ISSN 2218-5836 (online)

World Journal of *Orthopedics*

World J Orthop 2017 June 18; 8(6): 441-523



Published by Baishideng Publishing Group Inc

World Journal of Orthopedics

Contents

Monthly Volume 8 Number 6 June 18, 2017

REVIEW

441 Perioperative blood management strategies for patients undergoing total knee replacement: Where do we stand now?

Themistoklis T, Theodosia V, Konstantinos K, Georgios DI

MINIREVIEWS

455 Sternal metastasis - the forgotten column and its effect on thoracic spine stability

Piggott RP, Curtin M, Munigangaiah S, Jadaan M, McCabe JP, Devitt A

461 Role of fetuin A in the diagnosis and treatment of joint arthritis

Pappa E, Perrea DS, Pneumaticos S, Nikolaou VS

ORIGINAL ARTICLE

Retrospective Study

465 Emergent reintubation following elective cervical surgery: A case series

Schroeder J, Salzmann SN, Hughes AP, Beckman JD, Shue J, Girardi FP

471 Two-stage surgical treatment for septic non-union of the forearm

Perna F, Pilla F, Nanni M, Berti L, Lullini G, Traina F, Faldini C

Observational Study

478 Upper extremity disorders in heavy industry workers in Greece

Tsouvaltzidou T, Alexopoulos E, Fragkakis I, Jelastopulu E

484 Medial tibial plateau morphology and stress fracture location: A magnetic resonance imaging study

Yukata K, Yamanaka I, Ueda Y, Nakai S, Ogasa H, Oishi Y, Hamawaki J

SYSTEMATIC REVIEWS

491 Clinical application of concentrated bone marrow aspirate in orthopaedics: A systematic review

Gianakos AL, Sun L, Patel JN, Adams DM, Liporace FA

507 Distal triceps injuries (including snapping triceps): A systematic review of the literature

Shuttlewood K, Beazley J, Smith CD

514 Worldwide orthopaedic research activity 2010-2014: Publication rates in the top 15 orthopaedic journals related to population size and gross domestic product

Hohmann E, Glatt V, Tetsworth K

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WJO covers topics concerning arthroscopy, evidence-based medicine, epidemiology, nursing, sports medicine, therapy of bone and spinal diseases, bone trauma, osteoarthropathy, bone tumors and osteoporosis, minimally invasive therapy, diagnostic imaging. Priority publication will be given to articles concerning diagnosis and treatment of orthopedic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJO*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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World Journal of Orthopedics is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central and Scopus.

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NAME OF JOURNAL
World Journal of Orthopedics

ISSN
ISSN 2218-5836 (online)

LAUNCH DATE
November 18, 2010

FREQUENCY
Monthly

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PUBLICATION DATE
June 18, 2017

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World J Orthop 2017 June 18; 8(6): 491-506

DOI: 10.5312/wjo.v8.i6.491

ISSN 2218-5836 (online)

SYSTEMATIC REVIEWS

Clinical application of concentrated bone marrow aspirate in orthopaedics: A systematic review

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Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: Disclosures for Frank A Liporace include AO: Unpaid consultant, Biomet: IP royalties; Paid consultant; Medtronic: Paid consultant, Stryker: Paid consultant, Synthes: Paid consultant.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at algianakos@gmail.com, who will provide a permanent, citable and open-access home for the dataset.

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Manuscript source: Invited manuscript

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Received: January 23, 2017
Peer-review started: February 2, 2017
First decision: March 28, 2017
Revised: April 5, 2017
Accepted: May 3, 2017

Article in press: May 15, 2017
Published online: June 18, 2017

Abstract

AIM

To examine the evidence behind the use of concentrated bone marrow aspirate (cBMA) in cartilage, bone, and tendon repair; establish proof of concept for the use of cBMA in these biologic environments; and provide the level and quality of evidence substantiating the use of cBMA in the clinical setting.

METHODS

We conducted a systematic review according to PRISMA guidelines. EMBASE, MEDLINE, and Web of Knowledge databases were screened for the use of cBMA in the repair of cartilage, bone, and tendon repair. We extracted data on tissue type, cBMA preparation, cBMA concentration, study methods, outcomes, and level of evidence and reported the results in tables and text.

RESULTS

A total of 36 studies met inclusion/exclusion criteria and were included in this review. Thirty-one of 36 (86%) studies reported the method of centrifugation and preparation of cBMA with 15 (42%) studies reporting either a cell concentration or an increase from baseline. Variation of cBMA application was seen amongst the studies evaluated. Twenty-one of 36 (58%) were level of evidence Ⅳ, 12/36 (33%) were level of evidence Ⅲ, and 3/36 (8%) were level of evidence Ⅱ. Studies evaluated full thickness chondral lesions (7 studies), osteochondral lesions (10 studies), osteoarthritis (5 studies), nonunion or fracture (9 studies), or tendon injuries (5 studies). Significant clinical improvement with the presence of hyaline-like values and lower incidence of fibrocartilage on T2 mapping was found in patients receiving cBMA in the treatment of cartilaginous lesions. Bone consolidation and time to bone union was improved in patients receiving cBMA. Enhanced healing

rates, improved quality of the repair surface on ultrasound and magnetic resonance imaging, and a decreased risk of re-rupture was demonstrated in patients receiving cBMA as an adjunctive treatment in tendon repair.

CONCLUSION

The current literature demonstrates the potential benefits of utilizing cBMA for the repair of cartilaginous lesions, bony defects, and tendon injuries in the clinical setting. This study also demonstrates discrepancies between the literature with regards to various methods of centrifugation, variable cell count concentrations, and lack of standardized outcome measures. Future studies should attempt to examine the integral factors necessary for tissue regeneration and renewal including stem cells, growth factors and a biologic scaffold.

Key words: Concentrated bone marrow aspirate; Bone; Cartilage; Osteochondral lesion; Osteoarthritis; Tendon

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Core tip: With the widespread use of orthobiologics in everyday practice, attention must be directed to substantiate the evidence for their current use and to direct future practice guidelines. The use of concentrated bone marrow aspirate (cBMA) has become an increasingly popular alternative and adjunct in the treatment of cartilaginous lesions, bony defects, and tendinous injuries. This systematic review demonstrates the potential benefits of utilizing cBMA for the repair of different tissue types in the clinical setting. This systematic review also highlights discrepancies between the literature with regards to various methods of centrifugation, variable cell count concentrations, variable methods of application of cBMA, and the lack of standardized outcome measures.

Gianakos AL, Sun L, Patel JN, Adams DM, Liporace FA. Clinical application of concentrated bone marrow aspirate in orthopaedics: A systematic review. *World J Orthop* 2017; 8(6): 491-506 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i6/491.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i6.491

INTRODUCTION

With the widespread use of orthobiologics in everyday practice, attention must be directed to substantiate the evidence for their current use and to direct future practice guidelines. In any bioengineered environment, three components are required to provide the necessary biologic milieu for cell regeneration and renewal. The presence of stem cells, growth factors, and a biologic scaffold are integral to this process. Bone marrow aspirate (BMA) has been utilized as a source of bone marrow-derived mesenchymal stem cells (BM-MSC) with its relative ease of harvest, low morbidity, and feasible cost. BMA alone has a relatively low percentage of MSCs with only 0.001% to 0.01% of all nucleated cells in BMA being MSCs[1]. Therefore, the aspirate is typically concentrated by centrifugation in order to increase the ratio of MSCs. Concentrated bone marrow aspirate (cBMA) provides both stem cells and growth factors and relies on the host tissue to provide scaffold. The use of cBMA has become an increasingly popular alternative and adjunct in the treatment of cartilaginous lesions, bony defects, and tendinous injuries. Despite both basic science and clinical evidence of its efficacy, recent literature suggests that cBMA has different functions and roles in each biologic environment. Evidence suggests that stem cells act to direct local cells to stimulate regeneration and repair that is specific to each tissue. This process is mediated by secretomes from the stem cells, which allow their adaptation in each environment and therefore provides the appropriate growth factors and cytokines necessary to stimulate each tissue in a different fashion[2]. Growth factors derived from cBMA may be required for cell lineage differentiation although the exact growth factors have not to date been fully elucidated. The available literature regarding the use of cBMA in different tissue repair is highly heterogeneous with regards to indications, concentrations and overall functional outcomes.

