

E-ISSN: 2378-654X

Recent Advances in Biology
and Medicine

Review Article

Osteoarthritis and
Mesenchymal Stem Cell
Therapy: An Overview

HATASO, USA

Osteoarthritis and Mesenchymal Stem Cell Therapy: An Overview

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Received: Jul 1, 2017; Accepted: Aug 14, 2017

Abstract

Osteoarthritis (OA) is the most common form of arthritis that affects cartilage joints and leads to disability. OA becomes the major public health problem, as it is the most leading cause of disability and morbidity worldwide. Treatment choices for OA can be classified into several categories such as non-pharmacologic, pharmacologic, surgical therapy, and cell-based therapy. There is no curative treatment for OA, while conventional treatments that are commonly used focus on alleviating the pain as the main symptom of the disease. Mesenchymal stem cells (MSCs) that can be found in several tissues of human body offer a new strategy for OA treatment owing to their ability to differentiate into chondrocytes. This article provides an overview about the basic concept of osteoarthritis as well as an insight about the MSCs therapy, including their basic characteristics, source, and transplantation strategies in the OA area.

Keywords: Osteoarthritis; Cartilage joint; Stem cells therapy; Mesenchymal stem cells.

1. INTRODUCTION

Osteoarthritis (OA) is a chronic disorder of synovial joints characterized by destruction of articular cartilage followed by formation of osteophytes at the joint surfaces and margins. It is not primarily an inflammatory disorder and not purely a degenerative disorder. OA is a dynamic phenomenon; softening and disintegration of cartilage is accompanied by the formation of new bone hyperactivity, osteophytes, and remodeling. It commonly affects load-bearing joints such as hips, knees, and spine [1, 2].

More than 27 million people in the US are affected by OA. Moreover, OA is a leading cause of pain and disability worldwide [3-6]. According to the Indonesian Basic Health Research (Riskesdas) in 2013, the prevalence of OA in Indonesia is approximately 24.7% in people with age more than 15 years old [7]. Although the exact cause is idiopathic, the risk factors of OA include obesity, senility or old age, emotional stress, female sex, osteoporosis, occupational stress, past trauma, and repetitive injuries [2, 8-10]. In addition, the genetic contribution to OA is supported by many studies, and it is believed that at least 30% of the risk of OA is genetically determined [5-6, 11-12].

The pathogenesis of OA is related to the biomechanical changes in the cartilage of the knee joint [10]. Mechanical stress and other risk factors affect chondrocytes metabolism and release metalloproteinase enzymes (proteolytic enzyme) that result in the depletion of proteoglycans matrix, which ultimately leads to the defect of the cartilage. Secondary damage to chondrocytes may cause release of cell enzymes and further matrix breakdown, as the cartilage becomes less stiff. In addition, cartilage deformation leads to tissue breakdown, because it may add stress on the collagen network. This puts enormous pressure on the underlying bone, which causes sclerosis and later eburnation, as articular cartilage has an important role in distributing the forces caused by joint loading. Cysts may develop in the subchondral area because of microfractures that degenerate. Moreover, new bone formation takes place and results in osteophyte formation [1, 2].

OA commonly affects the load-bearing joints, although it can affect any joints. It is often asymmetric: a patient may have severe knee OA with almost normal function of the opposite leg [8]. The most common presenting symptom is pain and stiffness that result in a restricted mobility and reduce the quality of life. However, each joint has its unique physical examination findings (Herbeden nodes and Bouchard nodes on hand OA, sensory and motor weakness on spine OA, or hallux vagus deformity on foot OA, etc.). Joint swelling may be the first symptom that is shown in peripheral joints (wrists, fingers, knees, and toes) that may be due to an effusion [1, 2, 8].

OA is typically assessed by anamnesis and physical examination. Radiology examination may be required in order to confirm diagnosis and rule out other differential diagnosis [13]. The cardinal signs of OA can be viewed in a plain X-ray, such as narrowing of the "joint space," subchondral sclerosis, marginal osteophytes, subchondral cysts, and bone remodeling [1]. Laboratory testing is not typically performed for diagnosis while markers of inflammation such as C-reactive protein level and erythrocyte sedimentation rate are typically normal [8].

There is no curative treatment that can slow or arrest the progressivity of OA. This review was conducted to provide an insight about mesenchymal stem cells (MSCs) for OA therapy as well as current conventional treatments for the disease.

