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Can Osteoarthritis be Cured by Mesenchymal Stem Cells (MSCs): A Literature Review

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ABSTRACT Osteoarthritis (OA) is a prevalent, chronic degenerative joint disease with no definitive cure, affecting millions globally and significantly impairing quality of life. Despite available treatments, current management strategies primarily address symptoms rather than halting disease progression. Recently, mesenchymal stem cells (MSCs) have emerged as a promising regenerative therapy for OA due to their ability to differentiate into cartilage cells, modulate immune responses, and promote tissue repair. This literature review aims to investigate the potential therapeutic role of MSCs in OA treatment by analyzing clinical trial data from the last three years (2021–2023). Articles were sourced from PubMed using specific keywords based on the PICO framework. The review included only full-text clinical trials involving OA patients. The results highlight varied but generally favorable outcomes across different studies, with evidence of improvements in cartilage regeneration, pain reduction, and joint function. While some studies reported minimal adverse effects, heterogeneity in methodologies and patient responses suggests the need for further standardization and investigation. In conclusion, MSC therapy demonstrates encouraging potential in OA treatment but requires more robust, long-term clinical trials to establish efficacy, safety, and patient selection criteria.

INDEX TERMS Osteoarthritis, Mesenchymal Stem Cells, Cartilage Regeneration, Stem Cell Therapy, Clinical Trials.

I. INTRODUCTION

Osteoarthritis (OA) is one of the most common chronic musculoskeletal disorders, predominantly affecting older adults and women. Characterized by the progressive degeneration of articular cartilage and associated joint structures, OA leads to pain, stiffness, and reduced mobility, severely impacting the quality of life [1]–[4]. The knees and hips are particularly susceptible due to their weight-bearing function. Traditional treatments, including analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and physical therapy, focus primarily on symptom relief without addressing the underlying degenerative processes [5]–[8]. These approaches often lead to temporary improvements and may result in adverse effects with prolonged use.

Recent attention has turned toward regenerative medicine, particularly mesenchymal stem cells (MSCs), due to their unique biological properties. MSCs, derived from various tissues such as bone marrow, adipose tissue, and umbilical cords, possess the capacity for self-renewal, multipotent differentiation, and immunomodulatory effects [9]–[12]. Their ability to differentiate into chondrocytes makes them particularly relevant for cartilage repair in OA [13], [14]. In preclinical and clinical studies, MSCs have shown promise in promoting cartilage regeneration, reducing inflammation, and improving joint function [15]–[17].

Despite growing interest, the application of MSCs in OA treatment remains at an exploratory stage. Variations in stem cell sources, dosages, delivery methods, and patient characteristics have produced mixed results, highlighting a significant research gap. Some studies report substantial improvements in cartilage integrity and patient-reported outcomes, while others observe minimal benefits [18]–[20]. Moreover, the long-term efficacy and safety of MSC-based therapies are still under scrutiny, necessitating further rigorous clinical evaluations.

Given the global burden of OA and limitations of current therapies, investigating MSC-based interventions offers a promising avenue. This literature review aims to synthesize findings from recent clinical trials involving MSCs in OA therapy, specifically between 2021 and 2023. The study utilizes the PICO framework to ensure methodological relevance and focuses on patient outcomes, adverse effects, and therapeutic efficacy. The review contributes to existing knowledge by (1) mapping current evidence of MSC applications in OA, (2) identifying methodological trends and limitations across trials, and (3) suggesting directions for future research and clinical practice.

The remainder of this article is structured as follows: Section II outlines the methodology used for literature selection and analysis. Section III presents and discusses the findings of selected clinical trials. Section IV provides concluding remarks on the implications of MSC therapy in OA management and future research priorities.

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II. METHOD

This study employed a structured qualitative literature review methodology aimed at evaluating the clinical efficacy of mesenchymal stem cell (MSC) therapy for osteoarthritis (OA). Emphasis was placed on identifying consistent therapeutic outcomes, safety profiles, and methodological trends in recent clinical trials.

A. LITERATURE SEARCH STRATEGY

The primary source of literature was the PubMed database, focusing on clinical trials published from 2021 to 2023. The search was guided using the PICO framework: *Population* (patients with OA), *Intervention* (MSC-based therapy), *Comparison* (placebo or standard treatments), and *Outcome* (pain reduction, cartilage regeneration, and functional improvement). Keywords included: *"Mesenchymal Stem Cells"*, *"Osteoarthritis"*, and *"Clinical Trial"*, and were selected in accordance with Medical Subject Headings (MeSH).

B. ELIGIBILITY CRITERIA

Inclusion criteria consisted of:

1. Clinical trials conducted on human participants diagnosed with OA;
2. Use of MSCs from any biological source (e.g., bone marrow, adipose, umbilical cord);
3. Articles published in English;
4. Reporting on therapeutic outcomes such as joint pain, structural improvement, or function.

Exclusion criteria included:

a. Preclinical or animal studies
b. In vitro experimental designs
c. Meta-analyses, review articles, or studies unrelated to OA

C. DATA SELECTION AND ASSESSMENT

From the initial 25 articles retrieved, 15 studies met all inclusion criteria after thorough screening of titles, abstracts, and full texts. Selected studies were reviewed and analyzed using a standardized extraction protocol. This included data on sample size, MSC origin, cell administration technique, patient demographics, follow-up duration, and outcome metrics. The Cochrane Risk of Bias Tool was utilized to evaluate methodological quality and risk of bias in each study [32].

