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Intra-Articular Mesenchymal Stem Cells Versus Hyaluronic Acid in KNEE Osteoarthritis: A Systematic Review of Randomized and Controlled Trials

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ABSTRACT
Knee osteoarthritis (KOA) is a chronic degenerative joint disease characterized by progressive cartilage deterioration, persistent pain, functional impairment, and reduced quality of life. Although intra-articular hyaluronic acid (HA) injection is widely used as a non-surgical treatment to alleviate symptoms, its effects are generally temporary and provide limited regenerative potential. Mesenchymal stem cell (MSC) therapy has emerged as a promising regenerative approach due to its anti-inflammatory, immunomodulatory, and tissue-repair properties. This study aimed to systematically review and compare the clinical efficacy and safety of intra-articular MSC therapy and HA injection in patients with KOA. A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant randomized controlled trials and controlled clinical trials published between 2015 and 2025 were identified from the PubMed, Cochrane, and Wiley Online databases. Seven eligible studies involving 215 patients were included in the analysis, with outcomes assessed based on pain scores, functional evaluations, and structural changes. The findings demonstrated that MSC therapy consistently resulted in greater improvements in pain reduction, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, functional outcomes, and quality of life compared with HA treatment. Several studies also reported potential cartilage-preserving effects based on magnetic resonance imaging (MRI) evaluations; however, evidence supporting structural regeneration remains limited. MSC therapy showed a favorable safety profile, with minimal adverse events reported. In conclusion, intra-articular MSC injection appears to provide superior clinical improvements compared with HA injection in patients with KOA. However, larger randomized controlled trials with standardized protocols and longer follow-up periods are required to confirm its regenerative potential and support broader clinical application.

INTRODUCTION

Knee osteoarthritis (KOA) is a chronic, progressive degenerative joint disorder characterized by cartilage degradation, synovial inflammation, subchondral bone remodeling, and functional impairment. It is one of the leading causes of disability worldwide, particularly among older adults, and has a substantial impact on quality of life and healthcare systems. Current management strategies primarily focus on symptom control and functional

improvement rather than disease modification, highlighting the need for more effective regenerative treatment approaches (Hossain et al., 2026).

Intra-articular hyaluronic acid (HA) injection is an established non-surgical treatment for KOA. Its therapeutic effects are attributed to mechanical and biological mechanisms, including restoration of synovial fluid viscoelasticity, reduction of joint friction, and modulation of inflammatory pathways (Giarritiello, De La Motte, & Drago, 2025). HA may provide chondroprotective effects by inhibiting pro-inflammatory cytokines and matrix-degrading enzymes while promoting extracellular matrix synthesis. However, clinical outcomes following HA injection remain inconsistent, with benefits generally limited to modest and short-term improvements, particularly among patients with advanced-stage disease (Glinkowski & Tomaszewski, 2025).

In recent years, regenerative medicine has introduced mesenchymal stem cell (MSC) therapy as a promising approach for KOA management (Ho et al., 2022). MSCs possess self-renewal capacity, multilineage differentiation potential, and immunomodulatory properties, making them potential candidates for cartilage repair and disease modification (Yang et al., 2026). Preclinical and clinical studies have suggested that MSCs may reduce inflammation, promote chondrogenic activity, and improve cartilage-related outcomes (Sun et al., 2023). Several randomized controlled trials have reported that MSC therapy provides superior clinical outcomes compared with HA, particularly in terms of pain reduction and functional improvement during short- to mid-term follow-up periods (Cao et al., 2025; Zhu et al., 2021).

Despite these promising findings, the overall evidence remains heterogeneous and inconclusive. Variations in MSC sources, including bone marrow-derived MSCs, adipose tissue-derived MSCs, and umbilical cord-derived MSCs, as well as differences in cell processing methods, dosage regimens, and outcome assessment tools, contribute to inconsistent results across studies (Zhou & Shen, 2022). Furthermore, although clinical improvements are frequently reported, evidence supporting structural cartilage regeneration remains limited and inconsistent. High heterogeneity and relatively small sample sizes in existing trials further complicate the interpretation of comparative outcomes (Kennedy, Kitson, Okpara, Chow, & Gonzalez-Fernandez, 2024).

To date, several systematic reviews and meta-analyses have evaluated the efficacy of MSC therapy or HA individually; however, comprehensive evidence synthesis focusing specifically on high-quality comparative studies between intra-articular MSC therapy and HA remains limited. In particular, evidence from randomized controlled trials and controlled clinical trials is essential to determine the comparative effectiveness and safety of these interventions while minimizing potential bias.

