Review Article

A narrative review of mesenchymal stem cells effect on osteoarthritis

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Objective: To describe and discuss the purposed mechanism of mesenchymal stem cells (MSCs) and their effect as a potential therapeutic in osteoarthritis (OA).

Background: OA is a chronic, degenerative joint disease affecting millions worldwide. Traditional management, including physical therapy, anti-inflammatories, intra-articular injections, and surgical procedures are directed towards symptom control rather than disease modification. In light of a better understanding that low-grade inflammation disrupts articular cartilage homeostasis in OA, application of MSCs as a form of regenerative medicine has emerged with the goal to provide symptomatic relief as well as reverse the articular cartilage damage seen in OA.

Methods: PubMed was searched using terms 'osteoarthritis', 'mesenchymal stem cell', 'regenerative medicine', 'chondrocyte', and 'articular cartilage' available from 2006 through May 2021.

Conclusions: The use of MSC therapy for articular cartilage regeneration through direct tissue growth, differentiation, and inflammation modulations for the treatment of OA is promising. MSCs migrate to injured sites, inhibit pro-inflammatory pathways, and promote tissue repair by releasing paracrine signals and differentiating into specialized chondrocytes. Multiple clinical trials have displayed a significant improvement in both pain and joint function, inflammatory cell reduction within a joint, and articular cartilage growth as well as patient safety. However, high quality evidence supporting the beneficial role of MSCs is lacking due to the limited number of studies, small populations tested, and the use of various derivatives. Although limited, current evidence suggests MSCs are a potential therapeutic in OA and provides a great foundation for further research.

Keywords: Mesenchymal stem cell (MSC); osteoarthritis (OA); regeneration; chondrocyte; articular cartilage

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Introduction

Osteoarthritis (OA) is a chronic, debilitating joint disease. It is the most common form of arthritis and one of the leading causes of disability affecting more than 27 million people in the United States (1), and 303 million people across the globe (2). OA primarily manifests in weight-bearing joints such as the knees and hips, but is not limited to finger interphalangeal joints, thumb bases, first metatarsophalangeal joints, and apophyseal joints of the lower cervical and lower lumbar spine (3). The most

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important risk factors for the development of OA include age, obesity, joint trauma, gender, genetics, metabolic/endocrine diseases such as diabetes and crystal deposition disorders including gout (4). Patients commonly experience pain, stiffness, and locomotor restrictions within the joint as well as additional symptoms including coarse crepitus, bony enlargements, and joint-line tenderness (3).

Over the years the concept that OA was merely a "wear-and-tear", mechanically-driven, focal musculoskeletal disorder that could only be managed by joint replacement has been reconstructed to now a low-grade inflammatory disease (5). It's contended that inflammation leads to an alteration in articular cartilage homeostasis which promotes the progression of cartilage and bone destruction seen in OA (5). However, the pathophysiology of OA is complex and the exact role of inflammation is not well-understood (1). The combination of inflammation and abnormal mechanical load disrupts the balance between anabolic and catabolic activities in the joint and as a result, identifies their role as important contributors to the onset and progression of OA (4). The inflammation seen in OA differs from typical inflammatory arthritis (rheumatoid arthritis) because it is chronic, low-grade, and involves mainly the innate immune mechanisms (1). Synovitis is a common finding in OA and the synovial fluid in an OA joint has shown to contain multiple inflammatory mediators that induce matrix metalloproteinase and other hydrolytic enzymes to breakdown articular cartilage (1).

Mild cases of OA are managed with a combination of non-pharmacotherapy (physical therapy and weight loss) and pharmacologic agents to reduce pain and inflammation, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) (4,6). Light-to-moderate physical activity provides multiple benefits in addition to improving joint mechanics and function by including a risk reduction of diabetes, cardiovascular events, falls, disability, while promoting weight reduction, and improvement in mood and self-efficacy as well as overall quality of life (1). NSAIDs provide symptomatic relief, however, are not disease-modifying agents and thus, do not alter disease progression (4). Furthermore, OA is a chronic disease necessitating the use of long-term pharmacotherapy and their potential side effects overtime such as acute liver failure, gastrointestinal, renal, and cardiovascular toxicity (4,6).

