Intra-Articular Injections of Mesenchymal Stem Cells for Knee Osteoarthritis

Emérito Carlos Rodríguez-Merchán, MD, PhD

Abstract

Knee osteoarthritis (KOA) represents an enormous societal burden. This review article summarizes the knowledge on the efficacy of using intra-articular injections of mesenchymal stem cells (MSCs) to treat KOA.

PubMed (Medline) and the Cochrane Library were searched for literature related to MSC therapy and KOA up until January 31, 2014. The key search terms used were *stem cells* and *knee osteoarthritis*. One hundred thirty-five reports were found, but only the 25 fully focused on the topic were used for analysis.

Only 3 randomized controlled trials (level II evidence) found pain relief and functional improvement over the short term. The other human studies also reported encouraging results, but their evidence level was very low (IV).

Larger randomized controlled trials are needed to support these preliminary encouraging results. The relatively short duration of the studies is also a limitation for the technique at present.

Knee osteoarthritis (KOA), a common disabling disease with a high impact on quality of life, has a large societal cost. Yet no procedure halts progressive degeneration of the osteoarthritic knee joint.[1,2]

According to Barry,[3] mesenchymal stem cells (MSCs) differentiate into many different connective tissue cells, including cartilage. MSCs can be isolated from bone marrow, skeletal muscle, fat, and synovium. MSCs are multipotent cells with the capacity for self-renewal. Therefore, adult MSCs may regenerate tissues damaged by disease. In OA, the proliferative capacity and ability to differentiate are reduced in MSCs. Intra-articular injections of MSCs (MSC therapy) could repair progressively degenerated knee cartilage.

This review article summarizes the knowledge on the role of intra-articular injections of MSCs in the treatment of KOA, based on studies published in PubMed and the Cochrane Library. The article also reviews the methodology and results of the animal and clinical studies published so far on the topic.

Materials and Methods

PubMed (Medline) and the Cochrane Library were searched for literature on the role of MSC therapy in treating KOA. The key words used were *stem cells* and *knee osteoarthritis*. The period searched was from when these search engines began until January 31, 2014. One hundred thirty-five articles (including negative studies) were found, but only the 25 deeply focused on the topic were reviewed. The **Figure** shows the flow diagram of this study.

Results

Several experimental models of KOA have shown that MSC therapy can delay progressive degeneration of the knee joint (**Appendix 1**).[4-15] Using a rabbit massive meniscal defect model, Hatsushika and colleagues[13] found that a single intra-articular injection of synovial MSCs into the knee adhered around the meniscal defect and promoted meniscal regeneration. Park and colleagues[14] conducted an experimental study in dogs—the first demonstrating regional and systemic safety and systemic immunomodulatory effects of repeated local delivery of allogeneic MSCs in vivo. Regarding the observed systemic immunomodulatory effects, clinical and pathologic examinations revealed no severe consequences of repeated MSC transplantations. Results of mixed leukocyte reactions demonstrated suppression of T-cell proliferation after MSC transplantations.

Of the human studies published so far, only 3 were prospective randomized trials (level II evidence) included in the Cochrane Library (**Appendix 2**).[16-18] Varma and colleagues[16] found that intra-articular injections of MSCs considerably improved overall KOA outcome scores. Fifty patients with mild to moderate KOA were divided into 2 groups. Group A underwent arthroscopic débridement, and group B had buffy coat (MSC concentrate) injection and arthroscopic débridement. Patients were assessed on the basis of their visual analog scale (VAS) pain scores and osteoarthritis outcome scores.

Wong and colleagues[17] analyzed 56 knees in 56 patients (mean age, 51 years) with unicompartmental KOA and genu varum. Patients were randomly assigned to 2 groups, MSC and control. All patients underwent high tibial osteotomy (HTO) and microfracture. Patients in the MSC group received intra-articular injection of cultured MSCs with hyaluronic acid (HA) 3 weeks after surgery. Patients in the control group received

