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Can Osteoarthritis be Cured by Mesenchymal stem cells (MSCs): A Literature Review

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ABSTRACT Osteoarthritis (OA) is a degenerative joint disease that affects millions of people worldwide. The disease frequently results in discomfort, edema, and stiffness, which can impair movement, make everyday tasks challenging, and even render a person disabled. Since osteoarthritis is presently incurable, researchers are working hard to find new treatments. Adult Mesenchymal stem cells (MSCs) are the most common stem cells used in the therapy of OA in clinical trials. They are simple to extract for researchers from bone marrow or adipose. Depending on the kind of tissue that contains them, MSCs can develop into cartilage, bone, muscle, tendon, ligaments, or fat. For this reason, scientists are researching MSCs in OA stem cell therapies. According to research, MSCs produce substances that promote healing and reduce pain. According to some research, they may aid in reducing pain, swelling, and loss of motion when injected into a joint. Researcher conduct an examination of articles that are in accordance with the issue to be studied. Articles used in literature review are obtained through the database of international journal providers through PubMed, we investigated clinical studies and discussed what happened in these clinical studies and the extent of the effectiveness of stem cells in treatment of osteoarthritis. Different patients have responded differently to this therapy. While some people have experienced pain others have not. Research is still required to determine whether stem cell therapies for OA are effective and why some people respond to the therapy more favorably than others.

INDEX TERMS Osteoarthritis, Mesenchymal stem cells, edema

I. INTRODUCTION

All phases of life contain a special population of cells called stem cells, which have the capacity to self-renew and differentiate into various cell lineages. Due to the fact that they are the source from which particular cell types within differentiated tissues and organs are produced, these cells are essential mediators in the development of neonates as well as in restorative processes following injury or illness. The primary function of stem cells in adults is regenerative and restorative in nature, in contrast to the neonate stage of life where they serve to differentiate and proliferate into the myriad of cell types and lineages needed for continuing development. Since stem cells can perform only certain types of physiological functions, they are distinguished from finally differentiated cells by special qualities. Since stem cells can perform only certain types of physiological functions, they are distinguished from finally differentiated cells by special qualities. Potency, which describes a stem cell's capacity to differentiate into a variety of cell kinds, can be used to classify stem cells in addition to their origin [1].

MSCs are a diverse population of cells that come from the mesoderm at an early stage of embryonic development. They include stem cells as well as differentiated offspring from this period and later developmental stages. MSCs can be separated from numerous tissues, including the umbilical cord, adipose tissue, dermis, tendons, bone marrow, muscles, and dental pulp, making them one of the most accessible primary cells [2,3]. MSCs and MSC-Exos have been extensively researched to gauge their availability due to their therapeutic potential. MSCs are among the most extensively researched pluripotent stem cells because they are somatic precursor cells or stem cells. Additionally, the primary criterion for defining MSCs is their capacity to differentiate into numerous lineages and control inflammation [4,5]. Monocytes in bone marrow are where MSCs were first identified, according to studies. The characteristics of MSCs from different sources vary slightly due to different protein expression profiles, but they all generally have the ability to self-renew, have the potential for multidirectional differentiation, have immune regulation, and

meet the minimal identification standards set by the International Cell Therapy Association.

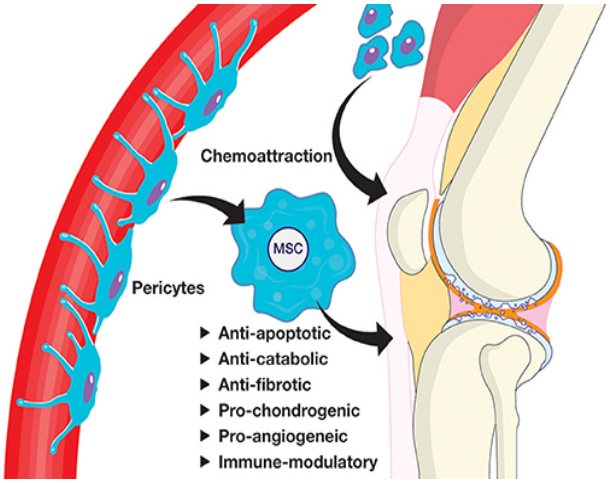
The characteristics of MSCs from different sources vary slightly due to different protein expression profiles, but they all generally have the ability to self-renew, have the potential for multidirectional differentiation, have immune regulation, and meet the minimal identification standards set by the International Cell Therapy Association. The following characteristics make up the fundamental definition of MSCs: (1) preserving plastic adhesion in a standard medium; (2) the expression of CD105, CD73, and CD90, but not CD45, CD34, CD14, CD11b, CD79a, CD19, or HLADR surface markers; and (3) the differentiation of osteoblasts, adipocytes, and chondroblasts under conventional in vitro circumstances [6].

