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The Effect of Exercise on Mesenchymal Stem Cells and their Application in Obesity Treatment

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Abstract

Mesenchymal stem cells (MSCs) have demonstrated considerable potential in tissue repair and the treatment of immune-related diseases, but there are problems with homing efficiency during MSCs transplantation. Exercise, as an intervention, has been shown to have an important impact on the properties of MSCs. This review summarizes the effects of exercise on the properties (including proliferation, apoptosis, differentiation, and homing) of bone marrow-derived MSCs and adipose-derived MSCs. Studies indicated that exercise enhances bone marrow-derived MSCs proliferation, osteogenic differentiation, and homing while reducing adipogenic differentiation. For adipose-derived MSCs, exercise enhances proliferation and reduces adipogenic differentiation. In addition, studies have investigated the therapeutic effects of combined therapy of MSCs transplantation with exercise on diseases of the bone, cardiac, and nervous systems. The combined therapy improves tissue repair by increasing the homing of transplanted MSCs and cytokine secretion (such as neurotrophin 4). Furthermore, MSCs transplantation also has potential for the treatment of obesity. Although the effect is not significant in weight loss, MSCs transplantation shows effects in controlling blood glucose, improving dyslipidemia, reducing inflammation, and improving liver disease. Finally, the potential role of combined MSCs transplantation and exercise therapy in addressing obesity is discussed.

Keywords Mesenchymal stem cells · Exercise · Obesity · Therapy

Introduction

Mesenchymal stem cells (MSCs) are fibroblast-like cells that can be extracted from various tissues such as bone marrow, adipose tissue, and umbilical cord [1]. They possess the capacity to self-renew and differentiate into osteoblasts, adipocytes, or chondrocytes [1]. MSCs secrete proteins, cytokines, and microRNAs, which exert effects such as inflammation modulation and immune regulation [2]. Consequently, MSCs are utilized for tissue regeneration, wound healing, and treatment of various diseases (e.g., bone and nervous system disorders) [3]. However, MSCs transplantation as a means of treating diseases still faces numerous challenges and hurdles, including the low survival rate and the efficiency of homing [4]. Homing refers to the process of MSCs migrating to damaged tissue, and MSCs will exert therapeutic effects after successfully homing to the damaged tissue [5, 6]. However, it is reported that after MSCs are injected into mice with fracture, most of the MSCs will be trapped in the lungs and migrate to the fracture site after 8 – 9 days [7]. Although MSCs home to the fracture site, less than 3% of MSCs survive 5 weeks after the fracture [7]. Administering a higher dose of MSCs could potentially offset the observed low survival rates. Nonetheless, this approach is associated with high costs and an elevated risk of adverse effects. Therefore, it is necessary to investigate optimal strategies to enhance the therapeutic efficacy of MSCs injections.

Exercise is recognized as a means of altering the biological properties of MSCs, as it can enhance their proliferation and osteogenic differentiation while reducing adipogenic differentiation of MSCs cultured in vitro [8–10]. Some previous

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studies have also demonstrated that treatment combined with exercise is beneficial to enhance the therapeutic effects of MSCs in various diseases [11]. This may be related to the fact that exercise can activate MSCs to secrete immune regulatory factors that promote tissue repair, while exercise also improves homing efficiency [11–13]. For example, in neurological disorders such as spinal cord injury (SCI), the combined treatment of MSCs transplantation and exercise has demonstrated enhanced neuroprotective effects and maintenance of motor function [12]. These results may be attributed to the exercise-induced increase in neurotrophin 4 [12]. In the acute myocardial infarction model, the combined treatment preserved left ventricular function greater than a single treatment [13]. Exercise also activated the stromal cell-derived factor 1 (SDF-1)/ CXC chemokine receptor type 4 (CXCR4) axis, which may enhance MSCs homing [13].

In addition to neurological, musculoskeletal, and cardiovascular disorders, there is increasing evidence suggesting the therapeutic potential of MSCs transplantation in addressing metabolic-related diseases, such as obesity and type 2 diabetes mellitus (T2DM) [14]. MSCs transplantation has been shown to ameliorate dyslipidemia, regulate blood glucose levels, and reduce inflammation in animal models [15–17].

In this review, we focus on bone marrow-derived MSCs (BMSCs) and adipose-derived MSCs (ADMSCs) and summarize the effects of exercise on the properties of MSCs. We also summarize the combination effects of MSCs transplantation and exercise on diseases, and the therapeutic efficacy of MSCs transplantation for obesity. Additionally, will explore the role of exercise in the future of MSCs treatment for obesity.

Effects of Exercise on Bone Marrow-derived MSCs (BMSCs) and Adipose-Derived MSCs (ADMSCs)

In this review, animal and cell studies were included to investigate the effects of exercise on BMSCs and ADMSCs. The exercise protocol in animal studies comprised treadmill running (8 studies), climbing exercise (1 study), and low-magnitude mechanical signals (LMMS, 1 study). Cell experiments, on the other hand, use mechanical stress and irisin pretreatment to simulate the effects of exercise. The exercise protocol and main findings from the included studies are summarized in Table 1 and Fig. 1.

Effects of Exercise on the Proliferation and Viability of BMSCs and ADMSCs

Exercise has been shown a tendency to enhance the proliferative capacity of BMSCs and ADMSCs. The number of colony-forming units (CFU) of BMSCs was higher in mice running on a treadmill for 5 weeks (21 ± 2) than in sedentary mice (16 ± 3) ($p < 0.05$) [8]. Additionally, an 8-week treadmill exercise protocol resulted in an increased number of CFU for both BMSCs and ADMSCs in rats [9]. Ocarino et al., reported that 12-week treadmill running increased the viability of BMSCs in ovariectomized rats [18]. A moderate-intensity treadmill running program increased the viability of BMSCs, while low- and high-intensity exercise did not induce significant change [10]. Except for treadmill running, 6-week of LMMS also increased the number of BMSCs in mice [19].

Conversely, some studies have indicated that exercise does not affect the proliferation or viability of MSCs. Baker et al., found a 29% increase in the number of CFU in bone marrow-isolated cells after 10 weeks of treadmill running, but this difference was not statistically significant [20]. It is important to note that in this study, the bone marrow-isolated cells were c-kit-positive and Sca-1-positive, indicating they may be hematopoietic stem cells rather than MSCs [20, 21]. Hell et al., adhered to the same exercise program as Ocarino et al., yet failed to observe an increase in the BMSCs' viability, which could be attributed to the utilization of a different animal model (normal vs. ostopenic) [18, 22]. Climbing a 100 cm meshed-wire tower, which is a different form of exercise than running, did not increase the number of CFU in mice BMSCs [23].

Exercise appears to enhance the proliferation and viability of MSCs. Yet the duration of exercise, which can vary from 4 to 10 weeks, and the type of exercise, such as treadmill running, LMMS, and climbing, can affect the benefits that are reported [8–10, 18–20, 22, 23].

