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A REVIEW OF BONE MARROW ASPIRATE CONCENTRATE THERAPY IN THE TREATMENT OF KNEE OSTEOARTHRITIS

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Abstract

Purpose: Bone marrow aspirate concentrate (BMAC) provides a novel therapeutic option for knee osteoarthritis. The authors aim to systematically evaluate functional and clinical outcomes after BMAC injection treatment for knee osteoarthritis.

Methods: We used articles found in PubMed and Google Scholar using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies published from January 2018 through November 2023 on patients treated with a bone marrow aspirate concentrate injection with a focus on grades I-IV Kellgren-Lawrence osteoarthritis of the knee. Reports contained functional and clinical outcomes.

Results: Eleven articles were used in the extraction of data. Eight hundred seventy-six patients were injected with BMAC and 1,010 knees with osteoarthritis were included in this literature review. For studies that passed inclusion and exclusion criteria, reported outcomes included improved pain, function, and quality of life post-procedure.

Conclusion: The literature reviewed indicates that the intraarticular injection of BMAC warrants additional investigation in treating mild to severe osteoarthritis (classified under Kellgren-Lawrence I-IV). Factors such as the preparation and concentration of BMAC remain subjects of ongoing debate and scrutiny. Consequently, further research is needed to determine the feasibility and effectiveness of BMAC as a treatment modality for knee osteoarthritis.

Level of Evidence: IV.

Keywords: *Regenerative Medicine, Knee Osteoarthritis, Bone Marrow Aspirate Concentrate, BMAC, Intraarticular Injection*

INTRODUCTION

Newly diagnosed knee osteoarthritis (OA) affects roughly 10% of adults over 60. These numbers are projected to increase due to the obesity pandemic.[1] It continues to limit the functional capabilities of those affected due to increased pain, which in turn negatively influences quality of life and ability to maintain employment. Conservative first-line therapies include exercise, weight loss, and injections intra-articularly with hyaluronic acid or corticosteroids. Orthobiologics is an emerging field that includes stem cell therapy and platelet-rich plasma.

Ongoing research challenges the long-term effectiveness of such therapies and the quality of evidence that supports their use.[2]

In particular, bone marrow aspirate concentrate (BMAC) injections for knee osteoarthritis has gained more traction during the past decade due to their inherent ability to repair, regenerate, and restore tissue homeostasis in culture.[3] In-vitro BMAC have the unique ability to differentiate into different types of cells, including bone and cartilage. There are a variety of mechanisms hypothesized through which BMAC are thought to positively impact knee osteoarthritis, including the recruitment of growth factors, apoptosis reduction, reduced inflammation, and angiogenesis stimulation.[4]

Knee OA affects a substantial portion of the elderly population, with prevalence rates increasing with age and being notably higher in women.[5] Contributing factors to the development of knee OA include genetics, obesity, joint injury, and mechanical stress. Current treatment options focus on symptom management and improving joint function, with a limited capacity to halt disease progression. However, emerging therapies such as BMAC offer promise in addressing the underlying pathophysiology of OA by promoting improvement in the homeostasis and viability of the arthritic joint. Preclinical and clinical studies have shown encouraging results regarding the efficacy and safety of BMAC therapy in knee OA, suggesting its potential as a promising therapeutic avenue for disease modification and long-term symptom relief.[6] Further research and clinical trials are warranted to elucidate optimal treatment protocols and long-term outcomes.

The literature continues to grow in favor of BMAC usage in knee osteoarthritis. BMAC treatments have shown to increase functional scores and decrease pain after intraarticular injections throughout multiple literature reviews and meta-analysis publications.[7–11] The authors' systematic review will focus on studies that used autologous minimally-processed BMAC since 2018. Studies will have applied BMAC using an intraarticular injection for mild to severe knee osteoarthritis. Patient-reported outcome measures (PROMs), complications, and radiological interpretation were used to measure post-injection effects.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) recommendations[12] guided information gathered in this literature review.