According to epidemiological data, osteoarthritis (OA) is one of the most prevalent chronic and degenerative diseases of the cartilage that impacts older individuals, particularly women. It is a prevalent musculoskeletal disorder that can affect any joint, including the spine or the upper limbs, but it is most frequently seen in the hip and knee joints of the lower extremities [7,8,9]. The majority of the loading tasks that call for the successful completion, smooth completion, and absorption of loads or vibrations are carried out by these joints. Additionally, the formation of osteophytes, inflammation of the synovial membrane, and decomposition of the hypochondriac bone are all associated with gradual degeneration and loss of articular cartilage. In addition to pain, stiffness, swelling, joint deformity, and functional impotence, the condition's clinical features also include muscle atrophy, which lowers patient quality of life [10,11,12].

Since there is no known cure for OA or successful long-term treatment, OA is acknowledged globally as an unmet clinical need. The disease is not modified by the current conservative treatment strategies for OA, which are focused on symptomatic management. It is significant to note that pharmaceutical therapies, such as the use of oral anti-inflammatories and simple analgesics, have a limited efficacy and may also carry a high risk of unfavorable side effects. With a 10% weight loss corresponding to a 50% decrease in pain for many people, education about weight loss is still an essential conservative measure. When compared to routine anti-inflammatory use, an appropriate functional and prescribed exercise regimen may be linked to a similar improvement in pain [13,14,15].

Osteoarthritis must be treated with targeted cartilage regeneration and joint function restoration. Mesenchymal stem cells/stromal cells (MSCs), in particular, transplantation, offer an effective method for tissue regeneration and repair because these pluripotent stem cells have the capacity to differentiate into cartilage **FIGURE 1**. In order to avoid or postpone the need for joint replacement surgery, MSCs can be used as seed cells that directly take part in local repair and control metabolism and immune function through their secretory functions. Due to their flexibility, MSCs might be essential in various phases of cartilage repair [16].

FIGURE 1. **Proposed mechanism of action for tissue repair Stem Cells [17].**



II. METHODS

Researchers conduct an examination of articles that are in accordance with the issue to be studied. Determination of literature search keywords (search string based on PI (E) COT framework (P=patient/problem;I/E=exposure/implementation; C= control/comparison intervention, O=outcome, T=time) because a good question will help determine the scope of the review and help the strategy of finding the article. Articles used in literature review are obtained through the database of international journal providers through PubMed, from 2021-2023, Clinical Trials only. Author opens www.PubMed.com. Researchers wrote keywords according to MESH (Medical Subject Heading) namely" Mesenchymal Stem Cells “, “Osteoarthritis “, and selected full text. 1.Inclusion Criteria Population or sample is Osteoarthritis. 2. Exclusion Criteria Population or sample other than Osteoarthritis.

III. RESULTS AND DISCUSSION

TABLE 1. shows the clinical studies using MSCs therapy in Osteoarthritis. R. Köhnke et al. [18] found that a significant increase in cartilage thickness in the stromal cell treated groups (HA + STx. vs. ABS, p = 0.028; HA + ST.x vs. HA, p = 0.042; STx. vs. ABS, p = 0.036). Scanning electron microscopy detected a similar heterogeneity of mineralization and tissue porosity in the subchondral zone in all groups. The single intra-articular injection of a stem cell containing, GMP-compliant advanced therapy medicinal product for the treatment of iatrogen induced osteoarthritis of the temporomandibular joint shows a chondroregenerative effect. Philippe Hernigou et al. [19] found that After treatment with MSCs injection in bone marrow lesions of the subchondral

