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# Mesenchymal Stem Cell Use in the Treatment of Osteoarthritis: A Literature Review

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# Mesenchymal Stem Cell Use in the Treatment of Osteoarthritis: A Literature Review

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## ABSTRACT

Mesenchymal stem cell (MSC) therapies have been growing in popularity in research due to their anti-inflammatory, immunomodulatory, and regenerative properties. Many ongoing clinical trials are investigating the safety and efficacy of MSC therapies to treat osteoarthritis, also known as “wear and tear” arthritis. As the average life expectancy increases, with age people are more prone to developing this disease, therefore, increasing its prevalence. This condition is progressive and will lead to functional decline, decreased quality of life, and increased medical costs. Our focus is to discuss the efficacy of mesenchymal stem cell injections in alleviating pain, improving functionality, and slowing the disease progression of osteoarthritis in adults. We systematically reviewed studies through multiple databases, including PubMed, ScienceDirect, AccessMedicine, and Iceberg using the search terms mesenchymal stem cells, osteoarthritis, stem cell therapy, and degenerative joint disease. We limited searches to 2018 and newer, studies in English, and human trials. A total of 20 studies that met the criteria out of 65 full-text studies were included in this review. Clinical outcomes such as pain, functionality, and tissue regeneration were assessed using WOMAC, KOOS, and other validated clinical outcome scales, and resonance imaging were used for disease progression rating. Studies reviewing mesenchymal stem cell injections in arthritic joints have shown positive clinical outcomes with results showing pain level, joint function and regeneration. To realize stem cell injections outside of studies, long-term and larger-scale randomized clinical trials are required to strengthen the interpretations and validity of current studies.

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# INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, affecting one in three people over the age of 65, with postmenopausal women being more at risk than men.[1] It most frequently affects the hips and the knees, causing pain, swelling, and stiffness around the joint, negatively impacting quality of life. There is significant debilitation associated with osteoarthritis as it accounts for 2.4% of all years lived with disability (YLD), and it is the third most rapidly increasing disability condition behind diabetes and dementia.[2] Other risk factors for OA include advanced age, decreased physical activity, obesity, bone density, and joint injury.

As OA progresses, some people may require medications to help manage their symptoms. First-line therapies typically consist of oral pain relievers or anti-inflammatory medications and topical steroids. Patients who do not respond to these may try injections of corticosteroids and hyaluronic acid (HA). Corticosteroid (cortisone) injections are anti-inflammatory agents most commonly administered to the affected joints. Benefits include inexpensive cost, quick (four to eight weeks) alleviation of joint pain, and increased joint mobility.[3] However, repeated cortisone injections can weaken the immune system, increase blood sugar levels in diabetic patients, cause fluid retention, and weaken surrounding tendons and cartilage. Thus, this treatment is inappropriate for long-term use, limiting injections to once every three months to prevent further complications.[4] Furthermore, hyaluronic injections are a natural substance found in joints and bones and administered in the same manner as cortisone to reduce pain and improve function. However, they are more costly, do not provide immediate relief (peak improvements at six to eight weeks), and only temporarily improve symptoms for six months.[5]

Patients resistant to first-line therapies and have significant joint damage may require surgical interventions. A possible treatment is an osteotomy, in which a piece of bone is

surgically removed to change its alignment. As the disease progresses, partial or total joint replacement surgery may become necessary. These more invasive procedures replace damaged joints with joints made of plastic, metal, or ceramic.[1] In a randomized, controlled trial, patients who received total knee replacements had greater pain relief and functional improvement after 12 months compared to those who underwent non-surgical treatment only.[6] Despite positive outcomes, the surgery patients experienced more severe side effects, such as deep vein thrombosis, heavy metal poisoning, and stiffness requiring forceful manipulation.[6] In addition, surgical implants only last 15 to 20 years, making them a nonviable option for younger patients who will have to receive follow-up surgeries. Thus, up-and-coming research on the effectiveness of mesenchymal stem cell therapy for OA is compelling as it may be without the aforementioned disadvantages and risks of current treatments.

MSCs are pluripotent adult stem cells isolated from tissues, such as bone marrow, umbilical tissue, and adipose tissue. They may now be the most versatile cell therapy products due to their chondrocyte differentiation and immunomodulatory properties, thus improving cartilage regeneration and joint restoration.[7] Though current research on MSC therapy alone is promising, there are few current studies that compare FDA-approved therapies in the United States with MSC trials in other countries. More research is required to determine the most effective overall long-term treatment for OA. With their ability for self-renewal, differentiation, and immunosuppression, MSCs have the potential to positively transform the lives of OA patients.[8] The purpose of our research is to assess the effectiveness of MSC therapy in improving pain, range of motion, quality of life, and potentially even the long-term prognosis of patients with OA.

