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Pooja Pithadia *

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Research Article

BMAC and Adipose-Derived MSCs Treatment for Knee Osteoarthritis: A Systematic Review

Pooja Pithadia[1]* MSc, Sharmila Tulpule[2] MBBS, M.S, MCh Ortho, Masud ur Rahman[3] MBBS, FRCS, Mrinalini Singh[4] PhD

[1]Medical Biotechnology, Medica Pain Management Clinic, London,UK.

[2]Medica Stem Cells, Dubai,UAE.

[3]Medica Stem Cells, Dublin, Ireland.

[4]Medica Institute Pvt Ltd, India.

***Corresponding Author:** Pooja Pithadia, Medical Biotechnology, Medica Pain Management Clinic, London,UK.

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Abstract

Background: Knee osteoarthritis is the most common musculoskeletal progressive disorder that affects nearly 303 million people worldwide. This condition prevails in 10% males and 13% females among the elders above 60. Although there is conventional non-surgical and surgical treatment available for knee osteoarthritis, there is a fascinating interest in bone marrow as pirate concentrate (BMAC) as well as adipose-derived mesenchymal stem cells (AD-MSC), including enzymatically treated stromal vascular fraction (SVF) and mechanically treated (microfat/nanofat) injections among physicians. Hence, this systematic review aims to determine the efficacy of BMAC and AD-MSCs (enzyme and mechanically treated) injections for knee osteoarthritis treatment.

Methods: A systematic review was performed on the following data sources (PubMed, Scopus, Google Scholar, EMBASE, and Cochrane Library) published on March 31, 2021. The keywords or MeSH terms include 'Knee Osteoarthritis with 'Bone marrow aspirate concentrate' OR 'BMAC' or with 'Adipose-derived mesenchymal stem cells (AD-MSC)' or with 'Stromal vascular fraction' OR 'SVF' or 'Mechanically treated AD-MSC (mfat/nanofat)'. In addition, the retrieved articles were further reviewed to identify relevant research studies.

Results: The authors reviewed and tabulated data based on the year of study, study type, therapy protocol, patient population, outcome measures, and interpretation. Among the 382 records screened, 43 studies (16 on BMAC and 27 on AD-MSCs) were included in the systematic review study. Among them, only 5 were randomized controlled trials. These selected studies demonstrated short-term positive outcomes such as improvement in knee pain and function with no adverse side effects. Moreover, researchers reported varied administration methods of BMAC or AD-MSC either as standalone or in combination with other conservative procedures such as PRP (Platelets Rich Plasma), HA (Hyaluronic acid), or surgery.

Conclusions: BMAC and AD-MSC (enzymatically and mechanically treated) injections prove safer and more efficacious in patients with knee osteoarthritis for a shorter duration of 2 years. However, the available literature lacks high-quality studies with no varied clinical settings and long-term follow-up of more than two years.

Keywords: bmac; stromal vascular fraction; adipose-derived mesenchymal stem cells; bone marrow aspirate concentrate; svf; knee osteoarthritis

Introduction

Osteoarthritis (OA) is the most common type of progressive musculoskeletal arthritic disorder affecting nearly 303 million people worldwide [1]. Compared to all the joint regions, OA commonly affects hip and knee joints [2]. Due to a steady increase in ageing, obesity, and life expectancy, knee OA is prevalent in 10% males and 13% females among the elderly population [3].

Knee osteoarthritis (KOA) arises from gradual deterioration of the articular cartilage, changes to the subchondral bone, osteophyte formation, degeneration of menisci and ligaments, and inflammation of the adjacent tissues [4].

Patients were suffering from KOA experience chronic pain, swelling, stiffness, and limited range of motion in the affected joint, leading to a reduced quality of life [5].

The well-accepted first-line conservative options include RICE (Rest, Ice therapy, Compression, and Elevation) exercise, activity modification, and physiotherapy. As symptoms worsen, NSAIDs (non-steroidal anti-inflammatory drugs), corticosteroids, and hyaluronic acid injections can relieve pain and improve joint function [6]. However, none of these treatments reverses or repair the degenerative nature of the disease [7]. Even the rapid disease progression to late-stage OA in patients who do not respond to conservative treatment would eventually require knee joint replacement [8].

