

# World Journal of *Stem Cells*

*World J Stem Cells* 2023 March 26; 15(3): 31-104



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Monthly Volume 15 Number 3 March 26, 2023

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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Xiang-Di Zhang; Production Department Director: Xu Guo; Editorial Office Director: Jia-Ru Fan.

**NAME OF JOURNAL**

*World Journal of Stem Cells*

**ISSN**

ISSN 1948-0210 (online)

**LAUNCH DATE**

December 31, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Shengwen Calvin Li, Carlo Ventura

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-0210/editorialboard.htm>

**PUBLICATION DATE**

March 26, 2023

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**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Mesenchymal stem/stromal cells-derived exosomes for osteoporosis treatment

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**Specialty type:** Medicine, research and experimental

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B, B  
Grade C (Good): C, C  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Gallone A, Italy; Jeyaraman M, India; Shalaby MN, Egypt; Ventura C, Italy

**Received:** December 26, 2022

**Peer-review started:** December 26, 2022

**First decision:** January 3, 2023

**Revised:** January 17, 2023

**Accepted:** March 16, 2023

**Article in press:** March 16, 2023

**Published online:** March 26, 2023



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### Abstract

Osteoporosis is a systemic bone disease, which leads to decreased bone mass and an increased risk of fragility fractures. Currently, there are many anti-resorption drugs and osteosynthesis drugs, which are effective in the treatment of osteoporosis, but their usage is limited due to their contraindications and side effects. In regenerative medicine, the unique repair ability of mesenchymal stem cells (MSCs) has been favored by researchers. The exosomes secreted by MSCs have signal transduction and molecular delivery mechanisms, which may have therapeutic effects. In this review, we describe the regulatory effects of MSCs-derived exosomes on osteoclasts, osteoblasts, and bone immunity. We aim to summarize the preclinical studies of exosome therapy in osteoporosis. Furthermore, we speculate that exosome therapy can be a future direction to improve bone health.

**Key Words:** Mesenchymal stem cells; Exosome; Osteoporosis; Osteoblasts; Osteoclasts; Bone immunity

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**Core Tip:** Osteoporosis is one of the major diseases endangering bone health in the elderly. The existing treatment drugs have problems such as long-term administration and side effects; thus, it is fundamentally difficult to cure osteoporosis. Exosomes derived from mesenchymal stem cells (MSCs) are vesicles that deliver signals and molecules between cells and have shown substantial positive effects in pre-clinical trials. In this review, we summarize the latest progress of MSCs-derived exosomes in the regulation of bone metabolism.

**Citation:** Huo KL, Yang TY, Zhang WW, Shao J. Mesenchymal stem/stromal cells-derived exosomes for osteoporosis treatment. *World J Stem Cells* 2023; 15(3): 83-89

**URL:** <https://www.wjgnet.com/1948-0210/full/v15/i3/83.htm>

**DOI:** <https://dx.doi.org/10.4252/wjsc.v15.i3.83>

## INTRODUCTION

Osteoporosis (OP) is a chronic systemic bone disease. It is characterized by decreased bone mass and destruction of bone microstructures, resulting in decreased bone mineral density (BMD) and ultimately an increased risk of fragility fractures[1]. The dynamic balance between bone formation and bone resorption is an important way to maintain normal bone metabolism. Osteoblasts promote bone formation by mineralizing the matrix, while osteoclasts degrade the bone matrix by secreting H<sup>+</sup> and releasing cathepsin K, accelerating bone dissolution[2].

At present, the prevention and treatment of OP can be divided into adjuvant therapy and drug therapy. The therapeutic effects of drugs are mainly divided into two aspects: Inhibition of osteoclasts (inhibition of bone resorption) and stimulation of osteoblasts (promotion of bone formation). Among them, the drugs that inhibit bone resorption are denosumab, bisphosphonates and selective estrogen receptor modulators; and drugs that promote bone formation are teriparatide and abaloparatide. Romosozumab, a monoclonal antibody directed against sclerostin, has a dual regulatory effect, inhibiting bone resorption and promoting bone formation at the same time[3].

