

[Orthopaedic Surgery]

Current Concepts: The Role of Mesenchymal Stem Cells in the Management of Knee Osteoarthritis

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Context: The number of adults with osteoarthritis in the United States is expected to nearly double from 21.4 million in 2005 to 41.1 million by 2030. As a result, medical costs and associated comorbidity will exponentially increase in the coming decades. In the past decade, mesenchymal stem cells (MSCs) have emerged as a novel treatment for degenerative joint disease.

Evidence Acquisition: PubMed (from 1990 to 2013) was searched to identify relevant studies. Reference lists of included studies were also reviewed.

Study Design: Clinical review.

Level of Evidence: Level 3.

Results: We identified 9 animal and 7 human studies investigating the use of MSCs in the treatment of osteoarthritis, with varying levels of support for this therapy.

Conclusion: While MSCs have shown potential for improving function and decreasing inflammation in animal studies, translation to patients is still in question. There is a great deal of heterogeneity in treatment methods. Standardizing the manufacturing and characterization of MSCs will allow for better comparisons.

Keywords: mesenchymal stem cells; osteoarthritis; treatment

Osteoarthritis (OA) is a disease process resulting from the failure of chondrocytes to repair damaged articular cartilage in synovial joints.² Increased synthesis of tissue-destructive proteinases such as matrix metalloproteinases, increased chondrocyte apoptosis, and insufficient extracellular matrix generation result in a cartilage matrix that is unable to withstand normal mechanical stresses.⁵ This leads to progressive cartilage loss, subchondral bone remodeling, osteophyte formation, and synovial inflammation.^{20,34} These degenerative changes can ultimately result in significant disability and chronic pain. The number of adults in the United States with osteoarthritis is expected to nearly double from 21.4 million in 2005 to 41.1 million by 2030.³¹ Direct and indirect medical costs relating to arthritis and associated comorbidities are estimated to

exponentially increase in the coming decades.⁶ In 1997, the total medical expenditures for arthritis and other rheumatic conditions were \$233.5 billion. These costs increased to \$321.8 billion by 2003 and have continued to rise on an annual basis.³¹

The prevalent strategy for managing OA is to exhaust conservative measures in an effort to delay major reconstructive joint surgery, particularly in younger adults. The goals of treatment are to decrease joint pain and improve function resulting in improved quality of life metrics for patients.

Low-impact, aerobic exercise significantly reduces pain and improves function in patients with early OA.⁶⁴ More specifically, strengthening exercises seem to be superior in reducing pain and impairment, and aerobic exercise leads to improved long-term functional outcomes.⁶⁴

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In patients with medial unicompartmental OA, valgus unloader braces reduce external varus moments and medial compartment load and improve pain and function when compared with simple neoprene sleeves.⁸ However, there is limited high-level evidence to suggest that valgus- or varus-directing knee braces for medial or lateral unicompartmental knee OA, respectively, are more effective than a placebo.^{8,25}

Pharmacological pain control remains the mainstay of treatment for symptomatic knee OA. Nonsteroidal anti-inflammatory drugs have a statistically significant pain-reducing effect when compared with placebo and acetaminophen, although this effect is not clinically significant.⁶⁴ Other options include nonselective oral nonsteroidal anti-inflammatory drugs plus a gastroprotective agent or cyclooxygenase-2 inhibitors. For patients with marked pain who are not good candidates for surgery, opioid analgesics may be considered in spite of physician and patient concerns regarding side effects and improper use.²⁹ Intra-articular corticosteroid treatment, although popular, only relieves pain in the short term, with its greatest effect after 1 week and diminishing thereafter.²⁹ In addition, intra-articular corticosteroid injections combined with lidocaine can be cytotoxic for chondrocytes. Its frequency and patient selection must be carefully considered.^{7,48}

Intra-articular viscosupplementation has become increasingly common for the treatment of symptomatic knee OA. However, its efficacy remains controversial. In several clinical studies, exogenous hyaluronic acid (HA) reduced the production and activity of pro-inflammatory mediators and matrix metalloproteinases, while enhancing native chondrocyte HA and proteoglycan synthesis, and even altering the behavior of immune cells.¹⁵ HA is also important for modulating tissue hydration and osmotic balance.¹⁵ A meta-analysis published in the *Journal of the American Medical Association* in 2003 suggests that intra-articular HA knee injections for OA may not result in a clinically significant difference when compared with placebo.³² However, a Cochrane review³ concluded that viscosupplementation, when used in specific clinical settings, is an effective treatment for knee OA and may provide longer term benefits when compared with intra-articular corticosteroids.²² The results of HA therapy may be related to variations in the molecular weights of HA products as well as varying degrees of heterogeneity of HA (viscosity and elasticity).

