Chapter

Mesenchymal Stem Cells from Fat: From Differentiation Mechanisms to Biomedical Application in Patients

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Abstract

Adipose tissue mesenchymal stem cells (AD-MSC or ADSC) are multipotent cells that do not show immune rejection. In this work, we analyze the route of administration and its possible differentiation into specific lineages of adipogenic, chondrogenic, osteogenic, myogenic, or neurogenic phenotypes. Transplanted cells induced tissue repair by inducing angiogenic, anti-inflammatory, and immunomodulatory effects (IDO, PG-2, nitric oxide, and some cytokine signaling). The ADSC exert these tissue repair processes through the release of chemokines and growth factors in a paracrine manner. Other fat-derived stem cells such as perivascular adipose tissue cells (PVAT) and muse cells induced reparative effects. Cell-free therapy using stromal vascular fraction (SVF) or the use of exosomes releasing miRNAs and cytokines also confirmed their safety and efficacy *in vitro*. Several published preclinical and clinical trials with AD-MSC confirmed their beneficial effects to repair and prevent chronic-degenerative pathologies. In this chapter, we review AD-MSC-based therapies that have used preclinical rodent models of disease for cartilage repair, regeneration of the peripheral and central nervous system, dental bone, myocardium, and liver, and in the treatment of perianal fistula in Chron's disease, and in wound and skin fibrosis repair. In addition, this work also includes clinical studies with AD-MSC or other fat-derived stem cells in patients with various pathologies.

Keywords: regenerative medicine, stem cells, adipose tissue mesenchymal stem cells (AD-MSC), adipose-derived stem cells (ADSC), exosomes, stromal vascular fraction (SVF), clinical applications of adipose stem cells; neurorepair, skin repair, cartilage repair, myocardium repair, liver regeneration, perianal fistula, aesthetic medicine, stem cell therapy, signalling pathways, chemokines

1. Introduction

1.1 Mesenchymal stem cells from adipose tissue (AD-MSC): Characteristics and markers

Adipose tissue secretes adiponectin, leptin, and other adipokines involved in metabolic functions [1]. The incidence of obesity in the world is high, and adipose tissue aspiration (liposuction-lipoaspiration) is an esthetic surgical procedure that reduces the amount of unwanted fat and also allows the isolation of autologous adipose-derived stem cells (SC) (ADSC) [2]. Adipose-derived mesenchymal stromal cells (AD-MSC) play a role in maintaining adipocyte populations and promote tissue's regenerative effects. Adipose tissue is an abundant, reliable, safe and feasible source for mesenchymal stromal cell isolation. Adipose tissue contains a large number of multipotent stem cells called adipose mesenchymal stromal cells (AD-MSC) and lipoblasts, among other components, capable of differentiating into specific lineages, such as adipogenic, chondrogenic, osteogenic, myogenic or neurogenic [3]. However, AD-MSC obtained from subcutaneous fat deposits or abdominal fat is a heterogeneous cell population, and individual differences could affect autologous transplants while allogenic transplants have the risk of immune rejection [4]. On the other hand, the efficacy and functionality of transplanted MSC depend on number of transplanted cells, route of infusion, and frequency of administration [5–9]. However, the number of AD-MSC transplants that reach the damaged tissue is low, although MSC can differentiate into the specific cell type to replace it, given its multipotentiality.

It is known that multiple doses infusion of AD-MSC offer longer cell persistence and are more effective than a single dose [9, 10]. It is also worthy to mention that intravenous infusion of ADSC (or stem cells in general) lead to their accumulation into the lung [11, 12], which could reduce the clinical efficacy of these transplanted SC [13]. Inflammation produces chemokines (chemotactic cytokines) that recruit MSC to damaged tissues. Homing or recruitment of stem cells to damaged tissues depends on the route of administration [14–20].

One advantage of fat is its safety and easy procedure for SC isolation under local anesthesia, making it less invasive than the puncture technique [21]. In addition, fat from liposuction can be preserved in biobanks for long periods of time at −85°C with cryoprotective agents. This fat can be isolated throughout life, although there are differences regarding the origin of fat in the number of cells obtained [1, 2]. In addition, the proliferative capacity of isolated cells is greater in fatty deposits of young than in older patients [22]. However, the composition of fat-derived SCs (or their subpopulations) varies between laboratories and preparations, probably due to the lack of standardization of *in vitro* isolation protocols [23–26]. The number of MSCs is limited and its proliferation capacity decreases with successive passages *in vitro* [27]. ADSC can adhere to plastic *in vitro* and maintain a normal karyotype *in vitro* through several growth passages (teen), although its capacity of expansion progressively decreases *in vitro* [28]. Thus, the multipotential capacity of differentiation into a wide variety of cell types converts them into good candidates for biomedical applications. In fact, several studies have confirmed the long-term safety of AD-MSC in rodent models of disease and clinical trials without adverse effects or tumorigenesis [29–31]. Finally, adipose/fat tissue provides an abundant source of stromal vascular fraction (SVF) cells while exosomes (exo) are nanovesicles derived vesicles released by SC that contain many soluble factors involved in cell repair [32].

Mesenchymal stem cells (MSC) are a multipotential heterogeneous population of stromal cells that adhere to the plastic, including AD-MSC [33–35]. MSC can be

isolated from bone marrow, adipose tissue, peripheral blood, Wharton's jelly from the umbilical cord, venous walls, placenta, periosteum, trabecular bone, or teeth, including the periodontal ligament, among other tissues [36–39]. The main criteria that identify MSC are their ability to adhere to the plastic *in vitro*, their fibroblast-type morphology, and the capacity of differentiation *in vitro* into cells of mesodermal origin (chondrocytes, adipocytes, and osteoblasts) [36–40]. The first characterization of these cells, obtained from human lipoaspirates, was demonstrated by Patricia Zuk and coworkers [41, 42]. It was in 2004 when the International Federation for Adipose Therapeutic and Science (IFATS) decided to unify the different nomenclatures of SC derived from the vasculo-stromal fraction of adipose tissue with the acronym ADSC (Adipose-derived Stem cells), including the mesenchymal stem cells from adipose tissues (MS-ADSC) [33, 35]. During the aforementioned congress, this type of cells was defined as fibroblast morphology cells able to adhere to the Petri dish *in vitro*, isolated from the stromal fraction of fat and with the capacity for self-renewal for long periods, and able to differentiate into adipocytes, chondrocytes, and osteocytes. ADSC are positive for the surface markers Stro-1 (stromal precursor antigen-1), CD73 CD29, CD44, CD90, CD105 and also are negative for the hematopoietic markers (CD34 and CD45) [36–45]. **Table 1** compares the properties of bone marrow-derived MSC (BM-MSC) with ADSC (see table). In addition, ADSC also expresses CD44 (hyaluronic acid receptor), and adhesion molecules such as CD29 (integrin β1), CD90 (Thy-1: thymocyte antigen-1), surface enzymes such as CD13 (aminopeptidase), CD71, CD105 (endoglin), CD73 (ecto-5′-nucleotidase). They also express CD49d (VLA4), CD106 (VCAM-1), and CD54 (ICAM-1) markers [46–48]. However, tissue-resident MSC may also express the hematopoietic stem cell (HSC) marker CD34 [49]. Although freshly isolated ADSC can express CD34, long-term cultured ADSC do not, perhaps due to the artificial environment of the tissue culture plate [50].

On the other hand, perivascular stem cells are located in blood vessels, such as pericytes or vascular precursor SC [51, 52]. ADSC is predominantly associated with vascular structures in the adipose microvasculature having a CD34+/CD31 phenotype of capillary endothelial cells [50–53]. In fact, in fresh adipose tissues, CD34+ cells are located in the intima and adventitia layers of blood vessels. However, MSC even appear to be pericytes capable of stabilizing blood vessels and also contribute to tissue

Parameter	BM-MSC (Bone marrow derived mesenchymal stem cells)	AD-MSC (Mesenchymal stem cells from fat)
Quantity of isolated cells from donnor	Less abundant	More abundant
Accessibility	Poorly accessible (located in the bone)	Highly accessible (located subcutaneously in fat)
Extraction procedure	It requires general anesthesia	It requires local anesthesia
Yield	Lower efficiency in the number of isolated stem cells	Higher efficiency in the number of isolated stem cells
Does it require the use of mobilizers?	Yes, the treatment with G-CSF (granulocyte-colony stimulating factor) enhances the number of isolated SC	Not required

BM-MSC: bone marrow mesenchymal stromal cells; MSC: mesenchymal stromal cells; AD-MSC: adipose-derived mesenchymal stromal cells.

