

Original Article

Functional Outcome of Mesenchymal Stem Cells Vs. Hyaluronic Acid in Knee Osteoarthritis Kellgren-Lawrence Grade I-III At 6-and 12-Months Follow-Up: A Meta-Analysis

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ABSTRACT

Background: Osteoarthritis (OA) is a degenerative synovial joint disease with progressive pain and deformity. Stem cell therapy, especially mesenchymal stem cells (MSCs), has revolutionized the treatment of knee OA. However, clinical evidence for MSCs in the treatment of knee OA is insufficient. The primary objective of this research is to offer substantiation and recommendations for advancing and utilizing MSC therapy in clinical settings, in contrast to the use of hyaluronic acid (HA) as the standard control group.

Methods: This study was a meta-analysis conducted through a search for relevant scientific reports in PubMed, Embase, and Google Scholar, using some keywords such as "mesenchymal stem cell," "hyaluronic acid," and "osteoarthritis."

Results: Mesenchymal stem cells showed promising results on a clinical basis. Among five included studies of 139 patients with knee osteoarthritis consisting of 70 patients treated with MSC and 69 patients treated with HA, mesenchymal stem cells provide significant short-term pain relief at 6- (I²=34%; SMD=-0.58 95% CI, -1.09 to -0.07; p=0.02) and 12-months follow-up (I²=28%; SMD=-0.79 95% CI, -1.22 to -0.37; p=0.0003), with relative clinical improvement. The highly differentiated MSC aids in tissue repair, regulation of immune response, and anti-inflammatory effect on knee osteoarthritis, including the chondrogenesis mechanism.

Conclusion: Mesenchymal stem cell therapy has shown effectiveness compared to hyaluronic acid injection for knee osteoarthritis, providing pain relief and improved functional outcomes on short-term intervals up to 12 months follow-up. Mesenchymal stem cells display some chondro-protective effects requiring further research and development.

Keywords: Hyaluronic acid; Human and medicine; Mesenchymal stem cell, Osteoarthritis

INTRODUCTION

Osteoarthritis is a degenerative disease of the synovial joints defined by clinical indications of joint pain and dysfunction as well as gradual joint deterioration. With a 3.8% global frequency, it is one of the most incapacitating diseases in existence.¹ For symptom relief, patients with knee OA may opt for medication, orthopaedic appliances, or surgery. The primary treatment is non-steroidal anti-inflammatory medicines (NSAIDs), although prolonged usage might have significant

adverse effects. Clinical options include injecting hyaluronic acid (HA), platelet-rich plasma (PRP), or corticosteroids directly into the affected joint. Patients with advanced knee OA are frequently urged to undergo surgery. However, this can have adverse effects on clinical outcomes.² Kellgren-Lawrence classification is used to describe OA grading using AP knee radiographs. They correlate to increasing severity of OA.²

The treatment of knee osteoarthritis has been revolutionized by stem cell therapy, particularly using mesenchymal stem cells. MSCs pos-



sess the capacity for self-renewal, the potential for multiple types of differentiation, and low immunogenicity, and they are straightforward to cultivate and obtain. Positive clinical results include pain alleviation, function recovery, and promising increases in cartilage volume and quality.³ Nonetheless, certain reports indicate an inadequate amount of clinical proof regarding the use of MSCs for knee osteoarthritis treatment. Albeit the high prevalence of OA in the population and the emergence of new and exciting branches of medicine working towards regenerative medicine, there has yet to be a summary of the treatment of knee OA using MSCs. This study aimed to provide a quantitative evaluation of the most recent, high-quality research on the clinical efficacy and safety of MSCs in treating knee OA. The study's findings will offer support and direction for promoting and applying MSC therapy in clinical practice. Results from this study will also help patients determine whether they need this therapy, as MSC therapy may be less affordable.

