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REVIEW

Exosomes as Emerging Therapeutic Strategies in Primary Osteoporosis: A Narrative Review

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Background: Primary osteoporosis imposes a growing global burden. While antiresorptive and anabolic agents reduce fractures, long-term adherence, adverse events, and limited tissue targeting leave unmet needs. Exosomes have emerged as promising, cell-free candidates.

Methods: We conducted a narrative synthesis of English-language studies (2010–May 2025) indexed in PubMed and Web of Science on exosomes and primary osteoporosis, including mechanistic, preclinical efficacy, delivery, and safety data.

Results: Exosomes modulate bone remodeling via osteoanabolic signaling, osteoclast inhibition, and antioxidative pathways. Across cell and animal models, exosome preparations improved osteoblast viability and function, enhanced mineralization, and mitigated glucocorticoid- or estrogen-deficiency–related bone loss. Key translational variables include source selection, isolation/characterization, cargo loading, dosing, route, targeting, and biocompatibility. Safety signals are preliminarily favorable but heterogeneous across platforms. The current evidence base is predominantly preclinical; standardized manufacturing, biodistribution and persistence profiling, and dose–response relationships remain insufficient.

Conclusion: Exosome-based approaches are promising adjuncts rather than immediate replacements for current osteoporosis therapies. Priorities include harmonized release criteria, head-to-head comparisons with standard agents, validated pharmacodynamic biomarkers, and early-phase clinical trials.

Clinical Relevance: For patients who are intolerant of or inadequately controlled by approved agents, exosome strategies may offer future targeted adjuncts once quality, safety, and efficacy are established in humans.

Keywords: exosomes, primary osteoporosis, bone regeneration, drug delivery, targeted therapy

Introduction

Osteoporosis is a metabolic bone disorder characterized by decreased bone mass and deterioration of bone microarchitecture, primarily due to an imbalance between bone resorption and bone formation processes.[1] Primary osteoporosis, particularly the postmenopausal and senile variants, has become an increasingly significant global public health issue.[2,3] In 2020, the prevalence of osteoporosis among Chinese adults aged 20 to 89 years was 13.54% according to the World Health Organization (WHO) diagnostic criteria and 29.49% based on the Chinese diagnostic criteria.[4] This indicates that osteoporosis is a significant public health issue in China, particularly among older women. Moreover, the epidemiological characteristics of osteoporosis vary substantially across different regions and populations. For example, in both Asian and Western countries, the diagnosis and treatment rates of osteoporosis in men are relatively low, especially in resource-limited settings.[5] These disparities may be associated with variations in peak bone mass and fracture risk among different populations. Evidence suggests that Asian men have a lower peak bone mass compared with Caucasians, which may contribute to misdiagnosis when Caucasian reference standards are applied.[5] Although traditional treatments, such as bisphosphonates and hormone replacement therapy, have shown some effectiveness, their use is limited by notable side effects and suboptimal target specificity.[6] As a result, the development of innovative therapeutic strategies has become a research priority. In recent years, exosomes—tiny membrane-bound vesicles released by cells—have shown

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great promise for treating osteoporosis because of their unique biological features.[7] Almost all types of cells can produce exosomes, which carry bioactive molecules including proteins, lipids, and nucleic acids. These exosomes are integral to intercellular communication.[8] Recent studies have highlighted their significant involvement in the pathogenesis and progression of osteoporosis, primarily through the modulation of osteoblast and osteoclast activity and the regulation of bone metabolic homeostasis. Furthermore, exosomes have the potential to function as natural drug delivery systems, capable of transporting therapeutic agents for targeted treatment. This presents a novel strategy to address the limitations associated with conventional therapies.[9]

Despite notable progress in fundamental research on exosomes within the context of osteoporosis, their clinical application continues to encounter several obstacles. These include the absence of standardized protocols for isolation and purification, significant heterogeneity, and the necessity for further validation regarding long-term safety. Future research endeavors should aim to elucidate the underlying mechanisms governing exosome function and to optimize their production and delivery methodologies, thereby facilitating their translational application in osteoporosis therapy. This review concentrates on the biological characteristics of exosomes, their roles in the pathophysiology of osteoporosis, and their therapeutic potential, with the objective of providing a theoretical foundation for the development of innovative treatment strategies. This narrative review focuses on primary osteoporosis and integrates mechanistic evidence with delivery considerations; our aim is to provide a concise, disease-specific synthesis to inform translational planning.

Unlike prior overviews that combined heterogeneous bone conditions or emphasized either biology or delivery in isolation, this narrative review is disease-specific to primary osteoporosis and couples mechanistic pathways (osteoblast–osteoclast crosstalk, oxidative stress, immunomodulation) with delivery/engineering issues (source selection, isolation/characterization, cargo loading, bone-targeting strategies) and standardization-to-translation considerations (release criteria, biodistribution/persistence profiling, pharmacodynamic biomarkers). We also synthesize recent 2023–2025 developments, including plant-derived exosome-like vesicles and bone-targeting strategies. Figure 1 provides an overview of exosome biogenesis, cargo classes, and bone-related recipient cells referenced throughout the review.

Application of Exosomes in Basic Research on Primary Osteoporosis

To clarify the cellular context, we organize the basic-research evidence by bone-related target cells and summarize representative exosome sources, pathways, and functional outcomes.

Effects on Osteoblasts/Pre-Osteoblasts

Bone Marrow Stromal Cells(BMSC)-derived exosomes deliver osteogenic microRNAs that enhance osteoblast proliferation and differentiation, upregulate runt-related transcription factor 2 (RUNX2) and Osterix, and activate Mitogen-Activated Protein Kinase (MAPK) signaling; they also reduce apoptosis and increase mineralization.[10–12] Additional evidence from myogenic exosomes indicates supportive effects on osteoblast function in vivo.[13] These findings position osteoblast-lineage cells as direct effectors of exosome-mediated osteogenesis.

Effects on Osteoclasts and Osteoblast–Osteoclast Crosstalk

Osteoclast-derived exosomes modulate the long non-coding RNA (lncRNA) AW011738/miR-24-2-5p/Triggering Receptor Expressed on Myeloid cells 1 (TREM1) axis, shaping osteogenic differentiation and bone mass, which underscores bidirectional coupling between bone resorption and formation.[14] Targeting this axis through exosomal cargo offers a route to rebalance remodeling in primary osteoporosis.