Table 1.
Differences between bone mesenchymal stem cells (BM-MSC) and adipose stem cells (AD-MSC).

homeostasis, playing an active role in repairing against injury [53]. Following ADSC transplants, controversial results on their repair capabilities were observed in both preclinical models of the disease and in clinical trials [53, 54]. These discrepancies can be explained by the infusion route used, differences in the cell type, and in the dose of MSC applied, which may affect their clinical efficacy [7, 55]. Even so, the therapeutic success of ADSC has been confirmed in multiple studies [56, 57], although there are particular cases where results differ, given the lack of standardization among multicenter clinical trials [58].

Finally, ADSC can be expanded *in vitro* as well as cryopreserved in biobanks under good manufacturing practices (GMP) [59]. In allogeneic transplants, the compatibility between donor and receptor depends on the histocompatibility antigens (HLA). Although allogeneic transplant often is well tolerated, the risk of immune rejection could occur after transplant [59–61].

1.2 Differentiation capacity of adipose-derived stem cells (ADSC) into various cell types

ADSC are progenitor cells that have a high capacity to differentiate into mesenchymal lineages such as osteocytes, adipocytes, and chondrocytes [28], although they can also differentiate into non-mesenchymal lineages (hepatocytes, pancreatic β cells) [28, 62–64]. ADSC can differentiate into adipocytes or osteoblasts, as fat-inducing factors inhibit osteogenesis, and conversely, bone-inducing factors hinder adipogenesis. Several external signals regulate the balance of adipo-osteogenic differentiation, and dysregulations of these balances contribute to aging, obesity, osteoporosis, osteopenia, etc. The process of MSC differentiation into adipocytes or osteoblasts has attracted great attention because of its potential repair capabilities in treating certain pathologies [29].

1.2.1 Differentiation of adipose stem cells (ADSC) into mesenchymal lineages

As mentioned above, ADSC can be differentiated into adipogenic, osteogenic, and chondrogenic lineages [65].

1.2.1.1 Adipogenic differentiation of ADSC

Given the origin of ADSC, undifferentiated cells express genes such as leptin, lipoprotein lipase, and PPARgmama-2 (peroxisome proliferator-activated receptor gamma-2). Their ability to differentiate into the adipogenic lineage is maintained even after the cells have been transplanted [65]. ADSC cells are grown in adipogenic medium with indomethacin, dexamethasone, 3-isobutyl-methylxanthine, penicillin/streptomycin, and rh-insulin, l-glutamine. Differentiated cells express the PPARγ2 marker (peroxisome proliferator-activated receptor gamma 2) or Glut4 [65].

1.2.1.2 Osteogenic differentiation of ADSC

Osteogenic induction of ADSC takes place for 21 days after adding osteogenic factors to the culture medium, such as TGF-β and bone morphogenetic proteins (BMP), dexamethasone, vitamin D3 and ascorbic acid/ascorbate, among others [65]. The capacity for osteogenic differentiation is confirmed by Von Kossa or Alizarin Red

staining that identify mineralized matrix and calcium deposits at the histological level [66]. During differentiation of ADSC into osteoblasts, the expression of bone markers and mineralized extracellular matrix (ECM) increases, such as Runx-related transcription factor 2 (Runx2), osteonectin, osteocalcin, alkaline phosphatase (ALP) and collagen type I [65, 67, 68]. In fact, osteogenic differentiation is enhanced by transfection of ADSC with BMP-2 and Runx2 [69, 70].

1.2.1.3 Chondrogenic differentiation of ADSC

Chondrogenic differentiation is induced by the addition of several factors in the culture medium such as transforming growth factor family members (TGF-β beta1 and 3), bone morphogenic protein (BMP-4) or basic fibroblast growth factor (bFGF). The differentiation of ADSC takes place during 21–28 days, and it is confirmed by Alcian Blue staining, which binds strongly to sulfated glycosamyglycans (GAGs) and glycoproteins [65]. Chondrogenic differentiation is also confirmed by TGF-β and SOX-9 expression, which is essential for the expression of type II collagen in chondrocytes [67, 68]. In this way, SOX-9 overexpression enhances chondrogenic differentiation and inhibits the osteogenic differentiation of MSC [71]. In addition, proteoglycans in the cartilage-like matrix can be identified by toluidine blue or safranin O staining [72]. Interestingly, the combination of L-ascorbic acid and platelet-rich plasma (PRP) can increase the survival of ADSC and improve chondrogenic function under appropriate concentrations [3].

1.2.2 Differentiation of adipose stem cells (ADSC) into non-mesenchymal phenotypes (muscle, cardiac, neurogenic, or endothelial cells)

ADSC can also differentiate into non-mesenchymal phenotypes, such as myogenic, neuronal, or endothelial lineages [69, 73]. Myogenic capacity of ADSC was demonstrated after transplantation into damaged rabbit muscles. In rodent models of cardiac injury, ADSC transplantation promotes regeneration of damaged myocardial tissue [64] On the other hand, human or rat ADSC can be differentiated into neuronal lineages by treatment with beta-mercaptoethanol, which induces the expression of beta-enolase, a neuronal marker [74]. In another study, treatment of ADSC with endothelin-1 (a paracrine factor released by endothelial cells) promotes their differentiation into endothelial cells with angiogenic properties. Finally, ADSC may be useful in treating preeclampsia, a complication of hypertension in pregnant women that leads to endothelial dysfunction [75].

1.3 Stromal vascular fraction (SVF) and exosomes (exo-ADSC) are adipose tissue-derived products

1.3.1 Stromal vascular fraction (SVF)

Lipoaspirate is a medical waste that contains stromal precursor stem cells called stromal vascular fraction (SVF). These cells are reliably and viably isolated from fat by enzymatic dissociation with collagenase [41, 42, 76] or using commercial kits [77]. The application of the local anesthetic method for SVF isolation with the collagenase kit, which is subsequently inactivated, allows the SVF to be obtained from the lipoaspirate [77]. The multipotent capacity of adipose tissue-resident stromal cells was demonstrated in 2000, when it was discovered that adipose tissue stromal

mesenchymal progenitor cells could differentiate into bone tissue *in vitro* under the right conditions [78]. In 2001, the presence of progenitor cells in subcutaneous adipose tissue with inherent properties of MSC was discovered, with potential ability to differentiate into chondrocytes, osteoblasts, and adipocytes. These cells exhibited good self-renewal capacity inherent to progenitor cells and typical mesenchymal-like markers on their surface, and at that time were termed processed lipoaspirate cells (PLA cells) [41, 76]. In SVF, ADSC are immunophenotypically characterized as CD45-/CD235a-/CD31-/CD31-/CD34+ markers, which represent approximately 20% of total SVF [33, 64]. In 2013, IFATS published a statement that included the minimum phenotypic criteria for characterizing uncultured SVF and also adherent ADSC isolated from adipose tissue, which typically account for up to 3%, approximately 2500 times more than bone marrow-derived cells (see **Figure 1**) [65].

Among the components of SVF, there are certain paracrine factors (VEGF, SDF1 alpha, BDNF, etc.) that protect against osteoarthritis in patients with joint injuries, especially of the knee [79]. The beneficial effects of SVF-associated therapy have been confirmed in preclinical models and also clinical trials, especially in patients with osteoarthrosis [80]. The clinical safety and efficacy of autologous SVF infusion performed in patients with grade 3 and 4 arthritis demonstrated 67% improvement in patients after stem cell therapy and with no adverse effects [81]. In this study, SVF-induced anti-inflammatory effects reduced osteoarticular injury through the release of nitric oxide, TGF-β1, stromal-derived factor (SDF-1 alpha), and other chemokines [80, 82, 83]. The exact composition of the paracrine factors in this SVF fraction and the exact molecular mechanism(s) by which SVF induces tissue repair are questions to be clarified in further studies. In addition, the combination of SVF

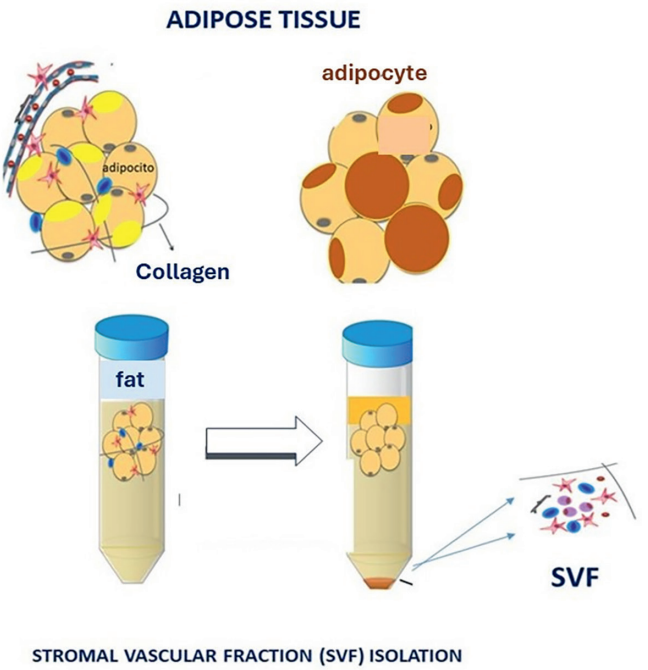

Figure 1.
Stromal vascular isolation fron fat.

with platelet-rich plasma (PRP) could enhance anti-inflammatory responses through the release of platelet-derived growth factor (PDGF) in patients [79].