MATERIAL AND METHODS

Search Strategy

The study was complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) policy statement. We carried out a comprehensive and systematic search, spanning from March 2013 to 2023, to identify studies that had the potential to be included in this research. The databases used are Google Scholar, PubMed,

and Embase with search queries of “Mesenchymal Stem Cell” AND “Hyaluronic Acid” AND “Osteoarthritis”. Two reviewers (F and IGNWA) examined the reference lists and abstracts independently. Any disagreements among the reviewers about whether to include or exclude a study will be determined through consensus and, if required, with consultation from a third reviewer. This study will involve a full-text, English-language, randomized controlled trial comparing mesenchymal stem cell derivatives and hyaluronic acid injection for knee osteoarthritis. The primary goal of this meta-analysis is to compare the functional outcomes of mesenchymal stem cell derivatives and hyaluronic acid injection for knee osteoarthritis. Our protocol has also been registered in PROSPERO (registration number: [CRD42023477087](https://www.crd42023477087)).

Inclusion Criteria

The requirements for studies to be included were as follows: 1) comparative prospective or retrospective RCT studies in English comparing mesenchymal stem cell-derived materials vs hyaluronic acid injection in patients with knee osteoarthritis Kellgren-Lawrence grade I-III, and 2) describing results measurements such as the Western Ontario and McMaster Universities Arthritis Index (WOMAC), the Visual Analog Scale (VAS), and the Whole-Organ Magnetic Resonance Imaging Score (WORMS) at 6- and 12-months follow-up. Studies involving patients with associated osteoarthritis in other joints, additional pathological knee pain reasons, and previous surgery were excluded (Table 1).

Table 1. PICO Criteria for Inclusion Study

	Inclusion	Exclusion
Population	Patient with knee osteoarthritis Kellgren-Lawrence grade I-III	Patient with associated osteoarthritis in other joints, other pathological causes of knee pain, and prior surgery
Intervention	Patients treated with mesenchymal stem cell derivatives	Patients treated with surgical treatment and conservative measures other than stem cell or hyaluronic acid injection
Comparison	Patients treated with hyaluronic acid injection.	Patients treated with surgical treatment and conservative measures other than stem cell or hyaluronic acid injection
Outcome	VAS score, WOMAC score, and WORMS score at 6- and 12-months follow-up	Outcomes not clearly mentioned work with another parameter than our inclusion criteria
Design	Randomized controlled trials (RCT)	Case reports, case series, cross-sectional studies, cohort studies, systematic reviews, or meta-analyses



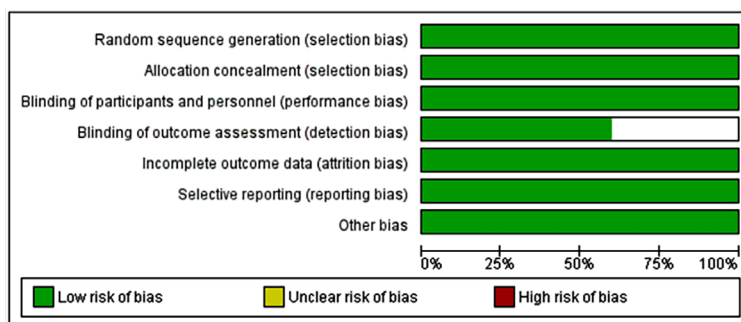
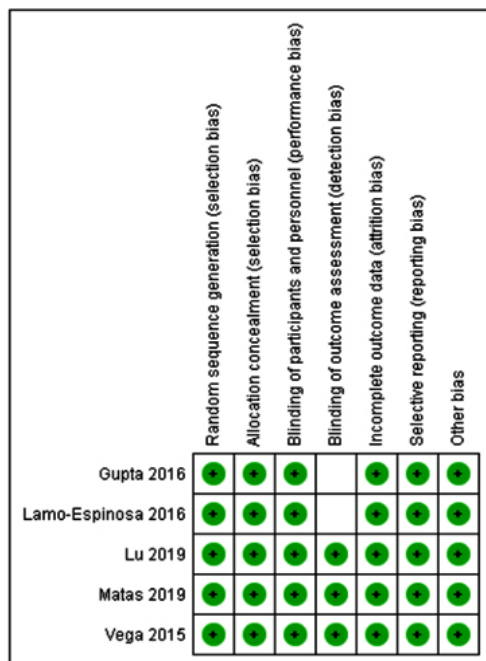
Figure 1. Risk of Bias Graph.⁴

Figure 2. Risk of Bias Summary.