bone, medial femorotibial compartment BML volume experienced regression over 24 months (mean regression 1.5 cm3, range 0.8 to 3.2 cm3). At the most recent follow up (average of 15 years, range 10 to 20 years), a total of 25 (18%) of the 140 patients underwent total knee arthroplasty performed at a mean of ten years (range, 5 to 15 years) after the date of the cell therapy. The overall incidence of knee arthroplasty after cell therapy was 1.19% per person-year which was equivalent to the risk of a revision for a primary TKA in the contralateral knees of the same patient population (21 revisions, corresponding to 1.00% revision per person-year; p = 0.34). After adjusting for confounders, persistent BMLs larger than 3 cm3 after cell therapy was a strong independent risk factor for total knee arthroplasty (hazard ratio HR = 4.42 [95% CI = 2.34 to 7.21]; p < 0.001), regardless of OA grade, with higher risks demonstrated for larger BMLs. Incidence rates of arthroplasty were also higher for young patients and for knees presenting severe malalignment. J. M. Lamo-Espinosa et al. [20] found that cell doses of 10, 40 and 100 million autologous cells per knee provided quite similar healing results and that much of the effect attained 1 year after cell application remained after 2 and 4 years. These results are encouraging because they indicate that, apart from safety and simplicity: (i) the beneficial effect is both significant and sizeable, (ii) it can be achieved with a single injection of cells, and (iii) the effect is perdurable for years. P. Hernigou et al. [21] found that at two-year follow-up, clinical and imaging (MRI) improvement was higher on the side that received cells in the subchondral bone. At the most recent follow-up (15 years), among the 60 knees treated with subchondral cell therapy, the yearly arthroplasty incidence was 1.3% per knee-year; for the 60 knees with intra-articular cell therapy, the yearly arthroplasty incidence was higher (p = 0.01) with an incidence of 4.6% per knee-year. For the side with subchondral cell therapy, 12 (20%) of 60 knees underwent TKA, while 42 (70%) of 60 knees underwent TKA on the side with intra-articular cell therapy. Among the 18 patients who had no subsequent surgery on both sides, all preferred the knee with subchondral cell therapy. J. D. Tucker et al. [22] found that novel biomarkers including levels of interleukin (IL)-5, IL-6, IL-10, and tumor necrosis factor-α were measured in synovial fluid 10 days after PRP treatment. Altered gene expression profiles in MSCs from patients treated with PRP were observed for matrix metalloproteinases and inflammatory markers (IL-6, IL-8, CCL2, TNF-α). A2M protease was significantly increased following PRP treatment (P = .005). WOMAC scores declined for up to 3 months from baseline levels and remained low at 6 and 12 months in the PRP group. In contrast, WOMAC scores for patients receiving the saline injection were relatively unchanged for up to 12 months. T. Weijie et al. [23] found that for 15 of them, in addition to implants, cartilage grafts were transplanted during surgery. All patients were monitored by the Oswestry Disability Index questionnaire, for one year. In general, the results showed that over time, patients with transplanted cartilage tissue and implants were in a better condition than patients who underwent only implant surgery. S. Zhang et al. [24] found that the VAS and WOMAC scores in the SVF group were significantly better than those in the HA group during the 5-year follow-up after treatment. The average responsive time to SVF treatment (61.52 months) was significantly longer than HA treatment (30.37 months). The adjusted Cox proportional hazards model showed that bone marrow lesion (BML) severity, body mass index (BMI) and treatment were independent risk factors and that the use of SVF reduced the risk of clinical failure by 2.602 times. The cartilage volume was reduced in both the SVF and control groups at 5 years but reduced less in the SVF group. O. Olufade et al. [25] found that, 51 patients were enrolled at the time of analysis (27 dCPC, 24 CSI). Both groups demonstrated improvement on the VAS, KOOS and EQOL. Largest differences were observed at 2 (p = 0.05), 3 (p = 0.012) and 6 months (p < 0.001) with a decrease of 1.66 in VAS at 6 months for dCPC (95% CI: -2.67 to -0.65) and 1.34 (95% CI: -2.37 to -0.3) for CSI. Time-averaged measures showed no difference between groups (p = 0.20). Limited data at 9 and 12 months trended toward improvement in the dCPC group. J.-H. Kim et al. [26] found that, the primary outcome was the serial changes of cartilage defect on periodic magnetic resonance imaging (MRI) evaluation using valid measurements until postoperative 24 months. Secondary outcomes were the 2-stage arthroscopic evaluation for macroscopic cartilage status and the postoperative functional improvements of patient-reported outcome measures until the latest follow-up. Furthermore, safety profiles after the treatment were evaluated. Cartilage regeneration on serial MRIs showed significantly better in the ADMSC group than in the control group. The arthroscopic assessment revealed that total cartilage regeneration was significantly better in the ADMSC group. Although it was not significant, functional improvements after the treatment showed a tendency to be greater in the ADMSC group than in the control group from 18 months after the treatment. No treatment-related adverse events, serious adverse events, and postoperative complications occurred in all cases. Concomitant intra-articular injection of ADMSCs with MOWHTO had advantages over MOWHTO alone in terms of cartilage regeneration with safety at 2-year follow-up, suggesting potential disease-modifying treatment for knee OA with varus malalignment. B. Sadri et al. [27] found that, the primary outcome of this study was safety and feasibility of allogeneic AD-MSCs injection during the 6 months follow-up. Fortunately, no serious adverse events (SAEs) were reported. Assessment of secondary outcomes of visual analogue scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and knee osteoarthritis outcome score (KOOS) indicated improvement in all patients. Comparison between baseline and endpoint findings of MRI demonstrated a slight improvement in two patients. In addition, decrease in serum cartilage oligomeric matrix

