International Journal of Research and Review
[Indexed, Peer-Reviewed Journal]
Volume 12; Issue: 6; June 2025
Website: www.ijrrjournal.com
Review Paper *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Effectiveness of Combination Therapy of Bone Marrow-Derived Mesenchymal Stem Cell for Enhancing Potential Therapeutic Effect on Ankle Arthritis: A Systematic Review

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DOI: https://doi.org/10.52403/ijrr.20250671

ABSTRACT

Background and Objectives: Current treatment options for ankle arthritis often provide only short-term therapeutic benefits, with frequent recurrence of symptoms. In recent years, various stem cell-based therapies have been developed due to their regenerative potential and ability to promote tissue repair in ankle arthritis. Bone marrow-derived mesenchymal stem cells (BM-MSCs) represent one such therapeutic approach, isolated from bone marrow and expanded in vitro, offering notable anti-inflammatory and osteoregenerative properties. The combination of BM-MSC therapy with existing treatment modalities is anticipated to enhance overall therapeutic efficacy.

Methods: This systematic review aims to evaluate the potential therapeutic effects of combining bone marrow-derived mesenchymal stem cell (BM-MSC) with existing treatment modalities. Comprehensive literature search was conducted using databases including PubMed, ResearchGate, Google Scholar, and ScienceDirect. Eligible studies included animal models, interventional and descriptive research, as well as other analytical and observational study designs.

Results: Five studies met the eligibility criteria and were included in the review. These studies utilized BM-MSC that had been isolated and cultured from bone marrow tissue. The experimental models involved rats in which arthritis had been experimentally induced. Overall, the combination of BM-MSCs with various therapeutic interventions demonstrated enhanced therapeutic effects on ankle arthritis, as evidenced by both pathological and radiological improvements. Additional benefits included augmented anti-inflammatory, antioxidant, and anti-arthritic properties.

Conclusion: The findings indicated that the combination of bone marrow-derived mesenchymal stem cells (BM-MSCs) effectively promotes tissue repair and delays joint degradation in ankle arthritis. The overall conclusion suggests that integrating BM-MSC therapy with existing treatment modalities may enhance therapeutic efficacy. However, additional research is warranted, particularly in human clinical trials, to address current limitations and to determine the optimal dosage, therapeutic safety, and potential side effects associated with each combination therapy.

Keywords: Ankle arthritis; Stem cell; Bone marrow; Mesenchymal; Therapeutic effect

INTRODUCTION

Osteoarthritis (OA) and Rheumatoid Arthritis (RA) are two distinct yet overlapping conditions that primarily affect the joints, synovial membranes, and periarticular soft tissues. The hallmark clinical manifestations include pain, which is typically followed by joint stiffness, swelling, effusion, synovitis, osteophyte hyperplasia, and progressive joint dysfunction.[1] However, in its approach, OA is more often associated with mechanical stress while RA has an increase in inflammatory markers such as rheumatoid factor, anti-cyclic citrullinated peptide antibodies.[2] There are approximately 595 million people affected by the disease leading to disruptions in daily activities.[3] Specifically, the most common predilections of OA in the body are the hip, knee, and hand. OA of the foot has a high prevalence rate of 17% of the population over 50 years of age which is similar to the prevalence of OA of the knee and can even be twice as large as OA of the hip but has a high level of neglect.[4]

Ankle osteoarthritis (OA) is a chronic degenerative condition that significantly disrupts daily functioning, with an impact comparable to that of hip and knee OA.[5] Etiologically, ankle OA is most commonly classified as post-traumatic, frequently developing as a consequence of specific preceding injuries.[6] Approximately 90% of ankle OA cases are associated with secondary trauma, with a strong correlation to a history of fractures, particularly involving the malleolus and tibia.[7] The incidence rate is related to the population of patients with Ankle OA which is dominated by young age (18-44 years) which is closely related to post-traumatic etiology with comparison to other conditions that can occur in the ankle and lower extremity area. Changes that occur in the ankle can develop within 12 to 18 months after the onset of trauma and can progress to advanced stages within 10 to 20 years after onset.[8] In RA, there is a high prevalence of the development of foot and ankle arthritis with 90% of patients reporting disability in walking and poor development of foot and ankle health that impairs quality of life.[9]