Search Strategy/Eligibility

The literature focused on databases, including Google Scholar and Medline (PubMed), conducted by three researchers (C.B., E.G., S.P.). Each article was assessed by its title and inclusion/exclusion criteria. Each article and reference were screened. Exclusion criteria was as follows: articles published before 2018, case reports, meta-analysis or literature reviews, studies that focused on joints other than knee OA, cells derived from sources other than bone marrow (lipo-aspirate, stromal vascular fraction), and non-human trials. The Memorial Regional Hospital database obtained full-text articles outside PubMed and Google Scholar.

Level of evidence and study quality

The studies included in the review were assessed using the Oxford Centre for Evidence-Based Medicine Working Group (OCEBM).[13] Each study was qualitatively reviewed and validated depending on whether it was a non-randomized trial (MINORS) or randomized-controlled trial (MJS).

Data compilation and analysis

The data from each study was isolated by publication year, first author, gender, study type, age, patient and knee sample size, OA grade, BMAC source and quantity, BMI, and follow-up ranges. The measures of outcomes were based upon visual analog scale (VAS), the Knee Injury and Osteoarthritis Outcome Score (KOOS), the Western Ontario Macmaster University Osteoarthritis Index (WOMAC), the International Knee Documentation Committee (IKDC), and Oxford Knee Score (OKS).

Statistical analysis

The RevMan 5.4 software (The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis. A pooled standardized mean

difference (SMD) with 95% confidence intervals (CI) was calculated to quantitatively evaluate the effects of BMAC injection compared to baseline values on outcomes of interest, such as VAS score, KOOS score, and WOMAC. Heterogeneity was assessed using the chi-square test and I^2 statistic, with I^2 statistic values of 25%, 50%, and 75% considered low, moderate, and high heterogeneity, respectively. As we anticipated clinical heterogeneity, a random-effects model was used in all pooled analyses. The between-study variance was estimated using tau-squared statistics in the random-effects model. Sensitivity analysis was conducted by excluding individual studies based on the follow-up time to evaluate each study's influence on the pooled estimate. In addition, subgroup analyses based on differences in the follow-up duration (< 12 months versus ≥ 12 months) were performed for pain scores to explore a potential source of heterogeneity. Publication bias was not reported in the pooled studies. A two-tailed test with $p < 0.05$ was considered statistically significant.

RESULTS

Literature search and identification of studies

When conducting the literature search from PubMed and Google Scholar, there were 1,124 relevant studies from PubMed and 1,090 from Google Scholar. The keywords used to search these databases were: bone marrow aspirate concentrate and knee osteoarthritis. Two articles were excluded due to being duplicates. From the 2,212 studies, 1,088 were found to be irrelevant to the topic. Based on the exclusion criteria, there were 1,116 studies excluded. This resulted in 8 eligible studies from PubMed and Google Scholar. A literature search was also conducted based on citations, which yielded 3 studies. Overall, 11 studies were eligible and included in this review. The PRISMA flowchart (Figure 1) depicts the systematic search, which shows how studies were identified and screened.[12]

Eligible patients and study characteristics

The review included 11 studies, which encompassed a total of 876 patients. Study patient sizes ranged from 15–195 patients (20 to 262 knees). These studies encompassed a range of study types, including prospective clinical trials, retrospective clinical trials, and case series, with evidence levels ranging from III to IV. The mean age of participants in the studies (for those provided) was 60.25, but the range was from 37- to 89-year-olds. Both genders were represented in the studies, but an uneven distribution was found depending on the study. Of the 11 studies, one study did not report the gender,[14] one had an equal distribution between male and female,[21] 5 studies had more males than females,[15,17–18,20,22] and the other 4 had more females than males.[16,19–21] Although BMI was not reported for every study, for those that did report, the BMIs fell between normal to extremely obese. All subjects' BMIs ranged from 19 to 39 kg/m^2. All studies had a follow-up period ranging from 1 month to 57 months, showing a very large range in how studies assessed the outcomes of their intervention. Characteristics of the studies and patients are shown in Table 1.

