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Review

THE THERAPEUTIC POTENTIAL OF MESENCHYMAL STROMAL CELLS AND THEIR SECRETOME IN SPORT-RELATED INJURIES

Nour Mobayed*[1], Dima Joujeh[1]

[2] *Biotechnology engineering, Faculty of Technical Engineering, University of Aleppo, Aleppo, Syria*

* Correspondence, e-mail: nourmobayed.nm@gmail.com

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ABSTRACT

As the prevalence of sports-related injuries continues to rise, there is an urgent need for innovative therapeutic strategies that not only expedite recovery but also enhance the quality of healing. The application of mesenchymal stromal cells (MSCs) therapy in the treatment of sports injuries represents a groundbreaking advancement in the field of regenerative medicine. This review aims to summarize and discuss the therapeutic effects of MSCs in facilitating tissue regeneration and expediting the healing process following sports-related injuries. It also aims to highlight current research findings regarding the efficacy, safety and administration routes in clinical MSCs therapy trials. Data was obtained by searching Pubmed and Google Scholar, using the keywords: 'sport injury, 'Osteoarthritis', 'mesenchymal stromal/stem cells', 'tendon', 'cartilage defect', 'ligament injury', 'MSC secretome', 'conditioned medium'. According to the U. S. National Library of Medicine, there have been a total of 7,146 registered clinical trials worldwide on stem cell therapy till 5/10/2024, with 1,626 specifically focusing on MSCs therapy. The safety and efficacy of MSCs and MSCs secretome therapies in treating sport-related injuries have been shown in many preclinical studies. The promising outcomes observed in experimental studies have propelled the transition to clinical trials, which have also shown positive results. MSCs therapy has the potential to accelerate healing processes, reduce downtime, and allow athletes to return to their sport faster and with greater confidence. This is crucial not only for professional athletes but also for recreational sports enthusiasts who seek to maintain an active lifestyle. However, bone marrow mesenchymal stromal cells (BM-MSCs), umbilical cord mesenchymal stromal cells (UCB-MSCs) and adipose-derived mesenchymal stromal cells (AD-MSCs) were predominantly utilized in these trials, indicating that there is unexplored therapeutic potential of MSCs from other sources. This review not only aims to contribute valuable knowledge to the field, but also aspires to inspire further exploration and innovation in the use of MSCs for enhancing athletic performance and recovery.

KEYWORDS: sport injury, mesenchymal stromal cells, cartilage defect, ligament injury, MSCs secretome.

1. Introduction

Sports injuries are injuries that occur during athletic activities and exercise, often resulting from accidents, inadequate equipment, poor training techniques, or overuse of specific body parts [1].

The diagnosis, prevention, and treatment of these injuries are crucial aspects of sports medicine. Fortunately, sport injuries are often treated efficiently, with many individuals successfully recovering and returning to their sports in satisfactory state [2]. Recently, there has been a growing interest among sports medicine physicians in incorporating regenerative medicine into their practice [3].

Regenerative medicine focuses on regenerating and replacing damaged human cells, tissues, and organs to restore normal function and activity in the body [4]. The concept of Regenerative Medicine combined with Cell based Therapy and Tissue Engineering is considered the fourth pillar of healthcare [5], and this technology holds promise for treating various diseases [4].

Mesenchymal stromal cells (MSCs) are gaining attention in regenerative medicine [6], due to their ability to differentiate into different cell types including bone cells, cartilage cells, muscle cells, and fat cells [7], and their role in post-injury signals by secreting trophic and immunomodulatory factors [8]. MSCs have been isolated from various fetal and adult tissues, such as cord blood, peripheral blood, adipose tissue, lung, skin, liver, pancreas, and dental pulp [6].

The safety and effectiveness of MSCs in treating sport injuries involving the ligament, tendon, bone, muscle,

cartilage, and nervous tissues have been demonstrated in many preclinical and clinical studies.

This review aims to summarize and discuss the therapeutic effects of MSCs from different sources in promoting tissue regeneration and accelerating the healing process after sport-related injuries, as well as indicate the current findings including efficacy, safety and administration routes in clinical MSC therapy trials. We hope that this review will provide valuable knowledge in the field of sport injuries treatment and help in development of innovative therapeutic strategies to enhance the quality of athletes' health.

2. Materials and Methods

Data was obtained by searching Pubmed and Google Scholar, covering studies published from [2012-2024], using the keywords: 'sport injury, 'mesenchymal stromal/stem cells', 'tendon', 'cartilage defect', 'ligament injury', 'MSC secretome', 'conditioned medium', "regenerative medicine". Original research articles, including clinical trials, in vitro studies, and animal model studies, that explored the role of mesenchymal stem cells (MSCs) or their secretome in the treatment of sport-related injuries were considered.

3. Sports Injuries

In modern society, sports have become an indispensable part of people's daily life [9]. However, athletes cannot avoid injuries during regular training and competitions, which causes inconvenience and hinder their learning, health, and daily life [10].