D. STUDY CHARACTERISTICS

The majority of studies were prospective randomized controlled trials (RCTs) involving adults aged 40–80 years diagnosed with knee OA based on radiographic or MRI findings. Randomization procedures and blinding were reported in most trials, thus minimizing selection bias and improving internal validity [33], [34].

E. STEM CELL SOURCES AND ADMINISTRATION

Mesenchymal stem cells were harvested from multiple sources, including bone marrow**,** adipose tissue**,** and umbilical cord tissue**.** Administration methods varied across studies and included intra-articular injection**,** subchondral implantation**,** scaffold-assisted delivery. Cell dosages ranged from 10 to 100 million cells per joint site, with some protocols involving single injections and others implementing multiple-dose regimens over specified time intervals [35]–[37].

F. OUTCOME EVALUATION

Therapeutic outcomes were assessed using validated clinical instruments such as:

1. Visual Analog Scale (VAS) for pain intensity
2. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for joint function
3. Magnetic Resonance Imaging (MRI) for cartilage quality and thickness

Most trials demonstrated statistically significant improvements in joint pain, physical performance, and cartilage regeneration among MSC-treated groups compared to control groups [38]–[40].

G. ETHICAL APPROVAL AND PATIENT RIGHTS

All studies included in this review were conducted in accordance with international ethical standards. Each clinical trial received prior approval from Institutional Review Boards (IRBs) or equivalent ethics committees. Informed consent was obtained from all participants before enrollment. Confidentiality and data protection were upheld as per standard research protocols [41], [42].

III. RESULTS

TABLE 1. shows the clinical studies using MSCs therapy in Osteoarthritis. R. Köhnke et al. [18] found that a significant increase in cartilage thickness in the stromal cell treated groups (HA + STx. vs. ABS, $p = 0.028$; HA + ST.x vs. HA, $p = 0.042$; STx. vs. ABS, $p = 0.036$). Scanning electron microscopy detected a similar heterogeneity of mineralization and tissue porosity in the subchondral zone in all groups. The single intra-articular injection of a stem cell containing, GMP-compliant advanced therapy medicinal product for the treatment of iatrogen induced osteoarthritis of the temporomandibular joint shows a chondroregenerative effect. Philippe Hernigou et al. [19] found that After treatment with MSCs injection in bone marrow lesions of the subchondral bone, medial femorotibial compartment BML volume experienced regression over 24 months (mean regression 1.5 cm3, range 0.8 to 3.2 cm3). At the most recent follow up (average of 15 years, range 10 to 20 years), a total of 25 (18%) of the 140 patients underwent total knee arthroplasty performed at a mean of ten years (range, 5 to 15 years) after the date of the cell therapy. The overall incidence of knee arthroplasty after cell therapy was 1.19% per person-year which was equivalent to the risk of a revision for a primary TKA in the contralateral knees of the same patient population (21 revisions, corresponding to 1.00% revision per person-year; $p = 0.34$). After adjusting for confounders, persistent BMLs larger than 3 cm3 after cell therapy was a strong independent risk factor for total knee arthroplasty (hazard ratio HR = 4.42 [95% CI = 2.34 to 7.21]; $p < 0.001$), regardless of OA grade, with higher risks demonstrated for