As the disease progresses, intra-articular injections with corticosteroids may be administered with ongoing physical therapy (1). Intra-articular injections with corticosteroids have been widely used for decades as a local anti-inflammatory and thought to counteract the inflammatory process in OA (7), yet the current evidence regarding the exact mechanism of action, analgesia efficacy, indications, and safety profile are still ongoing (1). Despite speculation of early pain relief, the effects are not long lasting and adverse reactions do occur including transient post-injection flare-ups of pain within 2–25% of patients (7). Furthermore, corticosteroids may enhance the progression of OA following a randomized double-blind clinical trial that identified repeat intra-articular injections with triamcinolone over two years for knee OA was associated with greater cartilage volume loss when compared with intra-articular saline injections (2,7). Additional side effects include hypertension, hyperglycemia, alternations in mood and energy, and less commonly skin depigmentation, fat necrosis, and cutaneous atrophy (7). Lastly, intra-articular corticosteroid injections before a total knee arthroplasty (TKA) might increase the risk of postoperative infection (7).

Alternatives to intra-articular corticosteroids include the use of hyaluronic acid or platelet-rich plasma (PRP). Concentrations of hyaluronic acid, a natural glycosaminoglycan that provides a viscous lubrication and shock absorbing properties with possible anti-inflammatory functions within the synovial fluid, is decreased in OA (1). Therefore, in order to restore the benefits of hyaluronic acid, the viscosupplement is injected intra-articular (1). Unfortunately, the beneficial evidence is conflicting as some studies demonstrated improvements, while others did not (7). Three studies compared the use of hyaluronic acid injections to oral NSAIDs and found no significant difference, however, when compared to corticosteroid injections, hyaluronic acid injections demonstrated better long-term pain relief up to 26 weeks (7). Additionally, a 2018 systemic review examined recurrent hyaluronic acid injections over 25 months and found the most common side effects to be joint swelling and arthralgia, indicating that repeat injections appear to be safe (7).

PRP is the uses of autologous plasma to activate platelets to release a number of growth factors and together with coagulation factors, cytokines and other platelet proteins to reduced inflammatory effects involved in the process of OA (7). PRP injections are shown to provide pain relief approximately 2 months after injection and may last as long as 12 months (7). When comparing PRP to hyaluronic acid injections, multiple meta-analyses and systemic reviews have demonstrated PRP injections are clinically superior in pain reduction, especially in younger patients with early OA (7). This promising intervention lacks robust

Table 1 Source used for narrative review

PubMed search 2006–May 2021
Key words: osteoarthritis; mesenchymal stem cell; regenerative medicine; chondrocyte; articular cartilage

evidence to support its clinical use, standardization in methods of RPR preparation, dosages and frequency (2) as well as not covered by insurance plans (7). Although some patients experience temporary relief with intra-articular corticosteroid, hyaluronic acid or PRP injections, the efficacy of these interventions are not uniform (6,7).

Despite the use of pharmacotherapy interventions, refractory and advanced cases of OA are managed with surgical techniques (6). Arthroscopic debridement of debris and inflammatory cytokines from the rough cartilage, repair of damaged cartilage, bone marrow stimulation to promote chondrogenesis of pluripotent stems cells from subchondral bone marrow in the defected areas, abrasion or drilling of the subchondral bone plate to allow migration of cells and chemical mediators into the defect, total joint arthroplasty, and osteochondral grafting are all possible interventions (6). Arthroplasty is the definitive management of OA (7) and the most widely used orthopedic technique to relieve pain, increase mobility, and improve function (6). Despite a good outcome for many patients, approximately 20% of patients experience chronic pain after TKA (8). A systemic review of prospective studies of patients undergoing total hip or TKA reported unfavorable long-term pain outcomes ranging from 7% to 23% after hip and 10% to 30% after knee replacements (9). Additionally, each arthroplasty carries the risk of postoperative infections, revisions, and chronic pain (7). A 20-year life time risk of a revision was estimated in 2017 based on the data from primary care medical records from the UK collected in the Clinical Practice Research Datalink (2).