According to the guidelines issued by the National Institute for Health and Care Excellence (NICE), the core principles of osteoarthritis (OA) management include patient education about the disease and its prognosis, engagement in strengthening and aerobic exercises, and weight reduction strategies for individuals who are overweight or obese.[10] These principles also include non-pharmacological strategies in ankle OA. Pharmacological therapies that can be given include analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids, viscosupplementation, platelet-rich plasma (PRP), and mesenchymal stem cells.[11] In the first phase, low-dose paracetamol may be used in combination with topical NSAIDs, but if there is no improvement, oral NSAIDs or cyclooxygenase-2 inhibitors may be added. In recent years, intra-articular therapies such as Hyaluronic acid, PRP, and Mesenchymal Stem Cell (MSC) have been developed.[12] Therapy from cell derivatives in Ankle OA is currently growing rapidly, especially in the treatment of OA because it can prevent further damage to bone cartilage. In experimental studies on MSCs, it was found that these derivatives can be effective in healing cartilage and have the effect of preventing further progression of OA. One of the MSC derivatives, Bone Marrow-derived Mesenchymal Stemcell (BM-MSC) is one of the most effective derivatives to reduce the progression of Ankle Arthitis.[13,14] The principle of therapy in RA by targeting Tumor Necrosis Factor Alpha (TNF-α) cells with first biological disease-modifying antirheumatic drugs (bDMARDs).[15] A systematic review is essential to examine the therapeutic effects of BM-MSCs that have regenerative and anti-inflammatory effects in the Ankle OA population. This review aims to investigate therapeutic combinations that may enhance the clinical efficacy of BM-MSCs, thereby optimizing outcomes for patients affected by ankle OA.

MATERIALS & METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was prospectively registered in the PROSPERO database (Registration ID: CRD420251036163).

Search Strategy

This study was searched based on Population Intervention Comparison/ Context Outcome (PICO) analysis by the combination of BM-MSC with various existing therapies. The literature search was conducted using the PubMed, ResearchGate, Google Scholar, and ScienceDirect platforms using journals published within the last 5 years. The search was linked with the help of relevant keywords and Medical Subject Headings (MeSH) terms namely "Combined Modality Therapy," "Bone Marrow," "Mesenchymal Stem Cell," "Ankle Arthritis," "Therapeutic Effect."

Inclusion and Exclusion Criteria:

The inclusion criteria sought in the study were as follows:

1. Population: Subjects of research that use animals or humans in their research by examining the results of the effects of BM-MSC combination therapy with existing drugs.
2. Intervention: Using BM-MSC in combination with several pre-existing therapies.
3. Study Design: Randomized controlled trials (RCTs), cohort studies, case-control studies, and experimental animal studies.
4. Language: Research publication in English

Studies with a case report design, meta-analyses, and review articles were excluded from this review. Additionally, studies were excluded if they lacked sufficient data, reported poor outcome quality, or did not directly involve animal or human subjects. Research that did not specifically investigate the combined effects of BM-MSC therapy with other pharmacological treatments was also excluded.

Data Extraction and Risk of Bias

Two reviewers independently extracted data, concentrating the study details, screened titles and abstracts for eligibility. Concentrating conducted the risk of bias analysis using the Risk of Bias tool for RCTs and the Newcastle Ottawa Scale (NOS) as guidelines. Disagreements will be resolved by discussion and a third person as the deciding factor.

RESULT

Study Selection

A comprehensive selection was made from several databases that had a total of 162 articles: 9 papers from PubMed, 100 papers from ResearchGate, and 53 papers from ScienceDirect. Two independent readers reviewed and screened 32 irrelevant articles and 54 duplicate articles, leaving 76 journals. After that, a total of 49 articles were excluded. Seeking for retrieval due to full-text review left 11 articles. The articles were analyzed and excluded 1 article that was not specific to BMMC and 5 journals that did not specifically discuss the combination therapy of BMMC with the result of 5 final studies (figure 1). Disagreements regarding the selection process will be resolved by discussion with a third party will review and make the final decision.