## METHODS

A systematic review was conducted, based on the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Using the PICOS model, (patient, intervention, control, outcome, study), inclusion and exclusion criteria were created.

A comprehensive literature search was conducted through the following four databases: PubMed, ScienceDirect, AccessMedicine, and Iceberg. The following search criteria were used: "((mesenchymal stem cells) AND (osteoarthritis OR wear and tear or degenerative joint disease)) AND ((pain OR function OR regeneration OR quality of life))." The following was used as inclusion criteria: randomized control trials that studied knee osteoarthritis and the use of stem cell injections to evaluate pain, range of motion, and regeneration. We limited our search to selected articles published after 2018, with human trials, and in the English language. This paper will review 15 quantitative studies and their findings surrounding the ability of MSCs to reduce pain and increase range of motion in OA patients. In addition, we will identify if these studies have clinically significant evidence to support the theory that MSCs promote the regeneration of degenerated cartilage.

To evaluate the endpoints of pain, range of motion, and quality of life, two common scales were used throughout studies to quantify osteoporosis. These include the widely used Western Ontario and McMaster Universities Arthritis Index (WOMAC) and The Knee Injury and Osteoarthritis Outcome Score (KOOS) scales. When assessing the regenerative ability of MSCs on osteoarthritic knees with degeneration, arthroscopy with biopsy, radiographs, and magnetic resonance imaging (MRI) were used in our studies. The reliability and validity of these methods have proven to be high.[9,10]

# DISCUSSION

## Pain

OA is a progressive degenerative joint disorder that is debilitating. The pain people experience due to OA negatively affects their ability to go about their activities of daily living. In addition to physical symptoms, OA causes mental health problems as well. An observational study found OA to be associated with 1.27 times higher rates of suicidal ideation.[11] It is a disease that is associated with aging meaning as time goes on, the cartilage becomes more worn down and bones rub against each other resulting in worsening pain, inflammation, and reduced movement in the joint. The natural shape of the joint changes and bony spurs form, causing more irritation.[12] Without intervention, patients will not find relief. MSCs have the potential to regenerate articular cartilage or at least slow down its deterioration, which would assuage the physical symptoms of OA.[11] While additional research and clinical trials need to be done to fine-tune the details, several studies have already produced results supporting the efficacy of MSCs in the treatment of OA.

A systematic review by Shoukrie et al. published in 2022 found six studies that utilized WOMAC and included a total of 160 patients who were followed for up to two years. A 55% reduction in the WOMAC total score and a 59% reduction in the WOMAC pain scores were reported six months after a single injection of MSCs.[13] In a systematic review by Ma et al. published in 2020 involving 335 patients across ten randomized controlled trials, they found WOMAC pain scores were greatly reduced (SMD, − 0.46; 95% CI: − 0.75 to −0.17, $P$=.002) across the groups that received MSCs as opposed to those in the control groups who received either hyaluronic acid or a placebo.[14] Additionally, seven studies within this systematic review reported VAS (Visual Analog Scale) pain scores for 194 patients at baseline and at the final

follow-up. The VAS scores were converted and they found that compared to the control groups, the scores of the MSCs groups decreased (MD, −19.24; 95% CI: − 26.31 to − 12.18, $P<.00001$).[14] The studies included in this systematic review followed up with the subjects for up to 12 months and the results held up. A phase I/II, randomized, active-control, single-blind, multiple-center clinical trial involving 57 study subjects by Chen et al. published in 2021 found that all subjects had a significant reduction in WOMAC total score after 24 weeks. The decrease in WOMAC pain scores is indicative of the safety and efficacy of using MSCs in the treatment of knee OA. Another clinical trial by Hernigou et al was published in 2021 in which 140 patients received total knee arthroplasty in one knee and a subchondral injection of MSCs during the same anesthetic. The patients were tracked for an average of 15 years, and it was found that MSCs were sufficient in managing pain, which then allowed either the postponement or avoidance of total knee arthroplasties.[15] They also found more than half the subjects preferred to have their knees treated with MSCs over total knee arthroplasties because of the improvement in pain even though treatment with MSCs did not provide more improvement in range of motion than treatment with TKA.[15]

MSCs as a treatment for OA is a relatively new procedure and further research is needed to optimize the process. However, from the clinical trials and systematic reviews that have already been performed, the trends in the results are promising. MSCs may soon become a way to provide pain relief for OA patients.

