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Review Article

Mesenchymal stem cell therapy for knee osteoarthritis: Clinical efficacy, mechanisms, and translational perspectives

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Abstract

Background: Knee osteoarthritis (KOA), a degenerative joint disorder, is characterized by a series of pathological changes, most notably cartilage degradation, inflammation, and alterations in bone tissue. Conventional treatment options, which involve NSAIDs, PT, corticosteroid agents, and hyaluronic acid, only provide symptomatic relief. Recently, mesenchymal stem cell-based therapy has been shown to target specific pathological aspects of knee osteoarthritis through immunomodulatory, paracrine, and chondroprotective actions, offering a potential therapeutic approach to address damaged cartilage in OA joints.

Aim and objective: To evaluate the clinical efficacy of mesenchymal stem cell (MSC) therapy in patients with knee osteoarthritis.

Materials and Methods: Electronic databases including PubMed, Scopus, and Google Scholar were utilized for a narrative review of literature between January 2019 and December 2025. A total of fifteen original studies including randomized controlled studies, prospective studies, and exploratory studies were included for this systematic review. The studies included relevant criteria for studies evaluating MSC therapy for KOA patients and reporting pain and functional data or imaging. Review articles were also included for mechanistic data.

Results: Mesenchymal stem cell (MSC) therapy was shown to have significant analgesic and functional benefits for patients suffering from knee osteoarthritis (KOA). There was significant analgesic benefit based on the Visual Analog Scale (VAS), WOMAC, and KOOS scores for all patients receiving MSC therapy, and adipose-derived MSCs (AD-MSCs) were shown to be more effective in providing short- to mid-term analgesic benefits when compared to single-dose bone marrow-derived MSCs (BM-MSCs). Functional benefits were also observed in all patients within 1-3 months of receiving MSC therapy, and these benefits were sustained for up to 48 weeks after treatment for some patients. Overall, MSC therapy was shown to be safe and well-tolerated, and adverse reactions were limited to minor local reactions at the injection site. A comparison of MSC therapy and other treatment modalities indicates that adipose-derived MSCs (AD-MSCs), umbilical cord-derived MSCs (UC-MSCs), and bone marrow-derived MSCs (BM-MSCs) combined with platelet-rich plasma (PRGF) all show significant symptomatic benefits for KOA sufferers, although cartilage regrowth has not been conclusively shown to occur through MSC therapy. MSCs were shown to exert their therapeutic effects through.

Conclusion: MSC therapy is a promising, safe biological intervention for KOA, showing consistent short- to mid-term symptomatic improvement. Dose and source of MSCs (AD-MSCs, UC-MSCs, BM-MSCs + PRGF) may improve symptomatic efficacy. Structural modification is poorly demonstrated. The mechanisms of action are more related to paracrine effects than to cartilage repair. Standardization of source, dose, and injection protocol of MSCs, together with large-scale multicentre studies, is essential to prove sustainability, potential structural modification, and long-term safety.

Keywords: Osteoarthritis of knee joint, Mesenchymal stem cells, Adipose tissue-derived MSCs, Umbilical cord MSCs, Extracellular vesicles, Pain management, Functional

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1. Introduction

Knee Osteoarthritis (KOA), or gonarthritis, is defined as a chronic, progressive degenerative disease of the knee joint that is characterized by the degeneration of intra-articular cartilage, pathological changes in subchondral bone, synovitis, and involvement of periarticular tissues. It is estimated that worldwide, there are more than 7% of the population, or 528 million people, with osteoarthritis (OA), with KOA being responsible for almost 85% of these cases.[1] KOA is characterized by its effects on middle-aged and older people, causing them pain, swelling, stiffness, and reduced

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mobility. KOA is believed to be caused by a combination of progressive cartilage degeneration, synovitis, and structural changes in subchondral bone, which includes sclerosis, bone marrow lesions, and osteophytes.[1,2]

The conservative treatment of KOA is mainly aimed at alleviating the symptoms but lacks a significant effect on the natural course of the disease. The traditional treatment options for the conservative management of KOA are NSAIDs, physiotherapy, and injections of corticosteroids and hyaluronic acid. Though the traditional treatment options can provide temporary pain relief, the natural course of the disease is not altered significantly because these treatment options are unable to influence the underlying pathophysiological processes of the disease. Therefore, the scope of regenerative medicine in the treatment of KOA through MSC therapy has been widened to overcome the limitations of the traditional treatment options.[3,4]

