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Use of mesenchymal stromal cells in the therapy of musculoskeletal disorders: A literature review

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Abstract. The rapid advancement of methods for obtaining multipotent progenitor cells, known as mesenchymal stromal/stem cells, from various human tissues and organs has driven progress in cellular therapy and regenerative medicine. This study aimed to review current scientific data on the use of mesenchymal stromal cells in the treatment of traumatic and orthopaedic disorders, providing clinicians with insights into the challenges and prospects of their clinical application. The sources of mesenchymal stromal cells, their characteristics, and their therapeutic effects on musculoskeletal disorders were analysed. These cells have been found to be applicable in both autologous and allogeneic forms due to their ability to differentiate into osteoblasts, chondrocytes, tenocytes, adipocytes, and other cell types, thereby promoting the regeneration of damaged tissues. Furthermore, mesenchymal stromal cells have been confirmed to exhibit paracrine activity by producing cytokines and growth factors, which contribute to their regenerative and regulatory effects both *in vitro* and *in vivo*. At the same time, it has been noted that despite their significant therapeutic potential, the clinical application of mesenchymal stromal cells is associated with several challenges, including immunocompatibility, stability, heterogeneity, and limited differentiation and migration capacities. The prospects for overcoming these limitations through cellfree approaches have been considered, particularly the use of exosomes secreted by mesenchymal stromal cells, which contain biologically active molecules such as mRNA, microRNA, proteins, and bioactive lipids. These components have been shown to promote cell proliferation, migration, regeneration, immunomodulation, and angiogenesis, making them a promising avenue in regenerative medicine. The findings of this study may contribute to the further development of effective therapeutic strategies in regenerative medicine, particularly in orthopaedics and traumatology. The practical significance of this research lies in the refinement of cellular therapy approaches aimed at restoring damaged tissues, which may serve as a foundation for future clinical trials and subsequent implementation in medical practice

Keywords: stem cells; exosomes; tissue regeneration; traumatology; orthopaedics

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INTRODUCTION

Mesenchymal stromal cells (MSCs) represent a promising avenue in regenerative medicine due to their unique biological properties. Current research highlights their pivotal role in regenerative processes, particularly in orthopaedics and traumatology. Damage to bone, cartilage, tendons, and ligaments is a common issue, especially among patients with degenerative musculoskeletal conditions and sports injuries. Existing treatment methods, including surgical interventions and pharmacological therapy, do not always provide full functional recovery of damaged tissues, driving a growing interest in cell-based technologies as an effective alternative.

Scientists are actively exploring the potential of MSCs as a source of regenerative therapy. A bibliometric analysis by Z. Deng *et al*. [1] demonstrated a significant increase in publications regarding their application in orthopaedics, specifically in the areas of osteogenic differentiation, cartilage regeneration, osteoarthritis treatment, and the use of biomaterials in combination with MSCs. MSCs can be obtained from various sources, including bone marrow, adipose tissue, synovial membrane, umbilical cord blood, dental pulp, and others. V.V. Maldonado *et al*. [2] note that each source has its own characteristics, which influence the cells' ability to differentiate and proliferate. For example, MSCs from adipose tissue are characterised by high availability and osteogenic potential.

MSCs are distinguished by their capacity for self-replication, self-division, and multipotent differentiation, forming various cell types: adipocytes, osteoblasts, chondrocytes, and myocytes. Scientists M. Sandonà *et al*. [3] have established that their migratory activity and interaction with the extracellular matrix contribute to tissue regeneration. According to reports by Y. Wang *et al*. [4], their proliferation and differentiation in *in vitro* conditions require biological signals formed through interactions with the extracellular matrix, cytokines, and growth factors.

J. Tang *et al*. [5] researched the role of exosomes secreted by MSCs in bone tissue regeneration processes. It was discovered that these extracellular vesicles contain growth factors and microRNAs, which stimulate osteogenesis and reduce inflammation in the affected area, opening up prospects for cell-free therapy. Despite their significant potential, the biological properties of MSCs depend on cultivation conditions, which can affect their clinical effectiveness. L.A. Costa *et al*. [6] emphasised the importance of the microenvironment for the functional activity of transplanted cells, highlighting the need to optimise methods for cultivating and administering MSCs.

MSCs are widely applied in the therapy of various diseases, including orthopaedic pathologies. Scientists Y. Zhang *et al*. [7] demonstrated that the use of MSCs accelerates the fusion of complex long bone fractures, stimulates osteogenesis, and improves the strength of newly formed bone tissue. Similar results were obtained by R. Ossendorff *et al*. [8], who proved that MSC injections significantly reduce bone tissue regeneration times, especially in cases of complicated healing.

In addition to fracture treatment, an important area of MSC application is the therapy of sports injuries. K.-I. Kim *et al*. [9] showed the effectiveness of their administration in meniscus and ligament ruptures, which promotes faster restoration of joint functional activity. Analogous results were obtained by J. Chen *et al*. [10] demonstrated that MSCs significantly improve tendon and ligament healing in professional athletes, reducing the risk of recurrence. Scientists O. Grabovyi *et al*. [11] established that the natural activation of MSCs in response to injuries contributes to their differentiation into fibroblasts, which form a connective scar tissue.

Particular attention is drawn to the potential of MSCs in cartilage tissue regeneration. Y. Jiang & R.S. Tuan [12] note that MSCs and their extracellular matrices are capable of activating chondrogenesis, promoting the repair of damaged cartilage in osteoarthritis and other degenerative joint diseases. The research by T. Frazier *et al*. [13], which focuses on the clinical application of MSCs in osteoarthritis treatment, is also of significant interest. The authors analysed the effectiveness of MSC transplantation in patients with knee joint pathology and found that cell therapy contributes to pain reduction, improved mobility, and slowed degenerative changes.

Thus, current research confirms the significant potential of mesenchymal stromal cells in the treatment of injuries and degenerative diseases of the musculoskeletal system. However, despite numerous studies, the use of MSCs in the therapy of orthopaedic diseases remains controversial. Achieving positive results requires consideration of several factors, including potential side effects. Therefore, it is important to systematise data on the positive and negative aspects of MSCs' impact on the treatment of musculoskeletal pathologies, predict development trends, and systematise literary information of the scientific base for further research in this field. This study aimed to analyse current scientific data on the use of MSCs in the treatment of orthopaedic and traumatological diseases in terms of their ability to differentiate and produce regulatory factors, as well as to highlight the challenges and prospects of their clinical use.

To achieve the stated aim, a systematic review of literature available in the MEDLINE/PubMed, Google Scholar, Scopus, and Web of Science databases, covering the period 2001-2024, was conducted; trends in publications for 2015-2024 were analysed separately. Review articles and described clinical cases related to the application of MSCs in traumatology and orthopaedics were considered. The study employed review-analytical and bibliosemantic methods to determine the current state of research on the problem. The literature search utilised various combinations of key terms, including "mesenchymal stem cells", "mesenchymal stromal cells", "*in vitro*", "*in vivo*", "differentiation", "regenerative medicine", "sports medicine", "clinical application", "treatment", "bone defect", "osteonecrosis", "fracture healing", "nonunion", "osteochondral defect", "cartilage repair", "cartilage defect", "osteoarthritis", "osteogenic differentiation", "knee", and "meniscus". All data were obtained from open sources; therefore, ethical approval or informed consent was not required.

INFORMATION SOURCES AND SEARCH STRATEGY

As shown in Figure 1, the database search in PubMed, Google Scholar, Web of Science, and Scopus yielded 1,057

literary sources in Ukrainian and English, which included studies utilising MSCs. After excluding duplicate articles based on titles and abstracts, 295 publications were selected, covering the use of MSCs in reconstructive and regenerative medicine. Following a review of the research results, examination of their full content with additional manual searching of references, and exclusion of articles unrelated to musculoskeletal disorders, 76 publications were selected that met the aim and criteria of the query. Approximately 65% of the studies focused on the treatment of knee joint diseases, predominantly osteoarthritis; about 30% concerned adipose tissue MSCs.