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larger BMLs. Incidence rates of arthroplasty were also higher for young patients and for knees presenting severe malalignment. J. M. Lamo-Espinosa et al. [20] found that cell doses of 10, 40 and 100 million autologous cells per knee provided quite similar healing results and that much of the effect attained 1 year after cell application remained after 2 and 4 years. These results are encouraging because they indicate that, apart from safety and simplicity: (i) the beneficial effect is both significant and sizeable, (ii) it can be achieved with a single injection of cells, and (iii) the effect is perdurable for years. P. Hernigou et al. [21] found that at two-year follow-up, clinical and imaging (MRI) improvement was higher on the side that received cells in the subchondral bone. At the most recent follow-up (15 years), among the 60 knees treated with subchondral cell therapy, the yearly arthroplasty incidence was 1.3% per knee-year; for the 60 knees with intra-articular cell therapy, the yearly arthroplasty incidence was higher ($p = 0.01$) with an incidence of 4.6% per knee-year. For the side with subchondral cell therapy, 12 (20%) of 60 knees underwent TKA, while 42 (70%) of 60 knees underwent TKA on the side with intra-articular cell therapy. Among the 18 patients who had no subsequent surgery on both sides, all preferred the knee with subchondral cell therapy. J. D. Tucker et al. [22] found that novel biomarkers including levels of interleukin (IL)-5, IL-6, IL-10, and tumor necrosis factor-α were measured in synovial fluid 10 days after PRP treatment. Altered gene expression profiles in MSCs from patients treated with PRP were observed for matrix metalloproteinases and inflammatory markers (IL-6, IL-8, CCL2, TNF-α). A2M protease was significantly increased following PRP treatment ($P = .005$). WOMAC scores declined for up to 3 months from baseline levels and remained low at 6 and 12 months in the PRP group. In contrast, WOMAC scores for patients receiving the saline injection were relatively unchanged for up to 12 months. T. Weijie et al. [23] found that for 15 of them, in addition to implants, cartilage grafts were transplanted during surgery. All patients were monitored by the Oswestry Disability Index questionnaire, for one year. In general, the results showed that over time, patients with transplanted cartilage tissue and implants were in a better condition than patients who underwent only implant surgery. S. Zhang et al. [24] found that the VAS and WOMAC scores in the SVF group were significantly better than those in the HA group during the 5-year follow-up after treatment. The average responsive time to SVF treatment (61.52 months) was significantly longer than HA treatment (30.37 months). The adjusted Cox proportional hazards model showed that bone marrow lesion (BML) severity, body mass index (BMI) and treatment were independent risk factors and that the use of SVF reduced the risk of clinical failure by 2.602 times. The cartilage volume was reduced in both the SVF and control groups at 5 years but reduced less in the SVF group. O. Olufade et al. [25] found that, 51 patients were enrolled at the time of analysis (27 dCPC, 24 CSI). Both groups demonstrated improvement on the VAS, KOOS and EQOL. Largest differences were observed at 2 ($p = 0.05$), 3 ($p = 0.012$) and 6 months ($p < 0.001$) with a decrease of 1.66 in VAS at 6 months for dCPC (95% CI: -2.67 to -0.65) and 1.34 (95% CI: -2.37 to -0.3) for CSI. Time-averaged measures showed no difference between groups ($p = 0.20$). Limited data at 9 and 12 months trended toward improvement in the dCPC group. J.-H. Kim et al. [26] found that, the primary outcome was the serial changes of cartilage defect on periodic magnetic resonance imaging (MRI) evaluation using valid measurements until postoperative 24 months. Secondary outcomes were the 2-stage arthroscopic evaluation for macroscopic cartilage status and the postoperative functional improvements of patient-reported outcome measures until the latest follow-up. Furthermore, safety profiles after the treatment were evaluated. Cartilage regeneration on serial MRIs showed significantly better in the ADMSC group than in the control group. The arthroscopic assessment revealed that total cartilage regeneration was significantly better in the ADMSC group. Although it was not significant, functional improvements after the treatment showed a tendency to be greater in the ADMSC group than in the control group from 18 months after the treatment. No treatment-related adverse events, serious adverse events, and postoperative complications occurred in all cases. Concomitant intra-articular injection of ADMSCs with MOWHTO had advantages over MOWHTO alone in terms of cartilage regeneration with safety at 2-year follow-up, suggesting potential disease-modifying treatment for knee OA with varus malalignment. B. Sadri et al. [27] found that, the primary outcome of this study was safety and feasibility of allogeneic AD-MSCs injection during the 6 months follow-up. Fortunately, no serious adverse events (SAEs) were reported. Assessment of secondary outcomes of visual analogue scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and knee osteoarthritis outcome score (KOOS) indicated improvement in all patients. Comparison between baseline and endpoint findings of MRI demonstrated a slight improvement in two patients. In addition, decrease in serum cartilage oligomeric matrix protein (COMP) and hyaluronic acid (HA) indicated the possibility of reduced cartilage degeneration. Moreover, quantification of serum interleukin-10 (IL-10) and interleukin-6 (IL-6) levels indicated that the host immune system immunomodulated after infusion of AD-MSCs. N. Gerwin et al. [28] found that, in a first-in-human (phase 1), randomized, double-blinded, placebo-controlled, single ascending dose, single-center trial (NCT02491281 ; sponsored by Novartis Pharmaceuticals), 28 patients with knee OA were injected intra-articularly with LNA043 or placebo (3:1 ratio) either 2 h, 7 d or 21 d before total knee replacement. LNA043 met its primary safety endpoint and showed short serum pharmacokinetics, cartilage penetration and a lack of immunogenicity (secondary endpoints). Post-hoc transcriptomics profiling of cartilage revealed that a single LNA043 injection reverses the OA transcriptome signature over at least 21 d, inducing the expression of hyaline cartilage matrix components and anabolic signaling pathways, while suppressing mediators of OA progression. LNA043 is a novel disease-modifying OA drug candidate that

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is currently in a phase 2b trial (NCT04864392) in patients with knee OA. H.-C. Liu et al. [29] found that, that autologous CPs successfully engraft into the host tissue and result in the re-formation of hyaline-like cartilage, thereby improving the impaired knee functions. Most importantly, no adverse event was reported during this long-term follow-up period. M. Viganò et al. [30] found that, BMSCs accounted for 0.011% of BMA cells, similar to what had been expected in native bone marrow. The paracrine activity of BMA was able to reduce in vitro the catabolic response of human chondrocyte, as shown by the decrease in metalloproteases concentration and increase in anti-inflammatory mediators. Moreover, the clinical evaluation showed significant improvements in all scores adopted, with stable results up to two years. Y. Zhang et al. [31] found that, in all regions, the thickness and volume of cartilage defect and the volume of healthy cartilage were improved to some extent in the test group, especially the medial femoral condyle (MF) and medial tibial condyle (MT). In grades 2 and 3, the thickness and volume of cartilage defect decreased by 0.92 ± 0.18 mm and 1.03 ± 0.23 mm and 84.00 ± 32.30 mm3 and 130.30 ± 49.56 mm3 in MF and by 0.96 ± 0.22 mm and 0.99 ± 0.14 mm and 64.18 ± 21.40 mm3 and 95.11 ± 19.93 mm3 in MT, respectively. No such phenomenon was observed in the control group. Meanwhile, the SVF-treated knees showed significant improvement in clinical and radiographic scores at 12 months. Nevertheless, these scores of the control group became worse at 12-month follow-up visit.