The regenerative strategies have the potential to move beyond the palliative measures to the healing of the damaged tissues in the joint. MSCs, which can be obtained from bone marrow, adipose tissue, and the umbilical cord, have been identified as a leading option for joint preservation strategies.[4,5] BMSCs, derived from bone marrow, have been extensively documented for their chondrogenic potential; however, the procedure is invasive, and the quality of the MSCs is compromised in older individuals.[4] ADSCs, derived from adipose tissue, have the advantage of high cell number and ease of access for autologous transplantation, while UC-MSCs, derived from the umbilical cord, have the advantage of high proliferative potential, making them more viable for allogenic transplantation.[6,4,5]

The therapeutic capability of MSCs has been ascribed mainly to their paracrine activity, which includes anti-inflammatory, immunomodulatory, and chondroprotective effects.[4,5] MSCs might be capable of inhibiting inflammatory pathways and stabilizing the microenvironment within the joint through the release of growth factors, cytokines, and extracellular vesicles such as exosomes. Such mechanisms support the possibility that MSC-based therapies could be used as disease-modifying treatments, although evidence for structural repair is currently being investigated.[6,4,5]

These trials have progressed from safety trials in phase I to efficacy trials in phase III. Results indicate that MSC injections are well tolerated. While local side effects of pain and swelling at the injection site have been noted in some patients, no severe adverse effects have been noted. In addition, a significant number of patients have noted a reduction in pain and improvement in functional scores.[7,8,9,10,11,3,12,13] While some studies have noted the maintenance of cartilage volume in patients undergoing repeated and high-dose injections of MSCs using MRI scans, this remains controversial in the current literature.[10,11,14]

Despite these encouraging trends, there are several important research gaps that need to be filled. Most clinical trials are conducted with short- or medium-term follow-up, generally up to two years. Therefore, there is a lack of information regarding long-term safety issues such as immune responses, tumorigenesis, and ectopic tissue formation.[2,12] In addition, considerable diversity exists regarding MSC source, dosage, and application methods used in various clinical trials, making it difficult to formulate standardized clinical guidelines. The present review aims to present a comprehensive overview of the status of MSC therapy for KOA, including its safety, functional efficacy, and its potential for structural modification.[1,2,12]

2. Aim and Objective

To evaluate the clinical efficacy of mesenchymal stem cell (MSC) therapy in patients with knee osteoarthritis.

3. Material and Methods

A narrative review was conducted using PubMed, Scopus, and Google Scholar, focusing on mesenchymal stem cell (MSC) therapy for knee osteoarthritis. Keywords included MSC therapy, knee osteoarthritis, adipose-derived MSCs, bone marrow MSCs, umbilical cord MSCs, extracellular vesicles, pain relief, and functional outcomes. Only studies published in English between January 2018, and December 2025 were considered. A total of 15 original studies were included, comprising randomized controlled trials, prospective clinical trials, and meta-analyses. Review articles were used solely for background and mechanistic context.

3.1. Inclusion criteria

1. Clinical or experimental studies evaluating MSC therapy in knee osteoarthritis.
2. Studies reporting pain, functional scores, or imaging outcomes.
3. Studies examining mechanistic effects, including immunomodulation, paracrine signaling, or extracellular vesicles.

3.2. Exclusion criteria

Non-English publications or studies without original clinical data and studies not involving MSC therapy or knee osteoarthritis.

4. Results

4.1. Analgesic efficacy of MSC therapy

Mesenchymal stem cell (MSC) therapy has shown statistically significant improvements in pain relief as well as functional improvement for individuals with knee osteoarthritis, as measured by Visual Analog Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), as well as Knee Injury and Osteoarthritis Outcome Score (KOOS) in a number of studies.[7,10,3] Comparison studies indicate that adipose tissue-derived MSCs as well as repeated injection methods may be more effective in terms of short- to mid-term analgesic relief compared to a one-time injection method for bone marrow-derived MSCs, although direct

comparison studies must be conducted to make a definitive conclusion. In some studies, a repeated injection method for MSCs has shown greater improvements in pain relief at 12 months compared to a control group that received hyaluronic acid injections, although caution should be exercised due to heterogeneity in study design as well as sample sizes.

