REVIEW

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Mesenchymal Stem Cell Injections for the Treatment of Osteoarthritis: A Systematic Review of Clinical Trials

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Objectives: **Osteoarthritis is a prevalent degenerative disease that affects many people worldwide. The use of mesenchymal stem cells (MSCs) in the setting of osteoarthritis has been explored by many clinical trials in the literature. Exploring these clinical trials is important for assessing the benefit of this modality in the setting of osteoarthritis.**
Methods: **On November 9, 2022, a search was conducted on PubMed/MEDLINE databases to explore clinical trials involving MSC injections for osteoarthritis. Only articles that were clinical trials, explored the use of MSC injections in osteoarthritis, involved human subjects, and written in English language, were included. Relevant data was extracted from the included trials.**
Results: **A total of 43 trials were included (N=43). The knee was most the commonly explored joint (95.4%), and adipose tissue was the most commonly utilized MSC source (49%). All but one trial (97.7%) reported clinical improvement in the MSC group on follow up, and 33 trials (76.7%) reported better clinical outcomes in the MSC groups when compared to control groups. Twenty-three trials (53.5%) used imaging to evaluate outcomes following MSC injections, out of which twenty (46.5%) reported improvements in the affected joint. Similarly, four trials (9.3%) used second look arthroscopy, out of which three (7%) reported better outcomes on follow up.**
Conclusion: **While published trials show good therapeutic potential for MSC injections in the setting of osteoarthritis, several discrepancies render the efficiency and reliability of this modality equivocal. The adoption of standardized protocols, employment of comprehensive evaluation tools, and reporting negative results is essential in order to appropriately assess the utility of MSC injections for the treatment of osteoarthritis.**

Keywords: Stem cells, regenerative medicine, arthritis, knee, injection, cartilage.

INTRODUCTION

Osteoarthritis is a prevalent degenerative disease that constitutes a major health issue worldwide. This disease causes the degradation of subchondral bone and articular cartilage, leading to pain, loss of joint mobility, and reduction in quality of life[1,2]. Global statistics estimate that around 18% of women and 9.6% of men suffer from osteoarthritis worldwide, with varying outcomes with respect to location, severity and prognosis[3]. The rise of both modifiable risk factors, like physical activity and sports, and nonmodifiable risk factors, like age and female gender, has contributed to the high incidence of osteoarthritis in our present time[4].

Osteoarthritis can affect any joint in the body, and can often present with mechanical pain, swelling, and reduced range of motion[5-7]. Additionally, it is often worsened by activity and relieved by rest. Etiology can be primary; idiopathic or non-traumatic, or secondary to trauma or injury[8,9]. It has been previously believed that osteoarthritis is purely degenerative in nature, and mainly affects cartilage. However, recent evidence suggested that the disease is multifactorial in its essence, involving many factors that include trauma, mechanical forces, biochemical reactions, inflammation, and metabolic derangements[10,11]. In addition, osteoarthritis has been shown to affect much more than the cartilaginous tissue in the joint, encompassing the subchondral bone, ligaments, synovium, peri-articular muscles, and joint capsule[12].

Multiple treatment protocols have been proposed for osteoarthritis. Classically, treatment options have been mainly clinically driven, aimed at mitigating the presenting symptoms and offering temporary relief[13].

This includes conservative management revolving around rest, ice, non-steroidal anti-inflammatory drugs, and corticosteroid injections[13]. When conservative management fails, operative therapeutic options may be necessary, and these often involve invasive procedures targeted at debriding the diseased joint surface or replacing the affected joint components. These options proved to be plagued with limitations, often due to their temporary effect, restricted efficacy, invasive nature or questionable outcomes. This, in turn, highlighted the need for novel therapeutic approaches, that are minimally invasive, and aim to restore joint integrity and homeostasis via stimulating and supporting the regeneration of articular tissue. As a result, the field of regenerative medicine rose in the domain of osteoarthritis and started garnering scientific attention.

Cell-based therapy has been the center of discussion for novel osteoarthritis treatments in the recent years. Mesenchymal stem cells (MSCs), in specific, have been regarded as an essential part of cell-based therapies in OA, and have garnered prominent attention in the last decade[14]. These cells are multipotent progenitors capable of transforming into other cell types, provided the right extracellular environmental requirements[14,15]. They possess immunomodulatory properties, have low alloreactivity, and are distributed in different sites throughout the body[16,17]. While numerous theoretic benefits of MSC-based treatments have been demonstrated in the literature, skepticism regarding its efficacy in the clinical setting has been conveyed and expressed. Accordingly, it is of essential importance to conduct continuous investigations into the recent literature, in order to appropriately assess the evidence supporting or opposing the use of a treatment in a certain clinical setting. As such the aim of our study is to explore the effects and outcomes of MSC-based injections in osteoarthritis, based on a holistic and systematic review of current and relevant literature.

METHODS

Search Strategy and Selection Criteria

On the 9th of November 2022, a literature search using the databases PubMed//MEDLINE was conducted in order to query studies reporting on the use of MSC injections for the treatment of osteoarthritis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to in this investigation. The following search strategy was used: (“mesenchymal stem cells” (MeSH Terms) OR (“mesenchymal” (All Fields) AND “stem” (All Fields) AND “cells” (All Fields)) OR “mesenchymal stem cells” (All Fields)) AND (“osteoarthritis” (MeSH Terms) OR “osteoarthritis” (All Fields) OR “osteoarthritides” (All Fields)). Reference lists of retrieved articles were screened for the addition of relevant articles. Only clinical trials pertaining to the use of MSC injections for osteoarthritis were included. Articles were excluded if they did not pertain to MSC-based injection therapies, did not pertain to osteoarthritis, were not written in the English language, or were not conducted on humans (Figure 1).

