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Potential Applications of Mesenchymal Stem Cells Derived From Autologous Microfragmented Adipose Tissue in the Treatment of Osteoarthritis

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ABSTRACT

Regenerative medicine is gaining increasing recognition in osteoarthritis treatment. Articular cartilage regeneration is central to regenerative strategies for managing osteoarthritis. Several surgical techniques have been employed to restore joint cartilage; however, their clinical efficacy remains limited. Mesenchymal stem cells are a promising source for cartilage regeneration owing to their capacity to differentiate into chondrocytes and bone cells and ability to secrete trophic factors with regenerative properties. Adipose tissue-derived mesenchymal stem cells are easily harvested, particularly from subcutaneous fat depots. This study outlines the methods of obtaining autologous microfragmented adipose tissue containing the stromal vascular fraction enriched with mesenchymal stem cells and discusses associated advantages and limitations. Moreover, the study synthesizes available clinical data on the safety and efficacy of intra-articular administration of autologous microfragmented adipose tissue with stromal vascular fraction in patients with osteoarthritis. Further long-term randomized controlled trials are warranted to assess the therapeutic potential and safety of adipose-derived mesenchymal stem cells in osteoarthritis management.

Keywords: osteoarthritis; regenerative medicine; mesenchymal stem cells; autologous microfragmented adipose tissue; stromal vascular fraction.

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Возможности применения мезенхимальных стволовых клеток, полученных из аутологичной микрофрагментированной жировой ткани, в лечении остеоартроза

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АННОТАЦИЯ

В настоящее время регенеративная медицина набирает всё большую популярность в лечении пациентов с остеоартрозом. В основе регенеративного лечения остеоартрита лежит восстановление суставного хряща. Для регенерации суставного хряща применяются различные хирургические процедуры, имеющие ограниченную клиническую эффективность. Мезенхимальные стволовые клетки принято считать перспективным источником для регенерации суставного хряща из-за их способности дифференцироваться в хрящевые и костные клетки и секретировать трофические факторы с регенеративными функциями. Мезенхимальные стволовые клетки жировой ткани легко изолируются и особенно доступны из подкожной жировой клетчатки. В статье описаны способы получения аутологичной микрофрагментированной жировой ткани со стромально-васкулярной фракцией, содержащей мезенхимальные стволовые клетки, их преимущества и недостатки. Авторами работы предпринята попытка объединения результатов исследований, которые посвящены изучению клинической эффективности и безопасности применения аутологичной микрофрагментированной жировой ткани со стромально-васкулярной фракцией, содержащей мезенхимальные стволовые клетки, у пациентов с остеоартрозом. Необходимо проведение дальнейших долгосрочных рандомизированных контролируемых исследований с целью детального анализа эффективности и безопасности применения мезенхимальных стволовых клеток жировой ткани в лечении пациентов с остеоартрозом.

Ключевые слова: остеоартроз; регенеративная медицина; мезенхимальные стволовые клетки; аутологичная микрофрагментированная жировая ткань; стромально-васкулярная фракция.

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Osteoarthritis (OA) is a progressive degenerative joint disease characterized by gradual degradation of hyaline cartilage and sclerosis of the adjacent bone tissue [1, 2]. According to recent epidemiological studies, the incidence of knee OA widely varies among adults worldwide. Using clinical criteria, radiological criteria, and a combination of the two, knee OA incidence ranges from 2.0% to 42.4%, 16.3% to 33.0%, and 1.5% to 15.9%, respectively [3]. There are approximately 81 million registered patients in five European countries (i.e., Germany, Italy, France, Great Britain, and Spain) and over 380 million in Russia, Brazil, India, and China [4]. According to official statistics, the number of patients with OA in the Russian Federation increased almost 2.5-fold in 2000–2010 [5]. A recent epidemiological study showed that 13% of the Russian population aged 18 years suffers from gonarthrosis and/or coxarthrosis [5]. OA is the fourth leading cause of disability worldwide and the second cause of disability among males [6, 7]. It is the most common joint disease in adults, with the knee being the most frequent localization [7]. Additionally, OA affects other joints with high functional loads, such as the hips, joints of the upper and lower extremities, and spinal column [7, 8]. OA of the hip and knee joints is the leading cause of disability worldwide [8]. It is primarily characterized by a molecular disorder or changes in cartilage metabolism, followed by structural changes, such as cartilage degradation, bone remodeling, and osteophyte formation. These changes result in the loss of normal joint function [9, 10].