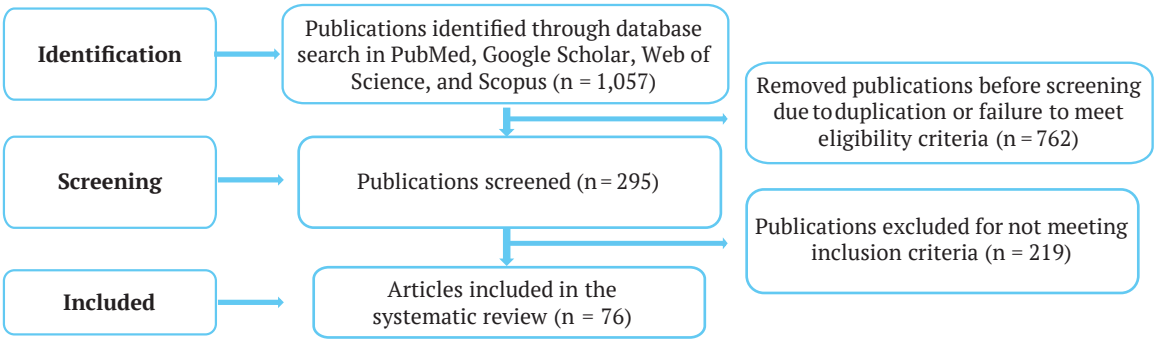

Figure 1. Flowchart of publication selection for the systematic review
Source: compiled by the authors

Scientific publications in this field are predominantly focused on fundamental research and clinical trials. As depicted in Figure 2, the analysis of the annual distribution of publications demonstrates a gradual increase in scientific activity within the field of orthopaedics from 2015 to 2024, except for a decrease in the number of studies in 2020. The authors of this article suggest that this reduction is likely related to the COVID-19 pandemic, during which an overall decline in scientific productivity was observed. The maximum number of publications (131) was recorded in 2019, while the minimum (77) occurred in 2015. The annual publication of over 80 articles confirms a sustained interest among researchers in the use of MSCs for treating orthopaedic diseases, fostering a robust research environment in this area. From the analysis of keyword cooccurrence across different topics in scientific publications (Fig. 3), it is evident that the primary research directions in traumatology include sources of stem cells, their differentiation into bone and cartilage tissue, exosomes, and regenerative medicine.

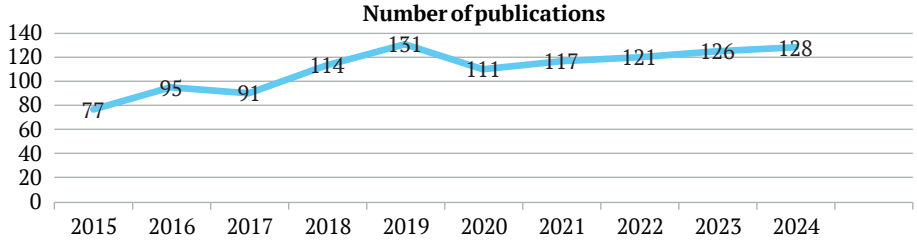

Figure 2. Dynamics of annual publication count and trends in MSC use for musculoskeletal regenerative medicine, 2015-2024
Source: compiled by the authors

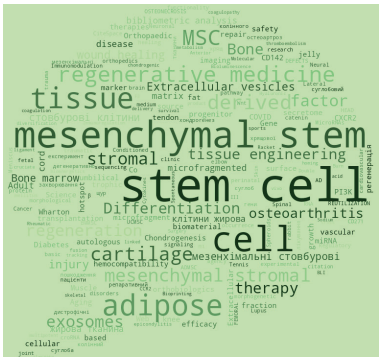

Figure 3. Cluster analysis of keywords
Source: compiled by the authors

Thus, the conducted literature analysis demonstrates a sustained interest within the scientific community in the application of MSCs in orthopaedic practice, particularly in the treatment of osteoarthritis and cartilage tissue regeneration. The identified trends confirm the increasing number of studies in this field, indicating the promising nature of MSC use in reconstructive medicine. Optimising MSC transplantation methods, studying their biological mechanisms, and conducting long-term evaluations of their clinical efficacy will contribute to the advancement of approaches for regenerating damaged tissues and the implementation of new therapeutic strategies.

SOURCES AND THERAPEUTIC POTENTIAL OF MSCS

The latest advancements in regenerative medicine have created new opportunities for the development of orthopaedics and traumatology, potentially transforming clinical practice approaches. Conditions that, as of 2025, are predominantly treated with surgical methods may in the future be effectively managed with less invasive approaches, such as MSC therapy. Research by C. Brown *et al*. [14] and L. da Silva Meirelles *et al*. [15] confirms that MSCs are capable of differentiating into cells of bone, cartilage, tendon, ligament, muscle, and other tissues. According to the classification by the International Society for Cellular Therapy, terms such as "mesenchymal stromal cells" are used for cells in the body (*in vivo*), and "multipotent stromal cells" are used for cells in culture (*in vitro*). The International Society for Cellular Therapy has defined basic criteria for MSC identification [16], including adherence to plastic under standard culture conditions; the presence of specific surface antigens CD73, CD90, CD105, and the absence of CD34, CD45, CD14/11b, CD79α/19, HLA-DR; and the ability to differentiate into osteoblasts, chondroblasts, and adipocytes *in vitro*.

The differentiation process is a crucial step in the transformation of MSCs into osteocytes and chondrocytes. This process is regulated by numerous signalling pathways, including BMP/Smad, Wnt/β-catenin, PI3K/AKT, MAPK, TGF-β, Notch, NF-kB, and others, which play a key role in regulating this process. For example, Q. Zhou *et al*. [17] demonstrated that the activation of BMP7/Smad5 promotes the selective differentiation of MSCs into chondrocytes. Furthermore, H.D. Fu *et al*. [18] established that BMP-7 can also accelerate the differentiation of MSCs into cartilage cells through the activation of the Wnt/β-catenin pathway. The PI3K/Akt pathway also plays an important role in bone regeneration: A. Yang *et al*. [19] showed that its activation involving IL-8 contributes to enhancing the therapeutic effect of MSCs in bone tissue repair. Research by U. Kozlowska *et al*. [20] indicated that MSCs obtained from different tissues share common characteristics, but their biological activity and markers vary depending on the source. It was found that prolonged cultivation affects the biological activity of MSCs; in particular, it can reduce their proliferative potential and alter the expression of certain markers. It has also been proven that bone marrow MSCs have the best capacity for multilineage differentiation. At the same time, adipose MSCs can serve as an alternative source due to their similar properties to bone marrow stromal cells.

Different sources of origin and differentiation ability allow MSCs to be classified into unipotent, multipotent, totipotent, and pluripotent cells, depending on their differentiation potential. Research by A. Vaish *et al*. [21] has shown that induced pluripotent MSCs, obtained by reprogramming somatic cells, retain the ability for multilineage differentiation, similar to embryonic stem cells, but have lower immunogenicity, which reduces the risk of rejection during transplantation. In another study by A. Vaish & R. Vaishya [22], the authors examined the molecular mechanisms that ensure MSC pluripotency. It was demonstrated that the transcription factors Sox2, Oct4, and Nanog play a key role in maintaining stem cell status and regulating the expression of genes associated with cell proliferation and self-renewal. The analysis also showed that the surrounding microenvironment (e.g., signals from growth factors and the extracellular matrix) can modulate the differentiation potential of MSCs, directing them towards a specific cellular phenotype.