Although a variety of therapeutic drugs for OP have emerged, all the drugs mentioned above have side effects[4], and more novel and effective drugs and therapies are needed. There are new advances in the research on stem cells and their exosomes in tissue repair and treatment. Therefore, the new scheme of MSCs-derived exosomes for the treatment of OP has gradually become a therapeutic option[5].

## EXOSOMES AND MESENCHYMAL STEM CELLS

Exosomes are small vesicles secreted by cells with a diameter of 40 to 160 nm, which carry signals and molecules among cells. In addition, the exosomes secreted by the cells in diseased states contain specific microRNAs (miRNAs), which is helpful for the diagnosis of diseases[6]. As a carrier of signal transduction and drug delivery, exosomes also have good potential in the treatment of diseases, and their effectiveness has been confirmed by numerous animal studies[7-13] (Figure 1). In 1974, Friedenstein *et al*[14] first discovered that mesenchymal stem cells (MSCs) in bone marrow have the potential for osteogenic differentiation. Later, researchers continued to explore the function of MSCs and found that MSCs are pluripotent stem cells, which have the ability to differentiate into osteoblasts, adipocytes, chondrocytes, cardiac muscle cells and skeletal muscle cells[15]. Previous studies have found that therapy with MSCs can accelerate bone tissue repair and regeneration and maintain bone mass in OP[16,17].

MSCs-derived exosomes are likely to play a major role in mediating the therapeutic effect of MSCs [18,19]. A schematic diagram illustrating the mechanisms of MSCs-derived exosomes in the treatment of OP is shown in Figure 2. Therefore, MSCs-derived exosomes are expected to be a new biological agent in the future.

## MSCS-DERIVED EXOSOMES IN THE TREATMENT OF OP

Exosomes have the characteristics of good targeting ability, high permeability and low toxicity. Therefore, exosomes therapy has become one of the hot spots in the study of OP treatment. Bone regeneration is one of the main modalities in the treatment of OP and bone fracture. MSCs-derived exosomes can promote the formation of new bone with vasculature, biomechanics, and histology[20]. MSCs-derived exosomes regulate bone metabolism and treat OP through signaling pathways, such as stimulating osteoblast differentiation from bone marrow stem cells, promoting osteoblast proliferation,