Therefore, this systematic review aimed to evaluate and compare the clinical efficacy and safety of intra-articular MSC therapy versus HA injection in patients with KOA, with a specific focus on evidence derived from randomized controlled trials and controlled clinical trials. By synthesizing high-quality evidence, this study sought to provide clearer guidance for clinical decision-making and clarify the potential role of MSC therapy as a regenerative alternative to conventional viscosupplementation.

METHOD

Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was performed from January 1, 2015, to January 1, 2025, using PubMed, Cochrane, and Wiley Online databases. The search strategy combined keywords and Medical Subject Headings (MeSH) terms, including "mesenchymal stem cells," "hyaluronic acid," "intra-articular injection," and "knee osteoarthritis" or "knee arthritis," using Boolean operators (AND/OR). Reference lists of relevant studies were also screened to identify additional eligible articles. Study selection was independently assessed by reviewers, and disagreements regarding inclusion were resolved through consensus or consultation with an external reviewer when necessary. Studies were included if they were available as full-text articles, published in English, and reported clinical outcomes related to the use of HA and MSC therapy in patients with KOA.

Inclusion Criteria

The inclusion criteria were as follows: (1) studies involving patients with knee osteoarthritis treated with intra-articular mesenchymal stem cell (MSC) injections compared to hyaluronic acid (HA); (2) randomized controlled trials or controlled clinical trials; (3) studies reporting clinical outcomes such as pain, functional scores, and/or structural outcomes; and (4) articles published in English. Studies were excluded if they involved osteoarthritis in joints other than the knee, did not include a direct comparison between MSC and HA or failed to report relevant outcome data (Table 1).

Table 1. PICO Criteria for Inclusion Study

	Inclusion	Exclusion
Patient	Patients with knee osteoarthritis (Kellgren–Lawrence grade I–IV)	Patients with osteoarthritis in joints other than the knee or secondary causes of knee pain (e.g., trauma, infection, inflammatory arthritis)
Intervention	Patients treated with intra-articular mesenchymal stem cell (MSC) injection	Patients treated with surgical interventions or non-MSC therapies (e.g., PRP, corticosteroids, oral medication alone)
Comparison	Patients treated with intra-articular hyaluronic acid (HA) injection	Studies without a direct comparison to HA injection
Outcome	Clinical outcomes including pain (VAS), function (WOMAC/KOOS), and/or structural outcomes (MRI, WORMS)	Outcomes not clearly reported or using parameters outside predefined clinical or structural outcomes
Design	Randomized controlled trials (RCTs) and controlled clinical trials	Case reports, case series, cross-sectional studies, systematic reviews, and meta-analyses

Quality Evaluation

Every manuscript was subjected to an impartial review by reviewers. Any disparities found were settled by thorough debate and consensus. The seven Cochrane criteria for assessing risk of bias in the "Risk of bias" assessment tool which include selection, performance, detection, attrition, reporting, and other bias will be used by the same independent reviewers to evaluate the quality of the included studies (Figure 1 and Figure 2).

Data Synthesis

Two authors conducted an independent title and abstract screening followed by a full-text screening of the study, and any inconsistencies were referred to a third author. For every study that was found and included, data extraction was gathered using specified tables under the headings of fundamental characteristics and results. The data extraction process was conducted by one author independently, and second author reviewed it.