In contrast, long-term results remain less consistent. While short-term improvements have consistently been noted in the first 1-2 months following injection, some studies note a reduction in analgesic effects over long-term follow-up, with some groups showing a partial regression towards baseline in pain scores after two years.[8] While meta-analyses consistently note statistically significant reductions in pain, the results do not consistently exceed minimal clinically important differences (MCID) at long-term follow-up.[2] While evidence currently supports symptomatic improvement, the degree to which analgesic effects depend on cell source, dosing regimen, disease severity, and study quality remains unclear.

4.2. Functional, mobility, and structural improvements

In all clinical studies conducted to assess the efficacy of MSC therapy in the treatment of knee osteoarthritis (KOA), significant improvement in patient-reported functional outcome measures has been consistently observed; however, the degree of improvement has been variable based on cell source, dosing regimen, and duration of follow-up.[8] In KOA patients treated with AD-MSCs, the total WOMAC score improved early and remained significantly improved for up to two years, although some attenuation was observed over time.[8] In another study, the treatment of KOA patients with ELIXCYE®, an allogeneic adipose-derived MSCs product, led to rapid and significant improvement in the total WOMAC score, pain, and stiffness, and this improvement was observed from Week 2 and sustained through Week 48; this improvement was noted to be superior to hyaluronic acid treatment within the follow-up period.[9]

Bone marrow-derived MSCs in combination with plasma rich in growth factors (PRGF) showed progressive improvement in WOMAC subscales at 12 months, whereas umbilical cord-derived MSCs (UC-MSCs) showed symptomatic relief at 3–6 months.[11,14] Taken together, these results suggest consistent symptomatic relief following MSC treatment, especially in pain and functional parameters.Objective mobility parameters also showed early improvement. Objective mobility parameters, including knee range of motion, 30-second sit-to-stand, and six-minute walk tests, improved within 1–3 months post-treatment.[8] Balance test scores on the Berg Balance Scale and functional activity scores (KSCRS, etc.) were maintained up to 48 weeks in ELIXCYE® groups.[9] However, in studies using BM-MSC + PRGF combinations, there was limited objective mobility improvement despite symptomatic relief.[11] Notably, structural imaging parameters are less conclusive. MRI and radiographic analysis showed minimal or no significant changes in cartilage thickness and joint space width following MSC treatment. Hence, although symptomatic relief is consistent, definitive structural cartilage regeneration has not been uniformly established. MSC treatment was generally safe, with adverse events being mostly mild and transient local injection site reactions.

4.3. Safety profile and adverse events

The short-term safety profile of mesenchymal stem cell (MSC) therapy for knee osteoarthritis has been found to be favourable across the available clinical studies. There has been no observed increase in serious adverse events when compared to a placebo or conventional intra-articular injections.[7] Mild to moderate local adverse events were observed to be self-limited in nature, such as pain at the site of injection, local swelling, and self-limited joint effusion. Systemic adverse events, hospitalization, immunologically mediated adverse events were not observed in the studies on the use of umbilical cord-derived MSCs. A dose-dependent trend was observed in local adverse events, with higher doses being more severe in duration and local adverse events being fewer in lower doses. A single febrile event was observed without any consequences.[14]

Findings regarding safety tended to be comparable irrespective of the source of MSCs, whether bone marrow or umbilical cord-derived products. Nonetheless, long-term safety profiles beyond 12 months of administration, the effects of cumulative dosing, and the possibility of delayed adverse reactions have not yet been adequately defined. Although the theoretical risks associated with cell-based therapies, such as tumorigenicity, heterotopic tissue formation, and immunogenicity, have not been observed in the current short-term studies, these issues should continue to be closely monitored in larger-scale trials.[7,15,14,3]