Source of MSCs and injection sites

The studies included in this literature review used autologous-derived bone marrow aspirate concentrate. All 11 studies used aspirate obtained from the iliac crest. Different devices were used to retrieve the bone marrow cells such as Arthrex, Ficoll-Paque Premium, BioCUE, Rotofix, with 5 studies not listing the machine used.[15,18,21-22,24] Three of the studies reported using ultrasound guidance, while the others did not report.[15,21-22] Cell number was calculated in one study.[16]

Clinical outcomes

A variety of clinical outcomes were assessed from the studies using differing methods to evaluate pain relief. Nine studies used the visual analog score (VAS),[14–22] thus making it the most widely used method to evaluate pain relief. This was followed by 5 studies that used the Western Ontario Macmaster University Osteoarthritis Index (WOMAC).[14-16,22,24] Two studies used the net promoter score (NPS)[14,17] and the Oxford Knee Score (OKS).[23,24] Three studies used the Knee Injury and Osteoarthritis Outcome Score (KOOS),[14–15,21] 2 studies used the International

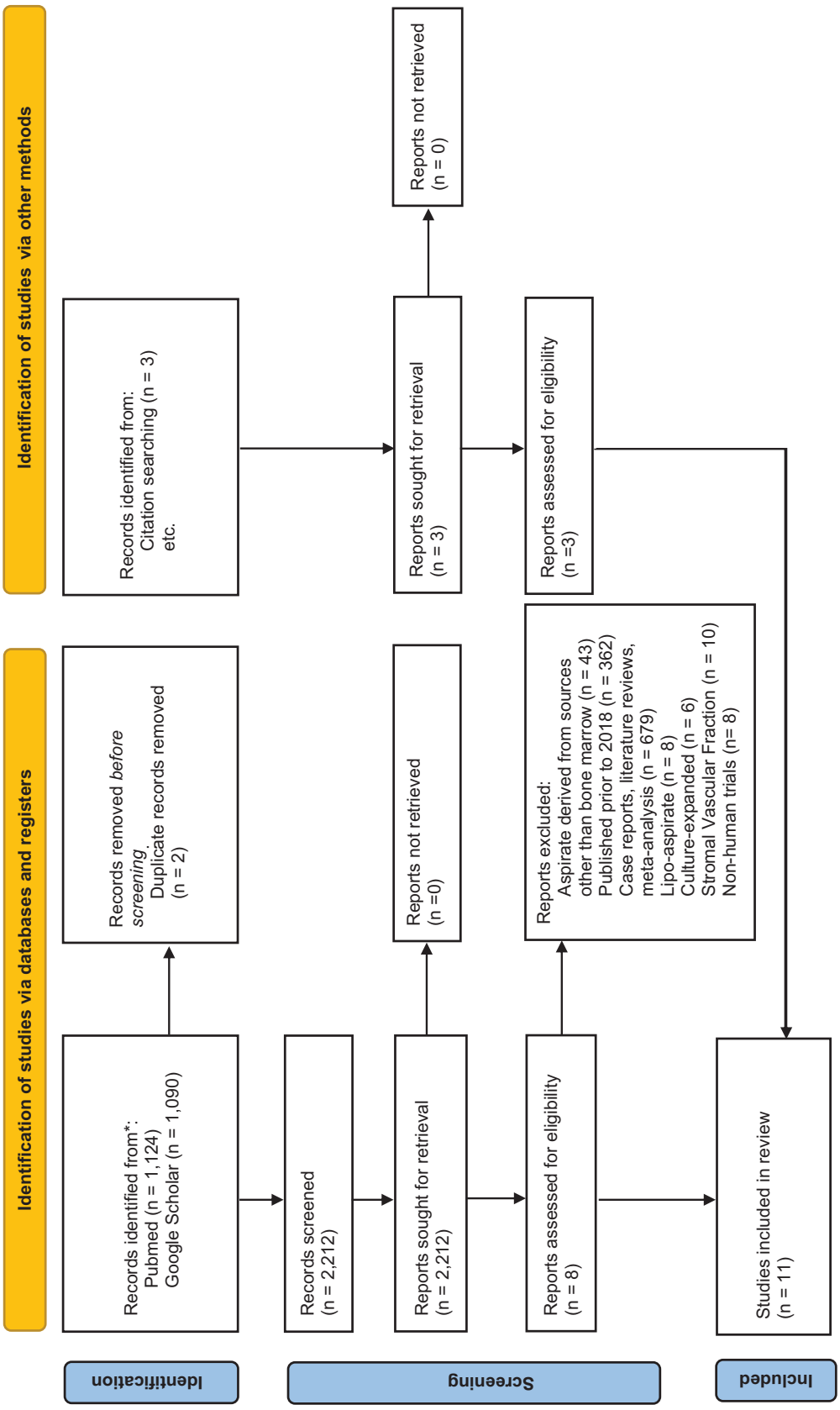

Figure 1. Identification and screening of databases and registers using the PRISMA flow diagram.