Effects of Exercise on the Apoptosis of BMSCs and ADMSCs

Following the transplantation of MSCs, a high apoptotic rate has been observed, potentially diminishing the therapeutic efficacy of MSCs [7]. The effect of exercise on apoptosis of MSCs is not yet clear. BMSCs (passage 4) from rats that exercised on a treadmill were cultured in osteogenic differentiation medium for 21 days and the expression level of *Casp3* mRNA was analyzed [22]. When comparing the BMSCs of the exercise group with age-matched control group, the exercise group demonstrated a significant upregulation of *Casp3* mRNA expression ($p < 0.05$) [22]. De Lisio et al., reported that exercise preconditioning can reduce the MSCs apoptosis and increase the survival rate in an animal model subjected to radiation exposure [24].

Moreover, the anti-apoptotic capability of MSCs not only depends on exercise but may also be influenced by exerkines released during exercise. In a study by Yan et al., mice ADMSCs were pretreated with or without irisin (a myokine

Table 1 Effects of exercise on bone marrow-derived and adipose-derived mesenchymal stem cells (MSCs) properties

Exercise type	Exercise intensity	Exercise time & duration	MSCs origin & Characterization	Effects				Reference
				Proliferation	Osteogenic differentiation	Adipogenic differentiation	Apoptosis	
Treadmill running	14 m/min (1st wk) to 24 m/min (10th wk)	45 min/day, 3 days/wk, 10 wk	Mice BM ($Sca\text{-}1^-$, Lin^-, $CD45^-$. $CD31^-$, $CD51^+$)	↑	↑	↓	N/A	Maredziak et al., 2015 [8]
	19.3 m/min	60 min/day, 8 wk	Rat BM & AD ($CD11b^-$, $CD45^-$, $CD79^+$, $CD90^+$)	↑ (BM & AD)	↑ (BM) ↔ (AD)	↓ (BM & AD)	↔ (BM & AD)	Liu et al., 2017 [9]
	15 m/min	30 min/day, 5 days/wk, 12 wk	Rat BM ($CD45^-$, $CD73^+$, $CD54^+$, $CD90^+$)	↑	↑	N/A	N/A	Ocarino et al., 2008 [18]
	15 m/min	30 min/day, 5 days/wk, 12 wk	Rat BM ($CD45^-$, $CD73^+$, $CD54^+$, $CD90^+$)	↔	↑	N/A	↓	Hell et al., 2012 [22]
	Low: 8 m/min Moderate: 18 m/min High: 28 m/min	50 min/day, 6 days/wk, 5 wk	Mice BM (adherence to plastic)	N/A	↑ (Moderate)	N/A	N/A	Zhang et al., 2017 [32]
	18 m/min	50 min/day, 6 days/wk, 6 wk	Rat BM (adherence to plastic)	N/A	↑	N/A	N/A	Zhang et al., 2020 [33]
	Low: 15.2 m/min Moderate: 19.3 m/min High: 26.8 m/min	60 min/day, 5 days/wk, 8 wk	Rat BM (adherence to plastic)	↑	↑ (Moderate)	N/A	N/A	Liu et al., 2018 [10]
	14 m/min (1st wk) to 24 m/min (10th wk)	45 min/day, 3 days/wk, 10 wk	Mice BM ($c\text{-}kit^+$, $Sca\text{-}1^+$)	↔	↑	↑	N/A	Baker et al., 2011 [20]
Climbing	61—73 m/day	11—13 min/day, 2 to 4 wk	Mice BM (adherence to plastic)	↔	↑	N/A	N/A	Mori et al., 2003 [23]
Mechanical Stimulation	LMMS, 0.2 g, 90-Hz signal	15 min/d, 5 days/wk, 6 wk	Mice BM ($Sca\text{-}1^+$, $Pref\text{-}1^+$)	↑	↑	↓	N/A	Luu et al., 2009 [19]

↑ increase, ↓ decrease, ↔ no change, *AD* adipose-derived, *BM* bone marrow-derived, *CD* cluster of differentiation, *LMMS* low-magnitude mechanical signals, *Pref-1* preadipocyte secreted factor-1, *Sca-1* stem cell antigen-1

released by muscles during exercise, 100 ng/ml) for 48 h [25, 26]. The ADMSCs were then washed to remove irisin and exposed to H_2O_2 (200 µM, 6 h) [25]. To assess apoptosis, protein expression levels of cleaved caspase-3 and TdT-mediated dUTP nick-end labeling analysis were performed [25]. The findings indicate that irisin pretreated ADMSCs had a higher anti-apoptotic capacity, suggesting that exercise may affects the apoptosis of MSCs [25].

On the other hand, no significant differences were observed between BMSCs and ADMSCs in terms of the exercise-induced alterations in apoptosis. BMSCs and ADMSCs were isolated from both sedentary and exercised rats and cultured

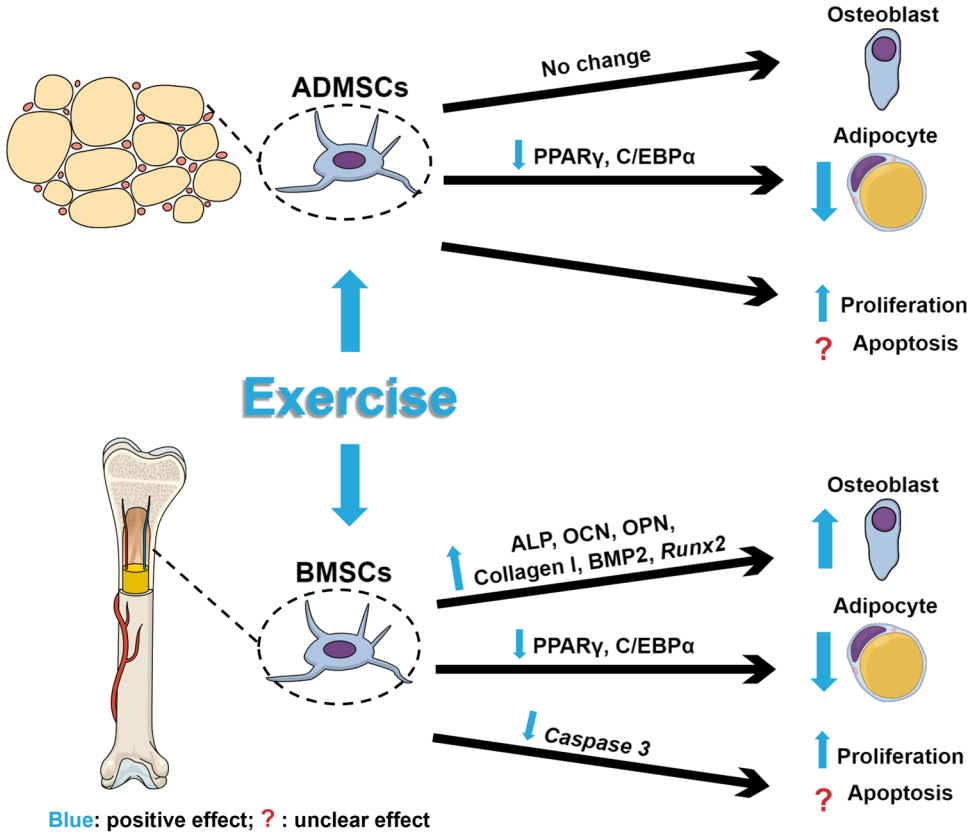

Fig. 1 Effects of exercise on bone marrow-derived and adipose-derived mesenchymal stem cells properties. ADMSCs, adipose-derived mesenchymal stem cells; ALP, alkaline phosphatase; BMP2, bone morphogenetic protein 2; BMSCs, bone marrow-derived mesenchymal stem cells; C/EBPα, CCAAT/enhancer-binding protein alpha; OCN, osteocalcin; OPN, osteopontin; PPARγ, peroxisome proliferator-activated receptor gamma; *Runx2*, runt-related transcription factor 2 protein coding gene