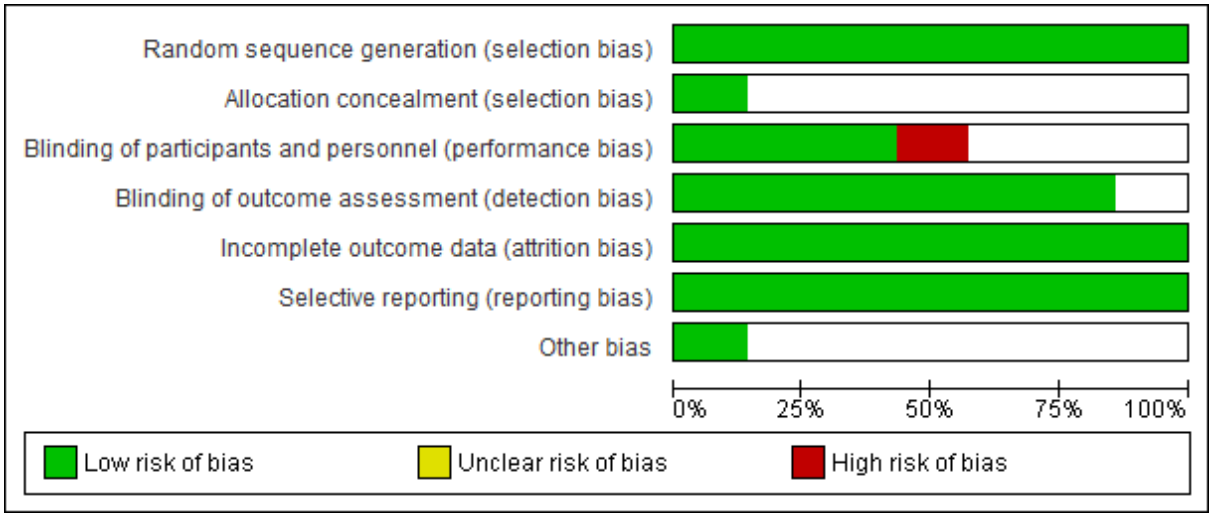

Figure 1. Risk of Bias Summary

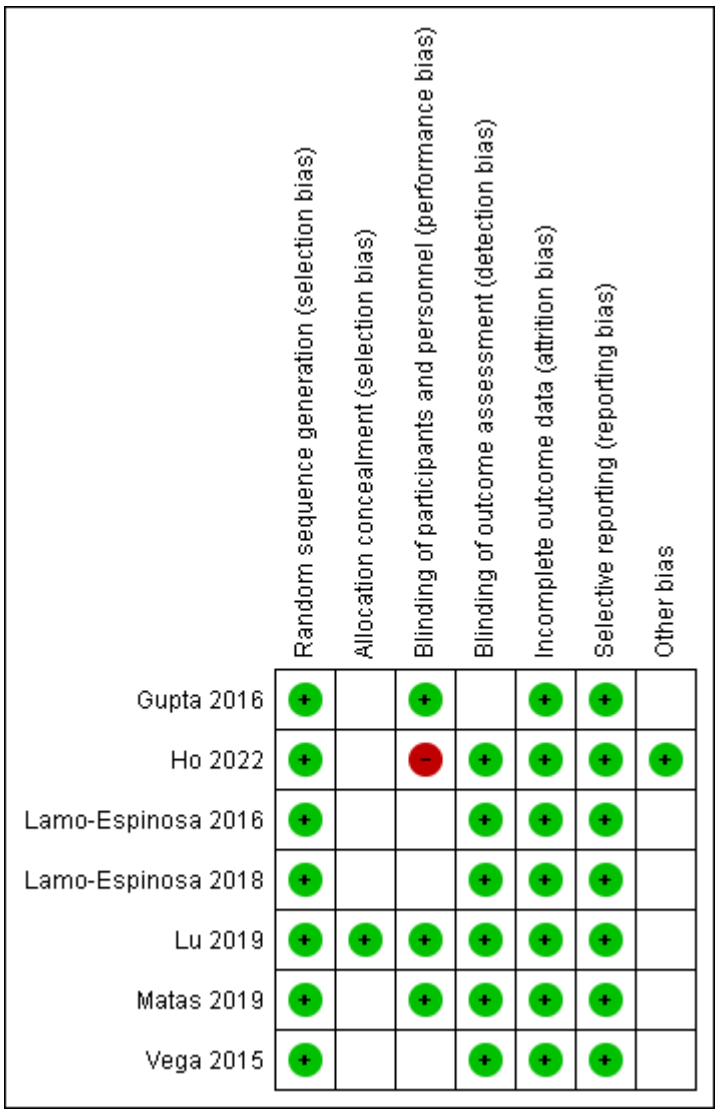

Figure 2. Risk of Bias Graph

RESULT AND DISCUSSION

Search and Selection Method

By searching the databases we utilized, we were able to find 2368 research publications. After removing duplicates, we had 1611 articles that needed to be evaluated. After assessing their titles, abstracts, and complete texts, we narrowed down to 7 studies5-11 that fit our criteria and were eligible for systematic review, as shown in Figure 3.

Baseline Characteristics

Seven studies5-11 with a total of 215 participants were included. Across the included studies, patients were predominantly middle-aged to older adults with symptomatic knee osteoarthritis, most commonly Kellgren–Lawrence grade II–III disease, while individuals with inflammatory arthritis, severe deformity, active infection, significant comorbidities, prior major knee interventions, or contraindications to intra-articular therapy were generally excluded, as shown in Table 1.