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Table 1. Study Type, Level of Evidence, Quality, and Further Study Demographics Included from the 11 Studies

Author	Study Type	Evidence Level	N patients (knees)	Lost to F/U	MSC Cell Count	Guidance Yes/No	Machine to extract cells, processing	Control group	Gender (M/F)	Mean Age (years)	BMI (kg/m^2)	F/U (months)	Study Period
Dulic et al.[14]	Prospective clinical trial	3	195	20	NA	No	Arthrex Angel, 150-micron filter	PRP (34) HA (30)	NA	NA	NA	1,3,6,9,12	April 2016–Dec 2017
El-Kadiry, et al.[15]	Prospective comparative study	3	30 (40)	1	NA	Yes, US	NA	PRP (13)	18/12	58.46	NA	1,3,6,9,12	Jan 2021–Jan 2022
Goncars et al.[16]	Prospective case series	4	32 (34)	0	45.56 ± 34.94 $\times 10^6$ cells	No	Ficoll-Paque Premium, 70-micron filter	None	16/16	53.96 ± 14.15	NA	1,3,6,12	Jan 2017–Jan 2018
Kon et al.[17]	Prospective multi-center	3	30 (45)	0	NA	No	BioCUE BMA	None	19/11	56.4 +/- 8.1	25.5 ± 3.5	1,3,6,12,24	Nov 2016–July 2019
Kuebler et al.[18]	Retrospective cohort study	3	160 (262)	41	NA	No	Machine NA, Marrow cellution kit	None	77/83	37-89	19-39	6 (wks), 6	March 2018–Dec 2019
Mariani et al.[19]	Retrospective case series	4	55	0	NA	No	SMART PREP2	None	38/17	45.3 ± 9.6	NA	18-57	May 2011–March 2019
Rasovic et al.[20]	Prospective clinical study	3	121	10	NA	No	Arthrex Angel	None	59/52	63.39 ± 10.1	28.0 ± 4.67	1,3,6,9,12	April 2016–Dec 2017
Shaw et al.[21]	Prospective clinical study	3	15 (20)	0	NA	Yes, US	NA	None	5/10	67.67 ± 7.90	24.87 ± 2.71	13.8, 21.4, 33.5, 86 (days avg)	July 2016–June 2017
Smith et al.[22]	Prospective case series	4	93	1	NA	Yes, US	NA	None	50/43	64.1 ± 9.5	NA	3,6	NA
Themistocleous et al.[23]	Retrospective clinical trial	3	121	0	NA	No	Rotofix 32A	None	36/85	70 (50-85)	NA	11	June 2014–Feb 2017
Vitali et al.[24]	Prospective case series	4	24	0	NA	No	Machine NA, SmartPreP2 Bone Marrow Pack	ACS	11/13	NA	NA	1,6	Dec 2017– Jan 2019

Knee Documentation Committee (IKDC),[14,17] and lastly 2 studies used the Numeric Pain Scale (NMS).[19,23]

Complications

The majority of studies reported no complications or adverse effects.[14-18,21-24] However, it is noteworthy that one study did report pain at the extraction site and inflammation at the injection site.[19] Furthermore, this study reported that some individuals experienced sensations such as knee grinding and joint stiffness. These effects were reported to be minor and resolved within a short period of time.

