World Journal of Diabetes

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World J Diabetes 2024 December 15; 15(12): 2399-2403

DOI: 10.4239/wjd.v15.i12.2399

ISSN 1948-9358 (online)

LETTER TO THE EDITOR

Mesenchymal stem cell-derived extracellular vesicles: A promising therapeutic strategy in diabetic osteoporosis

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Specialty type: Endocrinology and metabolism

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

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade A
Novelty: Grade B
Creativity or Innovation: Grade A
Scientific Significance: Grade A

P-Reviewer: Li Y

Received: August 11, 2024
Revised: September 27, 2024
Accepted: October 30, 2024
Published online: December 15, 2024
Processing time: 98 Days and 12.9 Hours

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Abstract

Diabetic osteoporosis (DOP) is a serious complication of diabetes mellitus. It is urgent to explore efficient clinical treatment strategies for DOP. It has been found that mesenchymal stem cell-derived extracellular vesicles (MSC-EVs), as an emerging cell-free therapy, show great potential in DOP treatment. MSC-EVs can effectively promote bone formation, inhibit bone resorption, and modulate the inflammatory microenvironment by delivering cargoes of microRNAs, long non-coding RNAs, and proteins to target cells, thereby ameliorating bone loss in DOP. However, there are limited reports on the treatment of DOP with MSC-EVs. To evoke more attention to this potential strategy, this article summarised the extant literature on MSC-EVs for DOP to provide new directions for further research and to promote the application of MSC-EVs in the clinical management of DOP.

Key Words: Bone marrow mesenchymal stem cells; Adipose-derived mesenchymal stem cells; extracellular vesicles; MicroRNAs; Long non-coding RNAs; Diabetic osteoporosis

Core Tip: A sustained high-glucose microenvironment may impair bone homeostasis leading to the initiation and progression of diabetic osteoporosis (DOP) in patients with diabetes mellitus (DM). Correcting the uncoupled bone remodelling and inflammatory microenvironment is the key to treating DOP. Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) have received widespread attention due to their ability to promote bone regeneration and inhibit bone loss in the treatment of osteoporosis by targeting the delivery of modifiable cargoes. This suggests that MSC-EVs also have great potential for the treatment of DOP, although the condition of DOP patients is more complex due to the fact that DOP patients are usually also accompanied by multiple cardiovascular and cerebrovascular complications and long-term use of multiple medications. Rapid advances in genetic engineering and bioengineering have also enabled modifiable MSC-EVs to show significant advantages in personalised and tailored treatment cases. More studies are needed to further demonstrate and develop the clinical therapeutic potential of MSC-EVs in DOP.

Citation: Yang YJ, Chen XE, Zhou XC, Liang FX. Mesenchymal stem cell-derived extracellular vesicles: A promising therapeutic strategy in diabetic osteoporosis. *World J Diabetes* 2024; 15(12): 2399-2403
URL: https://www.wjgnet.com/1948-9358/full/v15/i12/2399.htm
DOI: https://dx.doi.org/10.4239/wjd.v15.i12.2399

TO THE EDITOR

Based on the research by Wang *et al*[1], we believe that mesenchymal stem cell (MSC)-derived extracellular vesicles (MSC-EVs) for the treatment of diabetic osteoporosis (DOP) is a very promising therapeutic strategy, due to the fact that MSC-EVs have been widely used in the treatment of OP. However, there are only a few reports on MSC-EVs and DOP. Therefore, we wrote this paper to evoke the widespread interest in this MSC-EVs as an effective strategy for treating DOP, including clinical efficacy and mechanistic exploration.