protein (COMP) and hyaluronic acid (HA) indicated the possibility of reduced cartilage degeneration. Moreover, quantification of serum interleukin-10 (IL-10) and interleukin-6 (IL-6) levels indicated that the host immune system immunomodulated after infusion of AD-MSCs. N. Gerwin et al. [28] found that, in a first-in-human (phase 1), randomized, double-blinded, placebo-controlled, single ascending dose, single-center trial (NCT02491281 ; sponsored by Novartis Pharmaceuticals), 28 patients with knee OA were injected intra-articularly with LNA043 or placebo (3:1 ratio) either 2 h, 7 d or 21 d before total knee replacement. LNA043 met its primary safety endpoint and showed short serum pharmacokinetics, cartilage penetration and a lack of immunogenicity (secondary endpoints). Post-hoc transcriptomics profiling of cartilage revealed that a single LNA043 injection reverses the OA transcriptome signature over at least 21 d, inducing the expression of hyaline cartilage matrix components and anabolic signaling pathways, while suppressing mediators of OA progression. LNA043 is a novel disease-modifying OA drug candidate that is currently in a phase 2b trial (NCT04864392) in patients with knee OA. H.-C. Liu et al. [29] found that, that autologous CPs successfully engraft into the host tissue and result in the re-formation of hyaline-like cartilage, thereby improving the impaired knee functions. Most importantly, no adverse event was reported during this long-term follow-up period. M. Viganò et al. [30] found that, BMSCs accounted for 0.011% of BMA cells, similar to what had been expected in native bone marrow. The paracrine activity of BMA was able to reduce in vitro the catabolic response of human chondrocyte, as shown by the decrease in metalloproteases concentration and increase in anti-inflammatory mediators. Moreover, the clinical evaluation showed significant improvements in all scores adopted, with stable results up to two years. Y. Zhang et al. [31] found that, in all regions, the thickness and volume of cartilage defect and the volume of healthy cartilage were improved to some extent in the test group, especially the medial femoral condyle (MF) and medial tibial condyle (MT). In grades 2 and 3, the thickness and volume of cartilage defect decreased by 0.92 ± 0.18 mm and 1.03 ± 0.23 mm and 84.00 ± 32.30 mm3 and 130.30 ± 49.56 mm3 in MF and by 0.96 ± 0.22 mm and 0.99 ± 0.14 mm and 64.18 ± 21.40 mm3 and 95.11 ± 19.93 mm3 in MT, respectively. No such phenomenon was observed in the control group. Meanwhile, the SVF-treated knees showed significant improvement in clinical and radiographic scores at 12 months. Nevertheless, these scores of the control group became worse at 12-month follow-up visit.

