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Stem cell therapy in knee osteoarthritis, a recent literature review

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Abstract

Cell-based therapy and novel approaches using mesenchymal stromal cells (MSCs) has been explored in recent years as a new regenerative therapy for knee osteoarthritis. MSCs are envisioned as the most extensively explored new therapeutic drugs in the treatment of cell-based osteoarthritis due to their ability to differentiate into chondrocytes and their immunomodulatory properties. Various procedures for cell selection and preparation have been described in studies on MSCs. This article focuses on a review of the available literature on MSC based cell therapy in primary knee osteoarthritis. Promising results have been obtained for cartilage repair in around thirty human studies. These results are like other cartilage repair methods, with good results in approximately 80% of the cases. However, the number of patients in stem cell studies is small and the follow-up period is very short. The new cartilage formed is a repair tissue and does not have the original cartilage structure. Therefore, there is not enough information about the long-term results of this treatment. It has not been shown to be superior to other cartilage repair methods. Orthopedic use of stem cells is still in its infancy. Although the results obtained are promising, they are not yet included in standard treatment protocols. Stem cell research continues all over the world, but the ideal application method is unknown. There is a need for further clinical studies with a larger patient populations and longer follow-up periods.

Keywords: cartilage, mesenchymal stromal cells, osteoarthritis, regenerative therapy, knee

1. Introduction

Osteoarthritis (OA) is a significant public health problem. While there is remarkable international variation in the prevalence and incidence due to OA, the burden is increasing in most countries (1). Because life expectancy is increasing as the population ages, OA is becoming a more significant component of the global disease burden. OA has been defined as a synovial disease affecting articular cartilage and bone for many years. The American Council of Rheumatology (ACR) defined OA in 1986. According to this definition, OA is a heterogeneous, progressive, complex joint disease that develops due to deterioration of articular cartilage integrity, and causes clinical and radiological findings, as well as changes in bone and joint (2). OA is the most common joint disease in the world. It is the most common cause of pain and loss of function in adults in Western societies (3).

The pathogenesis of OA is quite complex, and not only related to so-called "wear and tear" mechanical stress (4). Even today, it is still not fully explained. The situation is simple because trauma causes OA, but when the cause of primary OA is questioned, the situation becomes quite complex. Is OA a cause of joint failure, or is it a result of the structural condition of the joint? Many studies are carried out to find an answer to this question and develop new treatment methods.

OA's joint damage should be considered organ failure like kidney or heart failure. The products formed in anabolic and catabolic processes play a role in the pathophysiology of OA. At the end of this process, joint failure develops. For many years, the pathogenesis of OA was based on the thesis that cartilage degeneration develops due to long-term mechanical stress on the joint. Still, it is believed that OA is a very complex multifactorial disease, thanks to the developments in molecular biology (4, 5). The extracellular matrix is produced by chondrocytes, while fibroblast-like synoviocytes produce the synovial fluid. These two cells are essential in maintaining the joint's microenvironment (These two cells are critical to the joint's microenvironment (much more fluent))(6). There is a balance between the anabolic and catabolic processes in the joint's microenvironment. While growth factors, transforming growth factor (TGF-β) and chondrocytes repair the damage in cartilage tissue, matrix metalloproteinase (MMP)-1,3,13 and anti-aggregant enzymes-ADAM-4 and 5 prevent this (7). The balance between these anabolic and catabolic processes is disturbed in OA. The chronicity of synovial inflammation in the joint causes macrophages to accelerate the catabolic process, which causes the release of more pro-inflammatory cytokines (IL-1β, IL-6, Tumor necrosis factor-alpha (TNF-α)) (8). In addition to these processes, pathological changes in the subchondral bone, which can be seen in all stages of OA, play an essential role in pathogenesis. In this pathological process,

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radiological findings can be detected as osteophyte formation, subchondral sclerosis, and chondral damage. Cartilage damage is thought to originate from subchondral bone (9). A pro-inflammatory environment associated with damaged cartilage combined with mechanical stress increases the release of pro-inflammatory cytokines and mediators, thereby accelerating the degradation of the cartilage matrix (10). Although the disease may be due to genetic and epigenetic factors, gender, ethnicity, and age (cellular ageing, apoptosis, and lubricin), it is also associated with obesity and overweight, dietary factors, sedentary lifestyle, and sports injuries (11).