Data Collection

The included articles were reviewed and appraised by the authors, who summarized findings and included what was deemed suitable and relevant to provide readers with a contemporary idea of the modalities and outcomes of MSC-based injections in the setting of osteoarthritis. The final data set from the included trials included number of participants, source of MSCs, interventional model, and clinical and radiographic outcomes of the employed treatment. Additional data on trial designs and characteristics were also extracted in order to comment on the quality of the available trials. Level of evidence was determined according to the Oxford Centre for Evidence-Based Medicine[18].

RESULTS

A total of 43 clinical trials were included in our study (Figure 1), and were summarized in (Table I) 19-61. These trials involved 1584 patients, out of whom 530 were males (33.5%), 840 were females (53%), and 214 were unspecified (13.5%) (Table II). The joint most commonly explored was the knee, with 1556 subsequent patients (98.2%) in 39 trials receiving MSC injections (Table II). One trial with 25 patients (1.6%) involved MSC injections in the shoulder and one trial (2.3%) with three patients (0.2%) involved MSC injections in the wrist (Table II).

Different sources of MSCs were explored in the clinical trials included in our study (Table II). Adipose tissue was the most common source for MSC generation, with 21 trials (49%) and 838 patients (53%), followed by bone marrow with 18 trials (42%) and 620 patients (39%) (Table II). Four trials (9%) involving 125 patients (8%) used MSCs from placental sources, like the umbilical cord or amniotic-derived tissue (Table II).

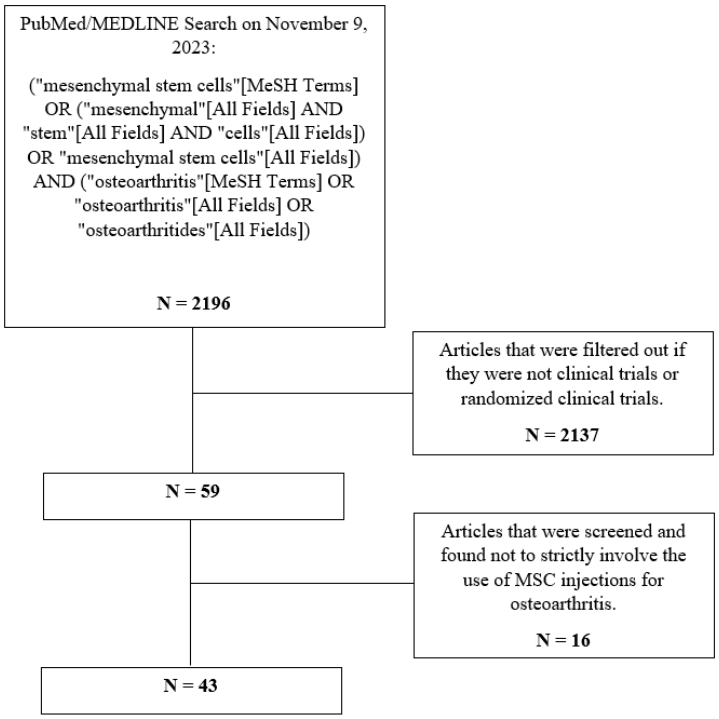

Fig. 1 — Article selection process.

Clinical scores were assessed using different patient reported outcome tools, with WOMAC and VAS being the most commonly used clinical scoring tools. Follow-up period ranged between six months and 15 years, with an average of 39.6 months. Forty-two included trials (97.7%) reported significant improvement in the clinical scores of their cohorts following MSC injections, and only one trial (2.3%) reported no significant change in clinical scores before and after intervention (Table III). In 33 trials (76.7%), MSC injections were reported to have better clinical outcomes when compared to the control treatment (Table III). One trial (2.3%) showed no significant difference in clinical outcomes between MSC group and control group, and nine trials (21%) did not report employing a control group, or did not compare outcomes between MSC injections and non-MSC-based controls (Table III).

Twenty-three trials (53.5%) used imaging to evaluate the outcomes of MSC injections in the setting of osteoarthritis (Table III). Twenty trials (46.5%) reported improvement, noted as cartilage regeneration, decrease in chondral defects or improvement in relevant imaging scores like MOCART (Table III). One trial (2.3%) showed no changes or improvement in cartilage integrity, and no change in damage or cartilage volume, and two trials (4.6) noted progression of cartilage damage and degeneration in the MSC group (Table III). Ten trials (23.2%) did not report using imaging to assess cartilage integrity following MSC injections (Table III).

Finally, four trials (9.3%) used second look arthroscopy to evaluate the integrity of the joint following intervention with MSC injections in their respective patient cohorts (Table III). Three of these trials (7%) reported improvement in joint cartilage, described as decreases in cartilage defects, regeneration of hyaline-like cartilage, and increases in Kanamiya grades (Table III). One trial (2.3%) showed no significant difference between the control group and the MSC group on second look arthroscopy (Table III). Remaining trials did not report arthroscopic findings.