Effects on Mesenchymal Stem Cells (MSCs)

Osteogenically induced Human Umbilical Cord Mesenchymal Stem Cell (HucMSC) exosomes are enriched for microRNAs linked to MAPK and osteoclast-differentiation pathways, thereby promoting MSC osteogenesis and improving bone density in estrogen-deficient models.[15] Young-donor plasma exosomes further enhance MSC proliferation and migration, Alkaline phosphatase (ALP) activity, and mineralization, with miR-142-5p acting as a key effector.[16] Plant-derived exosome-like nanovesicles (PELNs) promote human Bone Marrow-derived Mesenchymal Stem Cell (hBMSC) osteogenesis via autophagy enhancement and modulation of gut metabolites/microbiota.[17]

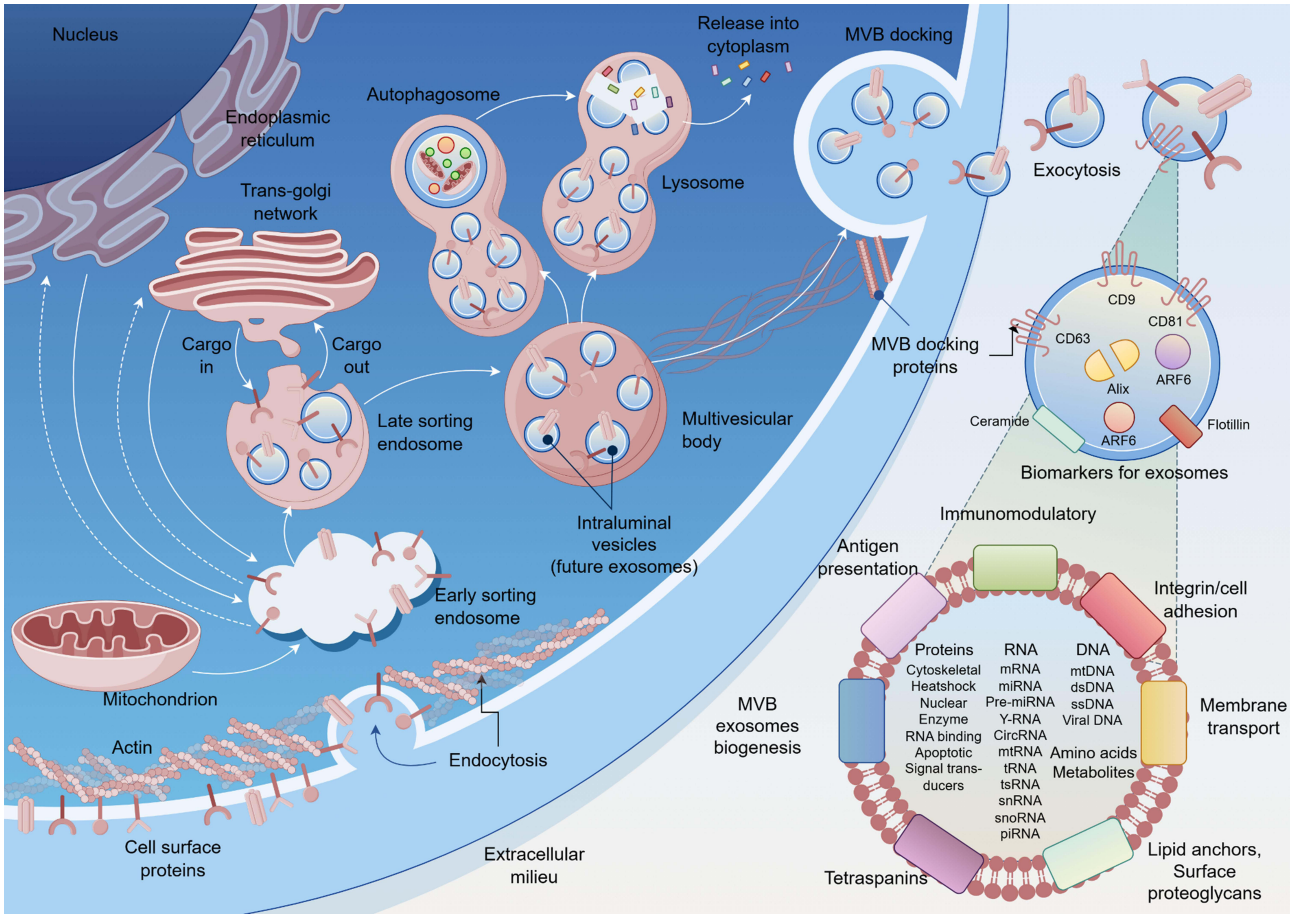

Figure 1 Exosome biogenesis, cargo, and bone-target cell interactions. Schematic of exosome formation via the endosomal pathway, representative cargo (proteins, lipids, RNAs; CD9/CD63), and uptake by osteoblasts, osteoclasts, MSCs, endothelial and immune cells. Through key pathways (eg, Wnt/β-catenin, RANKL–RANK–OPG, PI3K–AKT, MAPK, NF-κB), exosomes modulate bone remodeling in primary osteoporosis. Diagram not to scale.
Abbreviations: MSC, mesenchymal stromal/stem cell; MVB, multivesicular body.

Effects on Endothelial Cells and Angiogenesis

Endothelial Progenitor Cell (EPC) -derived exosomes stimulate endothelial proliferation, migration, and tubulogenesis through miR-126–mediated sprouty-related EVH1 domain-containing protein 1 (SPRED1) suppression and Rapidly Accelerated Fibrosarcoma/Extracellular signal-Regulated Kinase (Raf/ERK) activation, increasing vessel density and bone regeneration during distraction osteogenesis.[18] Endothelium-derived exosomes can also mitigate glucocorticoid-induced osteoporosis by limiting ferroptosis-related injury to osteoblasts.[19]

Effects on Immune Cells/Macrophages

BMSC-derived exosomes drive Macrophage2 (M2) macrophage polarization via Tripartite motif-containing 25 (TRIM25), dampen inflammatory signaling, and enhance bone formation in ovariectomized (OVX) models.[20] Preconditioned M2 macrophage exosomes activate β-catenin to stimulate MSC osteogenesis and accelerate bone-defect repair.[21]

Other Targets and Microenvironmental Context

Myogenic exosomes partially promote osteogenesis in sarcopenia-associated osteoporosis, highlighting muscle–bone axis communication.[13] In hyperglycemic/diabetic settings, adipose-derived mesenchymal stem cell (AD-MSC) exosomes suppress the NOD-like receptor family pyrin domain containing 3(NLRP3) inflammasome and reduce bone loss.[22]

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Collectively, these cell-type–specific effects contextualize how exosomes modulate the bone microenvironment in primary osteoporosis and inform target selection for translational studies.

Pathological Mechanisms of Primary Osteoporosis and the Role of Exosomes

The pathogenesis of primary osteoporosis is predominantly attributed to an imbalance in bone metabolism, characterized by excessive bone resorption relative to bone formation, which ultimately results in decreased bone mass and disruption of bone microarchitecture. Exosomes play multifaceted regulatory roles in this pathological process. From the perspective of intercellular communication, exosomes are involved in the regulation of bone metabolism by mediating signaling and material transfer between cells.[23] During bone remodeling, exosomes not only deliver signals that promote both osteogenesis and bone resorption but also modulate the differentiation, recruitment, and activity of bone-remodeling cells. Furthermore, they have been shown to contribute directly to extracellular matrix mineralization.[24] Research has demonstrated that exosomes derived from osteoclasts influence osteoblast differentiation via the lncRNA AW011738/miR-24-2-5p/TREM1 axis, thereby playing a role in the progression of osteoporosis.In particular, by employing a RANKL-induced osteoclast model alongside whole-transcriptome RNA sequencing, researchers identified significantly differentially expressed long non-coding RNAs (lncRNAs) and messenger RNAs (mRNAs). Exosomes derived from osteoclasts, which contained the lncRNA AW011738, were observed to suppress osteogenic markers and exacerbate bone loss in OVX mice. Conversely, the knockdown of AW011738 led to an increased expression of markers associated with osteogenic differentiation.[14]