Knee osteoarthritis (KOA) is the most common subtype of OA (12). KOA is a significant cause of pain and musculoskeletal dysfunction worldwide (13). The incidence of joint pain is directly proportional to age (11). Pain in joint movements, effusion, crepitation, cyst in the popliteal region (Baker), instability due to ligament laxity, valgus or varus deformity, and limitation in walking are the clinical features of KOA.

Many agents are used in OA treatment and are being studied to be developed. Each of these agents has advantages and disadvantages. The treatment should be shaped by taking into consideration the patient's specific comorbidity. No treatment definitively cures OA, stops its progression, or slows it down. Therefore, it is necessary to develop new treatment methods. These treatment methods should stop or slow down the progression of OA and have no or minimal side effects. Further studies should be encouraged.

Cell-based therapy and novel approaches using mesenchymal stromal cells (MSCs) have recently been explored as a new regenerative therapy for knee osteoarthritis (10, 14, 15). The International Society for Cell & Gene Therapy refers to MSCs as a bulk population with unique secretory, immunomodulatory, and homing properties. The minimal criteria include being plastic adherent, expressing specific surface markers, and being capable of in vitro differentiation into adipocyte or chondrocyte (16). MSCs, which can be differentiated into various functional tissue cells, have demonstrated a superior ability to regenerate damaged cartilage as well as provide significant and clinically relevant pain relief (17, 18). Conventional surgical OA treatment (arthroscopic debridement, microfracture, autologous or allogeneic cartilage transplantation, chondrocyte transplantation) is mainly effective in symptomatic treatment and pain management. It cannot contribute to the regeneration of degenerated cartilage or the reduction of joint inflammation. The fibrous cartilage tissue obtained from these treatments is not the same as natural hyaline cartilage. MSCs are envisioned as the most extensively explored new therapeutic drugs in the treatment of cell-based OA due to their ability to differentiate into chondrocytes and their immunomodulatory properties (19). In animal and clinical studies, MSCs have been reported to hold therapeutic potential for cartilage, regeneration, including stabilization of cartilage metabolic activity and chondrogenic differentiation (20-22). Various procedures for cell selection and preparation have been described in studies on MSCs. The mechanism of MSCs for KOA has not yet been clearly demonstrated. This article focuses on a review of the available literature on MSC-based cell therapy in primary knee osteoarthritis.

2. Mesenchymal Stem Cells Derived Therapies

Stem cells are derived from perivascular cells called pericytes in the human body and are involved in tissue repair and healing. When a pericyte leaves the basal lamina of a blood vessel, it is exposed to the surrounding tissue environment and becomes an MSCs (23). These resting cells play a role in the repair process by transforming into cells such as cartilage, bone, muscle and fat tissue needed in the injury area when damage occurs in the body. There are two types of stem cells; embryonic stem cells and adult stem cells (24). Embryonic stem cells can be obtained from the placenta, amniotic fluid, and umbilical cord. Adult stem cells are found in all tissues and blood in the body, but they are very rare. These cells must be replicated to be effective in therapy. Bone marrow (BM) (25), trabecular bone (26), adipose tissue (AT) (22), synovial fluid (27) and peripheral blood (28) are the sources from which adult stem cells can be obtained for the treatment of KOA.