until 80% confluence [9]. Subsequently, the cells were exposed to a hypoxia and serum-deprived environment (serum-free Dulbecco's Modified Eagle Medium, chamber conditions with oxygen concentration of 3%) for 24 h [9]. To evaluate apoptosis, flow cytometry was used to compare the number of Annexin V^+/propidium iodide- MSCs, while the activity of caspase-3 was assessed using a colorimetric assay [9]. The finding indicated no significant difference in the anti-apoptotic capability of BMSCs and ADMSCs from sedentary or exercise rats [9]. It was noted that BMSCs secreted more bone morphogenetic protein 2 under hypoxia and serum-deprived condition, which suggesting BMSCs isolated from exercised rats could be good source for bone repair applications [9].

Due to inconsistent findings in previous studies, the effects of exercise on MSCs apoptosis remain unclear. The effect of exercise on apoptosis seems to vary depending on the origin of MSCs [9, 25]. Future research needs to provide more evidence on the effect of exercise on MSCs apoptosis, and it is necessary to determine the role exercise plays in apoptosis during MSCs transplantation.

Effects of Exercise on the Differentiation Capacity of BMSCs and ADMSCs

Exercise is known to strengthen bones and reduce body fat [27, 28]. These changes are linked to exercise-induced changes in MSCs [29]. MSCs can differentiate into osteoblasts and adipocytes, contributing to bone and adipose tissue formation. Exercise influences this differentiation process.

Osteogenic Differentiation

Many studies proved that exercise increased the differentiation of BMSCs into osteoblasts [8–10, 18–20, 22, 23, 30–33]. BMSCs isolated from mice that trained on a treadmill for 10 weeks had higher levels of alkaline phosphatase (ALP), osteopontin, and osteocalcin compared to BMSCs from sedentary mice, showed more Alizarin Red S-positive BMSCs [8, 20]. Similarly, BMSCs isolated from rats subjected to treadmill running for 8 – 12 weeks show elevated levels of ALP activity and *Alpl* mRNA expression, as well as an increased number of mineralized nodules (at day 21 of osteogenic differentiation) compared to BMSCs from sedentary rats [9, 22]. However, there was no change in osteogenic differentiation of ADMSCs after exercise [9]. Following cell culture in osteogenic differentiation medium, the number of ALP^+CFU was higher in BMSCs from trained mice than sedentary mice [32, 33]. In particular, moderate-intensity exercise was more effective than low- and high-intensity exercise in enhancing ALP^+CFU [10, 32]. Even in an osteopenia model, exercise

can also increase the osteogenic differentiation capacity of BMSCs [18]. Moreover, Mori et al., has demonstrated that climbing exercise can also enhance the osteogenic differentiation capacity of BMSCs [23].

The observed enhanced osteogenic differentiation capacity of MSCs might be related to exercise-induced mechanical signals that are transmitted to the extracellular matrix and initiate intracellular signaling cascades [34]. These mechanotransduction processes involve the activation of pathways such as p38 mitogen-activated protein kinase and WNT/β-catenin, through cell surface integrins, ultimately converting these mechanical stimuli into biochemical signals that promote osteogenic lineage commitment [34].

Previous studies have confirmed the change in osteogenic differentiation markers following exercise or mechanical stimuli. These studies showed that exercise enhances osteogenesis by increasing the osteogenic protein (runt-related transcription factor 2, Osterix) and osteogenesis-related genes (*Runx2*, *Col1a1*, *Alpl* and *Bglap*) [9, 10, 30, 31].

Adipogenic Differentiation

Some studies reported that exercise reduced the adipogenic differentiation capacity [8, 9, 19, 20, 31]. Maredziak et al., and Baker et al., (employing identical exercise protocol) reported that treadmill training for 10 weeks reduces the adipogenic differentiation capacity of mice BMSCs as measured by Oil Red O (exercise < sedentary) [8, 20]. Liu et al., found that an 8-week treadmill training can inhibit the adipogenic differentiation capacity of rats BMSCs and ADMSCs, and the gene expression levels of *Pparg* (peroxisome proliferator-activated receptor coding gene) and *Cebpa* (CCAAT/enhancer-binding protein alpha coding gene) in exercise group were lower than sedentary group [9].

The same results with animal studies were obtained in a cell culture study that mimicked exercise by applying mechanical stimulation to cells [31]. After 10 days of strain stimulation, rats BMSCs showed fewer Oil Red O-positive cells than the unstimulated group [31]. Moreover, the protein and mRNA expression of PPARγ and C/EBPα in the strain-stimulated group were lower than unstrained group [31]. PPARγ and C/EBPα proteins are known to be the key transcription factors in adipogenic differentiation of MSCs and play critical roles in adipogenesis [35]. Possibly due to the change in these adipogenic differentiation makers, MSCs reduced adipogenic differentiation.

In animal studies, LMMS (acting as an exercise mimic) alone inhibits the adipogenic lineage and promotes MSCs toward the osteogenic lineage [19]. This highlights that mechanical stimulation plays a role in the regulation of MSCs differentiation that occurs due to exercise.

Effects of Exercise on the Homing of BMSCs and ADMSCs

The migration of MSCs across vascular endothelial cells to target tissue (damaged site) is known as MSCs homing [6]. Since MSCs release cytokines at the site of damage, it is essential that injected MSCs have high homing efficiency to the damaged region. MSCs homing is facilitated by inflammation, hypoxia, and SDF-1/ CXCR4 axis activation [36, 37].

Exercise can also serve as a way to promote the homing of MSCs. Previous studies have demonstrated that performing aerobic exercise before surgical procedure-induced acute myocardial infarction can activate SDF-1/CXCR4 axis [13]. Treadmill exercise (10 weeks, 5 times/week, 60 min/time) increases the expression of inflammatory factors in heart tissue of female spontaneously hypertensive rats, thereby enhancing the regenerative capacity of ADMSCs and facilitating cardiac function recovery [13]. Furthermore, pretreatment of ADMSCs with irisin (100 ng/ml, 2 days) promoted their homing to the myocardium via CSF/CSF2RB axis in a model of ischemia–reperfusion injury [25]. This evidence suggests the potential for exercise to increase homing efficiency. However, conflicting results have been reported. De Lisio et al., showed that more MSCs did not homing to the bone marrow in mice exposed to radiation after aerobic exercise compared to sedentary mice [24].

Due to conflicting findings, a definitive association between exercise and MSCs homing has yet to be established. Future research may explore whether exercise influences MSCs homing through different pathways. In addition, previous studies have only investigated the effects of exercise preconditioning on the efficiency of injected MSCs homing, and little is known about the effects of exercise simultaneously or post-MSCs transplantation [13, 24, 25].

