25. Hatzokos I, Stavridis SI, Iosifidou E, Karataglis D, Christodoulou A. Autologous bone marrow grafting combined with demineralized bone matrix improves consolidation of docking site after distraction osteogenesis. *J Bone Joint Surg Am*. 2011;93(7):671-678.
26. Hegde V, Shonuga O, Ellis S, et al. A prospective comparison of 3 approved systems for autologous bone marrow concentration demonstrated nonequivalency in progenitor cell number and concentration. *J Orthop Trauma*. 2014;28(10):591-598.
27. Hernigou P, Dubory A, Homma Y, Flouzat Lachaniette CH, Chevallier N, Rouard H. Single-stage treatment of infected tibial non-unions and osteomyelitis with bone marrow granulocytes precursors protecting bone graft. *Int Orthop*. 2018;42(10):2443-2450.
28. Hernigou P, Guissou I, Homma Y, et al. Percutaneous injection of bone marrow mesenchymal stem cells for ankle nonunions decreases complications in patients with diabetes. *Int Orthop*. 2015;39(8):1639-1643.
29. Hernigou P, Homma Y, Flouzat Lachaniette CH, et al. Benefits of small volume and small syringe for bone marrow aspirations of mesenchymal stem cells. *Int Orthop*. 2013;37(11):2279-2287.
30. Hernigou P, Homma Y, Flouzat-Lachaniette CH, Poignard A, Chevallier N, Rouard H. Cancer risk is not increased in patients treated for orthopaedic diseases with autologous bone marrow cell concentrate. *J Bone Joint Surg Am*. 2013;95(24):2215-2221.
31. Hernigou P, Poignard A, Beaujean F, Rouard H. Percutaneous autologous bone-marrow grafting for nonunions: influence of the number and concentration of progenitor cells. *J Bone Joint Surg Am*. 2005;87(7):1430-1437.
32. Hernigou PH, Mathieu G, Poignard A, et al. Percutaneous autologous bone-marrow grafting for nonunions: surgical technique. *J Bone Joint Surg*. 2006;88A(suppl 1):322.
33. Holton J, Imam M, Ward J, et al. The basic science of bone marrow aspirate concentrate in chondral injuries. *Orthop Rev (Padvia)*. 2016;8(3):6659.
34. Hunt KJ, Anderson RB. Treatment of Jones fracture nonunions and refractures in the elite athlete: outcomes of intramedullary screw fixation with bone grafting. *Am J Sports Med*. 2011;39(9):1948-1954.
35. Hyer CF, Berlet GC, Bussewitz BW, Hankins T, Ziegler HL, Philbin TM. Quantitative assessment of the yield of osteoblastic connective tissue progenitors in bone marrow aspirate from the iliac crest, tibia, and calcaneus. *J Bone Joint Surg Am*. 2013;95:1312-1316.
36. Jäger M, Herten M, Fochtmann U, et al. Bridging the gap: bone marrow aspiration concentrate reduces autologous bone grafting in osseous defects. *J Orthop Res*. 2011;29:173-180.
37. Kennedy JG, Murawski CD. The treatment of osteochondral lesions of the talus with autologous osteochondral

transplantation and bone marrow aspirate concentrate: surgical technique. *Cartilage*. 2011;2(4):327-336.
38. Kim GB, Seo MS, Park WT, Lee GW. Bone marrow aspirate concentrate: its uses in osteoarthritis. *Int J Mol Sci*. 2020;21(9):3224.
39. Kim YS, Lee HJ, Choi YJ, Kim YI, Koh YG. Does an injection of a stromal vascular fraction containing adipose-derived mesenchymal stem cells influence the outcomes of marrow stimulation in osteochondral lesions of the talus? A clinical and magnetic resonance imaging study. *Am J Sports Med*. 2014;42:2424-2434.
40. Lanham NS, Carroll JJ, Cooper MT, et al. A comparison of outcomes of particulated juvenile articular cartilage and bone marrow aspirate concentrate for articular cartilage lesions of the talus. *Foot Ankle Spec*. 2016;10(4):315-321.
41. Li C, Kilpatrick CD, Smith S, et al. Assessment of multipotent mesenchymal stromal cells in bone marrow aspirate from human calcaneus. *J Foot Ankle*. 2017;56(1):42-46.
42. Marx RE, Tursun R. A qualitative and quantitative analysis of autologous human multipotent adult stem cells derived from three anatomic areas by marrow aspiration: tibia, anterior ilium, and posterior ilium. *Int J Oral Maxillofac Implants*. 2013;28(5):e290-e294.
43. McCarrel T, Fortier L. Temporal growth factor release from platelet-rich plasma, trehalose lyophilized platelets, and bone marrow aspirate and their effect on tendon and ligament gene expression. *J Orthop Res*. 2009;27:1033-1042.