Diabetes mellitus (DM) is a common chronic metabolic disease with systemic complications. The persistent high-glycemic microenvironment in DM patients usually impairs bone homeostasis, leading to increased bone marrow fat and active osteoclasts and damaging bone regenerative function, ultimately leading to complications of DOP[2]. Both osteoporosis (OP) and DOP are characterised by reduced bone mineral density, destruction of bone microstructure and increased risk of secondary fractures. However, the onset of OP is primarily associated with estrogen deficiency and aging-related bone loss. The onset of OP is primarily associated with estrogen deficiency and aging-related bone loss, whereas DOP is caused by disturbances in phosphorus and calcium metabolism, advanced glycation end products, and cumulative oxidative stress due to prolonged exposure to hyperglycemia[3]. The rise in the prevalence of DM globally due to a diet high in sugar and fat and the ageing of the world's population has led to a gradual increase in the prevalence of DOP, which has become a public health problem[4]. Studies have reported a 60% prevalence of OP in DM patients, which is much higher than in non-diabetic patients. Currently, there are no effective clinical therapies to prevent and treat DOP. The development of new therapeutic strategies for DOP is urgent.

MSCs, including bone MSCs (BMSCs) and adipose-derived MSCs (ADSCs), have multidirectional differentiation potential and self-renewal ability, which can play an important role in tissue regeneration and repair, especially bone regeneration and reconstruction through a variety of secretory factors produced by paracrine action. However, currently, MSC transplantation has not become a mainstream clinical therapeutic strategy due to low cell transplantation survival, poor therapeutic efficacy, and short treatment duration[5]. MSC-EVs, as key carriers for cell-to-cell communication, are loaded with a variety of bioactive molecules such as DNA, RNA, proteins and lipids, showing promising potential as an alternative to cell-free therapies. Particularly, bone MSC-EVs (BMSC-EVs) have emerged as effective vehicles for bone disease treatment due to the innate ability to differentiate into different cell types[5]. It is suggested that BMSC-EVs are a promising potential therapeutic strategy for DOP. However, pathologically, the contents of BMSC-EVs change and their function changes accordingly. Studies have shown that EVs derived from young MSCs have a greater ability to promote osteogenesis than EVs derived from aging MSCs[6]. Wang *et al*[7] reported that diabetic BMSC-EVs showed lower potential to promote osteogenic differentiation than normal BMSC-EVs. Further studies found lower bone mass and higher bone marrow fat accumulation, known as bone-fat imbalance, in the DM mouse model. Normal BMSC-EVs enhance osteogenesis and inhibit adipogenesis, whereas these effects are attenuated in diabetic BMSC-EVs[8]. Single-stranded nucleic acid molecular aptamers are able to bind to targets by folding into three-dimensional structures with high affinity and selectivity[9]. Han *et al*[8] constructed an aptamer delivery system to specifically deliver normal BMSC-EVs to BMSCs, which could increase bone mass and reduce bone marrow fat accumulation, thereby promoting bone regeneration in diabetic mice. The above studies suggest that correcting the abnormal bone-fat dysfunction coupling is the crucial to treating DOP. Targeted delivery of BMSC-EVs may be a potential therapeutic strategy for DOP.

MicroRNAs (miRNAs), a non-coding RNA with a length of approximately 22 nt, play an important role in mediating intercellular communication. However, most miRNAs are not stable due to possible degradation and conversion by multiple pathways. In particular, circulating miRNAs are easily degraded by RNase, which limits miRNAs applications [10]. Cumulative evidence suggests that MSCs paracrine a variety of factors containing miRNAs and long non-coding RNAs (lncRNAs) in the form of extracellular vesicles (EVs), which provides the basis for stable transport and targeted delivery of miRNAs, showing strong therapeutic potential in the treatment of several diseases[11]. Nonetheless, there are still some technical drawbacks in the wide application of EVs, such as efficiency and long time preservation[5]. Recently,

cross-disciplinary co-operation between nanotechnology and regenerative medicine has opened up new directions for the treatment of bone diseases. As a natural delivery system, EVs can efficiently deliver cargoes to target cells, while modified nanoparticles enable precise control and localisation[12]. Magnetic nanoparticles (MNPs), as a class of nanomaterials, are widely used in magnetic separation and imaging as well as drug delivery. Recently, gold-coated MNPs (GMNPs) were found to be the optimal drug carriers due to their excellent biocompatibility and magnetic properties[13]. However, systemic administration of GMNPs is not targeted, resulting in low and uncontrolled concentrations of drug release from target tissues, which impairs therapeutic efficacy[14]. Recent studies have found that assembling Fe_3O_4, SiO_2, poly (ethylene glycol), and aldehyde (CHO; GMNPs) into a nanomaterial for loading into EVs can correct bone reconstruction and promote bone regeneration by targeting and modulating osteoblast and osteoclast functions[15,16], which may be an effective targeted therapeutic strategy for DOP.