Summary of the Effects of Exercise on BMSCs and ADMSCs

Exercise improve proliferation, osteogenic differentiation and reduce adipogenic differentiation of MSCs and these effects may relate to exercise intensity. Moderate-intensity exercise may be optimal for enhancing the properties of MSCs [9, 10]. Exercise at low-intensity may fail to provide the necessary mechanical stimulus, while excessively high-intensity could potentially lead to bone tissue damage and cell death, thereby negating the beneficial effects on MSCs characteristics [10]. Most research has used exercise training protocols lasting 5 to 12 weeks, with a total of 30 to 60 sessions. Despite this, there remains a significant gap in understanding the impact of varying exercise durations and frequencies on MSCs. It is imperative to conduct additional studies to elucidate the optimal exercise regimen that

can effectively enhance the properties and functionality of MSCs.

Therapeutic Effects of Combined Mesenchymal Stem Cells (MSCs) Transplantation and Exercise

Research on the combined MSCs transplantation and exercise had primarily focused on investigating their therapeutic effects on bone, heart tissue and nervous systems. The principal findings of studies examining the combined effects of MSCs transplantation are outlined in Table 2.

Bone Health

Exercise can enhance cartilage repair following BMSCs transplantation [38]. Osteochondral defects were induced through surgery in the center of the femoral groove of rats, and 4 weeks later, rats received injections of BMSCs (1×10^6 cells in 50 µL PBS) into the right knee and 50 µL PBS into the left knee. Two days post-injection, the exercise group started treadmill running for 2 to 8 weeks [38]. The combination of BMSCs transplantation and treadmill running led to improved cartilage repair scores, as observed in the second week [38]. Notably, the independent effects of BMSCs transplantation or exercise became apparent in the fourth week [38]. Moreover, the percent area stained with type II collagen was highest in the BMSCs transplantation and exercise combined group at week 4, but similar results were obtained at week 8 in the BMSCs transplantation group or exercise group [38]. This indicates that while the early combination of BMSCs transplantation and exercise has beneficial effects on cartilage repair, these effects may reduce over time [38].

Cardiac Disorders

Exercise boosts the therapeutic effects of MSCs in myocardial infarction (MI) [39]. After inducing MI in rats, the combined therapy of BMSCs injection (1×10^6 cells/animal via tail vein) and a 12-week exercise program improved exercise capacity and cardiac function while reducing left ventricular collagen content [40]. A 5-week exercise program combined with BMSCs treatment also improved exercise capacity and left ventricular ejection fraction in MI mice [41]. In this study, the combined treatment increased the number of $Ki67^+$ cells (a marker of proliferation) in the myocardial infarct area, supporting that exercise may enhance the retention of injected BMSCs in the heart and stimulate cardiomyocytes to enter the cell cycle [41]. Additionally, the study observed the effect of acute exercise on the therapeutic effect of BMSCs, revealing that injected BMSCs after acute exercise were retention in the infarcted area of the myocardium, which may be related to the activation of the SDF-1/CXCR4 axis by exercise, thereby enhancing the homing ability of MSCs [13, 41].

In addition to treadmill exercise, swimming has also been shown to enhance the therapeutic effects of MSCs, particularly when exercise preconditioning is performed [42, 43]. Prior to inducing MI in Fisher-344 rats, a 9-week swimming exercise program contributed to the preservation of ADMSCs in the myocardium and improved cardiac remodeling [42, 43]. Furthermore, the swimming and ADMSCs combined treatment showed synergy effects for MI treatment. This was attributed to exercise preconditioning, which fostered a pro-angiogenic and pro-inflammatory environment in the myocardial microenvironment [42, 43].

On the other hand, Lavorato et al., reported that BMSCs treatment restored the time-course of $[Ca2^+]_i$ transient in cardiomyocytes, while exercise restored the contractile time-course and amplitude of $[Ca2^+]_i$ transient in cardiomyocytes [44]. However, the therapeutic effects were not enhanced when combined with BMSCs and exercise [44].

Nervous System Disorders

SCI is a neurological disease in which damage to the spinal cord occurs due to external force [45]. MSCs transplantation has demonstrated efficacy in spinal cord repair, and exercise stans as the effective approach for improving motor function in individuals with SCI. Some studies have examined the effect of combining MSCs transplantation with exercise in SCI condition [12, 46].

In a study by Massoto et al., and his colleagues mice were transplanted with BMSCs (or culture medium as control) on the 7th day following surgery to induce SCI, and the exercise group performed treadmill running on the 14th day post-surgery [12]. In the combined therapy group (MSCs transplantation and exercise), the preserved white matter area and the level of myelinated fibers were higher than in the other treatment groups, and motor function was shown to be significantly improved [12]. Improvements in nerve regeneration ability and motor function through combined therapy are related to an increase in neurotrophin 4 level [12]. The immunomodulatory effect of MSCs and exercise are thought to release neurotrophin 4, which is known to promote nerve development [12, 47].

Similarly, in another study, after inducing SCI mice, followed by transplantation of BMSCs, treadmill running, or a combination of BMSCs transplantation and treadmill running [46]. After receiving BMSCs, the motor function improved following eight weeks of treadmill running [46]. Also, there was enhanced protection of axons and myelin, improved synaptic function, increased secretion of neurotrophic hormones, inhibited scar formation, and neuronal

Table 2 Therapeutic effects of combined MSCs transplantation and exercise therapy in disease condition

Disease model	Exercise protocol	MSCs origin	Injection method	Cell mass	Main results	Reference
Bone						
Osteochondral defect model	Treadmill running: 12 m/min, 30 min/day, 5 days/wk, 2—8 wk	Mice BMSCs	Injected into right knee	1×10^6 cells/animal	Exercise may enhance cartilage repair after BMSCs treatment	Yamaguchi et al., 2016 [38]
Cardiac disorders						
Acute MI	Treadmill running: 60—70% speed, 60 min, 5 days/wk, 10 wk	Mice ADMSCs	Injected into anterior wall of the left ventricle	2×10^5 cells/animal	Exercise prior to acute MI improves cardiac function and enhances the repair processes associated with ADMSCs treatment	Schaun et al., 2020 [13]
MI	Treadmill running: acute: 8—12 m/min, 45 min chronic: 10—13 m/min, 45 min/day, 4 days/wk, 5 wk	Mice BMSCs	IV	5×10^5 cells/animal	Acute exercise can increase BMSCs retention the post-MI heart Chronic exercise may enhance BMSCs-mediated effects on stimulating the cardiomyocyte cell cycle	Chirico et al., 2015 [41]
MI	Treadmill running: 60% of maximal speed, 60 min/day, 5 days/wk, 12 wk	Mice BMSCs	IV	1×10^6 cells/animal	BMSCs treatment has benefits for cardiac remodeling and exercise has positive effects on cardiac structure and function. However, combined BMSCs treatment and exercise do not enhance these benefits	Lavorato et al., 2016 [44]
MI	Treadmill running: 60% of the mean maximal running speed, 60 min/day, 5 days/wk, 12 wk	Rat BMSCs	IV	1×10^6 cells/animal	Exercise and BMSCs treatment improved exercise capacity and cardiac function, also reduced left ventricle collagen content	de Freitas et al., 2019 [40]
MI	Swimming: 90 min, 5 days/wk, 9 wk (before MI)	Rat ADMSCs	Injected into MI border zone	1×10^6 cells/animal	Exercise preconditioning improved the myocardial microenvironment for ADMSCs treatment and contributed to the restoration of cardiac remodeling	Vieira et al., 2019 [42]
MI	Swimming: 90 min, 5 days/wk, 9 wk (before MI)	Rat ADMSCs	Injected into MI border zone	1×10^6 cells/animal	Exercise preconditioning enhanced the effects of ADMSCs therapy and improved cardiac ADMSCs retention	Vieira et al., 2020 [43]