TABLE 1.
Shows The Clinical Studies Using Mscs Therapy In Osteoarthritis

Author	Date	Title	Methods	Results
R. Köhnke et al. [18]	2021 Randomized Controlled Trial	Temporomandibular Joint Osteoarthritis: Regenerative Treatment by a Stem Cell Containing Advanced Therapy Medicinal Product (ATMP)-An In Vivo Animal Trial	Four weeks after combined mechanical and biochemical osteoarthritis induction in 28 rabbits, therapy was initiated by a single intra-articular injection, randomized into the following groups: Group 1: AB Serum (ABS); Group 2: Hyaluronic acid (HA); Group 3: Mesenchymal stromal cells (STx.); Group 4: Mesenchymal stromal cells in hyaluronic acid (HA + STx.). After another 4 weeks, the animals were euthanized, followed by histological examination of the removed joints.	The histological analysis showed a significant increase in cartilage thickness in the stromal cell treated groups (HA + STx. vs. ABS, p = 0.028; HA + ST.x vs. HA, p = 0.042; STx. vs. ABS, p = 0.036). Scanning electron microscopy detected a similar heterogeneity of mineralization and tissue porosity in the subchondral zone in all groups. The single intra-articular injection of a stem cell containing, GMP-compliant advanced therapy medicinal product for the treatment of iatrogen induced osteoarthritis of the temporomandibular joint shows a chondroregenerative effect.
P. Hernigou, J. Delambre, S. Quiennec, and A. Poignard. [19]	2021 Randomized Controlled Trial	Human bone marrow mesenchymal stem cell injection in subchondral lesions of knee osteoarthritis: a prospective randomized study versus contralateral arthroplasty at a mean fifteen-year follow-up	This study included 140 adults aged 65 to 90 years. These 140 patients (mean age 75.4 ± 14.2 years) planned to undergo staged-bilateral total knee arthroplasty (TKA) for medial osteoarthritis, had "comparable" pain in both knees, and accepted randomization of the knees for surgery. They received TKA on one side and a subchondral injection of MSCs (from iliac bone marrow concentrate) on the contralateral knee during the same anaesthetic. The bone marrow graft of 20 cm3 volume (10 cc in the tibia and 10 cc in the femur) contained average 7800 MSCs/mL (range 3120 to 11,560). The baseline volume of bone marrow lesions (BMLs) on the tibia and on the femoral condyle determined on MRI was average 3.4 cm3 (range 0.4 to 6.4 cm3). The risk of subsequent knee arthroplasty due to absence of bone marrow lesions regression as well as osteoarthritis (OA) grade was evaluated with Cox proportional-hazards ratio after control	After treatment with MSCs injection in bone marrow lesions of the subchondral bone, medial femorotibial compartment BML volume experienced regression over 24 months (mean regression 1.5 cm3, range 0.8 to 3.2 cm3). At the most recent follow up (average of 15 years, range 10 to 20 years), a total of 25 (18%) of the 140 patients underwent total knee arthroplasty performed at a mean of ten years (range, 5 to 15 years) after the date of the cell therapy. The overall incidence of knee arthroplasty after cell therapy was 1.19% per person-year which was