Furthermore, exosomes are intricately linked to various pathological processes, including oxidative stress and apoptosis. Oxidative stress is acknowledged as a pivotal pathogenic factor in osteoporosis, and the microRNAs encapsulated within exosomes have the capacity to modulate this response, thereby influencing disease progression.[25] For example, endothelial cell-derived exosomes (EC-Exos) have been shown to mitigate glucocorticoid-induced osteoporosis by inhibiting ferritinophagy-dependent ferroptosis. Both in vitro and in vivo studies have demonstrated that EC-Exos can reverse the glucocorticoid-induced suppression of osteoblast activity, highlighting their essential regulatory function in the pathophysiology of osteoporosis.[19] Additionally, exosomes derived from MSCs play a significant role in bone metabolism through diverse signaling pathways. Exosomes derived from HucMSCs after osteogenic induction are enriched with microRNAs that regulate key signaling pathways involved in bone formation and differentiation, including osteoclast differentiation and the MAPK pathway, thus influencing osteoporosis. High-throughput microRNA sequencing has revealed 221 differentially expressed microRNAs in these osteogenically induced exosomes, among which 41 may play crucial roles in regulating osteogenesis in MSCs through exosomal mechanisms[15] Additionally, another study demonstrated that exosomes derived from bone marrow mesenchymal stem cells can protect intervertebral disc chondrocytes from apoptosis and calcification through the miR-31-5p/ATF6 axis, thus mitigating intervertebral disc degeneration.[26] Collectively, these findings elucidate the complex regulatory network mediated by exosomes in the pathogenesis of primary osteoporosis and provide novel insights into the mechanisms underlying the disease. Figure 2 summarizes representative signaling pathways through which exosomes modulate bone remodeling in primary osteoporosis. Representative exosome sources, cargo, recipient cells, and signaling pathways, together with their effects on bone formation and resorption, are summarized in Table 1. Figure 3 shows standard exosome characterization (TEM morphology and NTA size distribution) and representative in vivo micro-CT 3D reconstructions with the ROI highlighted.

Experimental Studies on Exosomes in Animal Models of Osteoporosis

In animal models of osteoporosis, the therapeutic potential and underlying mechanisms of exosomes have been extensively investigated. For example, in OVX rat models, which simulate postmenopausal osteoporosis, numerous studies have demonstrated that exosomes derived from various sources exert beneficial effects in mitigating bone loss. In OVX mouse models, exosomes derived from BMSCs have been shown to promote osteogenesis through TRIM25-mediated M2 macrophage polarization, thereby enhancing bone formation and improving bone microarchitecture.[20] Furthermore, exosomes isolated from the plasma of both young and elderly healthy individuals have been observed to enhance the proliferation and migration of MSCs, increase ALP activity, promote MSC mineralization, and reduce the

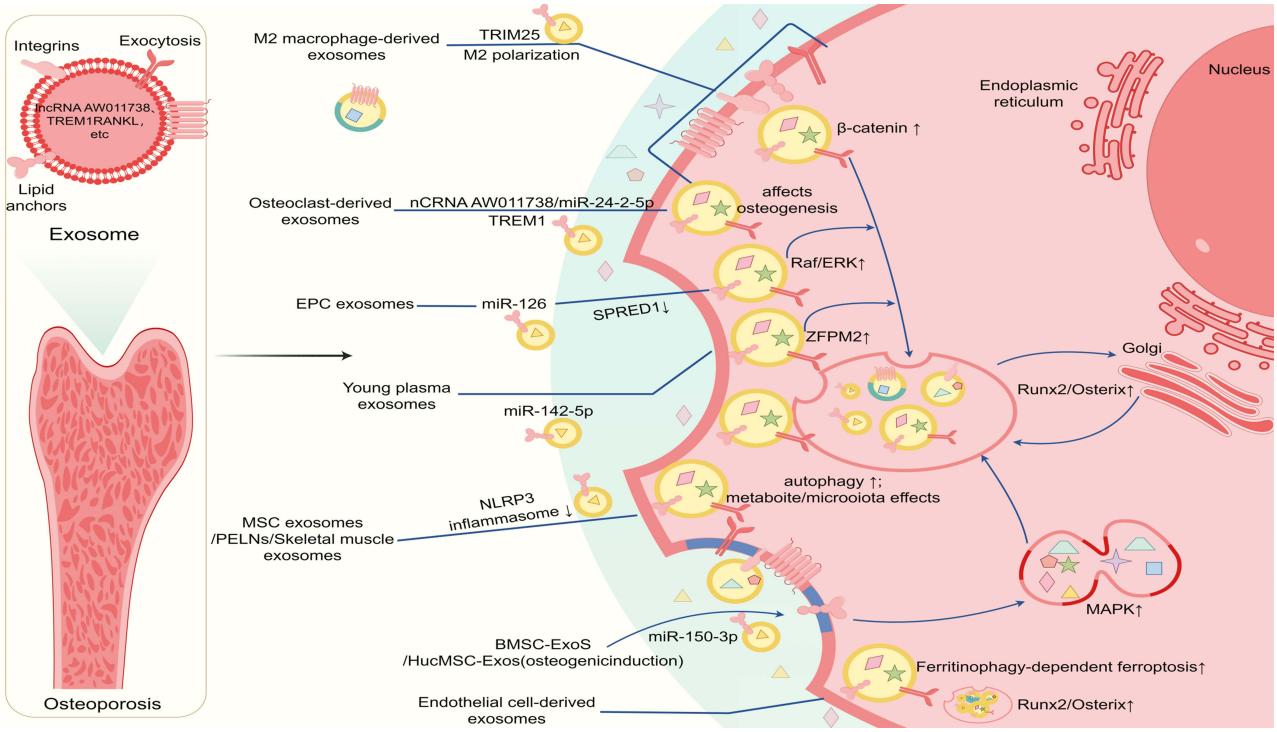

Figure 2 Mechanistic Pathways of Exosomes in Osteoporosis. Exosomes from osteoblasts, osteoclasts, stem cells, and immune cells regulate bone metabolism by transferring functional RNAs and proteins. They modulate osteogenesis and osteoclastogenesis mainly through Wnt/β-catenin, RANKL/RANK/OPG, PI3K/AKT, MAPK, and NF-κB signaling pathways.

number of osteoclasts.In an OVX–induced osteoporotic rat model, plasma-derived exosomes from young healthy individuals demonstrated superior protective effects on bone tissue compared to those from other sources. miRNA sequencing indicated elevated levels of miR-142-5p in exosomes from young donors. Overexpression of miR-142-5p replicated the pro-osteogenic effects observed with these exosomes, whereas its downregulation had the opposite effect;

Table 1 Mechanisms of Exosomes in Bone Regeneration

Functional Aspect	Specific Mechanism	Experimental Evidence
Promote Osteoblast Proliferation and Differentiation	Carry Specific microRNAs (eg miR-150-3p) to Regulate the Expression of Key Transcription Factors such as Runx2 and Osterix	Exosomes Derived from BMSCs
Inhibit Osteoblast Apoptosis	Enhance Osteoblast Viability and Reduce the Expression Levels of Apoptosis-Related Genes	Exosomes Derived from BMSCs
Regulate the MAPK Signaling Pathway	Upregulate the Expression of Proteins Related to the MAPK Signaling Pathway, Promoting Osteoblast Growth and Cell Cycle Progression	Exosomes Derived from BMSCs
Regulate Angiogenesis	Stimulate Endothelial Cell Proliferation, Migration, and Tube Formation to Promote Angiogenesis	Exosomes Secreted by EPC-Exos Downregulate SPRED1 in a miR-126-Dependent Manner and Activate the Raf/ERK Signaling Pathway
Regulate the Immune Microenvironment	Modulate Inflammatory Responses and Immune Cell Polarization to Create a Favorable Microenvironment for Bone Regeneration	Exosomes Derived from M2 Macrophages, Preconditioned with Hydrogen Sulfide (H_2S), Enhance Osteogenic Differentiation of MSCs by Activating the β-catenin Signaling Pathway

Notes: Summary of representative exosome-mediated mechanisms relevant to bone regeneration and remodeling in primary osteoporosis. The table lists exosome sources, key cargo (eg, miRNAs/lncRNAs/proteins), recipient cell types, principal signaling pathways (eg, Wnt/β-catenin, RANKL–RANK–OPG, PI3K–AKT, MAPK, NF-κB), and reported effects on osteogenesis/osteoclastogenesis.
Abbreviations: MSC, mesenchymal stromal/stem cell; EV, extracellular vesicle; EPC, endothelial progenitor cell.