*Table 1 Pain Outcomes Summarized*

| Study | Method | # of Participants in Study | Study Length | Findings |
|---|---|---|---|---|
| 2021 Hernigou et. al. Knee OA | Visual Analogue Scale (VAS) | 1 study, 140 subjects | 15 years | ✓ |
| 2022 Shoukrie et. al. Knee OA | Knee Injury and OA Outcome Score (KOOS)<br>Visual Analogue Scale (VAS)<br>Western Ontario and McMaster Universities OA Index (WOMAC) | 6 randomized controlled trials, 577 participants total | follow up ranged from 6 months to 24 months | ✓ |
| 2020 Ma et. al. Knee OA | Knee Injury and OA Outcome Score (KOOS)<br>Visual Analogue Scale (VAS)<br>Western Ontario and McMaster Universities OA Index (WOMAC) | 10 randomized controlled trials, 335 participants total | follow up ranged from 6 months to 12 months | ✓ |

**Joint Function/Range of Motion**

Moving on to the aspect of joint range of motion (ROM) in osteoarthritis, it is well known that OA reduces joint function and ROM due to the progressive deterioration of hyaline articular cartilage.[18] This reduction results in decreased joint movement and increased pain.[19] Various therapeutic interventions, including exercise therapy, hyaluronic acid injections, and injections of different forms of mesenchymal stem cells, have been studied.[18] Human adipose-derived mesenchymal stem cells (MSCs) offer immunomodulatory functions that can help restore the joint surface to its original shape, reduce inflammation, and prevent cartilage breakdown. The subsequent studies examined the clinical efficacy of MSC injections for knee osteoarthritis treatment, utilizing measures such as Visual Analog Scale (VAS) and WOMAC

scores to clinically assess pain and function at baseline, 3, 6, and 12 months post-treatment, where VAS scores range from 0 (no pain) to 10 (maximal pain).[18]

One study without a control group assessed the improvement in ROM (among many other parameters) in 11 patients with moderate to severe knee OA after a single injection of adipose-derived MSCs. The patients were then followed up for 18 months with assessments at 3, 6, 12, and 18 months. At the 3-month follow-up, the mean knee ROM improved by 17.3° with a p-value <.01. Another statistically significant improvement was seen at 6 months - a knee ROM increase of 7.8° relative to 3 months with a p-value <.05. ROM values then dipped 16.4° at the 12-month assessment and then slightly increased 2.3° at the final 18-month follow-up. Compared to baseline values, ROM increased by a non-significant measurement of 11°. The treatments were well tolerated with no adverse effects.[19]

In 2019, Lee et al conducted a double-blinded, randomized controlled study, comparing 12 subjects with Kellgren-Lawrence grade 2 to 4 (moderate to severe) OA in the test group were given a single injection of autologous adipose tissue-derived MSC and followed up after 1, 3, and 6 months.[16] These subjects were closely monitored at 1, 3, and 6 months post-injection. To minimize potential confounding factors, all participants refrained from using any other OA-related or pain medications for two weeks prior to the injection.[16] The control group received injections of normal saline. Before the injection, a comprehensive physical examination was conducted on all participants to establish baseline values for various parameters, including ROM. At the 6-month follow-up, the subjects in the saline control group displayed no significant change in knee ROM. In contrast, the MSC test group exhibited a substantial and statistically significant mean increase in knee ROM, amounting to 6.7° (p=0.0299), and a remarkable 55% reduction in their WOMAC score, with substantial reductions in WOMAC pain, stiffness, and

physical function scores by 59%, 54%, and 54%, respectively.[16] Treatment-related adverse effects were reported in 83% of the MSC group and 58% of the control group. However, all adverse effects were categorized as non-severe, falling below NCI-CTCAE scale 4-5, and they were effectively resolved with intermittent acetaminophen use within 3 days of injection.[16]