When assessing the quality and designs of the trials, it was found that 31 trials (72%) employed parallel assignment model for intervention, 11 trials (26%) employed single group assignment, and one trial (2%) employed a crossover assignment model (Table IV). In addition, the majority of the trials (30 trials, 70%) were randomized whereas 13 (30%) were not. Twenty-two trials (51%) reported blinding, whereas 21 (49%) did not report any blinding in their study design (Table IV). Finally, 28 trials (65%) were considered to be level II evidence, six trials (14%) were considered to be level III evidence, and nine trials (21%) were considered to be level IV evidence (Table IV).

DISCUSSION

Clinical trials exploring the use of MSC injections in OA have generally reported good outcomes in the

Table I. — Summary of all included clinical trials exploring the use of mesenchymal stem cells (MSCs) in osteoarthritis (OA).

Author	Year	Description	Results
Centeno et al.[19]	2008	1 knee OA patient received a percutaneous injection of autologous MSCs derived from bone marrow aspiration of the iliac crest into the knee.	VAS and range of motion improved significantly 24 weeks after the injection. In addition, MRI imaging showed statistically significant cartilage and meniscus growth 24 weeks post-injection.
Davatchi et al.[20]	2011	A total of 4 knee OA patients (Mean age = 57.75) received an injection 8-9 x 10(6) MSC derived from the patient's bone marrow into the worse knee of each patient.	VAS scores improved significantly at the 6-month follow-up in all 4 patients. In addition, patellar crepitus disappeared in 1 patient and improved for the other three patients.
Koh et al.[21]	2012	A total of 18 OA patients (Mean age= 54.6 years) received intra-articular injections of mesenchymal stem cells harvested from the infrapatellar fat pad into their affected knees.	WOMAC, Lysholm scores, and VAS scores improved significantly at final follow-up (24-26 months). In addition, the cartilage whole-organ MRI score noted significant improvement.
Wong et al.[22]	2013	A total of 56 patients with unicompartmental knee OA were randomly assigned to one of 2 groups (n=28 for cell-recipient group and n=28 for control group). The cell-recipient group received an intra-articular injection of MSC with hyaluronic acid 3 weeks after surgery in conjunction with a high tibial osteotomy (HTO) and microfracture. The control group received an HTO and microfracture with no injections.	1 year after the treatment, MOCART scores significantly better in the cell-recipient group. Integration of the regenerated cartilage was significantly better in 61% of the patients in the MSC group, while 86% of the control group showed incomplete integration with visible defects on MRI.
Orozco et al.[23]	2013	A total of 12 knee OA patients (6 male, 6 female, 6 right, 6 left) unresponsive to conservative treatments received an intra-articular injection of autologous expanded bone marrow MSCs.	VAS scores improved significantly at the 1-year follow-up. In addition, the Lequesne algofunctional index and the WOMAC index displayed a statistically significant positive correlation between improvement after 1 year and the initial pain score.
Jo et al.[24]	2014	A total of 18 OA patients were enrolled into a clinical trial to receive three doses of intra-articular adipose-derived MSC injection in the knee (low-, mid-, and high dose).	WOMAC scores improved prominently in the high-dose group. Arthroscopy showed that the size of cartilage defect decreased and volume of cartilage increased in the high dose group.
Vega et al.[25]	2015	A total of 30 OA patients were randomized into two treatment groups, each receiving an intra-articular injection of: hyaluronic acid (control) and allogeneic bone marrow (BM) MSCs into their affected knees.	Algofunctional indices showed significant improvement among the MSC-treated patients when compared to control group. A significant decrease in poor-cartilage areas and improvement of cartilage quality were observed in MSC-treated patients upon quantification of cartilage quality using T2 relaxation measurements.
Davatchi et al.[26]	2015	A total of 4 knee OA patients (Mean age = 57.75) received an injection of 8-9 x 10(6) MSC derived from the patient's bone marrow into the worse knee of each patient.	VAS scores improved until the 2-year follow-up, but then started to decline. However, VAS scores were significantly higher at the final follow-up (5-years) compared to baseline. At 5-year follow-up, the non-implanted knee was the worst knee.
Soler et al.[27]	2016	A total of 15 OA patients received intra-articular injections of autologous MSCs into their affected knees	A decrease in pain as well as an improvement in the SF-36 Quality of life test was observed. T2 mapping showed cartilage regeneration at the latest follow-up (12 months).
Gupta et al.[28]	2016	A total of 60 OA patients were enrolled into a clinical trial to receive intra-articular injection of allogeneic MSCs in the knee (different doses and placebo).	There was no difference in the WORMS, VAS, ICOAP and WOMAC-OA scores. Adverse events were predominant in the higher dose group consisting of knee pain and swelling.