2. MANAGEMENT OF OA

Treatment choice of OA comprises four main categories: non-pharmacologic, pharmacologic, surgical, and cell-based therapy. The treatment typically starts from the safest and least invasive considering the severity of the clinical features [8]. Stepped-care approach for OA treatment is recommended by the American and British specialty societies, as shown in Figure 3 [8, 14, 15].

2.1. Non-Pharmacologic Treatment

Non-pharmacologic therapy often starts with exercise and physiotherapy. Thomas *et al.* [16] found statistically significant reductions in knee pain at 6, 12, 18, and 24 months in a supervised home-based exercise patient (muscle strengthening and range-of-motion exercises) [16]. Current research also states that physiotherapy as an effective form of treatment to manage OA. A survey by Reid *et al.* [17] found that 86% patients who had received physiotherapy for their hip or knee OA believed that it is an important part of their management, with 80% reporting that it helped improve their condition with respect to the range of motion and strength [17]. A systematic review by Nelson *et al.* [3] stated that patients are advised to do low-impact aerobic exercise (land or water based), weightloss program for overweight patients, a range of motion and flexibility exercises, exercise in combination with manual therapy, endurance/strengthening exercises, and referral for physical/occupational therapy [3].

2.2. Pharmacologic Treatment

Pharmacologic treatments symptomatically treat and alleviate the pain associated with OA. Acetaminophen and NSAIDs are the drugs suggested for mild-to-moderate pain [18-20]. Acetaminophen is preferred as first-line therapy based on the side-effect

Figure 1: Cycle of articular cartilage deformation and collagen failure in OA [Solomon, 2010, p. 88].

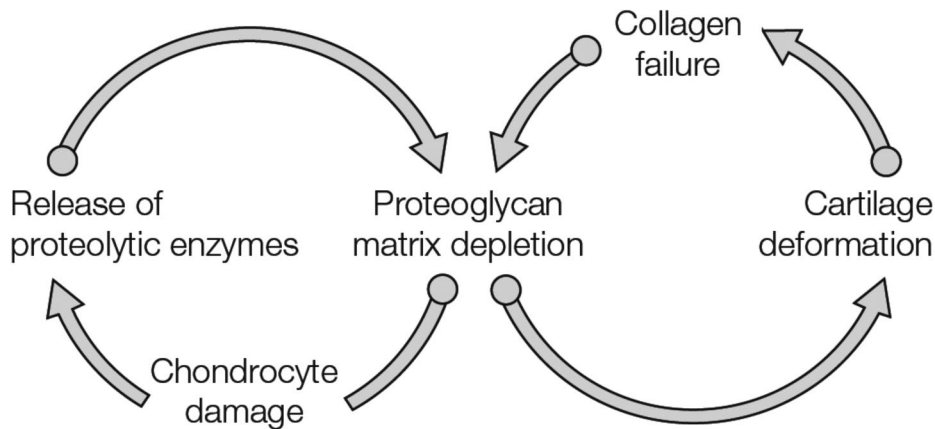


Figure 2: Radiograph of the knee in (a) anteroposterior view and (b) lateral view showing (1) joint space narrowing and (2) osteophyte formation. Radiograph of the hips (c) showing (1) joint space narrowing and (2) osteophyte formation [Sinusas, 2012, p. 50-51].