Quality Assessment of All Included Studies

Self-reported knee pain score (VAS)

Eight studies reported BMAC treatment on knee pain using the VAS score (Figure 2, Upper panel). The follow-up time period of these studies was from 21 days to 12 months. The heterogeneity analysis showed that I^2 = 99% among the studies, so the random-effects model was adopted. The pooled standardized mean difference (SMD) on the VAS knee pain was -3.46 (95% CI, –4.95 to –1.98; p <0.001) differed significantly between the baseline and post-treatment, suggesting the VAS knee pain was significantly reduced by the injection of BMAC when compared to the baseline. However, studies' effect estimates were highly heterogeneous (I^2 = 99%). To address the possibility that effect estimates on VAS pain score and heterogeneity change if only studies with 12 months follow-up were included in the meta-analysis, we performed a sensitivity analysis by omitting the studies with the follow-up time <6 months (Figure 2, Lower panel). The pooled SMD on the VAS knee pain was −1.78 (955 CI, –2.00 to –1.56) and the heterogeneity among the studies was significantly improved (I^2 = 0%). The studies with shorter follow-up periods were likely associated with the heterogeneity of the results. Although the pain relief effects were attenuated, the statistical significance persisted with a SMD of −1.78. This finding aligns with the combined analysis of all eight studies, suggesting that patients receiving BMAC experienced significant improvements in knee pain.

Self-reported physical function (WOMAC)

Six studies reported BMAC treatment on the self-reported physical function using WOMAC (Figure 3, upper panel). The follow-up time period of these studies was from 6 months to 57 months. The pooled SMD on the WOMAC was 0.8 (95% CI, −1.07 to 2.67; p = 0.40) and there was a statistically non-significant improvement in WOMAC in favor of the BMAC treatment when compared to the baseline. However, studies' effect estimates were highly heterogeneous (I^2 = 99%). We then performed a sensitivity analysis including only studies with 12 months of follow-up to assess the possible sources of the heterogeneity (Figure 3, Lower panel). The pooled SMD of the WOMAC score was 17.10 (95% CI, 15.43 to 18.77) and the heterogeneity among the studies was significantly improved (I^2 = 16%), indicating studies with a shorter follow-up duration were likely significant factors associated with the higher heterogeneity.

KOOS score

Three studies reported the KOOS score in patients with knee OA treated with BMAC. The follow-up time period of these studies was 12 months. The pooled SMD on the KOOS score was 1.29 (95% CI, 1.06 to 1.52; p <0.001) that differed significantly between the baseline and final follow-up, suggesting the KOOS score was significantly improved at 12 months when compared to the baseline.

IKDC score

Two studies reported the IKDC score in patients with knee OA treated with BMAC. The follow-up time period of these studies was 12 months. The pooled SMD on the IKDC score was 1.20 (95% CI, 0.94 to 1.45; p <0.001) that differed significantly between the baseline and final follow-up, suggesting the IKDC score was significantly improved at 12 months when compared to the baseline.

OKS score

Two studies reported the OKS score in patients with knee OA treated with BMAC. The follow-up time period of these studies was 12 months. The pooled SMD on the OKS score was −1.97 (95% CI,

(A)

Study of subgroup	Post-injection Mean	SD	Total	Pre-injection Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
Smith 2023	2.6	2.5	93	6.3	2.1	93	12.7%	–1.60 [–1.93,–1.27]
Shaw 2018	2.15	1.31	15	5.65	2.32	15	12.2%	–1.81 [–2.68,–0.94]
Rasovic 2023	2.45	1.7	111	7.21	1.64	111	12.7%	–2.84 [–3.21,–2.47]
Mariani 2023	3.3	2.5	55	7.8	1.9	55	12.6%	–2.01 [–2.47,–1.55]
Kuebler 2022	3.76	0.34	160	7.29	0.27	160	12.2%	–11.47 [–12.39,–10.55]
Kon 2022	3	1.9	30	6.3	1.8	30	12.5%	–1.76 [–2.36,–1.16]
El-Kadiry 2022	2.58	1.68	30	6.23	2.1	30	12.5%	–1.89 [–2.51,–1.28]
Dulic 2021	0.92	1.08	111	7.17	1.61	111	12.6%	–4.54 [–5.04,–4.04]
Total (95% CI)			**605**			**605**	**100.0%**	**–3.46 [–4.95,–1.98]**

Heterogeneity: $Tau^2 = 4.48$; $Chi^2 = 472.44$, df = 7 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 4.58$ ($P < 0.00001$)

(B)