In the same year, Lu et al conducted a double-blinded clinical trial involving 53 patients randomized to receive either Re-Join® or hyaluronic acid (HA) injections.[17] Re-Join® is a product combining in vitro expanded human adipose-derived mesenchymal progenitor cells (haMPCs) and a cell suspension solution.[17] WOMAC and VAS assessments at 6 and 12 months compared to baseline showed over 50% improvement in WOMAC scores in the Re-Join group, with a trend indicating an additional 70% improvement at 12 months.[17] Two additional double-blind randomized controlled trials (RCTs) similarly compared knee OA patients with Kellgren-Lawrence grade 2 to 4 who received injections of normal saline or MSC. In the first study by Emadedin et al, the MSC group had 19 participants, and the placebo group had 24. The results from a 6-month assessment showed a knee flexion increase of 1.8° between the test and control groups ($p=0.77$).[20] Lastly, a double-blind RCT conducted by Khalifeh SS et al, with a total of 20 subjects, showed an increase in knee ROM for the test group. The mean baseline ROM value of 81° increased to 86.7°, 117.3°, and 113.1° at the 2, 4, and 24-week follow-ups, respectively. This data represented a significant improvement between all time intervals, except between the pre-intervention and the 2-week assessment. In contrast, the control group did not exhibit any significant changes in ROM.[21]

In 2020, Lamo-Espinoza et al conducted a phase II multicenter, randomized clinical trial on 60 patients, with each group receiving either three weekly doses of platelet-rich plasma (PRGF) injections or intra-articular injections of bone marrow mesenchymal stem cells (BM-

MSCs) plus PRGF.[18] Both groups were followed for 12 months. The control group with PRGF injections displayed a VAS score of 5 to 4.5 ($p=0.389$) at 12 months, while the group receiving both BM-MSCs and PRGF injections improved significantly, going from 5.3 to 3.5 ($p=0.01$).[18] Their WOMAC scores also improved, demonstrating a 24.4% improvement for the PRGF group and a 28.6% improvement for the BM-MSCs and PRGF group.[18]

All of the evaluated studies showed a clear benefit in restoring joint function and ROM measurements for OA patients treated with MSCs up to the 6-month mark. However, beyond this timeframe, only one study continued to follow the participants, and the benefits did not persist. This suggests that additional injections may be necessary to maintain the ROM benefits of MSCs.

*Table 2 Range of Motion Outcomes Summarized*

| Study | Method | # of Participants in Study | Study Length | Findings |
|---|---|---|---|---|
| 2018 Spasovski et al. Knee OA. | Intra-articular injection of autologous adipose-derived MSC in patients with IKDC Grade B and D knee OA | 11 participants | 18 months w/ follow-ups at 3, 6, 12, and 18 months | ✓ at 3 & 6 months |
| 2018 Emadedin M et al. Knee OA. | Intra-articular implantation of autologous bone marrow–derived mesenchymal stromal cells in KL grade 2-4 knee OA. | 43 participants | 6 months | ✓ |
| 2019 Khalifeh S et al. Knee OA | Intra-articular injection allogenic placenta-derived MSC in KL grades 2-4 knee OA. | 20 participants | 6 months w/ follow-ups at 2, 4 and 24 weeks | ✓ |
| 2019 Lee WS et al. Knee OA | Intra-articular injected autologous adipose-derived MSC in participants with K and L grades 2-4 knee OA | 24 participants | 6 months | ✓ |
| 2019 Lu et al. Knee OA<br><br>phase IIb randomize, double blind study | intra-articular injection of bone marrow mesenchymal stem cell (Re Join) | 53 participants with Kellgren-Lawrence grade 1-3 knee OA | 12 months with follow up at 6 months and 12 months | ✓ |
| 2020 Lamo-Espinoza et al. Knee OA<br><br>phase II randomized controlled trial | 3 weekly doses of intra-articular administration of 100 x $10^6$ cultured autologous bone marrow mesenchymal stem cells injection | 60 participants total with knee OA | 3 weekly doses 12 months follow up | ✓ |

**Regeneration**

MSCs are unique as they have the ability to differentiate into various mesenchymal cell lineages including our focus for this paper, chondrocytes, making them optimal for tissue regeneration purposes.[22] The chondrocyte's primary role is maintaining cartilage tissue within joints to protect and cushion bones by balancing catabolic and anabolic activity. They reside in and produce an extracellular matrix containing type II collagen and proteoglycans that provide elasticity and durability. In OA of the knee, there is degeneration of the articular cartilage and synovial joint space narrowing either from the breakdown of cartilage through proteolysis (increased catabolic activity) or from the prevention of forming new cartilage (decreased anabolic activity).[23] With damage to the articular cartilage from increasing age, inflammation, joint injury, mechanical stress, and more, chondrocytes try to repair it by making type I collagen, which is incompatible with proteoglycans in the extracellular matrix, instead of type II collagen, which is compatible. This leads to decreased elasticity and breakdown of the cartilage matrix.[24] Over time the chondrocytes are unable to keep up with the demand and undergo apoptosis. Ultimately, this results in friction between the bones and can lead to joint stiffness, loss of mobility, swelling, and pain.