Sports injuries are physical discomforts that result from sports activities [11]. Sport injuries, most of the time, affect muscles, tendons, ligaments, cartilage and bones [12], and can lead to substantial pain and reduced activity capability, resulting in poor sports performance [13], reduced game or competition time, or worse, an early finish to the sports season [14].

Sports medicine is the discipline that treats injuries, pain, and physical damage resulting from sports, exercise, or physical activities [15].

Cryotherapy is a widely accepted treatment for acute sports injuries [16]. Current treatment modalities in modern medicine are non-steroidal anti-inflammatory drugs (NSAIDs), which showed potential health concerns of intolerable gastrointestinal side effects and other systemic side effects [17]. Conventional therapies often provide only temporary relief without addressing underlying tissue damage [18].

Tissue engineering has revolutionized the treatment of sports injuries [19], by developing biological substitutes to restore, replace, maintain, or enhance damaged tissue and organ functionality [20].

This field focuses on activating cells that have the capability to initiate and sustain the regeneration process, possibly through growth factors or genes, so that they generate new functional tissue [21]. Advancements in regenerative medicine are showcasing the potential of mesenchymal stromal cells (MSCs) as an effective treatment for damaged tissues [22].

4. Mesenchymal stromal cells (MSCs)

Multipotent mesenchymal stem/stromal cells (MSCs) are a key component of innovative therapeutic strategies aimed at tissue regeneration and the restoration of organ function [23].

These cells were first described by Friedenstein et al. who found that MSCs can be isolated by physical adherence to culture plates, and are capable of forming colonies with fibroblast-shaped cells in vitro [24]. According to the International Society for Cellular Therapy (ISCT) criteria, MSCs must meet specific requirements. These include specific surface antigen expression (CD44, CD90, CD105, CD73, ICAM-1, Stro-1, CD106, CD29, CD71, and CD166); absence of hematopoietic (CD34, CD11, CD14, and CD45), endothelial (CD31), and costimulatory markers (CD80, CD86); adherence to plastic surfaces; and the capability to differentiate into adipogenic, chondrogenic, and osteogenic lineages [25]. However, new criteria have also been introduced for identifying MSCs, such as spindle-shaped morphology, the absence of expression of iPSCs induction factors, the inability to form teratomas, and the release of MSC-relevant paracrine factors [26].

MSCs can be sourced from three main categories: prenatal-derived sources like the placenta, umbilical cord, and umbilical cord blood; embryonic sources such as amniotic fluid and embryonic tissue; and adult sources like adipose tissue, peripheral blood, muscles, and bone marrow [27]. Currently, MSCs have been classified as advanced therapy medicinal product (ATMPs) and must be manufactured in compliance with good manufacturing practices (cGMP) to ensure consistent production and quality standards in terms of potency, identity, and safety, as per EU Regulations 2003/94/EC and 91/356/EEC directives [28]. MSCs exhibit immunosuppressive and anti-inflammatory effects, and thus can accelerate tissue regeneration and reduce inflammation [29]. Additionally, MSCs offer advantages such as ethical considerations, ease of harvesting, and reduced risks of tumorigenesis [30]. Currently, two theories are proposed to elucidate the therapeutic mechanisms of MSCs: their potential differentiation into parenchymal cells or the secretion of bioactive factors like growth factors, cytokines, and proteins [31].

5. Conditioned Medium (CM)

Numerous studies have demonstrated that growth factors derived from MSCs can promote tissue repair independently of the cells themselves. The medium in which MSCs are cultured and release growth factors and cytokines is known as conditioned medium (CM) [32], which exerts a regenerative effect through paracrine mechanisms [33].

The collection of biologically active molecules and extracellular vesicles (EVs) released by cells are called "secretomes" [34].

These secretomes are now being considered as potential substitutes for MSCs in cell therapy due to their comparable capability to enhance tissue regeneration, and modulate the immune response [34]. MSCs possess an intrinsic functional plasticity, enabling them to promptly adapt and respond to the surrounding microenvironment when exposed to an inflammatory milieu [35] (Figure 1).

The activation of their immunosuppressive properties is primarily triggered by pro-inflammatory cytokines such as IFNγ, TNF, and IL1β [36].

Various soluble factors have been identified as mediators of this immunosuppressive effect, including transforming growth factor-β1 (TGF-β1), prostaglandin E2 (PGE2), hepatocyte growth factor (HGF), indoleamine 2,3-dioxygenase (IDO), nitric oxide (NO), and interleukin-10 (IL-10) [37].

Extracellular vesicles are categorized based on their size into apoptotic bodies (>1000 nm), microvesicles (100–1000 nm), and exosomes (30–150 nm) [38].

Exosomes are vesicles that contain proteins, lipids and nucleic acids and often act as mediators of cell-to-cell communication [39].