Study of subgroup	Post-injection Mean	SD	Total	Pre-injection Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
El-Kadiry 2022	2.58	1.38	30	6.23	2.1	30	12.3%	–2.03 [–2.66,–1.40]
Kon 2022	3	1.9	30	6.3	1.8	30	13.5%	–1.76 [–2.36,–1.16]
Mariani 2023	3.3	2.5	55	7.8	1.9	55	23.0%	–2.01 [–2.47,–1.55]
Shaw 2018	2.15	1.31	15	5.65	2.32	15	6.5%	–1.81 [–2.68,–0.94]
Smith 2023	2.6	2.5	93	6.3	2.1	93	44.7%	–1.60 [–1.93,–1.27]
Total (95% CI)			**223**			**223**	**100.0%**	**–1.78 [–2.00,–1.56]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.76$, df = 4 ($P = 0.60$); $I^2 = 0\%$
Test for overall effect: $Z = 15.78$ ($P < 0.00001$)

Figure 2. (A). Impact of BMAC treatment on VAS score. SMD and 95% CI for the VAS score between pre- and post-BMAC treatment at 12-month follow-up (n = 223). The diamond represents the pooled SMD. The vertical line at 0 represents no difference. BMAC treatment was effective in improving VAS score (pooled SMD: –3.46, 95% CI: –4.95, –1.98; $P < 0.001$). (B) Sensitivity analysis using only studies with 12-month follow-up (pooled SMD: –1.78, 95% CI: –2.00, –1.56; $P < 0.001$).

(A)

Study of subgroup	Post-injection Mean	SD	Total	Pre-injection Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
Dulic 2021	24.34	20.91	111	44.34	18.67	111	16.8%	–1.01 [–1.29,–0.73]
El-Kadiry 2022	75.12	16.87	30	50.38	19.99	30	16.6%	1.32 [0.76,1.88]
Kon 2022	79.3	19	30	59.5	14	30	16.6%	1.17 [0.62,1.72]
Kuebler 2022	66.3	4.08	160	49.3	4.27	160	16.8%	4.06 [3.68,4.45]
Mariani 2023	76.2	7.8	55	60.5	10.6	55	16.7%	1.68 [1.24,2.11]
Vitali 2022	20.55	15.41	24	60.42	16.3	24	16.4%	–2.47 [–3.24,–1.71]
Total (95% CI)			**410**			**410**	**100.0%**	**0.80 [1.07,2.67]**

Heterogeneity: $Tau^2 = 5.42$; $Chi^2 = 526.43$, df = 5 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: Z = 0.84 (P = 0.40)

(B)

Study of subgroup	Post-injection Mean	SD	Total	Pre-injection Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
El-Kadiry 2022	75.12	16.87	30	50.38	19.99	30	3.1%	24.74 [15.38,34.10]
Kon 2022	79.3	19	30	59.5	14	30	3.8%	19.80 [11.35,28.25]
Kuebler 2022	66.3	4.08	160	49.3	4.27	160	74.6%	17.00 [16.08,17.92]
Mariani 2023	76.2	7.8	55	60.5	10.6	55	18.6%	15.70 [12.22,19.18]
Total (95% CI)			**275**			**275**	**100.0%**	**17.10 [15.43,18.77]**

Heterogeneity: $Tau^2 = 0.75$; $Chi^2 = 3.58$, df = 3 ($P = 0.31$); $I^2 = 16\%$
Test for overall effect: Z = 20.08 ($P < 0.00001$)

Figure 3. (A) Impact of BMAC treatment on WOMAC score. SMD and 95% CI for the KOOS score between pre- and post-BMAC treatment at 12-month follow-up (n = 410). The diamond represents the pooled SMD. The vertical line at 0 represents no difference. BMAC treatment was effective in improving WOMAC score (pooled SMD: 0.80, 95% CI: −1.07, 2.67; $P < 0.001$). (B) Sensitivity analysis using only studies with 12-month follow-up (pooled SMD: 17.10, 95% CI: 15.43, 18.77; $P < 0.001$).