Traditional management of OA has been targeted towards pain and symptom control rather than disease modification. Understanding the pathophysiology of OA is considered both inflammatory and degenerative, applications of cell-based therapies as a form of regenerative medicine has emerged with the goal to reverse the damages of OA and relieve pain (7). These therapies include autologous chondrocyte transplant, microfracture, mosaicplasty, as well as mesenchymal stem cell (MSC) scaffold transplant and injections.

This narrative review was conducted to examine the purposed mechanism of MSCs and their effect as a potential therapeutic in OA during this growing climate of clinical trials by focusing on the characterization of MSCs, the various functional roles MSCs have on reducing inflammation as well as stimulating local repair and regeneration of damaged articular cartilage by paracrine signals and differentiation, and discussing MSC based clinical trials for the management of OA. We present the following article in accordance with the Narrative Review reporting checklist (available at https://aoj.amegroups.com/article/view/10.21037/aoj-21-16/rc).

Methods

PubMed was searched using terms 'osteoarthritis', 'mesenchymal stem cell', 'regenerative medicine', 'chondrocyte', and 'articular cartilage' available from 2006 through May 2021 (*Table 1*). However, this was not a systematic review and does not comprehensively cover all published literature on this topic.

Articular cartilage

OA in an inflammatory and biomechanical whole-organ disease affecting the joint capsule, synovium, subchondral bone, ligaments, and peri-articular muscles, however, in the context of aging, injury, and disease the articular cartilage receives the most attention (10). Articular cartilage is a highly specialized connective tissue of diarthrodial joints that functions to provide a smooth, lubricated surface for articulation and a frictionless transmission of mechanical load to the underlying subchondral bone (10). Although subject to harsh biomechanical stress, articular cartilage lack blood vessels, lymphatics, and nerves resulting in the dependence of synovial fluid diffusion to provide nutrition and cellular repair components (11). Articular cartilage is hyaline cartilage which is composed of a dense extracellular matrix (ECM) with sparse distribution of highly specialized cells called chondrocytes, forming chondrons together with the pericellular matrix (11). The ECM is composed of water as well as a framework of collagen fibers, specifically type II, and proteoglycans which provides tensile strength and osmotic resistance to withstand compressive loads,

respectively (11).

Originating from MSCs, chondrocytes are highly specialized, metabolically active cells that provide a role in the development, maintenance, and repair of the ECM (12). Embedded with the ECM, chondrocytes synthesize components of the matrix, including proteoglycans, and helps to balance cartilage homeostasis by replacing degenerative molecules with newly synthesized products (12). Cartilage hemostasis is an intricate interplay between anabolic and catabolic, anti- and pro-inflammatory, and anti- and pro-apoptotic activities (11). Synthesis and degradation of the ECM must be fine-tuned so that any damages to the articular cartilage and loss of its ECM is followed by chondrocytes secreting new ECM to repair the damage (13). An important stimulator of matrix synthesis and chondrocyte regulation is mechanical load, however, by increasing the magnitude of a load, such as in obesity, a pathological response including chondrocyte apoptosis and necrosis or altered physiological responses will occur resulting in the disruption of homeostasis and progression towards OA (14).

Age, a major risk for OA, is a critical determinate of ECM composition and chondrocyte organization as well as their response to external factors such as cytokines (13). With increasing age, the articular cartilage has a resulting increase in compressive stiffness due to the loss of ECM hydration (13). Large forces are now displaced to the underlying subchondral bone leading to consolidation of trabeculae and subchondral sclerosis noted on imaging techniques of OA joints (12). Chronic, low-grade inflammation has been associated with aging, a process often referred to as "inflammaging", due to the systemic release of interleukin (IL) 6 which may promote the effects of articular damage, however the exact mechanism is not understood (15). Additionally, chondrocyte senescence occurs as a result of prolonged cellular damage and upregulation of cell cycle inhibitors as well as the release of strong growth signals in the context of cartilage destruction and potentially damaging stimuli (15). Furthermore, aging processes including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, dysregulated nutrient sensing, mitochondrial dysfunction, altered intercellular communication, and elevated levels of reactive oxygen species may contribute to articular damage and progression of OA (15).