Table 2. Characteristic of the studies.

No.	Studies	Journal	Study Design	Level of evidence
1	Vega et al., 2015 ⁶	Transplantation	Randomized Controlled Trial	II
2	Gupta et al., 2016 ⁷	Arthritis Research & Therapy	Randomized Controlled Trial	II
3	Lamo-Espinosa et al., 2016 ⁸	Journal of Translational Medicine	Randomized Controlled Trial	II
4	Lu et al. 2019 ⁹	Stem Cell Research & Therapy	Randomized Controlled Trial	I
5	Matas et al. 2019 ¹⁰	Stem Cells Translational Medicine	Randomized Controlled Trial	II

Table 3. Characteristic of the study populations.

No.	Studies	Number of Subjects	Age (year)	Male	Female	OA KL Grade	Mesenchymal Stem Cell	Follow-up
1	Vega et al., 2015 ⁶	MSC: 15 HA: 15	MSC: 56.6±9.57 HA: 57.3±9.41	MSC: 6 HA: 5	MSC: 9 HA: 10	2-4	Bone marrow	12 months
2	Gupta et al., 2016 ⁷	MSC: 10 HA: 10	MSC: 58.1±8.23 HA: 54.9±8.27	MSC: 3 HA: 0	MSC: 7 HA: 10	2-3	Bone marrow	6, and 12 months
3	Lamo-Espinosa et al., 2016 ⁸	MSC: 10 HA: 10	MSC: 65.9 HA: 60.3	MSC: 4 HA: 7	MSC: 6 HA: 3	2-4	Bone marrow	6, and 12 months
4	Lu et al. 2019 ⁹	MSC: 26 HA: 26	MSC: 55.03±9.19 HA: 59.64±5.97	MSC: 3 HA: 3	MSC: 23 HA: 23	1-3	Adipose	6, and 12 months
5	Matas et al. 2019 ¹⁰	MSC: 9 HA: 8	MSC: 56.1±6.8 HA: 54.8±4.5	MSC: 3 HA: 3	MSC: 6 HA: 5	2-3	Umbilical cord	6, and 12 months

Quality Evaluation

Each article was evaluated independently by two reviewers (F and IGNWA). Any disputes are resolved by consensus following thorough debate. The same two independent reviewers

will evaluate the included RCTs' quality using the "Risk of bias" assessment tool seven Cochrane criteria for assessing bias, including selection, performance, detection, attrition, reporting, and others (Figure 1 and 2).