Until 2008, bone marrow was the primary source of MSCs. However, as noted by S. Konovalov *et al*. [23, 24] and M. Tronko *et al*. [25], in recent years, cells obtained from perinatal and adipose tissues have been increasingly used. They demonstrate a high safety and haemocompatibility profile, allowing for their use in systemic infusion. Similar conclusions were drawn by G. Moll *et al*. [26, 27], who emphasise the need to improve the minimum safety criteria for MSCs. They analysed the intravascular application of MSCs and highlighted the importance of assessing tissue factors and haemocompatibility to enhance clinical efficacy. Adipose tissue-derived MSCs provide a higher cell yield and greater longevity compared to bone marrow stem cells, although they are less capable of differentiating into bone and cartilage tissue. Despite this, their effectiveness in treating osteoarthritis has been confirmed by long-term clinical results. As noted by U. Kozlowska *et al*. [20], in addition to multipotent differentiation, the paracrine effect of MSCs – the secretion of growth factors (BMP, TGF-β, VEGF, etc.) that promote angiogenesis, proliferation, and cell regeneration – plays a key role in tissue regeneration. Similar data are provided by H.H. Maniar *et al*. [28], highlighting the significant potential of stem cells in orthopaedic practice.

As of 2025, genetically modified MSCs, capable of releasing growth factors over extended periods, are being actively developed. In particular, research by G.E. Salazar-Noratto *et al*. [29] explores approaches to enhance the survival of transplanted MSCs in tissue engineering and regenerative medicine. However, the majority of transplanted stromal cells accumulate in internal organs (liver, spleen, lungs), which limits their effectiveness and indicates the need for the development of cell-free therapeutic approaches. As an alternative, the use of secretomes – bioactive substances produced by MSCs, including exosomes and microvesicles – is proposed. This approach has been actively researched by scientists M.D. Hade *et al*. [30] and M. Maqsood *et al*. [31]. They note that secretomes contain a wide range of growth factors, cytokines, and exosomes, which promote tissue regeneration and may serve as a promising therapeutic agent in regenerative medicine.

Exosomes are nanoscale vesicles (30-100 nm) with a lipid bilayer membrane, typically produced by MSCs and present in various biological fluids. M.H. Gerami *et al*. [32]

examine the role of MSCs and their exosomes in the treatment of musculoskeletal disorders, particularly bone and joint pathologies, and emphasise their significant potential for orthopaedic applications. Recent studies have shown that exosomes contain various biologically active molecules, such as mRNA, microRNA, proteins, and bioactive lipids [33, 34]. C. Porcu *et al*. [34] analysed their involvement in skeletal muscle regeneration, opening new perspectives for the therapy of musculoskeletal pathologies. It is known that exosomes are involved in the regulation of many key biological processes, including cell proliferation, migration, enhancement of regenerative properties, inhibition of apoptosis, immunomodulation, and stimulation of angiogenesis. D.H. Hoang *et al*. [33] confirm their effectiveness in improving tissue healing and repair processes. Current research focuses on studying the molecular mechanisms that influence stem cell differentiation, paracrine signalling, immunomodulatory properties, and tissue remodelling processes in the orthopaedic microenvironment. L.L. Bagno *et al*. [35] analysed the impact of exosome delivery methods on their biological activity and therapy effectiveness. In 2025, clinical trials are ongoing to assess the safety and efficacy of stem cell use in the treatment of orthopaedic diseases.

THE ROLE OF MSCS IN BONE DEFECT REGENERATION

Nonunion of long tubular bones remains a complex challenge in achieving effective bone osteogenesis [36]. MSC therapy may represent an innovative approach to treating such lesions. Z. Zhou *et al*. [37] focus on improving methods for utilising stem cells, growth factors, and integrating MSCs with biomaterials, which contribute to accelerating bone tissue regeneration. Y. Jiang & R.S. Tuan [12] were among the first to investigate the impact of MSCs in the field of orthopaedics. They established that cells isolated from adult human bone fragments are capable of differentiating into various cell types of mesenchymal origin *in vitro*. Similar results were obtained by R. Berebichez-Fridman & P.R. Montero-Olvera [38], noting that MSCs obtained from damaged muscle tissues have similar phenotypes to bone marrow MSCs and exhibit the ability to transform into osteoblasts, chondrocytes, and adipocytes. Furthermore, researchers R. BerebichezFridman *et al*. [39] found that bone morphogenetic protein (BMP-2) stimulates DNA synthesis, activates replication, and promotes the directed differentiation of MSCs into osteoblasts.

Most existing clinical studies focused on bone tissue regeneration involving stem cells are cohort studies. According to reports by A.M. Theodosaki *et al*. [40], the use of autologous, genetically unmodified MSCs *in vivo* for bone tissue regeneration demonstrates the safety and therapeutic potential of this treatment. E. Lucarelli *et al*. [41] were among the first to investigate the possibility of using autologous bone marrow stromal cells, cultured *ex vivo*, for the reconstruction of large bone defects. The authors demonstrated that the application of such cells in combination with biomaterials promotes the formation of new bone tissue and successful defect repair, which is confirmed by radiological and clinical observations. In a study by Y. Liu *et al*. [42], it was established that the transplantation of MSCs along with their secreted extracellular matrix ensures robust bone tissue formation both *in vitro* and *in vivo*. This occurs through endochondral ossification under the influence of chondrogenic and osteogenic signals.

Combining MSCs with scaffolds or growth factors significantly enhances the healing of traumatic bone defects and nonunion fractures. The study by D. Dufrane [43] demonstrated the effectiveness of using 3D-printed grafts made from autologous adipose tissue stem cells to repair significant long bone defects. In a systematic review conducted by A.M. Theodosaki *et al*. [40], out of 10,091 retrieved clinical studies, 14 of which met the inclusion criteria, 138 patients underwent treatment with MSCs cultured on scaffolds. In all cases, bone tissue regeneration was observed, with better results than standard treatments. For the treatment of avascular necrosis of the femoral head, stem cell-enriched bone marrow aspirate concentrate is widely used. Its effectiveness is confirmed in the research by N. Pawar *et al*. [44].

The studies described above confirm the safety of using autologous MSCs for bone tissue repair in segmental long bone defects. None of the studies reviewed in this section reported complications such as inflammatory processes or excessive tissue growth. However, according to G.-I. Im [45] and B. Lukomska *et al*. [46], extensive cultivation of stromal tissues (4-5 months) can lead to genomic instability, which poses a risk of malignant transformation. On the other hand, a shorter period of *in vitro* expansion (up to 8 weeks) may explain the absence of reports of malignancy in the conducted clinical studies. Despite the promising results of successful bone tissue regeneration, G.-I. Im [36] and B. Lukomska *et al*. [46] emphasise that it is premature to draw definitive conclusions about the efficacy and safety of MSC-based methods. This is due to the limited number of controlled studies and the need for further randomised clinical trials.

CARTILAGE REGENERATION USING MSCS

Articular cartilage, unlike bone tissue, has limited regenerative capabilities. Its damage often leads to the development of degenerative joint diseases, such as osteoarthritis, and loss of mobility [12, 45]. Research by H. Le *et al*. [47] notes that due to the absence of blood vessels in articular cartilage tissue, mature chondrocytes exhibit a low capacity for proliferation and extracellular matrix synthesis to repair defects. Current research focuses on the use of MSCs, particularly those derived from adipose tissue, as they demonstrate the ability to divide and differentiate into chondrocytes [13, 47, 48]. However, even MSC differentiation does not always ensure successful tissue regeneration [20]. The stages of chondrogenesis include cell condensation, matrix synthesis, and maintenance of tissue homeostasis. Each stage requires specific growth factors [12]. In cartilage tissue lesions, meniscus injuries, cruciate ligament ruptures, and other knee joint pathologies, stromal cells are considered one of the most promising components of regenerative medicine [48]. Significant research has been conducted to study cartilage regeneration processes. For example, S. Rodeo [49] made substantial contributions to the study of the fundamental principles and clinical use of MSCs in orthopaedic sports medicine, particularly in the repair of menisci and cartilage in knee joints, shoulder joint tendons, and more. Additionally, research by Y.-M. Pers *et al*. [50] focuses on the use of mesenchymal stem cells to control

inflammation in osteoarthritis, opening new perspectives for regenerative therapy.