This review attempts to examine the evidence behind the use of cBMA in cartilage, bone, and tendon regeneration and repair and to establish proof of concept for the use of cBMA in these biologic environments. In addition our systematic review will provide the reader with a reference of the level and quality of evidence of the current available literature evaluating the uses of cBMA in the treatment of lesions in cartilage, tendon, and bone.

MATERIALS AND METHODS

A systematic review was conducted according to PRISMA guidelines[3]. The following search terms were used in MEDLINE, EMBASE, and Web of Science databases on November 22, 2016: "cBMA OR concentrated bone marrow aspirate OR BMC OR bone marrow concentrate OR bone marrow derived mesenchymal stem cells". This was paired with one of the following search strategies: (1) "cartilage OR chondrocytes OR chondrogenesis OR arthritis OR osteoarthritis OR osteochondral OR chondral"; (2) "tenocytes OR tendon OR tendinitis OR tendinosis OR tendinopathy"; or (3) "bone OR bone healing OR malunion OR delayed union OR osteocyte OR osteogenesis". Inclusion criteria were: (1) clinical studies demonstrating the effect of cBMA in cartilage, bone; or tendon (2) published in peer-reviewed journal; and (3) written in English. Exclusion criteria included review articles, case reports, basic science studies, and studies evaluating additional pathologic processes. Two independent reviewers performed the literature search screening both title and abstract for all results. Potentially

eligible studies received a full text review. The reference list of the identified articles in the results were manually screened for additional articles. A senior author was consulted if a consensus could not be reached. The following information was extracted and recorded from the included studies: Number of patients, preparation method of cBMA, cell count, treatment groups, adjunctive therapies/scaffolds, follow-up, objective and subjective outcomes, and level of evidence.

RESULTS

The initial literature search resulted in 1202 total studies. Once duplicates were removed and articles were screened for inclusion/exclusion criteria, 135 were included and full texts were assessed for eligibility. A total of 36 studies met inclusion/exclusion criteria and were included in this review.

Study characteristics

Thirty-one of 36 (86%) studies reported the method of centrifugation and preparation of cBMA. Fifteen of 36 (42%) studies reported either a cell concentration or an increase from baseline. There were no studies that reported on the minimal number of colony forming units in which below that number, cBMA did not provide significant benefit. Twenty-one of 36 (58%) were level of evidence Ⅳ, 12/36 (33%) were level of evidence Ⅲ, and 3/36 (8%) were level of evidence Ⅱ. Two studies were industry funded while 37 declared no conflict of interest.

cBMA in full thickness cartilage lesions

Seven studies evaluated the effect of cBMA in the treatment of full thickness cartilage defects in the knee and all reported significant clinical improvement post-operatively summarized in Table 1[4-10]. Three studies evaluated the effect of cBMA combined with microfracture and demonstrated improved clinical outcomes with reconstitution of original cartilage on magnetic resonance imaging (MRI). All three studies reported bone marrow edema and/or subchondral irregularities[4-6]. One study evaluated the effects of cBMA when compared with matrix-induced autologous chondrocyte implantation (MACI) and found that patients receiving cBMA had a significantly improved IKDC subjective score (P = 0.015) with 81% complete cartilage filling on MRI[7]. One study compared the effects of cBMA to PRP and reported that patients who received cBMA had T2 values closer to that of superficial hyaline cartilage (P = 0.01)[10]. Variation of cBMA application was seen amongst the studies evaluated. Several studies used cBMA in isolation, while other studies combined cBMA with either a collagen or hyaluronic acid scaffold. Many of these studies prepared the defect site and implanted cBMA through arthroscopic techniques.

cBMA in osteochondral lesions

Ten studies evaluated the effect of cBMA in the treatment of osteochondral defects in the talus (7/10) and the knee (3/10) summarized in Table 2[2,11-19]. All ten studies reported both clinical and radiologic improvements post-operatively after receiving cBMA. Six studies evaluated the effects of cBMA with no concomitant procedure and reported good clinical outcome scores including AOFAS, IDKS, and KOOS. For studies that utilized either a collagen or a hyaluronic acid scaffold, no significant difference was reported between the two groups. Buda[11] evaluated cBMA compared to autologous chondrocyte implantation (ACI) and reported no clinical difference between the two treatment strategies but found a higher presence of hyaline like values and lower incidence of fibrocartilage on T2 mapping in the cBMA group. One study favored treatment with cBMA when comparing cBMA to microfracture reporting 100% and 28% normal IDKC values at 5-year follow up, respectively[18]. Lastly, one study reported higher MOCART scores and T2 relaxation values with measurements resembling those of native cartilage in groups that received both microfracture with cBMA compared to groups that received microfracture alone[19]. cBMA had also been used as an adjunctive treatment to autologous osteochondral transplantation and resulted in overall improved FAOS scores post-operatively[2]. Variation of cBMA application was seen amongst the studies evaluated. These included the use of either a collagen powder or hyaluronic acid scaffold, with the majority of studies using arthroscopic techniques for cBMA implantation.

cBMA in osteoarthritis

Five studies evaluated cBMA in the treatment of knee osteoarthritis (OA) summarized in Table 3[20-24]. Only two studies evaluated the efficacy of cBMA without an adjunctive procedure. One reported better clinical outcomes at one week and three months in patients who received cBMA but found no difference in these scores after six months[24]. One study reported significant clinical improvements but found that 76% of patients had abnormal International Cartilage Repair Society repair scores[23]. Three studies evaluated cBMA combined with either PRP or PRF and found functional and clinical improvements in the cBMA groups with improvement in cartilage repair, although not significant[20-22]. Variation of cBMA application was seen amongst the studies evaluated, which utilized ultrasound or fluoroscopy for needle placement or was performed under arthroscopic guidance.

cBMA in bone healing

Nine studies evaluated the use of cBMA in bone healing summarized in Table 4[25-33]. Eight of nine studies reported on the use of cBMA in either non-union or delayed union. One study demonstrated initial radiographic and functional improvements in the cBMA group, but reported similar outcomes after one year post-operatively[31]. All studies reported either lower or similar complication rates post-operatively in groups that received cBMA compared to groups receiving no additional treatment. Bone

Table 1 Studies evaluating concentrated bone marrow aspirate in the treatment of full thickness chondral lesions