By transporting microribonucleic acid, mRNA, DNA, proteins, and soluble molecules to target cells, exosomes regulate the eventual fate of recipient cells [40].

Secretomes offer significant advantages over cells in terms of manufacturing, handling, preservation, product longevity, and potential as a ready-to-use biologic product [41].

Moreover, the utilization of MSCs secretome allows for controlled dosage and standardization of components to maximize therapeutic potential and ensure product safety [42].

The activity of exosomes can be easily manipulated by preconditioning MSCs, by simply adding cytokines or chemicals to the culture medium, introducing gene modifications, or using hypoxic culture conditions [38].

However, several factors such as gender, donor age, metabolic state, and phenotype can affect the effectiveness of MSCs secretome therapy. The lack of a standardized protocol for MSCs isolation/expansion (e.g., pH, oxygen tension, shear stress, chemical stimulus, seeding cell density, mechanical forces, and different types of culture systems), secretome production, collection, and bioprocessing, has also led to uncertainty about the biological effects of secretomes [43].

MSCs secretomes, particularly exosomes have been utilized as medicinal agents or delivery vehicles in the treatment of sport-related injuries. MSCs secretomes, especially exosomes, have been used as medical agents or delivery vehicles in the treatment of sport-related injuries. Exosomes contain a variety of biologically active molecules that promote tissue repair and reduce inflammation. Studies have shown that exosomes promote muscle regeneration by modulating immune responses, reducing fibrosis, and promoting myogenesis [44]. Furthermore, the regenerative capacity of MSCs-derived exosomes has been demonstrated in models of peripheral nerve injury and muscle injury, highlighting their promise as delivery vehicles for therapeutic agents [45].

The latest “Minimal Information for Studies of Extracellular Vesicles” (MISEV2023) guidelines from the International Society for Extracellular Vesicles (ISEV) provide a comprehensive update on best practices for the study of EVs. These guidelines are essential for ensuring accuracy, reproducibility, and transparency in EVs research. MISEV2023 includes new standards for the isolation, characterization, and function studies of EVs, highlighting how to handle pre-analytical variables such as different EVs sources. This update also addresses advances in understanding the mechanisms of EVs release and uptake, and expands recommendations for in vivo studies, helping researchers design experiments with improved reliability and relevance in biomedical applications. [46]

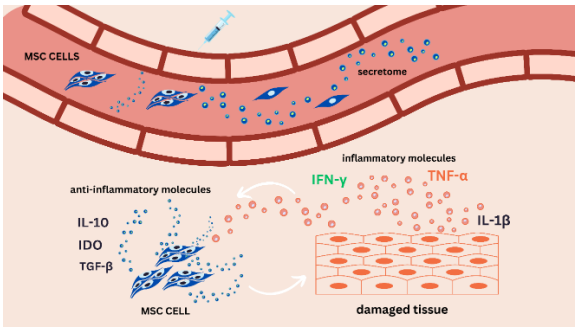

Figure 1. MSCs secretomes.

6. MSCs therapy for sport-related injuries

The prevalence of sports injuries is increasing alongside the rise in both professional and recreational sport practice, as highlighted in numerous epidemiological studies. Beyond the medical implications, the economic burden associated with the costs of conservative treatment, surgery, and rehabilitation is substantial [12].

Compared to traditional methods, stem cell therapy offers promising potential for repairing and functional plasticity following sports injuries. The application of stem cell therapy to an injured area can be achieved through various methods such as direct surgical application, stem-cell-bearing sutures, and injection [2]. Direct injection of the cells is the simplest delivery approach, but are only used for the early-stage injuries where the damage is limited to the cartilage layer [47].

Several studies - the recent ones being reviewed here (Tables 1, 2) - have demonstrated that MSCs and MSCs-secretomes based therapies are effective in sport-related injuries.

Table 1. Studies conducted on the effect of MSCs therapy in the treatment of sport-related injuries.