In a clinical study by K.-Y. Saw *et al*. [51], patients with cartilage defects in the knee joint were administered MSCs or hyaluronic acid weekly for five weeks. The results showed that patients receiving MSC injections experienced hyaline cartilage regeneration, which was not observed in the hyaluronic acid group. Experimental studies by V. Fishchenko *et al*. [52] confirmed the positive impact of adipose tissue-derived MSCs on the restoration of articular cartilage structure and function in rats after traumatic injuries. The researchers demonstrated the effect of MSCs on accelerating reparative chondrogenesis, as well as the formation of orderly osteogenesis without premature excessive matrix ossification or dystrophic changes in chondrocytes and chondroblasts. V. Fishchenko & L. Mammadov [53] also conducted clinical studies that demonstrated the high effectiveness of MSCs administered intra-articularly for the treatment of distal femoral fractures (19 patients) and deforming osteoarthritis of the knee joint (15 patients), regardless of the type of injury and the stage of gonarthrosis, confirming the promising nature of this approach.

Other studies have also demonstrated the safety and improvement in clinical and radiological parameters following MSC injections in patients with osteoarthritis [9, 54, 55]. F. Davatchi *et al*. [54] observed three patients with knee osteoarthritis for five years after intraarticular MSC administration, noting long-term pain reduction and improved joint function. In a larger study, D. Screpis *et al*. [55] developed a minimally invasive approach for treating knee osteoarthritis. The trial involved 202 patients aged 18 to 70 years who received intra-articular injections of MSCs derived from micro-fragmented adipose tissue at various stages of the disease. After 24 months of follow-up, the positive impact of the injections on joint functional status was confirmed. In the research by K.-I. Kim *et al*. [9], it was demonstrated that intra-articular administration of autologous MSCs, derived from adipose tissue and stromal vascular fractions, without additional therapy, results in high clinical efficacy, treatment safety and stimulates cartilage repair in patients with knee osteoarthritis. When comparing allogeneic and autologous MSCs, both sources showed effectiveness in reducing pain after six months of follow-up, but after a year, autologous MSCs demonstrated superiority, particularly in improving functional outcomes. At the same time, their regenerative potential depends on the patient's comorbidities, such as cardiovascular pathologies, which is an important factor for elderly patients with osteoarthritis.

Y. Jiang & R.S. Tuan [12] analysed the bioactivity, specifically the chondrogenic properties, of multipotent stem cells and progenitor cells derived from autologous adipose tissue, autologous bone marrow, and autologous articular cartilage. They established that different cell types exhibit distinct effectiveness in cartilage repair *in vivo*: articular cartilage stem cells best form cartilage-like tissue; bone marrow cells create a favourable environment for chondrogenesis, promoting the deposition of aggrecan and matrix proteins; conversely, adipose tissue cells more rapidly form fibrous tissue filling, which is less similar to cartilage tissue. The authors attribute these differences to the fact that adipose tissue cells synthesise 20-60% more proteins than other cell types and form an extracellular matrix with high levels of fibronectin and type I collagen. Meanwhile, articular cartilage stem cells produce more type III collagen and deposit less fibronectin and type I collagen. These results underscore the importance of selecting the stem cell source for stimulating cartilage regeneration, as the activation of chondrogenic differentiation and matrix formation depends on several key growth factors specific to each cell type.

Studies by K. Čamernik *et al*. [56] have demonstrated that MSCs derived from skeletal muscles, when compared to MSCs derived from the bones of 21 osteoarthritis patients, exhibited higher clonogenicity, faster growth rates, and shorter cell doubling times, as well as showing good osteogenic and myogenic properties. Furthermore, a positive correlation was observed between CD271 expression and adipogenesis. In preclinical studies by A. Vadhan *et al*. [57], it was proven that exosomes secreted by stromal cells are effective in osteoarthritis due to their chondroprotective and anti-inflammatory properties. The scientists found that these vesicles are capable of reducing the synthesis of pro-inflammatory cytokines while stimulating the production of anti-inflammatory factors and also inhibiting the activity of matrix metalloproteinases, which degrade the cartilage extracellular matrix. Exosomes can enhance cartilage tissue regeneration by promoting the differentiation of chondrogenic cells into chondrocytes, as well as stimulating the synthesis of collagen and proteoglycans [32]. In clinical studies conducted by K. Kawata *et al*. [58], it was shown that intra-articular administration of MSC-derived extracellular vesicles promotes the repair of meniscus defects and also stimulates the growth and migration of chondrocytes and synovial stem cells. Transcriptome/RNA analysis by comprehensive sequencing confirmed that MSC-derived extracellular vesicles upregulate CXCL5 and CXCL6 in chondrocytes, activating their growth and migration through the CXCR2 axis. The effectiveness of MSC-derived exosomes in repairing damaged intervertebral discs was also demonstrated in a study by A. Hajiesmailpoor *et al*. [59].

Tissue engineering, based on the use of stem cells in combination with scaffolds such as tricalcium phosphate, hydroxyapatite, and bioactive glass, has demonstrated its effectiveness in repairing bone and cartilage tissue defects. A systematic review by N. Montemurro *et al*. [60] describes the latest biomaterials (Compact-bio BoneR) and growth factors used in neurosurgery, dentistry, and orthopaedics for bone tissue regeneration. The authors highlight the promising application of bioactive materials in combination with MSCs to enhance osteogenesis and chondrogenesis. Research by S. Nedunchezian *et al*. [61] is dedicated to the creation of bioprinted hydrogel scaffolds based on hyaluronic acid-containing adipose tissue stem cells. The use of a dual crosslinking method allowed for the production of a biomaterial with improved mechanical characteristics, which promoted effective chondrogenic differentiation of MSCs. In turn, Y. Zhang *et al*. [62] demonstrated that the combination of MSCs derived from the human umbilical cord and cell-free cartilage matrix significantly improves cartilage tissue regeneration in a goat model compared to the microfracture method. After a period of observation, animals that received the transplants showed the formation of hyaline-like cartilage with appropriate structural

organisation. In a study by G. Wang *et al*. [63], a bilayer bionic cartilage matrix (membrane) was created, mimicking the structure, chemical, and mechanical characteristics of mature articular cartilage. The upper layer of the membrane consisted of a combination of collagen, sodium hyaluronate, and chitosan, while the transition layer included collagen, silk fibroin, and chitosan. The membrane was implanted into a cartilage defect in the knee joint of rabbits with osteoarthritis. Studies showed that this bionic membrane promotes MSC proliferation and differentiation, providing effective articular cartilage repair. In turn, Z. Wang *et al*. [64] used coral scaffolds with differentiated osteoblasts from rabbit adipose tissue stem cells and transplanted them into bone defects in mice. After 8 weeks, a significant acceleration in new bone tissue formation was recorded. MSCs are a promising tool for treating cartilage tissue pathologies. The selection of stem cell sources and usage protocols remains an important factor that requires further research to optimise treatment strategies.

THE ROLE OF MSCS IN TENDON AND LIGAMENT REPAIR: CHALLENGES AND PROSPECTS FOR CLINICAL APPLICATION

Tendons are tissues with limited blood supply and low cellular density, which complicates their ability to self-repair. According to a review by L. Jiang *et al.* [65], the tendon healing process involves three phases: inflammatory, proliferative, and remodelling, during which scar tissue often forms. The authors note that MSCs play a significant role in tendon and ligament repair due to their multidirectional differentiation potential. In tendon injuries, MSCs contribute to their repair through four main mechanisms: reducing inflammation, neovascularisation, cell proliferation, and differentiation into target cells. Stromal cells are capable of differentiating into tendon cells under specific *in vivo* or *in vitro* induction conditions, which promotes the stimulation of regeneration. Due to their pronounced paracrine effect, they secrete cytokines, growth factors, and chemokines, stimulating angiogenesis and cell proliferation in damaged tissue. Y. Wang *et al*. [66] in their study on a rat model of Achilles tendinopathy showed that the administration of exosomes derived from tendon stem cells (TSCs) significantly reduces the expression of matrix metalloproteinases (MMP)3, increases the expression of tissue inhibitor of metalloproteinases-3 (TIMP-3) and Col1a1, which improves tendon biomechanical properties and promotes their regeneration. The obtained results confirm that TSC-derived exosomes may be a promising therapeutic strategy in repairing damaged tendons by balancing extracellular matrix remodelling and stimulating tenogenesis. Concurrently, according to L. Jiang *et al.* [65], MSCs also contribute to the reorganisation of the extracellular matrix by activating collagen synthesis and stimulating the transformation of type III collagen into type I collagen, which is a crucial aspect of tendon structural remodelling after injury.