The known risk factors for OA include genetic predisposition, obesity, trauma, and age [10]. Patients aged >50 years are four times more likely to develop post-traumatic OA [10]. The regenerative response of chondrocytes, which make up 5% of the volume of articular cartilage, decreases with aging. This leads to progressive cartilage degeneration and loss of the matrix, which provides the articular cartilage its biomechanical properties and makes up 95% of the tissue. This loss may lead to complete destruction of the articular cartilage structure. Furthermore, chondrocytes produce inflammatory mediators that may severely damage the surrounding tissue, such as cytokines, chemokines, and proteolytic enzymes [11].

Regenerative medicine is gaining recognition in the treatment of OA [12, 13]. Regenerative OA treatment focuses on regenerating articular cartilage. Various surgical procedures with limited clinical efficacy are used for this purpose [13]. Mesenchymal stem cells (MSCs) are a promising source for articular cartilage regeneration owing to their ability to differentiate into cartilage and bone cells and secrete trophic factors that promote regeneration [14]. The paracrine, anti-apoptotic, anti-inflammatory, and anti-aging effects of MSCs are crucial to the regeneration process. The anti-aging effect of adipose tissue-derived MSCs (AT-MSCs) on OA chondrocytes was found to be characterized by a decrease in non-replicative aging markers, mainly 8-oxo-7,8-dihydroguanosine, interleukins 6 and 8, vascular endothelial growth factors, and transforming growth factor-beta, which is caused by the inflammatory process [15]. Stem cells contribute to critical biological processes, including cell proliferation, differentiation, and the modulation of inflammation [16]. Stem cells may be isolated from adipose tissue and from the bone marrow, umbilical cord blood, and placenta [17]. Currently, it is generally recognized that MSCs are present in the connective tissue of almost all organs [18].

In humans, AT-MSCs have demonstrated greater proliferative capacity than other types of MSCs [19]. These cells retain their differentiation potential even after prolonged culturing, and their proliferation is less influenced by donor age, which is particularly significant for elderly and senile patients with osteoporosis [20].

AT-MSCs were first identified in the early 2000s; they demonstrated self-renewal ability and high potential for multilineage differentiation [21]. These cells have several advantages, including faster and easier isolation in culture, long-term cultivation with a preserved phenotype, pluripotency, and reduced susceptibility to aging [22]. Additionally, AT-MSCs have comparable potential with bone marrow-derived MSCs in differentiating into cells and tissues of mesodermal origin, such as adipocytes, cartilage, bone, and skeletal muscle cells [23]. However, easy and repeated access to subcutaneous adipose tissue and the simple procedure for obtaining AT-MSCs provide clear advantages over other types of MSCs [24–26].

Autologous Microfragmented Adipose Tissue with Stromal Vascular Fraction Containing Adipose-Derived Mesenchymal Stromal Cells

Autologous microfragmented adipose tissue with stromal vascular fraction (SVF) contains a mixture of cells, including stromal/stem cells, endothelial cells, smooth muscle cells, fibroblasts, immune cells, and other cell types. These cells are separated from adipocytes and stroma using various methods [24].

The clinical use of AT-MSCs is strictly regulated because they are considered drugs, restricting their widespread clinical use in the Russian Federation, Europe, and the United States [27–30]. These restrictions have prompted new studies on alternative AT-MSC therapies involving minimal manipulations [31]. Consequently, if AT-MSCs are not cultivated in vitro, but rather extracted from adipose tissue in the operating room without substantial surgical manipulations and without the use of collagenase, this treatment modality for patients with OA is approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) [32]. FDA and EMA consider enzymatic digestion of tissues to be substantial manipulation, which falls under strict regulatory restrictions. Minimal manipulation of AT-MSCs is the process of isolating multiple cell populations using mechanical procedures that adhere to FDA and EMA guidelines worldwide [32]. Alteration of biological, physiological, or structural features of cells or tissues is considered substantial manipulation. Obtaining a bone marrow aspirate is an invasive procedure involving certain complications for

the donor. In contrast, liposuction to obtain SVF is minimally invasive [32, 33].