Figure 4. Impact of BMAC treatment on KOOS score. SMD and 95% CI for the KOOS score between pre- and post-BMAC treatment at 12-month follow-up (n = 173). The diamond represents the pooled SMD. The vertical line at 0 represents no difference. BMAC treatment was effective in improving KOOS score (pooled SMD: 1.29, 95% CI: 1.06, 1.52; P < 0.001).

Figure 5. Impact of BMAC treatment on IKDC score. SMD and 95% CI for the IKDC score between pre- and post-BMAC treatment at 12-month follow-up (n = 141). The diamond represents the pooled SMD. The vertical line at 0 represents no difference. BMAC treatment was effective in improving IKDC score (pooled SMD: 1.20, 95% CI: 0.94, 1.45; P < 0.001).

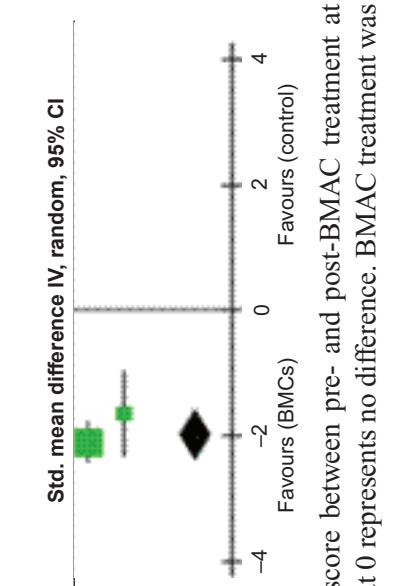

Figure 6. Impact of BMAC treatment on OKS score. SMD and 95% CI for the OKS score between pre- and post-BMAC treatment at 12-month follow-up (n = 145). The diamond represents the pooled SMD. The vertical line at 0 represents no difference. BMAC treatment was effective in improving OKS score (pooled SMD: −1.97, 95% CI: −2.38, −1.56; P < 0.001).

2.38 to 1.56; p <0.001) that differed significantly between the baseline and final follow-up, suggesting the OKS score was significantly improved at 12 months when compared to the baseline.

DISCUSSION

Among the 11 studies reviewed, the intraarticular administration of BMAC may be an option for patients as more robust prospective and randomized controlled studies become available.

Systematic reviews within the past 5 years at the time of publication showed favorable outcomes in managing knee OA. For example, a comprehensive meta-analysis consolidated the findings from 25 studies. This included 439 patients and highlighted the significant improvement of functional outcomes due to BMAC therapy in knee OA.[25] It was also shown that BMAC therapy led to improvements in cartilage volume, but improvements in cartilage quality were not statistically significant. Moreover, the analysis also brought various challenges and variability in BMAC therapy on knee OA such as bias, study methodology heterogeneity, blinding, and randomization. Further research is needed to refine treatment protocols and ensure consistency across interventions. This meta-analysis showed the efficacy of BMAC therapy in functional improvement and emphasized the need for ongoing investigation to optimize treatment outcomes.

The results demonstrated that intraarticular injection of BMAC represent an effective and safe treatment option for mild to severe knee osteoarthritis. The studies included in the review used autologous minimally-processed bone marrow aspirate concentrate sourced from the iliac crest. Various outcome measures were employed across studies, including visual analog scale (VAS), the Western Ontario Macmaster University Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC), and others. Statistical analysis revealed significant improvements in knee pain scores (VAS), physical function (WOMAC), KOOS score, IKDC score, and Oxford Knee Score (OKS) at different follow-up periods post-BMAC treatment.

Eight studies from the authors review assessed the efficacy of BMAC treatment using the VAS score, indicating a significant reduction in pain post-treatment compared to baseline across all studies. The follow-up period ranged from 21 days to 12 months, revealing consistent improvements in knee pain over various durations. However, as observed in the meta-analysis above, considerable heterogeneity was observed among the studies. This requires a sensitivity analysis to investigate the impact of follow-up duration on outcomes. Upon excluding studies with follow-up periods less than 6 months, heterogeneity significantly decreased, suggesting that shorter follow-up durations may contribute to variability in results. Despite the decline of pain relief effects, the statistical significance persisted, with patients consistently experiencing substantial improvements in knee pain following BMAC therapy.