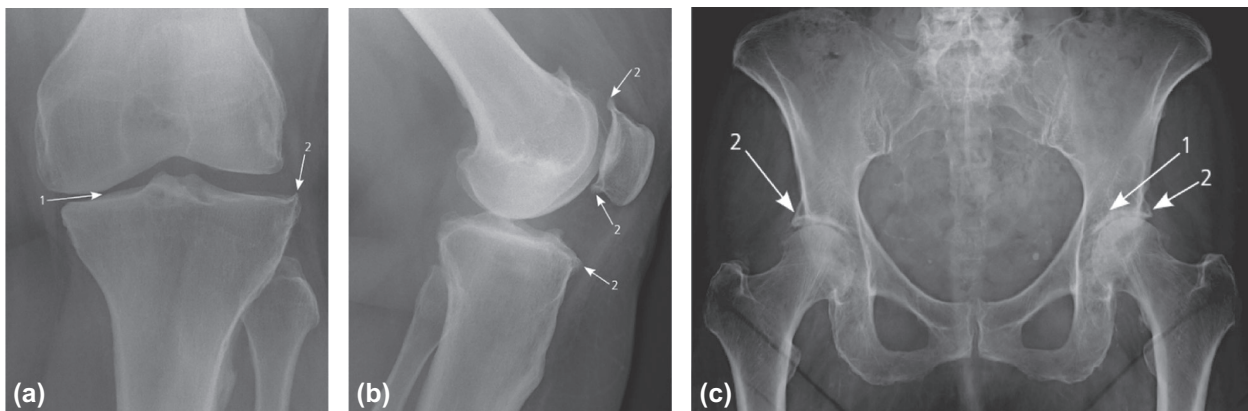
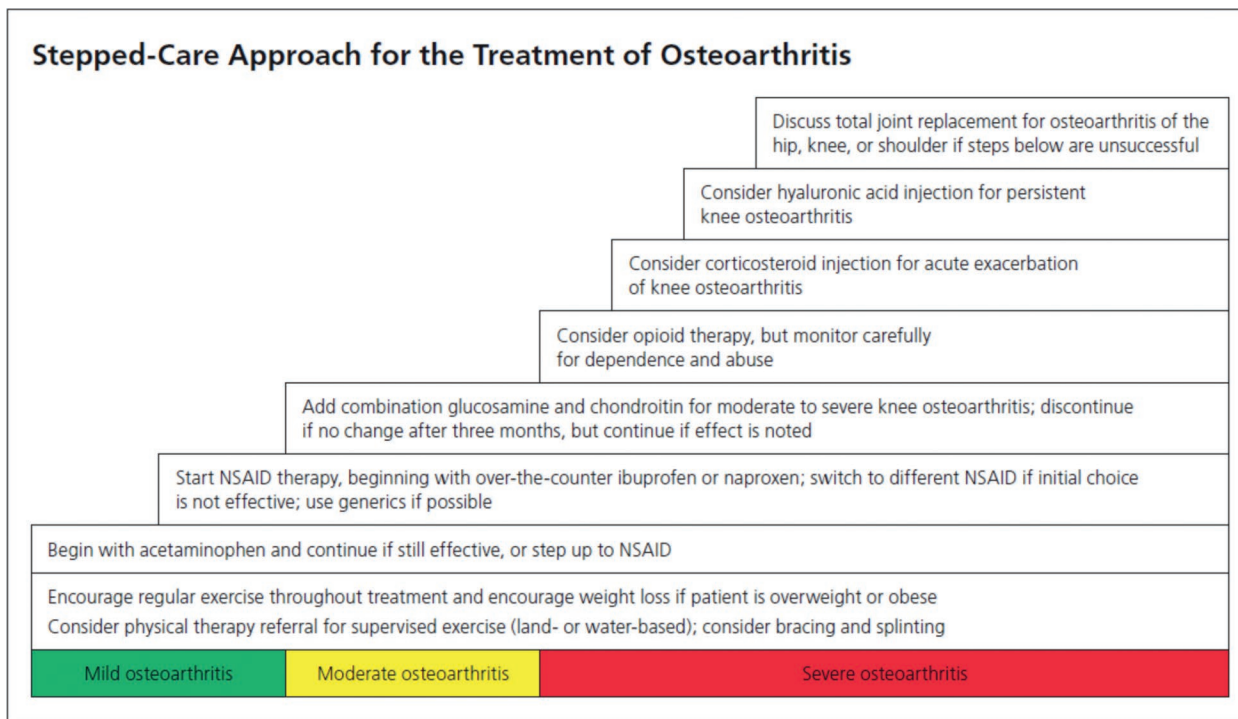


Figure 3: Recommended stepped-care approach for the treatment of OA (NSAID = nonsteroidal anti-inflammatory drug) [8, 14, 15].



profile of NSAIDs that can cause gastrointestinal (GI) discomfort and more importantly serious complications such as peptic ulcers, perforations, and bleeding [18, 21-23]. Opioid analgesics are the drugs suggested for severe OA, as it significantly reduces the intensity of the pain [18, 24].

Injection of viscosupplementation such as hyaluronic acid preparations into the knee and hip is widely used for treating OA with its ongoing controversy about the efficacy of the treatment, cost-effectiveness, and benefit-to-risk ratio. Hyaluronan helps in joint lubrication, buffers load transmission, and imparts anti-inflammatory properties to synovial fluid; however, the mechanism is still unknown [2]. Apart from injection of hyaluronic acid, corticosteroid intra-articular injection is commonly used for providing short-term relief from OA despite the unclear role of inflammation in the pathogenesis of OA [21-23].