MSCs are multipotent adult stem cells that are abundant in a variety of tissue types (Fig. 1). Stem cells from different sources have different differentiation capacities, clinical benefits, and cultural characteristics (29). MSCs-based cell therapy is of great interest because of the multifunctionality of MSCs, including self-renewal, differentiation into specialized cells with multiple functions and many tissues, secretion of regenerative growth factors, and immunomodulation. Therefore, the chosen cell source is essential for successful outcomes in MSCs-based cell treatments, including bone marrow, fat, synovial fluid, and synovium. In the literature review, bone marrow-derived MSCs (BM-MSCs) may be the predominant source of cells, followed by adipose tissue-derived MSCs (AT-MSCs).

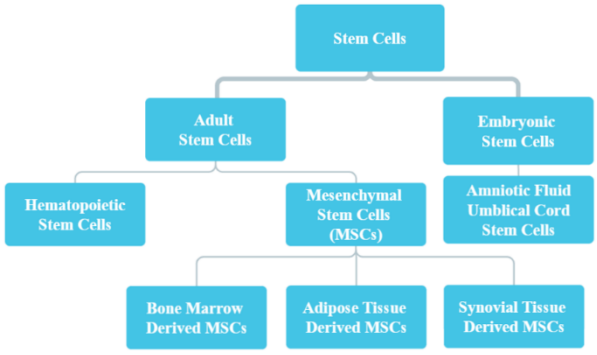

Fig. 1. MSCs are multipotent adult stem cells and highly present in multiple tissue types.

MSCs are an adult stem cell lineage and differ from pluripotent embryonic stem cells (ESCs) because they have a

more limited range of differentiation potential. ESCs can differentiate and self-renew in all cell types. Specific markers are available through cluster differentiation (CD) marker phenotypes of CD73, CD90, and CD105 that distinguish MSCs from other stem cell phenotypes (30). MSCs have multiple functionalities that include anti-inflammatory, immunomodulatory, and paracrine effects. MSCs can secrete several growth factors and anti-inflammatory proteins. The mechanisms of action of MSCs are very complex and beyond the scope of this review. For this reason, MSCs are preferred in the treatment of KOA because of their ability to differentiate directly into chondrocytes and their ability to optimize the catabolic and anabolic balance within the joint in the anabolic direction (31). It has been reported that MSC treatment effectively reduces pain and improves OA's clinical symptoms (32). This article will focus on orthopaedic applications of MSC therapy in primary knee osteoarthritis.

We emphasized the therapeutic potential of MSCs. However, there are many differences in current clinical practice (32). The lack of homogeneity in terms of treatment methods is thought-provoking. Patient selection, stem cell source selection, stem cell isolation methods, methods of applying stem cell therapy to the patient, the diversity of the place where stem cell therapy is applied, the diversity of treatments applied in addition to stem cell therapy, and the methods used to evaluate the success of stem cell therapy are not standardized. There is no standardization between studies in the literature. Therefore, there is a need to define a set of procedures to standardize MSC treatment modalities. This study aims to review the current MSC treatment methods and clinical studies used for KOA by reviewing the literature.

3. Patient Selection

Firstly, choose the appropriate origin of MSCs, then isolate MSCs from other cells, and inject the MSCs (Fig. 2). OA is a growing public health problem worldwide, affecting more than half of the population aged 65 and over. Since OA is a progressive disease, age is one of the most critical risk factors (11). In the literature, stem cell therapy was applied to patients between the ages of 18 and 75 who were diagnosed with OA symptomatically and radiologically (33). It is stated that ethnic and racial differences may affect pain and functional outcomes (34).

Existing comorbidities in patients can significantly affect the progression of OA. Various epidemiological studies have examined the prevalence of other chronic conditions in people with OA. It is estimated that 59% and/OR to? 87% of adults with OA have at least one other chronic illness, the most common being cardiovascular disease, diabetes mellitus, and hypertension (35, 36). Comorbidities reduce the quality of life and worsen joint functions in OA patients. The interaction between OA and comorbidities should be taken seriously, and patients with comorbidities should be carefully studied and excluded (33).