Disease	Cell source	Model	Injection route	Dosage	Duration of treatment	Key findings	Ref.
Muscle trauma	Tibial biopsies	Sprague-Dawley rats	Locally	2.5×10^6	3 weeks	MSCs transplantation improved skeletal muscle regeneration after injury	[48]
Spinal cord injury (SCI)	Bone marrow	Wistar adult female rats	Intravenously graft	1×10^6 MSCs in 500 µl	3 weeks	MSCs graft has been shown to enhance functional recovery following spinal cord compression injury	[49]
Peripheral nerve injury (sciatic nerve)	Bone marrow	Adult wild Sprague Dawley rats	Intravenous infusion	(1.0×10^6)	3 weeks	Results indicated that intravenous MSCs administration can lead to improved functional outcomes in a model of peripheral nerve injury, with some transplanted cells persisting and surviving in the lesion area for at least three weeks	[50]
Skeletal muscle trauma	Bone marrow from tibiae	Male Sprague Dawley rats	Local transplantation (TX)	2.5×10^6 MSCs	28 days	The transplantation of MSCs improved muscle forces significantly after fast-twitch stimulation	[51]
Knee osteoarthritis	Human umbilical cord blood (hUCB)	Albino rats of Wistar strain (adult males)	Intra-articular injection	$1.2–1.5 \times 10^6$ cells/ml	6 weeks	The intra-articular injection of hUCB MSCs is an effective method for cartilage repair in rats	[52]
Lateral epicondylosis (LE)	Allogeneic adipose-derived mesenchymal stem cells (allo-ASC)	Human patients (all more than 19 years old)	Intravenous injection	High-dose (10^7 cells in 1 ml) and low-dose (10^6 cells in 1 ml)	52 weeks	Results demonstrated that the intervention was safe and efficacious in improving pain, performance, and anatomical defects	[53]
Achilles tendon segmental defect	Rat bone marrow	Male Wistar rats	MSCs seeded into a 3D-PLG scaffold	1×10^6 TNF-α primed MSCs	4 weeks	Results showed enhanced strength, reduced inflammation, and a more favorable composition characterized by collagen I	[54]
Stretch Injury	Mouse bone marrow	C57BL/67 mice	Intramuscular injection	5×10^5 MSCs	14 days	Intramuscular injection of MSCs can result in transient improvement in isometric torque, and reduced susceptibility to reinjury following single stretch injury	[55]
Osteoarthritis (OA)	(PBMC) and AD-MSCs from sheep blood and their adipose tissue	Male small tail Han sheep	Intra-articular (IA) injections	AD-MSCs high (5×10^7 cells) and low (1×10^7 cells) doses	18 weeks	Intra-articular injection of allogeneic AD-MSCs combined with hyaluronic acid effectively prevented the development of osteoarthritis, and promoted cartilage regeneration in a sheep OA model	[56]
Rotator cuff disease or tendinopathy	Adipose tissue-derived mesenchymal stem cells (AD-MSCs) in patients	Human patients	Intratendinous injection	Low- (1.0×10^7 cells), mid- (5.0×10^7), and high-dose (1.0×10^8)	6 months	Intratendinous injection of AD-MSCs was found to be feasible, safe, and capable of regenerating tendon defects, leading to improved function and pain relief in the shoulder	[57]
Craniofacial bone defects	Bone marrow mesenchymal stem cells (BMSCs) and dental pulp mesenchymal stem cells (DPSCs)	Male New Zealand white rabbit	BMSCs and DPSCs were seeded on Bio-Oss® scaffolds and immediately implanted into the bone defects.	1×10^6 BMSCs and 1×10^6 DPSCs	3 and 6 weeks	When BMSCs and DPSCs were combined with Bio-Oss xenografts, they provided excellent support for bone regeneration in rabbit calvarial defects	[58]

Lateral elbow tendinopathy or tennis elbow (LET)	Adipose tissue from the periumbilical zone of patients (adipose tissue is an excellent source of adipose derived mesenchymal stromal cells (ASCs))	Human patients	injection	7.9×10^6 ASCs	12 months	Tennis players with recalcitrant lateral epicondylitis showed significant clinical improvement one month after receiving autologous ASCs, with structural repair observed at the origin of the common tendon origin after six months. These positive clinical outcomes persisted up to 12 months post-injection.	[59]
Osteoarthritis (OA)	Human umbilical cord blood (HUCMSCs) mixed with hyaluronan (HA)	New Zealand White (NZW) rabbit	Intra-articular injection	1×10^7	12 weeks	Transplantation of HUCMSCs and HA could attenuate cartilage destruction in osteoarthritis	[60]
Gastrocnemius muscle injury	(BM-MSCs) From male albino rats	Female albino rats	Local injection	$2.5x10^6$ cells	14 days	The results demonstrated that BM-MSCs are a promising option for skeletal muscle regeneration. They were capable of both accelerating the healing process and facilitating the repair of skeletal muscle	[61]
Spinal cord injury (SCI)	Bone marrow from femoral bones in Sprague-Dawley (SD) rats	Male SD rats	Intravenous infusion	1.0×10^6 MSCs	8 weeks	MSCs delivery has been associated with an increase in axonal diameter of pre-existing small caliber axons.	[62]
Skeletal muscle injury	BM-MSCs	Adult male albino rats	Local injection	$1x10^6$ MSCs cells	2 weeks and 4 weeks	Local injection of stem cells into injured muscles has been shown to activate, proliferate, and differentiate satellite cells, thereby accelerating muscle healing.	[63]
Muscle atrophy after peripheral nerve injury	Human umbilical cord	Sprague-Dawley (SD) male rats	Local injection	hucMSCs (1×10^6 cells) in 200 µl or (100 µg) in 200 µL of (hucMSCs-EXOs)	7 days	hucMSCs and hucMSC-EXOs through miR-23b-3p can improve muscle atrophy following nerve injury	[64]
Achilles tendinopathy	(hUC-MSCs)	Male Sprague–Dawley rats	Local injection	5×10^5 stem cells dissolved in 50 µl of normal saline	4–8 weeks	hUC-MSCs revealed a therapeutic effect in treating collagenase-induced Achilles tendinopathy	[65]

Table 2. Studies conducted on the effect of MSCs secretome-based therapies in the treatment of sport-related injuries.