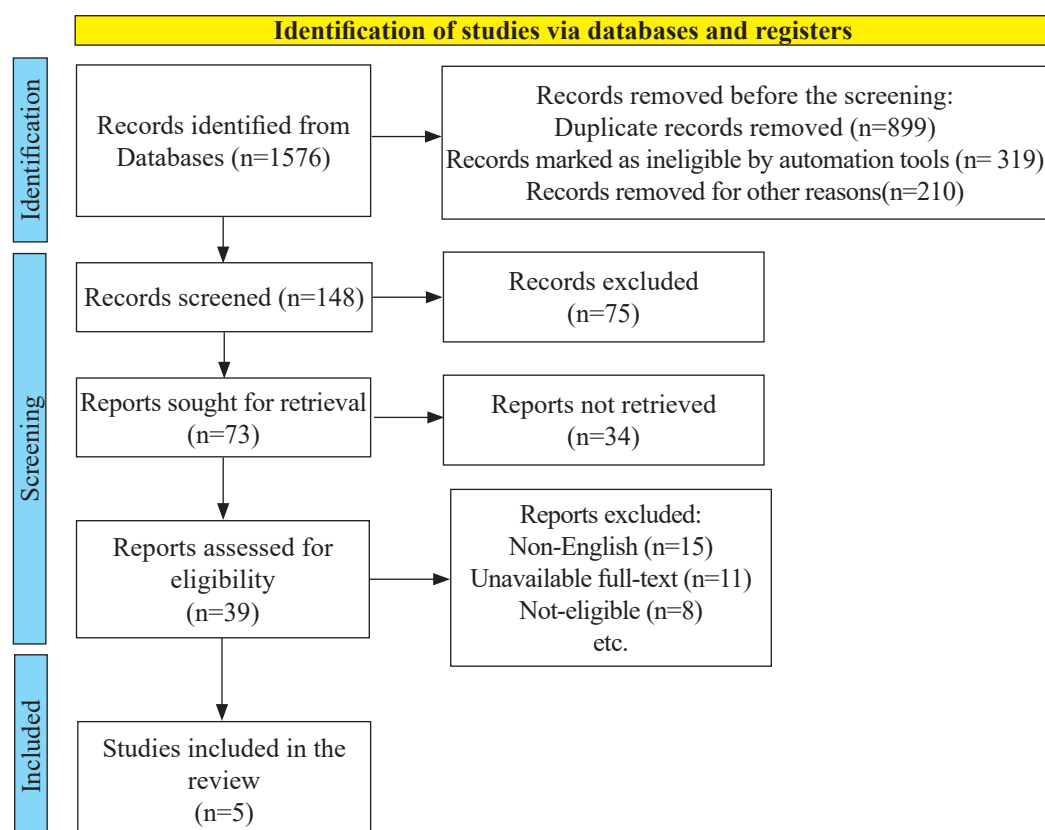
Figure 3. PRISMA flowchart for the included study.⁵

Table 4. Characteristic of the outcome of the studies.

No	Reference	Outcome Measure at 6 months			Outcome Measure at 12 months		
		VAS	WOMAC	WORMS	VAS	WOMAC	WORMS
1	Vega et al. 2015 ⁶	-	-	-	MSC: 3±2.7 HA: 5±3.4	MSC: 25±13.3 HA: 37.6±23.7	-
2	Gupta et al., 2016 ⁷	MSC:2.4±1.2 HA: 4.5±1.4	-	MSC:67.5±20.5 HA: 74.9±22.4	MSC: 2.1±1.2 HA: 3.9±1.4	-	MSC:66.1±19.2 HA:74.9±22.5
3	Lamo-Espinosa et al., 2016 ⁸	MSC: 3±2.9 HA: 5±4.4	MSC:22.6±13.3 HA: 11.3±11.8	MSC: 84.3±50 HA: 73±50	MSC: 2±1.4 HA: 4±1.4	MSC: 20.8±8.1 HA: 18.1±18.5	MSC: 99±50 HA: 67.7±50
4	Lu et al., 2019 ⁹	MSC:2.9±2.6 HA: 4.3±5.2	MSC:21.7±17.8 HA: 27.5±16.9	-	MSC: 2.7±2.5 HA: 3.5±2.5	MSC:21.3±18.2 HA: 27.2±16.3	-
5	Matas et al. 2019 ¹⁰	MSC:1.2±0.7 HA: 2.8±8.7	MSC: 13.8±9.2 HA: 18.6±14.7	MSC:46.6±18.1 HA: 33.2±25.7	MSC: 1.3±0.8 HA: 2.2±0.9	MSC:14.9±12.7 HA: 15.2±11	MSC:41.5±14.3 HA: 33.6±26.3

Data Synthesis

Using predefined tables in Microsoft Excel, data were extracted under important features and outcomes for all identified and included research (Microsoft Corporation, Redmond, WA, USA). When the data were accessible, Review Manager was used for quantitative analysis (RevMan, computer program version 5.3, the Cochrane Collaboration, 2014; The Nordic Cochrane Center, Copenhagen, Denmark). The results were displayed using forest plots. The mean differ-

ence for continuous outcomes and odds ratio for dichotomous outcomes with a 95% confidence interval (CI) were determined in each study. When the heterogeneity (I^2) was less than 50%, a fixed-effects model was used; while it was greater than 50%, a random-effects model was used.