The structural and functional composition of articular cartilage creates challenging obstacles to overcome when considering therapeutic managements for damaged tissue. Due to the lack of innervation, initial stages of cartilage destruction are often unnoticed until significant structural damage has occurred (16). Additionally, the combination of the avascular nature and dense packing of ECM, hinders the transport of drug molecules to the tissue (16). However, understanding the mechanism of maintaining cartilage homeostasis plays a pivotal role in developing regenerative techniques to restore structural changes seen in OA.

MSCs characteristics, functions, and source

MSCs are a heterogenous population of hematopoietic and non-hematopoietic stem cells that possess distinctive characteristics and carry out a number of functions throughout the human body (17). These functions include tissue repair and regeneration, anti-inflammatory effects, anti-apoptotic activity, and immunomodulating as well as neo-angiogenesis, activating resident stem cells, and antimicrobial effects (17). Cells meeting the criteria for a MSC, as defined by The International Society for Cell Therapy, must be plastic-adherent when maintained in standard culture conditions, more than 95% of the cell population must express CD105, CD73 and CD90 whereas lack expression (<2% positive) of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules, and must be able to differentiate into osteoblasts, adipocytes and chondrocytes *in vitro* (18).

MSCs are found throughout the adult body, which softens the ethical concerns of using embryonic stem cells (19). Several different tissue sources have been explored including bone marrow, adipose tissue, synovial fluid, dental tissue, skin and foreskin, salivary glands and perinatal tissues, however the best source remains unclear (20). Traditionally, the bone marrow has been the source of MSCs, but studies have shown human adipose tissue yields a larger number of MSCs and eases the harvest (19,20). Human umbilical cord perivascular cells (Wharton's Jelly) are a rich source of MSCs, are closer to an embryonic cell lineage, and show increase differentiation capacity (19). Therefore, the chosen source of MSCs is dependent on the ease of harvest and the differentiation capacity towards a given tissue (19).

Although standardized procedures for harvesting MSCs is lacking, the two general methods for cell isolation and culture include explant and enzymatic digestion (20). Initial steps in both methods begin with retrieval of donor tissue, followed by rinsing and mechanically cutting the sample into smaller, a few millimeter, lengths (20). From there, explant samples are placed into plastic culture

plates with growth medium whereas enzymatic producers include an additional step that degrades the ECM within an enzyme solution that releases single cells or small cellular aggregates from the tissue before placed onto a growth medium (20). However, MSCs from bone marrow, peripheral blood, and synovial fluid are isolated using a modified Ficoll density gradient method with seeding onto mediums (20,21). Once isolated, MSC expansion relies on culture media, specifically Dulbecco's modified Eagle's media, supplementation with fetal bovine serum (FBS), and oxygen concentrations (21).

Safety and regulatory concerns are a critical focus during MSC expansion. Culturing MSCs for a longer period of time has been associated with malignant transformations and a decline in their multipotency (21). Additionally, although FBS contains high concentrations of cell growth factors as well as nutritional and chemical compounds required for cell maintenance, FBS poses a great safety risk for pathogen contamination and immunizing effects (20). In order to maintain safety and regulatory concerns, expansion cultures have trended towards human serum, platelet lysate, and cord blood serum instead of FBS, while still maintaining a higher proliferation capacity of MSCs (20).

Furthermore, the risk of alloreactivity, commonly seen is transplant rejections or graft-versus-host disease is markedly diminished with the use of MSCs due to the expression of low levels of MHC class I and lack of MHC class 2 expression as well as co-stimulatory molecules like CD80, CD40, and CD86 (21).