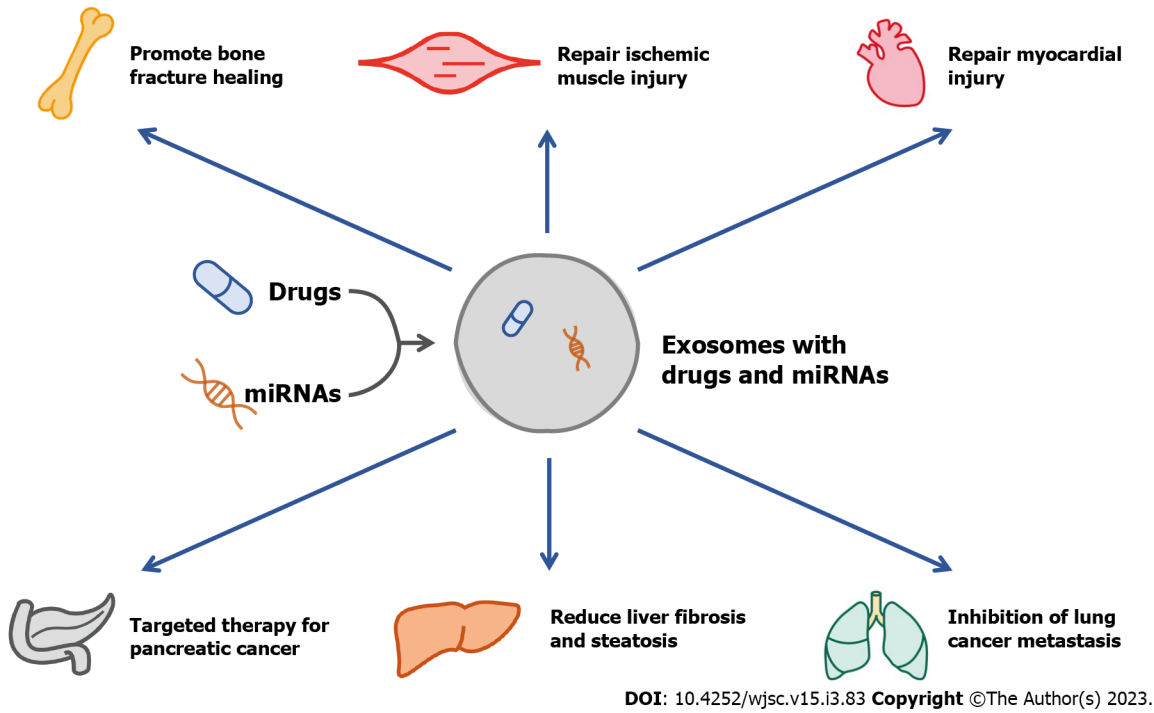


Figure 1 Schematic diagram illustrating the therapeutic potential of exosomes in diseases of multiple organs. miRNAs: MicroRNAs.

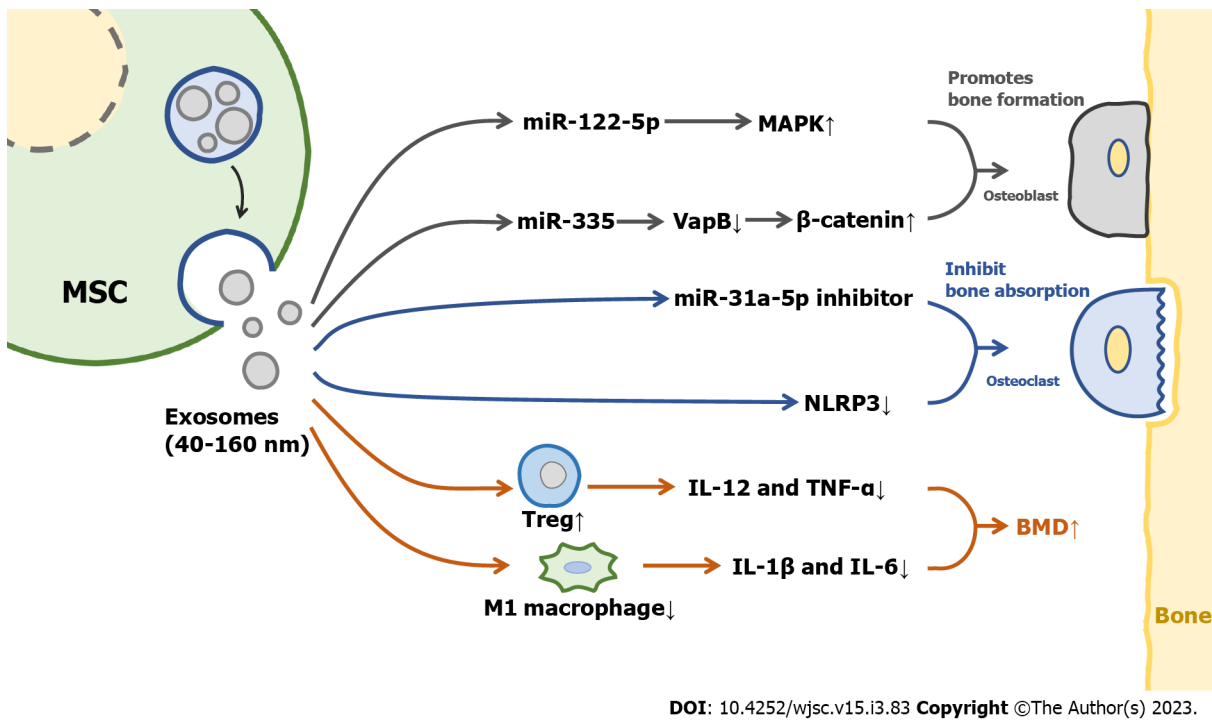


Figure 2 Schematic diagram illustrating the mechanisms of mesenchymal stem cells-derived exosomes in the treatment of osteoporosis. MSC: Mesenchymal stem cell; BMD: Bone mineral density.

inducing angiogenesis, and immunomodulation[21]. During treatment, MSCs-derived exosomes achieve the purpose of bone regeneration and treatment of OP by carrying and transporting proteins, miRNAs, and artificial synthetic drugs[22-24]. According to the pathogenesis of OP, exosomes are mainly involved in regulating the effects of osteoblasts, osteoclasts and bone immunity (Table 1).