The first step in the cartilage regenerative process is through chondrocyte activation.[25] Since MSCs can self-renew and secrete growth factors that stimulate tissue regeneration,[26, 27, 28] recent studies of participants with OA of the knee have shown promising results that MSC injections can promote positive cartilage regeneration depending on where the MSC was derived from.[17, 29, 30] Participants were eligible to enroll in these studies based on their K&L score which determines the severity of their osteoarthritis.[16, 17, 20, 29, 30, 31] In order to evaluate the cartilage in

the affected knee, MRI [16, 17, 19, 29, 30, 31] and arthroscopy with histological biopsy [29, 30] were performed.

The use of MRI to assess cartilage composition in participants with knee osteoarthritis is reliable and can distinguish between participants with and without OA, especially with the technique of T1rho relaxometry.[32] A study performed delayed gadolinium-enhanced MRI of articular cartilage (dGEMRIC) 3 years post-transplantation of a medicinal product (Cartistem), composed of allogeneic human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) and HA hydrogel, on participants with K&L grade 3 OA.[29] Results revealed continued regeneration of cartilage with a high glycosaminoglycan (GAG) content and the average ratio of [Gd-DTPA$^{2-}$] in regenerated cartilage to native cartilage was 1.44.[29] The quality of repaired cartilage was comparable to healthy natural cartilage as it contains copious amounts of GAG content and the perfect regeneration is 1.0.[29] Additionally, two studies examined the intra-articular injection of Re-Join®. The first study had participants with K&L grades 1 to 3 OA and completed an MRI analysis 12 months post-Re-Join® therapy, which displayed a statistically significant increase in the volume of articular cartilage (left knee p-value = 0.0042 and right knee p-value = 0.0307), and a trending decrease was observed in the control group that only received HA.[17] The second study's comparison of cartilage defects in MRIs pre-treatment and 6 months post-treatment in participants with K&L grade 3 OA that received microfracture and Re-Join® with HA treatment had a statistically significant ($p < 0.05$) outcome with a sizeable decrease in cartilage defects.[30] Another article investigated the treatment of intra-articular injection adipose-derived mesenchymal stem cells (AD-MSCs) in participants with International Knee Documentation Grade B and D OA with post-treatment MRIs that showed statistically significant improvement ($t = 0.970$, p-value = 0.001) in cartilage structure with visibly more

consistent cartilage throughout and less subchondral cysts and edema.[19] Two other studies reported no significant improvement in cartilage defects. The first study intra-articularly injected autologous adipose-derived mesenchymal stem cells (AD-MSCs) in participants with K&L grades 2 to 4 OA.[16] The second study intra-articularly injected human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) with HA in participants with K&L grades 1 to 4 OA.[31] However, in the control group of the first study[16] the cartilage defect was substantially increased with a statistically significant p-value of 0.0049. Ultimately, the majority of studies that used MRI to evaluate the regeneration of articular cartilage in participants with knee OA showed structural improvements and decreased defects.

Arthroscopy with histological biopsies were used in two studies to examine cartilage repair of participants' knees with OA. In the first study, arthroscopy along with staining of biopsy specimens occurred 1 year post-transplantation of Cartistem. The arthroscopy displayed notably improved defect sites with smoother, denser, firmer, and brighter white hyaline-like cartilage compared to the initial evaluation.[29] The histological analysis of the biopsied specimens with Masson's trichrome, Safranin O, and the immunohistochemical stains showed similar staining patterns to native articular hyaline cartilage.[29] In the second study, 6 months post-treatment of a microfracture and Re-Join® with HA second-look arthroscopy exhibited uniform, smooth, and firm white hyaline-like cartilage without abnormalities.[30] Furthermore, histological staining of cartilage biopsies with hematoxylin-eosin (H&E), safranin O/fast green (SOFG), Masson's trichrome, and immunohistochemistry for type I and II collagen overall had improved appearance than at baseline; however, it was a combination of fibrocartilage and hyaline-like cartilage and not the quality of native hyaline.[30] This study was limited in its biopsy results due to a small sample size and lack of consent from participants. Collectively, there were consistent

results from imaging, arthroscopy, and histological biopsy that promote the use of MSCs to decrease cartilage defects and stimulate cartilage regeneration in knee OA.