Ref.	Tissue	BMAC preparation	Concentration	Study design/ methods/follow up	Outcomes measured	Results	LOE
Enea *et al*[4]	Knee	60 mL BMA from iliac crest processed with MarrowStim Concentration Kit (Biomet) resulting in 3-4 mL of BMAC. Chondral lesion debrided and microfracture performed. Biocollagen MeRE collagen membrane (Bioteck) cut to match shape and immersed in BMAC until implantation. 10:1 mixture of 1-2 mL fibrin glue and BMAC laid on lesion. Membrane inserted and placed. 2-3 mL of fibrin glue-BMAC injected over and left to solidify	NS	n = 9. Arthroscopic microfracture covered with collagen membrane immersed in autologous BMAC from iliac crest. Follow up: 29 mo	Biopsy cartilage evaluated by surgeon using criteria of international cartilage repair society. The following items were utilized: Cartilage repair assessment, MRI, IKDC, Lysholm, VAS (pre and post op), Tegner (pre and post op). Four patients had second look arthroscopy and biopsy	Significant clinical improvement (P < 0.005). Cartilage macroscopic assessment at 12 mo revealed all repairs appeared almost normal. Histo-analysis showed hyaline-like cartilage repair in 1 lesion, fibrocartilaginous repair in 2 lesions and a mixture of both in 1 lesion. Post op MRIs (6-9 mo out) all showed reconstitution of original cartilage. Bone marrow edema and/or subchondral irregularities observed in all cases. Non-homogeneous cartilage signal and fissuring observed in 2 of 3 cases	Ⅳ
Enea *et al*[5]	Knee	60 mL of BMA from the iliac crest was obtained and processed with MarrowStim Concentration Kit (Biomet) to obtain 3-4 mL of BMAC. Cartilage was treated with arthroscopic microfracture and the defect was covered with PGA-HA scaffold matrix (Chondrotissue) seeded with autologous BMAC. 10:1 mixture of 1-2 mL of fibrin glue and BMAC was then applied to lesion bed. PGA-HA soaked in BMAC was then applied with 2-3 mL additional fibrin glue-BMAC mixture dispersed over the matrix until solidification at 2-3 min	NS	n = 9 (Outerbridge type III/IV) Consecutively treated with arthroscopic Polyglycolic acid/ hyaluronan - covered microfracture and BMAC. Follow up: 22 mo	Clinical scoring, IKDC, Lyshold, VAS, Tegner, cartilage microscopic examination at 12 mo, MRI at 8-12 mo post op. 5 patients underwent second look and 2 had biopsy	All patients but one showed improvement in clinical scoring from pre-op sto last follow-up (22 mo). All other variables increased from baseline to latest follow-up. Nineteen cartilage exams appeared normal, three almost normal, and one abnormal at 12 mo. Histo showed hyaline-like cartilage repair tissue formation in one case. MRI showed complete defect filling	Ⅳ
Gigante *et al*[6]	Knee	NA	NA	n = 5. MACI augmented with BMAC	Second look arthroscopy biopsy, CRA, ICRS Ⅱ Visual Histological Assessment Scale	Normal ICRS/CRA at arthroscopic evaluation and had mean overall histological ICRS Ⅱ of 59.8 ± 14.5. Hyaline-like matrix only found in one case. Mixture of hyaline/ fibrocartilage was found in one case and fibrocartilage was found three cases	Ⅳ
Gobbi *et al*[7]	Patello-femoral	60 mL of BMA from ipsilateral iliac crest concentrated by BMAC Harvest Smart PreP2 system to obtain concentration of BMC 4-6 times baseline value	4-6 × baseline	(1) MACI n = 19; (2) BMAC n = 18. Both with HYAFF1 scaffold. Follow up: 3 yr	XR, MRI, IKDC score, KIOOS score, VAS, Tegner	Both groups showed significant improvements in all scores from preop to final follow up (P = 0.002). There was no difference between the two groups except in the IKDC subjective scores which favored BMAC group (P = 0.015). MRI showed complete filling of defect in 76% of MACI and in 81% of BMAC	Ⅲ
Gobbi *et al*[8]	Knee	60 mL of BMA from ipsilateral iliac crest concentrated by BMAC Harvest Smart PreP2 system to obtain concentration of BMC 4-6 times baseline value. Activated using batroxobin enzyme to form sticky clot. Implanted and covered with collagen-based membrane scaffold (ChondroGide) and sealed with fibrin glue (Tissucol)	4-6 × baseline	n = 25. Cartilage transplantation with mulipotent stem cells and collagen type Ⅰ/Ⅲ matrix	XR, MRI, VAS, IKDC, KOOS, Lysholm, Marx, Tegner	Significant improvement at follow up across all measures. < 45-year-old and smaller lesions = better results. MRI = good stability of implant, hyaline-like cartilage found is histo analysis of biopsied tissue	Ⅳ

Gobbi *et al*[9]	Knee	60mL BMA from ipsilateral iliac crest (PreP2) and concentrated to 4-6 times baseline value, after activation with batroxobin enzyme (Plateltex Act) and pasted into lesion Covered with collagen type Ⅰ/Ⅲ matrix (Chondro-Gide) and sealed with fibrin glue (Tissucol)	4-6 × baseline	n = 15. One step surgery with BMAC and Collagen Ⅰ/Ⅲ matrix (chondro-gide)	XR, MRI at 1 and 2 yr. VAS, IKDC, KOOS, Lysholm, Marx, SF-36, Tegner at 6, 12, 24 mo. 3 had second look biopsy	Significant improvement at follow up across all measures (P < 0.0005). Single lesion and smaller lesions had better improvement. MRI showed greater hyaline-like tissue in all patients. Hyaline-like cartilage on histology in 3 biopsies	Ⅳ
Krych *et al*[10]	Distal femur	NS	NS	(1) n = 11 control scaffold; (2) n = 23 scaffold + PRP; (3) n = 12 scaffold + BMAC. Follow up: 12 mo	MRI, T2 mapping	BMAC and PRP groups had superior cartilage infill (P = 0.002, P = 0.03). BMAC demonstrated mean T2 value closer to that of superficial hyaline cartilage (P = 0.01)	Ⅲ

BMA: Bone marrow aspirate; NS: Not significant; CRA: Cartilage repair assessment; MRI: Magnetic resonance imaging; MACI: Matrix-induced autologous chondrocyte implantation; PRP: Platelet-rich plasma.

Table 2 Studies evaluating concentrated bone marrow aspirate in the treatment of osteochondral defects

Ref.	Tissue	BMAC preparation	Concentration	Study design/ methods/follow up	Outcomes measured	Results	LOE
Buda *et al*[11]	OCL of talus	Scaffold was a hyaluronic acid membrane loaded with previously cultured chondrocytes (ACI) or with BMAC. Platelet rich fibrin gel was produced the day before surgery using Vivostat System 1 (vivolution A/S). Harvested and processed 120 mL of the patient's venous blood to obtain 6 mL of platelet rich fibrin gel. 60 mL BMA was harvested from posterior iliac crest using Smart PRepI to obtain 6 mL of BMAC. 1 g powder mixed with 2 mL BMAC and 1 mL platelet rich fibrin gel. The hyaluronic acid membrane was cut and loaded with 2 mL BMAC and 1 mL platelet rich fibrin gel. A layer of platelet rich fibrin gel was placed over the implant once in place to provide additional stability	NS	n (total) = 80: (1) n = 40 - autologous chondrocytes implantation; (2) n = 40 with BMAC. Follow up: 48 mo	Clinical scores, XR, MRI Mocart score, T2 mapping	Groups had similar results at 48 mo. No statistically significant difference in clinical outcomes. Return to sport was slightly better with BMAC. MRI MOCART score was similar in both groups. T2 mapping highlighted a higher presence of hyaline like values and lower incidence of fibrocartilage in BMAC group	Ⅳ
Buda *et al*[12]	OCL of knee	Combined with either MAST or HA matrix	NS	n = 30. One step arthroscopic BMAC transplant with scaffold. Follow up: 29 mo	Clinical inspection, MRI, IKDC, KOOS	Good clinical outcome and osteochondral regeneration on MRI and biopsies in both groups	Ⅳ
Buda *et al*[13]	OCL of talus	Scaffolds either: (1) porcine collagen powder SpongostanI Powder (J and J) mixed with autologous cell concentrate and platelet gel; or (2) hyaluronic acid membrane (fidia advanced biopolymers) with addition of platelet gel. Platelet rich fibrin gel was produced the day before surgery using Vivostat System 1 (vivolution A/S). Harvested and processed 120 mL of the patient's venous blood to obtain 6 mL of platelet rich fibrin gel. 60 mL BMA was harvested from posterior iliac crest using Smart PRepI to obtain 6mL of BMAC. 1 g powder mixed with 2 mL BMAC and 1ml platelet rich fibrin gel. The hyaluronic acid membrane was cut and loaded with 2 mL BMAC and 1 mL platelet rich fibrin gel. A layer of platelet rich fibrin gel was placed over implant once in place to provide additional stability	NS	n = 64. One step arthroscopic BMAC transplant with scaffold (collagen powder of hyaluronic acid membrane) and platelet gel. Follow up: 53 mo	AOFAS scale score, radiographic, scaffold type, lesion area, previous surgery, lesion depth	Mean preop AOFAS was 65.2. Regardless of scaffolding type all patients showed similar pattern of clinical improvement at each follow-up. No correlation between area of lesion and pre-op AOFAS score but did observe relationship between area and AOFAS at each follow up post-operatively. No relationship between AOFAS score and depth of lesion	Ⅳ