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

Author	Date	Title	Methods	Results
R. Köhnke et al. [18]	2021 Randomized Controlled Trial	Temporomandibular Joint Osteoarthritis: Regenerative Treatment by a Stem Cell Containing Advanced Therapy Medicinal Product (ATMP)-An In Vivo Animal Trial	Four weeks after combined mechanical and biochemical osteoarthritis induction in 28 rabbits, therapy was initiated by a single intra-articular injection, randomized into the following groups: Group 1: AB Serum (ABS); Group 2: Hyaluronic acid (HA); Group 3: Mesenchymal stromal cells (STx.); Group 4: Mesenchymal stromal cells in hyaluronic acid (HA + STx.). After another 4 weeks, the animals were euthanized, followed by histological examination of the removed joints.	The histological analysis showed a significant increase in cartilage thickness in the stromal cell treated groups (HA + STx. vs. ABS, p = 0.028; HA + ST.x vs. HA, p = 0.042; STx. vs. ABS, p = 0.036). Scanning electron microscopy detected a similar heterogeneity of mineralization and tissue porosity in the subchondral zone in all groups. The single intra-articular injection of a stem cell containing, GMP-compliant advanced therapy medicinal product for the treatment of iatrogen induced osteoarthritis of the temporomandibular joint shows a chondroregenerative effect.
P. Hernigou, J. Delambre, S.	2021	Human bone marrow mesenchymal stem cell injection in	This study included 140 adults aged 65 to 90 years. These 140 patients (mean age 75.4 ± 14.2 years) planned to	After treatment with MSCs injection in bone marrow lesions of the

Quiennec, and A. Poignard. [19]	Randomized Controlled Trial	subchondral lesions of knee osteoarthritis: a prospective randomized study versus contralateral arthroplasty at a mean fifteen-year follow-up	undergo staged-bilateral total knee arthroplasty (TKA) for medial osteoarthritis, had "comparable" pain in both knees, and accepted randomization of the knees for surgery. They received TKA on one side and a subchondral injection of MSCs (from iliac bone marrow concentrate) on the contralateral knee during the same anaesthetic. The bone marrow graft of 20 cm3 volume (10 cc in the tibia and 10 cc in the femur) contained average 7800 MSCs/mL (range 3120 to 11,560). The baseline volume of bone marrow lesions (BMLs) on the tibia and on the femoral condyle determined on MRI was average 3.4 cm3 (range 0.4 to 6.4 cm3). The risk of subsequent knee arthroplasty due to absence of bone marrow lesions regression as well as osteoarthritis (OA) grade was evaluated with Cox proportional-hazards ratio after control of baseline variables (number of cells injected, age, knee alignment).	subchondral bone, medial femorotibial compartment BML volume experienced regression over 24 months (mean regression 1.5 cm3, range 0.8 to 3.2 cm3). At the most recent follow up (average of 15 years, range 10 to 20 years), a total of 25 (18%) of the 140 patients underwent total knee arthroplasty performed at a mean of ten years (range, 5 to 15 years) after the date of the cell therapy. The overall incidence of knee arthroplasty after cell therapy was 1.19% per person-year which was equivalent to the risk of a revision for a primary TKA in the contralateral knees of the same patient population (21 revisions, corresponding to 1.00% revision per person-year; $p = 0.34$). After adjusting for confounders, persistent BMLs larger than 3 cm3 after cell therapy was a strong independent risk factor for total knee arthroplasty (hazard ratio HR = 4.42 [95% CI = 2.34 to 7.21]; $p < 0.001$), regardless of OA grade, with higher risks demonstrated for larger BMLs. Incidence rates of arthroplasty were also higher for young patients and for knees presenting severe malalignment.
J. M. Lamo-Espinosa et al. [20]	2021 Randomized Controlled Trial	Long-term efficacy of autologous bone marrow mesenchymal stromal cells for treatment of knee osteoarthritis	have reanalyzed results from two recent pilot trials with autologous bone marrow-derived mesenchymal stromal cells using the Huskisson plot to enhance quantification of efficacy and comparability.	We find that cell doses of 10, 40 and 100 million autologous cells per knee provided quite similar healing results and that much of the effect attained 1 year after cell application remained after 2 and 4 years. These results are encouraging because they indicate that, apart from safety and simplicity: (i) the

