International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

The Emerging Roles of Nano Drug Delivery Systems in Treatment of Osteoporosis-Current Knowledge, Challenges and Future Perspectives

Peng Yin[1,2,*], Shilin Dong[1–3,*], Jiaoyang Yu[1,2,*], Zhengnan Zhao[1–3], Yunxiang Hu[1,2]

[1]Department of Orthopaedic Trauma, The Second Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, People's Republic of China; [2]School of Graduates, Dalian Medical University, Dalian, Liaoning, People's Republic of China; [3]Department of Hand and Foot Surgery, The Second Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhengnan Zhao, Department of Hand and Foot Surgery, The Second Affiliated Hospital of Dalian Medical University, No. 467 Zhongshan Road, Shahekou District, Dalian, Liaoning, 116027, People's Republic of China, Email zhengnanbx@163.com; Yunxiang Hu, Department of Orthopaedic Trauma, The Second Affiliated Hospital of Dalian Medical University, No. 467 Zhongshan Road, Shahekou District, Dalian, Liaoning, 116027, People's Republic of China, Email hooshawnzee@dmu.edu.cn

---

Abstract: Osteoporosis (OP) is a degenerative bone disease characterized by decreased bone mass and deterioration of bone tissue microstructure, which increases skeletal fragility and the risk of fractures. Currently, the drugs used clinically to treat OP are primarily classified into two types: bone resorption inhibitors and bone formation promoters. Although they demonstrate certain efficacy, most anti-OP medications do not specifically target bone tissue and may produce significant side effects. In recent years, bone-targeted therapies nano-drug delivery systems (NDDSs) for OP have gained attention due to their high drug loading capacity, strong targeting ability, ease of modification, and good biocompatibility. These characteristics effectively address the limitations of traditional therapies and have been widely applied in the treatment of OP. Therefore, this article systematically summarizes recent applications of NDDSs (including inorganic, organic, biogenic, and hybrid systems) in the treatment of OP, focusing on targeting design strategies, in vitro and in vivo efficacy validation, and clinical translation challenges, aiming to provide theoretical references for the development of the next generation of targeted nanomedicines.

Keywords: osteoporosis, nano-drug delivery systems, nanoparticles, nanomaterials, targeted therapy