**Table 1 Summary of studies on mesenchymal stem cells-derived exosomes in osteoporosis treatment**

Ref.	Exosome source	Cell type	Consequence
Zuo <i>et al</i> [24], 2019	BMSCs	BMSCs (after irradiation)	Alleviating radiation-induced bone loss by restoring Wnt/ $\beta$ -Catenin signaling pathway
Zhao <i>et al</i> [25], 2018	BMSCs	Osteoblasts (hFOB 1.19)	Promoting proliferation of osteoblasts <i>via</i> MAPK pathway
Liao <i>et al</i> [26], 2019	BMSCs	Osteoblasts	Promoting proliferation of osteoblasts by carrying miR-122-5p
Qi <i>et al</i> [27], 2016	hiPSC-MSCs	Osteoblasts	Promoting osteoblast proliferation, differentiation and bone formation
Hu <i>et al</i> [28], 2021	BMSCs	Osteoblasts	Promoting differentiation of osteoblasts by carrying miR-335
Zhang <i>et al</i> [31], 2021	AD-MSCs	Osteoclasts	Inhibiting NLRP3 inflammasome activation in osteoclasts
Nakao <i>et al</i> [32], 2021	GMSCs	Osteoclasts	Inhibiting RANKL and reducing osteoclast formation by carrying miR-1260b <i>via</i> Wnt5a/JNK signal pathway
Xu <i>et al</i> [33], 2018	BMSCs	Osteoclasts	Increasing the number of osteoclasts by carrying miR-31a-5p <i>via</i> RhoA pathway
Wei <i>et al</i> [40], 2019	BMSCs	Osteoblasts	Promoting osteoblast differentiation by inhibiting macrophage polarization and reducing the levels of inflammatory factors

BMSCs: Bone marrow mesenchymal stem cells; hiPSC-MSCs: Mesenchymal stem cells derived from human induced pluripotent stem cells; AD-MSCs: Adipose derived mesenchymal stem cells; GMSCs: Gingival tissue-derived mesenchymal stem cells; MAPK: Mitogen-activated protein kinase; NLRP3: NLR family pyrin domain containing 3; RANKL: Receptor activator of NF- $\kappa$ B ligand; Wnt5a: Wnt family member 5A; JNK: c-Jun N-terminal kinases.

## EFFECTS OF MSCS-DERIVED EXOSOMES ON OSTEOBLASTS

Osteoblasts are derived from pluripotent MSCs, which are major functional cells in bone matrix synthesis, secretion, and mineralization. Exosomes can directly regulate the activity of osteoblasts and then affect OP. MSCs-derived exosomes promoted the cell cycle of hFOB 1.19 cells, a type of osteoblast, and activated their proliferative activity through the MAPK pathway[25]. It was also found that overexpression of miR-122-5p in MSCs-derived exosomes of bone marrow can increase the BMD of the femoral head through the MAPK pathway[26]. Co-culture of MSCs-derived exosomes with bone marrow MSCs from osteoporotic rats resulted in increased levels of osteogenesis-related proteins and mineral deposition; in addition, the use of MSCs-derived exosomes promoted bone regeneration in a rat model of calvarial defects[27]. One study showed that the infusion of bone marrow MSCs-derived exosomes carrying miR-335 into mice with fractures significantly accelerated fracture healing, as miR-335 in exosomes was able to inhibit VapB, activate the Wnt/ $\beta$ -catenin pathway, and promote osteoblast differentiation[28]. Notably, exosomal miRNAs derived from MSCs are critical in regulating the function of osteoblasts. These miRNAs participate in and regulate some key signaling pathways and alter protein expression in osteoblasts. The positive roles of exosomes in osteoblast proliferation and differentiation, and the excellent therapeutic performance of exosomes in bone repair and bone mass recovery, indicate the potential of MSCs-derived exosomes in the treatment of OP.