Buda *et al*[14]	OCL of knee	Scaffold either MAST or HA matrix + PRF	NS	n = 20. Follow up: 24 mo	Clinical, MRI	Significant improvement at 12 and 24 mo, satisfactory MRI	Ⅳ
Giannini *et al*[15]	OCL of talus	Porcine collagen powder (J and J) or hyaluronic membrane scaffold. 60 mL of bone marrow harvested from posterior iliac crest and concentrated by SmartPrep to 6 mL of BMC. One step delivery system	NS	n = 49 received either BMA with collagen scaffold or BMA with HA membrane scaffold. Follow up: 48 ± 6 mo	AOFAS, radiograph, MRI	AOFAS improved P < 0.0005. T2 mapping analysis showed regenerated tissue with T2 values similar to hyaline cartilage in a mean of 78% of the repaired lesion area	Ⅳ
Giannini *et al*[16]	OCL of talus	One step arthroscopic transplantation. Platelet gel using Vivostat system. 60 mL BMA harvested from posterior iliac crest. Concentrated using SmartPReP in order to obtain 6 mL of concentrate. Scaffold: Either collagen powder (Spongostan1 Powder) or hyalyronic acid membrane. Scaffold was loaded with 2 mL BMAC and 1 mL PRF	NS	n = 25 in BMAC group. Study also compared to ACI	AOFAS, histology	Statistically significant improvement in mean AOFAS scores post-operatively (P < 0.0005). Only 1 superficial infection noted. Nearly homogeneous regenerated tissue on MOCART MRI in 82% of cases. Hypertrophy found in 2 cases on histology	Ⅳ
Giannini *et al*[17]	OCL of talus	Porcine collagen powder (J and J) or hyaluronic membrane scaffold. 60 mL of bone marrow harvested from posterior iliac crest and concentrated by SmartPrep to 6 mL of BMC. One step delivery system	NS	(1) n = 23 - Collagen scaffold + BMA; (2) n = 25 HA membrane scaffold + BMA. Follow up: 29 mo (24-35)	AOFAS, histology	AOFAS improved, Histology showed regenerated tissue in various degrees of remodeling	Ⅳ
Gobbi *et al*[18]	OCL of knee	Hyaluronic acid-based scaffold was used with BMAC	6 × baseline	n = 25 HA-BMAC, n = 25 microfracture. Observed prospectively for 5 yr	Patient-reported scoring tools: IKDC Subjective Knee Evaluation, KOOS, Lysholm Knee Questionnaire, and Tegner activity scale	Microfracture - 64% normal/nearly normal according to IKDC objective score at 2 yr and declined to 28% at 5 yr	Ⅱ
		60 cc of BMA from Iliac Crest spun to 6 × normal concentration. Batroxobin enzyme used to activate BMAC				HA-BMAC - 100% normal/nearly normal objective IKDC at 2 yr, 100% at 5 yr for ALL outcomes measured	
Hannon *et al*[19]	OCL of talus	60 mL of BMA from ipsilateral iliac crest, concentrated by Arteriocyte Magellan Autologous Platelet Separator System to obtain 3 mL of BMAC	NS	(1) n = 12 BMS; (2) n = 22 BMAC+BMS. Follow up: 48.3 mo for BMAC + BMS, 78.3 mo for BMS	AOFAS, FAOS, SF-12, MOCART	Mean FAOS and SF-12 PCS scores improved pre to post operatively (P < 0.01) for both groups. MOCART score significantly higher in cBMA + BMS (P = 0.023). T2 relaxation values in cBMA + BMS group significantly higher with measurements of adjacent cartilage	Ⅲ
Kennedy *et al*[2]	OCL of talus	60 mL of BMA from ipsilateral iliac crest, concentrated by commercially available BMAC centrifuge system to obtain 4 mL of pluripotent cells	NS	n = 72. AOT with BMAC. Follow up: 28 mo	FAOS, SF-12	FAOS, SF-12 significantly improved from pre to post-op	Ⅲ

KOOS: Knee injury and Osteoarthritis Outcome Score; NS: Not significant; OCL: Osteochondral lesions; BMA: Bone marrow aspirate; MRI: Magnetic resonance imaging.

consolidation and time to bone union was improved in patients receiving cBMA, with faster healing rates when

Table 3 Studies evaluating concentrated bone marrow aspirate in the treatment of osteoarthritis

Ref.	Tissue	BMAC preparation	Concentration	Study design/ methods/follow up	Outcomes measured	Results	LOE
Centeno *et al*[20]	Knee	60 mL of BMA from iliac crest was obtained toproduce 1-3 mL of BMAC. 60 cc of heparinized Ⅳ venous blood drawn to be used for isolating PRP and platelet lysate. Lipoaspirate - miniliposuction of the posterior superior buttocks or lateral thigh was performed under ultrasound and minimally processed (centrifuged) adipose tissue was injected into the articular space. Preparations were injected into the articular space of the knee together (5-10 cc) between the meniscus on the most painful side and over lying collateral ligament	NS	Data from registry. (1) n = 616 - BMAC+ PRP *vs* (2) BMAC + PRP + adipose graft. Outcomes and complication questionnaires at 1, 3, 6, 12 mo completed. 2 groups (A-BMAC and PRP protocol, B BMAC and PRP plus adipose fate graft (lipoaspirate)	LEFS, NPS, subjective percentage improvement rating, frequency and type of adverse events	Mean LEFS score increased in both groups and mean NPS decreased in both groups. AE rates were 6% without graft and 8.9% with graft. No difference between groups. Addition of adipose graft did not provide a detectible benefit over BMAC alone	Ⅳ
Centeno *et al*[21]	Knee	10-15 cc whole bone marrow aspirate harvested from 6-8 sites on posterior iliac crest (3-4 each side). Centrifuged and cells isolated. Patient heparinized blood for PRP and PL. Aspirates mixed together and injected into joint. Cell counts were counted four times and average was taken under microscope for total nucleated cell count	Lower and higher cell count groups defined using threshold of 4×10^4 cells	Data from registry. n = 373 patients that received BMAC combined with PRP and PL injections for 424 OA knees	Clinical scales assessed at baseline, 1, 3, 6, 12 and annually thereafter. NPS, LEFS, pain and functional outcome measures	Significant positive results with treatment for all pain and functional metrics. Higher cell group reported lower post treatment numeric pain scale values (P < 0.001). No significant difference detected for other metrics	Ⅳ
Haleem *et al*[22]	Femoral condyle	20 mL BMA from iliac crest isolated with density gradient (Ficoll-Paque), supplemented with 10% fetal bovine serum and penicillin streptomycin. Microfracture performed and sclerotic bone curetted. Autologous periosteal flap harvested from anteromedial ispilateral proximal tibia to fit defect size and stuffed into place. 1 mL platelet concentrate and 1 mL fibrinogen and 1 mL thrombin placed with BMAC PR fibrin glue	NS	n = 5, treated with BMAC + PRF	At 6 and 12 mo: Lysholm and Revised HHS Knee Score, XR and MRI. 2 patients had follow up arthroscopy at 12 mo rated by ICRS	All patients had statistically significant improvement at 6 and 12 mo (P < 0.005). No statistically significant difference between 6 and 12 mo post op in clinical scores. ICRS were near normal for 2 patients who consented to arthroscopy. MRI of 3 patients at 12 mo showed complete defect filling and complete surface congruity with native cartilage. Two patients showed incomplete congruity. BMAC on platelet rich fibrin gel as a scaffold may be effective to promote repair of articular cartilage defects	Ⅳ
Koh *et al*[23]	Knee	60 mL BMA from Iliac crest processed with MarrowStim Concentration Kit (Biomet) to obtain 3-4 mL of BMAC. Adipose tissue harvested from buttocks through liposuction. All fluid removed from knee arthroscopically. Lesion filled with cell suspension and held stationary for 10 minutes with defect facing upwards. Adherence of MSC confirmed. No marrow stimulation procedures were performed	Average of 3.8×10^6 ($2.5\text{-}6.1 \times 10^6$)	n = 37 knees using second-look arthroscopy after mesenchymal stem cell implantation for cartilage lesions done 12 mo post op	IKDC, Tegner, cartilage repair assessed using ICRS grading	IKDC and Tegner sores significantly improved (P < 0.001). ICRS overall repair grades 2/37 were normal, 7/37 were near normal, 20/37 abnormal, 8/37 severely abnormal.). Patient satisfaction: 33/34 reported good to excellent satisfaction. High BMI (> 27.5) and large lesion (> 5.4 cm^2) had significant prediction of poor clinical and arthroscopic outcomes (P < 0.05)	Ⅳ