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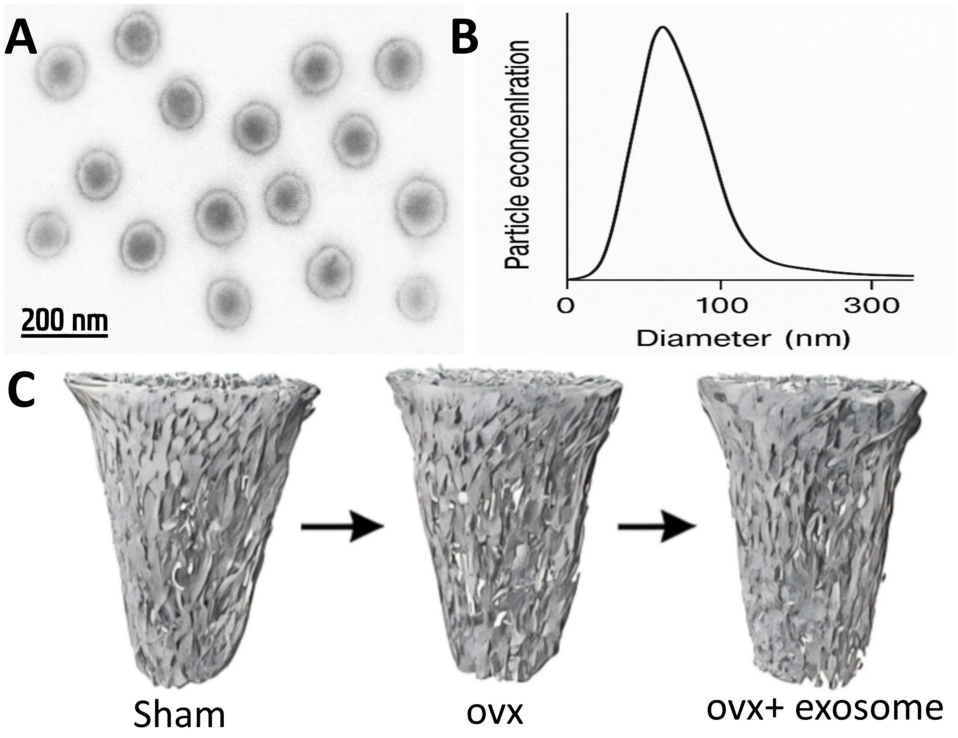

Figure 3 Exosome characterization and representative in vivo micro-CT reconstructions. (**A**) Transmission electron microscopy (TEM) images of isolated exosomes showing the typical spherical morphology (scale bar = 200 nm). (**B**) Nanoparticle tracking analysis (NTA) showing the particle size distribution of the exosome preparation. (**C**) Representative micro-CT 3D reconstructions of trabecular bone from sham-operated, ovariectomized (OVX), and OVX + exosome-treated groups. Quantitative analyses are reported in the text.

Abbreviations: TEM, transmission electron microscopy; NTA, nanoparticle tracking analysis; OVX, ovariectomy; μCT, micro-computed tomography.

these effects were reversible with miR-142-5p inhibitors. zinc finger protein, FOG family member 2(ZFPM2) was identified as a potential target of miR-142-5p in the context of osteoporosis.[16] Additionally, the functional properties of exosomes derived from HucMSC have been investigated, particularly following osteogenic induction. Exosomes subjected to osteogenic induction (Exo2) demonstrated enhanced effects on osteogenic differentiation compared to those derived from standard culture conditions (Exo1), although they exhibited reduced effects on proliferation. Both Exo1 and Exo2 were effective in improving tibial bone density and reversing osteoporosis in estrogen-deficient mouse models. High-throughput microRNA sequencing has identified 221 differentially expressed microRNAs in osteogenically induced exosomes derived from HucMSCs, among which 41 are posited to play pivotal roles in the exosomal regulation of osteogenesis. Mechanistically, microRNAs contained within Exo2 are implicated in bone development and differentiation processes, including osteoclast differentiation and the MAPK signaling pathways. Notably, the expression levels of hsa-miR-2110 and hsa-miR-328-3p were observed to increase with prolonged osteogenic differentiation, indicating their potential significance as key osteo-regulatory microRNAs within exosomes.[15] Additionally, exosomes derived from AD-MSCs have exhibited therapeutic potential in the context of diabetic osteoporosis by inhibiting the activation of the NLRP3 inflammasome and mitigating bone loss. In both cellular and animal models of diabetic osteoporosis, established through high-glucose exposure and streptozotocin injection, AD-MSC-derived exosomes have been shown to suppress the secretion of IL-1β and IL-18 in high glucose-treated osteoclasts, restore bone mass, and thereby underscore their therapeutic potential in this specific subtype of osteoporosis.[22,27]

Moreover, exosomes derived from MSCs have demonstrated significant therapeutic potential. The administration of MSC-derived exosomes into OVX mouse models resulted in enhanced bone formation and improved bone microarchitecture, as evidenced by micro-computed tomography (micro-CT), histological, and immunohistochemical analyses. Subsequent investigations suggested that these effects might be mediated through the activation of the Wnt/β-catenin signaling pathway, which promotes the proliferation and differentiation of osteoblasts, thereby exerting anti-osteoporotic effects.[13] Additionally, exosomes

Table 2 Summary of Preclinical Studies on Exosomal Therapy in Animal Models of Osteoporosis

Animal Model Type	Exosome Source	Main Mechanism of Action	Experimental Results
Ovariectomized Mouse Model	Exosomes Derived from BMSCs	Regulation of M2 Macrophage Polarization via TRIM25-Mediated Ubiquitination and Degradation of TREM1, Promoting Osteogenic Differentiation	Promotes Bone Formation and Improves Bone Microarchitecture
Ovariectomized Rat Model	Plasma-Derived Exosomes from Young and Elderly Healthy Humans	Enhance MSCs Proliferation and Migration, Increase ALP Activity, Promote MSC Mineralization, and Reduce Osteoclast Number	Both Types of Exosomes Are Beneficial, with Plasma Exosomes from Young Healthy Individuals Showing a Stronger Effect
Estrogen Deficiency Osteoporosis Mouse Model	Exosomes Derived from Osteogenically Induced HucMSCs	miRNAs Involved in Bone Development and Differentiation, Including Osteoclast Differentiation and the MAPK Signaling Pathway	Improves Tibial Bone Density and Reverses Osteoporosis
Diabetic Osteoporosis Rat Model	Exosomes Derived from AD-MSCs	Inhibition of NLRP3 Inflammasome Activation	Alleviation of Bone Loss
Ovariectomized Rat Model	Exosomes Derived from MSCs	Activate the Wnt/β-catenin Signaling Pathway to Stimulate Osteoblast Proliferation and Differentiation	Promote Bone Formation and Improve Bone Microarchitecture
Sarcopenic Osteoporosis Rat Model	Exosomes Obtained from DN Skeletal Muscle after Neuromuscular Electrical Stimulation Intervention (DN + ES-Exo)	Partially Promote Osteogenesis In Vivo and In Vitro	Exhibit Certain Anti-Osteoporotic Effects