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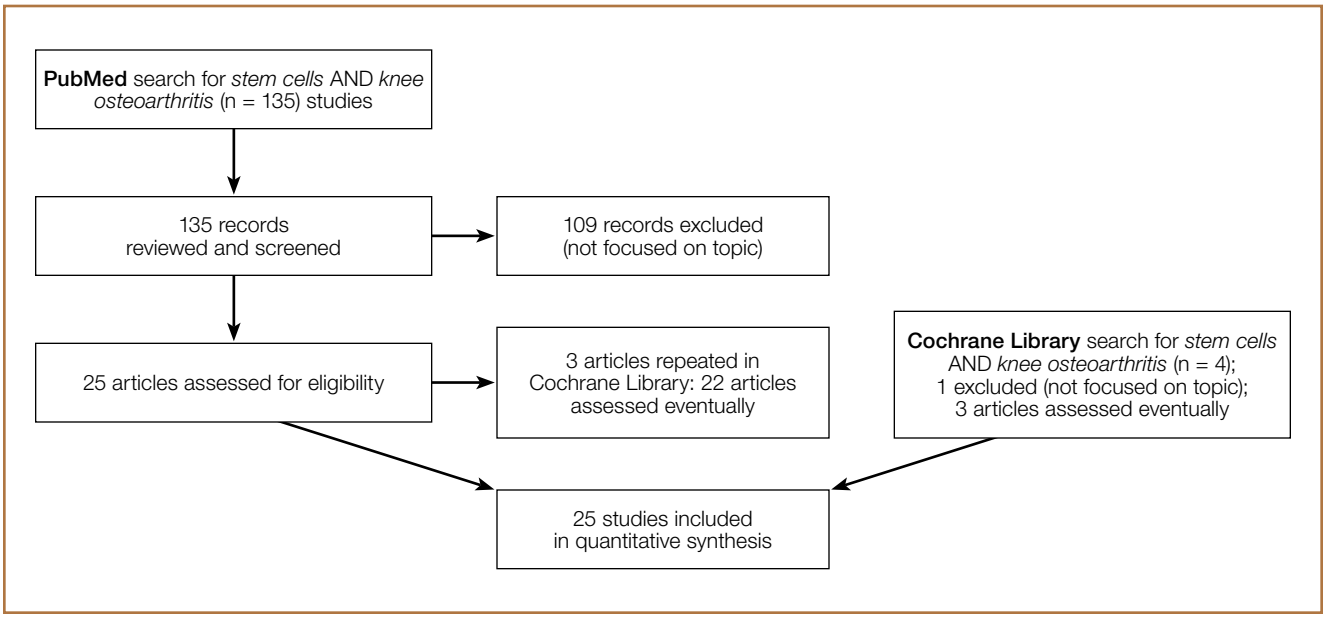

Figure. Flow diagram used in this study.

only HA. The primary outcome measure was International Knee Documentation Committee (IKDC) score 6 months, 1 year, and 2 years after surgery. Secondary outcome measures were Tegner and Lysholm clinical scores and 1-year postoperative Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scores. Both treatment arms achieved improvements in Tegner, Lysholm, and IKDC scores. After adjustment for age, baseline scores, and time of evaluation, the MSC group had significantly better scores. One year after surgery, magnetic resonance imaging (MRI) scans showed significantly better MOCART scores for the MSC group. Intra-articular injection of MSCs appeared to be effective in improving short-term clinical and MOCART outcomes in patients who underwent HTO and microfracture for varus knees with cartilage defects.

Saw and colleagues[18] compared histologic and MRI evaluation of articular cartilage regeneration in patients with chondral lesions treated by arthroscopic subchondral drilling followed by postoperative intra-articular injections of HA with and without peripheral blood stem cells (PBSCs). Fifty patients (ages, 18-50 years) with International Cartilage Repair Society grades 3 and 4 lesions of the knee joint underwent arthroscopic subchondral drilling; 25 patients were randomized to the intervention group (HA + PBSC) and 25 to the control group (HA). Both groups received 5 weekly injections starting 1 week after surgery. Three additional injections of either HA + PBSC or HA only were given at weekly intervals 6 months after surgery. After arthroscopic subchondral drilling into grades 3 and 4 chondral lesions, postoperative intra-articular injections of autologous PBSC combined with HA resulted in improved quality of articular cartilage repair over the same treatment without PBSC.

The other human studies analyzed had a low level of evidence (grade IV, case series) but found that intra-articular injections of MSCs reduced pain and improved function in patients with KOA over the short term, 1 year (**Appendix 3**).[19-25]

Discussion

This review aimed to define the role of MSC therapy in the treatment of KOA. MSC therapy has yielded encouraging outcomes in experimental models of KOA.[4-15] These experimental studies have suggested that MSCs can halt cartilage degeneration in KOA. So far, however, only 3 human studies with grade II evidence (randomized prospective trials) have been reported on the role of MSCs in KOA, but results of these studies have suggested that MSCs can reduce pain and improve function.[16-18]

Previous reviews of the literature[1,2] have analyzed the role of MSC therapy in KOA. Barry and Murphy[1] reported that several early-stage clinical trials, initiated or under way in 2013, were testing MSC delivery as an intra-articular injection into the knee, but optimal dose and vehicle were yet to be established. Filardo and colleagues[2] reported that, despite growing interest in this biological approach to cartilage regeneration, knowledge on the topic is still preliminary, as shown by the prevalence of preclinical studies and the presence of low-quality clinical studies.