Lamo-Espinosa et al.[29]	2016	A total of 30 OA patients were randomized into three treatment groups, each receiving an intra-articular injection of: hyaluronic acid (control), low-dose BM-MSCs, and high dose BM-MSCs into their affected knees.	VAS showed significant improvement in both test groups when compared to control. WOMAC scores showed significant dose-dependent improvement in low dose group (significance not sustained beyond 6 months) and in high-dose group (significant at 12 months). Improvement in range of motion was noted in test group but not in control group. Whole-organ MRI showed slightly decreased joint damage in the high-dose group.
Koh et al.[30]	2016	A total of 80 OA patients were enrolled into a clinical trial to receive arthroscopic microfracture (With and without adipose derived MSCs injection).	The mean KOOS symptoms and pain subgroup was better in the group with MSC injection as well as better signal intensity on the MRI. Second look arthroscopies showed no difference between both groups.
Pers et al.[31]	2016	A total of 18 OA patients were enrolled into a clinical trial to receive intra-articular injection of adipose MSCs in the knee (different doses).	The WOMAC improved from baseline in all the groups however it was statistically significant only in the low dose group.
Al Najar et al.[32]	2017	A total of 13 OA patients received intra-articular injections of MSCs harvested from the bone marrow into their affected knees.	No adverse events were noted. KOOS scores improved significantly at final follow-up (24 months). In addition, the thickness of the cartilage measured by the MRI noted significant improvement.
Bastos et al.[33]	2018	A total of 18 OA patients were enrolled into a clinical trial to receive intra-articular injection of MSCs in the knee (with and without PRP).	KOOS scores improved significantly in both groups without any statistical difference. The average number of fibroblast colony forming units was higher in the group without PRP.
Lamo-Espinosa et al.[34]	2018	A total of 30 OA patients were enrolled into a clinical trial to receive intra-articular injection of autologous bone marrow MSCs in the knee (different doses and hyaluronic acid).	MSC receiving patient had better WOMAC and VAS. No difference between the different doses of MSC was observed.
Song et al.[35]	2018	A total of 18 OA patients were enrolled into a clinical trial to receive intra-articular injection of adipose MSCs in the knee (different doses).	Pain, function and cartilage volume were improved in all three groups. However, the high dosage group had the highest improvement.
Peretti et al.[36]	2018	A total of 39 patients with grade 3-4 knee OA were enrolled into a clinical trial and randomized into two groups: arthroscopic debridement, and arthroscopic debridement + subsequent intra-articular injection of autologous micro-fragmented adipose tissue.	Preliminary results: Functional improvement and pain reduction at 6 months after treatment with subsequent intra-articular injection.
Emadedin et al.[37]	2018	A total of 43 patients with grade 2-4 OA were enrolled into a clinical trial and randomized into two groups for intra-articular injections in the knee: autologous bone marrow-derived MSCs, and normal saline.	WOMAC total score, WOMAC pain and physical function subscales, and painless walking distance improved significantly in patients who received MSC treatment after 6 months follow up.
Hong et al.[38]	2018	A total of 16 patients with bilateral OA were enrolled into a clinical trial to receive intra-articular injection of adipose-derived stromal vascular fraction (SVF) in one knee and Hyaluronic acid injection in the other.	The SVF treated knees had better improvement of VAS, WOMAC, ROM, as well as WORMS and MOCART measurements.

Table I. — Summary of all included clinical trials exploring the use of mesenchymal stem cells (MSCs) in osteoarthritis (OA)

Kim YS et al.[39]	2019	A total of 80 OA patients treated with concomitant HTO were randomized into two groups for implantations in the knee: MSC and MSC with allogenic cartilage (MSC-AC).	Lysholm and KOOS scores improved significantly in both groups at second-look arthroscopy (12.4-12.5 months); further improvement at final follow-up (27.3-27.8 months) was seen only in the MSC-AC group. Overall, Kanamiya grades were significantly higher in the MSC-AC group.
Freitag et al.[40]	2019	A total of 30 OA patients were randomized into three treatment groups: conservative management (control), single intra-articular injection, or two intra-articular injections of adipose-derived MSCs into their affected knees.	WOMAC, NPRS and KIOOS scores showed significant pain and functional improvements observed in both treatment groups against controls. Imaging analysis indicated showed modification of disease progression in treatment groups, with greater stabilization achieved in the two-injection group.
Lu et al.[41]	2019	A total of 53 patients with grade 1-3 knee OA were enrolled into a clinical trial and randomized into two groups for intra-articular injections in the knee: Adipose-derived MPCs, and HA.	WOMAC, VAS, and SF-36 scores improved significantly in both groups. The adipose-derived MPCs group improved significantly more in WOMAC score and had a greater increase in articular cartilage volume measured by MRI at 12 months.
Chahal et al.[42]	2019	A total of 12 patients with late-stage knee OA received a single intra-articular injection of 1, 10 or 50 million bone marrow-derived MSCs.	KOOS pain, symptoms, quality of life and WOMAC stiffness improved significantly after MSC treatment; the 50 million dose achieved clinically relevant improvements in almost all clinical outcome scores. Synovial pro-inflammatory macrocytes and IL-12 levels also decreased.
Mayoly et al.[43]	2019	A total of 3 stage four OA patients were enrolled into an experimental trial to receive intra-articular injections of autologous PRP mixed-microfat in the wrist.	VAS pain score improved by 50% and all 3 patients achieved MCID for DASH and PRWE scores at 12 months follow up. Microfat-PRP presented a good safety profile.
Lee et al.[44]	2019	A total of 12 OA patients were enrolled into a clinical trial and randomized into two groups for intra-articular injections in the knee: autologous adipose-derived MSCs, and normal saline.	WOMAC score improved significantly after a single injection of adipose-derived MSCs at 6 months follow up. Cartilage defect increased on MRI in normal saline group after six months; no significant change in cartilage defect in MSC group.
Matas et al.[45]	2019	A total of 25 OA patients were enrolled into a clinical trial and randomized into three groups for intra-articular injections in the knee: HA (at baseline and 6 months), umbilical cord-derived MSCs (at baseline), umbilical cord-derived MSCs (at baseline and 6 months)	Only MSC treated patients experienced significant pain and function improvements. WOMAC and VAS pain scores improved significantly in the two-dose MSC group compared to the HA group at 12 months follow up. No difference in MRI scores were detected.
Khalifeh Soltani et al.[46]	2019	A total of 20 OA patients were randomized into two groups for intra-articular injections in the knee: allogenic placenta-derived MSCs, and normal saline.	Quality of life, activity of daily living, sport/recreational activity, and OA symptoms improved significantly in the MSC group after 8 weeks. Improvement over six months were also noted, but not significant. Chondral thickness improved in 10% of total knee joint area in MSC group after 6 months follow up.
Zhao et al.[47]	2019	A total of 18 patients received intra-articular human adipose-derived MSCs at either low, medium or high doses.	Significant reduction in WOMAC and SF-36 scores. Improvement in cartilage was noted using the different MRI sequences.