MSCs can differentiate into fibroblasts, which comprise the main structural component of tendons and ligaments, thereby promoting their regeneration. Since the anterior cruciate ligament has low regenerative potential, its reconstruction is typically performed using autologous tendons. However, research on resident stem cells in tissues opens new possibilities for the repair of this structure. In a study by Y. Ogata *et al*. [67], it was established that MSCs isolated from the anterior cruciate ligament express CD90 and CD73 markers and have a high capacity for differentiation into fibroblasts.

A pilot study conducted by M. Khoury *et al*. [68] demonstrated significant clinical improvement and structural repair of tendons after the administration of autologous adipose tissue MSCs in 18 patients with chronic lateral epicondylitis of the elbow, resistant to conservative therapy. J.L. Ellera Gomes *et al*. [69] used mononuclear stem cells, isolated from iliac crest bone marrow aspirate, to treat 14 patients with rotator cuff tears. After 12 months of follow-up, clinical examinations and magnetic resonance imaging confirmed the complete healing of all 14 tears. Some MSC-based drugs have already undergone clinical trials. For example, the drug CARTISTEM, created from human umbilical cord blood MSCs, received approval from the Korean FDA in 2012 [70]. In December 2024, the FDA approved the drug Ryoncil (remestemcel-L-rknd), developed from allogeneic bone marrow mesenchymal stromal cells and intended for the treatment of steroidresistant acute graft-versus-host disease. These achievements indicate the growing interest and progress in the clinical application of mesenchymal stem cell-based drugs in various therapeutic areas.

Despite the significant potential of MSCs in the therapy of musculoskeletal disorders, their clinical application faces several challenges. For example, J. Xue & Y. Liu [70] note that, despite the pronounced immunomodulatory potential of MSCs, which affects innate and adaptive immunity through the production of immunosuppressive and immunomodulatory substances, their survival after infusion is quite low. This is due to the immediate inflammatory response that develops right after cell administration. U. Kozlowska *et al*. [20] emphasise that the rapid destruction of MSCs after administration is caused by the activation of the local immune response. Optimising transplantation conditions, including the use of anti-inflammatory agents or special carriers, can significantly improve treatment outcomes. V. Alonso-Goulart *et al*. [71] explored the possibility of using bioactive materials to increase MSC survival after implantation outside the bloodstream. The combination of MSCs with biomaterials allows for the creation of a favourable microenvironment, which reduces the risk of their destruction and improves integration into the recipient's tissues. Scientists J. Xue & Y. Liu [70] also draw attention to the effectiveness of biomaterial-carrier combinations based on bioceramics, hydrogels, and cell sheets, which improve cell survival after implantation and promote their effective functioning.

C. Tran & M.S. Damaser [72] found that MSCs are capable of synthesising a wide range of bioactive molecules, including cytokines, chemokines, angiogenesis and growth factors, which act in an autocrine and paracrine manner, regulating several physiological processes: recruitment of progenitor cells to damaged tissues, inhibition of apoptosis, scar formation, and tissue remodelling. J. He *et al*. [73] examined the features of using MSC spheroids in combination with hydrogels and confirmed their effectiveness in reducing the inflammatory response and improving cell survival. I. Mastrolia *et al*. [74] confirmed the ability of MSCs to actively migrate to injury sites, which promotes regeneration processes. The scientists

emphasise that the effectiveness of this mechanism can be increased using cytokines, chemical modifications, or bioparticles. It has been proven that MSCs integrated with biomaterials have a higher survival rate compared to cells after cryopreservation, which opens up wide prospects for the development of innovative approaches in regenerative medicine [26, 27].

G.E. Salazar-Noratto *et al*. [29] consider MSC transplantation as a safe and promising cell therapy strategy. However, the authors note that the effectiveness of this approach is characterised by significant variability, which is due to the complexity of the recipient's microenvironment. The study analysed various mechanisms that affect the survival of transplanted cells and proposed ways to optimise them to improve therapeutic efficacy. The use of vector materials in combination with MSCs has both advantages and limitations. In *in vitro* and *in vivo* studies, these materials enhanced the paracrine and autocrine effects of stem cells, as well as increased their therapeutic potential [70]. T. Zhou *et al*. [75] analyse the main challenges of MSC clinical application, including immunocompatibility, stability, heterogeneity, as well as differences in differentiation capacity between MSCs from different sources (bone marrow, umbilical cord, adipose tissue, muscles). They note that these factors can significantly affect the effectiveness of therapy and require an individual approach to the selection of cell sources for transplantation.

B. Lukomska *et al*. [46] investigated the issue of immunocompatibility between donor and recipient, which depended on environmental inflammatory molecules. Controlling these molecules is a key factor in reducing the risk of transplanted cell rejection. The authors also noted that inflammatory factors could stimulate MHC-II expression on MSCs, affecting their immune interaction. Y. Wang *et al.* [4] explored the immune response to stromal cell administration and their immunomodulatory properties in the orthopaedic microenvironment, emphasising the importance of understanding these mechanisms to reduce rejection risks and improve therapeutic outcomes.

A. Blandinières *et al*. [76] note that despite the confirmed multifunctional differentiation and paracrine capabilities of MSCs in *in vitro* studies, the mechanisms of their *in vivo* functioning remain poorly understood. The lack of standardised methods for isolating, characterising, and applying these cells complicates standardisation, which is critical for result reproducibility and regulatory compliance. This remains one of the key barriers to the widespread clinical application of MSCs.

Thus, the application of MSCs in tendon and ligament regeneration is a promising direction that requires further research. Optimising transplantation strategies, increasing cell survival, and minimising risks are key tasks for future studies. The use of bioengineering approaches and the combination of MSCs with biomaterials can significantly enhance the effectiveness of therapeutic strategies.

CONCLUSIONS

Thus, the conducted systematic review has summarised important information and analysed global research trends regarding the use of stem cells in regenerative medicine. A significant increase in the number of relevant publications has been noted, indicating the promising development of MSCs in the treatment of injuries and degenerative-dystrophic lesions of cartilage tissue. The therapeutic effect of MSCs is realised through mechanisms of migration, engraftment, and subsequent differentiation into target cells, which opens up broad possibilities for the treatment of musculoskeletal disorders. Along with this, there is a gradual transition of MSC research from the fundamental level to its clinical application. However, as of 2025, there is a limited amount of highvalue evidence regarding the routine use of MSCs for the repair and treatment of musculoskeletal injuries in clinical practice. For the successful clinical implementation of MSCs, large-scale trials with a larger patient sample and a long follow-up period are necessary. Standardising protocols for MSC isolation, cultivation, and transplantation is also important, ensuring their safety, effectiveness, and predictability of results. Special attention should be paid to the analysis of possible side effects and long-term consequences of MSC use. Given the promising nature of the field, it is important to continue interdisciplinary research to integrate regenerative medicine into routine clinical practice. This will open up new horizons for the personalised treatment of patients with musculoskeletal disorders, improve quality of life, and expand the possibilities for applying innovative approaches. In the future, active research is expected on combining MSCs with other biological components (PRP therapy, MFAT therapy), the use of stromal cells in tissue engineering, and the development of innovative drugs based on MSCs for the treatment of orthopaedic pathologies. The significant potential of this field requires further comprehensive study for effective implementation in clinical practice.