Study design weakness prevents effective comparison of the efficacy of MSC therapy with that of other treatments for relief of pain and other outcomes in KOA. The consistency of evidence of the clinical studies is low because of many uncontrolled variables.[1-3]

Conclusion

The results of MSC therapy in KOA are encouraging. However, optimal dose and vehicle are yet to be established.[1] Knowledge on this topic is still preliminary. Many aspects have to be optimized, and further randomized controlled trials are needed to

support the potential of this biological treatment for cartilage repair and to evaluate advantages and disadvantages with respect to the available treatments. The relative short duration of these studies is also a limitation for the technique at present.

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Appendix 1. Experimental Studies on the Role of Stem Cells in Knee Osteoarthritis

Study	Year	Experimental Model	Method	Results	Conclusions
Murphy et al[4]	2003	Goat	Adult stem cells were isolated from caprine bone marrow, expanded in culture, and transduced to express green fluorescent protein. OA was induced unilaterally in the knee joint of donor animals by complete excision of the medial meniscus and resection of the ACL. After 6 weeks, a single dose of 10 million autologous cells suspended in a dilute solution of sodium hyaluronan was delivered to the injured knee by direct intra-articular injection. Control animals received sodium hyaluronan alone.	In cell-treated joints, there was evidence of marked regeneration of the medial meniscus, and implanted cells were detected in the newly formed tissue. Degeneration of the articular cartilage, osteophytic remodeling, and subchondral sclerosis were reduced in cell-treated joints compared with joints treated with vehicle alone (no cells). There was no evidence of repair of the ligament in any of the joints.	Local delivery of adult MSCs to injured joints stimulates regeneration of meniscal tissue and retards the progressive destruction normally seen in this OA model.
Al Faqeh et al[5]	2008	Sheep	Sheep BMSCs were cultured in medium containing 5 ng/mL TGF-β3 + 50 ng/mL IGF-1 for 3 weeks. The cultured cells were then suspended at a density of 2×106 cells/mL and injected intra-articularly into the osteoarthritic knee joint. After 6 weeks, the distal head of the femur and the proximal tibial plateau were removed and stained with H&E.	The results indicated that knee joints treated with autologous BMSCs cultured in chondrogenic medium showed clear evidence of articular cartilage regeneration in comparison with other groups.	Knee joints treated with autologous BMSCs cultured in chondrogenic medium showed clear evidence of articular cartilage regeneration in comparison with other groups.
Grigolo et al[6]	2009	Rabbit	Rabbit knee joints were bilaterally subjected to ACL transection to surgically induce OA. After 8 weeks, the time necessary for development of cartilage surface damage, animals were treated with MSCs seeded onto Hyaff-11 scaffold in the left condyle and unseeded Hyaff-11 in the contralateral knee. Untreated rabbits were used as controls. All animals were sacrificed 3 or 6 months after surgery. Histologic, histomorphometric, and immunohistologic evaluations were performed.	OA changes developed in all animals subjected to ACL transection. The predominant macroscopically observed OA changes were mild (lateral femoral condyle) or moderate (medial femoral condyle) ulcerations. Statistically significant differences in the quality of the regenerated tissue were found between the implants with scaffolds carrying MSCs compared with implants with the scaffold alone or controls in particular at 6 months.	From the observations, it is possible to demonstrate that Hyaff-11 (a hyaluronan-based scaffold) has potential for MSC implantation and may have application for the treatment of early OA in humans.
Toghraie et al[7]	2011	Rabbit	In this study, scaffold-free MSCs obtained from an infrapatellar fat pad in an experimental animal model of OA by direct intra-articular injection were used. MSCs were isolated from a 2.8-kg white New Zealand rabbit. The cells were expanded and grown in vitro. OA was induced by unilateral ACL transection of knee joints. Twelve weeks after surgery, a single dose of 1 million cells suspended in 1 mL of medium was delivered to the injured knee by direct intra-articular injection. A control group received 1 mL of medium without cells. The knees were examined 16 and 20 weeks after surgery. Repair was investigated radiologically, grossly, and histologically with H&E, safranin-O, and toluidine blue stains.	Radiologic assessment confirmed development of OA changes after 12 weeks. Rabbits that received MSCs showed a lower degree of cartilage degeneration, osteophyte formation, and subchondral sclerosis than the control group 20 weeks after surgery. Quality of cartilage was significantly better in the cell-treated group than in the control group after 20 weeks.	Infrapatellar fat pad–derived MSCs could be the promising cell source for the treatment of OA.