1.3.2 Exosomes

Exosomes (exo) are small extracellular nanovesicles (size 40–150 nm) positive for CD63 and CD9 tetraspanin markers, and result from the fusion of vesicular bodies with the plasma membrane [80, 81]. Exo contains various nucleic acids (miRNA, RNA), proteins, and lipids and are involved in the cellular trafficking processes [81]. Soluble factors released by exo-ADSC promote anti-inflammatory and angiogenic effects as exo contains a cholesterol-rich lipid bilayer and also carries miRNAs that contribute to cellular repair mechanisms (miR-23a, miR-26b, miR-125b, miR-130b, miR-140, miR-203a, miR-223, miR-224), but also several proteins involved in many physiological processes [57, 84]. **Figure 2** shows several molecules involved in cell adhesion, prosurvival, and migration pathways of MSC, including fat MSC (ADSC, see **Figure 2**).

1.4 Repair mechanisms of adipose stem cells (ADSC)

ADSC release a plethora of paracrine factors involved in their protective/reparative effects, as demonstrated in several disease models in rodents, such as in diabetes, liver regeneration, ankle pathologies or neurological diseases [85–89]. The angiogenic capacity of ADSC depends on their origin [90], and they are cells carrying non-coding miRNAs involved in angiogenesis (e.g., miR-126, miR-296, miR-378, and miR-210 [91]). Activation of metalloproteases MMP-2 and 9 induces extracellular matrix remodeling, whereas ADSC stem cell transplantation reduces their activity [92] for the repair mechanisms of ADSC review (**Figures 2** and **3**).

The main protective and/or reparative mechanisms of transplanted ADSC are attributable to paracrine release of factors with angiogenic and/or immunomodulatory effects, making them ideal candidates for clinical transplants in patients [91, 93–96]. Indeed,

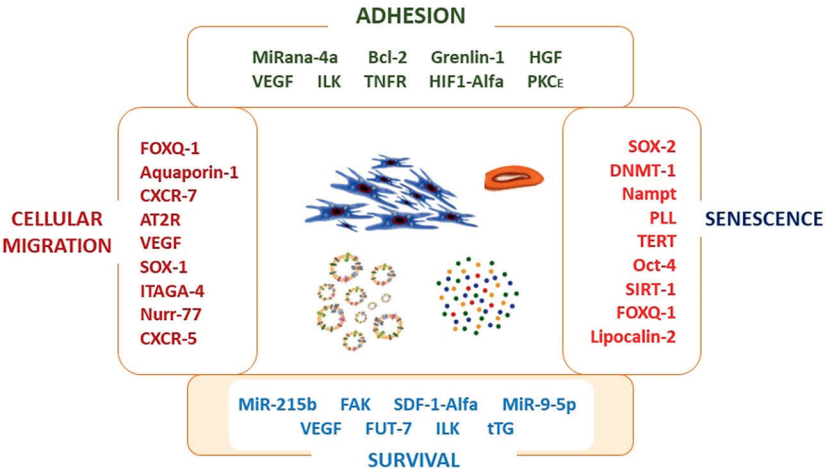

Figure 2.
Content of mesenchymal stem cell (MSC) exosomes (exo): miRNA and proteins involved in cell adhesion, migration, survival, and senescence.

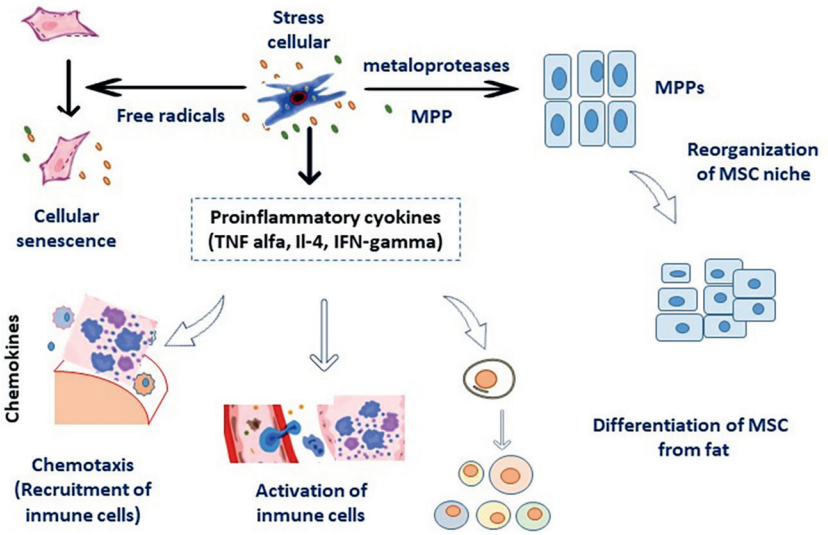

Figure 3.
Immunomodulatory properties of mesenchymal stem cells (MSC).

MSC favors the conversion of proinflammatory M1 macrophage phenotypes to an anti-inflammatory M2 phenotype and exerts immunomodulatory effects [97, 98]. MSC may act as antigen-presenting cells (APCs) with immunosuppressive properties for allogeneic stem cell therapy [98, 99]. Prostaglandin E-2 (PGE-2) and IDO are released by MSC [15, 100, 101] and involved in their immunosuppressive activities [102–106]. In addition,

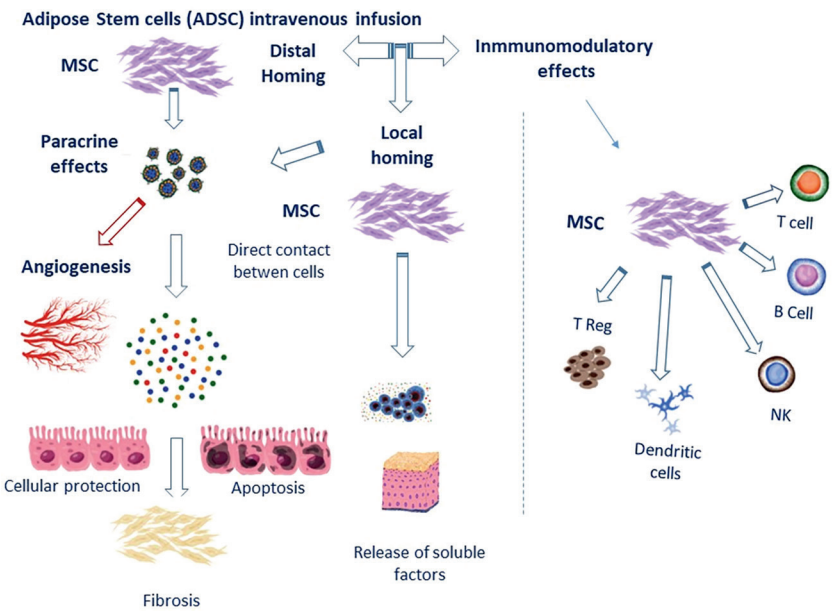

Figure 4.
Repair mechanisms of mesenchymal stromal cells, including ADSC, promote angiogenic, protective, anti-apoptotic, and immunomodulatory effects.