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REFERENCES

[1] Deng Z, Luo F, Lin Y, Luo J, Ke D, Song C, et al. Research trends of mesenchymal stem cells application in orthopedics: A bibliometric analysis of the past 2 decades. Front Public Health. 2022;10:1021818. DOI: 10.3389/fpubh.2022.1021818

[2] Maldonado VV, Patel NH, Smith EE, Barnes CL, Gustafson MP, Rao RR, et al. Clinical utility of mesenchymal stem/stromal cells in regenerative medicine and cellular therapy. J Biol Eng. 2023;17(1):44. DOI: 10.1186/s13036-023-00361-9

[3] Sandonà M, Di Pietro L, Esposito F, Ventura A, Silini AR, Parolini O, et al. Mesenchymal stromal cells and their secretome: New therapeutic perspectives for skeletal muscle regeneration. Front Bioeng Biotechnol. 2021;9:652970. DOI: 10.3389/fbioe.2021.652970

[4] Wang Y, Fang J, Liu B, Shao C, Shi Y. Reciprocal regulation of mesenchymal stem cells and immune responses. Cell Stem Cell. 2022;29(11):1515–30. DOI: 10.1016/j.stem.2022.10.001
[5] Tang J, Wang X, Lin X, Wu C. Mesenchymal stem cell-derived extracellular vesicles: A regulator and carrier for targeting bone-related diseases. Cell Death Discov. 2024;10(1):212. DOI: 10.1038/s41420-024-01973-w
[6] Costa LA, Eiro N, Fraile M, Gonzalez LO, Saá J, Garcia-Portabella P, et al. Functional heterogeneity of mesenchymal stem cells from natural niches to culture conditions: Implications for further clinical uses. Cell Mol Life Sci. 2021;78(2):447–67. DOI: 10.1007/s00018-020-03600-0
[7] Zhang Y, Fan M, Zhang Y. Revolutionizing bone defect healing: The power of mesenchymal stem cells as seeds. Front Bioeng Biotechnol. 2024;12:1421674. DOI: 10.3389/fbioe.2024.1421674
[8] Ossendorff R, Menon A, Schildberg FA, Randelli PS, Scheidt S, Burger C, et al. A worldwide analysis of adipose-derived stem cells and stromal vascular fraction in orthopedics: Current evidence and applications. J Clin Med. 2023;12(14):4719. DOI: 10.3390/jcm12144719
[9] Kim KI, Kim MS, Kim JH. Intra-articular injection of autologous adipose-derived stem cells or stromal vascular fractions: Are they effective for patients with knee osteoarthritis? A systematic review with meta-analysis of randomized controlled trials. Am J Sports Med. 2022;51(3):837–48. DOI: 10.1177/03635465211053893
[10] Chen J, Jiang C, Yin L, Liu Y, He Y, Li S, et al. A review of the role of tendon stem cells in tendon-bone regeneration. Med Sci Monit. 2023;29:e940805. DOI: 10.12659/MSM.940805
[11] Grabovyi O, Nevmerzhytska N, Yaremenko L, Kostynskyi H, Demydchuk A, Kondaurova H. Mesenchymal stem cells: Diversity. Pathologia. 2023;20(1):76–84. DOI: 10.14739/2310-1237.2023.1.272938
[12] Jiang Y, Tuan RS. Bioactivity of human adult stem cells and functional relevance of stem cell-derived extracellular matrix in chondrogenesis. Stem Cell Res Ther. 2023;14:160. DOI: 10.1186/s13287-023-03392-7
[13] Frazier T, March K, Garza JR, Bunnell BA, Darr KF, Rogers E, et al. Non-homologous use of adipose-derived cell and tissue therapies: Osteoarthritis as a case study. Bone Rep. 2022;17:101601. DOI: 10.1016/j.bonr.2022.101601
[14] Brown C, McKee C, Bakshi S, Walker K, Hakman E, Halassy S, et al. Mesenchymal stem cells: Cell therapy and regeneration potential. J Tissue Eng Regen Med. 2019;13(9):1738–55. DOI: 10.1002/term.2914
[15] Da Silva Meirelles L, Bieback K, Bolontrade MF. Editorial: Current progress in mesenchymal stem/stromal cell research. Front Cell Dev Biol. 2021;9:658903. DOI: 10.3389/fcell.2021.658903
[16] Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4):315–7. DOI: 10.1080/14653240600855905
[17] Zhou Q, Zhang JH, Yuan S, Shao JH, Cai ZY, Chen S, et al. A new insight of Kartogenin induced the mesenchymal stem cells (MSCs) selectively differentiate into chondrocytes by activating the bone morphogenetic protein 7 (BMP-7)/Smad5 pathway. Med Sci Monit. 2019;25:4960–7. DOI: 10.12659/MSM.916696
[18] Fu HD, Wang HR, Li DH. BMP-7 accelerates the differentiation of rabbit mesenchymal stem cells into cartilage through the Wnt/β-catenin pathway. Exp Ther Med. 2017;14(6):5424–8. DOI: 10.3892/etm.2017.5210
[19] Yang A, Lu Y, Xing J, Li Z, Yin X, Dou C, et al. IL-8 enhances therapeutic effects of BMSCs on bone regeneration via CXCR2-mediated PI3k/Akt signaling pathway. Cell Physiol Biochem. 2018;48(1):361–70. DOI: 10.1159/000491742
[20] Kozlowska U, Krawczenko A, Futoma K, Jurek T, Rorat M, Patrzalek D, et al. Similarities and differences between mesenchymal stem/progenitor cells derived from various human tissues. World J Stem Cells. 2019;11(6):347–74. DOI: 10.4252/wjsc.v11.i6.347
[21] Vaish A, Murrell W, Vaishya R. History of regenerative medicine in the field of orthopedics. J Arthrosc Surg Sport Med. 2020;1(1):154–8. DOI: 10.25259/JASSM_12_2020
[22] Vaish A, Vaishya R. Stem cells in orthopaedics and sports injuries: A comprehensive review and future research directions. J Ortho Rep. 2024;3(4):100344. DOI: 10.1016/j.jorep.2024.100344
[23] Konovalov S, Moroz V, Yoltukhivskyi M, Gadzhula N, Deryabina O, Kordium V. Comparative effects of mesenchymal stromal cells of various origins and sources on biochemical parameters in the hippocampus of rats during cerebral ischemia-reperfusion. Cell Organ Transpl. 2024;12(2):118–25. DOI: 10.22494/cot.v12i2.169
[24] Konovalov S, Moroz V, Yoltukhivskyy M, Gadzhula N, Gusakova I, Deryabina O, et al. Therapeutic potential of mesenchymal stromal cells on morphological parameters in the hippocampus of rats with brain ischemia-reperfusion modeling. Rep Morphol. 2024;30(3):52–62. DOI: 10.31393/morphology-journal-2024-30(3)-06
[25] Tronko M, Pushkarev V, Kovzun O, Sokolova L, Pushkarev V. Mesenchymal stem cells – the main resource of cell therapy. Use for diabetes mellitus treatment. Endokrynologia. 2022:27(3):214–35. DOI: 10.31793/1680-1466.2022.27-3.214
[26] Moll G, Ankrum JA, Kamhieh-Milz J, Bieback K, Ringdén O, Volk HD, et al. Intravascular mesenchymal stromal/stem cell therapy product diversification: Time for new clinical guidelines. Trends Mol Med. 2019;25(2):149–63. DOI: 10.1016/j.molmed.2018.12.006
[27] Moll G, Ankrum JA, Olson SD, Nolta JA. Improved MSC minimal criteria to maximize patient safety: A call to embrace tissue factor and hemocompatibility assessment of MSC products. Stem Cells Transl Med. 2022;11(1):2–13. DOI: 10.1093/stcltm/szab005
[28] Maniar HH, Tawari AA, Suk M, Horwitz DS. The current role of stem cells in orthopaedic surgery. Malays Orthop J. 2015;9(3). DOI: 10.5704/MOJ.1511.016