Hydroxyapatite-coated magnetite (Fe_3O_4) nanoparticles have been shown to be effective in preventing OP by enhancing osteoblast proliferation and differentiation through increased alkaline phosphatase, collagen and calcium deposition[17]. Xu *et al*[15] constructed a kind of nanoparticles GMNPs and combining it with anti-CD63 to prepare $GMNP_E$ to promote the enrichment of BMSC-EVs. Further studies revealed that $GMNP_E$-BMSC-EVs were able to target and inhibit matrix metalloproteinase 14 by delivering miR-150-5p, which activated the Wnt/β-catenin pathway to promote the proliferation and maturation of osteoblasts, thereby promoting osteogenesis[15], showing an attractive drug delivery strategy against DOP. In addition to being enriched with highly abundant miRNAs, BMSC-EVs are also capable of delivering multiple lncRNAs to target cells to activate downstream signaling cascades. Another study reported that $GMNP_E$-BMSC-EVs loaded with overexpressed lncRNA MEG3 were able to alleviate DOP in rats. This study found that osteoblasts could effectively uptake GMNPE-BMSC-EV-MEG3 to target inhibition of miR-3064-5p and enhance of nuclear receptor subfamily 4 member A3 expression by delivering highly expressed lncRNA MEG3 to osteoblasts, and subsequently, promote mitochondrial autophagy and differentiation of osteoblasts through activation of the PINK1/Parkin signaling pathway, which ultimately alleviated the bone loss in DOP rats[12], suggesting that $GMNP_E$-BMSC-EV-MEG3 is able to regulate bone formation by acting as a competing endogenous RNA for miR-3064-5p. The above studies emphasize the potential of $GMNP_E$-BMSC-EVs to promote bone formation. In addition, $GMNP_E$-BMSC-EVs can inhibit bone resorption. Studies have shown that $GMNP_E$-BMSC-EVs can effectively deliver miR-15b-5p to osteoclasts to downregulate GFAP expression and inhibit osteoclast differentiation, thereby alleviating bone loss in DOP rats[16]. The above studies suggest that $GMNP_E$-BMSC-EVs, as a potentially effective targeted delivery system, has a powerful role in promoting bone regeneration by simultaneously promoting bone formation and inhibiting bone resorption, which may provide a promising therapeutic approach for DOP.