2.3. Surgical Therapy

Surgical therapy is considered when the symptoms still persist despite the conservative treatment and result in complication and disability. Some surgical treatments that can be conducted for knee OA are arthroscopy, osteotomy, and knee arthroplasty. The indication of these procedures will depend on the site and severity of OA, patient characteristics, and the related risk factors. Total joint replacement procedure, which is commonly and successfully applied to the hip, knee, and shoulder joints, is the ultimate solution for OA. The range of the sites that can be treated is expanding in many other joints including the elbow, ankle, and at multiple locations in the hand. Despite these advanced techniques, some disadvantages still exist including the incompatibility of prosthetic joints with the functionality of a native joint, high cost for each procedure, and their invasive nature [8, 18, 25-27].

2.4. Cell-Based Therapy

Cell-based therapy has already been applied as an alternative method for OA treatment that comprises non-stem cell therapy and stem cell therapy. Cultured autologous chondrocyte implantation (ACI) is the first generation of non-stem cell therapy, which is widely applied to symptomatically treat the chondral and osteochondral defects of the knee [18, 28, 29].

The original ACI technique is ACI-P that involves a debrided chondral defect beneath a periosteal cover, under which a suspension of cultured chondrocytes is injected [29, 30]. Alternatively, a cover manufactured from porcine-derived type I/type III collagen (ACI-C) is used to produce a similar clinical outcome to ACI-P but with a lower incidence of hypertrophy of the graft. Both ACI-P and ACI-C have led to concerns about the unequal distribution of chondrocytes in the defect and the threat of cell leakage [29, 31]. Biodegradable scaffolds seeded with chondrocytes, named matrix-induced ACI (MACI), were developed in order to overcome that problem. This technique involves the attachment of cultured autologous chondrocytes into type I/III collagen scaffold [18, 29, 32].

In general, the success rate of ACI as a treatment option is approximately 76-86%. However, some problems, including de-differentiation of chondrocytes and their limitations to reach the location of cartilage damage, have emerged owing to this procedure. In addition, as the procedure uses cell culture, these therapies are invasive and relatively expensive. [18, 33-37].

3. MSCS CHARACTERISTICS

MSCs are multipotent stem cells that can differentiate toward mesodermal lineage, including osteoblasts, chondrocytes, and adipocytes [38-44]. The aim in using stem cells is to support the self-healing process of the knee joint cartilage that results in relief from OA symptoms [10]. MSCs have become a candidate to treat OA because of their availability in several tissues including the fluid inside the joint, capability to differentiate into chondrocytes, capacity to culture and expand *ex vivo*, ability for a faster proliferation, and capability to maintain their phenotype at a higher level during the proliferation process. In addition, MSCs are able to improve the lesions restricted to articular cartilage and more complex osteochondral lesions as well as tendons or ligaments, as they can specialize to all tissues within the joint while chondrocytes are terminally differentiated [10, 45-48]. MSCs are generally hypoimmunogenic. Moreover, owing to their immunosuppressive activity, Human Leucocyte Antigen (HLA) matching prior to allogeneic therapy is not required [49]. The other stem cell candidates to treat OA, which can be enabled to differentiate into chondrocytes or any type of cell, are induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs). Despite their ability to treat the cartilage defect in OA, some complications, such as teratoma growth and immunogenicity, are observed [34].

Other than their multi-lineage differentiation capacity, MSCs tend to migrate to the injury and inflammation site. The SDF1/CXCR pathway is a key regulator for MSCs migration, in which the absence of SDF1 signals impair the migration of these cells to the bone tissues. In addition, these cells express a large number of cytokines and growth factors (TGF β , VEGF, EGF), as well as chemokines (IL8 that involves in the recruitment of endothelial progenitor) that exhibit different roles. This paracrine activity of MSCs leads to the activation of several downstream processes such as chondrogenic differentiation, cartilage matrix formation, anti-inflammatory, anti-apoptotic, antifibrotic, angiogenic, mitogenic, and wound-healing properties [10, 49-54]. More importantly, the discovery of chondrocytes at the end stage of arthritis through the analysis of mRNA levels within the cartilage shows that endogenous cells are not inert and remain metabolically active to synthesize cartilage proteins. This fact supports the hypothesis that MSCs may also be able to assist the existing chondrocytes [41].