Bastos et al.[48]	2019	A total of 47 OA patients were enrolled into a clinical trial and randomized into three groups for intra-articular injections in the knee: autologous bone marrow-derived MSCs, autologous bone marrow-derived MSCs + PRP, and corticosteroid.	KOOS domains and global score improved the most in the MSCs and MSCs + PRP groups compared to the corticosteroid group at 12-month follow up. Intra-articular IL-10 cytokine levels were significantly reduced in all three groups.
Hernigou et al.[49]	2020	A total of 60 patients received bone marrow-derived MSC intraarticular and subchondral injections, one in each.	Subchondral bone injections showed better clinical and MRI improvements as well as lower yearly arthroplasty incidence vs intraarticular injections group.
Hernigou et al.[50]	2020	A total of 140 patients. TKA in one knee, subchondral MSC injection in the other knee.	BMLs regressed after MSC injections. Yearly TKA incidence after injection was equivalent to that of revision surgery. BML >3cm^2 independent RF for TKA after injection
Lu et al.[51]	2020	22 patients received two bilateral injections at week 0 and 3 (low, mid, high dose).	VAS and WOMAC improvements noted. MRI improvements were in low dose group.
Qiao et al.[52]	2020	30 patients with medial femoro-tibial condylar cartilage defects and 30 with trochlear-patellar defect received arthroscopic microfracture with injection of either normal saline (M), HA (MS) or HA plus haMPCs (MSR)	Improvement in WOMAC and SF-36 was seen in all three groups initially but only MS and MSR groups maintained the improvement. Arthroscopic and MRI evaluation of cartilage showed greatest reduction of defect in MSR followed by MS and M groups.
Dilogo et al.[53]	2020	57 patients received hUC-MSCs and HA the first week followed by HA injections in second and third weeks	VAS, WOMAC and IKDC scores significantly improved at 6 months follow up.
Garza et al.[54]	2020	A total of 39 OA patients were randomized into three treatment groups: placebo, low-dose or high dose (1:1:1) of intra-articular stromal vascular fraction (SVF) injection into their affected knees (SVF, derived from adipose tissue, is a collection of cells that include progenitors and MSCs).	WOMAC scores had significant dose-dependent improvements in the high and low-dose groups when compared to placebo. MRI review did not note any changes in cartilage thickness after treatment.
Vinet-Jones and Darr[55]	2020	A total of 25 OA patients received an injection of nondigested micro-fragmented adipose tissue (contains MSCs) injection into the affected shoulders.	VAS and DASH scores improved significantly in all study participants up to a year post-intervention.
Lamo-Espinosa et al[56]	2021	60 patients with knee OA received 3 weekly doses of PRGF or 100 million auto BM-MSCs plus PRGF.	VAS and WOMAC scores improved in both groups after 12mo follow up. OARSI criteria indicated only BM-MSC + PRGF group could be considered as OA treatment responders. XRs and MRIs showed no further damage
Chen et al.[57]	2021	A total of 64 OA patients were randomized into four treatment groups, each receiving an intra-articular injection of: hyaluronic acid (control), and three different doses of adipose-derived MSCs into their affected knees.	WOMAC scores showed significant improvement in test groups when compared to control at 4 weeks post treatment. VAS and KSCRS showed significant improvement at 48 weeks post treatment in test group when compared to control.
Sadri et al.[58]	2022	A total of three patients with knee OA received a total of 100×10^6 AD-MSCs injected into each affected knee.	VAS, WOMAC and KOOS scores improved in all patients after 6mo follow up. MRI findings showed slight improvement in 2 patients. Decrease in serum COMP and HA indicates possibility of reduced cartilage degeneration.

Table I. — Summary of all included clinical trials exploring the use of mesenchymal stem cells (MSCs) in osteoarthritis (OA).

Olufade et al.[59]	2022	A total of 51 patients with knee OA received either dehydrated cell and protein concentrate (dCPC) (27 patients) versus corticosteroid (CSI) (24)	Both groups demonstrated improvement on the VAS, KOOS and EQOL scores. Better improvement with dCPC starting 2, 3, 6 mo through 9 and 12 although limited data.
Zhang Y et al.[60]	2022	A total of 95 OA patients were randomized into two treatment groups, each receiving an intra-articular injection of stromal vascular fraction (SVF) or hyaluronic acid (control) into their affected knees.	Thickness and volume of cartilage defects, along with the volume of healthy cartilage showed improvements in the SVF group, unlike the control group, where no such changes were observed. SVF-treated patients also showed significant improvement according to clinical and radiographic scores at 12 months follow-up.
Zhang S et al.[61]	2022	A total of 126 OA patients were randomized into two groups, each receiving an intra-articular injection of: autologous SVF or hyaluronic acid (control) into their affected knees.	VAS and WOMAC scores were significantly better in the SVF group when compared to the control group at 5-year follow up. Responsive time to SVF treatment was significantly longer than that of control. Cartilage volume reduction was observed in both groups but was less in the SVF group.