Outcomes Measured Across the Studies

All included studies demonstrated that intra-articular MSC therapy resulted in significant improvement in pain, functional outcomes, and quality of life in patients with KOA compared

with HA alone. Clinical improvements were consistently observed in outcome measures such as Visual Analog Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) during follow-up periods ranging from 6 months to 4 years. Several studies also reported structural improvements on magnetic resonance imaging (MRI), including cartilage regeneration and improved WORMS scores, particularly in MSC-treated groups. Repeated or lower-dose MSC regimens appeared to provide more sustained clinical benefits compared with HA alone or single-dose administration.

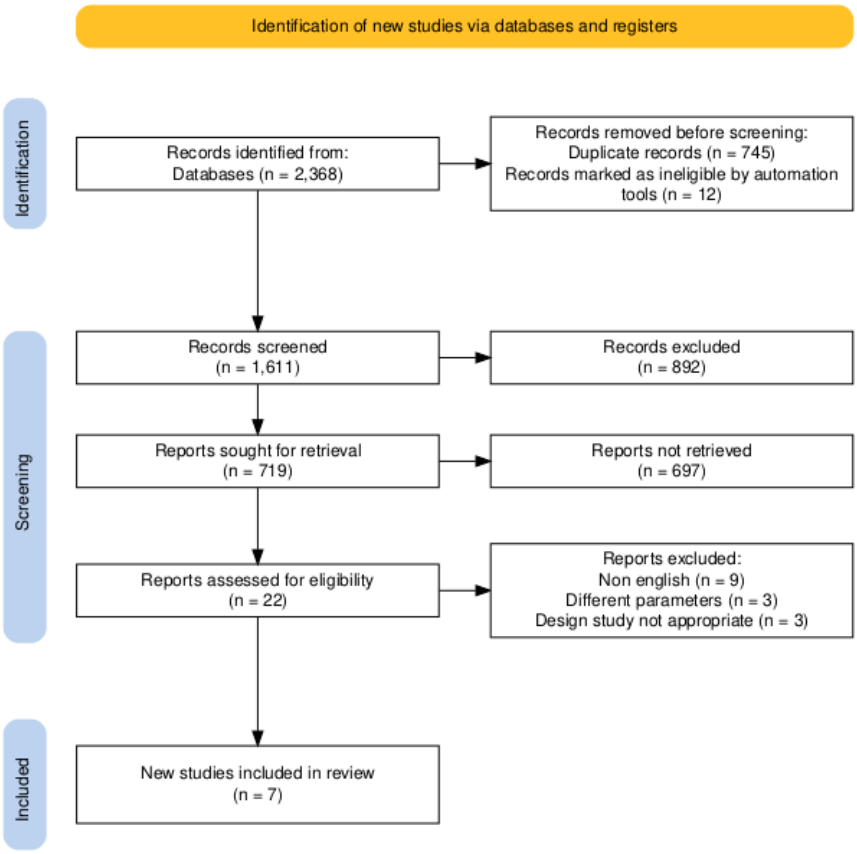

Figure 3. PRISMA flowchart for the included study

This systematic review evaluated the comparative efficacy and safety of intra-articular MSC therapy versus HA injection in patients with KOA. Overall, the included RCT consistently demonstrated that MSC therapy resulted in superior clinical improvement compared with HA, particularly regarding pain reduction and functional outcomes. Improvements were observed across multiple validated assessment tools, including the VAS, WOMAC, and several imaging-based structural evaluations such as MRI and WORMS scoring.

One of the most consistent findings across the included studies was the superior reduction in pain scores among patients receiving MSC therapy. Vega et al. reported significantly greater improvement in WOMAC and VAS scores in the MSC-treated group compared with HA at 12 months follow-up, accompanied by improvements in cartilage quality on quantitative MRI T2 mapping.5 Similarly, Lu et al. demonstrated that adipose-derived MSCs provided significant pain relief, improved functional capacity, and enhanced quality of life compared with HA

injection alone. Repeated umbilical cord-derived MSC administration in the study by Matas et al. also resulted in better symptomatic improvement than both single-dose MSC and HA treatment. These findings collectively suggest that MSC therapy may provide more sustained symptomatic relief than conventional viscosupplementation with HA.