In this scenario, there has been significant interest in developing efficacious conservative approaches classified as regenerative. Regenerative cell therapy uses the anti-inflammatory and healing properties of a patient's cells to treat inflamed and painful tissues [7] The use of Platelet Rich Plasma (PRP) and Prolotherapy are being evaluated to relieve the pain of OA [9, 10].

Recently, mesenchymal stem cells (MSCs) have appeared as a potential therapeutic regenerative option due to their ability of self-renewal, multilineage differentiation potential, immune-suppressive, anti-apoptotic, anti-fibrotic, angiogenic, mitogenic, anti-inflammatory, and wound healing properties [11,12]. These MSCs are present in many adult tissues such as bone marrow, adipose tissues, articular cartilage, synovial membrane, periosteum, and the dermis [13] Among these sources, bone marrow mesenchymal stem cells (BMSCs) and adipose-derived mesenchymal stem cells (AD-MSCs) received more attention [14] AD-MSCs are used in several forms, including stromal vascular fraction (SVF), culture-expanded adipose-derived stem cells, and minimally manipulated fat graft.

BMAC is obtained from the iliac crest via bone marrow needle aspiration, subsequently concentrated through dedicated centrifuges, and injected directly on the knee region [15]. Adipose tissue obtained through liposuction can be treated mechanically and enzymatically to extract adipose-derived mesenchymal stem cells (AD-MSCs). For mechanical extraction, adipose tissue was harvested mechanically in a closed system to extract the tissue-healing effect of micro-fragmented tissue [31]. For enzymatic extraction, collagenase is added to the non-enriched lipoaspirate, followed by its removal via a dilution step. In the dilution step, the lipid enzyme mixture is washed with normal saline followed by centrifugation. This final step extracts the SVF product, which can be directly administered to the patient [16].

This review aims to investigate the effectiveness of BMAC and AD-MSCs (enzymatic and mechanically derived) injections regarding pain reduction and functional improvement in adult patients with knee osteoarthritis.

Methods

This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [17,18].

A comprehensive, systematic literature search was performed in April 2021, and an analysis of these articles was conducted by all the authors involved in the study. The databases of PubMed, Scopus, Google Scholar, EMBASE, and Cochrane Library were searched from 2011 to March 31, 2021. The following keywords were used in different combinations: 'Knee Osteoarthritis with 'Bone marrow aspirate concentrate' OR 'BMAC' or 'Adipose-derived mesenchymal stem cells or 'Stromal vascular fraction' OR 'SVF' or 'Mechanically treated AD-MSC (mfat/nanofat)'.

Study selection

All participants in the trials had to have a clinical diagnosis of knee osteoarthritis under either intra-articular BMAC or AD-MSCs treatment.

We limited the search to articles in English, and only human studies were included. After assessing all titles and abstracts, all relevant articles were obtained. Even the bibliographies were also searched to identify further relevant literature that met our inclusion criteria.

All studies were included if their design could be classified into one of the following categories: open-label, randomized controlled trial, prospective, retrospective study, and pilot study.

We included studies in which adult participants were diagnosed with knee osteoarthritis by clinical or image evaluation. We excluded articles lacking access to the full text, conference presentations, narrative reviews, editorials, and expert opinions.

The articles found were pooled and subjected to inclusion and exclusion criteria established before the commencement of this systematic review. A PRISMA flowchart of this systematic review is provided in Figure I.

Data extraction

The researchers independently recorded the study design, therapy protocol, patient population, outcome measures, and interpretations.