Notes: Summary of study design, exosome source (cell type/species), cargo or engineering, delivery route and dosing, animal model (eg, OVX mouse/rat, senescence, glucocorticoid-induced), primary readouts (micro-CT, histomorphometry, biomechanical testing, serum markers), and main outcomes on bone formation/resorption.
Abbreviations: OVX, ovariectomized; MSC, mesenchymal stromal/stem cell; EV, extracellular vesicle.

derived from skeletal muscle have shown promise in osteoporosis treatment. Exosomes isolated from denervated skeletal muscle subjected to neuromuscular electrical stimulation (DN+ES-Exo) were administered to rats with sarcopenia-related osteoporosis. In vitro co-culture of DN+ES-Exo with differentiated Mouse Calvarial 3T3-E1 preosteoblastic cell line (MC3T3-E1) osteoblasts indicated that these exosomes partially facilitated osteogenesis both in vivo and in vitro, suggesting a potential therapeutic role for muscle-derived exosomes in osteoporosis management.[23] Collectively, these animal studies provide important preclinical evidence supporting the translational potential of exosome-based therapies for primary osteoporosis. Table 2 summarizes preclinical exosome-based studies in animal models of primary osteoporosis, including sources, delivery, outcomes, and key readouts.

Strength of Evidence

Reproducibility

Multiple groups report osteogenic rescue and partial prevention of bone loss in rodent or zebrafish osteoporosis models, supported by micro-architectural readouts and bone turnover markers.

Model Limitations

Study durations are short, comparator arms versus standard antiresorptives/anabolics are infrequent, and clinically representative populations (postmenopausal/senescent phenotypes, comorbidities, polypharmacy) are under-modeled.

Translational Gaps

Head-to-head studies with standard therapies, exposure–response characterization (both particle number and protein), skeletal biodistribution/residence-time profiles, and safety packages under clinically relevant dosing schedules are required to inform first-in-human designs.

Application of Exosomes in the Treatment of Primary Osteoporosis

Exosome-Mediated Drug Delivery Systems

Exosomes, as intrinsic nanoscale transporters, present notable advantages in drug delivery for the management of primary osteoporosis. Their superior biocompatibility, minimal immunogenicity, and capacity to penetrate biological barriers facilitate the transport of diverse bioactive molecules—including proteins, nucleic acids, and lipids—thereby playing pivotal roles in intercellular communication.[7,28] Within the framework of osteoporosis treatment, exosomes modulate intercellular signaling related to bone metabolism and influence the activities of osteoblasts and osteoclasts, thus exhibiting considerable diagnostic and therapeutic potential.[29,30] Furthermore, exosomes can serve as vehicles for the delivery of therapeutic agents or genetic material specific to osteoporosis, thereby enhancing drug targeting and efficacy.[31] Research indicates that methodologies such as electroporation and ultrasound can be utilized to incorporate estrogen into the interior or onto the surface of exosomes for targeted osteoporosis treatment. In particular, estrogen-loaded exosomes derived from BMMSCs have been developed using incubation and ultrasound-assisted techniques, with subsequent evaluation of their impact on BMMSC viability. The findings demonstrated that drug-loaded exosomes significantly enhanced BMMSC survival while preserving the characteristic spherical morphology of exosomes. Although the ultrasound loading method resulted in a minor increase in exosome particle size, the potential for effective delivery remained promising.[32]

Moreover, exosomes have the capability to achieve targeted delivery to specific cell types through the modification of surface ligands, a subject that has garnered significant attention in recent research.[33] Studies have demonstrated that the anchoring of specific glycosaminoglycans or other ligands to the exosomal surface can significantly enhance their targeting capabilities, thereby facilitating more precise drug delivery.[34] The functionalization of exosome surfaces can be accomplished through a variety of methods, including genetic engineering, covalent modification, and non-covalent interactions.[35] For example, genetic engineering can be utilized to express specific targeting molecules on the exosomal surface, thereby enhancing in vivo targeting and therapeutic efficacy.[36] Alternatively, chemical modification can introduce functional groups that increase binding affinity to target cells.[37] In the realm of cancer therapy, surface-engineered exosomes have been extensively utilized to enhance drug targeting. By modifying the surfaces of exosomes with antibodies or aptamers, researchers have facilitated the specific recognition and delivery of therapeutic agents to cancer cells, thereby augmenting treatment efficacy while minimizing adverse effects.[38] Additionally, exosomes can be engineered to deliver small interfering RNAs (siRNAs) or microRNAs (miRNAs) through surface modifications, thereby enabling gene silencing or regulation and playing a pivotal role in cancer treatment.[39] This exosome-based drug delivery strategy provides a precise and efficient approach for treating primary osteoporosis and shows significant potential in overcoming the limitations associated with conventional delivery methods. Building on findings from animal models, it is crucial to elucidate the molecular mechanisms by which exosomes promote bone regeneration.

Mechanisms of Exosome Action in Bone Regeneration

Exosomes are integral to bone regeneration, engaging multiple underlying mechanisms. Firstly, exosomes facilitate the proliferation and differentiation of osteoblasts. Empirical evidence indicates that exosomes derived from BMSCs enhance osteoblast proliferation and differentiation by delivering specific microRNAs, such as miR-150-3p. These exosomes modulate the expression of pivotal transcription factors, including Runx2 and Osterix, thereby augmenting osteoblastic function and offering therapeutic potential for osteoporosis.[10] Secondly, BMSC-derived exosomes contribute to osteoporosis mitigation by inhibiting osteoblast apoptosis. These exosomes significantly enhance osteoblast viability and decrease the expression levels of apoptosis-related genes, thus promoting osteoblast proliferation.[11] Furthermore, exosomes stimulate osteoblast proliferation by modulating the MAPK signaling pathway. Research has demonstrated

that BMSC-derived exosomes upregulate the expression of MAPK pathway-associated proteins, thereby facilitating osteoblast growth and progression through the cell cycle.[12]

Conversely, exosomes are integral to the regulation of angiogenesis, a process crucial for supplying the nutrients and oxygen necessary for bone regeneration. Exosomes derived from endothelial progenitor cells (EPC-Exos) have been demonstrated to enhance the proliferation, migration, and tube formation of vascular endothelial cells, thereby facilitating angiogenesis. In a rat model of distraction osteogenesis, the local administration of EPC-Exos was observed to expedite bone regeneration and augment vascular density. This effect is intricately linked to the downregulation of SPRED1 and the activation of the Raf/ERK signaling pathway, which occurs in a miR-126-dependent manner mediated by EPC-Exos.[18] Furthermore, exosomes play a pivotal role in bone regeneration by modulating the immune microenvironment. Specifically, macrophage-derived exosomes can promote bone healing by modulating inflammatory responses and guiding immune cell polarization, thus fostering a regenerative environment. Notably, exosomes from M2 macrophages preconditioned with hydrogen sulfide (H_2S) have been shown to facilitate the repair of cranial bone defects. This is achieved by enhancing the osteogenic differentiation of MSCs through the activation of the β-catenin signaling pathway.[21] These synergistic mechanisms underscore the substantial therapeutic potential of exosomes in bone regeneration and the repair of bone defects associated with primary osteoporosis.