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Study	Year	Experimental Model	Method	Results	Conclusions
Sato et al[8]	2012	Guinea pig	Commercially available human MSCs were cultured, labeled with CFDA-SE, suspended in either PBS or HA, and injected into the knee joints of 7-month-old animals. Control animals were injected with either PBS or HA alone. The animals were sacrificed 1, 3, or 5 weeks after transplantation, the knee joints were harvested, and fluorescent microscopic analysis was performed. Histologic and immunohistochemical analyses were performed 5 weeks after transplantation.	Five weeks after transplantation, partial cartilage repair was noted in the HA-MSC group but not in the other groups. Examination of CFDA-SE–labeled cells revealed migration, differentiation, and proliferation of MSCs in the HA-MSC group. There was strong immunostaining for type II collagen around both residual chondrocytes and transplanted MSCs in the OA cartilage. This scaffold-free, technically undemanding technique appears to result in the regeneration of articular cartilage in the spontaneous OA animal model.	The findings suggested that intra-articular injection of the HA-MSC mixture is potentially beneficial for OA, but further study of the long-term effects of transplantation is necessary.
Suhaeb et al[9]	2012	Rat	This study aimed to examine the effects of MSCs, HA, and the combination of MSCs and HA in treating OA in a rat model.	The histologic observations using the O'Driscoll score indicate that use of MSCs and HA independently, and not their combined use, delays OA progression.	Results of this preliminary study suggested that use of either MSCs or HA effectively reduces OA progression better than their combined use.
Al Faqeh et al[10]	2012	Sheep	Sheep BMSCs were isolated and divided into 2 groups. One group was cultured in chondrogenic media containing (Ham's F12:DMEM, 1:1) FD + 1% FBS + 5 ng/mL TGF-β3 + 50 ng/mL IGF-1 (CM), and the other was cultured in the basal media, FD + 10% FBS (BM). The procedure for surgically induced OA was performed on the donor sheep 6 weeks before intra-articular injection into the knee joint of a single dose of BMSCs from either group, suspended in 5 mL FD at a density of 2 million cells/mL. Control groups were injected with basal media (no cells).	Six weeks after injection, gross evidence of retardation of cartilage destruction was seen in the osteoarthritic knee joints treated with CM as well as BM. No significant ICRS scoring was detected between the 2 groups with cells. Macroscopically, however, meniscus repair was observed in the knee joint treated with CM. Severe OA and meniscal injury were observed in the control group. Interestingly, the CM group demonstrated good cartilage histoarchitecture, thickness, and quality, comparable to those of normal knee joint cartilage.	Intra-articular injection of a single dose of BMSCs, chondrogenically induced or not, could retard progression of OA in a sheep model, but the induced cells had better results, particularly in meniscus regeneration.
Toghraie et al[11]	2012	Rabbit	OA was induced in adult white New Zealand rabbits by unilateral ACL transection. The contralateral knee was considered the sham-operated group. Twelve weeks after surgery, the ASC-treated group was injected intra-articularly with a single dose of 1×10^6 cells suspended in 1 mL of medium. The control group received 1 mL of medium without cells, and the sham-operated group received no treatment. All rabbits were sacrificed 16 or 20 weeks after surgery. OA progression was evaluated radiologically, grossly, and histologically with H&E, safranin-O, and toluidine blue stain.	Twelve weeks after surgery, all knees subjected to ACL transection showed radiologic signs of OA. The findings showed significant differences in cartilage quality between the ASC-injected group and the control group, particularly 20 weeks after surgery.	Results of this study suggested that ASCs from subcutaneous adipose tissue could be a viable approach for treating OA.