TNF-stimulated gene 6 (TSG-6), another factor secreted by MSC, is stimulated by TNF-alpha or IL-1, resulting in anti-inflammatory effects [106] and prevention of vascular endothelial cell apoptosis ([107], see **Figures 2** and **3**). In a rodent infarction model, MSC transplantation reduced neutrophil recruitment by promoting anti-inflammatory effects dependent on TSG-6 protein levels concomitant with reduced MMP-6 activity in damaged areas ([108], and see **Figures 2** and **4**).

The inflammatory response is regulated by a delicate balance between proinflammatory signals released by M1-type macrophages as scavengers that remove cellular debris and M2-type macrophages that release cytokines that promote tissue repair. MSC can convert macrophages from an M1 proinflammatory phenotype toward an M2 anti-inflammatory effect. Activation of TNF-alpha-secreting macrophages by MSC could inhibit inflammatory responses [108]. The ability of MSC to regulate macrophage polarization through direct cell contact, although recent studies indicate that the immunomodulatory properties of MSC largely depend on paracrine mediators secreted by them [107].

2. Translational applications of adipose stem cells (ADSC)

Bone tissue engineering allows for improved therapeutic options of ADSC for the treatment of bone defects in situations such as reconstructive surgery, trauma, malformations, or other pathological conditions. The therapeutic role of bone tissue could also improve the quality of life of patients with osteoarticular problems. It is known that osteoprogenitor cells can grow *in vitro*, combined with an appropriate scaffold [65]. ADSC combined with various types of organic or inorganic scaffolds (polylactic acid, PLA, polyglycolic acid, PGA, glycolic acid, PLGA, fibrin, collagen, gelatin) have been shown to have improved their *in vitro* repair capabilities [107]. Ceramics are known to exhibit osteoconductive properties, support osteogenic potential, and affect growth direction *in vitro* [109]. ADSC growth, in combination with bioactive factors and scaffolds, exhibits strong osteoinductive properties (biocompatible and biodegradable) and increases osteogenic differentiation, enhancing bone trabeculae formation without forming toxic by products. Overall, ADSC treatments for bone regeneration are promising for the treatment of craniofacial defects [110].

2.1 Cell-based therapies for cartilage repair

The infusion route (intravenous, subcutaneous, etc.), dose, and frequency/timing of administration affect the safety and clinical efficacy of autologous or allogeneic human stem cell transplants [111]. Osteoarthritis (OA) is a progressive degenerative joint disease characterized by deterioration of articular cartilage as well as pathological changes in the adjacent subchondral bone. Cartilage injury is a leading cause of disability worldwide, and current conventional treatments (physical therapy, chondroitin sulfate supplementation, and arthroscopic surgery) can improve joint function but without complete reversal of pain. Since cartilage injury is a leading cause of disability worldwide [110], autologous stem cell therapy treatment could promote cartilage regeneration [111]. However, stem cells injected directly into the pain site often have limited cell retention and a low survival rate, especially in large cartilage lesions, which might reduce their clinical efficacy [112, 113]. In a mouse model of OA injury, a single injection of AD-MSC into the knee during the early stage of OA inhibits cartilage destruction [114]. However, there was no effect when ADSC were infused at an

advanced stage of the disease [115]. Given the limited efficacy of conventional treatments against OA, intra-articular infusion of autologous stem cells could be a potential approach for cartilage regeneration, including the application of exosomes or MSC-derived advanced therapy drugs (ATMPs) against osteoarticular lesions [115, 116].

MSC can differentiate into chondrocytes, osteoblasts, and myocytes, among other types of mesodermal cells (for review, see [117]). In one study, the authors demonstrated that clinical symptoms improved during a 6-month follow-up after intra-arterial injection of ADSC, in patients with osteoarticular problems [118, 119]. In another study, an MSC-conditioned culture medium protected against bone defects. However, the properties of MSC are affected by sex, age, and body mass index of donors [120], leading to inter-individual differences between patients. On the other hand, the use of scaffolds increases the viability of ADSC and their aggregation capacity *in vitro* [121]. The three-dimensional structure of ADSC loaded on scaffolds, as well as the pore size, the type of material, and the stiffness of the scaffolds, are important factors that could affect the osteoarticular regeneration processes. Indeed, certain biomaterials (scaffolds) can enhance cartilage formation *in vitro*, as ADSC can be differentiated into chondrocytes by the addition of certain recombinant proteins (IGF-1, TGF-β, or BMP) to the medium [117]. MSC-derived cartilage increases mineralization and promotes angiogenesis for bone formation in a SCID mouse model [116]. The use of biomimetic injectable hydrogels can induce the release of soluble factors capable of retaining stem cells at the target site. For example, natural materials favor cell adhesion, promote their biodegradability, and regulate their mechanical properties [122].

Scaffolds with smaller pore sizes (90–250 μm) preserved cell adhesion properties and favored proliferation, and also increased collagen type II expression [123]. In this sense, a combination of a 3D type I collagen scaffold with platelet-derived growth factor (PDGF) and insulin are biocompatible materials *in vitro* and increase the chondrogenic differentiation of ADSC [124]. Other studies have confirmed that hydrogel-based scaffold systems can create cartilage but with better mechanical properties [125]. ADSC cells in a PLGA-gelatin scaffold with immobilized TGF-β1 reduce cartilage damage and improve cartilage quality [116]. The efficacy of intra-articular injections of hydrogels (with and without ADSC) was evaluated in a collagenase-induced OA rat model 7 days after induction of cartilage degeneration. The results showed that both hydrogel and ADSC-hydrogel treated groups showed chondroprotective and anti-inflammatory effects, suggesting that the hydrogel induces cartilage tissue regeneration [126–128]. In this model, the OA lesion and inflammation were reduced by ADSC-hydrogel treatment. In conclusion, the use of biomaterials combined with stem cells could be a good therapeutic option for OA patients. Although it is important to establish a specific therapeutic option for each patient based on their degree of osteoarticular injury.

A recent systemic review of 4348 articles has evaluated the use of ADSC for ankle orthopedy treatment, demonstrating the beneficial effects of AD-MSC against osteoarticular lesions. For example, improvements in MRI outcomes after SVF treatment together with marrow stimulation were demonstrated as compared to marrow stimulation alone [129]. Other meta-analyses evaluated the effect of ADSC and SVF in 82 studies with a total of 3594 treated patients with osteoarticular diseases. 70% of these studies evaluated the effect of stem cells in osteoarthritis, and 26% dealt with expanded ADSC. This review confirmed the heterogeneity of cell types used for osteoarticular lesions from different sources of adipose tissue (for review consult [129]). Thus, the safety and efficacy of SVF treatment to treat osteoarticular lesions are associated with many protective mechanisms, among them the induction of immunomodulatory effects and graft survival, leading to cell repair [130]. However,

differences in the methodology for SVF isolation, donor age, etc., are limitations that may reduce the efficacy of ADSC and adipose tissue-derived products. On the other hand, lack of standardization of clinical procedures, as well as hormonal status or comorbidities such as obesity may also affect the efficacy of ADSC transplantation. Finally, differences in international regulations between countries may affect the products available on the market. In some cases, conducting double-blind randomized trials without a true control group is another limitation [131]. Despite these limitations, promising results highlight the clinical use of ADSC treatments for osteoarthritis pathologies (in general) by inducing anti-inflammatory and chondroprotective effects without serious complications [132]. Due to regulatory issues, most of the research is still in the experimental phase, and most are preclinical results; therefore, we are still far from reaching the generation of new cartilage due to the cellular and molecular complexity of this tissue (see, **Figure 5**, [133]).

2.2 Regeneration of the central and peripheral nervous system by fat-derived stem cells (ADSC)

Neuroprotective and promyelinating properties of conditioned culture medium have been demonstrated in human adipose mesenchymal stromal cells [134]. This study confirmed the repair capacity of isolated ADSC from intact adipose tissue of 10 subjects undergoing abdominal plastic surgery [134]. The therapeutic potential of ADSC in the central and peripheral nervous system has been associated with its capacity to differentiate into neurons, endothelial cells and Schwann cells, to the expression of neuronal markers and to a faster proliferation rate than other types of stem cells [135]. Neuronal differentiation of ADSC is mediated by several neurotrophins (NGF, BDNF, GDNF, FGF) and hormones (IGF-1), which regenerate damaged nerves and induce neuroprotective effects [89]. Neuronal degeneration and vascular damage can lead to inflammation, followed by loss of oligodendrocytes and neurons in the lesions.