Shapiro *et al*[24]	Knee	52 mL BMA from iliac crest concentrated in Arteriocyte Magellan Autologous Platelet Separator System centrifuge to yield 6 mL of cellular product	NS	n = 25 BMAC, n = 25 saline (patients had bilateral knee pain)	OARSI measure, VAS score, safety outcomes, pain relief, function	OARSI and VAS decreased significantly from baseline at 1wk, 3 mo, 6 mo (P < 0.019), no difference in pain relief	Ⅱ

BMA: Bone marrow aspirate; MRI: Magnetic resonance imaging; NS: Not significant; OA: Osteoarthritis; BMI: Body mass index; VAS: Visual analogue scale; OARSI: Osteoarthritis Research Society International.

Table 4 Studies evaluating concentrated bone marrow aspirate in bone healing

Ref.	Tissue	BMAC preparation	Concentration	Study design/methods/follow up	Outcomes measured	Results	LOE
Bastos Filho *et al*[25]	Tibia/femur nonunion	11G × 10 cm bone marrow aspiration needle into posterior iliac crest to obtain a total of 100 to 110 mL for each patient - concentrated to 20 mL with Sepax system	NS	n = 6 patients with nonunion of tibia or femur. Four received percutaneous infusion of autologous bone marrow aspirated without Sepax processing. Two received with processing. Follow up to 6 mo	Clinical examination and radiographic evaluation at 2, 4, 6 mo. Clinical criteria included full weight bearing tolerance and absence of pain upon palpation at the fracture site. Radiographic healing checked with AP, lateral and oblique films to look for bone callus. Patient satisfaction questionnaire scale from 0-10	Bone consolidation obtained in all the patients. Bone callus observed in the radiographic between 3 and 24 wk, average 13.8 wk in group without processing. Mean satisfaction increased in all patients	Ⅱ
Desai *et al*[26]	Nonunion/delayed union of tibia	Total of 60 cc bone marrow aspirated from iliac crest with 16 gauge Jamshidi needle (Harvest system). Concentrated to 10 cc for injection	101.48 ± 64.13/cc	n = 49 patients with tibial nonunion had BMAC injection with DBM and/or rhBMP-2. Follow up until radiographic union or another procedure was performed	Radiographic healing (bridging of 3 out of 4 cortices on AP and lateral films)	No difference in healing rate between patients with fracture gaps less than and greater than 5 mm	Ⅲ
Garnavos *et al*[27]	Humeral shaft delayed union	With the use of a 10 cm long and 3 mm wide biopsy needle, 60 mL of bone marrow was aspirated from each patient's iliac wing and was centrifuged to provide 10 mL of concentrated mesenchymal stem cells. The concentrated bone marrow mixed with 10 cc of DBM putty	NS	n = 5. Intramedullary nailing with antegrade/unreamed technique was performed for 4 patients. One patient was treated previously with retrograde/unreamed nailing left in situ. The concentrated mixture was infused percutaneously in the area of nonunion with a biopsy needle under fluoroscopy. Patients were followed up every 4-6 wk for 12 mo	Patients were assessed for union process, discomfort, level of activities and functional improvement	There were no peri- or postoperative complications. Sound union was obtained in all cases from 12 to 20 wk after the operation. At final followup, all patients had regained a satisfactory range of shoulder and elbow motion. They had also returned to pre-injury level of activities and were happy with their treatment and outcome	Ⅳ
Guimaraes *et al*[28]	Femoral shaft nonunion	11G × 10 cm needle used for aspiration from iliac crest. The marrow samples were harvested in small amount (2 mL) and the contents of each syringe were pooled in the container of the bone-marrow-collection kit containing anticoagulant solution. The final volume of bone marrow aspirate (200 mL) was then filtered through a sequence of successively	9.8 ± 4.3 × 10^6 *vs* 20.2 ± 8.6 × 10^6	n = 16 patients with aseptic nonunion of femur were treated with injection of BM-MSCs who had locked IMN. Follow up: 3-8 mo	Radiographic RUST scores	Bone union occurred in 8 of 16 patients according to RUST. The grafts used in patients whom treatment failed contained significantly lower number of total nucleated cells (9.8 ± 4.3 × 10^6 *vs* 20.2 ± 8.6 × 10^6)	Ⅳ

		smaller-diameter mesh filters. The cells were finally collected in a blood transfer pack unit. The aspirated material was reduced to a final volume of 40 mL by removing most of the RBC the plasma by centrifugation					
Hernigou *et al*[29]	Ankle nonunion	150 mL of bone marrow aspirate obtained from anterior portion of the ipsilateral iliac crest then treated with a cell separator	27.3 ± 14.6 × 10^6	*n* = 86 ankle nonunion in diabetic patients treated with BM-MSCs *vs* *n* = 86 diabetic matched nonunion treated with a standard bone iliac crest autograft	Time of union, callus volume, complication, morbidity of graft harvesting *vs* bone marrow aspiration in diabetic patients	70 out of 86 patients (82.1%) treated with BMC achieved healing with a low number of complications; 53 (62.3%) of patients treated with iliac bone graft had healing and major complications were observed: Amputations, osteonecrosis of fracture wound edge, infections	Ⅲ
Hernigou *et al*[30]	Tibial shaft nonunion	Bone marrow aspirated from anterior iliac crest total of 300 mL then concentrated to 50 mL	18 ± 7 million	BMAC injected into 60 noninfected atrophic nonunion of tibia. Follow up until union	Radiographic union; healing time; volume of callus	Patients who did not achieve union had significantly lower number of progenitor cells comparing to the 53 patients who achieved union. There was positive correlation between the volume of mineralized callus at 4 mo and the number and concentration of fibroblast colony-forming units in the graft; there was a negative correlation between the time needed to obtain union and the concentration of CFU in the graft	Ⅳ
Ismail *et al*[31]	Long bone nonunion	40 mL of bone marrow was aspirated from posterior iliac crest and transferred into a container prefilled with 5000 U/mL of heparin. Aspirate was diluted with phosphate-buffered saline at a ratio of 1:1 and centrifuged at room temperature at 3000 rpm for 30 min. The collected buffy coat was washed and transferred into a culture flask containing Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum. Cells were incubated at 37 ℃ at 5% CO_2 with a routine culture medium change every two to three days. Subculture was performed between	14-18 million BMSCs	*n* (total) = 10. *n* = 5, treated with combination of 15 million BM-MSCs, 5 g/cm^3 (HA) granules and internal fixation. *n* = 5, control subjects were treated with iliac crest autograft, 5 g/cm^3 HA granules with internal fixation. Follow up = 12 mo	VAS, LEFS, DASH score. Radiological assessments for union were conducted by a blinded radiologist using two radiological scoring systems: The Lane-Sandhu and Tiedeman radiological scores	No significant differences in post-op pain between the two groups. The treatment group demonstrated initial radiographic and functional improvements. Statistically significant differences in functional scores were present during the first (P = 0.002), second (P = 0.005) and third (P = 0.01) month. Both groups achieved similar outcomes by the end of one year follow up	Ⅲ