Despite the considerable potential and successful results, many challenges and questions, such as the suitability of MSCs tissue origin or the appropriate condition for cartilage repair, still persist [18, 55]. Some therapeutic strategies were studied to increase the therapeutic effects such as MSCs implantation in a scaffold, mixed injection with other anti-inflammatory, and pro-chondrogenic factors to enhance the retention and survival of the cells [18].

3.1. MSCs Sources

MSCs are heterogeneous stromal cells that are derived from various sources including bone marrow, adipose tissue, and synovium [34]. Adult MSCs were first isolated from bone marrow (BM-MSCs) in 1999 by Pittenger *et al.* [56], who demonstrated their multi-lineage differentiation potential, and have been extensively studied since then [56]. Adipose-derived MSCs (ADSCs) are typically harvested from the patients' adipose tissue through surgical resection or liposuction and infrapatellar fat pads (IFPs) that provide higher chondrogenic potential cells compared to other sources [34, 57].

Despite the numerous studies that have been conducted on ADSCs and BM-MSCs for OA treatment, only a few studies related to synovial fluid-derived MSCs (SF-MSCs) are recently available [34]. Compared to other sources, SF-MSCs are proposed as an attractive source for OA treatment owing to their high proliferative activity and chondrogenic potential. The advantages of these cells are they are specific for patients' bodies and can be easily harvested during arthrocentesis or routine arthroscopic examination without the risk of damaging normal tissues [18].

Other than derived from bone marrow, adipose tissue and synovium, MSCs are also located in other tissues of the human body such as in chorionic villi of the placenta, umbilical cord blood, amniotic fluid, peripheral blood, fetal liver, lung, and even exfoliated deciduous teeth. However, the best source of adult MSCs is still unknown. More studies should be done in order to compare the chondrogenic abilities of different classes and sources of stem cells [34, 58].

3.2. Delivery Strategies for MSCs into OA Area

For OA treatment, several clinical trials conducted various strategies for MSCs transplantation to increase their therapeutic effects, including direct intra-articular injection of MSCs, MSCs with scaffolds, and injection of MSCs mixed with cytokines and/or growth factors. The indication of these procedures typically depends on the extent of the damage. Direct intra-articular injection might be more effective in the early stages of OA where the defect is only about the cartilage layer while a scaffold or matrix is required to support the implanted cells in the area of large defects [59].

3.2.1. Intra-articular MSCs Injection

Intra-articular injection of MSCs has some benefits other than the enhancement of joint repair and reduction of the joint degenerative changes. The method is the simplest and easiest procedure for stem cell treatment of OA [18]. Koh Y G *et al.*

[60] concluded that the intra-articular injection of infrapatellar fat pad-derived MSCs is effective for alleviating the pain and improving knee function in patients with knee OA. Stem cells were prepared with platelet-rich plasma and injected directly into the knee with OA. Clinical improvement was monitored pre-operatively and during follow up with the Western Ontario and McMaster Universities Osteoarthritis Index, the Lysholm score, and the visual analog scale (VAS) as well as magnetic resonance imaging (MRI) at the final follow up [60].

In a study performed in Iran (2012) by Emadedin *et al.* [61], intra-articular injection of culture-expanded MSCs was used for OA therapy in six females with radiological evidence of knee OA. Up to 6 months post injection, all measured parameters improved [61]. Gao *et al.* [62] reported the enhancement of bone formation as the result from fibroblast growth factor receptor (FGFR) 3+/+ MSCs transplantation into the intra-femoral area in osteopenic FGFR 3-/- recipient mice [62]. In addition, Murphy *et al.* [63] reported the therapeutic effects of transplanted human BMSCs in a caprine model of OA where they suggested that local delivery of implanted cells stimulated the regeneration of meniscal tissue where those cells were detected in the newly formed tissue and reduced the damaged progression of the injured area [63].

3.2.2. Transplantation of MSCs with Scaffold

According to Kim *et al.* [64], the weakness of local injection of MSCs is the limited cell retention and survival at the damaged site [64]. In their previous study, they conducted MSCs implantation with arthroscopic guidance based on the local adherent technique performed by Koga *et al.* [65] to further prevent the cell leakage. However, they found that large cartilage lesions showed significantly worse outcomes, and it was concluded that a more advanced surgical procedure with scaffolds was required to support these cells in patients with large cartilage lesions [64, 65].