Fig. 2. The flow diagram of applying MSC-based therapy. First, choose the appropriate origin of MSCs, isolate MSCs from other cells, and inject the MSCs

4. Cell Selection and Isolation

Autologous or allogeneic MSC options can be used in treatment. Maybe the best treatment option is as there is a less immune reaction to autologous MSCs (22). The Autologous MSC option was preferred in many studies in which knee osteoarthritis was treated with stem cells (33). Adipose tissue and bone marrow are the most common sources of autologous MSC (14). It was seen in the literature review that bone marrow was the most frequently used MSC resource (14, 37, 38), and AT was the second most commonly used (21, 22). There are several sources of allogeneic MSCs. Allogeneic MSCs derived from adipose tissue or bone marrow can be obtained from other humans. Allogeneic MSCs from the placenta or umbilical cord can be donated with consent by a healthy mother just in time. In addition, various medicinal products are available as sources of allogeneic MSC. Administration of allogeneic MSCs may be more convenient than autologous MSCs because the process does not require invasive MSC collection and saves the time associated with waiting for cell expansion (39). A possible limitation of implanting allogeneic MSCs is host immune rejection; however, MSCs can be tolerated due to their immunomodulatory properties (39).

5. Adult Stem Cell Sources

5.1. Adipose Tissue Derived Mesenchymal Stem Cells

Adipose Tissue-Derived Mesenchymal Stem Cells (AT-MSCs) are MSCs thought to be isolated from pericytes, the stromal vascular fraction (SVF), located in the capillary and perivascular advent of large blood vessels in adipose tissue (40). Adipose tissue has been recognized as a potential source of autologous MSC due to its relative ease of harvest, the abundance of MSCs, and high chondrogenic potential compared to other sources such as bone marrow (21). AT-MSCs share features in morphology and phenotype with Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs) (41). Some literature publications comparing AT-MSCs with BM-MSCs indicate that AT-MSCs are present in higher numbers per unit of tissue volume, multiply faster in culture, and are less susceptible to ageing caused by culture expansion (42). AT-MSCs are not affected by the patient's age, sex, or

physiological condition (43). Because of these advantages, SVF and culture-augmented AT-MSCs are becoming more common. Adipose tissue is mostly taken from abdominal subcutaneous fat tissue by lipoaspiration.

5.2. Bone Marrow Derived Mesenchymal Stem Cells

BM-MSCs are mesenchymal stem cells isolated from bone marrow aspirate (BMA) or bone marrow concentrate (BMAC). Just as AT-MSCs are found in high volume in adipose tissue stroma, BM-MSCs are found in high volume in bone marrow spaces. It shares standard features with BM-MSCs and AT-MSCs (41). For example, pericyte origin, expression of common cell surface markers, gene expression profiles and differentiation potential are similar. Bone marrow is the gold standard for deriving MSCs for transplantation (44). BM-MSCs are a reliable source of MSCs, and such MSCs have superior osteogenic potency (38). MSCs should have plastic attachment and express CD105, CD73 and CD90 under standard culture conditions and also lack expression of CD45, CD34, CD14, CD11b, CD79a, CD19 and human leukocyte antigen isotype DR surface molecules (45). Differentiation of MSCs into osteoblasts, adipocytes, and chondroblasts should be confirmed in vitro. While these criteria will likely require modification, these minimum criteria will encourage a more uniform characterization of MSCs and facilitate data exchange between researchers. (46).

6. Culture

MSCs are multipotent adult stem cells and are highly present in multiple tissue types. Stem cells from different sources have different differentiation capacities, clinical benefits, and cultural characteristics (29). One of the characteristic features of MSCs is their ability to adhere to tissue culture plastic and generate colonies when plated at low densities (47). We know the ability of MSCs to undergo chondrogenic, osteogenic, and adipogenic differentiation.

MSCs grow from individual foci, or colonies from the microscopic view, and these colonies generated from progenitor cells have been called the colony-forming unit fibroblast (48). Fibroblasts express the same cell immunophenotypic markers, as well as the genes known to be expressed in stem cells, and were expressed in adipose and dermal stem cells OR stem cells in dermis. Fibroblasts can also differentiate into the three cell lineages mentioned above, adipocytes, osteocytes, and chondrocytes (49).