				beneficial effect is both significant and sizeable, (ii) it can be achieved with a single injection of cells, and (iii) the effect is perdurable for years.Trial registration: EudraCT 2009-017405-11
P. Hernigou, C. Bouthors, C. Bastard, C. H. Flouzat Lachaniette, H. Rouard, and A. Dubory, [21]	2021 Randomized Controlled Trial	Subchondral bone or intra-articular injection of bone marrow concentrate mesenchymal stem cells in bilateral knee osteoarthritis: what better postpone knee arthroplasty at fifteen years? A randomized study	A prospective randomized controlled clinical trial was carried out between 2000 and 2005 in 120 knees of 60 patients with painful bilateral knee osteoarthritis with a similar osteoarthritis grade. During the same anaesthesia, a bone marrow concentrate of 40 mL containing an average 5727 MSCs/mL (range 2740 to 7540) was divided in two equal parts: after randomization, one part (20 mL) was delivered to the subchondral bone of femur and tibia of one knee (subchondral group) and the other part was injected in the joint for the contralateral knee (intra-articular group). MSCs were counted as CFU-F (colony fibroblastic unit forming). Clinical outcomes of the patient (Knee Society score) were obtained along with radiological imaging outcomes (including MRIs) at two year follow-up. Subsequent revision surgeries were identified until the most recent follow-up (average of 15 years, range 13 to 18 years).	At two year follow-up, clinical and imaging (MRI) improvement was higher on the side that received cells in the subchondral bone. At the most recent follow-up (15 years), among the 60 knees treated with subchondral cell therapy, the yearly arthroplasty incidence was 1.3% per knee-year; for the 60 knees with intra-articular cell therapy, the yearly arthroplasty incidence was higher ($p = 0.01$) with an incidence of 4.6% per knee-year. For the side with subchondral cell therapy, 12 (20%) of 60 knees underwent TKA, while 42 (70%) of 60 knees underwent TKA on the side with intra-articular cell therapy. Among the 18 patients who had no subsequent surgery on both sides, all preferred the knee with subchondral cell therapy.
J. D. Tucker et al., [22]	2021 Randomized Controlled Trial	Randomized, Placebo-Controlled Analysis of the Knee Synovial Environment Following Platelet-Rich Plasma Treatment for Knee Osteoarthritis	Knee synovial fluid was analyzed before the respective injections and again 10 days following injection. Participants were followed up to 12 months completing visual analog scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaires at intervals over that period.	Novel biomarkers including levels of interleukin (IL)-5, IL-6, IL-10, and tumor necrosis factor-α were measured in synovial fluid 10 days after PRP treatment. Altered gene expression profiles in MSCs from patients treated with PRP were observed for matrix metalloproteinases and inflammatory markers (IL-6, IL-8, CCL2, TNF-α). A2M protease was significantly increased following PRP treatment ($P = .005$). WOMAC scores declined for up to 3

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

			and the Emory Quality of Life (EQOL) measure at 1, 2, 3, 6, 9 and 12 months.	differences were observed at 2 ($p = 0.05$), 3 ($p = 0.012$) and 6 months ($p < 0.001$) with a decrease of 1.66 in VAS at 6 months for dCPC (95% CI: -2.67 to -0.65) and 1.34 (95% CI: -2.37 to -0.3) for CSI. Time-averaged measures showed no difference between groups ($p = 0.20$). Limited data at 9 and 12 months trended toward improvement in the dCPC group.
J.-H. Kim, K.-I. Kim, W. K. Yoon, S.-J. Song, and W. Jin, [26]	2022 Randomized Controlled Trial	Intra-articular Injection of Mesenchymal Stem Cells After High Tibial Osteotomy in Osteoarthritic Knee: Two-Year Follow-up of Randomized Control Trial	This randomized controlled trial (RCT) was aimed to assess regeneration of cartilage defect, functional improvement, and safety of intra-articular injection of ADMSCs after MOWHTO compared with MOWHTO alone for osteoarthritic knee with varus malalignment. This RCT allocated 26 patients into the MOWHTO with ADMSC-injection group (n = 13) and control (MOWHTO-alone) group (n = 13).	The primary outcome was the serial changes of cartilage defect on periodic magnetic resonance imaging (MRI) evaluation using valid measurements until postoperative 24 months. Secondary outcomes were the 2-stage arthroscopic evaluation for macroscopic cartilage status and the postoperative functional improvements of patient-reported outcome measures until the latest follow-up. Furthermore, safety profiles after the treatment were evaluated. Cartilage regeneration on serial MRIs showed significantly better in the ADMSC group than in the control group. The arthroscopic assessment revealed that total cartilage regeneration was significantly better in the ADMSC group. Although it was not significant, functional improvements after the treatment showed a tendency to be greater in the ADMSC group than in the control group from 18 months after the treatment. No treatment-related adverse events, serious adverse events, and postoperative complications occurred