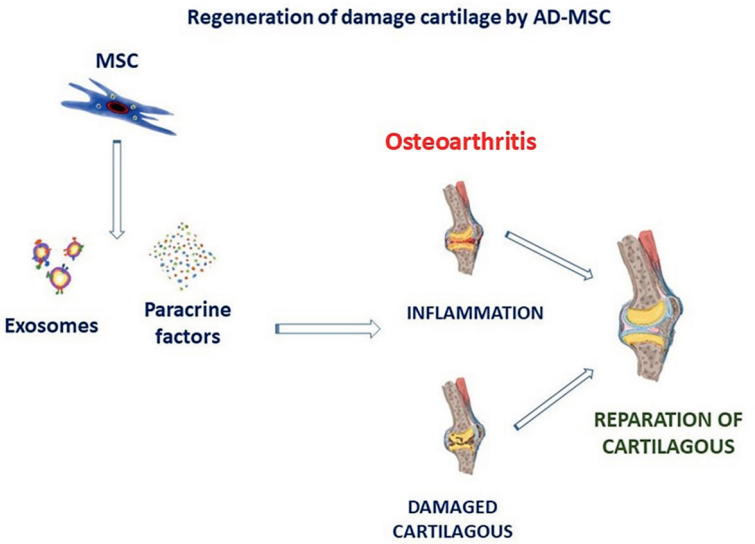

Figure 5.
Repairing effects of ADSC in osteoarthritis.

Therefore, ADSC administration could control the inflammatory response after injury and could also improve regenerative capacity, given the contribution of vascular factors in repair [136]. In fact, vascularization is another factor involved in cell survival and proliferation, and released vascular factors released by damaged endothelium enhance ADSC-mediated regenerative effects (**Figure 5**, [137]).

ADSC exo-derivatives produce neuroprotective effects in rodent models of multiple sclerosis, cerebral ischemia, and traumatic brain injury (TBI) [138, 139]. ADSC infusion prevented TBI-induced neuroinflammation and also decreased secondary injury as a consequence of TSG-6 release, leading to reduced microglial overactivation [140].

ADSC exo-derivatives can decrease the cytotoxic effect of overactivated microglia by reducing the nuclear factor kappa-beta (NF-β) transactivation and regulating mitogen-activated protein kinase (MAPK) pathway [92]. Axonal regeneration and less reactive gliosis were evident after ADSC treatment in rats with spinal cord injury [141]. In a multidisciplinary clinical trial, intrathecal infusion of ADSC decreased the medullar lesion at L3–4 level of the spinal cord, and the evaluation of lesions with objective criteria following the International Standards for Neurological Classification of Spinal Cord Injury scores demonstrated improvements in these patients [142]. Preclinical findings confirmed that the combination of scaffolds and ADSC could prevent symptomatology in certain neurological disorders, such as amyotrophic lateral sclerosis, Alzheimer's (AD), Parkinson's (PD), or Huntington's disease [142, 143]. Some clinical trials evaluated the safety and efficacy of ADSC to treat pathological conditions in patients with Alzheimer's, Parkinson's or Huntington's, or amyotrophic disease (see ClinicalTrials.gov, www.clnicaltrials.gov identification numbers NCT03117738 and NCT02184546) [144–149].

2.2.1 Regeneration of the peripheral nervous system by ADSC

ADSC infusion in rodent models promoted regenerative effects of the peripheral nervous system after sciatic nerve damage with varying degrees of severity. ADSC treatment enhanced Schwann cell regeneration by increasing the number of myelinated fibers in the damaged nerves. In fact, ADSC can be differentiated into Schwann cells [150], and the use of compatible biomaterials *in vitro*, such as PGA, PCL, and collagen, increase the repair capacity of ADSC [151, 152].

2.3 Regeneration of the dental pulp by ADSC

ADSC treatment also promotes the regeneration of bone tissue in alveolar bone defects, specifically in patients with periodontal disease [153]. The inclusion of ADSC in PLGA matrices enhances bone growth in animal models. The synergic combination of ADSC with fibrin also prevented inflammation and reduced bone resorption in the tooth, suggesting that MSC from the oral cavity contributes to repair [154]. The combination of autologous ADSC and Platelet-Rich Plasma (PRP) induces periodontal tissue regeneration. For example, CD31 positive adipose population contributes to promoting repair in dental pulp cells in dogs [153]. However, their applications in regenerative dentistry need further confirmation with clinical trials [154].

2.4 Regeneration of the myocardium by ADSC

Several routes of infusion have been evaluated in transplants with ADSC into the myocardium, such as intramyocardial, intravenous, or intracoronary injection.

Transplantation with ADSC has promoted beneficial effects in cardiovascular pathology due to its capacity for differentiation to the required cell type [155] and the release of paracrine factors involved in angiogenic, anti-apoptotic, and anti-inflammatory effects [156, 157]. Intramuscular and intracoronary infusion of ADSC improved the left ventricular ejection fraction (LVEF) function [158], and inhibit the fibrosis process [159]. The efficacy of direct infusion of ADSC into infarcted myocardium in rodent models is limited, given the low survival rate of transplanted cells [158]. Intravenous administration of resistin-treated ADSC improved LVEF function, reduced fibrosis, and decreased cardiomyocyte apoptosis [160]. Intracoronary administration of ADSC also reduced apoptosis (programmed cell death) in the infarcted area of the myocardium without significantly affecting LVEF [161], clearly indicating the relevance of the infusion route for ADSC transplantation. This intravenous administration significantly reduced infarct size and induced angiogenesis [161].

On the other hand, the combination of biomaterials with ADSC creates a favorable microenvironment for tissue repair in the infarcted area [162]. Some studies have addressed the factors involved in the reparative effect of ADSC. For example, the overexpression of the Stromal Cell Derived Factor (SDF-1 alpha) chemokine as a regenerative factor in stem cell therapy since it reduces apoptosis and enhances angiogenesis, leading to protective effects [162, 163] and its overexpression prevented detrimental consequences of myocardial infarction [164]. Overexpression of other trophic factors such as IGF-1, VEGF, hepatic growth factor (HGF), and FGF-2 also decreased apoptosis and enhanced angiogenesis [165, 166]. From this perspective, several clinical trials have reported that intracardiac ADSC transplantation improved the scales with improvement in cardiac function [164, 165].

2.5 Liver regeneration by ADSC

Acute liver failure or chronic liver diseases can be the consequence of infection with viruses, toxins or even genetic factors. These liver diseases are characterized by fibrosis and can provoke liver damage and inflammation with the consequent activation of hepatic stellate cells (HSC) [167]. Given that ADSC can differentiate into various types of liver cells and have anti-apoptotic and immunomodulatory effects, they could be useful for treating liver pathologies [168]. The administration of ADSC suppresses the expression of proinflammatory cytokines and decreases the proliferation of activated HSC cells [168, 169]. In a rodent model of induced liver fibrosis by CCl4 treatment, ADSC transplant or exosomes infusion markedly decreased liver fibrosis, leading to apoptosis of HSC cells [170, 171]. In another study, ADSC injection into liver parenchyma protected cells against liver injury by inducing Superoxide dismutase-1 (SOD-1) and produced anti-inflammatory effects by reducing IL-1 beta levels [172]. The culture of ADSC under hypoxia increase the expression Nrf2 transcription factor *in vitro* (a nuclear factor erythroid 2 with antioxidant effects) that protects against free radical-mediated toxicity in the liver [173]. Another factor released by ADSC, such as hepatic growth factor (HGF), induced anti-inflammatory effects by increasing IL-10, an anti-inflammatory cytokine [174, 175]. In addition, exosomes from ADSC infusion reduced the levels of liver enzymes such as aminotransferase (AST), alanine aminotransferase (ALT) activities and reduced lactate dehydrogenase (LDH) activity [168]. Intravenous infusion of ADSC in a murine model of liver injury prevented liver damage concomitant with decreased serum ALT and AST activities. In a carbon chloride liver injury model, ADSC-derived exosomes

carrying the modified miRNA-181-5p reduced liver fibrosis [176, 177]. The combination of ADSC with scaffolds such as PLGA markedly improved liver function and reduced necrotic areas in the tissue [178]. Umbilical cord MSC (UC-MSC) infusion reduces fibrosis and increases caveolin-1 in hepatic stellate cells [179]. Finally, some clinical trials confirmed that ADSC infusion is safe and effective in treating liver cirrhosis in patients. In these clinical trials, ADSC transplantation improved liver function without any adverse effects [180, 181]. However, further clinical trials with a larger sample size should confirm the long-term safety of ADSC in patients.