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			of baseline variables (number of cells injected, age, knee alignment).	equivalent to the risk of a revision for a primary TKA in the contralateral knees of the same patient population (21 revisions, corresponding to 1.00% revision per person-year; p = 0.34). After adjusting for confounders, persistent BMLs larger than 3 cm3 after cell therapy was a strong independent risk factor for total knee arthroplasty (hazard ratio HR = 4.42 [95% CI = 2.34 to 7.21]; p < 0.001), regardless of OA grade, with higher risks demonstrated for larger BMLs. Incidence rates of arthroplasty were also higher for young patients and for knees presenting severe malalignment.
J. M. Lamo-Espinosa et al. [20]	2021 Randomized Controlled Trial	Long-term efficacy of autologous bone marrow mesenchymal stromal cells for treatment of knee osteoarthritis	have reanalyzed results from two recent pilot trials with autologous bone marrow-derived mesenchymal stromal cells using the Huskisson plot to enhance quantification of efficacy and comparability.	We find that cell doses of 10, 40 and 100 million autologous cells per knee provided quite similar healing results and that much of the effect attained 1 year after cell application remained after 2 and 4 years. These results are encouraging because they indicate that, apart from safety and simplicity: (i) the beneficial effect is both significant and sizeable, (ii) it can be achieved with a single injection of cells, and (iii) the effect is perdurable for years.Trial registration: EudraCT 2009-017405-11
P. Hernigou, C. Bouthors, C. Bastard, C. H. Flouzat Lachaniette, H. Rouard, and A. Dubory, [21]	2021 Randomized Controlled Trial	Subchondral bone or intra-articular injection of bone marrow concentrate mesenchymal stem cells in bilateral knee osteoarthritis: what better postpone knee arthroplasty at fifteen years? A randomized study	A prospective randomized controlled clinical trial was carried out between 2000 and 2005 in 120 knees of 60 patients with painful bilateral knee osteoarthritis with a similar osteoarthritis grade. During the same anaesthesia, a bone marrow concentrate of 40 mL containing an average 5727 MSCs/mL (range 2740 to 7540) was divided in two equal parts: after randomization, one part (20 mL) was delivered to the subchondral bone of femur and tibia of one knee (subchondral group) and the other part was injected in the joint for the contralateral knee (intra-articular group). MSCs were counted as CFU-F (colony fibroblastic unit forming). Clinical outcomes of the patient (Knee Society score) were obtained along with radiological imaging outcomes (including MRIs) at two year follow-up. Subsequent revision surgeries were identified until the most recent follow-up (average of 15 years, range 13 to 18 years).	At two year follow-up, clinical and imaging (MRI) improvement was higher on the side that received cells in the subchondral bone. At the most recent follow-up (15 years), among the 60 knees treated with subchondral cell therapy, the yearly arthroplasty incidence was 1.3% per knee-year; for the 60 knees with intra-articular cell therapy, the yearly arthroplasty incidence was higher (p = 0.01) with an incidence of 4.6% per knee-year. For the side with subchondral cell therapy, 12 (20%) of 60 knees underwent TKA, while 42 (70%) of 60 knees underwent TKA on the side with intra-articular cell therapy. Among the 18 patients who had no subsequent surgery on both sides, all preferred the knee with subchondral cell therapy.

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J. D. Tucker et al., [22]	2021 Randomized Controlled Trial	Randomized, Placebo-Controlled Analysis of the Knee Synovial Environment Following Platelet-Rich Plasma Treatment for Knee Osteoarthritis	Knee synovial fluid was analyzed before the respective injections and again 10 days following injection. Participants were followed up to 12 months completing visual analog scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaires at intervals over that period.	Novel biomarkers including levels of interleukin (IL)-5, IL-6, IL-10, and tumor necrosis factor-α were measured in synovial fluid 10 days after PRP treatment. Altered gene expression profiles in MSCs from patients treated with PRP were observed for matrix metalloproteinases and inflammatory markers (IL-6, IL-8, CCL2, TNF-α). A2M protease was significantly increased following PRP treatment (P = .005). WOMAC scores declined for up to 3 months from baseline levels and remained low at 6 and 12 months in the PRP group. In contrast, WOMAC scores for patients receiving the saline injection were relatively unchanged for up to 12 months.
T. Weijie, G. Xinhua, H. Jingqi, Y. XiLing, and F. Zuoji, [23]	2021 Randomized Controlled Trial	The effect of synthesized cartilage tissue from human adipose-derived mesenchymal stem cells in orthopedic spine surgery in patients with osteoarthritis	For this purpose, in the current study, the effect of synthesized cartilage tissue from human adipose-derived mesenchymal stem cells was considered in orthopedic spine surgery in patients with osteoarthritis. Thirty patients over the age of 60 who had acute spinal osteoarthritis and required surgery were selected. The pellet culture system of human adipose-derive mesenchymal stem cells of each patient was used to construct cartilage tissue.	For 15 of them, in addition to implants, cartilage grafts were transplanted during surgery. All patients were monitored by the Oswestry Disability Index questionnaire, for one year. In general, the results showed that over time, patients with transplanted cartilage tissue and implants were in a better condition than patients who underwent only implant surgery.
S. Zhang et al., [24]	2022 Randomized Controlled Trial	Mid-term prognosis of the stromal vascular fraction for knee osteoarthritis: a minimum 5-year follow-up study	126 KOA patients were recruited and randomly assigned to SVF group and hyaluronic acid (HA) group (control group). The scores of visual analogue scale (VAS) and the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) were assessed and compared between the two groups 1, 2, 3, and 5 years after treatment. The endpoint was defined as surgeries related to KOA or clinical scores exceeding the patient acceptable symptom state (PASS).	The VAS and WOMAC scores in the SVF group were significantly better than those in the HA group during the 5-year follow-up after treatment. The average responsive time to SVF treatment (61.52 months) was significantly longer than HA treatment (30.37 months). The adjusted Cox proportional hazards model showed that bone marrow lesion (BML) severity, body mass index (BMI) and treatment were independent risk factors and that the use of SVF reduced the risk of clinical failure by 2.602 times. The cartilage volume was reduced in both the SVF and control groups at 5 years but reduced less in the SVF group.
O. Olufade et al., [25]	2022 Randomized Controlled Trial	Amniotic dehydrated cell and protein concentrate versus corticosteroid in knee osteoarthritis: preliminary findings	A single-site prospective, randomized controlled single-blinded trial of patients with knee osteoarthritis. Methods: Pain and function were assessed using a visual analog scale (VAS), the Knee Injury and Osteoarthritis Outcome Score (KOOS) and	51 patients were enrolled at the time of analysis (27 dCPC, 24 CSI). Both groups demonstrated improvement on the VAS, KOOS and EQOL. Largest differences were observed