Figure 1. Flow diagram strategy based on PRISMA 2020 Flow Diagram Guidline

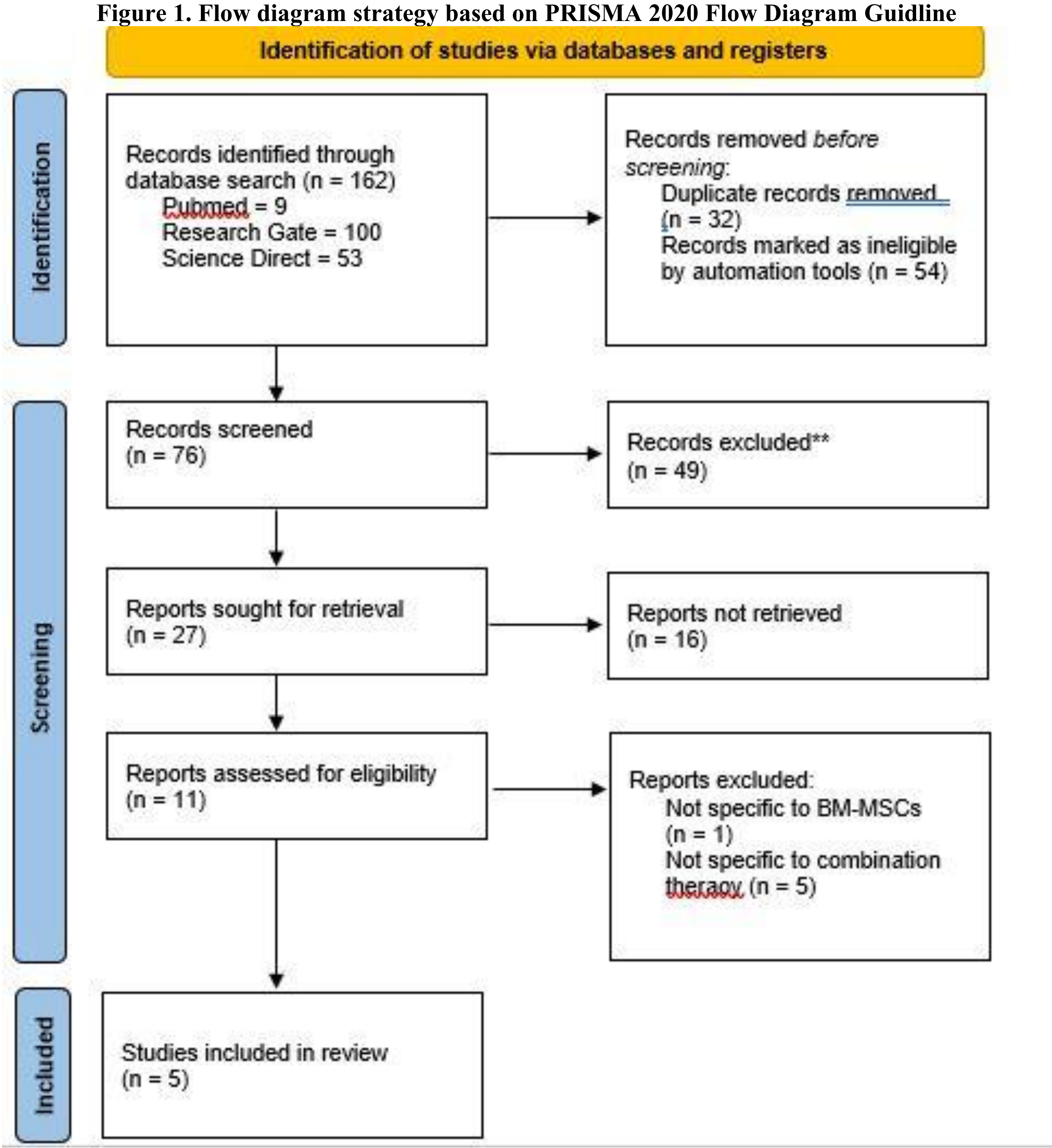

Table 1. Systematic Qualitative Review

No	Authors	Combination Existing Therapy	Number of Participant	Follow Up Time	Outcome
1	RH Ahmed et al. 2024	Curcumin	48 male rats and 48 female rats *(divided into 16 groups, 6 rats for each)*	21 days	Curcumin and BM-MSCs are effective at reducing inflammation while also having beneficial effects on the ankle joint that can restore high serum PGE2 and IL-17 level and lower the IL-13 level in arthritic rat to normal.
2	UI Hagag et al. 2024	Hyaluronic Acid	50 adult male wistar rats *(divided into 5 groups)*	Every weeks until 6 weeks	The combination of BM-MSCs and HA has substantial anti-inflammatory, antioxidant, and effects anti-arthritic in Wistar rats with MIA-induced OA. Also have ability to regulate inflammation, oxidative stress and reduce MMP-13.
3	Z Zhao, et al.	Autologous Oxygen-Releasing	SD rats *(unknown*	1 weeks 4 weeks	Autologous oxygen-releasing nano-bionic materials and BM-MSCs can

	2023	Nano-Bionic Scaffold	*number or rats)*	8 weeks	promote tissue engineering repairing and delay the scaffold degradation by effectively carry lipids, proteins, nutritional factors, and growth factors.
4	D Guss et al. 2022	Chondrocyte Conditioned Medium (CCM)	50 male rats *(divided into 5 groups)*	3 months	Several pathological scores were as indicators including joint surface, matrix, cell distribution, cell viability, subchondral bone, and mineralization. The combination of BM-MSCs and CCM showed good results in pathological and radiological evaluations.
5	EA Ahmed et al. 2021	Indomethacin	50 male wistar rats *(divided into 5 groups)*	7 days 14 days 21 days	BM-MSCs and IMC can effectively produce anti-inflammatory and anti-arthritic effects when used together, rather than when used alone, in CFA-induced arthritic Wistar rats.