Although enzymatic digestion is effective, it requires xenogeneic substances that may cause immune reactions. This contradicts the European principles of good manufacturing practice (regulation no. 1394/2007 of the European Parliament and of the European Council). To address this issue, separate devices have been employed in isolating SVF from adipose tissue [33].

Nonenzymatic fraction isolation methods utilize mechanical or physical phenomena to alter the structural integrity of adipose tissue. These methods are less specific and may isolate SVF cells from their own function. Some studies have introduced the concept of stromal vascular niche [34]. The final product obtained by nonenzymatic mechanical separation is not strictly cellular stromal vascular material, as is usually obtained by enzymatic separation. It is a combination of cellular debris, blood cells, and components of the extracellular matrix [35]. Moreover, mechanical devices can maintain cell clusters or their native environment, promoting longer preservation of cell function, including exosome release and secretion. The stromal vascular niche protects activated AT-MSCs, enhancing their efficiency in the recipient environment and triggering biological events that mimic the natural healing process [35]. Currently, several devices have been developed for the nonenzymatic separation and isolation of the SVF from adipose tissue [35].

Methods of Obtaining Autologous Microfragmented Adipose Tissue Containing Stromal Vascular Fraction and Adipose-Derived Mesenchymal Stromal Cells

These devices differ in separation methods, tissue dissociation times and degrees, and quality of the final SVF product. Nonenzymatic methods of SVF isolation generally rely on one of four techniques: centrifugation, pressure, filtration, and washing. The most common devices for collecting and purifying adipose tissue to obtain SVF containing AT-MSCs include PureGraft (Bimini Technologies LLC, USA), LipiVage (Genesis Biosystems, USA), Lipogems (Lipogems Int Spa, Italy), Rigenera (HBW srl, Italy), Lipo-Kit GT (Medikan-International Inc, Korea), Hy-Tissue Nanofat (Fidia Farmaceutici, Italy), Hy-Tissue SVF (Fidia Farmaceutici, Italy), StromaCell (MicroAire Surgical Instruments, USA), MyStem (MyStem LLC, Wilmington, USA), Revolve (Life Cell Corporation, USA), Wal Body-Jet и Q-Graft system (Human Med AG, Germany), and IntelliCell (Biosciences Inc, USA). Many of these devices have been evaluated in preclinical and clinical trials. Outdated systems for collecting and separating adipose tissue, such as the LipiVage and PureGraft devices, were among the first products in the regenerative medicine field of OA to be commercialized [36, 37].

The LipiVage system uses tissue collection, washing, and transfer technology to collect fat grafts under controlled conditions with vacuum, thus avoiding the need for centrifugation or decantation. An integrated filter rapidly (⩽15 min) separates the aspirated adipose tissue inside the cannula from oils and fluids. The fragmented adipose tissue obtained using the LipiVage system was similar to normal adipose tissue, which enabled the collection of large volumes of aspirate. However, microanalysis of the lipoaspirate was not performed.

PureGraft technology filters adipose tissue through a special membrane in a short period of time (up to 15 min). Furthermore, the lipoaspirate obtained from the PureGraft system contains larger particles (>1000 μm), enabling "dialysis" of adipose tissue without resorting to more destructive methods such as centrifugation [38–40]. These technologies are mainly applied in plastic surgery [41].

Lipogems is the most studied and frequently used system in clinical practice. This system allows for collecting tissue containing pericytes and AT-MSCs with minimal mechanical force. After aspirate processing, the final product is pulverized adipose tissue (600/400 μm) that is free of impurities and blood and extremely rich in AT-MSCs [42]. Lipogems devices are used in traumatology and orthopedics to treat tendinopathies and OA [43].

Alternatively, several researchers have developed an easy-to-use and cost-effective "clean" mechanical tissue disintegration system. This technology, called the Rigenera microtransplantation system, disaggregates autologous adipose tissue by collecting micrografts enriched with progenitor cells, growth factors, and AT-MSCs into a special receiver. This was confirmed in an in vitro study [44].