Table 2 (continued)

Disease model	Exercise protocol	MSCs origin	Injection method	Cell mass	Main results	Reference
Nervous system disorders						
SCI	Treadmill running: 6—12 m/min, 10 min/day, 3 days/wk, 8 wk	Mice BMSCs	Injected into the epicenter of the lesion	8×10^5 cells/animal	Exercise and BMSCs combined treatment improved locomotor performance and had the highest neurotrophin 4 expressions than exercise or BMSCs alone Exercise and BMSCs treatment can enhance preservation of white-matter sparing, the total number of myelinated fibers, and the G-ratio	Massoto et al., 2020 [12]
SCI	Treadmill running: 4—9 m/min, 20 min/day, 6 days/wk, 8 wk	Mice BMSCs	Injected into the contusion epicenter	1×10^5 cells/animal	Exercise and BMSCs combined treatment improved motor function Exercise and BMSCs combined treatment can reduced fibrotic scar tissue, protected neurons and promoted axon and myelin protection	Sun et al., 2023 [46]
SCI	Wheel running	Human ADMSCs	Injected into the thoracic spinal cord dorsal horn	1×10^6 cells/animal	Exercise and ADMSCs combined treatment improved motor function, mechanical allodynia, and hypoalgesia ADMSCs alone reduced white and gray matter loss at the lesion site	Cheng et al., 2023 [48]
SNI (crush)	Swimming: 16.5℃, 10 min/day, 7 days	Rat BMSCs	Infused into the crush site of the nerve	1×10^5 cells/animal	Cold water swimming and BMSCs combined treatment showed greater functional recovery than treatment of exercise or MSCs alone	Yang et al., 2015 [50]
SNI (transection)	Swimming: 30℃, 30 min/d, 7 days	Rat BMSCs	Infused into the lesion site of the nerve	1×10^5 cells/animal	Swimming and BMSCs combined treatment and swimming both showed beneficial effects on sciatic nerve injury, but combined treatment did not show greater functional recovery than swimming alone	Wang et al., 2010 [49]

Table 2 (continued)

Disease model	Exercise protocol	MSCs origin	Injection method	Cell mass	Main results	Reference
Parkinson's disease	Treadmill running: 16 m/min, 30—60 min/day, 5 days/wk, 5 wk	Human ADMSCs;	Injected into the striatum	2×10^5 cells/animal	Exercise alone and exercise + ADMSCs combined treatment showed best improvement on motor deficits	Cucarian et al., 2019 [51]
Alzheimer's disease	Treadmill running: 25 m/min, 30 min/day, 5 days/wk, 4 wk	Rat BMSCs (pretreated with DMOG)	IV	1×10^6 cells/animal	Exercise and BMSCs combined treatment improved memory function, enhanced neurogenesis in the hippocampus, increased antioxidant capacity and serum levels of BDNF	Abshenas et al., 2020 [52]

ADMSCs adipose-derived mesenchymal stem cells, *BDNF* brain-derived neurotrophic factor, *BMSCs* bone marrow-derived mesenchymal stem cells, *DMOG* dimethyloxalylglycine, *MI* myocardial infarction, *IV* intravenous injection, *SCI* spinal cord injury, *SNI* sciatic nerve injury

preservation [46]. Through in vitro experiments, the authors propose that the combination therapy of BMSCs transplantation and exercise enhances SCI recovery by activating the PI3K/AKT/mTOR pathway [46].

A combination of ADMSCs and exercise (wheel running) therapy has been reported to improve motor function recovery and mitigate SCI-induced hyperalgesia and hypoalgesia at the early stage of SCI recovery [48]. These effects may be related to the therapy-induced downregulation of lba1 and GFAP expression in the lumbar spinal cord dorsal horn [48].

In the sciatic nerve injury model, the combined therapy of swimming (30 min/day, 7 days) and MSCs transplantation shows different effects depending on water temperature [49, 50]. Sprague–Dawley rats received sciatic nerve transection surgery, and then BMSCs were transplanted, and swimming (30 °C) was started 12 h after surgery [49]. Combining transplantation of BMSCs with swimming can recover motor function as measured by sciatic function index, ankle activity, vertical locomotor activity, and electrophysiological studies [49]. However, these recoveries were greater than BMSCs transplantation alone but not greater than swimming alone [49]. Rats with a crush model of sciatic nerve injury underwent the same protocol (swimming and BMSCs) but the average water temperature was 16.5 °C [50]. In this study, the combination of BMSCs transplantation and cold-water swimming showed greater recovery effects on motor function than swimming alone or BMSCs transplantation alone [50].

The combined therapy of ADMSCs transplantation and exercise demonstrated a notable recovery in motor function in a Parkinson's disease (PD) model [51]. Following the induction of PD model in Wistar rats through 6-hydroxydopamine injection, and treadmill running exercise (16 m/min, 60 min/day, 5 days/week, 5 weeks) was performed, along with a single injection of ADMSCs [51]. Motor function was evaluated using the foot fault walking task, which showed a significantly higher total number of foot-slip in both untreated group and ADMSCs group compared to the sham, while there was no difference between exercise group and combined (exercise + ADMSCs) group compared to sham [51]. In other words, exercise can improve motor function in the PD model and can be considered an adjuvant intervention to treat PD with MSCs transplantation [51].

One study reported the effects of BMSCs and exercise combined therapy in Alzheimer's disease animal model. In this study, Alzheimer's disease was induced in Wistar rats using an intracerebroventricular injection of Amyloid-β [52]. Two weeks after the induction, treadmill exercise (25 m/min, 30 min/day, 4 days/week, 4 weeks) and BMSCs injections (1×10^6 cells/animal via tail vein) were performed [52]. The result showed that the combined therapy improved memory function, enhanced BMSCs migration and neurogenesis in the hippocampus, protected the pyramidal cells from

apoptosis in hippocampus, and increased antioxidant capacity and serum level of brain-derived neurotrophic factor [52].

In summary, the combination of MSCs transplantation and exercise can effectively treat various diseases. Current research trends indicate that injecting MSCs into the site of injury is more common than intravenous injection. This could be attributed to the potential for intravenous injections to result in MSCs becoming trapped in the lungs instead of homing to the tissues requiring repair [5]. Furthermore, both forced exercises (treadmill running or swimming) and voluntary exercises (wheel running) significantly enhance the therapeutic effects of MSCs. Exercise preconditioning improves the microenvironment, which helps to increase the retention rate of MSCs, thereby enhancing their therapeutic effects [42, 43].

