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Short review of therapeutic applications of adipose-derived stromal vascular fractions in osteoarthritis

Tang Q *et al.* The review of osteoarthritis

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Abstract

Osteoarthritis (OA) is considered to be a highly heterogeneous disease with progressive cartilage loss, subchondral bone remodeling, and low-grade inflammation. It is one of the world's leading causes of disability. Most conventional clinical treatments for OA are palliative drugs, which cannot fundamentally cure this disease. The stromal vascular fraction (SVF) from adipose tissues is a heterogeneous cell population. According to previous studies, it contains a large number of mesenchymal stem cells, which have been used to treat OA with good therapeutic results. This safe, simple, and effective therapy is expected to be applied and promoted in the future.

In this paper, the detailed pathogenesis, diagnosis, and current clinical treatments for OA is introduced. Then, clinical studies and the therapeutic mechanism of SVF for the treatment of OA is summarized.

Key Words: Arthritis; Articular cartilage; Stromal vascular fraction; Mesenchymal stem cells; Cell therapy

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Core Tip: Osteoarthritis (OA) stromal vascular fraction (SVF).

INTRODUCTION

Osteoarthritis (OA) was once thought to be a degenerative joint disease, but recent research has revealed that cartilage, subchondral bone, and synovium in the joints can all develop and form varying degrees of inflammation. As a result, OA is considered a whole joint disease. It is marked by an imbalance in the catabolic and anabolic processes of articular cartilage, as well as compensatory changes in bone and synovial inflammation, all of which ultimately lead to joint dysfunction^[1,2].

The major feature of OA is the degeneration of articular cartilage and subchondral bone, which eventually results in joint swelling, pain, stiffness, limited mobility, effusion and inflammation, and even disability. This disease not only causes patients to experience considerable pain but also places a great economic burden on them and on society. Aging, genetic susceptibility, obesity, high bone mineral density (BMD), joint overuse, and injury are among the main causes of OA, according to researchers^[3].

The Global Burden of Disease study for 2017 was published in The Lancet in 2018, and Safiri used it to conduct a systematic analysis of OA. From 1990 to 2017, the global age-standardized point prevalence, annual incidence, and years lived with disability rates of OA increased by 9.3% (95% UI: 8%-10.7%), 8.2% (95% UI: 7.1%-9.4%), and 9.6% (95% UI: 8.3%-11.1%), respectively. It is worth noting that the prevalence of OA in females was higher than that in males. Furthermore, both the morbidity and prevalence of OA rise with age, with the prevalence of cases peaking at 60-64 years old^[4].

Obesity, in addition to age, is a significant risk factor for OA. Obesity puts more strain on weight-bearing joints. At the same time, adipocytes may also play a role in the pathogenesis of OA by secreting inflammatory factors. These factors increase the production of matrix metalloproteinases (MMPs) and prostaglandins while inhibiting

the synthesis of proteoglycans and type II collagen, affecting cartilage function^[5]. Obese patients (BMI > 30 kg/m²) are more likely to need total knee arthroplasty and have higher rates of postoperative complications, according to studies^[6].

Genetic factors account for 30%-65% of OA cases. A genome-wide association scanning study has identified 21 independent OA susceptibility loci^[7]. Articular cartilage injury, anterior cruciate ligament (ACL) rupture, and meniscus tear (MT) all greatly increase the risk of OA. According to one study, people who have had knee injuries are four times more likely to develop OA than those who have not had knee injuries^[8]. In addition, a low vitamin D diet^[9] and excessive joint use^[10] may also increase the risk of OA. High BMD increases the risk of knee OA and joint space narrowing, but does not worsen the imaging progression of existing knee OA, according to one study^[11].

Since OA can cause great personal and economic losses, we must pay attention to it. The purpose of this paper is to introduce the pathogenesis, diagnosis and current clinical treatment methods of OA and briefly summarize the clinical research and mechanism of SVF in the treatment of osteoarthritis.

PATHOGENESIS OF OA

Cartilage destruction, subchondral bone remodeling, osteophyte formation, and joint capsule thickening are all part of the pathogenesis of OA, which may take several years. It should be noted that prearthritic deformities of the limbs could also lead to osteoarthritis. For example, severe valgus or varus malalignment leads to lateral or medial gonarthrosis. This can produce a change in the distribution of high stresses within the joint, resulting in a force imbalance, which in turn accelerates arthritic pathology^[12]. The inflammation of OA is low-grade and chronic, causing both the innate and adaptive immune systems to be activated (primarily the innate immune system), distinguishing OA from rheumatoid arthritis^[13].