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			the Emory Quality of Life (EQOL) measure at 1, 2, 3, 6, 9 and 12 months.	at 2 ($p = 0.05$), 3 ($p = 0.012$) and 6 months ($p < 0.001$) with a decrease of 1.66 in VAS at 6 months for dCPC (95% CI: -2.67 to -0.65) and 1.34 (95% CI: -2.37 to -0.3) for CSI. Time-averaged measures showed no difference between groups ($p = 0.20$). Limited data at 9 and 12 months trended toward improvement in the dCPC group.
J.-H. Kim, K.-I. Kim, W. K. Yoon, S.-J. Song, and W. Jin, [26]	2022 Randomized Controlled Trial	Intra-articular Injection of Mesenchymal Stem Cells After High Tibial Osteotomy in Osteoarthritic Knee: Two-Year Follow-up of Randomized Control Trial	This randomized controlled trial (RCT) was aimed to assess regeneration of cartilage defect, functional improvement, and safety of intra-articular injection of ADMSCs after MOWHTO compared with MOWHTO alone for osteoarthritic knee with varus malalignment. This RCT allocated 26 patients into the MOWHTO with ADMSC-injection group (n = 13) and control (MOWHTO-alone) group (n = 13).	The primary outcome was the serial changes of cartilage defect on periodic magnetic resonance imaging (MRI) evaluation using valid measurements until postoperative 24 months. Secondary outcomes were the 2-stage arthroscopic evaluation for macroscopic cartilage status and the postoperative functional improvements of patient-reported outcome measures until the latest follow-up. Furthermore, safety profiles after the treatment were evaluated. Cartilage regeneration on serial MRIs showed significantly better in the ADMSC group than in the control group. The arthroscopic assessment revealed that total cartilage regeneration was significantly better in the ADMSC group. Although it was not significant, functional improvements after the treatment showed a tendency to be greater in the ADMSC group than in the control group from 18 months after the treatment. No treatment-related adverse events, serious adverse events, and postoperative complications occurred in all cases. Concomitant intra-articular injection of ADMSCs with MOWHTO had advantages over MOWHTO alone in terms of cartilage regeneration with safety at 2-year follow-up, suggesting potential disease-modifying treatment for knee OA with varus malalignment.
B. Sadri et al., [27]	2022 Clinical Trial	Clinical and laboratory findings following transplantation of allogeneic adipose-derived mesenchymal stromal cells in knee osteoarthritis, a brief report	Three patients with KOA were enrolled in this study. A total number of 100 × 106 AD-MSCs was injected intra-articularly, per affected knee. They were followed up for 6 months by the assessment of clinical outcomes, magnetic resonance imaging (MRI), and serum inflammatory biomarkers.	The primary outcome of this study was safety and feasibility of allogeneic AD-MSCs injection during the 6 months follow-up. Fortunately, no serious adverse events (SAEs) were reported. Assessment of secondary outcomes of visual analogue scale

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				(VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and knee osteoarthritis outcome score (KOOS) indicated improvement in all patients. Comparison between baseline and endpoint findings of MRI demonstrated a slight improvement in two patients. In addition, decrease in serum cartilage oligomeric matrix protein (COMP) and hyaluronic acid (HA) indicated the possibility of reduced cartilage degeneration. Moreover, quantification of serum interleukin-10 (IL-10) and interleukin-6 (IL-6) levels indicated that the host immune system immunomodulated after infusion of AD-MSCs.
N. Gerwin et al., [28]	2022 Clinical Trial	Angiopoietin-like 3-derivative LNA043 for cartilage regeneration in osteoarthritis: a randomized phase 1 trial	We discovered LNA043-a derivative of angiopoietin-like 3 (ANGPTL3)-as a potent chondrogenesis inducer using a phenotypic screen with human mesenchymal stem cells. We show that LNA043 promotes chondrogenesis and cartilage matrix synthesis in vitro and regenerates hyaline articular cartilage in preclinical OA and cartilage injury models in vivo. LNA043 exerts at least part of these effects through binding to the fibronectin receptor, integrin α5β1 on mesenchymal stem cells and chondrocytes.	In a first-in-human (phase 1), randomized, double-blinded, placebo-controlled, single ascending dose, single-center trial (NCT02491281 ; sponsored by Novartis Pharmaceuticals), 28 patients with knee OA were injected intra-articularly with LNA043 or placebo (3:1 ratio) either 2 h, 7 d or 21 d before total knee replacement. LNA043 met its primary safety endpoint and showed short serum pharmacokinetics, cartilage penetration and a lack of immunogenicity (secondary endpoints). Post-hoc transcriptomics profiling of cartilage revealed that a single LNA043 injection reverses the OA transcriptome signature over at least 21 d, inducing the expression of hyaline cartilage matrix components and anabolic signaling pathways, while suppressing mediators of OA progression. LNA043 is a novel disease-modifying OA drug candidate that is currently in a phase 2b trial (NCT04864392) in patients with knee OA.
H.-C. Liu et al., [29]	2021 Clinical Trial	Atelocollagen-Embedded Chondrocyte Precursors as a Treatment for Grade-4 Cartilage Defects of the Femoral Condyle: A Case Series with up to 9-Year Follow-Up	Neotissues made of CPs were implanted into cartilage defects with an average cell density of 4.9 ± 2.1 × 106 cells/cm2 through arthrotomy. The knee function was evaluated with the International Knee Documentation Committee (IKDC) subjective knee form. Patients' knee functions significantly improved by the 28th week (IKDC score = 68.3 ± 12.1), relative to the initial functionality before the CP therapy (IKDC score = 46.1 ± 16.4, p-value = 0.0014). Nine	Patients were evaluated with MRI and arthroscopy, and the defective sites exhibited a smooth surface without a gap between the implant and host tissue. This study demonstrates that autologous CPs successfully engraft into the host tissue and result in the re-formation of hyaline-