Platelet-rich plasma (PRP) is autologous blood, minus red blood cells, with higher-than-baseline concentrations of platelets prepared by centrifugal separation. Various growth factors, such as platelet-derived growth factor, vascular endothelial growth factor, and transforming growth factor β 1 (TGF- β 1), among others, are present. Current evidence suggests that PRP stimulates chondrogenesis and regeneration while increasing HA production and stabilizing angiogenesis.^{18,30} Compared with intra-articular HA or placebo controls, PRP injections in the knee appear to be superior for pain control and functional improvement during the first 6 months in the treatment of OA.^{23,41,49} At this time, more substantiated clinical data are required to determine the efficacy of PRP in the treatment of

symptomatic OA. Certainly, there are less data to suggest that PRP can influence the natural history of an osteoarthritic knee. Rather, its mechanism of action is likely anti-inflammatory, which can alter the local intra-articular milieu of catabolic and anabolic growth factors and cytokines.³³

Appropriate surgical management of OA is determined by specific patient symptoms, clinical and radiographic findings, circumstances, and expectations. While younger patients with isolated unicompartmental OA may benefit from a high tibial osteotomy or unicompartmental knee arthroplasty, patients with advanced, multiple compartmental OA are more likely to benefit from total knee arthroplasty. The routine use of arthroscopic debridement for the treatment of OA has been challenged recently by several randomized control studies demonstrating no significant difference between arthroscopic management and placebo in the treatment of knee OA.^{24,35}

Although many nonsurgical and surgical treatment modalities improve pain and function in OA patients, none alter the natural history of the disease process. Recently, there has been increased focus on the potential role of stem cells in the management of OA. The following sections provide a brief overview on the different types of stem cells that can be used, with particular emphasis on the potential role of mesenchymal stem cells (MSCs), also known as mesenchymal stromal cells.

ROLE OF MESENCHYMAL STEM CELLS IN THE MANAGEMENT OF OSTEOARTHRITIS

Rationale

In the past decade, MSCs have emerged as an option in the armamentarium for the treatment of OA. MSCs, derived from bone marrow, can differentiate into cells of chondrogenic lineage.¹⁹ MSCs are abundant in many adult tissue types and are precursors to the mesodermal lineage of cells/tissues including bone, cartilage, fat, and connective tissues (including tendon and ligament).^{9,16} MSCs can be isolated from bone marrow, adipose tissue, and umbilical cord tissue/blood as well as synovium and periosteum.^{16,40,57} Since MSCs are somatic (adult) stem cells, they have limited replicative potential and, importantly, are non-transformative.^{26,51}

Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are 2 other stem cell types that can differentiate into multiple lineages of cell/tissue types, including chondrogenic cells. However, among all potential allogeneic stem cell sources, MSCs seem to hold the most promise at present.^{11,38,50,55} There are also unresolved safety concerns with potential tumorigenicity and immunologic compatibility with ESCs and/or iPSCs as allogeneic cell sources, as well as ethical/religious considerations.^{4,37,58,61}

Regulatory Pathways

A cartilage product may be defined as a tissue, non-tissue biologic, device, drug, or a combination of these terms as per Section 361 of the Public Health Service Act.⁵³ Tissues that are

minimally manipulated (autologous bone marrow aspirate concentrate), intended for homologous use, and do not have a systemic effect are categorized as human cells, tissues, and cellular- and tissue-based products and do not require a formal clinical trial for Food and Drug Administration (FDA) approval and market release. Cartilage products regulated as biological drugs require an investigational new drug application for clinical evaluation and premarket demonstration. The product must be safe, pure, potent, and effective. Finally, for cartilage products regulated as devices, associated clinical studies must be conducted under an investigational device exemption, and a premarket approval is required.

Products such as Orthokine, an autologous PRP procedure (Orthogen, Düsseldorf, Germany; known as Regenokine in the United States) or ex vivo expanded autologous/allogeneic MSCs would be regulated as biological drugs by the FDA but may be regulated differently depending on the country and regulatory jurisdiction.^{53,56} While the use of minimally manipulated (eg, not ex vivo culture-expanded) autologous bone marrow cell aspirates (of which the exact number and/or proportion of MSCs may not be known at the time of administration) may pose some potential clinical merit, any significant benefit of autologous or allogeneic MSC treatment will likely be associated with ex vivo culture expansion that in turn will require standardized and quality controlled manufacturing processes. A key point to consider is that the autologous MSC therapy (eg, bone marrow aspirate concentrate) with un-expanded cells can be performed at the discretion of a physician without a formal approval/registration status of “a device or biological drug” in most regulatory jurisdictions, including Canada and the United States. The downside of this is 2-fold: (1) There may be no quality control measure that can be applied for each preparation and patient and (2) because of decreases in quality of the MSCs with increases in patient age, older patients may not get significant clinical benefits from autologous MSC procedures aside from a potential placebo effect. The evidence for procedures such as bone marrow aspirate concentrate, however, remains quite limited at the present time.