		days 7 and 10. Mixed with 5 g/cm^3 defect of HA granules				
Le Nail *et al*[32]	Open tibia fracture	Hernigou's technique. Bone marrow from posterior iliac crest by needle aspiration. Around 500 mL concentrated by centrifugation to obtain 50 mL	171 ± 107 × 10^6 *vs* 118 ± 28 × 10^6	*n* = 43 cases of open tibial fractures with initial surgical treatment that developed nonunion or delayed union, subsequently treated with injection of BMAC	Clinical success (consolidation without any subsequent procedure): Non painful callus palpation and a full weight bearing without any contention system. Radiographic bone healing 3 out of 4 cortices	23 successes (53.5%) within 17 wk after BMAC	Ⅳ
Thua *et al*[33]	Long bone nonunion	BMA (300-350 mL) were obtained by Jamshidi vacuum. Both posterior iliac crests of patients were harvested under loco-regional anaesthesia. BMAC was produced *via* density gradient centrifugation using the Sorvall centrifuge at 3670 rpm for 7 min. Afterwards, a total volume of 8 mL BMAC was mixed with freeze-dried allograft cancellous bone chips. BMAC was incubated for 15 min with bone chips as a composite of BMAC-ACB prior to transplantation	2.43 ± 1.03 (× 10^6) CD34 cells/mL (staining)	*n* (total) = 27. *n* = 9 control treated with autologous cancellous bone graft from iliac crest. *n* = 18 clinical trial group treated with BMSCs and allograft cancellous bone chips. Correction and optimization of fixation device were done for previously failed procedures. Patients were followed up in outpatient clinic for 1, 3, 6, 9 12, 18, 24 mo	Functional outcomes, radiographic outcomes based on modified Lane and Sandhu radiological scoring system	Bone consolidation was obtained in 88.9% and mean interval between cell transplantation and union was 4.6 ± 1.5 months in autograft group. Bone union rate was 94.4% in group of composite BMAC-ACB implantation. The time to union in BMAC-ACB grafting group was 3.3 ± 0.9 mo, and led to faster healing when compared to the autograft	Ⅲ

NS: Not significant; BM-MSC: Bone marrow-derived mesenchymal stem cell; BMA: Bone marrow aspirate; RBC: Red blood cell; CFU: Colony-forming units; BMSC: Bone marrow derived stroma cell.

compared to patients in the autograft group[33]. One study found a significantly lower number of progenitor cells in patients who did not achieve union as well as a negative correlation between the time needed to obtain union and the concentration of colony forming units in the graft[30]. Lastly, one study evaluated the efficacy of cBMA in the treatment of open tibia fractures and found adequate bone consolidation and bone callus formation in all patients[25]. Variation of cBMA application was seen amongst the studies evaluated. These methods utilized cBMA in isolation or in combination with DBM/rhBMP-2, freeze-dried allograft, or cancellous bone chips. Application of cBMA to the site of nonunion was accomplished by either fluoroscopic visualization or percutaneous injection.

cBMA in tendon repair

Five studies evaluating cBMA in tendon repair were included and summarized in Table 5[34-38]. One study evaluated open Achilles tendon repair augmented with cBMA and reported excellent functional outcomes, early mobilization, normal range of motion, and no re-ruptures at a mean follow up of 29.7 mo[38]. One study evaluated the use of cBMA during rotator cuff repair and reported enhanced healing rates, improved quality of the repair surface on ultrasound and MRI, and a decreased risk of re-rupture when compared to the control group[34]. The MSC content in rotator cuff tears was evaluated in one study, which demonstrated a moderate-to-severe reduction in content at the tendon-bone interface tuberosity relative to the control[35]. Lastly, one study showed that MSCs treated with insulin had an increase in tendon-specific markers, content of tendon specific proteins, and receptors on the cell surface compared with control cells[36]. None of the studies specifically described the method of cBMA injection.

DISCUSSION

cBMA in cartilage repair

Articular cartilage injury presents orthopedic surgeons with a difficult challenge as its inherent avascularity and poor healing potential can hinder its self-regenerative capacity. This poor repair capacity has been implicated in the development of post-traumatic osteoarthritis (PTOA) and osteochondral lesions (OCL). Traditional techniques for surgical stimulation of cartilage repair include microfracture and micropicking. These techniques penetrate the subchondral bone in order to stimulate blood flow and allow MSCs access to the cartilage defect. In addition,

Table 5 Studies evaluating concentrated bone marrow aspirate in tendon repair

Ref.	Tissue	BMAC preparation	Concentration	Study design/ methods/follow up	Outcomes measured	Results	Level of evidence
Hernigou *et al*[34]	Rotator cuff	150 mL BMA from iliac crest mixed with an anticoagulant solution (citric acid, sodium citrate, dextrose). MSCs were injected in the tendon at the junction between the bone and tendon (4 mL), and in the bone at the site of the footprint (8 mL). Each patient in the MSC-treated group received a total of 12 mL of bone marrow concentrate	51000 ± 25000 cells in 12 mL of injected BMC	n = 45 received MSCs during repair. n = 45 matched control group of 45 patients who did not receive MSCs. Follow up: 3, 6, 12, 24 mo and 10 yr	RTC healing and re-tear rate confirmed by ultrasound and MRI	45/45 repairs with MSC augmentation had healed by six months *vs* 30/45 repairs without MSC treatment by 6 mo. Intact rotator cuffs were found in 39/45 patients in the MSC-treated group, but just 20/45 patients in the control group. Patients with a loss of tendon integrity at any time up to the ten-year follow-up milestone received fewer MSCs as compared with those who had maintained a successful repair during the same interval	Ⅲ
Hernigou *et al*[35]	Tendon-bone interface rotator cuff	NS	NS	n = 125 symptomatic patients. n = 75 control patients. Assessed the level of MSCs in the tuberosity of the shoulder of patients undergoing a rotator cuff repair	Mesenchymal stem cell content at the tendon–bone interface tuberosity was evaluated by bone marrow aspiration collected in the humeral tuberosities of patients at the beginning of surgery	A significant reduction in MSC content (from moderate, 30%-50%, to severe > 70%) at the tendon–bone interface tuberosity relative to the MSC content of the control was seen in all rotator cuff repair study patients. Severity of the decrease was statistically correlated to the delay between onset of symptoms and surgery, number of involved tendons, fatty infiltration stage and increasing patient age	Ⅲ
Mazzocca *et al*[36]	Rotator cuff	MSCs were exposed to either insulin or tendon-inducing growth factors or were left untreated to serve as a control. The BMA was overlaid onto a 17.5% sucrose gradient and centrifuged for 5 min at 1500 rpm (205 g), and the resulting pink middle layer was obtained. After the isolation of bone marrow, MSCs were exposed to a 1-time dose of 10-9-mol/L, 10-10-mol/L, 10-12-mol/L, or 10-13-mol/L insulin from bovine pancreas or were left untreated to serve as a control	NS	n = 11 patients undergoing arthroscopic RCR. After the determination of the optimal dose of insulin, MSCs were (1) exposed to the hormone insulin; (2) exposed to the growth factors IGF-1, bFGF, and GDF-5, which served as a positive control for MSCs' differentiation into a tendon; or (3) left untreated to serve as a negative control. In the growth factor group, MSCs were treated with a 1-time dose, 10 ng/L, of IGF-1, bFGF, and GDF-5 or 10–10-mol/L insulin	Cell count, gene expression, protein analysis, and immunocytochemical analysis. Confirmation of protein levels was verified on immunocytochemistry analysis by 4 independent evaluators blinded to group assignment	MSCs treated with insulin showed increased gene expression of tendon-specific markers (P > 0.05), increased content of tendon-specific proteins (P > 0.05), and increased receptors on the cell surface (P > 0.05) compared with control cells. Histologic analysis showed a tendon-like appearance compared with the control cells	Ⅲ
Mazzocca *et al*[37]	Rotator cuff	Isolation 1: one 5 min centrifugation at 1500 rpm in which BMA was overlaid onto a 17.5% sucrose gradient in a 50-mL conical tube followed by extraction of CTPs in the fractional layer. Isolation 2:30 min	Nucleated cells harvested from fractionated layer were counted and plated	n = 23 BMAC harvested through the anchor tunnel of the humeral head during arthroscopy. n = 23 matched controls. Mean time to follow-up was	Reverse transcription polymerase chain reaction analysis, Single Assessment Numeric Evaluation score	Reverse transcription polymerase chain reaction analysis and cellular staining confirmed the osteogenic potential of the connective tissue progenitor cells. There was no statistically	Ⅲ