WOMAC: Western Ontario and McMaster Universities OA Index; VAS: Visual Analogue Score; NPRS: Numeric Pain Rating Scale; KIOOS: Knee Injury and OA Outcome Score; DASH: Disabilities of the Arm, Shoulder and Hand; KSCRS: Knee Society Clinical Rating System; SF-36: 36-Item Short Form Survey

Table II. — Demographic and clinical characteristics of the patients in the included trials.

		Number of Patients	Percent (%)
Sex	Male	530	33.5
	Female	840	53
	Unspecified	214	13.5
	Total	1584	100
Source of MSC	Adipose Tissue	838	53
	Bone Marrow	620	39
	Umbilical Cord	55	3.5
	Placental Tissue	20	1.3
	Amniotic-Derived Tissue	51	3.2
	Total	1584	100
Affected Joint	Knee	1556	98.3
	Shoulder	25	1.6
	Wrist	3	0.1
	Total	1584	100

literature (Table I). The theorized rationale behind the benefits of MSC use in osteoarthritis have been implicated in in-vitro studies through four main functions: stimulating chondrogenesis, modulating the immune response in the joint, inhibiting osteoclast (OC) proliferation, and maintaining joint homeostasis (Figure 2)[14]. These benefits have translated into clinical trials that used MSCs of different sources on different osteoarthritic joints, and noted general improvement on clinical, radiographic, and arthroscopic outcomes[19-27,29-61]. Nevertheless, and while the majority of clinical trials note positive outcomes, some report negative or inconsistent outcomes. Accordingly, a thorough exploration of different aspects of trial designs and results is warranted to appropriately interpret trial results.

Affected joints and MSC source

The vast majority of clinical trials exploring the use of MSC in osteoarthritis involved the knee joint[19-27,29-42,44-54,56-61], with only a few trials exploring other joints like the shoulder and the wrist[43,55]. While osteoarthritis can affect any joint in the body, the knee

Table III. — Summary of clinical, radiographic, and arthroscopic outcomes of included trials.

		Number of trials	Percentage from all trials (N=43)
Improvement with MSC group on clinical scores	Yes	42	97.7
	No	1	2.3
Clinical improvement superior to control group	Yes	33	76.7
	No	1	2.3
	Unspecified	9	21
Improvement with MSC group on Imaging	Cartilage regeneration/decrease in defect/ improvement in MRI scores (i.e. WORMS, MOCART… etc.)	23	53.5
	No significant improvement/ No change in damage or cartilage volume	7	16.3
	Progression of cartilage damage	1	2.3
	Unspecified	12	27.9
Improvement with MSC group on second arthroscopy	Showed Improvement	3	7
	No improvement	1	2.3
	Unspecified	39	86

Table IV. — Summary of trial characteristics and designs.

		Number of trials	Percent (%)
Intervention Model	Parallel Assignment	31	72
	Single Group Assignment	11	26
	Crossover Assignment	1	2
Allocation Model	Randomized	30	70
	Non-Randomized	13	30
Masking Status	Blinding Reported	22	51
	No Blinding Reported	21	49
Level of Evidence	II	28	65
	III	6	14
	IV	9	21

is one of the most commonly affected, accounting for more than 80% of the total burden of the disease[62,63]. This is not surprising given the recent increases in obesity rates and life expectancy, as well as the location and size of the knee joint which predispose it to high mechanical loading and articular degeneration[64]. Accordingly, it is warranted that the researchers would be interested in the knee more so than other joints when exploring treatments for osteoarthritis.

MSCs can be extracted from different sites in the body, like the bone marrow, adipose tissue, and placenta, among others (Figure 2)[65]. This variety constitutes a challenge in cell-based studies since each set of MSCs possesses different therapeutic capabilities and different characteristics depending on the site it was obtained from[65]. The most common sources for MSC extraction in our study were adipose tissue[21,24,30,31,35,36,39-41,43,44,47,51,52,55,57,58], and bone marrow[19,20,22,23,25-29,32-34,37,42,48-50,56], with a few trials utilizing placental sources (9%) like the umbilical cord, and amniotic-derived tissue[38,45,46,53,54,59-61].

Adipose-derived MSCs are popular in the setting of regenerative medicine, due to their abundance, accessibility, and great proliferative and immunomodulatory capacity when compared to other types[14,66]. As such, adipose-derived MSCs are currently considered the most widely used stem cell type in clinical therapy, and this has been reflected by the results of our study[14,66]. While the capacity for chondrogenic and osteogenic differentiation is superior in the bone marrow than the adipose tissue, the clinical advantages and the high MSC yield shown in adipose tissue render it a more favorable source for many investigators worldwide[67].