Mechanism of Action

The most important hallmark of MSCs, regardless of their tissue sources of origin, is that the MSCs do not express major histocompatibility complex class II antigens (human leukocyte antigen, DR receptors), thereby not provoking the host's T-cell response on implantation.⁴⁷ Furthermore, the MSCs can modulate and control inflammation, inhibit apoptosis, stimulate endogenous cell proliferation and repair, and improve blood flow in joints.⁵⁷ MSCs can hone to injured tissue and secrete a milieu of proteins via a paracrine effect leading to a healing or trophic effect, thus contributing to endogenous tissue repair.¹⁶ The mechanism of action is related to the secretion of cytokines, chemokines, and growth factors from the MSCs.⁹

One of the attractive features of MSCs is the ability to readily harvest from the patient's own tissue source such as bone marrow, although the quantity and quality of MSCs decrease

with age.^{2,21} While minimally manipulated (ie, not ex vivo culture-expanded) autologous cell aspirates may pose some potential clinical merit, the immune-privileged nature of the MSCs allows development of allogeneic MSC products for the treatment of OA with standardized and quality-controlled manufacturing process.

Clinical Use of Mesenchymal Stem Cells in Osteoarthritis

The optimal source of MSCs has yet to be determined.^{16,50,57} There are various advantages and disadvantages associated with bone marrow, synovium, adipose tissue, and umbilical cord (Table 1).^{45,63}

At the present time, administration usually involves placing the MSCs via intra-articular injection. The ideal approach remains to be determined as the intra-articular microenvironment can be influenced by local pro- and anti-inflammatory actions from the cells. Alternatively, MSCs can be implanted in a scaffold, encapsulated, or injected in combination with other factors such as transforming growth factor- β .⁵⁰ They can be engineered to express anti-inflammatory or pro-chondrogenic factors. Another option is to inject bone marrow concentrate,⁵⁷ which does not require ex vivo culture expansion.²

A systematic review of the safety of intra-articular autologous bone marrow MSC injections in humans found 22 adverse events and 4 serious adverse events following 844 procedures (mean follow-up, 21 months).⁴² Two serious adverse events were related to the procedure (pulmonary embolism and infection at the iliac crest harvest site) and 2 were unrelated (tumors in areas not involving the cell collection or implantation site). The mild adverse events were related to transient pain or swelling, with a rate comparable with other injectable joint therapies. Nevertheless, controversy still exists about the relative risks of MSC injections. MSCs not cultured in an authorized good manufacturing practice facility using approved culture protocols may risk bacterial contamination, cellular transformation, and/or premature differentiation of cells.¹⁶ There have been no reported adverse events associated with MSC transformation,^{45,44} but there remains a theoretical concern that cells may differentiate/transform into unwanted cell types or become tumorigenic, especially over the long term. To date, there are no long-term safety problems following either allogeneic or autologous MSC use.

The recent identification of subtypes of MSCs that may demonstrate pro-inflammatory versus anti-inflammatory responses based on activation of toll-like receptors 4 and 3, respectively,⁶² is particularly relevant for choosing appropriate treatment strategies targeting inflammatory diseases.

SUMMARY OF ANIMAL MODELS USING MESENCHYMAL STEM CELLS IN THE TREATMENT OF OSTEOARTHRITIS

A full summary of animal models using MSCs to treat OA is provided in Appendix 1 (available at <http://sph.sagepub.com/content/suppl>). Knees of mice injected with adipose-derived

Table 1. Sources for mesenchymal stem cells

Tissue Type	Advantages	Disadvantages
Bone marrow ⁴⁵	<ul style="list-style-type: none"> • Good chondrogenic and osteogenic potential • Easy to harvest and exist in large numbers • High proliferative activity 	<ul style="list-style-type: none"> • Risks of harvesting, such as infection and pain
Synovium ⁴⁵	<ul style="list-style-type: none"> • Best chondrogenic potential • High proliferative activity 	<ul style="list-style-type: none"> • Poor osteogenic potential • Only preclinical studies available
Adipose tissue ⁴⁵	<ul style="list-style-type: none"> • Easily harvested • Available in large numbers 	<ul style="list-style-type: none"> • Lower chondrogenic potential, but may be improved through the use of growth factors
Umbilical cord ⁶³	<ul style="list-style-type: none"> • No morbidity with collection • Large capacity for ex vivo expansion • Full potential to differentiate into chondrogenic, adipogenic, and osteogenic lineages 	<ul style="list-style-type: none"> • Allogenic source • Less well studied

MSCs with collagenase-induced OA were protected against synovial thickening, formation of enthesophytes, and cartilage destruction when compared with the control group.⁵² However, knees injected on post-OA day 14 did not show the same protective effect, suggesting that early intervention is important in mitigating OA progression.