Nonetheless, to successfully apply these research findings to clinical practice, it is necessary to further investigate the mechanisms underlying MSCs and exercise combination therapy. This includes determining the best injection method, types of exercise, and optimal timing for exercise to achieve the best therapeutic outcomes.

MSCs and Obesity

Effects of Obesity on MSCs

Previous studies have demonstrated that obesity induces chronic inflammation, leading to an increase in the number of MSCs within adipose tissues while concurrently diminishing the migration and proliferation capacities of MSCs [53–55]. Treating BMSCs with tumor necrosis factor-α (TNF-α), an inflammatory factor highly expressed in obesity, increases CXCR4 expression and causes MSCs to migrate to adipose tissue [53]. When comparing ADMSCs from obese mice to those from lean mice, obese mice ADMSCs exhibited decreased proliferative capacity and diminished migratory ability [54]. Furthermore, the decreased proliferative capacity of ADMSCs due to obesity is associated with reduced telomerase activity, leading to genomic destabilization, telomere shortening, and cellular senescence [56, 57]. Additionally, the upregulation of cell cycle regulators such as *p16*, *p21*, and *p53* mRNA expression in the obese state may induce apoptosis in ADMSCs [54, 55].

There is conflicting evidence in the studies on the effects of obesity on MSCs ability to differentiate into osteogenic and adipogenic lineages. Shu et al., reported that BMSCs isolated from 12-week diet-induced obesity (DIO) mice exhibited elevated expression levels of bone formation-related genes such as *Runx2* (runt-related transcription factor 2), *Sp7* (osterix), and *Bglap* (osteocalcin), as well as adipogenesis-related genes including *Pparg*, *Cebpa, Cebpb, and Cebpd* compared to the lean control group [58]. da Silva et al., reported that the protein expression levels of C/EBPα and PPARγ in BMSCs isolated from 10-week DIO mice were found to be higher compared to those in BMSCs isolated from lean mice [59]. This is probably attributed to the elevated levels of TNF-α in the bone marrow due to obesity, leading to an inflammatory bone marrow microenvironment that promotes adipogenic differentiation of BMSCs [59]. On the contrary, Wu et al., revealed that BMSCs produced from obese mice had lower osteogenic and adipogenic differentiation capacities than those derived from lean mice [60]. Also, authors found that obese mice had stronger osteogenic and adipogenic differentiation capacity in subcutaneous adipose-derived stem cells and infrapatellar fat pad-derived stem cells than lean mice [60].

Based on the findings of prior studies, it is conceivable that chronic inflammation induced by obesity impacts MSCs, and this influence may vary depending on the tissue of origin.

The Therapeutic Effects of MSCs Transplantation on Obesity

Numerous ongoing studies are dedicated to unraveling the potential of MSCs in ameliorating obesity and obesity-related complications. Most studies investigating the effects of MSCs transplantation on obesity used ADMSCs, and only some used BMSCs. A potential reason for the preference for ADMSCs versus BMSCs could be that the ADMSCs tend to secrete more insulin [61]. The main results of papers related to the effect of MSCs transplantation on obesity are summarized in Table 3.

The Impact of MSCs Transplantation on Body Weight and Body Composition

Weight loss is crucial for addressing obesity, but the effects of MSCs transplantation on DIO and T2DM animal models are inconsistent [15–17, 62–75]. Out of 17 studies investigating the impact of MSCs transplantation on body weight, 35% of the studies showed a reduction in body weight following the MSCs transplantation [17, 62–66], and 65% of the studies showed either no change in body weight or no superior effect compared to alternative treatments [15, 16, 67–75].

The impact of MSCs transplantation on body weight appears to be related to the injection method, injection times, and the genetic modification of MSCs. It seems that intraperitoneal injection (IP) is a more effective method for inducing weight loss. Specifically, administering IP injections two or more times can effectively reduce weight gain induced by a high-fat diet [17, 62, 63]. Moreover, genetically modified MSCs have been shown to effectively reduce high-fat diet-induced weight gain. Such as neuregulin 4-overexpressing human ADMSCs, metformin-pretreated human

Table 3 The therapeutic effect of MSCs in the treatment of obesity and metabolism complications in animal models

Obese animal model	MSCs origin	Injection methods	Injection dose	Injection times	Time points of sacrifice	MSCs treatment main effects	Reference
6-week-old male B6 (60% HFD for 36 weeks)	Mice BMSCs	IV	5×10^5 cells/animal/time	2	12 weeks after the 2nd MSCs treatment	Improved HFD induced arrhythmias, cardiac fibrosis and increased exercise capacity	Daltro et al., 2017 [75]
7 weeks old B6 mice (60% HFD for 20 weeks)	Mice ADMSCs	IV	2×10^6 cells/animal	1	45 days after MSCs treatment	Improved blood glucose homeostasis and lipid profile (TG, HDL). Reduced liver fat cell deposition and inflammation. The mass of pancreas β-cells was protected	Cao et al., 2015 [67]
6-week-old male B6 (60% HFD for 8 weeks)	Mice ADMSCs (over-expressing *Nrg4*)	IV	2×10^6 cells/animal	1	8 weeks after MSCs treatment	*Nrg4*-tADMSCs reduced body weight, plasma levels of TG, CHOL, and liver fat cell deposition. *Nrg4*-tADMSCs show greater improvement than ADMSCs in insulin sensitivity improvement	Wang et al., 2019 [65]
8-week-old male B6 (60% HFD)	Mice ADMSCs (CPT1AM-expressing)	Subcutaneously implanted into back	1×10^6 cells (embedded in Matrigel)	1	10 weeks after MSCs treatment	CPT1AM-expressing ADMSCs treatment reduced body weight. Improved TG, CHOL, glycerol and glucose clearance. Also improved liver steatosis, adipose tissue dysfunction	Soler-Vázquez et al., 2023 [66]
8-week-old male B6 (60% HFD for 16 weeks)	Human ADMSCs	IV	1×10^6 cells/animal	1	2 weeks after MSCs treatment	Increased fat mass percentage and decreased lean mass percentage. Reduced white adipose tissue weight and adipocyte size. Improved lipid profile (TG, LDL-c and HDL-c) and inflammation	Xie et al., 2021 [72]

Table 3 (continued)