Disease	CM source	Model	Injection route	Dosage	Outcome measures	Key findings	Ref.
Ligament injury	BM-MSC-exosomes	Male Wistar rats	Local injections	5×10^6 exosomes from TNF α-primed MSCs (TNF), or 5×10^6 exosomes from CRX-527-primed MSCs (CRX)	14 days	The study highlighted the impact of changes in the MSCs environment on the efficacy of exosomes in ligament recovery, shedding light on the adaptability and versatile role of MSCs-derived exosomes in tissue regeneration	[66]
Posterior cruciate ligament rupture	Allogeneic umbilical cord mesenchymal stem cell	Human	MSCs secretome was injected into the remains of the posterior cruciate ligament	10 cc	1 year after surgery	The secretome generated from allogenic UC-MSCs produced excellent functional and radiographic results in grade I-II PCL rupture	[67]

Chronic rotator cuff tears (RCTs)	Exosomes derived from kartogenin (KGN)-preconditioned human bone marrow mesenchymal stem cells (KGN-Exos)	Rats	Local injections	_	8 weeks	KGN-Exos injection could serve as a cell-free treatment option to accelerate tendon-to-bone healing in chronic RCT cases	[68]
Muscle crush injury	Bone marrow-derived MSCs from Sprague Dawley rats	Male and female Sprague Dawley rats	L6 rat myoblasts (ATCC, Manassas, VA) were cultured in DMEM (Invitrogen)	1×10^6 cells per gel	6 weeks	The use of sulfated alginate in combination with MSCs spheroids resulted in reduced collagen deposition, enhanced myogenic marker expression, and increased neuromuscular junctions two weeks post-injury	[69]
Achilles tendon rupture	Extracellular vesicles from inflammation-primed adipose-derived stem cells (iEVs)	NF-κB-GFP-luciferase transgenic reporter mice	2-strand modified Kessler technique	0.1×10^9, or 5×10^9 iEVs (CRTL, +iEVL, or +iEVH)	28 days	Results indicated that iEVs could effectively boost Achilles tendon healing by targeting macrophages to attenuate inflammation and stimulating tendon cells to enhance intrinsic healing and functional recovery	[70]
Tendinopathy	Small extracellular vesicles released from induced pluripotent stem cell-derived mesenchymal stem cells (iMSC-sEVs)	Female Sprague Dawley rats	Local injection	iMSC-sEVs (1×10^{10} particles of iMSC-sEVs in 100 µL PBS)	4 weeks	Local injection of iMSC-sEVs led to increased tenocyte proliferation, decreased proinflammatory cytokine expression, effective pain relief in tendinopathy rats, and improved tendon histology	[71]
Shoulder stiffness (SS)	Extracellular vesicles derived from human bone marrow mesenchymal stem cells (BMSC-EVs)	Male C57/6J mice	Intra-articular injection	From 1.2×10^8 to 3×10^8 EVs	6 weeks	The results demonstrated the antifibrotic role of BMSC-EVs in capsular fibrosis, which was achieved by transferring let-7a-5p and suppressing the expression of TGFBR1	[72]
Anterior cruciate ligament reconstruction (ACLR)	Exosome derived from magnetically actuated (iron oxide nanoparticles (IONPs) combined with a magnetic field) bone mesenchymal stem cells (BMSCs) (IONP-Exos)	Sprague-Dawley rats	Local injection	(100 µg/tunnel) of IONP-Exos.	8 weeks	The study demonstrated that therapeutic molecule-enriched IONP-Exos could enhance tendon-bone integration, offering a promising strategy to improve tendon-bone healing post-ACLR	[73]
Anterior cruciate ligament reconstruction (ACLR)	Exosomes from hypoxia-cultured Sprague–Dawley rats bone-marrow mesenchymal stem cells (Hypo-Exos)	Male mature SD rats	Hydrogel injection	Uniform injection of Hypo-Exos with the adhesive hydrogel (300 µL, 10 mg/ml)	8 weeks	Peri-graft Hypo-Exos injection accelerated grafted tendon-bone tunnel integration after ACL reconstruction by enhancing peri-graft bone microarchitecture	[74]
Chondral defects of the knee	MSC-EVs were derived from immortalized E1-MYC 16.3 human embryonic stem cell	Male Göttingen minipigs	Intra-articular injections	1 mg MSC-EVs in 1 mL PBS	6 months	Intraarticular injections of MSC-EVs in conjunction with BMS resulted in osseous ingrowth, affecting optimal cartilage repair, while improving subchondral bone healing	[75]