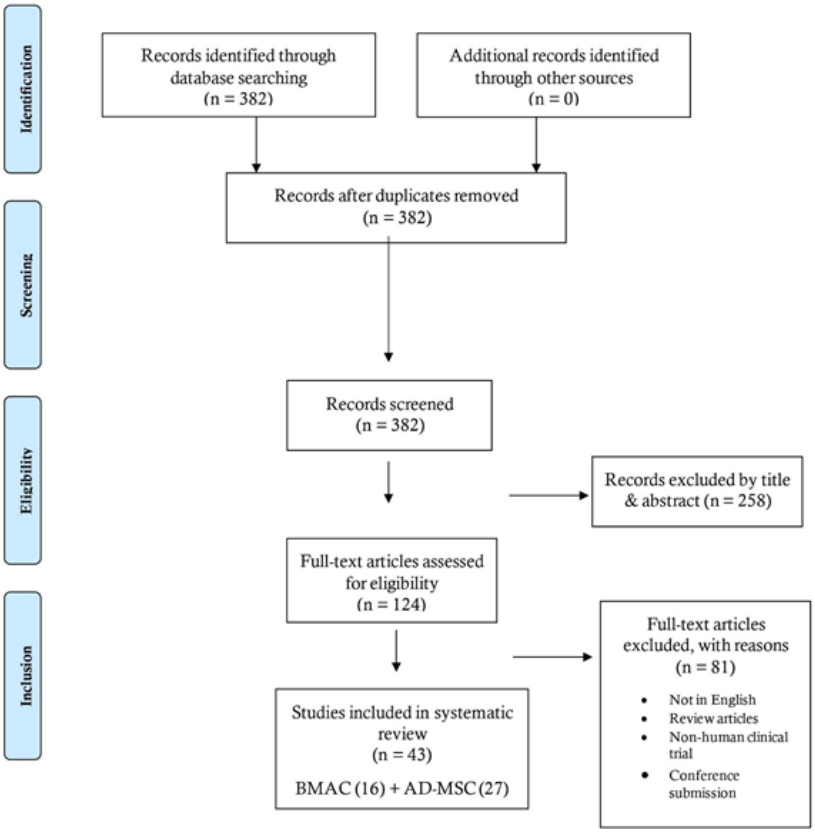

Figure 1: *A flow diagram of study inclusions: BMAC and AD-MSCs [PRISMA 2009 flow diagram]*

Results

Literature search

Of the 382 articles initially identified by the search, 16 [19,30,32,35] on BMAC and 27 [36,62,16]. on AD-MSCs, including SVF, met the inclusion criteria. Therefore, the relevant data is given in Tables III and IV.

Participants

The 16 studies under BMAC involved 10 to 681 patients with the age group of between 18-85 affected by knee OA [Table I), while 27 studies under AD-MSCs, including SVF, involved 2 to 2586 knee OA patients between 18-89 age group [Table II]. Among these 44 studies, only 5 were randomized controlled trials. Fourteen papers were prospective studies, with three of them being comparative, two being open-label, one being a pilot study. The rest were retrospective studies, with two of them being comparative.

Therapeutic approaches

Regarding the therapeutic protocol, BMAC was either injected alone or combined with PRP in the same session, alternatively as a booster dose after a certain period. Very few authors injected BMAC in association with adipose tissue or scaffold. Under AD-MSCs, it was either injected alone or combined with PRP, adipose tissue, HA, or scaffold.

Outcome measures

Regarding outcomes, varied clinical scores such as WOMAC, VAS, KOOS, IKDC, KSS, ICOAP, NPS, and LEFS were used to evaluate the outcomes of BMAC injections (Table 1) and AD-MSCs injections (Table 2). Even MRI was performed before and after the procedure to detect positive changes in the resultant images. Very few authors used ICRS, OKS, NRS, ROM, Tegner activity, Lysholm patient satisfaction scores, and PROMIS questionnaires. Immunohistochemical analysis was reported only in Roato et al. 55. 's study involving AD-MSCs injections.