RESULTS

Literature Search, Study Selection, and Study characteristics



A total of 1576 documents were found using the electronic search across several databases. The remaining five studies were included in the qualitative synthesis after duplication was eliminated, screening, and exclusion. The remaining studies were removed because they did not meet the inclusion and exclusion criteria, lacked mean and standard deviation data, were non-English studies, were unavailable in their whole, and other reasons (Figure 3). Characteristics of the included studies are shown in Table 2 and characteristics of the study populations are shown in Table 3.

One hundred thirty-nine individuals with knee osteoarthritis were included in this meta-analysis, including 70 patients who were treated with mesenchymal stem cell injection and 69 patients who were treated with a hyaluronic acid injection. The patient's average age is 57.87 years old. Gender-wise, female is more dominant, with 102 females and 37 males. According to the Kellgren-Lawrence classification, our patients had grade 2 and 3 knee osteoarthritis. The mesenchymal stem cell used in this study includes bone marrow-derived mesenchymal stem cells in three studies and one study, each using Adipose-derived mesenchymal stem cell and umbilical cord mesenchymal stem cell. The follow-up period was perceived at 6- and 12-months following treatment (Table 4).

VAS Score

After a six-month follow-up period, VAS scores from four studies were examined. These studies involved a combined total of 55 patients in the mesenchymal stem cells group and 54 patients in the hyaluronic acid group. Figure 4 (A) demonstrates the significant differences between the MSC and HA on VAS score (heterogeneity, $I^2 = 34\%$; SMD = -0.58, 95%CI, -1.09 to -0.07; $p = 0.02$).

Similar results are shown at 12 months follow-up. Figure 4 (B) demonstrates the significant differences between MSC and HA in five studies, including a total of 70 patients in the mesenchymal stem cells and 70 patients in the hyaluronic acid group (heterogeneity, $I^2 = 28\%$; SMD = -0.79, 95%CI, -1.22 to -0.37; $p = 0.0003$).

WOMAC score

At six months follow-up, WOMAC scores were analyzed in three studies, including a total of 45 patients in the mesenchymal stem cells and 44 patients in the hyaluronic acid group. Figure 4 (C) demonstrates the insignificant differences between the MSC and HA on WOMAC score (heterogeneity, $I^2 = 60\%$; SMD = 0.01 95%CI, -0.73 to 0.75; $p = 0.98$). Similar results are shown at 12 months follow-up. Figure 4 (D) demonstrates the insignificant differences between MSC and HA in four studies, including a total of 60 patients in the mesenchymal stem cells and 59 patients in the hyaluronic acid group (heterogeneity, $I^2 = 0\%$; SMD = -0.28 95%CI, -0.64 to 0.09; $p = 0.14$).

WORMS Score

At six months follow-up, WORMS scores were examined in three studies, including a total of 29 patients in the mesenchymal stem cells and 28 patients in the hyaluronic acid group. Figure 4 (E) demonstrates the insignificant differences between the MSC and HA on WOMAC score (heterogeneity, $I^2 = 0\%$; SMD = 0.13 95%CI, -0.40 to 0.65; $p = 0.63$). Similar results are shown at 12 months follow-up. Figure 4 (F) demonstrates the insignificant differences between MSC and HA in three studies, including a total of 29 patients in the mesenchymal stem cells and 28 patients in the hyaluronic acid group (heterogeneity, $I^2 = 24\%$; SMD = 0.18 95%CI, -0.43 to 0.78; $p = 0.57$).