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Study	Year	Experimental Model	Method	Results	Conclusions
ter Huurne et al[12]	2012	Mouse	ASCs were isolated from fat surrounding the inguinal lymph nodes and cultured for 2 weeks. Experimental OA was induced by injecting collagenase into the knee joints of C57BL/6 mice. OA phenotypes were measured within 8 weeks after induction. Histologic analysis was performed, and synovial thickening, enthesophyte formation, and cartilage destruction were measured in the knee joint. ASCs were injected into the knee joints of mice 7 days after induction of collagenase-induced OA. On day 1, green fluorescent protein-labeled ASCs were attached to the lining layer in close contact with macrophages.	Thickening of synovial lining, formation of enthesophytes associated with medial collateral ligaments, and formation of enthesophytes associated with cruciate ligaments were significantly inhibited on day 42 after ASC treatment, by 31%, 89%, and 44%, respectively. Cartilage destruction was inhibited on day 14 (65%) and day 42 (35%). In contrast to early treatment, injection of ASCs on day 14 after OA induction had no significant effect on synovial activation or joint pathology on day 42.	A single injection of ASCs into the knee joints of mice with early-stage collagenase-induced OA inhibited synovial thickening, formation of enthesophytes associated with ligaments, and cartilage destruction.
Hatsushika et al[13]	2013	Rabbit	Synovium was harvested from the knee joint of rabbits, and the colony-forming cells were collected. Two weeks after the anterior half of the medial menisci was excised in both knees, 1×10^7 MSCs in 100 µL PBS were injected into the right knee. MSC and control groups were compared macroscopically and histologically at 1, 3, 4, and 6 months (n = 4). Articular cartilage of the medial femoral condyle was also evaluated histologically at 6 months. Multipotentiality of the colony-forming cells was confirmed. Injected MSCs labeled with DiI were detected and remained in the meniscal defect at 14 days.	The meniscus was larger in the MSC group than in the control group at 1 and 3 months. The difference in size between the groups was indistinct at 4 and 6 months. However, the histologic score was better in the MSC group than in the control group at 1, 3, 4, and 6 months. Macroscopically, the surface of the medial femoral condyle was fibrillated in the control group but looked nearly intact in the MSC group at 6 months. Histologically, a defect or thinning of the articular cartilage with sclerosis of the subchondral bone was observed in the control group; contrarily, articular cartilage and subchondral bone were better preserved in the MSC group.	Synovial MSCs injected into the knee adhered around the meniscal defect and promoted meniscal regeneration in rabbits.
Park et al[14]	2013	Beagle	Allogeneic adipose-derived canine MSCs were delivered to the regions of the lacrimal gland and the third eyelid gland and into the knee joints of 6 healthy laboratory beagles as follows: 6 times with 1-week intervals for delivery to the lacrimal gland and the third eyelid gland regions and 3 to 4 times with 1- to 2-week intervals for intra-articular transplantations. The beagles were sequentially evaluated by clinical examination. At the end of the study, the beagles were humanely euthanized, and complete gross and histopathologic examinations of all organ systems were performed. Mixed leukocyte reactions were also performed before the first transplantation and after the final transplantation.	Clinical and pathologic examinations revealed no severe consequences of repeated MSC transplantations. Results of mixed leukocyte reactions demonstrated suppression of T-cell proliferation after MSC transplantations.	Results of this study showed regional and systemic safety and systemic immunomodulatory effects of repeated local delivery of allogeneic MSCs in vivo.

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Study	Year	Experimental Model	Method	Results	Conclusions
Nam et al[15]	2013	Boer goat	Two full-thickness chondral defects 5 mm in diameter were created in tandem on the medial condyle of the left stifle joints of 18 Boer goats, which were then divided into 3 groups of 6. Simultaneously, bone marrow aspirates were taken from the iliac crests of the goats in group 1 and were sent for BM-MSC isolation and expansion in vitro. Six weeks later, BMS surgery, which involves subchondral drilling at the defect sites, was performed. After 2 weeks, group 1 knees were given autologous intra-articular BM-MSCs (n = 6). In group 2, though BMS surgery was performed, supplementations were not provided. In group 3, no intervention was administered. The goats were sacrificed after 6 months. Repairs were macroscopically assessed with ICRS scoring, histologic grading by O'Driscoll score, biochemical assays for glycosaminoglycans, and gene expressions for aggrecan, collagen II, and Sox9.	Histologic and immunohistochemical analyses revealed hyaline-like cartilage regeneration in the transplanted sites, particularly in group 1. In contrast, tissues in groups 2 and 3 showed mainly fibrocartilage. The highest ICRS and O'Driscoll scorings were also observed in group 1; the lowest score was seen in group 3. Similarly, total glycosaminoglycan/total protein as well as chondrogenic gene levels were expressed in the same order (highest in group 1, lowest in group 3). Significant differences were found between the 3 groups.	Results of this study suggested that supplementing intra-articular injections of BM-MSCs after BMS surgery provides superior cartilage repair outcomes.