2.6 ADSC infusion for the treatment of perianal fistula

Perianal fistulas are a complication suffered by 20 to 25% of Crohn's patients, and the infusion of autologous or allogenic ADSC can promote reparative effects through the release of paracrine, immunomodulatory, anti-apoptotic, and angiogenic factors. Several clinical trials have confirmed a complete cure rate of anoperineal fistulas in these patients. A phase III controlled trial confirmed the safety of treatment with allogenic ADSC (Alofisel®), which induced a radiological remission in 60% of cases [41, 42, 76, 182, 183]. Another phase II multicenter randomized controlled trial has shown that infusion of expanded ADSC (20 to 60 million cells) in combination with fibrin glue is safe and achieves higher cure rates than fibrin glue treatment alone [184].

2.7 Skin repair by ADSC

Subcutaneous administration of AD-MSC is well-studied in esthetic medicine, especially in cases of facial rejuvenation [185, 186]. Topical administration of ADSC increases skin graft survival as well as wound healing capacity [187, 188]. Furthermore, subcutaneous injection of AD-MSC from different human donors did not form teratomas in immunodeficient SCID mice up to 17 months after infusion. Furthermore, increased cell survival, exclusively at the injection site, was observed for at least 17 months after infusion, as well as these infused ADSC were able to differentiate into subdermal tissue fibroblasts without migration to organs [188]. ADSC transplantation normalized blood flow at the wound site [189], facilitated fibroblast migration and proliferation, inhibited collagen deposition, and also decreased α-smooth muscle α-actin expression in scar fibroblasts [189, 190]. ADSC differentiate into skin stem cells and promote the accumulation of autologous skin SC. Several trophic factors are involved in skin repair by ADSC, including epithelial growth factor (EGF) receptor, while the increased release of GDF11 factor promotes skin anti-aging effects. In addition, severe burn injuries and intractable ulcers are reduced after ADSC transplantation during wound healing [191]. Reduced inflammation by ADSC infusion promotes the polarization of proinflammatory M1 macrophages into their anti-inflammatory M2 phenotype, contributing to wound healing repair in rodent models of skin injury [192]. Autologous fat grafts with ADSC induce antifibrotic and anti-inflammatory effects, but the exact mechanism of repair is not yet fully understood.

Infusion of ADSC promotes reparative effects associated with the release of cytokines (G-CSF, PDGF, HGF, IL-6, and IL-8), chemokines (Il-8, SDF-1 alpha), and vascular factors (VEGF). Since ADSC are also modulators of metalloprotease activity [193, 194], it is possible that they may promote anti-fibrotic effects by decreasing their activity. By simulating the interaction of ADSC with fibroblasts and endothelial cells

(ECs) in the skin, the ADSC secretome could alter scleroderma vascular inflammatory foci (SSc) in the skin *in silico* [192]. In a study using ADSC expressing Bcl-2 embedded in collagen scaffolds to treat diabetic wounds, significant improvement in wound healing [194, 195], enhanced neovascularization, and decreased healing time compared to controls were observed [196]. ADSC exosomes stimulated wound healing by increasing fibroblast, keratinocyte, and endothelial cell proliferation [196, 197].

Several clinical trials have shown that ADSC transplantation has corrected facial skin defects in patients with radiation injury [196] and that ADSC are safe and effective in the treatment of this type of radiation injury [198]. In contrast, a single dose of autologous fat grafting was insufficient to improve burn scars, perhaps due to the small patient sample size. Overall, more clinical trials should confirm the clinical efficacy of ADSC to treat wound healing [199].

Author	**Tissue**	**Rodent model and implantation of cells**	**Results**
Arrigoni et al.	Bone/rabbit	Surgery implantation/ rabbit	ADSC-induced bone formation with increased bone density
Chen et al.	Bone/human	Surgery implantation/ rabbit	Overexpression of miR-375 enhances osteogenesis in vitro and in vivo Efficiently reduced inflammatory responses
Li et al.	Cartilagous	Injection or surgery implantation/rabbit	ADSC with scaffold promote long-term regeneration
Cho et al.	Cartilagous	Surgery implantation	The transplant of ADSC was able to improves the quality of cartilage
ter Huerne et al.	Cartilagous	injection	ADSC infusion improved synovial inflammation
Yin et al.	Cartilagous	Surgery implantation	ADSC combined with an immobilized TGF beta scaffold improves regeneration of defective cartilage
Hu et al.	Nerves	surgery implantation	Improves nerve regeneration by ADSC treatment
Khingam et al.	Nerves	surgery implantation	ADSC promotes axonal regeneration
Li et al.	Nerves	Injection	ADSC reduces neurodegeneration
Durco et al.	Nerves	Surgery implantation	The ADSC infusion increase the number of nerve fibers
Nagata et al.	miocardium	Transfusión	ADSC Transplant Promotes Better Cardiac Recovery
Bobi et al.	miocardium	Surgery implantation	ADSC infusion improves perfusion in the periischemic area of the myocardium
Mori et al.	miocardium	Surgery implantation	Increases vascular density in the peri-infarct area by ADSC infusion in the myocardial
Qiao et al.	miocardium	injection	The combination of scaffolds with ADSCs increase angiogenesis, decreases fibrosis, and reduces the infarct size.
Zhang et al.	liver	injection	ADSC combined with matrices increased angiogenesis, reduced fibrosis, and reduced infarct size

Table 2.
Preclinical studies with adipose stem cells (ADSC).

3. Preclinical trials developed with fat-derived stem cells (ADSC) in murine models

The following **Table 2** indicates the preclinical findings with ADSC infusion in murine models of disease, as well as the route of administration of the cells (for a review refer to Dong et al. [61]) [65, 200].

4. Clinical trials with ADSC in patients with various pathologies

ADSC treatment of corneal and retinal lesions or optic nerve degeneration is associated with corneal epithelial proliferation [61] and promotes anti-inflammatory and immunomodulatory effects [61, 201]. The feasibility of ADSC to stabilize retinal microvasculature has been conclusively demonstrated in a diabetic retinopathy model [88, 202]. Another study reported that ADSC-loaded collagen sponge promoted repair of tracheal defects and restored cilia motility function [203], as well as for the treatment of silicosis (2010), asthma, or even inflammatory diseases [204, 205]. On the other hand, autologous transplantation of ADSC can improve the functional recovery of skeletal muscle and also favor its differentiation without direct involvement of new myofiber formation [206]. ADSC have been used to treat autoimmune diseases [207] such as systemic lupus erythematosus (SLE), Sjörgren's syndrome, or Crohn's syndrome [208] or even for the treatment of type I diabetes mellitus [172]. Moreover, the anti-inflammatory capacity of ADSC makes them ideal candidates for the treatment of tendon injuries [209]. Furthermore, ADSC-derived extracellular vesicles also prevent metabolic dysfunction due to steatosis liver disease [210]. The administration of fat from subcutaneous abdominal adipose tissue (lipoaspirate) was evaluated in patients with type 2 diabetes with insulin resistance compared with healthy donors. In this study, patients with insulin resistance had a lower capacity for proliferation of ADSC, which is usually the first stage of diabetes [211]. In addition, the expression of osteogenesis markers is higher in cells from patients with type 2 diabetes (T2D), leading to the conclusion that type 2 diabetes modifies stem cell activity and that insulin resistance reduces ADSC proliferation [212]. Stem cell therapy is a novel therapeutic strategy for erectile dysfunction in patients with bilateral cavernous nerve injury. A meta-analysis of 12 studies with 319 rats analyzed the efficacy of stem cell transplants. Further studies will investigate the role of nerve restoration and vascular cell recovery in urology [116].

Several trials have confirmed the safety and efficacy of autologous ADSC to treat different pathologies [200, 213]. For example, fat is ideal for treating vocal problems because it is a biocompatible material and is readily available. The main disadvantage of its use is that resorption can cause long-term failure after its transplantation. In one study, fat harvested from the liposuction procedure was centrifuged, and the fat cell layer was injected directly into the vocal muscle. Fourteen patients received ADSC treatment (18–74 years, mean age: 48 years) with respiratory dysphonia secondary to laryngeal hemiplegia (n = 7) or anatomical defects (n = 7). The results confirmed an improvement in voice quality after ADSC transplantation, and these patients remained stable for 3–26 months (mean 10.6) [214]. In addition, seven patients improved their paralytic dysphonia after stem cell therapy [206].