On the other hand, the bone marrow had traditionally been considered one of the most used sources for MSC

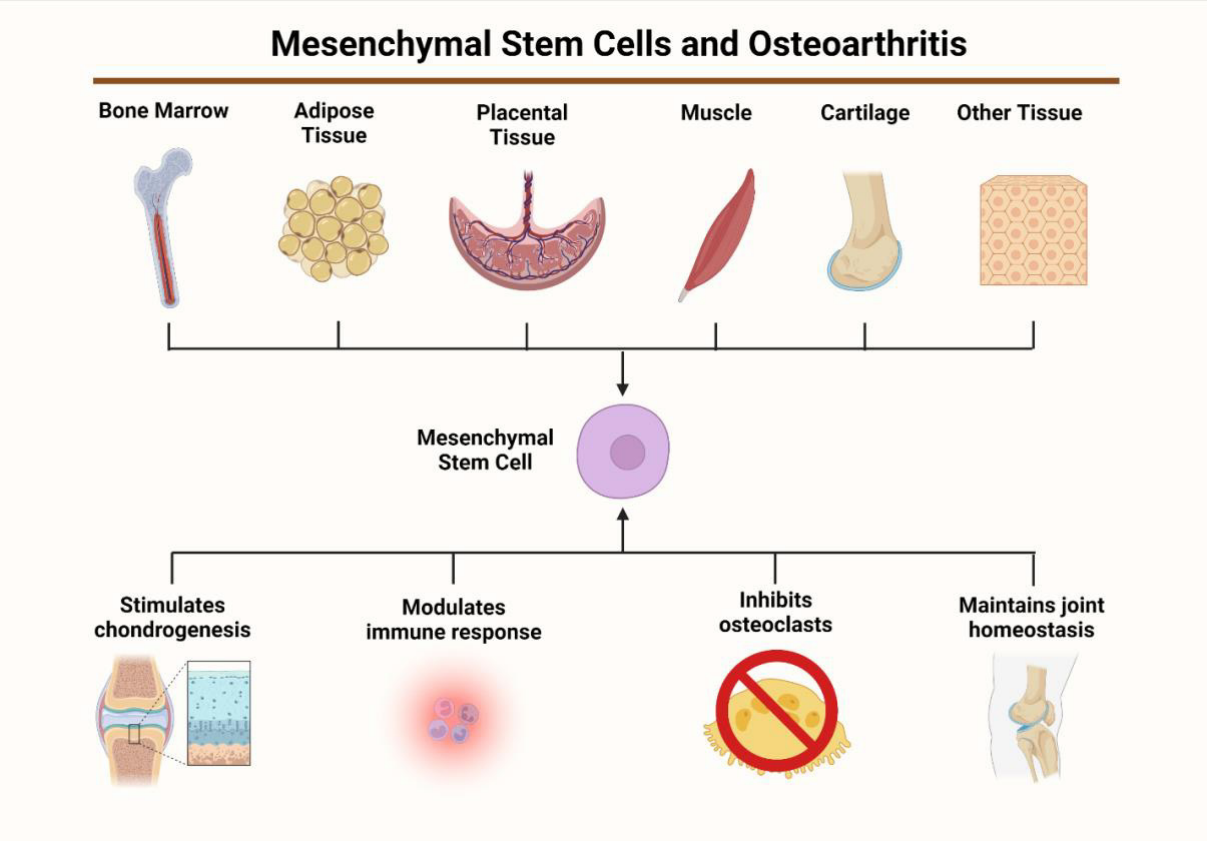

Fig. 2 — Mesenchymal stem cells (MSCs) can be extracted from different sites and sources inside the human body. These cells have been suggested to aid in the treatment of osteoarthritis through stimulating chondrogenesis, modulating the joint immune response, inhibiting osteoclasts, and maintaining joint homeostasis.

extraction, especially in the setting of pathologies that involve cartilage degeneration[67]. MSCs extracted from the marrow show strong chondrogenic differentiation but are limited by the invasiveness of their extraction procedure and their low yield[67]. Similarly, the placental tissue has been reported to be highly beneficial in treatment of osteoarthritis. A systematic review by Wei et al compared the efficacy of different MSC sources in the treatment of osteoarthritis and suggested that while MSCs from adipose tissue had the best pain-relieving potential, those that were derived from the umbilical cord had the best potential to improve function[67,68]. Nevertheless, the utility of placental tissue in this setting remains limited due to the fewer number of trials employing it as a source of MSC, along with the difficulties in acquiring and expanding MSCs from it when compared to other sources, like adipose tissue[67,68].

Improvement of clinical outcomes and sources

The majority of trials showed improvement in clinical outcomes and scores upon treatment with MSC injections, with different follow up periods that varied between six months and 15 years[19-27,29-61]. However, several inconsistencies between the trials were worth noting. Some trials noted dose-dependent improvements, where higher clinical scores were shown at higher MSC doses like Jo et al, Lamo-Espinosa et al, Chahal et al, Matas et al, Garza et al, and Song et al.[24,29,35,42,45,54]. Interestingly though, Pers et al noted improvement only in the low dose MSC group, and Gupta et al noted more adverse events in the higher dose group[28,31]. One trial by Hernigou et al explored whether mode of injection affected clinical outcomes, and noted better clinical scores with subchondral injections when compared to intraarticular injections[49]. In addition, even though 42 trials noted improvements with MSC injections, only 33 reported improvement to be superior to the control group[19-27,29-61]. Nine trials did not report any superiority for MSC injection therapy, mainly due to lack of non-MSC-based control groups[19,23,26,43,47,49,51,53,55]. One trial by Gupta et al showed no difference in clinical outcomes between MSC and control groups, and noted higher adverse effects in some of the test groups, evident by knee pain and swelling[28]. While the clinical scores of the included trials entail good

therapeutic potential, the inconsistent trial designs, different follow-up periods, and varying results raise concerns regarding the efficacy of this treatment modality and highlight the need for further research in this domain.