Abbreviations: ACL, anterior cruciate ligament; ASC, adipose-derived stem cell; BM, bone marrow stem cell cultured in basal media; BMS, bone marrow stimulation; BM-MSC, bone marrow–derived mesenchymal stem cells; BMSC, bone marrow stem cell; CFDA-SE, carboxyfluorescein diacetate succinimidyl ester; CM, chondrogenic-induced bone marrow stem cells; FBS, fetal bovine serum; FD, freeze drying; F12:DMEM, Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12; HA, hyaluronic acid; H&E, hematoxylin-eosin; ICRS, International Cartilage Repair Society; IGF-1, insulinlike growth factor 1; MSC, mesenchymal stem cell; OA, osteoarthritis; PBS, phosphate-buffered saline; TGF-β3, transforming growth factor β3.

Appendix 2. Clinical Studies With High Level of Evidence on Stem Cells in Knee Osteoarthritis

Study	Year	Methods	Results	Conclusions
Varma et al[16]	2010	In this study, 50 patients with mild to moderate knee OA were selected and divided into 2 groups. Group A underwent arthroscopic débridement, and group B had buffy coat (MSC concentrate) injection and arthroscopic débridement. On follow-up, patients were assessed on the basis of visual analog scale pain scores and OA outcome scores to compare the groups' results and determine the efficacy of arthroscopic injection of buffy coat in OA management.	The results suggested the technique used in the study considerably improved overall OA outcome scores, particularly QOL during and at the end of the studied follow-up period.	The technique used in the study considerably improved overall OA outcome scores, particularly QOL during and at the end of the studied follow-up period.
Wong et al[17]	2013	Fifty-six patients (56 knees) with unicompartmental knee OA and genu varum were randomly assigned to a cell-recipient group (n = 28) or a control group (n = 28). Exclusion criteria were joint-line congruity angle of >2°, knee malalignment from femoral causes, fixed flexion deformity, and age older than 55 years. All patients underwent HTO and microfracture. The cell-recipient group had intra-articular injection of cultured MSCs with HA 3 weeks after surgery. The control group received only HA. Primary outcome measure was IKDC score at 6 months, 1 year, and 2 years after surgery. Secondary outcome measures were Tegner and Lysholm clinical scores and 1-year postoperative MOCART scores.	Median age was 51 years. Mean body mass index was 23.85. Both treatment arms achieved improvements in Tegner, Lysholm, and IKDC scores. After adjustment for age, baseline scores, and time of evaluation, the cell-recipient group had significantly better scores. The effect of treatment showed added improvement of 7.65 for IKDC scores, 7.61 for Lysholm scores, and 0.64 for Tegner scores. One year after surgical intervention, MRIs showed significantly better MOCART scores for the cell-recipient group. Age-adjusted mean difference in MOCART scores was 19.6.	Intra-articular injection of cultured MSCs was effective in improving short-term clinical and MOCART outcomes in patients who underwent HTO and microfracture for varus knees with cartilage defects.

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Study	Year	Methods	Results	Conclusions
Saw et al[18]	2013	Fifty patients (ages 18-50 years) with ICRS grades 3 and 4 lesions of the knee joint underwent arthroscopic subchondral drilling; 25 were randomized to the intervention group (HA + PBSC) and 25 to the control group (HA). Both groups received 5 weekly injections starting 1 week after surgery. Three additional injections of either HA + PBSC or HA only were given at weekly intervals 6 months after surgery. Subjective IKDC scores and MRIs were obtained before surgery and at serial visits after surgery. At 18 months, we performed second-look arthroscopy and biopsy on 16 patients in each group. We graded biopsy specimens using 14 ICRS II components and obtained a total score. MRIs at 18 months were assessed with a morphologic scoring system.	Total ICRS II histologic scores averaged 957 (control group) and 1066 (intervention group), MRI morphologic scores averaged 8.5 (control) and 9.9 (intervention), and mean 24-month IKDC scores were 71.1 (control) and 74.8 (intervention). One patient was lost to follow-up. There were no notable adverse events.	After arthroscopic subchondral drilling into grades 3 and 4 chondral lesions, postoperative intra-articular injections of autologous PBSCs combined with HA resulted in improvement in quality of articular cartilage repair, over that provided by the same treatment without PBSCs, as shown by histologic and MRI evaluation.

Abbreviations: HA, hyaluronic acid; HTO, high tibial osteotomy; ICRS, International Cartilage Repair Society; ICRS II, ICRS Visual Assessment Scale II; IKDC, International Knee Documentation Committee; MOCART, Magnetic Resonance Observation of Cartilage Repair Tissue; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; OA, osteoarthritis; PBSC, peripheral blood stem cell; QOL, quality of life.