4.4. Comparative efficacy of MSC sources

Adipose-derived mesenchymal stem cells (ADSCs), including the allogenic product ELIXCYE®, have shown early and significant improvements in pain and functional outcomes for patients with knee osteoarthritis. Studies have shown a decrease in visual analog scale (VAS) pain scores as early as week 2, with WOMAC scores and Knee Scoring System for Osteoarthritis (KSCRS) index improvements within the first month of therapy.[9,8] These studies indicated a quick response to intra-articularly injected ADSCs. Nevertheless, despite these positive outcomes, objective evidence of cartilage regeneration was not shown using Magnetic Resonance Imaging (MRI).[9] The adverse events experienced by these patients were mild to moderate injection site reactions, which are self-limiting, indicating a good safety profile for these cells.[9,14]

Umbilical cord-derived MSCs (UC-MSCs) and their small EVs have shown efficacy in providing sustained symptomatic relief, particularly in clinical trials that have assessed the efficacy of multiple doses.[6,10,1] In the early clinical trials, there have been significant reductions in VAS pain scores, as well as substantial improvements in WOMAC scores, over 6- to 12-month periods, with some trials demonstrating the efficacy of MSCs over hyaluronic acid

in long-term pain relief.[10,1] Although immunomodulatory properties have been shown in animal models, as well as the formation of hyaline-like cartilage, the translation of such cartilage formation, as confirmed by MRI, in the osteoarthritic joint is still in its infancy.[6,10] On the other hand, the use of autologous BM-MSCs in combination with Plasma Rich in Growth Factors (PRGF) has shown symptomatic improvement without clear evidence of the modification of the osteoarthritic joint structure.[11] Different MSC sources show comparable symptomatic efficacy, but definitive structural modification of the osteoarthritis joint has not been established.[9,6,10,11]

4.5. Mechanistic insights and clinical implications

Randomized trials and meta-analyses have shown that mesenchymal stem cell (MSC) therapy has been associated with consistent symptomatic relief in patients with knee osteoarthritis, including reduction in total and functional WOMAC scores at 6-12 months and up to two years, as well as reduction in Visual Analog Scale (VAS) pain scores. There is also evidence to suggest that higher concentrations of MSCs and adipose-derived sources may be associated with greater functional benefits than placebo or conventional supplementation therapy.[7,12,13]

Therapeutic properties of MSCs are mainly related to the immunomodulatory effect and paracrine activities, but not the regeneration of cartilaginous tissue. For example, small vesicles from MSCs of the umbilical cord (UC-MSC-sEVs) can be involved in the polarization of M2b macrophages, as well as the protection of chondrocytes from oxidative stress-induced apoptosis. In addition, MSCs can be involved in the modulation of inflammatory cytokines, pain, and stabilization of cartilaginous tissue. However, the existence of disease-modifying properties of MSCs, including the regeneration of cartilaginous tissue, is limited and varies depending on the study.[6,4,5]

5. Conclusion

Cumulative data suggest that MSC therapy is a promising biological intervention for knee OA, which is associated with symptomatic efficacy for pain relief and functional improvement. A series of meta-analyses of randomized clinical trials demonstrated that MSC therapy is more effective than a placebo and non-surgical interventions in short- to mid-term outcomes.[7,12] Multiple doses of MSC therapy may be more effective than a single dose for symptomatic improvement.[8,10] The efficacy of MSCs is also related to their source, preparation, and culture condition, and preliminary results suggest that umbilical cord-derived MSCs (UC-MSCs) and a combination of bone marrow-derived MSCs and platelet-rich plasma (MSC-PRGF) may be more effective than hyaluronic acid for OA. Although preliminary data suggest potential structural efficacy, this is yet to be consistently demonstrated.[9,11]

MSC therapy is considered safe, with most adverse reactions being mild, local, and self-limiting, such as injection site pain and swelling.[7,12] In terms of mechanism, MSCs mainly work through paracrine action, immunomodulation, and extracellular vesicles, rather than direct cartilage regeneration.[6,4,5] Although promising, there is still a great deal of variability in MSC origin, dose, and injection technique that prevents standardization of clinical practice. Large-scale, multicenter randomized controlled trials using standardized MSC preparations and extended follow-up are required to determine the durability of clinical response, possibility of structural change, and long-term safety.[7,8,12]

6. Authors Contributions

All authors contributed equally to the conception, data collection, analysis, and writing of this study.

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None.

8. Conflict of Interest

None.

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