Normally, articular cartilage consists of water, chondrocytes, and extracellular matrices. The extracellular matrix is synthesized and secreted by chondrocytes and

contains collagen (mainly type II collagen), proteoglycans, hyaluronic acid (HA), and small-molecule glycoproteins. Type II collagen and other extracellular matrices can form a reticular structure, which provides pressure resistance for articular cartilage^[14]. When OA occurs, chondrocytes produce a variety of inflammatory cytokines and chemokines that cause inflammation, such as interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6). Concurrently, chondrocytes produce MMPs, as well as disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTS). Type II collagen is the target of disintegrin, and proteoglycans are the target of ADAMTS; together, these proteins eventually lead to increased cartilage catabolism and reduced synthetic metabolism and repair^[15]. It is worth noting that osteoblasts, synovial cells, and monocytes in joints can produce IL-1 β , TNF- α , MMPs, *etc.*^[15].

Subchondral bone, which is located beneath the calcified layer of articular cartilage and contains blood vessels and nerves, may provide mechanical support for articular cartilage. In the early stage of OA, osteoclasts mediate the remodeling of subchondral bones. Magnetic resonance imaging (MRI) can detect various degrees of subchondral bone sclerosis, osteophytes, and subchondral bone cysts as OA progresses^[16,17]. This modification may reduce the mechanical support provided by subchondral bones to articular cartilage, making the articular cartilage vulnerable to damage.

Synovitis is one of the most common complications of OA. The synovium may proliferate significantly during the progression of OA, and synovial cells may also secrete proinflammatory factors and MMPs to aid in the development of OA^[18]. In addition to the local inflammatory mechanism of joints, increasing evidence suggests that obesity can keep the human body in a low-degree inflammatory environment for an extended period of time. Obese people have a significantly higher risk of OA than people with a normal BMI^[6].

DIAGNOSIS AND THERAPY OF OA

The primary method of diagnosing OA is imaging examination, which mainly includes

X-rays, computed tomography (CT), MRI, ultrasonography, and arthroscopy. X-ray examination is one of the preferred methods for the clinical diagnosis of OA^[19,20]. It can detect key features of OA, such as joint space narrowing, osteophytes, subchondral bone sclerosis, and cysts. However, because X-ray images can only visualize cartilage damage indirectly by observing changes in joint spaces and bones, it cannot be used as the sole criterion for OA diagnosis, and it is not suitable for OA diagnosis in the early stages^[21]. CT scan can reveal subtle bone changes in the subchondral bone. The images can clearly show the loose bodies formed by osteophyte shedding around the joints on different sides. As a result, it is more sensitive for detecting osteophytes and subchondral cysts^[22]. Because MRI has higher tissue resolution, it can provide information about the size and structural integrity of cartilage, as well as directly show articular cartilage damage and changes in thickness^[23]. Furthermore, because MRI can detect OA-inducing factors such as injuries to the ACL and meniscus, it is useful for detecting OA at an early stage^[23]. Although ultrasonography can detect joint exudation and inflammation, it cannot diagnose deeper joints as well as MRI^[24]. Arthroscopy is the use of an arthroscope to penetrate deep into the joint cavity and directly observe tissues such as the articular cartilage and meniscus. It can not only pinpoint the location of synovitis but can also clean up the joints by removing loose bodies, removing torn meniscus tissue, and trimming bone surfaces. This diagnostic method can both diagnose and treat OA, making it the most promising diagnostic tool for assessing joint damage^[25]. When features of OA appear on images in the clinic, it usually means that the patient has irreversible cartilage damage.

Biomarkers have won a place in the diagnosis of OA because they can be used as indicators for its early diagnosis and prognosis. Biomarkers of OA are distributed in the blood, urine, and joint fluid and primarily consist of cytokines related to joint metabolism, extracellular matrix components, inflammatory factors, *etc.* Currently, commonly used indicators are cartilage oligomeric matrix protein, HA, proteoglycan, MMP, C-telopeptide of type II collagen (CTX-II), IL-6, and lactate dehydrogenase^[26]. Although biomarkers can be used to make an early diagnosis of OA, their sensitivity

and specificity are not satisfactory^[27]. Because each of the methods listed above has advantages and disadvantages, it is necessary to combine them to provide comprehensive and reliable information for the diagnosis of OA, as well as a scientific reference for developing an OA treatment plan.