The superiority of MSC therapy may be explained by its regenerative and immunomodulatory properties. Unlike HA, which primarily acts as a viscosupplement by restoring synovial fluid viscoelasticity and temporarily reducing joint friction, MSCs exert broader biological effects through anti-inflammatory signaling, tissue repair, and chondrogenic differentiation. MSCs can inhibit pro-inflammatory cytokines and modulate macrophage polarization, thereby reducing synovial inflammation and slowing cartilage degeneration. MSCs possess the potential to differentiate into chondrocyte-like cells and stimulate extracellular matrix synthesis, contributing to cartilage preservation and repair. Consequently, these disease-modifying effects may require a longer period before producing clinically observable improvements in pain and joint function, as gradual stabilization of cartilage degeneration and restoration of tissue homeostasis evolve over time. The sustained clinical improvement observed up to 24 months further suggests that MSC therapy may influence the long-term progression of osteoarthritis rather than merely providing temporary symptomatic relief (Li et al., 2023; Wang et al., 2026).

Interestingly several studies suggested that higher or repeated doses of MSCs may produce superior outcomes. Lamo-Espinosa et al. demonstrated that high-dose bone marrow-derived MSCs resulted in sustained improvement in WOMAC and VAS scores compared with HA alone, with benefits persisting up to four years follow-up in their subsequent long-term study (Lamo-Espinosa et al., 2016; Lamo-Espinosa et al., 2018). Matas et al. also reported that repeated dosing of umbilical cord-derived MSCs achieved better clinical improvement than single-dose therapy, suggesting a potential dose-response relationship in MSC treatment (Matas et al., 2019). These findings support the hypothesis that prolonged regenerative stimulation and immunomodulation may enhance long-term clinical efficacy.

Despite the encouraging clinical outcomes, evidence regarding structural cartilage regeneration remains inconsistent. Some studies reported favorable MRI findings following MSC therapy. Vega et al. (2015) demonstrated a reduction in poor cartilage areas on MRI T2 mapping, while Lamo-Espinosa et al. observed modest improvement in WORMS scores, particularly in the high-dose MSC group. However not all imaging outcomes reached statistical significance and several studies showed only trends toward structural improvement without definitive radiological superiority over HA. Similar findings were reported in previous meta-analyses, where MSC therapy demonstrated promising chondroprotective effects but inconsistent evidence regarding true cartilage regeneration (Alfarhan, 2025; Aryana et al., 2023). Therefore, although MSC therapy appears clinically beneficial, further studies with longer follow-up and standardized imaging evaluation are required to clarify its structural regenerative capacity.

Another important finding of this review was the favorable safety profile of MSC therapy. Most included studies reported no serious treatment-related adverse events. Gupta et al. described transient joint pain and swelling after MSC injection, while only one synovial effusion requiring prolonged hospitalization was reported (Gupta et al., 2016). Lu et al. reported no serious adverse events in the MSC group, whereas a severe joint infection occurred

in the HA group (Lu et al., 2019). Long-term follow-up by Lamo-Espinosa et al. also demonstrated sustained safety without evidence of major complications up to four years after treatment. Overall, these findings support the relative safety and feasibility of intra-articular MSC administration in KOA management.

Several limitations should be acknowledged in this review. First, significant heterogeneity existed among the included studies regarding MSC source, preparation methods, cell dose, injection frequency, and outcome assessment. Bone marrow-derived, adipose-derived, and umbilical cord-derived MSCs were all included, each with potentially different biological characteristics and regenerative potential. Second, most studies involved relatively small sample sizes and phase I/II trial designs, limiting the generalizability of findings. Third, follow-up duration was predominantly limited to 12 months, with only one study providing long-term follow-up data. Finally, structural outcomes were inconsistently reported, and MRI evaluation methods varied across studies, making pooled interpretation difficult.

Despite these limitations, the current evidence suggests that intra-articular MSC therapy may provide superior pain relief and functional improvement compared with HA injection in patients with knee osteoarthritis. The regenerative and immunomodulatory properties of MSCs offer a promising therapeutic approach beyond symptomatic treatment alone. Additional large-scale RCT with standardized MSC protocols, longer follow-up duration, and consistent structural outcome assessment are necessary to establish the long-term efficacy and optimal clinical application of MSC therapy in KOA.

CONCLUSION

Intra-articular MSC therapy appeared to demonstrate superior clinical efficacy compared with HA injection in the management of KOA, particularly in improving pain relief, functional outcomes, and quality of life. The included studies also suggested potential chondroprotective and regenerative effects, as evidenced by favorable MRI-based structural findings and reduced progression of joint degeneration. The therapeutic benefits of MSCs are likely associated with their anti-inflammatory, immunomodulatory, and regenerative properties, which may provide advantages beyond the temporary viscosupplementation effects of HA. However, larger, high-quality randomized controlled trials (RCTs) with standardized treatment protocols and long-term structural outcome assessments are still required to establish the optimal clinical role of MSC therapy in KOA management.

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