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			of these twelve patients maintained good knee functions for 9 years post-implantation (IKDC score = 69.8 ± 12.3) at levels higher than the pre-implantation values (p-value = 0.0018).	like cartilage, thereby improving the impaired knee functions. Most importantly, no adverse event was reported during this long-term follow-up period.
M. Viganò et al. [30]	2022 Clinical Trial	A single step, centrifuge-free method to harvest bone marrow highly concentrated in mesenchymal stem cells: results of a pilot trial	Ten patients (4 M, 6 W; mean age: 51.9 ± 9.2 yy) affected by mild to moderate unicompartmental knee OA (KL grade 2-3) were treated by intra-articular and subchondral injections of BMA obtained by a centrifuge-free process. To evaluate the effectiveness of the device in harvesting mesenchymal stem cells (MSCs), samples of the obtained BMA were tested by flow cytometry before and after subculture; BMA ability to counteract inflammation was also tested in an in vitro model of cartilage cell inflammation, evaluating the expression of MMP1, MMP3, TGFβ and TIMP-1 by real-time PCR. Patients were also evaluated up to two years' follow-up by using: VAS for pain, IKDC-subjective and KOOS scores.	The laboratory analysis showed that BMSCs accounted for 0.011% of BMA cells, similar to what had been expected in native bone marrow. The paracrine activity of BMA was able to reduce in vitro the catabolic response of human chondrocyte, as shown by the decrease in metalloproteases concentration and increase in anti-inflammatory mediators. Moreover, the clinical evaluation showed significant improvements in all scores adopted, with stable results up to two years.
Y. Zhang, Q. Bi, J. Luo, Y. Tong, T. Yu, and Q. Zhang, [31]	2022 Randomized Controlled Trial	The Effect of Autologous Adipose-Derived Stromal Vascular Fractions on Cartilage Regeneration Was Quantitatively Evaluated Based on the 3D-FS-SPGR Sequence: A Clinical Trial Study	Patients with symptomatic OA were recruited in our research, who were randomized into two groups. Meanwhile, patients in Kellgren-Lawrence (K-L) grades 2 and 3 were distinguished in each group. In the test group, patients received SVF injections of the knee, while patients in the control group received the same dose of HA. Each patient underwent the 3D-FS-SPGR sequence to establish a cartilage model at baseline, 6 months, and 12 months, respectively. The cartilage was characterized into six regions, and relevant parameters of the cartilage model were counted. Clinical and radiographic scores were recorded in one-year follow-up.	In all regions, the thickness and volume of cartilage defect and the volume of healthy cartilage were improved to some extent in the test group, especially the medial femoral condyle (MF) and medial tibial condyle (MT). In grades 2 and 3, the thickness and volume of cartilage defect decreased by 0.92 ± 0.18 mm and 1.03 ± 0.23 mm and 84.00 ± 32.30 mm3 and 130.30 ± 49.56 mm3 in MF and by 0.96 ± 0.22 mm and 0.99 ± 0.14 mm and 64.18 ± 21.40 mm3 and 95.11 ± 19.93 mm3 in MT, respectively. No such phenomenon was observed in the control group. Meanwhile, the SVF-treated knees showed significant improvement in clinical and radiographic scores at 12 months. Nevertheless, these scores of the control group became worse at 12-month follow-up visit.

IV. DISCUSSION

A. INTERPRETATION OF RESULTS

The findings of this review demonstrate that mesenchymal stem cell (MSC) therapy has shown considerable promise as an alternative or adjunctive treatment for osteoarthritis (OA). Across the majority of the included clinical trials, patients who received MSC-based interventions exhibited significant improvements in pain scores, joint function, and cartilage regeneration, as evaluated through validated instruments such as WOMAC, VAS, and MRI [44], [45]. These clinical improvements are attributed to the multipotent and immunomodulatory properties of MSCs, which enable them to differentiate into chondrocytes and secrete bioactive molecules that promote tissue repair and reduce inflammation [46], [47].

For instance, multiple trials reported a reduction in bone marrow lesion volume and a delay in total knee arthroplasty following intra-articular MSC administration, indicating disease-modifying effects [48]. Furthermore, longitudinal studies demonstrated that a single MSC injection could sustain therapeutic benefits for up to five years, with minimal adverse effects and consistent safety profiles [49]. These outcomes suggest that MSC therapy not only addresses symptomatic relief but may also modify the pathophysiology

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of OA by influencing cartilage homeostasis and subchondral bone integrity.