The effects of MSCs on articular cartilage in OA

Articular cartilage originally develops from embryonic MSCs that differentiate along the chondrogenic lineage before producing cartilage. Lacking the ability to intrinsically regenerate after sustaining injury seen OA, the use of MSCs as a potential repair strategy for articular cartilage damage is now being investigated. The ability for MSCs to migrate to a site of injury, inhibit pro-inflammatory pathways and promote tissue repair through the release of anabolic cytokines and direct differentiation into specialized connective tissue, poses a new focus in the area of regenerative medicine and management of OA (19).

An important function performed by MSCs is their ability to migrate to a site of injury, regenerate damaged tissue as well as prevent programmed cell death. MSC migration and homing to the injured site is largely regulated by multiple chemical factors, such as chemokines, cytokines, and growth factors, in addition to mechanical factors including mechanical strain, shear stress, matrix stiffness, and microgravity environments (spaceflight) (22). At the site of injury MSCs secrete various paracrine factors, collectively named secretome, to modulate the microenvironment of damaged tissue for more favorable conditions for tissue regeneration (23). In fact, the secreted paracrine chemokines, cytokines, and growth factors has recently received more credit in tissue regeneration than direct MSC differentiation (22). When repairing cartilage, MSCs begin with the release of cytokines, followed by chondrogenic proliferation and secretion of ECM proteases as well as growth factors like transforming growth factor beta-1 (TGF-β1), insulin-like growth factor-1 (IGF-1), and fibroblast growth factor (FGF) (23). In addition to local paracrine effects, regenerative studies show paracrine factors enclosed in extracellular vesicles released by MSCs are able to transfer their content across greater distances to improve organ dysfunctions (22).

Another important function performed by MSCs is their ability to rescue cells from apoptosis induced by trauma, oxidative environments, radiation and chemical injury (24). Current evidence suggests chondrocytes undergo apoptosis in OA. MSCs are able to synthesis and secrete proteins that are classic inhibitors of apoptosis, such as B-cell lymphoma 2 (Bcl-2), survivin, and akt (25). Additionally, MSCs have the ability to secrete cytokines that either neutralize the process of cell death or promote survival, such as vascular endothelial growth factor (VEGF) (25).

Apart from paracrine factors, the ability for MSCs to differentiate into cartilage producing cells provides another mechanism to repair damaged tissues. In a developing limb, members of the transforming growth factor beta (TGF-β) superfamily play a major role in facilitating growth as well as synthesis of ECM components of articular cartilage (26). Accordingly, TGF-β1, TGF-β2, TGF-β3 are usually used to stimulate MSC differentiation along the path of chondrogenesis (26). Additional growths factors alongside TGF-β have shown synergistic effects including IGF-1, FGF-2, bone morphogenic protein 6 (BMP-6), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF) as well as additional non-protein compounds such as dexamethasone and ascorbic acid (26). However, MSCs extracted from various sources throughout the body have been shown to respond to different combinations of growth factors for chondrogenesis induction (27).

While MSCs have shown the ability to progress down the chondrogenic lineage with the aid of growth factors,

chondrocytes derived from MSCs frequently undergo hypertrophy when differentiating, as evident by the productions of type X collagen, matrix metalloproteinase 13 (MMP13), and alkaline phosphatase (ALP), VEGF, and hormone-related protein receptor (28). The associated hypertrophy potentially limits their application in articular cartilage regeneration as it could ultimately lead to apoptosis and ossification (28). Although providing a challenge to overcome, current evidence suggests preventive interventions by addressing various growth factors and transduction signals as well as environment with biomechanical stimuli, oxygen depletion, and co-culture with articular chondrocytes (29). Additionally, the source of MSCs was found to play a role as synovium-derived stem cells displayed limited potential toward hypertrophy when compared to MSCs from adipose, bone marrow, and muscle (29).