Improvement observed on imaging

Around 31 trials in our study reported using imaging to explore any evidence of cartilage changes following MSC treatment[19,21-25,27-29,31,32,35,37,38,40-47,49-56,58,60,61]. Several validated MRI scores were used in the process, and results varied between different studies (Table III). Twenty-three trials reported improvement of cartilage status on follow-up imaging, evident by cartilage regeneration, decrease in size of chondral defects, increased joint spacing, or achievement of higher MRI scores[19,21-25,27,32,35,37,38,41,43,44,46,47,49-53,55,60,61].

While these findings are promising, one particular challenge in cartilage regeneration is developing cartilage that is of good quality and can be integrated appropriately into the host joint[69,70]. Ideally, hyaline-like cartilage should be obtained in the joint to achieve native joint integrity and biomechanics[69,70]. Without postoperative histological analyses, it would be difficult to assess the quality of the regenerated cartilage and as such, comment on the success of the MSC injection therapy.

Seven trials did not note any significant improvement or change in cartilage damage or volume, while one trial noted progression of cartilage damage on postoperative imaging[28,29,31,40,42,45,54,56,58]. These findings raise questions about the clinical improvement observed following MSC injections for osteoarthritis. The lack of correlation between imaging and clinical findings warrants further research regarding the effects of MSC injections beyond regenerative capabilities. Whether these cells played an anti-inflammatory roles or simple placebo effects, the discrepancy between clinical and radiographic outcomes should be explored by translational scientists in the future.

Second look arthroscopy

Four of the forty-two trials reported exploring cartilage changes via second look arthroscopy on follow up[24,30,39,52]. Three of these trials reported improvement evident by decreased cartilage defects, regeneration of cartilaginous tissues and increased chondral thickness[24,39,52]. Qiao Z et al used histological analysis to confirm the growth of fibrocartilage and hyaline-like cartilage in the joint[52]. The use of second-look arthroscopy is important to quantify the tangible effects of MSC treatment on osteoarthritis knee joints. While clinical scores can be dampened by placebo effects, objective parameters like imaging and second look arthroscopy allow the researchers to appropriately assess the degree of chondral improvement and evaluate the regenerative capabilities of the cell-based treatment modality. One trial, however, by Koh et al explored the use of MSCs and microfracture for osteoarthritis and compared the outcomes to the use of microfracture alone[30]. The authors noted no significant differences in second look arthroscopy between the control and test groups, even though significant improvement was noted on clinical scores and imaging findings[30]. These discrepancies highlight the gap of knowledge that exists in the domain of cell-based regenerative medicine. In addition, these inconsistencies question the conclusiveness and the efficacy of MSC therapy in the setting of osteoarthritis.

Recommendations

Our findings allow us to extrapolate several recommendations for future research exploring the use of MSC-based therapy in the setting of osteoarthritis. While clinical outcomes following the use of MSC injections in osteoarthritis are generally positive, several discrepancies and inconsistencies question the reliability of this treatment. Several trials exhibited no correlations between clinical, imaging, and arthroscopic findings, and this raises concerns about the validity of this treatment and the quantitative benefit it entails. While clinical scoring tools are important to assess the satisfaction of the patient with the treatment, more objective methods like imaging, second look arthroscopy, and histological analyses should be conducted to appropriately assess and evaluate the benefits exhibited by MSC injections. In our study, not all trials reported the use of imaging, and only four studies reported the use of second look arthroscopy.

In addition, inconsistent trial designs limit the reproducibility of the research findings and the reliability of the results. The different MSC sources and the variety of trial protocols constitute prominent hurdles that should be overcome in future research. In addition, the lack of randomization, absence of blinding, and low level of evidence exhibited in some trials decrease the credibility and reliability of the proposed results and diminish the impact of published work. Finally, it is important to note that there is

an inherent bias towards reporting and publishing positive results in the literature. This should be kept in mind when considering the use of MSC injections for the treatment of osteoarthritis in prospective patients. In light of these considerations, it is important to conduct additional research that explore the use of regenerative modalities for the treatment of different degenerative pathologies like osteoarthritis. The adoption of unified trial designs with comprehensive assessment tools is important to decrease bias and obtain reliable and reproducible results. It is also essential to report negative results as that can help guide future researchers and scientists towards employing better experimental designs and exploring other promising treatment options.

CONCLUSION

Osteoarthritis is a worldwide prevalent degenerative disease that affects many people worldwide. MSC-based injections have shown great potential in treating the degenerative symptoms of the disease, and as such, a good number of clinical trials have explored the use of this therapeutic modality in the clinical setting of osteoarthritis.

Our study showed that the majority of clinical trials exploring the use of MSC injections for osteoarthritis involve the knee joint and employ adipose-derived MSCs in their trial designs. The majority of trials also reported clinical improvement following MSC injections, and some reported regenerative changes on imaging and second look arthroscopy. Nevertheless, the inconsistent trial designs, conflicting results, and variety of MSC sources used, entail limitations that should be addressed for future research. In addition, the lack of control groups, absence of objective parameters like imaging or second look arthroscopy, and the discrepancies between clinical, imaging and arthroscopic scores, constitute important weaknesses in some trials that should be noted prior to using MSC-based injections for treating prospective osteoarthritis patients. Researchers exploring the use of this modality should adopt standardized trial protocols, employ comprehensive objective and subjective assessment tools, and report both positive and negative results, in order to accurately evaluate the efficiency and reliability of MSC injections in the setting of osteoarthritis.

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