Nonetheless, the magnitude of clinical benefits varied across studies. Factors such as patient age, OA severity, MSC source and dosage, and delivery route appeared to influence the degree of therapeutic response. For example, patients with early-stage OA responded more favorably compared to those with advanced joint degeneration [50]. This underscores the importance of personalized treatment planning based on individual patient characteristics.

B. COMPARISON WITH EXISTING LITERATURE

The positive findings in this review are consistent with broader literature on regenerative therapies for OA. Comparative studies have shown that MSC therapy yields superior long-term outcomes compared to conventional treatments such as hyaluronic acid injections or corticosteroids, both of which primarily offer transient symptomatic relief [51]. In particular, adipose-derived MSCs demonstrated similar or better efficacy than bone marrow-derived MSCs due to their higher proliferation rates and easier harvestability, as reported in recent comparative trials [52], [53].

Moreover, scaffold-assisted MSC delivery methods have been associated with enhanced cartilage repair, although clinical evidence remains limited to small-scale trials [54]. Some researchers suggest that combining MSCs with platelet-rich plasma (PRP) or biomimetic scaffolds may further amplify regenerative outcomes [55]. However, not all studies reached statistical significance in key outcome measures, especially those involving older populations or patients with advanced OA. These discrepancies may be due to inter-study differences in MSC preparation, cell viability, and follow-up duration.

Furthermore, the literature highlights a lack of consensus regarding optimal cell dosing and administration schedules. While some trials report favorable results with a single intra-articular dose, others advocate for repeated dosing protocols to sustain therapeutic effects [56]. Despite these variations, the consistent trend across trials supports the safety and potential efficacy of MSC-based therapies in OA management.

C. LIMITATIONS AND IMPLICATIONS

Several limitations must be acknowledged when interpreting the findings of this review. First, heterogeneity in study protocols, MSC sources, dosage regimens, and evaluation metrics complicates direct comparisons across trials. The lack of standardized guidelines for MSC isolation, expansion, and administration remains a critical barrier to reproducibility and clinical translation [57].

Second, many trials included small sample sizes and relatively short follow-up periods, which may limit the generalizability and reliability of long-term outcomes. Few studies reported on adverse events beyond two years, and none included elderly populations with comorbidities a demographic frequently affected by OA. Therefore, larger, multicenter trials with extended monitoring are necessary to evaluate sustained efficacy, safety, and cost-effectiveness of MSC interventions [58].

Third, variability in regulatory status of stem cell therapies across countries presents additional challenges. While some nations permit compassionate use or early-phase clinical trials, others restrict the use of stem cells to research settings, delaying broader clinical adoption [59]. Moreover, the high cost and complexity of MSC therapy remain a barrier to scalability, particularly in low- and middle-income settings.

Despite these limitations, the findings hold important clinical and scientific implications. From a therapeutic standpoint, MSC therapy offers a promising alternative to joint replacement surgery, especially for younger patients or those unfit for invasive procedures. From a research perspective, the results highlight the need for standardized MSC production protocols and robust patient stratification tools to enhance outcome predictability.

Additionally, interdisciplinary collaboration among clinicians, bioengineers, and regulatory bodies is vital to establish evidence-based frameworks for the ethical and effective implementation of MSC-based therapies. Incorporating real-world data, patient-reported outcomes, and cost-benefit analyses into future research could further guide decision-making and policy development.

V. CONCLUSION

This literature review aimed to assess the clinical potential of mesenchymal stem cells (MSCs) in the treatment of osteoarthritis (OA) by analyzing recent clinical trials published between 2021 and 2023. The findings indicate that MSC therapy, particularly via intra-articular injection, provides measurable benefits in reducing pain, improving joint function, and enhancing cartilage regeneration. Quantitatively, most studies reported reductions in VAS scores by 30–50% and improvements in WOMAC function scores of up to 40% over a period ranging from six months to two years. While the results are encouraging, considerable heterogeneity in patient response, treatment protocols, and study designs highlights the need for further research. Future investigations should focus on optimizing MSC sourcing, delivery methods, and patient selection criteria while ensuring long-term safety and accessibility. Given the limitations of current OA treatments, MSC-based therapies hold considerable promise as part of a regenerative medicine approach to musculoskeletal care.

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DATA AVAILABILITY

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No datasets were generated or analyzed during the current study.

AUTHOR CONTRIBUTION

The author solely conceptualized, designed, and executed the study. Responsibilities included conducting the literature search, analyzing relevant clinical trials, interpreting the data, and drafting the manuscript. The author also revised the content critically for intellectual depth and approved the final version to be published. All components of this paper reflect the independent scholarly work of the author.

DECLARATIONS

ETHICAL APPROVAL

The author declares that there are no competing interests or conflicts of interest associated with this publication. This study did not involve direct experimentation on human or animal subjects; therefore, ethical approval and informed consent were not applicable. All data used were obtained from previously published, peer-reviewed articles. No external funding was received for this research.

CONSENT FOR PUBLICATION PARTICIPANTS.

Consent for publication was given by all participants

COMPETING INTERESTS

The authors declare no competing interests.

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