Obese animal model	MSCs origin	Injection methods	Injection dose	Injection times	Time points of sacrifice	MSCs treatment main effects	Reference
6-week-old male B6 (60% HFD for 10 weeks)	Human ADMSCs	IV	5×10^5 cells/animal	2	4 weeks after the 2nd MSCs treatment	Reduced the levels of TG in serum and liver tissue, and serum oxidized LDL. Improved glucose tolerance with decreased insulin resistance. Reduced the serum insulin and IL-6 levels	Shree et al., 2019 [16]
8-week-old male B6 (60% HFD for 15 weeks)	Human ADMSCs	IP	4.2×10^7 cells/kg/animal	2	6 weeks after the 2nd MSCs treatment	Reduced fat mass percentage, atherogenic index of plasma, blood glucose levels and HbA1c, and the serum levels of TNF-α and IL-6	Jaber et al., 2021 [15]
7 weeks old B6 (60% HFD for 10 weeks)	Human ADMSCs	IP	4.2×10^7 cells/kg/animal	3	4 weeks after the 2nd MSCs treatment	Reduced body weight. Improved glucose tolerance and blood glucose homeostasis. Improved pancreas and inflammation	Ji et al., 2015 [62]
6 weeks old B6 *db*/*db* (60% HFD for 6 weeks)	Human ADMSCs	IP	2×10^6 cells/animal/time	3	4 weeks after the 3rd MSCs treatment	Reduced body weight, CHOL, TG, and fasting glucose. Improved *β*-cell percentage in pancreatic islets	Liu et al., 2016 [63]
4-week-old male B6 (60% HFD for 30 weeks)	Human ADMSCs	IP	5×10^6 cells/kg/animal	5	2 weeks after the 5th MSCs injection	Reduced body weight and improved lipid profile. Reduced liver fat accumulation, fibrosis and inflammation	Lee et al., 2017 [17]

Table 3 (continued)

Obese animal model	MSCs origin	Injection methods	Injection dose	Injection times	Time points of sacrifice	MSCs treatment main effects	Reference
4—6 weeks old male B6 (45% HFD for 14—16 weeks; 60% HFD for 8—10 weeks)	Human ADMSCs (overexpressing *Sod2* or *Cat*)	IP	1.5×10^7 cells/animal	1	4 weeks after MSCs treatment	*Sod2*- or *Cat*-MSCs treatment reduced adipocytes area, and improved glucose tolerance. Also, reduced liver fat accumulation and TG, and improved systemic inflammation	Domingues et al., 2019 [68]
6-week-old male B6 (60% HFD for 10 weeks)	Human ADMSCs (pretreat with Met)	IM	5×10^5 cells/animal	1	4 weeks after the 2nd MSCs treatment	Met-ADMSCs reduced body weight. Both ADMSCs and Met-ADMSCs improved insulin resistance, only Met-ADMSCs improved lipid profile and serum IL-6	Shree et al., 2016 [64]
4-week-old male B6 mice HFD/HSD (55% fat, 28% carbohydrate for 14—16 weeks)	Mice ADMSCs (sheet)	Subcutaneously implanted into back	1×10^6 cells/dish of sheet	1	10 days after MSCs treatment	Improved glucose intolerance and insulin resistance. Increased and decreased serum levels and expressions of adiponectin and TNF-α in the adipose tissues	Ishida et al., 2020 [70]
8-week-old male SD rats (60% HFD for 8 weeks, STZ injection at week 8 + 24 more weeks HFD)	Rat ADMSCs	IV	3×10^6 cells/animal	1/week	1 week after MSCs treatment	Improved glucose clearance and insulin sensitivity. Reduced liver damage (steatosis, inflammation, ballooning and fibrosis) and systemic inflammation	Yu et al., 2019 [74]
5-week-old male B6 (60% HFD for 24 weeks, STZ injection at week 23)	Mice ADMSCs	IV	5×10^5 cells/animal	1	5 weeks after MSCs treatment	Reduced adipocyte size. Improved glucose homeostasis and insulin sensitivity. Increased mass of pancreas β-cells and improved liver steatosis and inflammation	Wang et al., 2018 [71]

Table 3 (continued)

Obese animal model	MSCs origin	Injection methods	Injection dose	Injection times	Time points of sacrifice	MSCs treatment main effects	Reference
8-week-old male SD (40% HFD for 8 weeks, STZ injection at week 8)	Rat ADMSCs	IV	3×10^6 cells/animal	1	24 h after MSCs treatment	Improved glucose homeostasis and insulin sensitivity. ADMSCs treatment promoting hepatic glycogen synthesis and inhibiting hepatic glucose production	Xie et al., 2017 [80]
8-week-old male SD rats (58% HFD for 4 weeks, STZ injection once at week 4)	Rat ADMSCs	IV	2×10^6 cells/animal	1	8 weeks after MSCs treatment	Improved hyperglycemia and insulin sensitivity, and inflammation. Increased the number of β-cells	Hu et al., 2015 [69]
8-week-old male SD rats (40% HFD for 5 weeks, STZ injection at week 5)	Rat BMSCs	IV	1×10^6 cells/animal/time	1 vs. 5	35 days after MSCs injection or 1 week after MSCs treatment	Single or multiple injections both reduced blood glucose and improved pancreatic islets damage. Multiple injections could restore these damages near to normal	Hao et al., 2013 [79]
12—14 weeks old female B6 (AT-HFD for 12 weeks)	Mice ADMSCs	Injected into the spleens	1×10^5 cells/animal	1—2	2 weeks after last MSCs treatment	Improved liver fibrosis and liver inflammation	Yamato et al., 2019 [73]

ADMSCs adipose-derived mesenchymal stem cells, *AT* atherogenic, *BMSCs* bone marrow-derived mesenchymal stem cells, *B6* C57BL/6 mice, *Cat* catalase, *CHOL* cholesterol, *CPT1AM* active Carnitine palmitoyltransferase 1A form, *HbA1c* glycated hemoglobin, *HDL-c* high-density lipoprotein cholesterol, *HFD* high-fat diet, *HSD* high-sucrose diet, *IL-6* interleukin-6, *IM* intramuscular injection, *IP* intraperitoneal injection, *IV* intravenous injection, *LDL-c* low-density lipoprotein cholesterol, *Met* metformin, *Nrg4* neuregulin 4 coding gene, *Sod2* superoxide dismutase 2 coding gene, *SD* Sprague–Dawley rats, *STZ* streptozotocin, *TG* triglyceride, *TNF-α* tumor necrosis factor alpha

ADMSCs, and carnitine palmitoyltransferase 1A-expressing human ADMSCs, all of which have demonstrated the ability to induce weight loss [64–66].

Other studies have reported that MSCs transplantation improved body composition even without causing weight loss. Jaber et al., demonstrated that IP of human-ADMSCs in DIO mice reduced the percentage of fat mass, even though it did not lead to significant weight loss [15]. Domingues et al., reported that transplanting human-ADMSCs overexpressing *Sod2* or *Cat* (catalase) into DIO mice reduced adipocyte area more effectively than null-human ADMSCs [68]. Additionally, Xie et al., observed a reduction in fat mass and an increase in lean mass two weeks after human-ADMSCs transplantation through tail vein injection in DIO mice [72]. Furthermore, ADMSCs transplantation resulted in decreased weight and adipocyte area in epididymal adipose tissue and inguinal subcutaneous adipose tissue [72]. Similar effects of ADMSCs injection were also observed in a DIO + streptozotocin-induced T2DM mouse model. Wang et al., reported that injecting ADMSCs from normal, T2DM, or db/db mice into T2DM mice effectively reduced adipocyte size [71].

MSCs-induced weight loss or improved body composition may be related to increased uncoupling protein-1 expression or M2 macrophage in white adipose tissue [68, 72]. Increased uncoupling protein-1 can induce heat release and enhance energy expenditure, while increased M2 macrophages have been shown to be effective in improving obesity [76, 77].