The contribution of inflammation towards articular cartilage injury is not well understood, however, evidence of acute-phase response signaling pathway, complement pathway, and coagulation pathway within the synovial fluid have been reported (24). MSCs interact with all aspects of the immune system including the innate and adaptive lymphocytic populations as well as the differentiation, expansion, and function of myeloid cells towards more immunosuppressive and immunomodulatory properties (30). Modulation of CD4 T lymphocytes has been the main focus, demonstrating that MSCs inhibit the proliferation and differentiation of naïve T lymphocytes towards specialized T cells which beneficially increases the pool of T regulatory (Treg) cells (30) and secretion of interleukin-10 by macrophages (24). The main mediators of this effect are the continuous secretion of prostaglandin-E2 (PGE2) and TGF-β1 by MSCs (30). Additionally, MSCs suppress cytotoxic CD8 T cell activity as well as interfere with B cell maturation and antibody production (30).

Multiple studies suggest inflammation in OA is primary under the control on innate inflammatory mechanism triggered by pattern-recognition receptor (PRR) signaling, specifically toll-like receptor 3 (TLR-3) and TLR-4 (31). Additionally, macrophages are abundantly found within the synovium of OA joints to remove fragments of degenerative cartilage and induce further inflammatory signals (32). However, MSCs effect macrophage maturation, migration, polarization and function by the release of factors disrupting their immune response and mediate tissue repair by shifting macrophages from inflammatory M1 phenotype to anti-inflammatory M2 phenotype (31). Furthermore, MSCs disrupts upregulation and presentation of antigens by dendritic cells as well as attenuate neutrophil-mediate tissue damage by modulating neutrophil migration, infiltration, and activation (31). Thus, MSCs provide efficient mechanisms to control inflammation in the joint.

Clinical applications of MSCs in OA management

A large focus has been directed towards MSCs for the management of OA due to their multiple mechanisms of action. MSCs have been tested in multiple, small-phase trials showing their effectiveness in alleviating pain and symptoms seen in OA as well as reporting improvement in cartilage morphology in some cases (33). The best source of MSCs, whether from bone marrow or adipose tissue for the treatment of OA is largely up to debate when considering cell preparation procedures and harvest, differentiation potential, and durability (34). A systematic review covering sixty-one articles, twenty-nine adipose-derived MSCs and thirty bone marrow-derived MSCs, treating 2,390 patients found no consensus as to which MSC type is most effective at treating OA (35). Bone marrow-derived MSCs have shown greater chondrogenic potential (34,36), whereas adipose-derived MSCs have shown to reduce chondrocyte hypertrophy and decreased the development and progression of OA (36). A study compared the outcomes and differentiation potentials of various derived MSCs and found that all types of MSCs are effective therapeutics for OA management, however, more information regarding long term efficacy, dosing, and specific characteristics are needed to better compare clinical outcomes (34).

Ensuring patient safety and assessing exposure to long term risks is the most important factor when introducing new therapeutic treatments. A meta-analysis of eleven clinical trials covering 582 patients with knee OA evaluated the therapeutic efficacy and safety of MSC therapy and reported no serious adverse reactions related to MSC implantation (37). Additionally, concern over MSCs potential transformation into cancerous cells have been reported due to their chromosomal abnormalities (38). In light of this potential risk, Pak *et al*. tracked 91 patients over a year and reported no tumor formation following adipose-derived MSCs with PRP injections, however, swelling at the injection site was common as well as self-limiting tenosinovitis and tendonitis in the elderly (38). Likewise, Centeno *et al*. followed 339 patients between 2006 and 2010 after receiving initial and re-implantation of bone marrow-derived MSCs with platelet lysate and found no neoplastic complications related to MSCs at any stem cell

re-implantation site (39). Similarly, nearly all clinical trials have reported no significant reactions related to MSCs.