				in all cases. Concomitant intra-articular injection of ADMSCs with MOWHTO had advantages over MOWHTO alone in terms of cartilage regeneration with safety at 2-year follow-up, suggesting potential disease-modifying treatment for knee OA with varus malalignment.
B. Sadri et al., [27]	2022 Clinical Trial	Clinical and laboratory findings following transplantation of allogeneic adipose-derived mesenchymal stromal cells in knee osteoarthritis, a brief report	Three patients with KOA were enrolled in this study. A total number of 100 × 106 AD-MSCs was injected intra-articularly, per affected knee. They were followed up for 6 months by the assessment of clinical outcomes, magnetic resonance imaging (MRI), and serum inflammatory biomarkers.	The primary outcome of this study was safety and feasibility of allogeneic AD-MSCs injection during the 6 months follow-up. Fortunately, no serious adverse events (SAEs) were reported. Assessment of secondary outcomes of visual analogue scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and knee osteoarthritis outcome score (KOOS) indicated improvement in all patients. Comparison between baseline and endpoint findings of MRI demonstrated a slight improvement in two patients. In addition, decrease in serum cartilage oligomeric matrix protein (COMP) and hyaluronic acid (HA) indicated the possibility of reduced cartilage degeneration. Moreover, quantification of serum interleukin-10 (IL-10) and interleukin-6 (IL-6) levels indicated that the host immune system immunomodulated after infusion of AD-MSCs.
N. Gerwin et al., [28]	2022 Clinical Trial	Angiopoietin-like 3-derivative LNA043 for cartilage regeneration in osteoarthritis: a randomized phase 1 trial	We discovered LNA043-a derivative of angiopoietin-like 3 (ANGPTL3)-as a potent chondrogenesis inducer using a phenotypic screen with human mesenchymal stem cells. We show that LNA043 promotes chondrogenesis and cartilage matrix synthesis in vitro and regenerates hyaline articular cartilage in	In a first-in-human (phase 1), randomized, double-blinded, placebo-controlled, single ascending dose, single-center trial (NCT02491281 ; sponsored by Novartis

			preclinical OA and cartilage injury models in vivo. LNA043 exerts at least part of these effects through binding to the fibronectin receptor, integrin α5β1 on mesenchymal stem cells and chondrocytes.	Pharmaceuticals), 28 patients with knee OA were injected intra-articularly with LNA043 or placebo (3:1 ratio) either 2 h, 7 d or 21 d before total knee replacement. LNA043 met its primary safety endpoint and showed short serum pharmacokinetics, cartilage penetration and a lack of immunogenicity (secondary endpoints). Post-hoc transcriptomics profiling of cartilage revealed that a single LNA043 injection reverses the OA transcriptome signature over at least 21 d, inducing the expression of hyaline cartilage matrix components and anabolic signaling pathways, while suppressing mediators of OA progression. LNA043 is a novel disease-modifying OA drug candidate that is currently in a phase 2b trial (NCT04864392) in patients with knee OA.
H.-C. Liu et al., [29]	2021 Clinical Trial	Atelocollagen-Embedded Chondrocyte Precursors as a Treatment for Grade-4 Cartilage Defects of the Femoral Condyle: A Case Series with up to 9-Year Follow-Up	Neotissues made of CPs were implanted into cartilage defects with an average cell density of 4.9 ± 2.1 × 106 cells/cm2 through arthrotomy. The knee function was evaluated with the International Knee Documentation Committee (IKDC) subjective knee form. Patients' knee functions significantly improved by the 28th week (IKDC score = 68.3 ± 12.1), relative to the initial functionality before the CP therapy (IKDC score = 46.1 ± 16.4, p-value = 0.0014). Nine of these twelve patients maintained good knee functions for 9 years post-implantation (IKDC score = 69.8 ± 12.3) at levels higher than the pre-implantation values (p-value = 0.0018).	Patients were evaluated with MRI and arthroscopy, and the defective sites exhibited a smooth surface without a gap between the implant and host tissue. This study demonstrates that autologous CPs successfully engraft into the host tissue and result in the re-formation of hyaline-like cartilage, thereby improving the impaired knee functions. Most importantly, no adverse event was reported during this long-term follow-up period.
M. Viganò et al. [30]	2022 Clinical Trial	A single step, centrifuge-free method to harvest bone marrow highly concentrated in mesenchymal stem	Ten patients (4 M, 6 W; mean age: 51.9 ± 9.2 yy) affected by mild to moderate unicompartmental knee OA (KL grade 2-3) were treated by intra-articular and subchondral injections of BMA obtained by a centrifuge-free process.	The laboratory analysis showed that BMSCs accounted for 0.011% of BMA cells, similar to what had been expected in native bone marrow.