Synergistic Effects of Exosomes with Existing Therapeutic Strategies

In the management of primary osteoporosis, the integration of exosomes with existing therapeutic modalities presents an innovative approach to enhancing clinical outcomes. From a pharmacological synergy perspective, exosomes can function as drug delivery vehicles in conjunction with conventional anti-osteoporotic agents, such as bisphosphonates and parathyroid hormone (PTH). Bisphosphonates act by inhibiting osteoclast activity and reducing bone resorption, whereas exosomes facilitate the precise delivery of these agents to osteoporotic sites. This targeted delivery not only enhances drug efficacy but also mitigates systemic distribution and associated adverse effects. Empirical evidence indicates that exosomes loaded with bisphosphonates more effectively suppress osteoclast differentiation and activity while concurrently promoting the proliferation and differentiation of osteoblasts. Compared to the administration of bisphosphonates alone, this combined strategy results in a significantly greater increase in bone mass in osteoporotic animal models.[40] Results remain heterogeneous across laboratories, and several studies report limited or null effects depending on isolation method, dose normalization, and biodistribution, underscoring the need for standardized protocols.

In the context of synergy with physical therapies, electrical stimulation exemplifies a significant approach. Exosomes derived from BMSCs that have been preconditioned with electrical stimulation (referred to as Elec-exo) demonstrate an enhanced regenerative capacity in bone repair. Electrical stimulation induces alterations in the protein and gene expression profiles of BMSC-derived exosomes, enriching proteins associated with oxidative phosphorylation and activating bone formation-related pathways, such as PI3K-Akt and MAPK. When Elec-exo is encapsulated within a chondroitin sulfate methacrylate (CSMA) hydrogel and applied to a rat femoral defect model, it markedly accelerates early-stage bone regeneration. This combined treatment yields superior outcomes compared to either physical stimulation or exosome therapy alone.[41] This synergistic strategy, which integrates exosomes with existing therapeutic modalities, optimizes the advantages of each approach and holds significant promise for providing more effective treatment options for patients with primary osteoporosis.

Comparison with Current Standard Therapies

Although conventional anti-osteoporotic drugs are effective to some extent, their long-term use is often accompanied by adverse side effects, limiting their widespread clinical application.[42] While guideline-endorsed antiresorptive agents (eg, oral or intravenous bisphosphonates, denosumab) and anabolic agents (eg, teriparatide, abaloparatide, romosozumab) are available, their effectiveness in real-world practice is constrained by challenges in long-term adherence and by adverse events such as gastrointestinal intolerance, hypocalcemia, osteonecrosis of the jaw, and atypical femoral fractures.[43,44] In certain circumstances, abrupt discontinuation may even trigger rebound vertebral fractures (eg, denosumab).

Furthermore, individualized sequencing or combination strategies remain insufficiently defined, underscoring unmet needs in specificity, safety, and durability of benefit.[45]

In recent years, exosomes have emerged as a promising therapeutic strategy, attracting attention for their natural origin, selectivity, adaptability, and minimal side effects.[46] The therapeutic advantage of exosomes in osteoporosis lies in their ability to modulate key cells involved in bone metabolism, such as osteoblasts and osteoclasts, thereby promoting bone formation and inhibiting bone resorption to improve bone mineral density and microarchitecture.[47,48] Beyond their established role as vesicular carriers, exosomes also provide cell-free delivery with low immunogenicity, inherent protection for unstable cargos, and compatibility with scalable bioprocessing and quality control frameworks.[49,50] They are amenable to targeted engineering approaches (eg, surface ligand display or cargo loading) to enhance homing to the bone microenvironment, regulate osteoblast–osteoclast crosstalk and antioxidant responses, and potentiate osteoanabolic signaling pathways associated with primary osteoporosis.[51]

While standard therapies are supported by extensive clinical trial data, exosome strategies remain largely preclinical, with no osteoporosis-specific human studies completed to date. Therefore, exosomes should currently be considered as potential adjuncts rather than replacements for established drugs, offering a promising avenue to address unmet needs in safety, durability, and tissue specificity.

Strength of Evidence

Reproducibility

Emerging strategies such as bone-targeting ligands, engineered cargo loading, and plant-derived exosome-like vesicles show convergent improvements in osteogenic endpoints, though effect sizes vary by source, isolation (dUC vs SEC/affinity), and loading method.

Model Limitations

Manufacturing heterogeneity, limited stability/transport data, and inconsistent reporting of negative markers, contaminants, endotoxin, and mycoplasma.

Translational Gaps

GMP-compatible scale-up, batch-release criteria (identity, purity, potency, safety), validated targeting performance benchmarks, and comparator-anchored efficacy frameworks versus bisphosphonates, denosumab, or anabolic agents are not yet established.

Advances in Exosome Therapy for Primary Osteoporosis

Recent Progress in Exosome Isolation and Purification Technologies

The isolation and purification of exosomes are essential prerequisites for their therapeutic application in osteoporosis. Conventional methodologies, including ultracentrifugation, density gradient centrifugation, and polymer-based precipitation, have been extensively employed. Nonetheless, these techniques are hindered by several limitations, such as prolonged processing durations, suboptimal purity, and restricted yield. In response to the increasing demand for exosome research and clinical applications, innovative isolation and purification technologies have been developed in recent years.

Microfluidic technology has emerged as a promising methodology due to its capabilities for high throughput, high resolution, and minimal sample consumption. By engineering specific physical or chemical environments within microchannels, microfluidics facilitates the efficient isolation and enrichment of exosomes. For instance, the use of inertial focusing and sieving effects within microfluidic chips enables precise separation of exosomes based on their size and shape, thereby significantly enhancing isolation efficiency and purity.[52] Additionally, immunoaffinity capture techniques exploit the specific binding interactions between antibodies and surface markers on exosomes to achieve selective isolation. While this method can further improve exosome purity, it necessitates the careful selection of appropriate markers and antibodies based on the exosome source and is often associated with higher costs. Concurrently, nanomaterial-based separation methods have garnered considerable attention. By leveraging the interactions between nanoparticles and

Table 3 Comparison of Exosome Isolation Methods: Principles, Advantages, Limitations, and Applications

Technology Category	Specific Method	Advantages	Limitations	Application Examples
Traditional Isolation Technique	Ultracentrifugation	Simple Operation, Low Cost	Low Purity, Potential Damage to structure of exosomes	Preliminary exosome enrichment
Emerging Isolation Technology	Microfluidic Chip	High Throughput, High Purity (>90%)	High Equipment Cost, Requires Optimization for Clinical Adaptation	Precise Isolation of Bone-Targeted Exosomes (eg miR-142-5p Carriers)
Chemical Loading	Estrogen Incubation/ Ultrasound Treatment	High Drug Encapsulation Efficiency (~70%)	May Affect the Integrity of the exosomal membrane	Treatment of Postmenopausal Osteoporosis
Genetic Engineering Modification	Bone-Targeting Peptide (DSS)6 Modification	Specifically Targets Bone Tissue (Accumulation Efficiency Increased by 50%)	Complex Manufacturing Process	(DSS)6-mEV-SRT2104 System (MRI-Visible Therapy)

Notes: Summary of major exosome isolation methods with core principles, typical input matrices, and use-case fit. Columns list yield and purity, EV integrity/bioactivity retention, co-isolated contaminants (eg, lipoproteins/albumin), scalability/throughput, hands-on time/cost, and recommended applications (discovery vs functional assays vs manufacturing).