Appendix 3. Clinical Studies With Low Level of Evidence on Stem Cells in Knee Osteoarthritis

Study	Year	Methods	Results	Conclusions
Davatchi et al[19]	2011	Four patients (ages, 55, 57, 65, 54 years) with moderate to severe knee OA were selected for the study. After signed written consent was obtained, 30 mL of bone marrow was taken and cultured for MSC growth. With enough MSCs in culture (4-5 weeks) and with all safety measures having been taken, cells were injected into 1 knee of each patient.	Time spent walking before pain appeared improved for 3 patients and remained unchanged for 1. Number of stairs climbed and VAS pain scores improved for all patients. Physical examination revealed improvement was mainly for crepitus and improvement in range of motion was minor.	Results were encouraging but not excellent. Improved technique may improve results.
Koh & Choi[20]	2012	Patients with knee OA had 25 stem cell injections combined with arthroscopic débridement. A mean of 1.89×10^6 stem cells were prepared with approximately 3.0 mL of PRP and injected into selected knees of patients in the study group.	For the study group, mean Lysholm, Tegner, and VAS pain scores were significantly improved by final follow-up, and no major adverse events related to the injections were observed during the treatment and follow-up periods. Results for the study and control groups were compared. Although the study group's preoperative mean Lysholm, Tegner, and VAS pain scores were significantly poorer than the control group's, clinical results at final follow-up were similar and not significantly different between the groups.	The short-term results of this study are encouraging. They demonstrate that infrapatellar fat pad–derived MSC therapy with intra-articular injections is safe and assists in reducing pain and improving function in patients with knee OA.
Orozco et al[21]	2013	Twelve patients with chronic knee pain unresponsive to conservative treatments and with radiologic evidence of OA were treated with autologous expanded bone marrow MSCs by intra-articular injection (40×10 cells). Clinical outcomes, including pain, disability, and QOL, were followed for 1 year. Quality of articular cartilage was assessed by quantitative MRI T2 mapping.	Feasibility and safety were confirmed, and strong indications of clinical efficacy were identified. Patients exhibited rapid and progressive improvement (approaching 65%-78%) on algofunctional indices by 1 year. This outcome compares favorably with the results of conventional treatments. In addition, quantification of cartilage quality by T2 relaxation measurements demonstrated a highly significant decrease in poor cartilage areas (mean, 27%), with improvement in cartilage quality in 11 of the 12 patients.	MSC therapy may be a valid alternative treatment for chronic knee OA. The intervention is simple, does not require hospitalization or surgery, provides pain relief, and significantly improves cartilage quality.