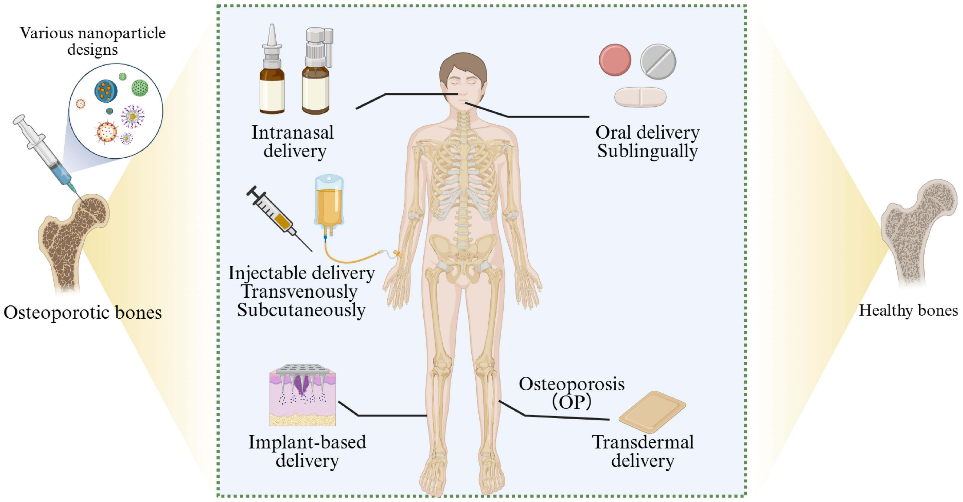
---

Introduction

Osteoporosis (OP) is a systemic bone metabolic disorder characterized by reduced bone mass and compromised bone microarchitecture, significantly increasing the risk of fractures, particularly threatening the health of elderly and postmenopausal women. Approximately 200 million people worldwide suffer from OP, leading to over 8.9 million fractures annually, resulting in a substantial economic burden on healthcare systems.[1,2] The core pathological mechanism underlying OP is an imbalance in bone remodeling: excessive bone resorption mediated by osteoclasts (OCs) and insufficient compensatory bone formation by osteoblasts (OBs), leading to dysregulation of the RANKL/OPG system and suppression of pro-osteogenic signaling pathways such as Wnt/β-catenin, alongside a chronic inflammatory and oxidative stress microenvironment.[3–5] Traditional OP treatments, primarily anti-resorptive agents like bisphosphonates and denosumab, and anabolic agents such as teriparatide, exhibit notable limitations. These include low bioavailability, as oral bisphosphonates have a gastrointestinal absorption rate of less than 1%, necessitating high doses and frequent administration. Additionally, off-target toxicity is a concern; bisphosphonates can induce osteonecrosis of the jaw, while estrogen therapies are associated with an increased risk of thrombosis. Furthermore, these treatments are often single-target, struggling to concurrently modulate both bone resorption and formation. Prolonged use may also result in "adynamic bone", highlighting the need for more effective therapeutic strategies.[6–8] Nano-drug delivery systems

Received: 12 May 2025
Accepted: 28 August 2025
Published: 10 September 2025

Graphical Abstract



(NDDSs) leverage the distinctive physicochemical properties of nanomaterials, presenting innovative solutions for osteoporosis treatment. These systems enable precise targeting through surface modifications that enhance drug accumulation in bone tissue and facilitate controlled release in response to the acidic pH or elevated reactive oxygen species (ROS) present in pathological environments.[9,10] They enable synergistic delivery by co-loading anti-resorptive drugs (such as siRNA to silence RANK) with osteogenic factors (like BMP-2) for "bidirectional regulation.[11–13] Additionally, polymeric nanoparticles (such as PLGA) can extend the drug half-life, reducing dosing frequency;[14] and nanonization improves the solubility of hydrophobic drugs (such as raloxifene), allowing them to penetrate the dense matrix of bone tissue.[15] This article offers a comprehensive overview of the recent applications of NNDSs, encompassing a range of materials including inorganic, organic, biogenic, and hybrid systems, in the treatment of osteoporotic conditions. It emphasizes the design strategies aimed at targeted delivery, the validation of efficacy through both in vitro and in vivo studies, and the challenges associated with clinical translation. The objective of this review is to provide valuable theoretical insights that will support the development of the next generation of targeted nanomedicines, thereby advancing therapeutic strategies for osteoporotic patients.

Differences Between Traditional Treatments and NDDSs

Traditional pharmacological treatments for OP primarily fall into two categories: anti-resorptive drugs and anabolic agents, aimed at restoring the balance of bone metabolism (suppressing osteoclast activity or stimulating osteoblast function) to improve bone density. Below are the main drug classifications and their mechanisms of action.[16] Anti-resorptive medications, which aim to inhibit bone loss, include bisphosphonates such as alendronate, zoledronic acid, and risedronate. Their mechanism of action involves the inhibition of osteoclast activity and the induction of apoptosis through selective binding to bone hydroxyapatite, resulting in deposition at sites of bone resorption.[17,18] Selective estrogen receptor modulators, such as raloxifene, mimic estrogen's protective effects on bone by suppressing osteoclast activity while avoiding stimulation of breast and endometrial tissues. They are particularly suitable for postmenopausal women, as they reduce the risk of breast cancer; however, they may increase thrombosis risk and are contraindicated in individuals with a history of thrombotic events.[19] RANKL inhibitors, such as denosumab, function by specifically binding to RANKL, thereby blocking osteoclast differentiation and activation.[20] Hormone replacement therapy includes drugs like estradiol and conjugated estrogens, which directly supplement estrogen levels to inhibit bone resorption.[21] Anabolic agents, such as PTH analogs teriparatide and abaloparatide, stimulate new bone formation by intermittently activating PTH receptors, which promotes the proliferation and differentiation of osteoblasts.[22] Sclerostin inhibitors, such as romosozumab, function by inhibiting sclerostin, thereby promoting bone formation while simultaneously suppressing bone resorption.[23] Other adjuvant therapies include calcium and vitamin D supplements, with recommended dosages of 1000–1200 mg/day and 800–2000 IU/day, respectively. These nutrients are essential for all osteoporosis treatments, as they help maintain calcium balance, enhance intestinal calcium absorption, and support bone mineralization. Additionally, vitamin K2 activates osteocalcin, promoting calcium deposition in bone tissue.[24] Strontium ranelate demonstrates dual actions by weakly stimulating bone formation and inhibiting bone resorption; however, its use is restricted in Europe due to associated cardiovascular risks.[25] NDDSs enhance the pharmacokinetic profiles of drugs by specifically targeting active pharmaceutical ingredients to lesions and regulating drug release. Recent advancements in nanotechnology have significantly increased the potential of NDDSs in the medical field, making them a focal point of research.[26–28] Common nanomaterials used in OP treatment include organic materials, inorganic materials, biologically derived materials, hybrid materials in general.[29–33] (Table 1, Figure 1)