Abbreviations: UC, ultracentrifugation; dUC, differential UC; SEC, size-exclusion chromatography; PEG, polyethylene glycol precipitation; TFF, tangential-flow filtration; IAC, immunoaffinity capture; MF, microfluidics.

exosomes, these methods facilitate rapid isolation and enrichment, offering advantages such as simplicity and high efficiency.[53] Microfluidic technology has emerged as a prominent candidate in the domain of exosome isolation, owing to its precise microscale manipulation and automation potential. Its label-free separation techniques not only streamline operational procedures and reduce both time and cost, but also effectively preserve the bioactivity of exosomes. However, existing microfluidic platforms encounter several challenges and limitations when processing clinical samples.[54] In addition to microfluidics, polyethylene glycol (PEG) precipitation remains a popular method due to its high yield and cost-effectiveness. Despite certain limitations in purity, the convenience and productivity of PEG precipitation make it a favored approach among researchers. The integration of PEG precipitation with other separation techniques can further enhance the efficiency and purity of exosome isolation.[55] Table 3 compares commonly used exosome isolation methods, highlighting principles, performance, and recommended applications across research and translational contexts.

Application of Exosome-Based Drug Delivery Systems in Osteoporosis Treatment

Exosomes, as intrinsic nanoscale carriers, exhibit remarkable biocompatibility, minimal immunogenicity, and robust cell-targeting capabilities, indicating significant potential in drug delivery applications. In the context of osteoporosis treatment, exosome-based drug delivery systems offer precise transport of therapeutic agents to lesion sites, thereby enhancing drug efficacy and reducing side effects. Researchers have developed a targeted drug delivery system by encapsulating estrogen within exosomes derived from BMMSCs. This approach not only preserves the inherent properties of exosomes but also significantly increases estrogen accumulation in bone tissue, supports BMMSC survival, and consequently improves therapeutic outcomes in the treatment of osteoporosis.[33] Additionally, various anti-osteoporotic agents, including simvastatin and icariin, have been encapsulated within exosomes in several studies. The exosome-mediated delivery of these drugs has demonstrated enhanced bioavailability and targeting efficiency, thereby augmenting their therapeutic efficacy against osteoporosis. Although exosome-based drug delivery represents a promising novel strategy for the treatment of osteoporosis, challenges persist concerning the low drug loading efficiency, as well as the stability and targeting capability of drug-loaded exosomes. These aspects require further optimization. Table 4 summarizes bone-targeting and delivery strategies for exosome-based therapies in primary osteoporosis.

Table 4 Challenges and Future Directions of Exosome Therapy for Osteoporosis

Category	Specific Content	Solutions/Research Directions
Isolation and Standardization Challenges	Current Methods (eg Ultracentrifugation) Have Low Purity and Efficiency; High Exosome Heterogeneity	Develop Efficient Isolation Methods Such as Microfluidic Technology and Immunoaffinity Capture; Establish Standardized Production Processes
Targeting and Drug-Loading Efficiency	Low Drug Loading Efficiency and Insufficient Targeting Ability	Enhance Exosome Targeting Through Surface Modifications (eg Bone-Targeting Peptides) and Genetic Engineering Optimization
Long-Term Safety and Efficacy	Limited Data from Animal Studies and Short-Term Clinical Trials; Long-Term Effects (eg Immune Response, Tumor Risk) Remain Unclear	Conduct Large-Scale, Long-Term Clinical Trials and Integrate Multidisciplinary Research to Assess Safety
Synergistic Treatment Strategies	The Synergistic Mechanisms with Conventional Drugs (eg Bisphosphonates) or Physical Therapies (eg Electrical Stimulation) Require Further Validation	Investigate the Combined Application of Exosomes with Existing Therapies and Optimize Synergistic Protocols

Notes: Summary of exosome-based bone-targeting and delivery strategies relevant to primary osteoporosis. Columns list the exosome source, targeting approach (eg, surface engineering or ligand decoration), cargo and loading method, route and dosing, targeting/biodistribution readouts, and reported effects on osteogenesis/osteoclastogenesis.
Abbreviations: EV, extracellular vesicle; MSC, mesenchymal stromal/stem cell; siRNA, small interfering RNA; miRNA, microRNA.

Strength of Evidence

Reproducibility

Emerging strategies such as bone-targeting ligands, engineered cargo loading, and plant-derived exosome-like vesicles show convergent improvements in osteogenic endpoints, though effect sizes vary by source, isolation (dUC vs SEC/affinity), and loading method.

Model Limitations

Manufacturing heterogeneity, limited stability/transport data, and inconsistent reporting of negative markers, contaminants, endotoxin, and mycoplasma.

Translational Gaps

GMP-compatible scale-up, batch-release criteria (identity, purity, potency, safety), validated targeting performance benchmarks, and comparator-anchored efficacy frameworks versus bisphosphonates, denosumab, or anabolic agents are not yet established.

Future Prospects of Exosome Therapy for Primary Osteoporosis

Clinical Application Challenges of Exosome Therapy for Osteoporosis

Despite the significant potential of exosome therapy for osteoporosis, its clinical application is hindered by several challenges. Primarily, the production and isolation techniques for exosomes have not been fully standardized, leading to issues with consistency and reproducibility in clinical settings. Current isolation methods often exhibit low purity and efficiency, thereby limiting the broader application of exosomes.[56,57] Exosomal heterogeneity remains a major obstacle to clinical translation, as variations in cell source, culture conditions, and isolation techniques contribute to batch-to-batch variability. This variability affects cargo content, targeting efficiency, and therapeutic predictability. Although recent advancements in single-vesicle profiling and high-throughput RNA sequencing may provide potential solutions, these techniques still require standardization for regulatory approval. To enhance the therapeutic efficacy of exosomes, researchers are investigating engineering modifications to optimize their targeting capabilities and drug-loading capacity.[58,59] In the realm of cancer therapy, exosomes are increasingly recognized as a promising drug delivery system due to their low immunogenicity and high biocompatibility, which facilitate the safe transport of therapeutic agents in vivo. Nonetheless, improving the drug-loading efficiency and targeting specificity of exosomes continues to be a significant area of research.[60,61] Furthermore, the utilization of exosomes in cancer immunotherapy has garnered

Table 5 Registered or Ongoing Exosome/EV Clinical Trials in Bone-Related Indications with TRL Assignment

Indication	Registry ID	Title/Intervention	Phase	Geography	Assigned TRL
Knee osteoarthritis	NCT05060107	Intra-articular MSC-derived small EVs (ExoOA-1)	Phase 1	Chile	TRL-6
Knee osteoarthritis	NCT06431152	Intra-articular UC-MSC exosome	Early Phase 1	Chile	TRL-6
Knee osteoarthritis	NCT06463132	PEP ± hyaluronic acid (Euflexxa)	Phase 1b	USA	TRL-6
Periodontitis with alveolar bone involvement	NCT04270006	Autologous adipose-derived stem-cell exosomes adjunctive to SRP	Early Phase 1	Egypt	TRL-6
Degenerative meniscal injury (knee)	NCT05261360	Autologous synovial MSC-derived exosomes, intra-articular	Phase 2	Turkey	TRL-7