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Study	Year	Methods	Results	Conclusions
Koh et al[22]	2013	The study group had 18 patients (6 men, 12 women). Mean age was 54.6 years (range, 41-69 years). In each patient, adipose synovium was harvested from the inner side of the infrapatellar fat pad by skin incision extension at the arthroscopic lateral portal site after arthroscopic débridement. After stem cells were isolated, a mean of 1.18×10^6 stem cells (range, 0.3×10^6 to 2.7×10^6 stem cells) were prepared with approximately 3.0 mL of PRP (mean, 1.28×10^6 platelets/μL) and injected into the selected knees. Clinical outcomes were evaluated with WOMAC and Lysholm scores and VAS pain scores. Also compared were MRI data collected both before surgery and at final follow-up.	WOMAC scores decreased significantly ($P < .001$), from 49.9 points before surgery to 30.3 points at final follow-up (mean follow-up, 24.3 mo; range, 24-26 mo). Lysholm scores also improved significantly ($P < .001$) by final follow-up, increasing from a mean of 40.1 points before surgery to 73.4 points by end of study. Likewise, there were significant ($P = .005$) changes in VAS pain scores throughout the follow-up period. Mean VAS score decreased from 4.8 before surgery to 2.0 at final follow-up. Radiography showed that, at final follow-up, the whole-organ MRI score had significantly ($P < .001$) improved, from 60.0 points to 48.3 points. Particularly notable was the change in cartilage whole-organ MRI score, which improved from 28.3 points to 21.7 points ($P < .001$). Further analysis revealed that improvements in clinical and MRI results were positively related to number of stem cells injected.	The encouraging results of this study showed that intra-articular injection of infrapatellar fat pad–derived MSCs is effective in reducing pain and improving knee function in patients being treated for knee OA.
Koh et al[23]	2013	Stem cell injections combined with arthroscopic lavage were administered to 30 elderly patients (≥65 years) with knee OA. Subcutaneous adipose tissue was harvested from both buttocks by liposuction. After stromal vascular fractions were isolated, a mean of 4.04×10^6 stem cells (9.7% of 4.16×10^7 stromal vascular fraction cells) were prepared and injected into the selected knees of patients after arthroscopic lavage. Outcome measures included KOOS, VAS pain scores, and Lysholm scores before surgery and at 3-month, 12-month, and 2-year follow-up. Sixteen patients had second-look arthroscopy.	Almost all the patients had significant improvement in all clinical outcomes by final follow-up. All clinical results were significantly ($P < .05$) improved at 2-year versus 12-month follow-up. Of the patients older than 65 years, only 5 had worsening of Kellgren-Lawrence grade. On second-look arthroscopy, 14 (87.5%) of 16 elderly patients improved or maintained cartilage status at least 2 years after surgery. Moreover, no patient underwent total knee arthroplasty during this 2-year period.	ASC therapy for elderly patients with knee OA was effective in healing cartilage, reducing pain, and improving function. Therefore, ASC therapy seems to be a good treatment option for OA in elderly patients.
Jo et al[24]	2014	AD-MSCs were injected into the knees of 18 patients with knee OA. Phase 1 of the study had 3 dose-escalation cohorts (3 patients each): low dose (1.0×10^7 cells), mid dose (5.0×10^7 cells), and high dose (1.0×10^8 cells). In phase 2, 9 patients were receiving the high dose. Primary outcomes were safety and WOMAC scores at 6 months. Secondary outcomes were clinical, radiologic, arthroscopic, and histologic evaluations.	There were no treatment-related adverse events. WOMAC scores were improved in the high-dose group 6 months after injection. Size of cartilage defect was decreased and volume of cartilage was increased in the medial femoral and medial tibial condyles of the high-dose group. Arthroscopy revealed decreased size of the cartilage defect in the medial femoral and medial tibial condyles of the high-dose group. Histology revealed thick, hyaline-like cartilage regeneration.	These results showed that intra-articular injection of 1.0×10^8 AD-MSCs into osteoarthritic knees improved function and pain in the knee joints without causing adverse events and reduced cartilage defects by regenerating hyaline-like articular cartilage.

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Study	Year	Methods	Results	Conclusions
Gobbi et al[25]	2014	From January 2007 to February 2010, 25 patients (mean age, 46.5 years) with symptomatic large chondral defects of the knee (ICRS grade 4) underwent cartilage transplantation with MSCs and a collagen type I/III matrix. Minimum follow-up was 3 years. Mean lesion size was 8.3 cm^2. In 18 of these patients, coexisting injuries were treated concurrent with the surgery. All patients participated in a standard postoperative rehabilitation program. Several evaluations were done before surgery and at 1- and 2-year and final follow-up: radiographs, MRI, and VAS pain, IKDC, KOOS, Lysholm, Marx, and Tegner scores. Seven patients had second-look arthroscopic surgery, with 4 consenting to tissue biopsy.	No patients were lost at final follow-up. Mean (SD) preoperative scores were significantly ($P < .001$) improved at final follow-up: VAS pain improved from 5.4 (0.37) to 0.48 (0.19); IKDC subjective, from 37.92 (4.52) to 81.73 (2.42); KOOS pain, from 61.04 (3.95) to 93.32 (1.92); KOOS symptoms, from 55.64 (3.23) to 89.32 (2.32); KOOS activities of daily living, from 63.96 (4.48) to 91.20 (2.74); KOOS sports, from 34.20 (5.04) to 80.00 (3.92); KOOS QOL, from 32.20 (4.43) to 83.04 (3.37); Lysholm, from 46.36 (2.25) to 86.52 (2.73); Marx, from 3.00 (0.79) to 9.04 (0.79); Tegner, from 2.12 (0.32) to 5.64 (0.26). Patients younger than 45 years and patients with smaller or single lesions had better outcomes. MRIs showed good implant stability and complete filling of defect in 80% of patients. Histologic analysis of the biopsied tissue revealed hyaline-like cartilage. No adverse reactions or postoperative complications were noted.	Large chondral defects can be effectively treated with MSCs. This treatment can be done routinely in clinical practice. Moreover, it can be achieved with 1-step surgery, avoiding a previous surgical procedure to harvest cartilage and subsequent chondrocyte cultivation.

Abbreviations: AD-MSC, adipose-derived mesenchymal stem cell; ASC, adipose-derived stem cell; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; OA, osteoarthritis; PRP, platelet-rich plasma; QOL, quality of life; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.