		centrifugation at 1500 rpm followed by fractionated layer extraction of CTPs using a Histopaque gradient	on 100 mm Primaria dishes at a concentration of 0.5×10^6 cells/9.6 cm^2 then incubated	10.6 ± 6.7 mo in the aspirate group and 10.0 ± 6.2 mo in the control group		significant difference in the Single Assessment Numeric Evaluation score, range of motion measures or post-operative strength measures between groups	
Stein *et al*[38]	Achilles	30 to 60 mL of BMA, combined with a standardized mixture of anticoagulant citrate dextrose solution A and separated by centrifugation at 3200 rpm for 15 min. The aspirate was concentrated to yield a volume of 6-9 mL of BMAC	NS	*n* = 28 open repairs with BMAC. Mean follow up: 29.7 mo. Patients were followed postoperatively at two weeks, six weeks, three months, six months, one year and annually thereafter	Calf atrophy, maximum dorsi- and plantarflexion, and fatigue limit during single-limb heel raise. Functional and activity status was measured in terms of time to walking, light activity (such as cycling or jogging) and return to sport, as with the validated Achilles Total Rupture Score. Self-reported functional status, activity level and ATRS	All patients achieved good or excellent outcomes postoperatively by attaining functional use or return to sport. At final follow-up of 29.7 ± 6.1 mo, mean calf circumference for paired operative and nonoperative extremities was 37.7 ± 2.0 and 38.2 ± 2.0 (difference -0.5 ± 1.3) cm, respectively, for the 26 patients with single Achilles tendon repair. Walking without a boot was at 1.8 ± 0.7 mo, and participation in light activity was at 3.4 ± 1.8 mo. Overall, 92% (25 of 27) patients returned to their preferred sport successfully at 5.9 ± 1.8 mo. Mean ATRS at final follow-up was 91 (range 72-100) points, with no single mean item score below 8 points. All patients were able to achieve a ROM of neutral dorsiflexion or greater and were able to successfully perform a single-limb heel raise at final follow-up	Ⅳ

NS: Not significant; MSC: Mesenchymal stem cell; BMA: Bone marrow aspirate.

mosaicplasty and autologous chondrocyte implantation (ACI) have been utilized to repair chondral damage. First and second-generation ACI procedures, as well as mosaicplasty, have several concerns including donor site morbidity, cost, and lack of availability to all surgeons due to FDA restrictions. The inability of chondrocytes to self-regenerate and self-renew has directed surgeons to investigate alternative biologic augments in the traditional surgical treatment for cartilage defects. cBMA is a rich source of mesenchymal stem cells and has emerged as a treatment strategy to regenerate cartilage defects in OCL and PTOA.

Several *in vivo* models have demonstrated production of type II collagen and hyaline-like repair tissue when introducing MSCs to a cartilage defect, therefore the use of cBMA may provide further stimulation of chondrogenesis when addressing cartilaginous lesions[19]. There have been a number of studies evaluating the use of cBMA in cartilage regeneration and repair in the animal model. Saw *et al*[39] investigated the use of cBMA combined with hyaluronic acid in the treatment of full-thickness chondral defects in a goat model and reported hyaline regeneration after 24 wk. Fortier *et al*[40] evaluated the treatment of full-thickness cartilage defects with cBMA combined with microfracture in the equine model. Improvements in both macroscopic and histologic scores in tissue treated with cBMA were reported with MRI demonstrating an increase in defect filling and improved repair tissue integration with normal surrounding cartilage[40].

The current literature demonstrates the potential benefits of utilizing cBMA for the repair of cartilage injury in the clinical setting. Significant clinical improvement in functional scores was demonstrated with the use of cBMA in the treatment of full thickness cartilage injury, post-traumatic osteoarthritis, and osteochondral lesions. Improved clinical and histologic results were reported when cBMA was used as an adjunctive procedure with either microfracture or MACI in the treatment of full thickness chondral lesions[4,6,7]. On MRI, groups treated with cBMA demonstrated superior cartilage ingrowth with T2 values closer to that of superficial hyaline cartilage when compared to either a control scaffold or MACI alone[7,10]. These positive results were also demonstrated when utilizing cBMA in the treatment of OCLs. Gobbi *et al*[18] compared with microfracture with cBMA in the treatment of OCLs and found that microfracture resulted

in 65% normal IKDC at 2 years with decline to 27% at 5 years *vs* 100% normal at 2 years and no decline at 5 years for patients treated with cBMA. Buda *et al*[11] reported a higher presence of hyaline like values and lower incidence of fibrocartilage on T2 mapping in patients who received cBMA when compared to those who received ACI. Hannon *et al*[19] also demonstrated better T2 relaxation values with higher measurements of adjacent cartilage in patients treated with bone marrow stimulation (BMS) with cBMA than those treated with BMS alone. Surprisingly, these positive results were not translated as effectively when evaluating cBMA in the treatment of knee OA. Overall, studies demonstrated positive results with improved pain and clinical scores initially but after one-year follow-up, there was no significant difference between groups receiving cBMA and those that did not.

cBMA in bone regeneration

Nonunion is a catastrophic failure of bone healing, which has gained increased attention over the last two decades. It is estimated that 5% to 10% of fractures will result in delayed union or nonunion resulting in prolonged treatment and repeated hospitalizations, longer rehabilitation protocols, and increased overall morbidity[41]. The financial burden posed by nonunion remains a challenge for orthopedic surgeons with a total estimated cost of these complications ranging between $23000 and $60000 per patient[42]. Numerous techniques of treating nonunion have been described in the literature including invasive interventions such as open reduction internal fixation with the use of bone graft or bone graft substitutes. Autologous cancellous bone graft derived from the iliac crest is still considered the gold standard graft option due to its high potentials of osteoconduction, osteoinduction, and osteogenesis. However, there is a limit to the amount of bone graft from iliac crest donor site that can be harvested in the reconstruction of large osseous defects. In addition, there are disadvantages of chronic donor site pain, cosmetic concern, and nerve injury, which have been documented in the literature[33].

The use of cBMA as an adjunctive procedure has gained attention in the treatment of nonunions[30]. The current literature demonstrates faster healing with greater than 94% union rate when using cBMA combined with allograft compared with conventional autologous cancellous bone graft[33]. Ismail *et al*[31] reported similar union rates and outcomes when comparing cBMA and iliac crest autograft. The benefits of cBMA as an adjunctive therapy has also been demonstrated in the treatment of upper extremity long bone nonunion. Garnavos *et al*[27] described successfully using a minimal invasive approach by injecting cBMA to address humeral diaphyseal fractures, thereby avoiding potential complications associated with the conventional compression plating technique for treating humeral nonunions. Hernigou *et al*[29] utilized the same minimally invasive technique to treat diabetic ankle fractures nonunion. The diabetic population poses a challenge for orthopedic surgeons with well-documented increased complications and increased time to bony union. Hernigou *et al*[29] also reported a union rate of 82.1% with minimal complications in patients who received cBMA compared to a union rate of 62.3% with major complications in patients who received iliac bone graft alone.