Table I: Patients' demographics [BMAC]

Articles	Total enrolled	M/F	Age group	KL grade
19Shapiro et al., 2017	25	7/18	-	-
20Shapiro et al., 2018	25	7/18	42-68	I-II
21Kim et al., 2014	41	17/24	53-80	I-IV
22Sampson et al., 2016	73	-	23-79	III-IV
23Krych et al, 2016	46 (23+12+11)	23:15/8 12:8/4 11:8/3	Mean 38	-
24Anz et al., 2020	90	-	18-80	I-III

25Centeno et al, 2014	681 (616 vs 224)	616: 397/219 224:119/105	54.3 vs. 59.9	I-IV
26Centeno et al, 2015	373 (224 vs 185)	224: 143/81 185: 140/45	54.5 vs. 50.2	I-IV
27Rodriguez et al, 2018	19	3/16	58 (30-80)	I-II
28Themistocleous et al., 2018	121	36/85	70 (50-85)	III-IV
29Ryu et al., 2020	52 (25 vs 27)	-	-	-
30Kristin et al., 2015	70	-	-	II-IV
32Oliver et al., 2015	70	21/49	-	II-IV
33Shaw et al., 2018	15	5/10	Mean 67.7	-
34Vad et al, 2016	10	4/6	63.5 (52-73)	III-IV
35Hernigou et al, 2018	30	12/18	28 (18-41)	IV

Table II: *Patients' demographics [AD-MSCs]*

Articles	Total enrolled	M/F	Age group	KL grade
36Gibbs et al., 2015	4	2/2	23–50	-
37Bansal et al., 2017	10	-	≥50	I-II
7Fodor et al., 2016	6	-	51-69	I-III
38Garza et al., 2015	6	-	59 (52-69)	II-III
39Hong et al., 2019	16	-	18-70	II-III
40Mautner et al., 2019	110	24/17 12/23	59 ± 11 63 ± 11	-
41Pak J, 2011	2	-	60-87	-
42Pak et al., 2013	74	-	-	-
43Pak et al., 2016	3	-	60–87	III
44Pintat et al., 2017	19	10/9	-	-
45Yokota et al., 2017	13	2/11	74.5	III-IV
46Hudetz et al., 2017	17	12/5	40-85	III-IV
47Pers et al., 2016	18	-	50-75	III-IV
48Berman et al, 2019	2,586	-	-	-
16Zhang et al., 2021	47 (29 vs 24)	-	-	II-III
49Lapuente et al., 2020	50	-	50-89	-
50Simunec et al, 2020	12	5/7	61 (51-80)	III-IV
51Koh et al, 2013	18	6/12	54.6 (41-69)	-
52Koh et al., 2014	44 (23 vs 21)	-	-	-
53Koh et al., 2014	37 knees	-	57.4 (48-69)	-
54Koh et al., 2015	30	-	-	-
55Roato et al, 2019	20	9/11	59.6	I-III
56Jones et al., 2018	54 (27 vs 27)	-	-	-
57Bui et al., 2014	21	-	≤18	II-II
58Nguyen et al, 2017	30 (15 vs. 15)	3/12 vs 3/12	58.60 vs. 58.20	II-III
59Kim et al., 2015	49 (55 knees)	-	-	I-II
60Kim et al., 2015	54 (56 knees): 37 (39 knees) vs 17 (17 knees)	-	-	-

Table III: *Clinical studies regarding the use of BMAC to treat knee osteoarthritis*

Ref	Study	Therapy protocol	Outcome	Follow up (mon)	Conclusion
[36]	Case series	SVF + PRP + moderate exercise for 4 months	KOOS Physical function tests: GUG, SCT RPE	12	Less Pain & better knee function
[37]	Prospective	SVF + PRP	WOMAC, 6-minute walking distance, MRI	24	Significant improvement of WOMAC scores and 6-minute walking distance. MRI showed increase in cartilage thickness in all but 2 patients. All patients are satisfied with therapy.