Rotator cuff tendon	Exosomes derived from mesenchymal stem cells (BMSC-Exos)	Sprague-Dawley (SD) rats	Intravenous injection	200 μg of total protein of BMSC-Exos precipitated in 200 μL of PBS	8 weeks	BMSC-Exos promoted tendon-bone healing after rotator cuff reconstruction in rats, by promoting angiogenesis and inhibiting inflammation	[76]
Defects in the patellar tendons	Extracellular vesicles from bone marrow-derived multipotent mesenchymal stromal cells (BMSC-EVs)	Sprague-Dawley rats	Fibrin glue containing EVs was placed in the window defect of patellar tendon after rat tendon injury model	BMSC-EVs and fibrin glue (25 μg in 10 μL)	4 weeks after surgery	Local administration of BMSC-EVs was found to enhance tendon healing by reducing inflammation and apoptotic cell accumulation, while increasing the proportion of tendon-resident stem/progenitor cells	[77]
Soleus muscle crush injury	Secretome from adipose-derived mesenchymal stem cells (ADSC)	C57BL/6 mice	Intra-venous (IV) injection	100 μL EV (from 1×10^6 cells)	21 days	The secretome from ADSC exhibited robust effects on cellular processes that support tissue regeneration, and accelerated skeletal muscle regeneration following acute damage	[78]
Suspensory ligament injury (SL)	Extracellular microvesicles derived from ASC from Horses	Dutch Warmblood gelding horse	A USG-guided injection of MVsAZA/RES directly into the injury site	2×10^4 cells in 25 μg/mlMVsAZA/RES	12 months	Application of MVsAZA/RES resulted in increased lesion filling, improved angiogenesis, and enhanced elasticity in injured tissue	[79]
Cartilage degradation	Exosomes derived from miR-92a-3p-overexpressing human mesenchymal stem cells	Female C57B/L10 mice	Injection	15 μl MSC-Exos (500 μg/mL) or 15 μl MSC-miR-92a-3p-Exos in PBS (500 μg/mL)	28 days	Results suggested that exosomal miR-92a-3p could regulate cartilage development and homeostasis by targeting WNT5A directly	[80]
Osteoarthritis (OA)	Exosomes were harvested from conditioned culture media of ESC-MSCs	C57BL/6 J mice	Intra-articular injection	5 μL ESC-MSCs (1×10^6/joint)	8 weeks	Exosomes from ESC-MSCs showed beneficial therapeutic effects on OA by balancing chondrocyte extracellular matrix synthesis and degradation	[81]
Osteochondral defects	MSCs were derived from HuES9 human embryonic stem cells (hESCs)	Sprague Dawley (SD) female rats	Intra-articular injections	100 μg exosomes	12 weeks after surgery.	Human embryonic MSCs exosomes were effective in cartilage repair	[82]

7. Cartilage defects

Articular cartilage has a limited capacity for self-repair [83]. Injuries to cartilage caused by trauma, inflammation, or degenerative joint disease often lead to osteochondral defects, ultimately resulting in osteoarthritis [84].

The treatment of cartilage defect in trauma injury and degenerative disease poses a challenge for orthopedic specialists. Advanced MSC based therapy has emerged as a promising approach for repairing damaged cartilage [85].

MSCs exhibit the ability to differentiate into chondrocytes at the site of a lesion, and secrete cytokines and growth factors that facilitate cartilage regeneration [86].

8. Osteoarthritis (OA)

Osteoarthritis (OA) stands as the most prevalent degenerative joint disease characterized by irreversible cartilage damage [87]. While OA is commonly perceived as a progressive condition affecting adults and the elderly, various risk factors beyond age, including race, genetics, joint injuries, gender, obesity, and specific activities, predispose individuals to OA [88].

Notably, certain types of joint injuries prevalent in athletes are strongly linked to the development of OA [89]. The general view is that OA is the result of “wear and tear”; because athletes and young individuals use their joints more and the risk is higher [88].

Current non-surgical treatments for OA encompass non-pharmacological and pharmacological approaches. However, current pharmacological treatments primarily focus on symptom relief without addressing regeneration or reconstruction [60]. MSCs therapy holds promise for regenerating damaged cartilage, alleviating pain, enhancing function, and potentially delaying the necessity for surgery. This minimally invasive and safe procedure offers a hopeful path for patients seeking long-lasting relief from knee OA [90]. In addition, exosomes derived from MSCs can transport various molecules to promote MSCs migration and aid in cartilage repair [91]. Nonetheless, the tissue source of MSCs may significantly impact the efficacy of MSCs therapies, and thus far, no ideal source, dosage, preparation method, or specific characteristics of MSCs have been definitively established for OA treatment [92].

9. MSCs for tendon injuries

Tendons are vital in facilitating skeletal movement as they connect muscles to bones. They are found in both synovial joints, such as the flexor tendons in the hands and feet, and non-synovial joints, including the Achilles, rotator cuff, and patellar tendons [93]. Tendinopathy is a common cause of recurring pain and long-term impairment in athletes [94].