Several studies evaluated the effect of BMA concentration on functional outcomes when treating long bone nonunions. Hernigou *et al*[30] demonstrated that improved time to union with the use of cBMA was potentially related to the number of progenitors in the graft. The amount of bone healing may be directly related to the concentration of cells and the time to union may be indirectly related to the number of cells[30]. This finding was also supported by Guimaraes *et al*[28] demonstrating that grafts used in patients whom treatment failed contained significantly lower number of total nucleated cells. Bastos Filho *et al*[25] compared using cBMA *vs* whole volume BMA reporting no significant difference in time to union and patient satisfaction score. Although no significant difference was reported, this may be attributed to the small sample size in the cBMA group (n = 2) and minimal follow up. In addition, this study highlighted that unprocessed cBMA contains larger volume and fatty content in the graft increasing the risk of pulmonary embolism, therefore the smaller volume of cBMA may in fact be a safer alternative.

cBMA in tendon repair

Tendon injuries typically result from repetitive motions or overuse and can be difficult to treat as many patients either present late or after a prolonged period of non-operative management making treatment challenging due to the chronicity of the injury. It has been well documented that delayed presentation of rotator cuff tears decreases the MSC content and healing potential in patients[35]. A study by Hernigou *et al*[35] reported a significant reduction in the number of MSCs at the tendon-bone interface of the greater tuberosity in patients with a rotator cuff injury. In addition, they found that the severity of the decrease in MSC content correlated to increasing patient age, delay between onset of symptoms and surgery, fatty infiltration stage of muscle, and the number of involved tendons[35]. It has been demonstrated that MSCs have the potential to develop into tenocytes and can be a source of growth factors to establish an environment conducive to tendon tissue regeneration. MSCs in the form of cBMA have been shown to improve the strength and quality of tissue formed when used in tendon repair[34,35,38].

The current literature has demonstrated that the addition of cBMA can help to heal tendon injuries and at times may decrease the healing time and rate of re-rupture. Hernigou *et al*[35] reported enhanced healing and improved quality of the repair surface on ultrasound and MRI in patients receiving cBMA during rotator cuff repair. They reported that 100% of the rotator cuff repairs healed by six months compared to 67% in the control group. Furthermore, 87% of the study group had an intact rotator cuff repair compared to 44% of the control at ten year follow up indicating superior outcomes in the longer term[34]. The benefits of cBMA in tendon repair

have also been demonstrated in the Achilles tendon model. Stein *et al*[38] reported excellent results with no re-ruptures, decreased calf atrophy, early mobilization, a 92% return to sport, and better ankle range of motion in patients receiving adjunctive cBMA during Achilles tendon repair compared to those who received no additional treatment.

One of the difficulties in analyzing BMA literature is the variable methods of harvesting, preparing, and concentrating cBMA. Mazzocca *et al*[37] devised a novel technique for harvesting BMA in patients undergoing rotator cuff repair with no donor site morbidity. BMA was harvested through the anchor tunnel of the humeral head during routine arthroscopic rotator cuff repair. No additional complications during the procedure, no significant delay in the procedure, and no difference in functional patient outcomes were reported when using this harvest technique[37]. Lee *et al*[43] studied the use of two different concentrations of allogenic cBMA in patients with lateral epicondylitis. They found no significant differences in the changes of elbow pain and performance between the two groups on follow up visits but they did note faster pain improvement and an earlier plateau of performance scores in the group that received a higher concentration of MSCs[43]. Lastly, Mazzocca *et al*[36] showed that MSCs treated with insulin showed statistically significant increase in gene expression of tendon-specific markers, increase in content of tendon-specific proteins, and increase in receptors on the cell surface. Therefore, these studies demonstrate that there are many factors that can increase the potential for tenocyte differentiation and enhanced tendon repair and regeneration.

Level of evidence

Although the literature highlights the potential benefit of cBMA as either a primary or adjunctive treatment strategy in the treatment of cartilaginous lesions, bony defects, and tendon injury, the majority of these studies were of clinical level of evidence Ⅲ or Ⅳ. This review demonstrates the need for future randomized clinical trials with larger numbers of subjects and standardization of harvesting and application. Although several studies evaluated the effect of cell concentration on healing potential, an effective therapeutic range has yet to be established for each tissue environment.

Summary of MSC mechanism

Adult BMSCs have two primary functions: (1) to differentiate into distinctive end-stage cell types such as bone, cartilage, and tendon; and (2) to secrete bioactive macromolecules that are both immunoregulatory and regenerative[44]. Every cell has a half-life with a turnover sequence mechanism that gives rise to the phenotypes in complex tissues. This allows for both replacement of cells, as well as, the capacity for differentiation into bone, cartilage, and tendon. BMSCs also have characteristic markers of pericytes, which are smooth muscle vascular support cells that may play an important role in stem cell differentiation[44,45]. MSCs also demonstrate trophic activity through secretion of both cytokines and growth factors[46]. The intrinsic secretory activity of MSCs affords a regenerative environment for the repair of injured or damaged tissues[44]. Tissue-specific scaffolds have also been utilized in tissue engineering to reform tissues when MSCs are implanted into different tissue sites. The capacity for cell regeneration and repair relies on several additional factors including patient age, extent of injury/damage, and the functional ability of MSCs to grow and repair. Tissue engineering allows for the manipulation of both the delivery of MSCs to targeted tissue sites and the microenviroment for which cells grow in order to enhance differentiation[44]. Future investigations will continue to focus on harnessing the therapeutic potential of MSCs in tissue specific environments to enhance regeneration and repair of cartilage, bone, and tendon.

Conclusion

The current literature demonstrates the potential benefits of utilizing cBMA for the repair of cartilaginous lesions, bony defects, and tendon injuries in the clinical setting. The studies have demonstrated using cBMA as an adjunctive procedure can result in cartilage healing similar to that of native hyaline tissue, faster time to bony union, and a lower rate of tendon re-rupture. This systematic review also demonstrates discrepancies between the literature with regards to various methods of centrifugation, variable cell count concentrations, and lack of standardized outcome measures. Although several studies evaluated the effect of cell concentration on healing potential, an effective therapeutic range has yet to be established for each tissue environment. Future studies should attempt to examine the integral factors necessary for tissue regeneration and renewal including stem cells, growth factors and a biologic scaffold.

COMMENTS

Background

Bone marrow aspirate (BMA) has been utilized as a source of bone marrow-derived mesenchymal stem cells (BM-MSC) with its relative ease of harvest, low morbidity, and feasible cost. BMA alone has a relatively low percentage of MSCs and therefore concentrated bone marrow aspirate (cBMA) has gained increased attention. cBMA stimulates tissue regeneration and repair and has become an increasingly popular alternative and adjunct in the treatment of cartilaginous lesions, bony defects, and tendinous injuries.

Research frontiers

Current research has focused on the use of cBMA in cartilage, bone, and tendon regeneration and repair. The available literature regarding the use of cBMA in different tissue environments is highly heterogeneous with regards to indications, concentrations and overall functional outcomes. This systematic review attempts to establish proof of concept for the use of cBMA in these biologic environments.

Innovations and breakthroughs

This systematic review demonstrates the potential benefits of utilizing cBMA for the repair of different tissue types in the clinical setting based on the most up-to-date published clinical studies. This systematic review also highlights

discrepancies between the literature with regards to various methods of centrifugation, variable cell count concentrations, variable methods of application of cBMA, and the lack of standardized outcome measures.

Applications

The current literature demonstrates the potential benefits of utilizing cBMA for the repair of cartilaginous lesions, bony defects, and tendon injuries in the clinical setting. The studies have demonstrated using cBMA as an adjunctive procedure can result in cartilage healing similar to that of native hyaline tissue, faster time to bony union, and a lower rate of tendon re-rupture.

Terminology

cBMA: Concentrated bone marrow aspirate; BMA: Bone marrow aspirate concentrated by centrifugation in order to increase the ratio of MSCs.

Peer-review

The authors present a well written systematic review examining the use of BMA in the management of cartilage, bone, and tendon injuries. Overall, the paper is very well organized and reads well.

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