Ref	Study	Therapy protocol	Outcome measures	Follow up (mon)	Conclusion
[19]	Single-blind, prospective RCT	BMAC + Platelet-poor bone marrow plasma vs. saline	VAS, ICOAP, WOMAC, KOOS	6	No significant improvement
[20]	Single-blind RCT	BMAC + Platelet poor plasma vs. saline	VAS, ICOAP, algometer	12	Significant improvement in pain & QoL. No superiority to saline. MRI - No cartilage regeneration
[21]	Retrospective	BMAC+ adipose tissue inj.	VAS, IKDC, SF-36, KOOS, Lysholm	8.7	Significant improvement of pain & function.
[22]	Retrospective	BMAC followed by PRP at 8th week	VAS, global patient satisfaction score	5	Significant improvement of pain with high patient satisfaction
[23]	Cohort, prospective	Scaffold + PRP vs scaffold + BMAC vs control scaffold	MRI	12	Improved cartilage maturation with greater fill and mean T2 values closer to that of superficial native hyaline cartilage
[24]	RCT	BMAC vs leukocyte rich PRP	WOMAC, IKDC	1, 3, 6, 9, & 12 before & after	PRP & BMC were effective in improving patient-reported outcomes; neither treatment provided a superior benefit
[25]	Comparative retrospective Group A vs B	(A) BMAC+PRP vs. (B) BMAC+PRP+ adipose graft	NPS, LEFS, improvement rating score	6-10	Significant improvement of pain and function. No significant benefit with the addition of adipose graft to BMAC.
[26]	Comparative retrospective Group A vs B	A- 4 × 108 cells BMAC+PRP vs B- >4 × 108 cells BMAC+PRP	NPS, LEFS, IKDC, improvement rating score	3-15	Significant improvement of pain and function. Significantly higher pain reduction with high cell content.
[27]	Retrospective	BMAC only	WOMAC & Satisfaction rate score	6-24	Better WOMAC score. No significant difference between 6-month and latest follow-up scores. Variable satisfaction rate (63.2% yes, 36.8% no).
[28]	Retrospective	BMAC only	NPS & OKS	11	Significant improvement of pain & function
[29]	Retrospective	BMAC vs hUCB-MSCs	VAS, IKDC, KOOS, M-MOCART, & ICRS	24	Significantly improvement in all outcomes in both groups; but no differences between two groups
[30]	Prospective case series	BMAC only	Adverse events, KOOS	Baseline, 3, & 6	Transient pain and swelling. Positive KOOS with improved pain, QoL, daily activities, & sports/recreation score without major complication
[32]	Prospective case series	BMAC + SVF	Adverse events, KOOS	Baseline, 3, & 6	Transient pain and swelling. Positive KOOS with improved pain, QoL, daily activities, & sports/recreation score without major complication
[33]	Retrospective	4 sequential BMAC injections in 3 months	Resting/active NPS, overall percentage improvement & LEFS	24 days	Significant improvement of pain & function. Multiple injections are more effective than a single one.
[34]	Pilot trial	BMAC only	MRI, WOMAC, NRS	14 (13-15)	Significant improvement in WOMAC and NRS scores. MRI - increase in extracellular matrix thickness by an average of 14%. Better improvement for patients younger than 63.5 years old.
[35]	RCT	BMAC vs TKA	MRI, bone marrow lesion volume, Knee society score	12 (8-16) years	Decrease in lesion size by 40% with better cartilage and bone repair. No significant difference in outcomes between BMAC & TKA. Majority preferred BMAC.