Table 2. Characteristics Study

No	Studies	Journal	Study Design
1	RH Ahmed et al. 2024	Endocrine, Metabolic & Immune Disorders-Drug Targets	Randomized Controlled Trial
2	UI Hagag et al. 2024	World Journal of Orthopedics	Randomized Controlled Trial
3	Z Zhao, et al. 2023	Journal of Biomedical Nanotechnology	Randomized Controlled Trial
4	D Guss et al. 2022	American Orthopaedic Foot & Ankle Society	Randomized Controlled Trial
5	EA Ahmed et al. 2021	*Evidence-Based Complementary and Alternative Medicine*	Randomized Controlled Trial

DISCUSSION

Ankle arthritis is a degenerative condition that can significantly reduce individual productivity across both younger and older age groups. Mesenchymal stem cell (MSC) therapy has gained increasing attention due to its strong potential for differentiation into osteocytes, chondrocytes, and adipocytes in vitro, as well as its regenerative properties that play a crucial role in the treatment of osteoarthritis (OA).[16] BM-MSC can be isolated from mesenchymal tissues such as cartilage, tendons, muscle, and bone, and subsequently expanded through culture while preserving their multipotent differentiation capacity. MSCs exhibit key biological properties, including anti-inflammatory activity, cellular renewal, and tissue regeneration. These capabilities are expected to facilitate the repair and regeneration of damaged tissues in affected patients .[17]

The therapeutic effects of BM-MSC and Hyaluronic Acid (HA) produced can be seen from the initial assessment, namely reducing the symptoms of swelling in Ankle OA caused by a decrease in edema, improvement in the inflammatory process, and synovial hyperplasia in histological research conducted. The therapeutic effect specifically works by regulating pro-inflammatory cytokines, TNF-α and IL-17 and by increasing anti-inflammatory cytokines and IL-4, but furthermore if the two are combined it will have a better effect in regulating serum TNF-α and IL-17. In addition, the effect of this combination therapy also works better in reducing Lipid Preoxidation (LPO) which is a marker of degenerative processes by having an impact on the destruction of cell membranes and other lipid structures and increasing Serum Glutathione (GSH) and GSH-S-transferase (GST) levels which are an antioxidant system in protecting cells from oxidative damage and free radicals compared to non-combined controls.[17]

Combined therapeutic effects of BM-MSC and Indomethacin (IMC) can efficiently suppress inflammation in Complete Freund's

Adjuvant (CFA) induced objects which provide edema improvement effects up to 30% and 35%. Histopathologically, it is explained that in RA Ankle there will be an increase in Reactive Oxygen Species (ROS) and Lipid Preoxidation (LPO) levels that are uncontrollable and will reduce the antioxidant protection system, resulting in oxidative stress which will have an impact on the disruption of cellular function and mediators in the pathogenesis of cartilage and tissue damage. The group treated with BM-MSC and IMC combination therapy provided better protection than the control therapy in joint gap repair, less leukocyte infiltration, and cartilage repair. This combination therapy also had the effect of suppressing LPO levels in the study subjects.[18]

The combination of BM-MSC therapy with Curcumin was also found to have a good therapeutic effect by reducing high serum PGE2 and IL-17 and reducing IL-13 levels. In addition, obtained good results on COX-1 and IL-6 gene expression and decreased IL-4 in CFA-induced objects.[19] In addition, another combination studied is the combination of BM-MSCs with secretome Chondrocyte Conditioned Medium (CCM) which has a positive impact on joint surfaces, subchondral bone, cell distribution, cell matrix, and mineralization. In addition, there was an improvement in the joint gap score and osteophytes in the tibia and talus in Monoiodoacetate (MIA)-induced Ankle OA objects. [20] The combination of BM-MSCs with Autologous Oxygen-Releasing nano-bionic material also has a good impact on the improvement of cell proliferation and apoptosis and there is good regulation in carrying lipids, proteins, nutritional factors, and growth factors for the development of cell repair and decreased cell degradation, osteoblast proliferation, and osteogenic differentiation especially for ankle joint repair.[21]

CONCLUSION

This systematic review highlights various combination therapies involving bone marrow-derived mesenchymal stem cells BM-MSC that have demonstrated improved outcomes in the treatment of ankle arthritis. Existing studies have reported a significant enhancement in therapeutic effects with combination approaches, particularly in terms of anti-inflammatory, antioxidant, anti-rheumatic activity, and tissue regeneration. However, further research is warranted, especially in human subjects, to better understand the benefits and limitations of each combination therapy and to optimize their clinical application.

Declaration by Authors

Ethical Approval: None
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: I Komang Gede Satria Mulyana Nugraha, I Gusti Lanang Agung Wiradinata, Ida Bagus Anom Krishna Caitanya. Effectiveness of combination therapy of bone marrow-derived mesenchymal stem cell for enhancing potential therapeutic effect on ankle arthritis: a systematic review. *International Journal of Research and Review*. 2025; 12(6): 628-634. DOI: 10.52403/ijrr.20250671

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