Some studies have comparatively analyzed different mechanical and enzymatic systems for obtaining SVF [45–47]. Raposio et al. [45] compared two procedures for isolating AT-MSCs: one based on enzymatic and mechanical methods (centrifugation and vibration using collagenase) and the other based solely on mechanical methods (centrifugation and vibration). The results show that the enzymatic and mechanical treatment of the aspirate revealed significantly more AT-MSCs than the mechanical method of adipose tissue isolation alone.

Additionally, Domenis et al. [46] demonstrated that AT-MSCs obtained using a mechanical device (Fastem kit) are less efficient than those obtained using enzymatic systems (Lipo-kit and Celution) for isolating SVF. Nevertheless, all three systems enable the collection of an adequate amount of adipose tissue.

However, Senesi et al. [47] revealed that AT-MSCs exhibit good cell viability and express the CD90+, CD105+, CD44+, CD119+, CD34-, CD45-, CD31-, and CD14- markers. Moreover, they showed the ability of AT-MSCs to differentiate in a chondrogenic or osteogenic direction using mechanical devices (Rigenera and Lipogems), as opposed to enzymatic separation.

Additionally, mechanical separation methods are used to obtain AT-MSCs from various perivascular functions. In such cases, enzymatic separation yields a "pure" population of

AT-MSCs that rapidly differentiate into mesodermal cell lines. This significantly increases the method's clinical efficiency [45, 46]. Among the two analyzed mechanical systems, only the AT-MSCs obtained with the Rigenera device were able to differentiate into mesodermal lines. However, the process was slower than enzymatic separation [47].

A new device called the Hy-Tissue SVF has been recently introduced into the wide clinical practice of orthopedic traumatologists. This device allows for SVF isolation in the form of free cells and microfragments (30/70 μm) of connective tissue containing stromal cells and extracellular matrix [48]. The system disaggregates autologous adipose tissue using a double bag with an inner filter bag consisting of a mesh with a permeability of up to 120 μm. When lipoaspirate is processed in this system, the main structural and morphological unit, namely, the fat niche, is preserved after disintegration. This protects the activated AT-MSCs and increases their efficiency in the biological medium. This makes this system different from the others because preserving fatty structural niches increases AT-MSC efficiency. Additionally, the lack of enzymatic influence on lipoaspirate decreases tissue trauma and maintains the structural and functional integrity of AT-MSCs. The decrease in fat granule size contributes to enhanced engraftment owing to the micrograft's effective and rapid revascularization in direct contact with the receiving vascular microenvironment [49, 50].

Clinical Efficiency of Autologous Microfragmented Adipose Tissue Containing Stromal Vascular Fraction and Adipose-Derived Mesenchymal Stromal Cells

Notably, MSCs promote the regeneration of articular cartilage and are actively used in clinical practice [15, 16, 18]. Several studies have confirmed the clinical and instrumental efficiency of using MSCs to treat OA [51–55]. The use of AT-MSCs in OA is relatively recent; however, over the past 10 years, AT-MSCs have gained popularity in regenerative medicine because of their proven safety and efficacy in regenerating articular cartilage [16].

The efficacy of intra-articular injection of AT-MSCs in knee OA has been clearly demonstrated by clinical, radiological, arthroscopic, and histological studies with an average follow-up period of at least 6 months [51].

Another clinical series showed that an intra-articular injection of AT-MSCs in patients with severe knee OA stopped the progression of the disease's clinical manifestations and achieved the study's primary endpoints (i.e., pain severity, joint function, and return to physical therapy) for at least 24 months [52].

Spasovski et al. [53] reported that AT-MSC therapy significantly decreases the severity of the clinical symptoms of knee OA after 3 months of manipulation, reaching maximum efficacy after 6 months.

Therapy using AT-MSCs for OA has demonstrated the high chondrogenic potential of AT-MSCs obtained from the infrapatellar and suprapatellar regions when injected into the knee joint cavity [54]. *In vitro* and *in vivo* studies have confirmed that AT-MSCs collected from the infrapatellar region have a higher chondrogenic potential [54].