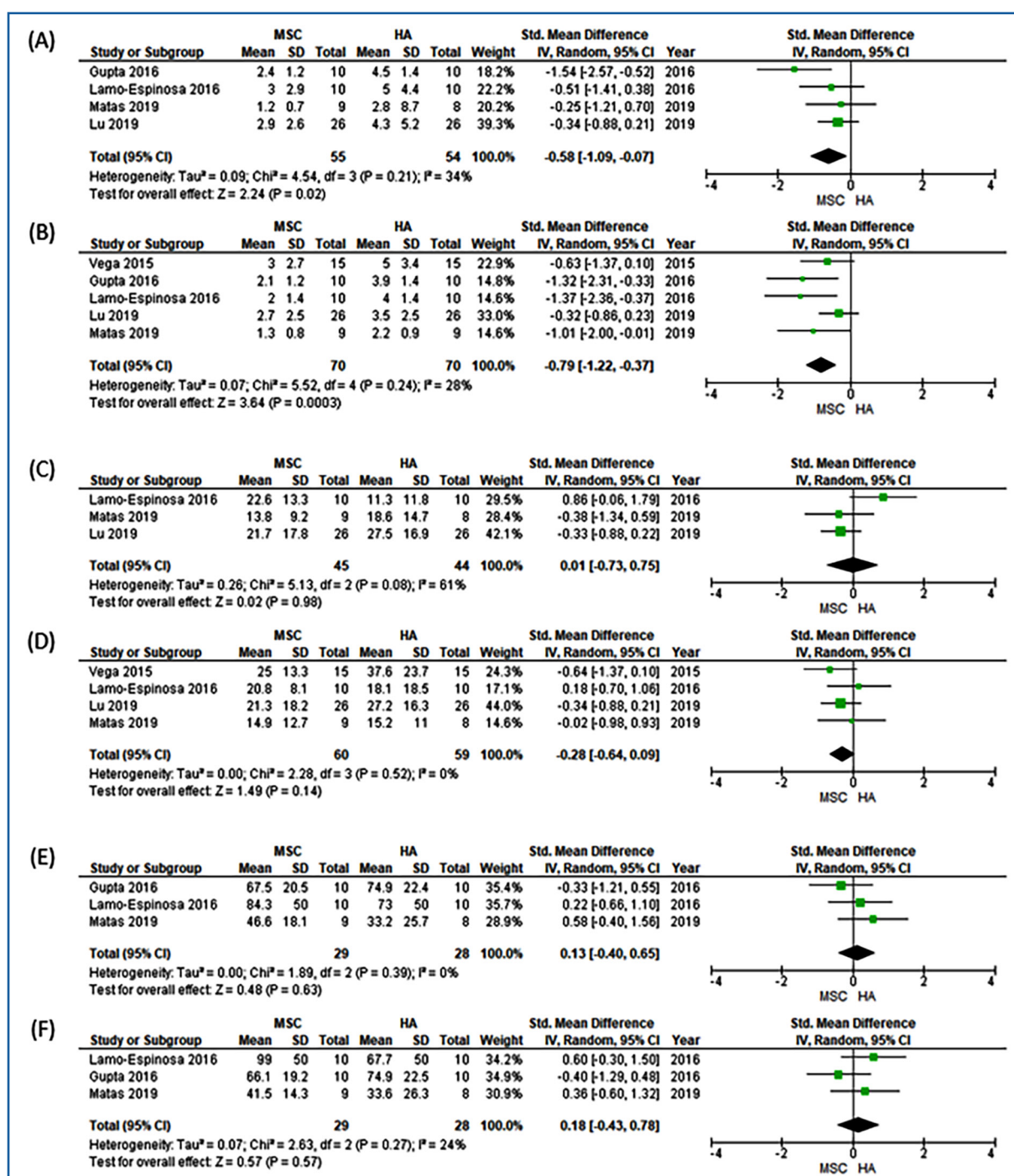


Figure 4. (A and B) Forest plot analysis VAS, (C and D) WOMAC, and (E and F) WOMRS score at 6 months and 12 months follow-up, respectively.