The differentiation of mesenchymal stem cells (MSCs) into cartilage-producing cells - chondrocytes is highly dependent on culture conditions. Mediators capable of promoting chondrogenesis, such as transforming growth factor-beta (TGF-β) have been described using simplified in vitro models (50). In a recent study by Yin et al., histological evaluation and gene expression analysis showed that BMSCs differentiated into mature chondrocytes after 21 days of culture without using exogenous growth factors (TGF-β) (51). Chondrogenesis can be performed in vitro in 2-dimensional or 3-dimensional culture systems. A 3-dimensional culture system allows cells to adapt to their natural morphology, facilitating more excellent/effective cell contact and interaction with the ECM. Also, the efficiency of chondrogenesis tends to be lower in the 2-dimensional culture system (52). Co-culture of platelet-rich plasma (PRP), MSCs and chondrocyte will promote chondrogenesis without hypertrophic and pathological responses (53).

7. Transplantation

Transplantation of MSCs is a promising strategy given the high proliferative capacity of MSCs and their potential to differentiate into cartilage-producing cells - chondrocytes. Transplantation is a process in which MSCs isolated or cultured on a supporting material such as collagen membranes or scaffolds are inserted and fixed directly into the lesion area of the cartilage. This method minimizes the dispersal of MSCs in the graft so that they can differentiate into chondrocytes in the cartilage. Koh et al. (2016) used a commercially available fibrin sealant product containing lyophilized human plasma fibrinogen and thrombin solution loaded with MSC suspension. When the two solutions were mixed, the adhesive instantly formed a gel, and the gel was implanted into the cartilage lesion surface under arthroscopic guidance (17). Akgun et al. (2015) planted MSCs on the surface of type I/III collagen membranes, then transplanted the membrane directly to the lesion site on subchondral bone and fixed cells using fibrinogen and thrombin (54).

Recently, paracrine effects of transplanted MSCs have received more attention than the differentiation of MSCs into chondrocytes. Donor MSCs were not preserved in the host tissue of patients who received MSC injections for different diseases after one year. Other studies have consistently reported that engraftment of transplanted MSCs in host tissues is not (not what? Not possible?) (10). The lack of engraftment may be partly due to the lack of transplantation technology and its less frequent use than injections.

8. Applying MSCs

Injection is the most common method used to introduce mesenchymal stem cells into the joint cavity. MSC and MSC-derived exosomes, chemokines and cytokines secreted by MSCs exert a paracrine effect within the joint that creates a regenerative environment by chondrogenesis, chondrocyte proliferation, reduction of apoptosis and regulation of catabolism (14).

Most substances, such as hyaluronic acid (55), platelet-rich plasma (55, 56), and saline (56), are known to improve OA symptoms on their own; therefore, it is essential to exclude background effects and carefully analyze clinical outcomes. Injection of MSCs may include single or multiple doses of different concentrations; however, the therapeutic effects of treatment with different doses and concentrations are controversial.

Although there are hundreds of experimental studies on cartilage repair and the alleviation of osteoarthritis symptoms, there are few human studies. Promising results have been obtained for cartilage repair in around thirty human studies. These results are similar to other cartilage repair methods, with good results in approximately 80% of the cases. However, the number of patients in stem cell studies is small, and the follow-up period is very short. The new cartilage formed is a repair tissue and does not have the original cartilage structure. Therefore, there is not enough information about the long-term results of this treatment. It is not superior to other cartilage repair methods. Orthopaedic use of stem cells is still in its infancy. Although the results are promising, they are not yet included in standard treatment protocols. Stem cell research is continuing worldwide, yet it is not known what the ideal application method is. There is a need for further clinical studies with larger patient populations and longer follow-up periods.

Conflict of interest

The authors declared no conflict of interest.

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Authors' contributions

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