Diekman et al¹³ used a closed tibial plateau fracture model to induce posttraumatic arthritis (PTA) in the knees of C57BL/6 mice. A single intra-articular injection of MSCs at the time of fracture prevented the development of PTA. Control mice showed evidence of PTA 8 weeks after the induced fracture. An increase in the cytokine levels of the MSC-treated mice included elevated systemic IL-10 levels, suggesting an anti-inflammatory effect from MSC injections. However, the immune mechanisms of murine and human MSCs differ, and clinical applications in humans may result in different outcomes.

A hemimiscectomy model in 12-week-old rats was used to evaluate single, intra-articular injections of rat- (rMSCs) and human-derived MSCs (hMSCs).¹⁹ At 2 and 4 weeks, there was regeneration of the meniscus in a similar manner with both rMSCs and hMSCs. At 8 weeks, hMSCs appeared to inhibit osteoarthritis progression compared with controls.

In a second study, hMSCs were injected into 7-month-old guinea pigs with spontaneous knee arthritis that occurs naturally as early as 3 months of age.⁴⁶ This study had 4 groups: a control group with phosphate-buffered saline (PBS), a control group with HA injection, a PBS + hMSC group, and an HA + hMSC group. Single injections of HA + hMSCs resulted in significantly lower OA scores and partial cartilage repair. These changes were found neither in the control groups injected with PBS or HA only nor in the group injected with PBS + hMSCs.

The potential benefits of MSCs in the treatment of OA were shown using a model of induced subchondral defects in the knees of adult white New Zealand rabbits.⁵⁹ Bone marrow- or periosteum-derived MSCs injected into the knees showed an

improvement in the macroscopic appearance and histologic scores (with hyaline-like cartilage) compared with control knees.

Adipose-derived stem cells injected into the medial compartment of rabbit anterior cruciate ligament (ACL)-transected knees showed improved radiologic and histologic scores compared with controls.⁵⁴

Goat knees injected with MSCs 6 weeks after complete excision of the medial meniscus and resection of the ACL demonstrated marked regeneration of the medial meniscus and less cartilage damage when compared with control knees.³⁶

Sheep knees were injected 6 weeks post-ACL transection with either a control (basal media without cells), chondrogenic media-induced bone marrow MSCs, or basal media-induced bone marrow MSCs.¹ Chondrogenic media-induced bone marrow MSCs resulted in better repair of cartilage lesions as well as repair of some of the meniscal lesions with meniscus-like tissue. This suggests that predifferentiation might be an effective strategy compared with the use of undifferentiated MSCs.

Intra-articular injections 14 days after surgery of an adipose-derived stromal vascular fraction and bone marrow-derived MSCs were compared with controls for the treatment of knee OA induced arthroscopically in horses (placebo, adipose-derived stromal vascular fraction, and bone marrow-derived MSCs).¹⁷ There were no significant treatment effects in pain scores, radiographic evaluations, or histologic examinations. The only significant beneficial effect was a decrease in the PGE2 levels in the synovial fluid of bone marrow-MSC horses on day 35.

In summary, most animal studies are based on histologic evidence rather than functional evaluation, making preclinical work difficult to translate to symptomatic OA patients. Results may vary with severity of the model/injury, timing, type of MSCs, culture method, or dose.

CLINICAL STUDIES IN HUMANS USING MESENCHYMAL STEM CELLS IN THE TREATMENT OF OSTEOARTHRITIS

A full summary of clinical studies using MSCs in the treatment of OA in humans is provided in Appendix 2 (available at <http://sph.sagepub.com/content/suppl>). Regeneration of extensive unicompartmental articular cartilage defects in OA knees was promoted by the implantation of autologous MSCs in 12 patients compared with a cell-free control group.⁶⁰ There was improvement in the histologic and arthroscopic scores as well as clinical outcome scores in the treatment group, but no significant difference between the clinical outcome scores.