DISCUSSION

Regenerative medicine has emerged as a potential approach in the management of knee osteoarthritis, offering potential solutions beyond traditional treatments. Currently, disease-modifying drugs alter the natural course of osteoarthritis and offer structural improvement in destroyed particular cartilage and the

associated structures. This innovative field focuses on implementing the natural healing mechanism by restoring damaged tissue and asymptomatic relief. Unfortunately, according to the American College of Rheumatology and Arthritis Foundation, advanced regenerative treatment has not yet been recommended in the guideline management of osteoarthritis due to the ongoing growing research under-



way. While the American Academy of Orthopaedic Surgeon Clinical Practice Guideline has only admitted using PRP with limited strength of recommendation, it may reduce pain and improve functions in asymptomatic knee osteoarthritis.^{2,11,12}

Mesenchymal stem cells are used as one of the main products in regenerative medicine for knee osteoarthritis. These cells have the extraordinary capacity to develop into multiple cell types, including cartilage cells, which are required for joint healing. This targeted method attempts to encourage the regeneration of damaged cartilage, reduce inflammation, and enhance joint function.¹³ Mesenchymal stem cells originating from various sources, such as adipose tissue, umbilical cord, and bone marrow, have received a great deal of attention in the field of regenerative medicine.

According to Hernigou et al., bone marrow mesenchymal stem cells (BM-MSCs) provide significant pain relief to postpone and avoid total knee arthroplasty.¹⁴ In a similar vein, Zhang et al. noted that exosomes derived from BM-MSCs might alleviate osteoarthritis by facilitating the shift of synovial macrophages from the M1 to M2 phenotype, preserving chondrogenic traits and preventing chondrocyte hypertrophy.¹⁵ The utilization of umbilical cord-derived MSCs (UC-MSCs) has emerged as a promising alternative, obtained from Wharton's jelly of the umbilical cord after birth. UC-MSCs possess similar characteristics to BM-MSCs but offer the advantage of being easily accessible without invasive procedures. Dhillon et al. support the administration of UC-MSCs for the treatment of knee osteoarthritis by providing significant improvement in clinical outcomes.^{16,17} Another easily obtained material is adipose tissue-derived MSCs (AD-MSCs) through minimally invasive techniques like liposuction. AD-MSCs are abundant in adipose tissue and

exhibit considerable regenerative potential. These MSCs hold great promise in regenerative therapies, offering the potential for tissue repair, anti-inflammatory effects, and immunomodulatory properties. The versatility and therapeutic potential of MSCs from bone marrow, umbilical cord, and adipose tissue make them invaluable tools in advancing the field of regenerative medicine. According to Freitag et al., AD-MSC is a safe and effective management of knee osteoarthritis, with the potential to prevent disease progression.¹⁸ A study by Issa et al. mentioned that AD-MSCs is highly efficient in managing knee osteoarthritis, providing significant improvement in functional and pain outcomes. Furthermore, AD-MSC is capable of cartilage repair and maintaining the integrity of articular cartilage.¹⁹

Several animal studies have investigated the effects of mesenchymal stem cells in knee osteoarthritis, leading to way or subsequent human injuries. In these animal experiments, a range of animal models, such as rabbits, rats, dogs, and goats, were intentionally induced with knee osteoarthritis and subsequently subjected to treatment involving mesenchymal stem cells obtained from various sources, which included bone marrow, umbilical cord, and adipose tissue. These preclinical studies consistently demonstrated promising outcomes, showing that MSC therapy could effectively improve cartilage regeneration, reduce inflammation, and enhance joint function in animal models of knee OA.²⁰ The animal studies provided crucial insights into the safety and efficacy of MSCs, leading to the initiation of human clinical trials. Human studies evaluating the use of MSCs in knee OA have shown encouraging results, demonstrating pain reduction, improved joint function, and cartilage regeneration. Mesenchymal stem cells display encouraging chondrogenic properties that were not present in previous standard treatments for knee osteo-



arthritis. Furthermore, these human studies build upon the foundation laid by animal studies, further supporting the potential of MSC therapy as a viable treatment option for knee osteoarthritis. Continued research and clinical trials are essential to optimize MSC-based treatments and establish their long-term effectiveness and safety in human patients.²¹