[29] Salazar-Noratto GE, Luo G, Denoeud C, Padrona M, Moya A, Bensidhoum M, et al. Understanding and leveraging cell metabolism to enhance mesenchymal stem cell transplantation survival in tissue engineering and regenerative medicine applications. Stem Cells. 2020;38(1):22–33. DOI: 10.1002/stem.3079
[30] Hade MD, Suire CN, Suo Z. Mesenchymal stem cell-derived exosomes: Applications in regenerative medicine. Cells. 2021;10(8):1959. DOI: 10.3390/cells10081959
[31] Maqsood M, Kang M, Wu X, Chen J, Teng L, Qiu L. Adult mesenchymal stem cells and their exosomes: Sources, characteristics, and application in regenerative medicine. Life Sci. 2020;256:118002. DOI: 10.1016/j.lfs.2020.118002
[32] Gerami MH, Khorram R, Rasoolzadegan S, Mardpour S, Nakhaei P, Hashemi S, et al. Emerging role of mesenchymal stem/stromal cells (MSCs) and MSCs-derived exosomes in bone- and joint-associated musculoskeletal disorders: A new frontier. Eur J Med Res. 2023;28:86. DOI: 10.1186/s40001-023-01034-5
[33] Hoang DH, Nguyen TD, Nguyen HP, Nguyen XH, Do PTX, Dang VD, et al. Differential wound healing capacity of mesenchymal stem cell-derived exosomes originated from bone marrow, adipose tissue and umbilical cord under serum- and xeno-free condition. Front Mol Biosci. 2020;7:119. DOI: 10.3389/fmolb.2020.00119
[34] Porcu C, Dobrowolny G, Scicchitano BM. Exploring the role of extracellular vesicles in skeletal muscle regeneration. Int J Mol Sci. 2024;25(11):5811. DOI: 10.3390/ijms25115811
[35] Bagno LL, Salerno AG, Balkan W, Hare JM. Mechanism of action of mesenchymal stem cells (MSCs): Impact of delivery method. Expet Opin Biol Ther. 2022;22(4):449–63. DOI: 10.1080/14712598.2022.2016695
[36] Im GI. Clinical use of stem cells in orthopaedics. Eur Cell Mater. 2017;33:183–96. DOI: 10.22203/eCM.v033a14
[37] Zhou Z, Guo C, Sun X, Ren Z, Tao J. Extracellular vesicles secreted by TGF-β1-treated mesenchymal stem cells promote fracture healing by SCD1-regulated transference of LRP5. Stem Cell Int. 2023;2023:4980871. DOI: 10.1155/2023/4980871
[38] Berebichez-Fridman R, Montero-Olvera PR. Sources and clinical applications of mesenchymal stem cells: State-of-the-art review. Sultan Qaboos Univ Med J. 2018;18(3):e264–77. DOI: 10.18295/squmj.2018.18.03.002
[39] Berebichez-Fridman R, Gómez-García R, Granados-Montiel J, Berebichez-Fastlicht E, Olivos-Meza A, Granados J, et al. The holy grail of orthopedic surgery: Mesenchymal stem cells-their current uses and potential applications. Stem Cells Int. 2017;2017:2638305. DOI: 10.1155/2017/2638305
[40] Theodosaki AM, Tzemi M, Galanis N, Bakopoulou A, Kotsiomiti E, Aggelidou E, et al. Bone regeneration with mesenchymal stem cells in scaffolds: Systematic review of human clinical trials. Stem Cell Rev Rep. 2024;20(4):938–66. DOI: 10.1007/s12015-024-10696-5
[41] Lucarelli E, Donati D, Cenacchi A, Fornasari PM. Bone reconstruction of large defects using bone marrow derived autologous stem cells. Transfus Apher Sci. 2004;30(2):169–74. DOI: 10.1016/j.transci.2003.11.008
[42] Liu Y, Kuang B, Rothrauff BB, Tuan RS, Lin H. Robust bone regeneration through endochondral ossification of human mesenchymal stem cells within their own extracellular matrix. Biomaterials. 2019;218:119336. DOI: 10.1016/j.biomaterials.2019.119336
[43] Dufrane D. Impact of age on human adipose stem cells for bone tissue engineering. Cell Transplant. 2017;26(9):1496–504. DOI: 10.1177/0963689717721203
[44] Pawar N, Vaish A, Vaishya R. Core decompression and bone marrow aspirate concentrate injection for Avascular Necrosis (AVN) of the femoral head: A scoping review. J Clin Orthop Trauma. 2021;24:101691. DOI: 10.1016/j.jcot.2021.101691
[45] Im GI. Stem cells for reutilization in bone regeneration. J Cell Biochem. 2015;116(4):487–93. DOI: 10.1002/jcb.25027
[46] Lukomska B, Stanaszek L, ZubaSurma E, Legosz P, Sarzynska S, Drela K. Challenges and controversies in human mesenchymal stem cell therapy. Stem Cells Int. 2019;2019:9628536. DOI: 10.1155/2019/9628536
[47] Le H, Xu W, Zhuang X, Chang F, Wang Y, Ding J. Mesenchymal stem cells for cartilage regeneration. J Tissue Eng. 2020;11. DOI: 10.1177/2041731420943839
[48] Xia D, Wu J, Zhou F, Wang S, Zhang Z, Zhou P, et al. Mapping thematic trends and analysing hotspots concerning the use of stem cells for cartilage regeneration: A bibliometric analysis from 2010 to 2020. Front Pharmacol. 2021;12:737939. DOI: 10.3389/fphar.2021.737939
[49] Rodeo S. Stem cells 101. Amer J Sports Med. 2021;49(6):1417–20. DOI: 10.1177/03635465211011082
[50] Pers YM, Ruiz M, Noël D, Jorgensen C. Mesenchymal stem cells for the management of inflammation in osteoarthritis: State of the art and perspectives. Osteoarthr Cartil. 2015;23(11):2027–35. DOI: 10.1016/j.joca.2015.07.004
[51] Saw KY, Anz A, Merican S, Tay YG, Ragavanaidu K, Jee CSY, et al. Articular cartilage regeneration with autologous peripheral blood progenitor cells and hyaluronic acid after arthroscopic subchondral drilling: A report of 5 cases with histology. Arthroscopy. 2011;27(4):493–506. DOI: 10.1016/j.arthro.2010.11.054
[52] Fishchenko V, Gavrilyuk A, Rosha L, Botsul O, Bevz V, Sukhan D, et al. Reparative chondrogenesis at rats shinbone proximal epiphyphis traumatic injury with the use of Warton drugs star cells mezenchenichemis in the experiment. World Med Biol. 2021;3(77):249–54. DOI: 10.26724/2079-8334-2021-3-77-249-254
[53] Fishchenko O, Mammadov L. Possibilities of using adipose tissue-derived stem cells in deforming osteoarthritis of the knee joint. Bull Probl Biol Med. 2022;1(163):167–71. DOI: 10.29254/2077-4214-2022-1-163-167-171
[54] Davatchi F, Sadeghi Abdollahi B, Mohyeddin M, Nikbin B. Mesenchymal stem cell therapy for knee osteoarthritis: 5 years follow-up of three patients. Int J Rheum Dis. 2016;19(3):219–25. DOI: 10.1111/1756-185X.12670