*Table 3 Regeneration Outcomes Summarized*

| Study | Method | # of Participants in Study | Study Length | Findings |
|---|---|---|---|---|
| 2017 Park et.al Knee OA | Post-transplantation of Cartistem on participants with K&L grade 3 OA | Total: 7 participants (4 participants received low-dose MSCs; 3 participants received high-dose MSCs) | Total: 7 yrs<br>MRI assessed 12 wks and 3 yrs post-transplantation. Second-look arthroscopy and biopsy at 1 year | MRI ✓<br>Arthroscopy ✓<br>Histological Biopsy ✓ |
| 2022 Qiao et. al. Knee OA | Arthroscopic microfracture in combo with intra-articular injection of Re-Join® with HA treatment in participants with K&L grade 3 OA | Total: 60 participants (20 only with Re-Join®; 10 for second-look arthroscopy, biopsy, and MRI) | Total: 24 mo<br>Second-look arthroscopy, biopsy, & MRI 6 months post-treatment | MRI ✓<br>Arthroscopy ✓<br>Histological Biopsy ✓ |
| 2019 Lu et. al. Knee OA | Intra-articular injection of Re-Join® in participants with K&L grades 1-3 OA | 53 participants (26 received Re-Join®) | Total: 12 mo<br>MRI evaluated at screening and week 48 | MRI ✓ |
| 2018 Spasovski et. al. Knee OA | Intra-articular injection AD-MSCs in participants with International Knee Documentation Grade B and D OA | 9 participants treated with AD-MSCs (2 patients had both knees treated = 11 knees total treated) | Total: 18 mo<br>MRI performed pre-treatment and after 6 and 18 mo post-treatment | MRI ✓ |
| 2019 Lee et. al. Knee OA | Intra-articular injected AD-MSCs in participants with K&L grades 2-4 OA | 24 participants (12 treated with AD-MSCs and 12 control with normal saline) | Total: 6 mo<br>Follow up 1, Total: 6 mo. MRI obtained pre-injection and 3 and 6 mo post-injection | MRI ✗ |
| 2020 Dilogo et. al. Knee OA | Intra-articular injected hUC-MSCs with HA in participants with K&L grades 1-4 OA | 29 participants (57 knees; 33 knees K&L grade 1-2 and 24 kness K&L grade 3-4 | Total: 12 mo<br>MRI obtained at 6 mo and 12 mo | MRI ✗ |

## CONCLUSION

To conclude, osteoarthritis is a debilitating condition, characterized by pain, reduced joint function, and cartilage degeneration, that requires a need for more effective and less invasive treatment options. Our research paper has explored the benefits of mesenchymal stem cell therapy in managing and potentially improving the challenges patients with osteoarthritis face on a day-to-day basis.

Our analysis of the different studies performed with MSC therapy highlights its potential to improve joint function, promote cartilage regeneration, and most importantly alleviate pain in OA patients. The majority of the studies we interpreted showed a significant reduction in short-term and long-term pain scores measured by WOMAC and VAS scales. Joint function showed improvements with the ability of patients to increase their range of motion in the affected knee. Lastly, structural improvements in cartilage defects were confirmed through imaging studies like MRIs, arthroscopy, and histological biopsies suggesting the development of new hyaline-like cartilage in participants receiving the injections. However, several studies also showed no regeneration differences after injections suggesting more studies are needed to confirm benefit.

Despite these promising results, there continue to be limitations and research gaps. The need for further comprehensive and long-term studies are necessary to validate the safety and longevity of MSC therapy. Comparative research with treatments currently in use and the potential side effects of the therapy are crucial for informed decision-making. In light of our positive findings, we also encountered limitations in many of the studies. Standardized treatment protocols including type and quantity of stem cells per injection, number of injections over time, patient selection criteria, and continued monitoring and follow-up visits should be established to ensure consistency and higher-quality treatments. We would also propose a strategy to increase

awareness and education among healthcare professionals and patients regarding the potential therapeutic benefits of MSC, in the hopes of it leading to early intervention and prevention of OA.

In summary, our research regarding MSC therapy suggests it is a promising and valuable addition to the treatment options already approved for OA. With continued investigations and a standardized approach, MSC therapy can offer a more effective and less invasive solution to OA patients, helping improve their quality of life, reducing pain, and improving their joint functionality.

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