The efficacy of MSCs in treating knee OA has been the subject of extensive research and clinical trials. MSC-based therapies have shown promising results in improving the symptoms and functional outcomes of knee OA. Wang et al. reported significant improvements in pain reduction joint function and quality of life in patients receiving MSC therapy for knee OA, with a mean difference of -13.24 (VAS score, $p = 0.010$) and -7.22 (WOMAC score, $p = 0.010$). In terms of dosage, low-dose AD-MSCs (25 million cells) provide better results than higher-dose AD-MSCs.²² Moreover, MSC-based treatments have demonstrated a favorable safety profile with minimal adverse effects. Although further research is needed to optimize the dosage, delivery methods, and long-term effects, the emerging evidence suggests that MSCs hold great potential as a viable therapeutic option for managing knee OA.^{23,24}

Our study presents similar results to previous research about the efficacy of MSCs for managing knee osteoarthritis. In comparison to the standard hyaluronic acid injection for the management of early-stage knee osteoarthritis, all types of MSCs among the four included studies (BM-MSCs, AD-MSCs, and UC-MSCs) have shown significant pain relief at 6- and 12-months follow-up ($p < 0.05$). Mesenchymal stem cells exert anti-inflammatory capabilities and immunomodulatory functions that are supposedly said in Spain relief. According to Kyurkchiev et al., MSCs have a widespread inhibitory effect on developing dendritic cells, macrophages, Natural

Killer (NK), and cytotoxic T lymphocytes. Alongside the anti-inflammatory response, MSCs represent a wide range of immunomodulatory activities on cell-mediated and humoral immune responses.²⁵

When the pain level is reduced, patients with knee osteoarthritis are expected to perform better knee function. According to Koh et al., the administration of AD-MSCs significantly improves knee functional scores.²⁶ On the contrary, in your findings, despite the overall trending favouring MSCs, there is an insignificant difference in functional WOMAC score between MSCs and HA at 6- and 12- months follow-up, respectively ($p = 0.08$ and $p = 0.14$). The small number of samples and short-term follow-up are considered the major influencing factors affecting the statistical analysis. Hence, further research is necessary to conclude the efficacy of MSCs and the long-term outcomes beyond 12 months, which seems very promising due to the chondroprotective and chondrogenic properties of MSCs. Hankenson et al. found an increased level of thrombospondin 2 (TSP-2) as the cartilage and bone differentiation regulator after administration of MSCs. Jeong et al. mentioned that TSP-2 promotes cartilage differentiation and inhibits cartilage hypertrophic maturation through autocrine signaling from UC-MSCs.^{27,28}

Regarding radiological outcome, the Whole-Organ Magnetic Resonance Imaging Score (WORMS) has been used in clinical studies to assess the efficacy of MSCs products in treating knee OA according to the cartilage structural integrity. According to Jo et al., an arthroscopic examination of the knee joint at six months following administration of AD-MSCs showed smaller cartilage defect size with thick hyaline cartilage information seen on histology.²⁹ These findings suggest that MSC-based therapies have the potential to impact the radiological progression of knee OA positively. Nevertheless, despite



the excellent outcomes of macroscopic and microscopic histopathology studies as well as laboratory chondrocyte markers in previous studies, your findings at short-term follow-up have yet to show relevant results. There are similar radiological outcomes in MRI imaging based on WORMS scoring between the MSCs and HA group up to 12 months follow-up with positive trends to promising overall outcomes. Hence, further research on the radiological benefits of MSCs invalidating the chondroprotective and chondrogenic properties of MSCs is mandatory, primarily investigating the long-term outcomes beyond 12 months of follow-up.³⁰

In your perspective, a mesenchymal stem cell has great potential for the management of knee osteoarthritis; furthermore, a certain newly developed derivative product of mesenchymal stem cells, such as secretome and exosome, which has equally effective outcomes with much lower cost than the standard mesenchymal stem cell. Nevertheless, further research involving regenerative medicine is necessary in the management of early knee osteoarthritis in Kellgren Lawrence grade II-III.^{31,32}

CONCLUSION

Mesenchymal stem cell therapy has shown effectiveness compared to hyaluronic acid injection for knee osteoarthritis, providing pain relief and improved functional outcomes in short-term intervals up to 12 months follow-up. However, chondroprotective effects in mesenchymal stem cell therapy require further research and development.

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