[7]	Phase I open label single-arm	SVF	WOMAC, VAS, ROM, OA index, knee motion, timed up-and-go (TUG), & MRI	12	No infections, acute pain flares, or other adverse events. significant improvement in WOMAC, VAS, ROM & TUG. MRI- no detectable structural differences. Full activity with decreased knee pain
[38]	Feasibility & safety study	SVF	PROMIS questionnaire, pain & mobility questionnaire	2, 4, 6, & 12 weeks	Decreased pain and increased mobility with no side effects
[39]	Double-blind RCT	SVF vs HA. Bilateral OA	VAS, WOMAC, ROM, whole-organ MRI score	12	VAS, WOMAC, & ROM improved significantly for both groups, but these improvements were not long lasting in the control group. MRI - significantly increased cartilage repair in the SVF group compared to the control.
[40]	Retrospective	MFAT vs BMAC	KOOS, EQOL, VAS	6	Significant improvement in pain and function, EQOL, VAS, & KOOS with both treatments, with no significant difference between them.
[41]	Case series	SVF + PRP + HA + Calcium chloride + 1ng dexamethasone	VAS, Knee motion range, Functional rating index, MRI	3	Improvement in pain & knee function
[42]	Safety study	SVF + PRP	VAS, MRI	12	Safe with no adverse side effects. Improvement in VAS & cartilage repair
[43]	Case series	SVF + PRP + HA + Calcium chloride	VAS, Knee motion range, functional rating index, MRI	5	Safe with improvement in pain and knee function
[44]	Prospective	AD-MSC+ PRP	WOMAC, MRI, & ICRS	12	Improvement in WOMAC & cartilage repair with no adverse side effects
[45]	Prospective	SVF	VAS, WOMAC, JKOM	6	VAS, WOMAC, & JKOM improved significantly
[46]	Prospective	MFAT	VAS, dGEMRIC MRI, IgG isolation from plasma and synovial fluid	12	Significant decrease in VAS scores. No change in IgG. MRI displayed increase in proteoglycan content within the ECM.
[47]	Phase I multicentric, prospective, single-arm, open-label, dose escalating	SVF injection with 3 varied stromal cell doses 2×106 10×106 50×106	VAS, WOMAC, OA index Patient global assessment Knee injury, OA outcome score, short arthritis assessment scale SF-36 quality-of-life questionnaire	6	Less pain and better knee function only in the low-dose group
[48]	Prospective	SVF + PRP	VAS, WOMAC, adverse events score	12 & 24	No difference in outcomes between SVF alone or with PRP added to SVF. Very few minor side effects. Less pain and greater ease of mobility. 82% overall improvement
[16]	Clinical trial	SVF	WOMAC, VAS, ROM, WORMS, & MOCART	before & after 1-, 3-, 6-, & 12	WOMAC, VAS, ROM – significant improvement. MRI - thickness, volume, surface of cartilage defect decreased. WORMS & MOCART – improvement in cartilage repair with no adverse side effects
[49]	Retrospective	SVF	Lequesne, WOMAC, VAS, quantification of the biochemical profiles of synovial fluid	12	Safe & effective with no adverse effects. Significant improvement in all scores after 1-year follow-up for all ages & OA degree groups.
[50]	Comparative case series	SVF+PRP vs SVF only	KOOS & MRI	12	Significant improvement KOOS in 3 of the 4 treatment groups. 67% of the patients were satisfied or very satisfied with the procedure and would recommend it to others. No serious adverse events
[51]	Case series	infrapatellar fat pad derived MSC + PRP	Lysholm score, VAS, MRI, OA Index, WOMAC	24.3 (24-26)	Significant improvement in all these scores. Effective for reducing pain & improving knee function

[52]	Prospective, comparative observational study	HTO + PRP Vs HTO + PRP + SVF	Lysholm score, KOOS, VAS		PRP + SVF showed improved cartilage healing, better KOOS, & VAS score when compared with PRP only
[53]	Retrospective Case series	AD-MSC	IKDC, Tegner activity scale, cartilage repair using ICRS grading	26.5 (24-34)	Improvement in all scores with encouraging outcomes in cartilage repair
[54]	Therapeutic case series	SVF + arthro. lavage	KOOS, VAS, Lysholm score	Before and after 3, 12, & 24	Almost all patients showed significant improvement in all clinical outcomes at the final follow-up examination. None of the patients underwent TKS during this 2-year period. Adipose-derived SVF – good option in elderly patients
[55]	Prospective	autologous conc. adipose tissue after lipoaspirate centrifugation	WOMAC, VAS, MRI, immunohistochemistry	18	Both WOMAC & VAS scores improved significantly, WOMAC showed progressively better outcomes. MRI: Outerbridge grade did not show significant changes. Immunohistochemistry displayed new tissue growth.
[56]	Comparative prospective, single-center, parallel-group RCT	SVF vs HA	WOMAC, PROMIS questionnaire, synovial fluid analysis, sway velocity assessment	6	Ongoing
[57]	Prospective	SVF + PRP	VAS, Lysholm scores, MRI	6	Significant improvement in VAS & Lysholm scores. MRI analysis showed partial regeneration & thickening of articular cartilage
[58]	Comparative prospective	AM + SVF + PRP injection vs. AM alone	WOMAC, VAS, Lysholm scores, MRI, knee joint function	18	WOMAC, Lysholm, & VAS scores improved for both groups up to 12 months, but at 18 months, the SVF group was significantly better than the control group. At 12 months, the SVF group displayed significantly less bone marrow edema than the control group.
[59]	Case series retrospective	AD-MSC	IKDC, Tegner activity score, patients' overall satisfaction score	-	Significant improvement in all scores. The clinical outcomes of MSC implantation for knee OA are encouraging.
[60]	Cohort study	MSCs loaded as a scaffold vs MSC without scaffold	IKDC, Tegner activity scale, cartilage repair assessed with ICRS grade	28.6 (24-34)	Clinical & arthroscopic outcomes of MSC implant were encouraging in both groups, although there were no significant differences between groups. However, second-look arthroscopy showed better ICRS grades in Group 2.