Scaffolds were used to improve cell attachment and support the growth and nutrition supply of the implanted cells. It was used as the substrate support and the microenvironment of the cell carrier in a gel or a 3D structure form. Collagen, fibrin, and hyaluronic acid are some of the commonly used scaffolds. [18]. In a retrospective study by Kim *et al.* [64], two groups of patients were studied: group 1 was treated with adipose-derived MSCs implantation without scaffold, and another group (group 2) underwent the same procedure but with fibrin glue as scaffold. The outcome of the clinical and arthroscopic examination was encouraging in both groups without significant differences in the outcome scores. However, there were significantly better International Cartilage Repair Society (ICRS) grades in group 2 at the final follow up [64].

In addition, Kuroda *et al.* [65], using the same protocol as in Wakitani *et al.* [66] study, reported the therapeutic effects of autologous transplantation of bone-marrow cells seeded within collagen type I hydrogels to treat a patient with a full-thickness cartilage defect of the medial femoral condyle. The data obtained from the arthroscopic procedure showed that the defect was completely covered by smooth tissues in 7 months after surgery and the clinical symptoms had improved significantly in 1 year after surgery without any pain and complication. From the histological finding, the defect was filled with a hyaline-like type of cartilage tissue, which proved that the transplanted cells had successfully differentiated into chondrocytes [59, 65, 66].

Transplantation of MSCs with a scaffold for proliferation and matrix production provides more accessible, easy-to-manipulate, and self-renewing source of progenitor cells. The scaffold also provides sufficient functional properties at the time of implantation, resulting in initial mechanical integrity for the procedure [59, 64].

3.2.3. Mixed Injection of MSCs

There were several reports associated with transplantation of mixed MSCs with cytokines or growth factors with scaffold to improve the therapeutic effects [18]. Mrugala *et al.* [67] demonstrated the comparison of transplantation of ovine MSCs (oMSCs) mixed with or without chitosan as well as TGF β 3 in a fibrin clot for OA treatment. They suggested that transplantation of oMSCs mixed with chitosan and TGF β 3 had effects in clinical improvement [67].

Platelet-rich plasma (PRP) is an autologous platelet gel that contains hundreds of chondrogenic growth factors including TGF- β and platelet-derived growth factor (PDGF) as well as platelet concentrate that is important to repair injury in osteochondral defect [18, 68]. Seo *et al.* [68] confirmed that the therapeutic effects of bilayer gelatin/ β -TCP (GT) combined with stem cells, chondrocyte, BMP-2, and PRP (Ch/MSC/PRP/GT) on osteochondral defects of the talus in horse stimulated osteochondral regeneration [68].

Chiang *et al.* [69] in 2016 used allogeneic BM-MSCs mixed with hyaluronic acid to treat knee OA in an *in vivo* anterior cruciate ligament transection (ACLT) in OA-induced rabbits. The study compared the knee that received injection of MSCs mixed with hyaluronic acid with the contralateral OA knee that received hyaluronic acid alone. In addition, there were control groups that consist of sham operational group and untreated OA group. The knees treated with BM-MSCs and hyaluronic acid showed less cartilage loss, fewer surface abrasions, and improved cartilage content compared with those that received injection of hyaluronic acids alone [69].

Centeno and colleagues had reported two observational case studies about improvement in both chondral volume and meniscus volume using a combination of both isolated bone-marrow MSCs, bone-marrow aspirates (BMA) and platelet lysate. Centeno later published a case series and reported that only 6.9% patients still required joint replacement surgery after MSC therapy from those who initially required total knee replacement in 2011. After the procedure, 60% of patients reported >50% pain relief and 40% reported >75% pain relief at 11 months [41, 70-72].

4. CONCLUSION

OA is the most common disease that affects joint cartilage and leads to disability. As there is no curative treatment to slow or arrest OA progression, current standard treatments only focus on the management of symptoms. MSCs therapy is considered to be an attractive candidate for advanced OA treatment owing to its ability to differentiate into chondrocytes. Several studies and transplantation strategies were conducted to increase the therapeutic effects of these cells such as direct intra-articular injection of MSCs and transplantation of MSCs with scaffold and mixed injection. Despite many successful reports associated with this treatment, more studies and clinical trials in human should be performed to determine the best source for these cells, and also the comparison of each delivery strategies as well as the treatment efficacy and safety should be done.

Author Contributions

All authors contributed equally to this review.

Source of Funding

None.

Conflict of Interest

None.

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Citation: Purwanthi IGAP, Marta KKA, Adiwardhana IGKS. Osteoarthritis and mesenchymal stem cell therapy: an overview. *Recent Adv Biol Med*. 2017; 3:69-76.