		cells: results of a pilot trial	To evaluate the effectiveness of the device in harvesting mesenchymal stem cells (MSCs), samples of the obtained BMA were tested by flow cytometry before and after subculture; BMA ability to counteract inflammation was also tested in an in vitro model of cartilage cell inflammation, evaluating the expression of MMP1, MMP3, TGFβ and TIMP-1 by real-time PCR. Patients were also evaluated up to two years' follow-up by using: VAS for pain, IKDC-subjective and KOOS scores.	The paracrine activity of BMA was able to reduce in vitro the catabolic response of human chondrocyte, as shown by the decrease in metalloproteases concentration and increase in anti-inflammatory mediators. Moreover, the clinical evaluation showed significant improvements in all scores adopted, with stable results up to two years.
Y. Zhang, Q. Bi, J. Luo, Y. Tong, T. Yu, and Q. Zhang, [31]	2022 Randomized Controlled Trial	The Effect of Autologous Adipose-Derived Stromal Vascular Fractions on Cartilage Regeneration Was Quantitatively Evaluated Based on the 3D-FS-SPGR Sequence: A Clinical Trial Study	Patients with symptomatic OA were recruited in our research, who were randomized into two groups. Meanwhile, patients in Kellgren-Lawrence (K-L) grades 2 and 3 were distinguished in each group. In the test group, patients received SVF injections of the knee, while patients in the control group received the same dose of HA. Each patient underwent the 3D-FS-SPGR sequence to establish a cartilage model at baseline, 6 months, and 12 months, respectively. The cartilage was characterized into six regions, and relevant parameters of the cartilage model were counted. Clinical and radiographic scores were recorded in one-year follow-up.	In all regions, the thickness and volume of cartilage defect and the volume of healthy cartilage were improved to some extent in the test group, especially the medial femoral condyle (MF) and medial tibial condyle (MT). In grades 2 and 3, the thickness and volume of cartilage defect decreased by 0.92 ± 0.18 mm and 1.03 ± 0.23 mm and 84.00 ± 32.30 mm3 and 130.30 ± 49.56 mm3 in MF and by 0.96 ± 0.22 mm and 0.99 ± 0.14 mm and 64.18 ± 21.40 mm3 and 95.11 ± 19.93 mm3 in MT, respectively. No such phenomenon was observed in the control group. Meanwhile, the SVF-treated knees showed significant improvement in clinical and radiographic scores at 12 months. Nevertheless, these scores of the control group became worse at 12-month follow-up visit.

IV. CONCLUSION

Osteoarthritis affects the joints, the part of the skeleton where two bones meet, and is a prevalent, chronic, and incurable degenerative disorder. The connective tissue known as cartilage, which serves as a cushion of protection for the extremities of the bones, deteriorates over time, along with tendons, ligaments, and inflammation. Joints become painful and rigid as a result. Medications are frequently given to OA patients to treat pain and inflammation. Drugs can be ingested, administered topically, or injected directly into the joint. Anti-inflammatory treatments like corticosteroid injections or oral nonsteroidal anti-inflammatory drugs often provide patients with momentary respite.

Patients with OA may undergo surgery in severe instances where there has been significant joint damage and other treatments have failed to relieve pain or disability. It might be necessary to substitute the joint if it cannot be fixed surgically.

Stem cell therapies have the potential to assist in the repair of damaged joints in a variety of ways, including immune response regulation, cell delivery that can be directed to form cartilage, transplantation of cartilage produced by stem cells, or activation of a patient's own cells for regeneration. These possible stem cell treatments aim to treat pain, reduce inflammation, and regenerate or replace joint tissues. Mesenchymal stromal cells (MSCs), also known as mesenchymal stem cells, are frequently used in therapies. These cells, however, frequently lack any sign that they contain live stem cells and instead are a mixed population of cells from bone marrow, fat, and blood. These mixed populations of cells can either be produced in a facility and processed to select for a particular subpopulation before injection, or they can be taken from a patient and injected back into that patient. In some early clinical trials, lab-grown cells were found to have anti-inflammatory properties and to stimulate other cells to enhance tissue repair. Clinical studies are still being conducted to evaluate these cells' capacity for regeneration. "Stem cell" injections are promoted as a treatment for OA patients who wish to alter their joints or regrow cartilage.

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