44. McCright B, Dang JM, Hursh DA, et al. Synopsis of the Food and Drug Administration–National Institute of Standards and Technology co-sponsored "In Vitro Analyses of Cell/Scaffold Products" Workshop. *Tissue Eng Part A*. 2009;15(3):455-460.
45. McIlwraith CW, Frisbie DD, Rodkey WG, et al. Evaluation of intra-articular mesenchymal stem cells to augment healing of microfractured chondral defects. *Arthroscopy*. 2011;27:1552-1561.
46. McLain RF, Fleming JE, Boehm CA, Muschler GF. Aspiration of osteoprogenitor cells for augmenting spinal fusion: comparison of progenitor cell concentrations from the vertebral body and iliac crest. *J Bone Joint Surg Am*. 2005; 87(12):2655-2661.
47. Murawski CD, Kennedy JG. Percutaneous internal fixation of proximal fifth metatarsal jones fractures (zones II and III) with Charlotte Carolina screw and bone marrow aspirate concentrate: an outcome study in athletes. *Am J Sports Med*. 2011;39(6):1295-1301.
48. Muschler GF, Nitto H, Boehm CA, Easley KA. Age- and gender-related changes in the cellularity of human bone marrow and the prevalence of osteoblastic progenitors. *J Orthop Res*. 2001;19:117-125.
49. O'Malley M, DeSandis B, Allen A, et al. Operative treatment of fifth metatarsal jones fractures (zones II and III) in the NBA. *Foot Ankle Int*. 2016;37(5):488-500.
50. Pinzur MS. Use of platelet-rich concentrate and bone marrow aspirate in high-risk patients with Charcot arthropathy of the foot. *Foot Ankle Int*. 2009;30:124-127.
51. Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. *Science*. 1999;284(5411):143-147.
52. Roukis TS, Hyer CF, Philbin TM, Berlet GC, Lee TH. Complications associated with autogenous bone marrow aspirate harvest from the lower extremity: an observational cohort study. *J Foot Ankle Surg*. 2009;48:668-671.
53. Rush SM, Hamilton GA, Ackerson LM. Mesenchymal stem cell allograft in revision foot and ankle surgery: a clinical and radiographic analysis. *J Foot Ankle Surg*. 2009;48:163-169.
54. Sakai S, Mishima H, Ishii T, et al. Concentration of bone marrow aspirate for osteogenic repair using simple centrifugal methods. *Acta Orthop*. 2008;79(3):445-448.
55. Saw KY, Hussin P, Loke SC, et al. Articular cartilage regeneration with autologous marrow aspirate and hyaluronic acid: an experimental study in a goat model. *Arthroscopy*. 2009;25(12):1391-1400.
56. Schade V, Roukis T. Percutaneous bone marrow aspirate and bone graft harvesting techniques in the lower extremity. *Clin Podiatr Med Surg*. 2008;25(4):733-742.
57. Schweinberger M, Roukis T. Percutaneous autologous bone-marrow harvest from the calcaneus and proximal tibia: surgical technique. *J Foot Ankle Surg*. 2007;46(5):411-414.
58. Shimozono Y, Yasui Y, Hurley ET, Paugh RA, Deyer TW, Kennedy JG. Concentrated bone marrow aspirate may decrease postoperative cyst occurrence rate in autologous osteochondral transplantation for osteochondral lesions of the talus. *Arthroscopy*. 2019;35(1):99-105.
59. Stein BE, Stroh DA, Schon LC. Outcomes of acute Achilles tendon rupture repair with bone marrow aspirate concentrate augmentation. *Int Orthop*. 2015;39(5):901-905.
60. Udehiya RK, Amarpal A, Aithal HP, et al. Comparison of autogenic and allogenic bone marrow derived mesenchymal stem cells for repair of segmental bone defects in rabbits. *Res Vet Sci*. 2013;94:743-752.
61. Urdzikova LM, Sedlacek R, Suchy T, et al. Human multipotent mesenchymal stem cells improve healing after collagenase tendon injury in the rat. *Biomed Eng Online*. 2014;13:42.
62. Wehling P, Moser C, Frisbie D, et al. Autologous conditioned serum in the treatment of orthopaedic diseases: the orthokine therapy. *BioDrugs*. 2007;21:323-332.
63. Yamaguchi Y, Kubo T, Murakami T, et al. Bone marrow cells differentiate into wound myofibroblasts and accelerate the healing of wounds with exposed bones when combined with an occlusive dressing. *Br J Dermatol*. 2005;152(4):616-627.
64. Yao J, Woon CY, Behn A, et al. The effect of suture coated with mesenchymal stem cells and bioactive substrate on tendon repair strength in a rat model. *J Hand Surg Am*. 2012;37:1639-1645.