Tendon injuries can be caused by acute overloading, chronic repetitive stress, and various internal and external factors. Genetics, tendon location, and individual health status also contribute to the likelihood of injury [95]. Rotator cuff injuries, classified as bone-tendon interface injuries, are prevalent in modern sports activities and often result in severe symptoms such as shoulder pain and dysfunction [96]. Tendon regeneration processes are slower compared to other connective tissues due to their hypoxic and hypovascular structure [97].

MSCs have emerged as a promising therapeutic approach for tendon regeneration [98]. The concept of utilizing MSCs for tendon repair was initially proposed in 1998 and, notably, a case report involving an equine patient was published as early as 2003. Since then, numerous experimental studies on animals and case series in equine patients have instilled optimism regarding the potential benefits of locally implanting MSCs into acute tendon injuries to enhance the healing process [94]. When transplanted, MSCs can modulate the inflammatory environment and abundant the balance of extracellular matrix (ECM) to promote tendon regeneration [100]. The paracrine response is believed to be the primary mechanism through which MSCs exert their effects and is being harnessed for the treatment of various musculoskeletal pathologies, including tendinopathies [101].

10. MSCs for ligament injuries

Sports injuries are commonly caused by overuse, with half of these injuries affecting tendon, tendon sheets, and tendon insertions into the bone [12]. Tendon and ligament fibers possess elasticity, allowing for elongation during exercise; however, injury occurs when the strain exceeds the physiological limits of these structures [102]. The incidence of ligament injuries, particularly anterior cruciate ligament (ACL) injuries, is on the rise [12].

The ACL is a main structure for maintaining knee stability, and its rupture, a frequent athletic injury, can lead to serious consequences such as knee joint instability, damage to other ligaments, dislocation, and osteoarthritis [103]. While ACL reconstruction has shown favorable clinical outcomes, challenges persist in achieving successful biological healing of ACL grafting as a cause of failed ACL reconstruction [104].

Advancements in MSCs-based therapies for treating musculoskeletal injuries have paved the way for utilizing MSCs to enhance healing following ACL injuries [105]. Furthermore, MSCs-EVs have demonstrated promise in the treatment of tendon and ligament injuries, offering a method that eliminates the necessity of transplanting live cells into the human body [106].

11. Clinical trials

The encouraging results observed in the experimental studies motivated the progression of MSC therapy into clinical trials. According to the U. S. National Library of Medicine (https://clinicaltrials.gov), there have been a total of 7,146 registered clinical trials worldwide on stem cell therapy till 5/10/2024, with 1,626 specifically focusing on mesenchymal stem/stromal cell therapy. A significant number of trials dedicated to MSC therapy highlights the importance of this therapy from point of view of scientists.

Various clinical trials demonstrated the safety and effectiveness of MSCs therapy in several types of sports injuries including cartilage, tendon, and bone injuries (Table 3). However, UCB-MSCs AD-MSCs, and BM-MSCs were the cell type choices in most of the clinical trials (Figure 2), indicating that there is unexplored therapeutic potential of MSCs from other sources.

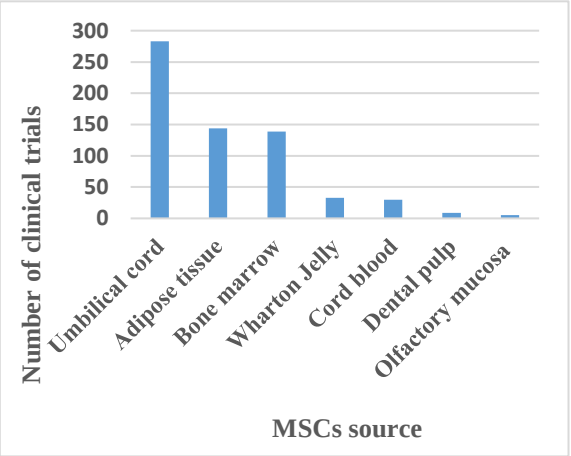

Figure 2. Frequency of MSC source contributions in clinical trials on MSC therapy during 2016-2024 (https://clinicaltrials.gov/)

The use of MSCs in clinical applications faces significant challenges. One key issue is the variability in MSCs properties depending on their source, which impacts their stability of stemness and differentiation capacities. Additionally, concerns over the safety of MSC therapies, including potential tumorigenicity and immune rejection. the interactions between MSCs and the host environment, including immune system responses, can significantly affect the outcomes of therapy. Another challenge lies in the scalability of MSC production, as ensuring consistent quality across large-scale manufacturing remains difficult, potentially limiting their widespread clinical use [107].

However, advances in bioprocess engineering for mesenchymal stem cells (MSCs) have facilitated cGMP-compliant production, essential for clinical applications. Current strategies, including serum-free media, microcarrier-based expansion, and automated closed systems, ensure high-quality MSCs with minimized risk of contamination, which is crucial for regenerative and therapeutic applications. These scalable methods enable efficient cell growth while preserving MSC potency and functionality for safe clinical use [108].