Treatment for OA primarily consists of lifestyle changes, physical therapy, drug therapy, intra-articular therapy, and surgery. However, there is no complete cure for OA. The goal of treatment in the early stage of OA is to reduce pain and stiffness. Therapeutic approaches normally involve moderate exercise, diet, and oral medication. The goal of treatment in the intermediate and late stages of OA is to maintain physical function. The therapeutic approaches normally include intraarticular injection therapy and surgery. According to the Osteoarthritis Research Society International, suitable structured land-based exercise is one of the most effective ways to treat OA, as it can reduce joint pain and stiffness. Furthermore, losing weight is also one of the important ways for obese patients to improve OA^[28]. Physical therapy includes electrotherapy, thermotherapy, and acupuncture. Analgesic, anti-inflammatory, and cartilage-protecting drugs are commonly used in drug therapy. However, these therapies can only alleviate pain symptoms and slow the inflammatory process; they cannot prevent the development of OA. In clinical practice, articular cavity injection therapy is a minimally invasive treatment method. The injected treatment agents include glucocorticoids, sodium hyaluronate, platelet-rich plasma (PRP), bone morphogenetic protein 7 (BMP-7), and stem cells. It should be noted that ultrasound can be used to guide the use of intraarticular injections in patients with advanced osteoarthritis and obesity. A novel intraarticular injectable drug-loaded delivery system using nanoscale materials, including micelles, liposomes, and dendrimers, has been proposed. This method can slow drug release and prolong drug retention time in the joint cavity^[29]. The surgical therapies for OA treatment mainly include arthroscopic debridement, microfracture, allogeneic/autologous cartilage transplantation, and artificial joint replacement. For example, for frontal malalignment and varus or valgus malalignment, high tibial osteotomy could be used to correct the proximal tibial angle, thereby

reducing pain and delaying the progression of arthritis^[30]. However, surgery is invasive and comes with certain risks. Therefore, it is only applicable for patients who have severe degenerative changes in their joints, such as reduced or eliminated joint space, which severely impairs their quality of life^[31]. This therapy is not appropriate for the treatment of early-stage OA.

STROMAL VASCULAR FRACTION

SVF is a multicellular component extracted from adipose tissues through a process that includes collagenase digestion, centrifugation, washing, and filtration. Clinically, liposuction, for example, can be used to obtain adipose tissues from areas such as the abdomen, groin, forearm, and hip. Methods currently used to extract SVF mainly include enzyme digestion and mechanical separation. Because the cell yield obtained by enzyme digestion is higher than that obtained by mechanical separation, researchers prefer enzyme digestion^[32-34]. However, if the final product of the enzyme digestion method is not completely washed, it may retain exogenous collagenase, so it is subject to strict regulatory standards in use.

The cell components of SVF could be identified by cell surface molecules such as the cluster of differentiation (CD)^[35]. ³ According to the International Federation for Adipose Therapeutics and Science and the International Society for Cellular Therapy, SVF is primarily composed of adipose mesenchymal stem cells (ADSCs), hematopoietic stem/progenitor cells, lymphocytes, monocytes/macrophages, endothelial cells, and pericytes^[36]. According to research, CD45-CD235a-CD31-CD34+ is a marker combination to identify SVF cells. ADSCs are a critical component of SVF, accounting for approximately 10% of the SVF cell population^[37]. ADSCs endow SVF with characteristics of stem cells, and other cells also play a positive role in secreting active cytokines and regulating body immunity. Because SVF has demonstrated excellent therapeutic value in tissue regeneration, vascular reconstruction, and anti-inflammatory properties, it is widely used in clinical practice.

The keywords "stromal vascular fraction" and "osteoarthritis" were used to search the

clinical research database (www.ClinicalTrials.gov). After the withdrawn studies were removed, the current clinical trial studies of SVF in the treatment of osteoarthritis were obtained, as shown in Table 1.

CLINICAL RESEARCH OF SVF IN OA

Clinically, drug therapy for OA can relieve pain and some symptoms, but it cannot repair or inhibit the damage to cartilage and other joint tissues. As a result, it can neither fundamentally solve the problem of cartilage degeneration nor prevent the progression of OA. Although surgical therapy may be used to repair cartilage damage, the long-term treatment effect of OA is limited, and there are numerous drawbacks and risks. Additionally, it should be noted that surgical treatment is only suitable for the treatment of patients with OA in the middle and late stages. Therefore, the minimally invasive, safe, and rapid therapy of stem cell injection into the joint cavity has gained more attention and use.