## EFFECTS OF MSCS-DERIVED EXOSOMES ON OSTEOCLASTS

Osteoclasts originate from hematopoietic progenitor cells in the bone marrow, and play an osteolytic role by secreting H<sup>+</sup> and cathepsin K[29,30]. Adipose MSCs-derived exosomes inhibited NLRP3 in the osteoclasts of diabetic OP rat models and increased BMD[31]. RANKL is a major factor in promoting the differentiation of preosteoclasts into osteoclasts, gingiva MSCs-derived exosomes can target Wnt5a in periodontal osteoclasts and inhibit the expression of RANKL, thus reducing the differentiation of osteoclasts[32]. Of course, as a carrier of miRNA, exosomes will also have an effect on osteoclasts by carrying miRNA. Bone marrow MSCs-derived exosomes delivered miR-31a-5p to osteoclasts, which increased osteoclast number and bone resorption. In addition, BMD significantly increased in a rat model treated with miR-31a-5p inhibitor[33]. These findings suggested that MSCs-derived exosomes can regulate osteoclast differentiation, increase bone density, and inhibit OP. Notably, bone marrow stromal cell-derived exosomes do not have any effect on osteoclasts at the surface of trabecular bone, and therefore do not play a role in preventing bone resorption[34]. There are few studies on the regulation of osteoclast differentiation by MSCs-derived exosomes. Therefore, we need to further explore the potential of MSCs-derived exosomes in the treatment of OP by regulating osteoclast differ-

entiation.

## EFFECTS OF MSCS-DERIVED EXOSOMES ON BONE IMMUNITY

There is an intricate relationship between the immune system and the skeletal system. Activated immune cells release inflammatory mediators and cytokines that upset the balance of bone remodeling and activate osteoclasts, leading to bone loss and OP[35,36]. MSCs-derived exosomes can regulate the immune system[37]. After treatment with adipose MSCs-derived exosomes in mice with colitis, regulatory T cells returned to normal baseline level, and the levels of inflammatory factors such as interleukin (IL)-12 and tumor necrosis factor- $\alpha$  reduced[38]. Exosomes derived from adipose and bone marrow MSCs can significantly increase the level of type II collagen in articular cartilage, promote articular cartilage formation and accelerate the recovery of osteoarthritis in mice[39]. MSCs-derived exosomes promote the differentiation of bone marrow MSCs into osteoblasts by inhibiting the polarization of M1 macrophages and reducing the levels of inflammatory cytokines such as IL-1 $\beta$  and IL-6[40]. MSCs-derived exosomes can regulate immunity and inflammation *in vivo*. Unfortunately, little is known about their role in bone immunity. However, available findings suggest the potential of MSCs-derived exosomes in the treatment of OP by modulating bone immunity.

## CONCLUSION

At present, drug treatment of OP still focuses on inhibiting bone resorption and promoting bone formation. Drug therapy has a good effect, but long-term use of drugs can cause serious side effects. In the field of bone regeneration, stem cell therapy has significant efficacy, and exosomes are one of the important carriers of cell information and factors. Therefore, MSCs-derived exosomes may be a promising biological agent in the treatment of OP. This review focuses on the mechanism of MSCs-derived exosomes in the treatment of OP, by delivering miRNA, regulating related targets, and regulating bone immunity. Therefore, the potential of MSCs-derived exosomes in the treatment of OP is anticipated, but further preclinical studies are needed to prove the safety and reliability of exosome therapy and provide strong evidence for the clinical conversion of exosome therapy.

## FOOTNOTES

**Author contributions:** Shao J and Zhang WW were responsible for the concept design; Huo KL, Shao J and Zhang WW wrote the main manuscript text and prepared Figures 1 and 2; Yang TY provided technical support; all authors reviewed the manuscript.

**Supported by** National Natural Science Foundation of China, No. 81703533; Natural Science Foundation of Shanghai, No. 20ZR1449500; Shanghai Jiao Tong University Medical Engineering Cross Fund, No. YG2019GD02; Science Technology Development Fund of Shanghai Pudong New Area, No. PKJ2020-Y28; and Medical Discipline Construction Project of Pudong Health Committee of Shanghai, No. PWYts2021-05.

**Conflict-of-interest statement:** The authors declare no conflict of interests.

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**S-Editor:** Yan JP

**L-Editor:** A

**P-Editor:** Yan JP

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