[55] Screpis D, Natali S, Farinelli L, Piovan G, Iacono V, de Girolamo L, et al. Autologous microfragmented adipose tissue for the treatment of knee osteoarthritis: Real-world data at two years follow-up. J Clin Med. 2022;11(5):1268. DOI: 10.3390/jcm11051268
[56] Čamernik K, Mihelič A, Mihalič R, Marolt Presen D, Janež A, Trebše R, et al. Skeletal-muscle-derived mesenchymal stem/stromal cells from patients with osteoarthritis show superior biological properties compared to bone-derived cells. Stem Cell Res. 2019;38:101465. DOI: 10.1016/j.scr.2019.101465
[57] Vadhan A, Gupta T, Hsu WL. Mesenchymal stem cell-derived exosomes as a treatment option for osteoarthritis. Int J Mol Sci. 2024;25(17):9149. DOI: 10.3390/ijms25179149
[58] Kawata K, Koga H, Tsuji K, Miyatake K, Nakagawa Y, Yokota T, et al. Extracellular vesicles derived from mesenchymal stromal cells mediate endogenous cell growth and migration via the CXCL5 and CXCL6/CXCR2 axes and repair menisci. Stem Cell Res Ther. 2021;12(1):414. DOI: 10.1186/s13287-021-02481-9
[59] Hajiesmailpoor A, Mohamadi O, Farzanegan G, Emami P, Ghorbani M. Overview of stem cell therapy in intervertebral disc disease: Clinical perspective. Curr Stem Cell Res Ther. 2023;18(5):595–607. DOI: 10.2174/1574888X17666220628123912
[60] Montemurro N, Pierozzi E, Inchingolo AM, Pahwa B, De Carlo A, Palermo A, et al. New biograft solution, growth factors and bone regenerative approaches in neurosurgery, dentistry, and orthopedics: A review. Eur Rev Med Pharmacol Sci. 2023;27(16):7653–64. DOI: 10.26355/eurrev_202308_33419
[61] Nedunchezian S, Banerjee P, Lee CY, Lee SS, Lin CW, Wu CW, et al. Generating adipose stem cell-laden hyaluronic acid-based scaffolds using 3D bioprinting via the double crosslinked strategy for chondrogenesis. Mater Sci Eng C Mater Biol Appl. 2021;124:112072. DOI: 10.1016/j.msec.2021.112072
[62] Zhang Y, Liu S, Guo W, Wang M, Hao C, Gao S, et al. Human umbilical cord Wharton's jelly mesenchymal stem cells combined with an acellular cartilage extracellular matrix scaffold improve cartilage repair compared with microfracture in a caprine model. Osteoarthr Cartil. 2018;26(7):954–65. DOI: 10.1016/j.joca.2018.01.019
[63] Wang G, Cao K, Liu K, Xue Y, Roberts AI, Li F, et al. Kynurenic acid, an IDO metabolite, controls TSG-6-mediated immunosuppression of human mesenchymal stem cells. Cell Death Differ. 2018;25(7):1209–23. DOI: 10.1038/s41418-017-0006-2
[64] Wang Z, Han L, Sun T, Wang W, Li X, Wu B. Construction of tissue-engineered bone with differentiated osteoblasts from adipose-derived stem cell and coral scaffolds at an ectopic site. Br J Oral Maxillofac Surg. 2021;59(1):46–51. DOI: 10.1016/j.bjoms.2020.07.006
[65] Jiang L, Lu J, Chen Y, Lyu K, Long L, Wang X, et al. Mesenchymal stem cells: An efficient cell therapy for tendon repair (review). Int J Mol Med. 2023;52(2):70. DOI: 10.3892/ijmm.2023.5273
[66] Wang Y, He G, Guo Y, Tang H, Shi Y, Bian X, et al. Exosomes from tendon stem cells promote injury tendon healing through balancing synthesis and degradation of the tendon extracellular matrix. J Cell Mol Med. 2019;23(8):5475–85. DOI: 10.1111/jcmm.14430
[67] Ogata Y, Mabuchi Y, Shinoda K, Horiike Y, Mizuno M, Otabe K, et al. Anterior cruciate ligament-derived mesenchymal stromal cells have a propensity to differentiate into the ligament lineage. Regen Ther. 2018;8:20–8. DOI: 10.1016/j.reth.2017.12.001
[68] Khoury M, Tabben M, Rolón AU, Levi L, Chamari K, D'Hooghe P. Promising improvement of chronic lateral elbow tendinopathy by using adipose derived mesenchymal stromal cells: A pilot study. J Exp Orthop. 2021;8(1):6. DOI: 10.1186/s40634-020-00320-z
[69] Ellera Gomes JL, da Silva RC, Silla LMR, Abreu MR, Pellanda R. Conventional rotator cuff repair complemented by the aid of mononuclear autologous stem cells. Knee Surg Sports Traumatol Arthrosc. 2012;20(2):373–7. DOI: 10.1007/s00167-011-1607-9
[70] Xue J, Liu Y. Mesenchymal stromal/stem cell (MSC)-based vector biomaterials for clinical tissue engineering and inflammation research: A narrative mini review. J Inflamm Res. 2023;16:257–67. DOI: 10.2147/JIR.S396064
[71] AlonsoGoulart V, Carvalho LN, Marinho ALG, de Oliveira Souza BL, de Aquino Pinto Palis G, Lage HGD, et al. Biomaterials and adiposederived mesenchymal stem cells for regenerative medicine: A systematic review. Materials. 2021;14(16):4641. DOI: 10.3390/ma14164641
[72] Tran C, Damaser MS. Stem cells as drug delivery methods: Application of stem cell secretome for regeneration. Adv Drug Deliv Rev. 2015;82–83:1–11. DOI: 10.1016/j.addr.2014.10.007
[73] He J, Zhang N, Zhu Y, Jin R, Wu F. MSC spheroids-loaded collagen hydrogels simultaneously promote neuronal differentiation and suppress inflammatory reaction through PI3K-Akt signaling pathway. Biomaterials. 2021;265:120448. DOI: 10.1016/j.biomaterials.2020.120448
[74] Mastrolia I, Foppiani EM, Murgia A, Candini O, Samarelli AV, Grisendi G, et al. Challenges in clinical development of mesenchymal stromal/stem cells: Concise review. Stem Cells Transl Med. 2019;8(11):1135–48. DOI: 10.1002/sctm.19-0044
[75] Zhou T, Yuan Z, Weng J, Pei D, Du X, He C, et al. Challenges and advances in clinical applications of mesenchymal stromal cells. J Hematol Oncol. 2021;14(1):24. DOI: 10.1186/s1304502101037x
[76] Blandinières A, Randi AM, Paschalaki KE, Guerin CL, Melero-Martin JM, Smadja DM. Results of an international survey about methods used to isolate human endothelial colony-forming cells: Guidance from the SSC on Vascular Biology of the ISTH. J Thromb Haemostasis. 2023;21(9):2611–9. DOI: 10.1016/j.jtha.2023.06.014

Використання мезенхімальних стромальних клітин в терапії захворювань опорно-рухового апарату: огляд літератури

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Анотація. Швидкий розвиток методів отримання мультипотентних клітин-попередників, відомих як мезенхімальні стромальні/стовбурові клітини, з різноманітних тканин та органів людини сприяв прогресу у сфері клітинної терапії та регенеративної медицини. Метою цього дослідження став огляд сучасних наукових даних щодо використання мезенхімальних стромальних клітин у лікуванні травматичних і ортопедичних захворювань, а також ознайомлення клініцистів із викликами та перспективами їх клінічного застосування. У ході дослідження було проаналізовано джерела отримання мезенхімальних стромальних клітин, їхні характеристики та терапевтичний вплив при захворюваннях опорно-рухового апарату. Було встановлено, що ці клітини можуть використовуватися як в аутологічній, так і в алогенній формах завдяки їх здатності до диференціювання в остеобласти, хондроцити, теноцити, адипоцити та інші типи клітин, що сприяє регенерації ушкоджених тканин. Було підтверджено, що мезенхімальні стромальні клітини володіють паракринною активністю, продукуючи цитокіни та фактори росту, що забезпечує їх регенеративний і регуляторний вплив як *in vitro*, так і *in vivo*. Водночас було зазначено, що, попри значний терапевтичний потенціал, їх клінічне застосування пов'язане з низкою викликів, зокрема, питаннями імуносумісності, стабільності, гетерогенності, а також обмеженою здатністю до диференціювання та міграції. Було розглянуто перспективи подолання цих обмежень за допомогою безклітинних підходів, зокрема застосування екзосом, що виділяються мезенхімальними стромальними клітинами, та містять біологічно активні молекули мРНК, мікроРНК, білки та біоактивні ліпіди. Було відзначено, що ці компоненти сприяють клітинній проліферації, міграції, регенерації, імуномодуляції та ангіогенезу, що є перспективним напрямом у регенеративній медицині. Отримані результати можуть бути використані для подальшої розробки ефективних терапевтичних стратегій у регенеративній медицині, зокрема в ортопедії та травматології. Практичне значення дослідження полягає в удосконаленні підходів до клітинної терапії, спрямованих на відновлення уражених тканин, що може слугувати основою для майбутніх клінічних випробувань і подальшого впровадження в медичну практику

Ключові слова: стовбурові клітини; екзосоми; регенерація тканин; травматологія; ортопедія