Mesenchymal stem cells (MSCs) are derived from the mesoderm and can differentiate into adipocytes, osteoblasts, chondrocytes, and other mesoderm cells^[38]. This differentiation potential makes MSCs a promising alternative treatment for OA. MSCs can be derived from the umbilical cord, bone marrow, and adipose tissue. When compared to other source tissues, adipose tissues are rich in content, easier to obtain (through liposuction), and contain more stem cells (ADSCs)^[39]. ADSCs are a type of MSC. Furthermore, ADSCs have higher genetic stability, a higher ability for proliferation and differentiation, a lower rate of aging, and longer telomere length^[40], making them the most promising treatment option for OA.

ADSCs can be obtained by SVF after *in vitro* adherence culture and amplification. However, because the cumbersome and time-consuming *in vitro* amplification step poses a contamination risk, as well as time and economic costs, the researchers shifted their focus to SVF, which does not require culture. The rich cellular components in SVF can not only differentiate into chondrocytes to aid in tissue repair but also secrete active cytokines and regulate the body's immune system to exert anti-inflammatory effects,

among other things. As a result, clinical researchers prefer SVF.

This study used the keywords "stromal vascular fraction" and "osteoarthritis" to search PubMed, Web of Science, Cochrane Library, and Google Scholar, and after removing duplicates and non-English literature, we screened clinical trials of SVF treatment for OA published between 2016 and 2020. Finally, 23 studies were obtained, as shown in Table 2^[41-63].

The majority of the studies in Table 2 are for knee OA, and approximately half of the clinical studies are uncontrolled and without combination therapy, with only SVF being used to treat OA. No serious adverse reactions, such as infection, acute pain, or cancer, were reported in any of these studies, indicating that SVF treatment for OA is safe. Most studies used adipose tissue from the abdomen, buttocks, and lateral thigh, with a volume (for one knee) ranging from 60 to 215 mL; the number of SVF cells varied from 2×10^6 to 3×10^7 ; and the final volume of SVF preparation used for intra-articular injection varied from 2.5 to 5 mL. Although it is difficult to maintain a unified standard for the degree of OA, the volume of adipose tissues, and the number and viability of SVF cells, existing studies have demonstrated a positive therapeutic effect, with VAS, WOMAC, ROM, MRI, KOOS, Lysholm, and other scores improving, the patient's pain decreasing, and inflammation symptoms decreasing. Simultaneously, joint function has been improved to a certain extent^[43,44,48-56,61-63]. Figure 1 depicts the general steps of using SVF to treat OA in a current clinical setting.

It is worth noting that Garza found a significant difference in the final treatment effect of OA patients between the high-dose SVF (3×10^7) and low-dose SVF (1.5×10^7) groups. They pointed out that the median WOMAC score changes in the two groups after 6 mo of treatment were 83.9% and 51.5%, respectively. At the same time, the WOMAC scores of the high-dose and low-dose groups differed significantly from that of the control group, indicating that the degree of OA improvement is SVF dose-dependent^[61].

Interestingly, Michalek used collagenase digestion and mechanical methods to obtain SVF. The results showed that the cell yield of the former was 3.4 times higher than that

of the latter, and the cell activity was similar. The researchers then used the obtained SVF to randomly treat OA patients, and they discovered that the SVF obtained by the two extraction methods had the same therapeutic effect on OA, with no significant difference. As a result, it can be concluded that the SVF extraction method has little effect on OA treatment^[48].

THERAPEUTIC MECHANISM OF SVF IN OA TREATMENT

When the body is damaged, signaling molecules are produced in the damaged area, activating the homing effect of stem cells, causing them to migrate to the damaged location and play a role in tissue repair^[64]. However, cartilage tissues lack blood vessels. Even for bone marrow MSCs, it is difficult to migrate to the injury, so exogenous stem cell injection is needed. After SVF is injected into the joint cavity of patients, the ADSCs in the SVF can migrate to the damaged area through the interaction of various chemokine receptors (such as CXCR4, integrin, selectin, and vascular cell adhesion molecule-1)^[65].