The Impact of MSCs Transplantation on Lipid Profile

MSCs transplantation seems to be effective in improving dyslipidemia. Obesity can result in the excessive accumulation of body fat, leading to dyslipidemia and an increased prevalence of cardiovascular diseases. Thus, it is important to focus on the prevention and management of dyslipidemia associated with obesity. Liu et al., transplanted human-ADMSCs into *db*/*db* mice and found that ADMSCs through activated adenosine monophosphate-activated protein kinase and hormone-sensitive lipase improved dyslipidemia and reduced weight [63]. Lee et al., transplanted human-ADMSCs into DIO mice, and the result showed that MSCs treatment improved lipid profile and liver fat accumulation, which means ADMSCs transplantation induced upregulation of *Pparg* and downregulation of *Ppara* in the liver, which is associated with increased fatty acid uptake and lipogenesis, as well as decreased triglyceride storage in the liver [17].

Daltro et al., observed that the total cholesterol levels decreased in the group that received BMSCs transplantation compared to levels before transplantation [75]. However, this reduction in cholesterol levels does not appear to be solely attributed to the effect of MSCs transplantation. Because the high-fat diet was withdrawn at the same time as MSCs transplantation [75].

The Impact of MSCs Transplantation on Blood Glucose and Insulin

The transition from obesity to T2DM occurs due to a gradual decline in insulin secretion accompanied by a gradual increase in insulin resistance and is also associated with glucose dysregulation [78]. Insulin sensitivity and disturbed blood glucose homeostasis in obesity and T2DM have been demonstrated to improve with MSCs transplantation [15–17, 62–71, 74, 79, 80]. The improvement in insulin sensitivity and fasting blood glucose levels can probably be ascribed to the protective effects on pancreatic β-cells [67]. Particularly, studies have demonstrated that ADMSCs transplantation increases pancreatic β-cells mass in both DIO mice and T2DM mice [67, 71]. This protects these cells from inflammation by reducing the mRNA expression of *Tnf-α* and *Adgre1* [67, 71]. Moreover, the transplantation of MSCs decreases pro-inflammatory factors such as IL-6, IL-1β, and TNF-α, while concurrently increasing the levels of anti-inflammatory factors such as IL-10 [15–17, 62, 64–74].

The Impact of MSCs Transplantation on Liver

MSCs transplantation in obese animals also has notable effects on the liver [16, 17, 64, 67–69, 71, 73, 74, 80]. Studies have demonstrated that ADMSCs transplantation effectively reduced liver fat accumulation and triglyceride levels [16, 17, 67, 68], while also alleviating liver fibrosis and steatosis [17, 71, 73, 74].

Limitations of MSCs Transplantation on Obesity Treatment

The existing research findings suggest that MSCs transplantation, particularly ADMSCs, has a therapeutic effect on improving obesity and obesity complications. However, the protocols employed in the investigations (cell-derived tissue, number and frequency of injections, injection site, observation period after injection, etc.) are different, making it challenging to compare results between studies. Therefore, there is a need to establish an optimal protocol for the treatment of obesity in future investigations.

On the other hand, it is necessary to find ways to enhance the therapeutic potential of MSCs for obesity, as some studies have shown that transplanted MSCs exhibit lower survival and proliferation rates, which may reduce the effectiveness of obesity treatment [81]. Recently, genetic modification was used to enhance the therapeutic potential of MSCs. For example, before MSCs transplantation it was treated by *Sod2* or *Cat*, to upregulate antioxidants, or

neuregulin 4 (a factor that can regulate lipogenesis in the liver) was overexpressed in ADMSCs to improve insulin resistance and other obesity-related metabolic disorders [65, 68].

Side Effects and Adverse Events in MSCs Treatment

Several reviews have previously summarized the side effects and adverse events linked to MSCs transplantation [82, 83]. These reviews point out that although MSCs transplantation has shown great potential in several diseases, its application still carries various risks [82, 83]. The side effects and adverse events may include immune rejection, fever, and cancer.

Autologous or allogeneic MSCs can be used for MSCs treatment. Autologous MSCs has advantage in reducing the risk of immune rejection. However, the donor's health state may exert an influence on the therapeutic efficacy of MSCs. For example, inflammation caused by obesity can lead to reduced proliferative capacity in MSCs [54]. Furthermore, MSCs isolated from T2DM patients exhibit enhanced characteristics such as apoptosis and autophagy, which may reduce their therapeutic efficacy [84]. Although MSCs lack major histocompatibility complex class II molecules, which makes them hypoimmunogenic and makes them commonly utilized in allogeneic MSCs treatment, some studies suggest that allogeneic MSCs treatment can still induce immune response [2]. Fever represents a commonly observed adverse event after MSCs treatment, potentially associated with immune response [82]. Therefore, it is necessary to consider some strategies to reduce the potential immune response.

To perform gene editing and expand a sufficient number for transplantation, MSCs in vitro culture are often used. However, with the increase in the number of cell divisions, the accumulation of mutations within the cells also increases, thereby elevating the risk of oncogenic mutations [85].

Although many studies have reported side effects associated with MSCs treatment, few studies on MSCs and exercise combined treatment have reported such side effects. Future research should focus on whether MSCs and exercise combined treatment may elicit any side effects.

Future Research

Exercise is known to be an effective approach for improving obesity, as it leads to reductions in body fat mass, improvements in insulin resistance, and alleviation of inflammation [28, 86, 87]. Under normal conditions, exercise has been shown to enhance the proliferation, differentiation, and migration of MSCs. However, it is also unknown whether exercise may have the potential to restore MSCs function impaired by inflammation under obese conditions. Furthermore, while weight loss through MSCs transplantation alone may be challenging, exercise has been demonstrated as an effective means to achieve this goal and enhance the quality of life in obese individuals [88]. Nonetheless, there remains a lack of research investigating the combined therapy of exercise and MSCs transplantation for improving obesity.

Conclusions

Exercise can impact the properties of MSCs through mechanical signaling. The improvement in proliferation, osteogenic differentiation, and homing of MSCs induced by exercise suggests potential for improving the homing efficiency of transplanted MSCs. However, conflicting research findings relate to various exercise protocols, origin tissue of MSCs, and cell culture protocols. More research is needed to determine the specific effects of exercise on MSCs, and for this purpose, experiments considering the differences between MSCs in vivo and in vitro should also be performed.

MSCs transplantation plays a pivotal role in treating bone, cardiac, and neurological disorders, and exercise serves as a factor to enhance that role. Exercise increased the homing efficiency of transplanted MSCs and promoted cytokine secretion, resulting in better therapeutic effects.

In obesity, the properties of MSCs change, leading to a propensity for adipose tissue differentiation. Despite these changes, MSCs transplantation has demonstrated efficacy in addressing obesity. Several studies have shown that improving blood glucose levels, dyslipidemia, insulin resistance, inflammation, and liver diseases without significant alterations in body weight. Exercise represents another approach that can help improve the quality of life of obese patients, improve body weight, blood glucose, and dyslipidemia, and perhaps also enhance the effectiveness of obesity treatment along with MSCs transplantation. In the future, it will be necessary to confirm the treatment effect more clearly on obesity by combining exercise and MSCs transplantation.

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Declarations

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