Table 3. Clinical trials of MSCs in the treatment of sport-related injuries.

Disease	Phase	Number of participants	Source of MSC	Dose	Administration	Transplantation	Outcomes	CT code	Ref.
Chronic patellar tendinopathy (with gap >3 mm)	Phase I/II	20 participants (age 18-48 years)	BM-MSCs	20 x10^6 cells	Intratendinous	Autologous	Treatment with BM-MSC or Lp-PRP in combination with rehabilitation in chronic patellar tendinopathy is effective in reducing pain and improving activity levels	NCT03454737	[109]
Tendon tear	Phase II	23 patients (older than 18 years of age)	AD-MSCs	-	Intra-lesional	Allogenic	Treatment was not effective	NCT02298023	[110]
Low back pain	Phase I	11 patients (age: 18-70 years)	AD-MSCs	6 x 10^6 cells/disc combined with hyaluronic acid	Intradiscal administration	Autologous	The intradiscal application of matrilin-3-primed ASC spheroids with hyaluronic acid is a safe and feasible treatment option for chronic discogenic LBP	NCT05011474	[111]
Low back pain	Phase I	11 patients (age 19 to 70 years)	AD-MSCs	2 x 10^7 cells/disc	Intradiscal injection	Autologous	Combined implantation of MSCs and hyaluronic acid derivative in chronic discogenic LBP is safe and tolerable	NCT02338271	[112]
Knee osteoarthritis	Not applicable	26 patients (20-80 years)	AD-MSCs	1 x 10^8	Intra-articular	Autologous	Concomitant intra-articular injection of AD-MSCs offered advantages in cartilage regeneration with safety observed at the 2-year follow-up	NCT03000712	[113]
Knee osteoarthritis	Phase III	125 patients	AD-MSCs	-	Intra-articular	Autologous	Intra-articular injection of autologous MSCs provided significant pain relief and functional improvements in patients with K-L grade 3 osteoarthritis	NCT03990805	[114]
Knee osteoarthritis	Phase II	40 patients	AD-MSCs	100 x 10^6	Intra-articular	Allogenic	Notable articular cartilage regeneration and significant improvement were shown in the treatment group	IRCT20080728001031N23	[115]
Knee osteoarthritis	Phase I/II	29 patients (40 - 65 years)	UC-MSC	20 x 10^6	Intra-articular	Allogeneic	UC-MSCs treatment was safe and superior to active comparator in knee OA at 1-year follow-up	NCT02580695	[116]
Knee osteoarthritis	Phase II	60 patients	BM-MSCs	25 x 10^6	Intra-articular	Allogeneic	MSCs treatment was safe, with a dose of twenty-five million cells showing the most effective results in pain reduction	NCT01453738	[117]
Knee osteoarthritis	-	30 participant	AD-MSCs	100 × 10^6	Intra-articular	Autologous	Autologous AD-MSCs therapy appears to be a safe and effective therapy for knee osteoarthritis	ACTRN12614000814673	[118]
Knee osteoarthritis	Phase II	60 patients (18–80 years)	BM-MSCs	100 × 10^6	Intra-articular	Autologous	Treatment with BM-MSCs associated with Platelet Rich Plasma was shown to be a viable therapeutic option for osteoarthritis of the knee	NCT02365142	[119]

Knee osteoarthritis	-	20 patients	BM-MSCs	1×10^6	Intra-articular	Autologous	MSCs injection resulted in reduced pain, functional assessment score improvement, and enhancing quality of life parameters	CUHK_CCT00469	[120]
Cartilage defects	Phase III	89 (mean age, 55.9 years)	UCB-MSCs	7.5×10^6 cells	Through mini-arthrotomy or with microfracture	Allogeneic	MSCs- hyaluronate implantation resulted in improved cartilage grade at second-look arthroscopy and provided more improvement in pain	NCT01041001, NCT01626677	[121]
Articular cartilage lesions in the knee	-	11 patients	BM-MSCs	1– 10 x 10^7	Around the cartilage lesion under arthroscopy	Autologous	B-MSCs transplantation with microfracture resulted in better postoperative healing of the cartilage and subchondral bone	R000008607	[122]

12. Conclusion

Despite the progress in MSCs therapy development, it has not been commonly used to treat sports injuries, as there are still many questions that need precise and clear answers before effective treatments can be widely applied in clinical applications. It is necessary to determine the appropriate number of passages for MSCs expanding in culture, the best MSCs source, the optimal dose and injection route, and whether it is better to inject undifferentiated MSCs or induce MSCs differentiation in vitro before being injected into the body. Therefore, further extensive studies are needed to understand the precise mechanisms by which MSCs repair damage and to explore cellular therapeutic alternatives for currently incurable diseases.

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