Table IV: *Clinical studies regarding the use of AD-MSCs to treat knee osteoarthritis*

Safety and efficacy of BMAC and AD-MSCs therapy

None of the studies analyzed in this systematic review recorded any complication or adverse effect of BMAC and AD-MSCs administration. Only mild pain and swelling have been observed in very few patients within the initial few days following BMAC/AD-MSCs injection procedure. Furthermore, both BMAC and AD-MSCs showed positive clinical outcomes with significant improvement in pain, articular function, and range of movement.

Discussion

The results of this systematic review validate that both BMAC and AD-MSCs treatments are safe and effective to treat knee OA. However, the therapeutic use of BMAC and AD-MSCs, especially SVF, is restricted across the United States, Europe, and many other countries based on safety and efficacy concerns.

The significant finding of this systematic review is that most of the studies are of low quality with a lack of well-defined methodologies, with very few RCTs, thus preventing us from providing any substantial conclusions on the therapeutic potential of these AD-MSCs and BMAC injections.

Furthermore, there is an inadequate patient selection process, although these studies reported good reliability. The inclusion and exclusion criteria, recruitment rate, and a well-defined selection process were rarely reported. Hence, further studies including larger patient cohorts should be performed to demonstrate the long-term effect of both BMAC and AD-MSCs injections.

Many patients underwent conservative treatments such as steroid treatment or surgical procedures in most of these studies, such as microfracture, arthroscopic debridement, or high tibial osteotomy. Hence there is no clear understanding of the exclusive clinical potential of these BMAC and AD-MSCs injections.

We can find the release of platelet-rich plasma (PRP) treatment without adequate evidence in the recent past. This treatment has been used clinically due to high media exposure only [61]. There is a possibility to exempt 510(k) regulations [62]. New medical devices "substantially equivalent" to those already prevalent in the market can skip the standard FDA approval process. Hence, there was an increase in the production of PRP kits. However, this market saturated due to overproduction by various preparation systems, thereby preventing a "standardization" of PRP therapy for knee OA treatment.

This same scenario is now approaching AD-MSCs and BMAC therapies that are not affected by the regulatory burden. Moreover, they can be quickly harvested from the OA patient and administered immediately through an intra-articular injection with PRP or HA (hyaluronic acid). HA provides an environment where MSCs can easily adhere to the target area around the lesion and differentiate into cells to build damaged bone and cartilage. Similarly, PRP consists of highly concentrated platelets and varied growth factors to exacerbate the proliferation of MSCs [68,69]. Hence, this simultaneous use of other biological agents or administering these treatments following the conventional procedures prevent a reasonable comparison of the studies performed so far.

The available RCTs have several biases since most of the patients were treated bilaterally [20,63]. This is not the ideal condition to determine the efficacy of a treatment since the patients cannot evaluate one knee independently from the other. There was no proper clarity on the number of cells administered and the exact number of injections for the best outcome. It was even difficult to interpret which one of the two treatments provide better outcomes. Although their immunophenotypes are more than 90% identical [64,65], they still have many distinct characteristics, especially in their cell surface markers, differentiation potentials, and distribution within the body. An in vitro analysis revealed that almost 300-fold more SVF can be derived from 100 g of adipose tissue when compared to 100 ml of bone marrow aspirate [66,67]. However, there is no apparent connection between the quantity and the dose-effect. Furthermore, there is no substantial evidence to define the patient's profile that could respond better to a specific treatment compared to others. Hence, this topic demands more research to understand the effect of both BMAC and AD-MSCs therapies.