Immunophenotyping of SVF-enriched fresh fat grafts has been evaluated for enhancing reconstructed breasts. Although fat injection into and around the reconstructed breast may require repeated injections and fat necrosis may occur, it

appears to be a safe technique that corrects significant contour deformities [215]. The performance of both grafts was evaluated through volume measurement by magnetic resonance imaging before and after 6 months of the operation in women for breast reconstruction. The finding of this study indicates that fat injection corrects contour deformities in the reconstructed breast [215].

A recent clinical trial has demonstrated the beneficial effects of allogenic ADSC treatment in acute stroke. In this single-center, randomized, double-blind, placebo-controlled, phase II pilot clinical trial, the safety and efficacy of allogeneic ADSC therapy has been confirmed [216]. The American Diabetes Association indicates that 85 percent of amputations result from complications arising from diabetic foot ulcers or peripheral arterial disease. In this context, cell therapy could prevent limb amputation by inducing the blood vessel formation and also reduce neuropathy relief in diabetic patients (**Table 3**) [216].

Clinical trials with ADSC	**Treatment with ADSC**	**Diseases conditions or Therapeutic indication**
Japanese UMIN clinical trial registry (UMIN000022601)	The 3.3×10^5/kg was administered via the hepatic artery using microcatheter IV. The follow-up period was 24 weeks after implantation.	The patients underwent liver biopsies prior to treatment. 24 weeks after treatment the evolution of nonalcoholic fatty liver disease (NAFLD) and fibrosis were measured [200]
NCT02904824	Injection using autologous fat enriched with ADSC vs. autologous fat for the functional reconstruction of the glottal gap provoked by unilateral vocal cord paralysis by laryngoplasty	Unilateral vocal cord paralysis (unilateral)
NCT02387723 without results yet (results will be published in 2025).	Phase I-II, multicenter, randomized, controlled clinical trial for the study of factibility of the cutaneous adult allogenic adipose-derived mesenchymal stem cells (AD-MSC) application expanded on fibrin hyaluronic biological matrix to treat venous ulcer of the lower limbs (fistula).	Adipose tissue stem cells (ADSC) on biological matrix for the treatment of venous ulcer of the lower limbs The incidence of adverse events (time frame through study completion, an average of 1 year) were evaluated.
NCT02287974 Andalusian network for design and translation of advanced Therapies n = 48 treated patients (Spain) Clinical Trial I/II opened, randomized and controlled for the study of the Use of stem Cells therapy in insulinized diabetic patients type 2 with critical ischemia in lower limbs (CLI): study of the needs of insulin	To study the effect of the stem cells autologous mononuclear treatment from the bone marrow (n = 12), autologous progenitor endothelial CD133 cells from the bone marrow (n = 12) and autologous mesenchymal stem cells from adipose tissue (n = 12) on proinflammatory cytokines, the resistance to insulin as well as the reduction of insulin treatment. Inclusion criteria: diabetic type 2 (treated with insulin at least 3 previous months). vascular disease infrapopliteal, atherosclerotic of severe degree	The critical ischemia of the foot is defined as a persistent/persistent pain that needs analgesia and/or not healing present sores>4 weeks, without evidence of improvement with conventional therapies patients were included by the criteria of impossibility of revascularization or fail in the surgery of revascularization (evaluated at least 30 days before, or entry in phase of critical ischemia).

Clinical trials with ADSC	Treatment with ADSC	Diseases conditions or Therapeutic indication
NCT01828723 Interventional (Clinical trial phase I, interventional) Estimated enrollment: phase one, open Label, single arm study single group assignment	Inclusion criteria: female or male: age 18 years or older that are scheduled for liposuction (BMI between and including 23 and 28) and facial fat grafting procedures for cosmetic purposes. Facial volume defects treated with a total graft volume of between 1 mL and 50 ml. Aim: to evaluate the safety of concentrated SVF-enriched fat graft by monitoring the number and types of adverse events, physical examinations, blood draws (CBC/LFT/BMP), and urinalysis (time Frame: 6 months) were also evaluated	Conditions of disease: lipoatrophy/aging/ wrinkles Demonstrate the safety of antria cell preparation process during facial fat grafting assisted with autologous SVF treatment. Outcome: to demonstrate the efficacy of autologous SVF treatment via antria cell preparation process by observing graft survival time, volume, and quality of facial re-contouring (time frame: 6 months)
NCT01678534 (AMASCIS-01: phase II) Reparative effect of acute allogenic mesenchymal stem cells from adipose tissue against ischemic stroke; evaluation of safety assessment, in a randomized, double blind placebo controlled single center pilot clinical trial (n = 19) Masking: quadruple (Participant, care provider, Investigator, outcomes assessor) Intervention: ischemic Stroke and placebo group Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Aim: safety evaluation with allogeneic MSC-ADSC Study group: allogeneic stem cells from adipose tissue A single intravenous AD-MSC infusion, dose (1 million units/kg) infused within the first 2 weeks after the onset of stroke symptoms. Drug: allogenic mesenchymal stem cells from adipose in acute ischemic stroke patients (Follow-up 24 months) Inclusion criteria: Male or women with acute ischemia (aged 60–80 years with symptoms of acute cerebral infarction). • Patients should be treated within 2 weeks from the onset of stroke symptoms. • Patients with a focal neurological that must persist to the time of treatment without clinically improvement by computerized tomography (CT) and/or MRI. Patients must have a score on the NIH Stroke Scale 8–20, with at least 2 of these points and motor deficit at the time of inclusion.	Primary Outcome Measures: number of participants with Adverse events, complications. (Time Frame: 24 months) Adverse events (AES) were recorded during all the study period (24 months) Neurological and systemic complications (brain oedema, seizures, respiratory infections, deep venous thrombosis, development of tumors, etc) were measured. Secondary outcome measures: to assess the potential efficacy of allogeneic stem cells from adipose tissue in acute ischemic stroke patients by evaluating the outcome at 3 months (NIH Stroke Scale, total volume of stroke by performing MRI). Changes in biochemical markers for brain repair as VEGF, BDNF, MMP-9 and its relationship to neurological and functional outcomes were evaluated
NCT01649687 Phase 1 and II (n = 7)	Aim: Allogeneic SC treatment for the Treatment of cerebellar ataxia with fat-derived MSC (ADSC) Patients will receive intravenously one dose of 5–7 × 10^7 cells of allogeneic adipose-derived mesenchymal stem cells	Allogeneic adult adipose-derived mesenchymal stem cells for cerebellar ataxia treatment Biological: allogeneic adult adipose-derived mesenchymal stem cells for the treatment of diagnosed of spinocerebellar ataxia 3 (SCA3) or multiple system atrophy-cerebellar (MSA-C, ages between 20 ~ 70 years).

Clinical trials with ADSC	Treatment with ADSC	Diseases conditions or Therapeutic indication
NCT01585857 A Phase I, prospective, bi-centric, single-arm, open-label (n = 18)	Aim: to study the safety (primary aim) and efficacy (secondary aim) of a single injection of autologous ADSC on patients with moderate or severe osteoarthritis of the knee. Autologous ADSC for intra-articular infusion (three study groups with doses (2, 5, and 10 millions of ADSC intra-articular injection in 5 ml) Each patient will receive one single administration for 3 months. They will be follow-up during 1 year with routinely examinations for safety issues. The first patient will be followed during 12 weeks before inclusion of the second patient.	Osteoarthritis treatment with ADSC to evaluate safety of a single injection of autologous AD-MSC to treat severe osteoarthritis of the knee joint Primary outcome evaluation of adverse events (Time frame: during 1 year, following injection) Secondary outcome measures: functional status of the knee. Efficacy will be assessed by scales for evaluating the osteoarthritis index and range of motion of the target knee joint, pain-specific assessment and image analysis.
NCT01532076 Effectiveness of Adipose tissue derived mesenchymal stem cells as osteogenic. Composite Grafts Prospective randomized first in men proof of principle trial	Aim: to study the effectiveness of AD-MSC as osteogenic component in composite grafts vs. acellular bone graft substitutes for augmentation in the treatment of proximal humeral fractures as model for fractures of osteoporotic bone. Experimental: graft by lipoaspiration, SVF and embebed in fibrin gel, wrapping around hydroxyapatite granules The control acellular composite graft augmentation open reduction internal fixation (ORIF) of the fracture, augmentation with acellular bone graft substitute.	Primary outcome measurements: development of secondary dislocation within 12 months postoperative (Time frame: 12 months postoperative). Secondary outcome measures: functional outcome 6 weeks, 6 and 12 months after fixation (Time frame: 12 months postoperative). Pain at either surgical site will be recorded via the visual analogue scale. Finally, bone mineral density (Time frame: 12 months postoperative) in case of implant removal was analyzed with microcomputed tomography) for bone mineral density.
NCT0125776	Autologous hhAD-MSC (human adipose tissue-derived MSC) to treat lower extremity ischemia in diabetes	Critical limb ischemia in diabetes
NCT01222039 Multicenter clinical trial phase I/II randomized, controlled, for the evaluation of safety and feasibility of two different doses of allogenic AD-MSC in patients with graft versus host disease GVHD (n = 19).	Aim: to assess the safety and feasibility of two-dose of allogeneic AD-MSC infusion expanded in vitro in patients undergoing hematopoietic stem cell transplantation, who have developed chronic and extensive GVHD. Conventional treatment: gradually descending dosage of prednisone and cyclosporin or tacrolimus for at least 46 weeks. Starting dose: 1 mg/Kg/24 h prednisone and 3 mg/Kg/12 h cyclosporin. Intravenous infusion of allogenic AD-MSC (Low dose: 1×10^6/Kg).	Conventional treatment plus intravenous infusion of allogenic mesenchymal stem cells from adipose tissue for the treatment of GVHD.