The application of ADSC-EVs in the field of bone regeneration has also been widely reported due to the fact that ADSCs are more readily available in large quantities compared to BMSCs[18]. Studies have shown that oxidative stress is higher in diabetics, which in turn promotes the progression of diabetes and its complications. Epidemiologic studies have shown that elevated inflammation in diabetic patients disrupts the immune system leading to lipid peroxidation, which induces osteoclast apoptosis and activates osteoblasts to promote bone resorption, ultimately inducing the complication DOP. In the DOP inflammatory environment, Expression of NLRP3 and pro-IL-1β is induced to activate the assembly of the NLRP3 inflammasome (composed of pro-caspase-1, NLRP3, and ASC), which triggers caspase-1-mediated extracellular secretion of IL-1β and IL-18, ultimately initiating pyroptosis. Tofiño-Vian *et al*[19] demonstrated that ADSC-EVs were able to alleviate osteoarthritis by reducing chondrocyte inflammation through inhibition of nitric oxide synthase activity. Moreover, Zhang *et al*[20] found that ADSC-EVs mitigated bone resorption by reducing the production of inflammatory mediators including IL-6, PGE2, and NO, thereby alleviating DOP. Subsequent studies by this team found that ADSC-EVs may be inhibiting pro-inflammatory cytokines and bone resorption by delivering enriched miR-146a in streptozotocin-induced DOP rats[21]. Mechanistically, ADSC-EVs inactivates NLRP3 inflammasome by delivering miR-146a thereby inhibiting the release of IL-18 and IL-1β inflammatory factors and eventually reducing bone resorption[21]. The above results suggest that ADSC-EVs may ameliorate bone loss in DOP by modulating the inflammatory microenvironment. In addition, surine-derived stem cells-EVs (USC-EVs) have gained attention as a relatively low-cost, non-invasive source of stem cells. Previous studies have confirmed that USC-EVs can enhance osteogenesis and inhibit osteoclastogenesis[22]. Zhang *et al*[23] found that USC-EVs could prevent secondary OP in diabetic rats by transferring miR-26a-5p into osteoblast precursor cells to enhance osteoblast activity and induce osteoblast precursor cell differentiation and inhibit osteoclast activity through inhibiting HDAC4 to initiate the HIF-1α/VEGFA pathway. The above results suggest that in addition to BMSC-EVs, ADSC-EVs and USC-EVs also have significant advantages in the treatment of DOP due to their easier accessibility.

Conclusions and perspectives

Current studies have shown that BMSC-EVs, ADSC-EVs and USC-EVs can effectively promote bone formation, inhibit bone resorption and improve the inflammatory bone microenvironment, thereby ameliorating DOP bone loss. On the one hand, the cargoes of MSC-EVs can be modified by strategies such as gene editing to enhance its therapeutic effect. On the other hand, bioengineering strategies such as nano-modification can be used to enhance the target delivery ability of EVs and thus enhance the local drug concentration in target tissues/organs. This shows that MSC-EVs have highly modifiable properties (optimizing efficacy and enhancing targeted delivery), offering unlimited possibilities for the therapeutic potential of MSC-EVs for bone regeneration. This also suggests that in the future, the efficacy of MSC-EVs can be further enhanced by diversely modifying MSC-EVs cargoes or modifying MSC-EVs, even providing the possibility of specific personalized and tailored therapies.

Although cumulative studies have shown MSC-EVs to be a promising treatment strategy for DOP, it has to be recognized that the current studies on the efficacy of MSC-EVs in DOP temporarily remain at the level of animal disease models. Patients with DOP exhibit a wide range of heterogeneity; for example, patients with diabetes may also have

multiple concurrent cardiovascular and cerebrovascular comorbidities and be taking multiple medications at the same time, which complicates the clinical treatment of patients with DOP. Therefore, on the basis of existing experimental animal studies, substantial future clinical trials are needed to accurately evaluate the therapeutic efficacy of MSC-EVs in heterogeneous patient populations. Moreover, the validation of the safety and efficacy of MSC-EVs in humans should not be neglected. The exploration of long-term effects of MSC-EVs in DOP is also a concern for future research. In addition, the purification, transportation, storage and cost of MSC-EVs are also difficult issues that are currently pending. Prior to the clinical application of MSC-EVs, future research should also focus on the purified production, storage stability and safety of MSC-EVs. Furthermore, as mentioned earlier, MSC-EVs lack tissue targeting specificity. The assembly of nanomaterials can confer good bone tissue targeting properties to MSC-EVs. However, nanomaterials loaded with MSC-EVs are expensive which prevents them from being introduced into clinical applications, at least for the time being. Exploring ways to reduce the production cost of nanomaterials loaded with MSC-EVs or to develop more cost-effective targeted delivery systems is a critical part of the clinical translation of MSC-EVs.

FOOTNOTES

Author contributions: Yang YJ and Chen XE contribute equally to this study as co-first authors. Liang FX and Zhou XC designed and coordinated the article; Yang YJ and Chen XE wrote the manuscript; all authors approved the final version of the article.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country of origin: China

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S-Editor: Lin C
L-Editor: A
P-Editor: Xu ZH

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