Six studies from the authors review investigated the impact of BMAC treatment on self-reported physical function using the WOMAC score. The follow-up periods varied significantly, ranging from 6 months to 57 months. However, the pooled analysis revealed a non-significant improvement in WOMAC scores following BMAC treatment compared to baseline, with a standardized mean difference (SMD) of 0.8 (95% CI, −1.07 to 2.67; $p = 0.40$). Notably, significant heterogeneity was observed again among the studies, prompting further sensitivity analysis focusing on studies with a 12-month follow-up duration. This analysis revealed a substantial improvement in WOMAC scores, with a pooled SMD of 17.10 (95% CI, 15.43 to 18.77), and a significant reduction in heterogeneity ($I^2 = 16\%$). Shorter follow-up durations may contribute to the heterogeneity observed in outcomes, emphasizing the importance of considering follow-up duration in interpreting the efficacy of BMAC treatment for improving physical function in knee osteoarthritis patients. Additionally, while the overall improvement in WOMAC scores was significant in the longer-term follow-up studies, caution should be exercised in interpreting these results, especially given the variability in study durations and potential confounding factors influencing outcomes.

Three studies utilized KOOS for their pain score with a follow-up period of 12 months. The pooled analysis revealed a significant improvement in KOOS scores at the 12-month follow-up compared to baseline, with a standardized mean difference (SMD) of 1.29 (95% CI, 1.06 to 1.52; $p<0.001$). Similarly, two studies investigated the impact of BMAC treatment on the KOOS pain score and found a significant improvement at the 12-month follow-up, with a pooled SMD of 1.24 (95% CI, 0.99 to 1.50; $p<0.001$). Additionally, two studies assessed the International Knee Documentation Committee (IKDC) score and the Oxford Knee Score (OKS) in patients with knee OA treated with BMAC over a 12-month follow-up period. The pooled analysis demonstrated significant improvements in both IKDC score (SMD: 1.20; 95% CI, 0.94 to 1.45; $p<0.001$) and OKS score (SMD: −1.97; 95% CI, 2.38 to 1.56; $p<0.001$) compared to baseline. These findings suggest that BMAC treatment significantly improves various clinical outcomes related to knee OA, including pain, function, and overall knee health, further highlighting the potential of BMAC therapy as an effective and safe treatment option for knee OA patients.

These studies had various strengths and grades of KL showing improvement with BMAC, regardless of the variation. The recent literature compared to prior years and meta-analysis reveals larger cohorts and endorses the effectiveness even with larger studies. Additionally, significant improvements were found in various clinical outcomes post-BMAC treatment, including pain relief, physical function, and overall knee health, demonstrating the efficacy of BMAC therapy across multiple domains. The quality of research and its clinical application has improved in just the last few years to support the use of BMAC for knee OA, confirmed by the authors most recent literature review. Moreover, the thorough assessment of potential sources of heterogeneity and sensitivity analyses conducted in this review enhance the robustness and reliability of the findings, further strengthening its contribution to regenerative medicine in knee osteoarthritis management.

Despite these findings, challenges remain in orthobiologic therapy for therapeutic intervention.

Obstacles such as the preparation of BMAC and sources of MSC variability remain. Heterogeneity among studies and varying follow-up durations were observed in the authors review, emphasizing the need for further investigation to standardize treatment protocols and assess long-term outcomes. Risk bias and reliability of the authors studies need to be questioned. Single intraarticular injections vs. multiple sites and injecting without guidance contribute to orthobiologic knee OA treatment inconsistencies. All studies except one were performed without measuring BMAC counts appropriately and many without a control group for comparison. This leaves the authors questioning the accuracy of the results without a consistent protocol. While BMAC therapy holds potential as a promising treatment for knee OA, continued research efforts are warranted to optimize its efficacy and further cement its role in clinical practice. Future studies should aim to create a protocol that provides more consistent data to standardize knee OA treatment and further the usage of orthobiologics in general.

CONCLUSION

Based on the review of BMAC treatment for knee OA, intraarticular BMAC injection could be considered an orthobiologic option. However, the studies' lack of consistent treatment protocols and homogeneity results in a large variance. More high-level studies are warranted to formulate stringent treatment algorithms and protocols for treatment.

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