Notes: Registered or ongoing exosome/extracellular vesicle clinical trials in bone-related indications with Technology Readiness Level (TRL) assignment (as of August 27, 2025). Trials were identified from ClinicalTrials.gov and mapped to TRLs using drug/biologic conventions. Early human safety studies (Phase 1 or Early Phase 1) correspond to TRL-6; Phase 2 corresponds to TRL-7. No osteoporosis-specific interventional exosome trials were identified as of the search date; listed bone/joint indications serve as clinical maturity anchors. Registry information is continually updated; readers should verify current status on the registry.
Abbreviations: EV, extracellular vesicle; UC-MSC, umbilical cord-derived mesenchymal stromal cell; PEP, purified exosome product; SRP, scaling and root planing; OA, osteoarthritis; TRL, Technology Readiness Level.

considerable attention, as they function as natural immune modulators capable of augmenting antitumor immune responses.[62] Despite these challenges, the potential for the clinical translation of exosomes remains expansive. Ongoing optimization of production and isolation methodologies, coupled with comprehensive investigations into their biological functions and mechanisms, may enable exosomes to assume pivotal roles in regenerative medicine, cancer therapy, and other domains.[63,64] Future research must persist in emphasizing standardized production, optimization targeting, and the application of exosome-based therapies across various diseases to facilitate successful clinical translation. Additionally, comprehensive investigation into the long-term safety and efficacy of exosome therapy is imperative. The majority of existing studies predominantly rely on animal models and short-term clinical trials, leaving the long-term effects in humans—such as potential immune responses or tumorigenic risks—insufficiently understood. Overcoming these challenges requires multidisciplinary collaboration, integrating expertise from materials science, biology, medicine, and related fields, to collectively advance the clinical translation of exosome-based therapies. Results remain heterogeneous across laboratories, and several studies report limited or null effects depending on isolation method, dose normalization, and biodistribution, underscoring the need for standardized protocols.

To contextualize clinical translation with a quantitative metric, we compiled registered or ongoing exosome/EV trials in bone-related diseases and mapped each to a Technology Readiness Level (TRL) according to drug/biologic conventions (Phase 1 ≈ TRL-6; Phase 2 ≈ TRL-7) (Table 5). This approach complements narrative appraisal by situating the field on a common maturity scale that is comparable across modalities and therapeutic areas.

As of August 27, 2025, osteoporosis-specific interventional trials were not identified; neighboring musculoskeletal indications (for example, knee osteoarthritis and periodontitis) have entered early human evaluation (TRL-6), with only limited programs progressing to Phase 2 (TRL-7) in joint conditions. Accordingly, most osteoporosis-focused exosome strategies remain at TRL-3 to TRL-5 (preclinical to IND-enabling). These data emphasize the need for standardized potency assays, exposure metrics (particles and protein), systematic biodistribution/safety packages, and comparator-anchored designs to bridge the gap to TRL-6+. These barriers delineate the near-term priorities for translation and are addressed in the next subsection.

Future Research Directions of Exosome Therapy for Osteoporosis

Future work should prioritize concrete, testable steps to advance exosome therapy toward clinical translation, rather than reiterating existing barriers. Standardized protocols for isolation, characterization, and potency assays will be essential to ensure reproducibility and regulatory compliance, and improved large-scale manufacturing techniques are needed to produce exosomes with consistent quality. For instance, further elucidation of the regulatory networks involving specific microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and proteins within exosomes on the functions of osteoblasts and osteoclasts will provide a theoretical foundation for designing exosome therapies with enhanced targeting capabilities.[65]

Conversely, a significant area of research is the optimization of exosome preparation and delivery technologies. The development of standardized and efficient large-scale production methods is essential for enhancing exosome yield and ensuring quality stability. Concurrently, advancements in exosome targeting and delivery techniques are crucial for improving specificity and delivery efficiency to bone tissue and specific cell types, while minimizing impacts on non-target tissues. Comparator-anchored early-phase studies will clarify positioning and support subsequent randomized trials with clinically meaningful outcomes. Through comprehensive research endeavors in these domains, exosome therapy holds promise as an effective strategy for the treatment of osteoporosis.

Strength of Evidence

Reproducibility

The preclinical signal across platforms supports a plausible therapeutic window, but heterogeneity in sources, characterization panels, and outcome measures constrains meta-analytic confidence.

Model Limitations

Current pipelines inadequately capture age-related biology, frailty, and long-term safety; most data derive from short-course interventions without chronic exposure assessments.

Translational Gaps

Clear patient selection, dose-finding rules, pharmacodynamic biomarkers, and comparator-controlled early-phase trials are needed, alongside regulatory-grade CMC documentation and long-term safety surveillance plans to enable sustainable clinical translation.

Conclusion

Exosome-based approaches for primary osteoporosis show encouraging preclinical efficacy across cell and animal models by enhancing osteo-anabolic signaling, modulating osteoclast activity, and mitigating oxidative stress. Their translational potential rests on rigorous standardization of source selection, isolation and characterization, cargo loading, and release criteria, together with robust biodistribution, targeting, and safety evaluation. Current evidence remains heterogeneous across laboratories, and some studies report limited or null effects, underscoring the need for harmonized protocols and dose normalization. Priority next steps include head-to-head comparisons with standard agents, mechanism-to-product alignment (including targeting strategies and quality control), validated pharmacodynamic biomarkers, and early-phase clinical trials designed to assess safety and preliminary efficacy. Overall, exosomes are promising adjuncts to existing therapies rather than immediate replacements, and focused translational work will determine their clinical value in primary osteoporosis.

Abbreviations

AD-MSC, adipose-derived mesenchymal stem cell; ALP, Alkaline phosphatase; BMSC, Bone Marrow Stromal Cells; BMMSCs, BMSC, bone marrow mesenchymal stem cells; CD44, cluster of differentiation 44; CD63, cluster of differentiation 63; CD9, cluster of differentiation 9; DN, denervated; DEX, Dexamethasone; EPC, electrical stimulation; ES, extracellular vesicle; EV, extracellular vesicle; EVs, extracellular vesicles; ERK, Extracellular signal-Regulated Kinase; GCLC, glutamate-cysteine ligase catalytic subunit; GFP, green fluorescent protein; GIOP, Glucocorticoid-Induced Osteoporosis; GSTP, glutathione S-transferase pi; hBMSC, human Bone Marrow-derived Mesenchymal Stem Cell; HucMSC, Human Umbilical Cord Mesenchymal Stem Cell; lncRNA, long non-coding RNA; MAPK, Mitogen-Activated Protein Kinase; MC3T3-E1, mouse calvaria pre-osteoblast cell line; MSC, Mesenchymal Stem Cell; NLRP3, NOD-like receptor family pyrin domain containing 3; NQO1, NAD(P)H quinone dehydrogenase 1; Nrf2, Nuclear factor erythroid 2–related factor 2; PDN, Prednisolone; PI3K-Akt, Phosphoinositide 3-Kinase – Protein Kinase B (PKB/Akt) signaling pathway; Raf, Rapidly Accelerated Fibrosarcoma; RUNX2, runt-related transcription factor 2; SPRED1, sprouty-related EVH1 domain-containing protein 1; SPRY1, sprouty homolog 1.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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