Clinical trials with ADSC	**Treatment with ADSC**	**Diseases conditions or Therapeutic indication**
NCT01157650 Interventional (clinical trial, n = 15)	Aim: evaluation of viability, security and tolerance of allogenic AD-MSC in fistulizing Chron's disease patients, collecting the reactions and adverse events (3 years of study) Experimental: Autologous mesenchymal stem cells Fistulizing Crohn's disease	Treatment of Fistulous Crohn's Disease by Implant of Autologous AD-MSC Tissue. Evaluating the ADSC therapeutic effect, in particular Fistulas healing efficiency.
NCT01056471 Multicenter clinical trial phase I/II randomized, placebo-controlled study.	Aim: to evaluate safety and feasibility of two different doses of autologous AD-MSC from patients with secondary progressive multiple sclerosis who do not respond to treatment Intravenous infusion of autologous AD-MSC (low 10^6 cells/Kg and high dose: $4*10^6$ cells/Kg), including placebo control.	Condition of diseases: autoimmune Diseases immune System Diseases demyelinating Diseases nervous System Diseases demyelinating autoimmune diseases, CNS Autoimmune diseases of the nervous system
NCT00442806 A randomized clinical trial of adipose-derived The APOLLO Trial (n = 14).	Subjects who have coronary artery disease and have suffered acute myocardial infarct Eligible subjects will undergo standard treatment after admission and will then undergo liposuction for further ADRC's or placebo treatment.	Stem cells for the treatment of myocardial Infarction. Primary outcome measures: to evaluate safety determined by major adverse cardiac and cerebral events (MACCE) (Time frame: 6 months) Secondary outcome measures: feasibility - assessment of cardiac function by MRI, SPECT, and Echocardiography (Time frame: 6 months)
NCT0177191324 Immunophenotyping of Fresh SVF from adipose tissue or enriched Fat grafts for refinements of reconstructed Breasts	Inclusion criteria for women: contour irregularities and volume insufficiency in reconstructed breasts. local flaps with conditions to receive fat grafts good health condition Exclusion criteria: breast cancer patients under chemotherapy bad health condition patients too thin patients that require secondary reconstruction	Study groups: centrifuged fat graft in women who underwent breast reconstruction. Study-2: ADSCs enriched centrifuged fat graft. ADSCs enriched from the abdominal subcutaneous tissue is isolated by lipectomy and SVF isolated and immediately added to the fat graft in order- to increase the volume insufficiency or correct contour irregularities for reconstructed breasts.
This is the first development safety update report FIBHGM-ECNC007–2010	The aim is to induce the overexpression and production of microvessels at local level. Route of administration: injection into the thickness of a parlay (Phase I/II). Clinical unicentric trial, randomized, controlled, two parallel-groups, to evaluate the safety of ADSC derived from fat in the glottal Gap zed vocal cord.	

Clinical trials with ADSC	Treatment with ADSC	Diseases conditions or Therapeutic indication
NCT02904824	The facial recontouring by fat was evaluated in the treatment of glottic incompetence. Study design and setting: fourteen patients (aged 18–74 years) with breathy dysphonia secondary to laryngeal hemiplegia or anatomical defects underwent vocal fold lipoinjection. Fat harvested by liposuction was centrifuged, and the fat cell layer injected into the vocalis muscle. The patients underwent pre- and postoperative video laryngostroboscopy, maximum phonation time (MPT) measurements, and voice handicap index (VHI) self-assessments	Unilateral vocal cord paralysis (unilateral)
NCT02387723	Allogeneic ADSC in patients with heart failure Patients with heart failure will be treated with culture expanded AD-MSC from healthy donors stored in nitrogen until use.	Heart failure The cells will be injected directly into the myocardium. The patients will be followed for 6 months for safety and efficacy registration.
Phase II multicenter, clinical trial, randomized controlled trial	Aim: to investigate the effectiveness and safety of ADSC for the treatment of complex perianal fistulas safety of stem cell-based therapy with expanded ADSC against Crohn's disease, and perianal cryptoglandular fistulas (n = 35; n = 14) Patients were randomly assigned to fibrin glue or 20 million ADSC cells plus plus fibrin glue treatment. Fistula healing was tested at 8 weeks and 1 year. If healing was not seen at 8 weeks, they received these treatments	Fistula healing was observed in 71 percent of ADSC-treated patients. The proportion of patients with healing was similar in Crohn's and non-Crohn's subgroups. However, ADSC were also more effective than fibrin glue alone in patients with a suprasphincteric fistulous tract. At 1 year follow-up, both treatments were well tolerated.

Table 3.
Clinical trials conducted with fat stem cells in patients (consult number of each trial for more detail in www.clinicaltrials.gov).

5. Future perspectives

ADSC are widely used to treat a wide range of clinical indications. Short follow-up periods in some studies and low power of findings in clinical trials are explained by low patient numbers. Furthermore, differences in regulatory practices between countries may hamper the application of stem cell therapies. Standardization of protocols and safety of long-term clinical trials need to be demonstrated before

clinical application of AD-MSC and SVF against chronic diseases. Since complications in adipose tissue are strongly associated with obesity, cardiovascular disease and type 2 diabetes, a better understanding of the cellular and repair mechanisms associated with adipose organoids as promising tools together with stromal vascular fraction or pluripotent stem cells as stem cell sources in the future is also needed [116].

Future perspectives should focus on mechanistic pathways for a better understanding of SVF properties. Long-term clinical studies are needed to truly confirm safety in patients, as well as studying their optimal dosages for SVF-based therapies over time in chronic diseases. Furthermore, studying the signaling pathways associated with the repair effect of ADSC, including the specific function of each SVF cell type, may provide insight into the knowledge and clinical application of fat stem cell therapies [217]. Small sample sizes of some studies reduce the power to detect significant effects.

6. Conclusions

The application and development of ADSC are boosted by the field of biomaterials and tissue engineering, which contribute to the improvement of the field of regenerative medicine. Given its abundance and easy isolation procedure as a waste material, liposuction fat is a good source for the isolation of ADSC for biomedical applications. These ADSC infusion promotes anti-inflammatory and immunomodulatory effects and the release of autocrine and paracrine functions, including chemokines and growth factors contribute to repair processes. Finally, the differentiation capacity of ADSC into various cell types could into specific local cell types in damage tissue also prevent tissular damage. Several clinical trials with ADSC confirmed their protective effects against chronic-degenerative osteoarticular injuries. However, further studies are required to evaluate the long-term biosafety and efficacy of ADSC stem cell therapy. Standardization of protocols and the inclusion of a larger sample size are required to confirm their long-term safety. However, a systematic review confirmed the safety and efficacy of intra-articular application of autologous stem cells, fat-derived against knee osteoarthritis with good results [218].

Acknowledgements

We appreciate María Eugenia Cabaña-Muñoz's support.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

GVHD	chronic graft versus host disease.
AD-MSC	mesenchymal stem cells from adipose tissue

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