Bone marrow-derived MSCs were evaluated in 6 female patients with radiographic and magnetic resonance imaging (MRI) evidence of Kellgren-Lawrence grade IV knee OA.¹⁰ Patients were injected with bone marrow-MSCs that were cultured for 7 days. At 1-year follow-up, there were no local or systemic adverse events. Patients all had statistically significant improvements in their visual analog scale (VAS) and Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scores, improved function (increased range of motion, increased walking distance to pain, and decreased patellar crepitus), and MRI evidence of increased cartilage repair, extension of repair tissue, and decreased subchondral edema.

A pilot study in 4 patients with moderate to severe knee OA who received bone marrow-MSC injections and were followed for 6 months were found to have improvements in walking time for onset of pain, stair climbing, knee crepitus, and swelling.¹² There were no adverse events noted. There were no radiographic changes noted on postinjection knee radiography.

Emadedin et al¹⁴ evaluated the use of bone marrow-MSCs in 6 female patients with radiographic and MRI evidence of Kellgren-Lawrence grade IV knee OA. At 1-year follow-up, there were no local or systemic adverse events. The patients all had improvements in their VAS and WOMAC pain scores, improved function (increased range of motion, increased walking distance to pain, and decreased patellar crepitus), and MRI evidence of increased cartilage repair, extension of repair tissue, and decreased subchondral edema.

Pain scores improved following the injection of infrapatellar fat pad derived-MSCs into knees following arthroscopic procedures.^{27,28} The improvements correlated with the number of MSCs injected. Both studies suggested a better response in knees affected by International Cartilage Repair Society grade 3 OA compared with grade 4 OA.^{27,28} The first study reported no significant adverse events associated with the injections, although some patients reported a slight increase in their knee pain for 2 to 3 days postinjection.²⁷

Eighty to 90 mL of bone marrow was extracted from the iliac bone in an ambulatory setting from 12 patients with knee OA using local anesthesia and slight sedation.³⁹ After a mean cell expansion period of approximately 3 weeks, the MSC concentrate was injected into the affected knee and the patients were followed for a minimum of 1 year. Patients tolerated the

procedures well (both bone marrow aspiration and knee injection), and there was a statistically significant improvement in pain scores and function, measured by VAS and WOMAC scores, at 12-month follow-up.

CARTISTEM (MEDIPOST, Seoul, Korea) is the only commercially available MSC product for OA using allogeneic, umbilical cord blood as the cell source. CARTISTEM is approved in Korea and is undergoing US FDA investigational new drug cleared phase I/IIa clinical trials in the United States for the treatment of cartilage defects in combination with an HA scaffold.

FURTHER AREAS OF INVESTIGATION

Despite recent advancements, the use of MSCs for the treatment of OA needs to be better defined. Barry and Murphy² list 13 ongoing studies investigating the use of MSCs in knee, hip, or ankle OA in humans. However, there are several important hurdles that must be addressed before reliable conclusions from the body of literature regarding the role of MSCs in the treatment of knee OA can be drawn:

- (1) Is the role of MSCs predominantly symptom management or as a disease-modifying osteoarthritis drug? Human studies have shown that intra-articular injections of MSCs improve pain and function scores in knee OA.^{10,27,28,39,60} However, there is very little evidence to support MSCs having a disease-modifying effect.
- (2) The optimal method of MSC administration remains unknown. Specific studies have not compared MSC injections in suspension versus scaffold media.^{2,46}
- (3) The optimal dose, frequency, timing, and number of injections remains unclear (see Appendix 1). There is a distinct lack of homogeneity among animal studies investigating the use of MSCs in the treatment of OA. Although animal and clinical studies have suggested dose ranges anywhere from 1×10^6 to 4×10^7 cells per injection, there is no clear indication of what the initial dose should be.
- (4) The optimal source of MSCs (bone marrow, adipose tissue, synovium, umbilical cord blood/tissue) is yet to be identified.⁴⁵ The majority of clinical studies use bone marrow- or adipose-derived MSCs.
- (5) There is a need for clinical imaging studies to determine where the MSCs end up after injection.
- (6) Knee OA may be associated with malalignment, specifically varus and valgus knee deformities. It is possible that patients who also have a mechanical axis deformity in addition to OA would benefit from a concurrent procedure to correct the deformity in addition to treatment with MSCs. Other mechanical factors to consider include the stability of the knee as well as the integrity of the meniscus. Certainly, the health of the surrounding musculotendinous structures also contributes to the structure and function of the knee joint.

CONCLUSION

Mesenchymal stem cells are an exciting and relatively novel treatment for osteoarthritis. MSCs may improve symptoms and function in osteoarthritic joints but also decrease inflammation and induce cartilage healing. This is likely related to the secretion of cytokines, chemokines, and growth factors from MSCs.

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