Both bone marrow harvesting and lipoaspiration are minimally invasive procedures with minimal side effects. However, lipoaspiration was more severe due to the associated risks of pain and hematoma. Anyway, the surgeon who opts for these treatments depends on the availability of preparation kits in different countries. Moreover, industries have been releasing their proprietary kits for BMAC and AD-MSCs preparation, with new methods still being developed. However, there is no adequate research evidence to support the ability of MSCs.

At present, stem cell treatment is expensive and cannot be considered a "routine" treatment for knee cartilage degeneration. From a clinical viewpoint, the use of BMAC and AD-MSCs for knee OA treatment seems to be safe and deliver positive clinical outcomes. Moreover, this treatment can be a minimally invasive therapeutic option for patients who are ineligible for surgery. However, their promising outcomes for a shorter duration (3 months–24 months) must sustain for the long term of more than two years compared to the available conventional treatments. Hence, the use of BMAC or AD-MSCs therapies must be thoroughly discussed between the physician and the patient before proposing them as a first-line therapeutic approach to avoid surgery.

However, increasing the number of treatment options for knee OA does not always intend to improve the standard of care, especially when there is a lack of enough comparative trials that determine the effectiveness of a novel treatment compared to established ones.

Limitations

It is possible that BMAC and AD-MSCs injections could deliver positive outcomes in treating knee osteoarthritis, according to the results from our study. Nonetheless, the factors affecting the outcomes are but not limited to the lack of control group, a small number of studies and co-interventions, a small sample size, lack of long-term follow-up of not more than two years, the possibility of bias, and lack of objective assessment on the interventions

Although these above findings provide encouraging results, the lack of comparative study with corticosteroids and hyaluronic acid limits definitive conclusions, furthermore, the relationship of sex, age, and the severity of knee osteoarthritis could not be figured out clearly.

Additionally, MRI evaluation was not performed in all the studies to complement the clinical parameters, including the quantification of knee cartilage regeneration following the treatment. Moreover, there is a lack of comparison among the outcomes for different KL grades. Hence, more studies are required to confirm the positive long-term effects of AD-MSCs and BMAC therapies for knee osteoarthritis.

Despite having all these limitations, the treatment of knee osteoarthritis with BMAC and AD-MSCs seems to be safe by delivering positive clinical outcomes. This treatment can be a potential minimally invasive option for those who are ineligible for invasive approaches.

Conclusion

BMAC and AD-MSCs injections prove safer and more efficacious in treating knee osteoarthritis on a short-term duration (3 months-24 months) without any adverse side effects. However, only very few randomized control studies are published to support this result. Additionally, there is a lack of high-quality research studies for more than 2 years with varied trial settings.

List of abbreviations

Abbreviations	Full form
BMAC	Bone marrow aspirate concentrate
SVF	Stromal vascular fraction
AD-MSCs	Adipose-Derived Mesenchymal Stem Cells
PRP	Platelet-rich Plasma
EMBASE	Excerpta Medica dataBASE
RCT	Randomized Controlled Trial
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
HA	Hyaluronic Acid
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

KOOS	Knee Injury and Osteoarthritis Outcome Score
IKDC	*International Knee Documentation Committee*
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
MRI	Magnetic Resonance Imaging
ROM	Range of Motion
VAS	Visual Analogue Scale
KSS	Knee Society Score
ICOAP	Intermittent and Constant Osteoarthritis Pain Score
NPS	Neuropathic Pain Scale
LEFS	Low Extremity Functional Score
ICRS	International Cartilage Repair Society
OKS	Oxford Knee Score
NRS	Numerical Rating Scale
QoL	Quality of Life
HTO	High Tibial Osteotomy
AM	Arthroscopic Microfracture
MFAT	Microfragmented adipose tissue
TKA	Total Knee Arthroplasty

Declarations

Ethics approval and consent to participate: Not Applicable

Consent for publication: Not Applicable

Availability of data and materials: Not Applicable

Competing Interests: The authors declare that they have no competing interests

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