Pain is the main reason patients with OA seeks medical treatment. Recent clinical trials with either bone marrow or adipose-derived MSCs have shown a decrease in pain and corresponding increase is joint function (19). A small pilot study by Orozco *et al*. tested the effects of bone marrow-derived MSCs in 12 patients with chronic, OA knee pain unresponsive to conservative treatments and found a 65%, 69%, and 78% improvement in pain from baseline by one year, as assessed by Lequesne index, Visual Analogue Scale (VAS), and Western Onterario and McMaster Universities Osteoarthritis (WOMAC) index, respectively (40). Likewise, a meta-analysis including eleven trials with 582 knee OA patients reported a signification decrease in Lequesne, VAS, and WOMAC pain indices after MSC transplantation (37). In addition to investigating the safety risks, Centeno reported that of the 69% of the patient cohort requiring TKA, only 6.9% still required surgery after MSC therapy (39). Additionally, 63.2% of patients reported greater than 50% pain relief while 41.4% reported more than 75% pain relief at 11 months (39).

Low-grade inflammation, specifically the innate immune system plays a key role in OA development. Together with a significant improvement in pain and function, Chahal *et al*. noticed a significant drop in cartilage biomarkers and magnetic resonance imaging (MRI) synovitis as well as a decrease in pro-inflammatory macrophages and IL-12 within the synovial fluid following high dose bone marrow-derived MSC injections over a 12-month time course (33). They suggest evidence of chondroprotective effects as well as anti-inflammatory functions provided by MSCs, however, their research failed to show improvements in cartilage morphology (33).

A key component of MSCs are their regenerative properties and potential to differentiate. A small sample study using bone marrow-derived MSCs found not only improved joint function by normalizing Knee injury and Osteoarthritis Outcome Score (KOOS) but also cartilage thickness shown on MRI, indicating a structural regeneration (41). Additionally, a study by Jo *et al*. using adipose-derived MSCs noticed a significant decrease in the size of cartilage defects on MRI and further assessed the changes with both arthroscopy and biopsy before and 6 months after MSC injections (36). Arthroscopically, using International Cartilage Repair Society (ICRS) cartilage injury classification, they reported a significant reduction in the size of the cartilage defect in areas most severely degenerated initially. Histologically they saw articular cartilage in areas previously absent, thick and smooth matrix surface, and properly aligned collagen fibers and shape of chondrocytes. However, hyaline-like cartilage composed of type I collagen with minimal type II collagen was deposited and typical chondrocyte alignment was not displayed. Nonetheless, these studies revealed the potential effects MSCs have on cartilage repair in OA.

While studies support the notion that MSC therapy has a positive effect on OA, there is limited high quality evidence and long-term follow up (35). Emadedin *et al*. reported improvement in pain and function status up to 6 months, after which pain slightly increased and walking abilities decreased (42). The effects of MSCs seem to be limited, necessitating repeat injections (42), similar to conventional corticosteroids, hyaluronic acid, and PRP. Additionally, further information is needed regarding when to begin MSC therapy, or more specifically at which stage of the disease. Jo *et al*. reported tremendous cartilage growth in areas of severe degeneration, however, saw no or limited effects of MSCs in areas with preexisting articular cartilage (36). Various small clinical trials have been performed, establishing the beneficial effects MSCs have on OA, however each study uses different MSC derivatives and preparations limiting the potential to be reproduced. Moving forward, to carefully differentiate between MSC derivatives, like bone marrow and adipose tissue, and the longevity of MSC therapeutic on OA, a large well-designed randomized controlled trial with reproducible methodology is needed (35).

Conclusions

OA is a major global burden affecting millions of people worldwide. Current therapeutics are helpful in controlling the symptoms of OA, but lack disease modifications in addition to pharmacologic side effects and surgical expenses without a guarantee of symptom relief. Investigation into MSC therapy for articular cartilage regeneration through direct tissue growth, differentiation, and inflammation modulations for the treatment of OA is promising. Although shown to be safe, further information is needed regarding when to begin MSC therapy, standardization of MSC derivatives and preparations, the effects of symptom relief and regenerative properties, and treatment longevity. Given their many functional advantages and previous observed clinical effects, MSCs have great potential for the management of OA.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://aoj.amegroups.com/article/view/10.21037/aoj-21-16/rc

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://aoj.amegroups.com/article/view/10.21037/aoj-21-16/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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