An experimental model of severe OA in mice showed that administering AT-MSCs obtained from the suprapatellar region decreased inflammation and cartilage degeneration by increasing glycosaminoglycan synthesis and activating endogenous chondrogenesis [55]. These effects of AT-MSCs appear to be associated with the reduction of pro-inflammatory cytokines and chemokines in articular cartilage, inhibition of chondrocyte apoptosis, limitation of hypertrophic and fibrotic chondrocyte phenotypes, and decreased collagenase activity [55]. A significant limitation of the abovementioned studies on the efficiency of AT-MSCs in treating OA is the short patient follow-up period.

Jo et al. [50] and Pers et al. [55] revealed the high clinical efficacy of intra-articular AT-MSC injections for knee OA with an average follow-up period of at least 24 weeks. Additionally, Song et al. [56] demonstrated the high clinical and instrumental efficacy of AT-MSCs in patients with knee OA, with an average follow-up period of at least 96 weeks. However, in some cases, the researchers repeated intra-articular injections of AT-MSCs. Magnetic resonance imaging data indicated that the studied group of patients showed a decrease in pain severity, an increase in knee joint movement amplitude, and an increase in cartilage thickness [52, 57].

Zhang et al. [57] presented the results of a comparison of the clinical efficacy of AT-MSCs and hyaluronic acid salt preparations in 126 patients with OA who had a follow-up period of at least 5 years. They concluded that the long-term intra-articular application of AT-MSCs derived from autologous microfragmented adipose tissue with SVF allowed for the control of OA symptoms in 60% of patients and preservation of articular cartilage volume.

A recent systematic review exhibited the high clinical and instrumental efficacy of intra-articular AT-MSC injections for patients with knee OA [58]. Six months after the procedure, most patients showed decreased disease severity, increased daily activity, improved quality of life, and hyaline cartilage thickening in the affected joints [58]. A systematic review by Goncharov et al. [59] yielded similar results regarding the use of AT-MSCs in patients with OA of large joints. The review included data from 22 studies involving >1500 respondents.

CONCLUSION

OA is an urgent problem in modern medicine that requires the search for new and promising treatment methods, especially for elderly and senile patients. Cell therapy combined with traditional therapeutic approaches is a new OA treatment method that may improve patients' quality of life.

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In recent years, the use of AT-MSCs to treat OA has significantly gained increasing interest owing to their ease of obtaining, preparing, and implanting without traditional surgical intervention. AT-MSCs can stimulate tissue regeneration, reduce inflammation, and alleviate pain.

AT-MSCs have several advantages. They are easily cryopreserved, proliferate rapidly in culture, and contain a greater number of active cells that retain stem cell phenotype and pluripotency. Furthermore, harvesting adipose tissue is more cost-effective than obtaining bone marrow, and the procedure is minimally invasive and may be repeated.

Notably, AT-MSCs indirectly decrease the levels of proinflammatory cytokines and chemokines in articular cartilage, inhibit chondrocyte apoptosis, and limit the number of hypertrophic and fibrotic chondrocyte phenotypes. Additionally, AT-MSCs decrease collagenase activity. These mechanisms lead to decreased pain intensity, increased joint function, and improved quality of life for patients with OA.

Nevertheless, more long-term randomized controlled trials are required to thoroughly analyze the efficacy and safety of AT-MSCs in treating patients with OA.

ADDITIONAL INFORMATION

Authors contributions: B.V.A.: conceptualization; S.I.A.: writing—original draft; M.A.V.: writing—original draft; S.S.V.: writing—original draft; F.A.P.: writing—review & editing. All authors approved the version of the manuscript to be published and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Б.В.А. — разработка концепции; С.И.А. — написание черновика рукописи; М.А.В. — написание черновика рукописи; С.С.В. — написание черновика рукописи; Ф.А.П. — написание рукописи — рецензирование и редактирование. Все авторы одобрили рукопись (версию для публикации), а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой её части.
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Источники финансирования. Отсутствуют.
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Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали два внешних рецензента, член редакционной коллегии и научный редактор издания.

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