Although numerous studies have demonstrated that ADSCs can be induced to differentiate into chondrocytes *in vitro*, there is insufficient evidence to prove that ADSCs can differentiate into chondrocytes *in vivo* to repair damaged cartilage tissues during OA treatment. Existing evidence indicates that an important mechanism of the therapeutic effect of ADSCs is the nourishing effect of ADSCs; they can secrete growth factors and cytokines, such as transforming growth factor- β (TGF- β), bone morphogenetic proteins (BMP-2, BMP-4, and BMP-7), insulin-like growth factor 1 (IGF 1), and fibroblast growth factor-2 (FGF-2). As a result, ADSCs may promote cartilage formation, induce cell proliferation, differentiation, and migration and ultimately promote cartilage injury repair^[66]. Furthermore, ADSCs may secrete NO, TNF- α , IL, and other cytokines, which play a role in regulating the body's immunity and anti-inflammatory response^[67]. At the same time, ADSCs can inhibit chondrocyte apoptosis by expressing antiapoptotic proteins, thereby slowing the onset of OA^[68].

Many researchers have used PRP in combination with stem cells to treat OA and have

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achieved satisfactory therapeutic effects. This is because PRP can release a variety of growth factors, such as platelet-derived growth factor, TGF, FGF, and various ILs. These growth factors can not only regulate the body's immune response but can also promote and enhance the repair function of stem cells. Therefore, PRP can stimulate the proliferation and differentiation of chondrocytes, regulate the synthesis of endogenous hyaluronic acid, and help to repair cartilage tissue damage^[69].

SVF is a multicellular component that, in addition to ADSCs, also contains progenitor cells, pericytes, endothelial cells, fibroblasts, and various immune cells. These cells also aid in the promotion of cartilage repair by forming the microenvironment, secreting cytokines, and regulating immunity^[57].

DISCUSSION

Unfortunately, no complete cure exists for OA, and once a cartilage lesion occurs, it will gradually degenerate. As a result, the early diagnosis and treatment of OA is critical. Considering that osteoarthritis is a whole joint disease, OA should be treated with combined therapy. Through intraarticular injection therapy, treatment agents can directly reach the damaged site, which can not only allow drugs and especially stem cells to avoid being cleared by the body but also reduce the potential systemic effects of drugs^[70]. Especially for traumatic arthritis, cartilage adipose stem cells provide a new avenue for the treatment of this type of arthritis through their powerful differentiation ability and paracrine and anti-inflammatory effects. Therefore, intraarticular injection therapy should be added to the combined treatment of OA. Increasing evidence shows that intraarticular injection of SVF is an effective treatment option for repairing articular cartilage damage, but there is a lack of clinical outcome data for long-term follow-up. Furthermore, the use of SVF to treat OA has certain individual differences, such as differences in extraction methods and equipment, which result in a variation in the number and quality of extracted cells. Simultaneously, the amount of fat acquired and the final cell yield of different patients are difficult to reconcile. The number of SVF cells used in the final treatment of OA varies by up to 10-fold in different studies. As a result,

more detailed and comprehensive extraction standards and treatment guidelines for the use of SVF for OA treatment are needed.

The fact that SVF has a high safety profile in the treatment of OA is encouraging. Some researchers have used SVF in conjunction with other measures (such as the use of HA, microfracture, and PRP), and the results have been promising. As a result, in the future, a combination of multiple treatments, such as SVF combined with weight loss, exercise, and acupuncture to treat OA, may be considered, providing new treatment options for this disease. All of the patients who received SVF treatment had no serious adverse reactions, such as infection, acute pain, or cancer. Although patients occasionally experience minor reactions, such as joint effusion, swelling, pain congestion, and itching at the liposuction site, they can recover without intervention or improve with simple treatment. However, most clinical studies have certain limitations, such as a small number of clinical patients, a short follow-up period, and a lack of randomized controlled trials. As a result, in future studies, a more comprehensive and appropriate study design is needed. Recently, it has been concluded that clodronate can reduce pain and improve joint mobility by intraarticular injection for OA treatment. Combined with HA, clodronate can also relieve pain and reduce bone marrow lesions in early OA. In the future, it may be used in conjunction with SVF for better results^[71].

CONCLUSION

In conclusion, SVF is an effective treatment for repairing articular cartilage damage, especially for relieving pain and other symptoms and improving joint function in OA patients. At the same time, clinical treatment with SVF is very safe. Relevant mechanistic studies reveal the beneficial role of SVF and its paracrine molecules in the treatment of osteoarthritis, which can mediate intercellular communication and interact with the cellular microenvironment and a variety of cell types, thus triggering appropriate cellular responses, inhibiting inflammation, promoting cartilage repair and regeneration and restoring joint homeostasis to reduce pain. However, various factors can change the characteristics of SVF and its secretion, such as individual differences in

donors and different preparation standards, which may limit its therapeutic effect. Therefore, further in-depth research is still needed to make stem cells a routine clinical treatment for diseases such as osteoarthritis.

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