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

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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 aspirate 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.
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.

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    |

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

Table II: Patients' demographics [AD-MSCs]

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. |
| Study Type            | Intervention | Measurements                                                                 | Duration | Results/Outcomes                                                                                                                                                                                                 |
|-----------------------|--------------|-------------------------------------------------------------------------------|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| [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 liposuction are minimally invasive procedures with minimal side effects. However, liposuction 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

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