Representative Delivery Approaches of NDDSs in OP

The current administration methods primarily include intravenous, sublingual, subcutaneous, implantation, intranasal, and transdermal routes. Each drug administration route presents specific limitations. Intravenous methods require skilled personnel and pose infection risks, while sublingual routes are limited to small doses and may compromise patient compliance due to taste. Subcutaneous injections have slower absorption rates and can cause irritation, making them suitable for limited volumes. Implantation methods, though effective for sustained release, are invasive and carry risks of infection and rejection. Intranasal delivery suffers from variable absorption and limited volume capacity, potentially leading to discomfort. Lastly, transdermal systems are restricted to small molecular weight drugs and can cause skin irritation, with absorption variability among individuals. These challenges highlight the need for innovative solutions to optimize drug delivery across various routes.[34–36] Nanomaterials provide innovative solutions for overcoming biological barriers in drug delivery across various administration routes. Intravenous and subcutaneous delivery of nanohydroxyapatite (nHA), nanocomposites like nCh/HA, and silver nanoparticles (nAg/HA) effectively repress biomarkers associated with bone turnover in osteoporotic models, enhancing bone health. A study by Fouand-Elhady et al demonstrated that treatment with nHA, nCh/HA, or nAg/HA resulted in significant repression of serum SOST, BALP, and BSP levels, accompanied by a notable down-regulation of RANKL and CtsK gene expression. Conversely, a significant enhancement in the calcification intensity of femoral bone was observed. These findings underscore the potential of nHA, nCh/HA, and nAg/HA as promising nanomaterials for mitigating excessive bone turnover in a primary osteoporotic rat model.[37] Sublingual delivery of SCT-HAP-NPs yields comparable pharmacodynamic effects to subcutaneous injections, offering a non-invasive alternative that bypasses gastrointestinal barriers. Kotak et al reported a significant and comparable improvement in serum biomarkers, alongside increases in bone mass and mechanical strength, and decreases in bone erosion when compared to subcutaneous SCT, in an ovariectomized (OVX) OP rat model. The comparable pharmacodynamic effects at equivalent dosages suggest that sublingual SCT-HAP-NPs may serve as a non-invasive alternative to injection for targeted bone delivery.[38] By implanting in a femur defect, Qayoom et al provided proof of concept for the application of exosomes in bone regeneration therapy, proposing that they could function as a booster dose to reduce the overall dosage of bone morphogenetic protein (BMP), thus addressing the limitations associated with BMP use.[39]

Table 1 Advantages and Disadvantages of Different Types of Nano-Delivery Materials

Material Type	Representative Materials	Advantages	Limitations
Organic materials	Liposomes; PLGA; Chitosan	Good biocompatibility; Biodegradable	Limited drug loading capacity; Low mechanical strength
Inorganic materials	HAP; MSNs; CeO_2	High stability; Strong bone targeting	Poor biodegradability; Potential toxicity
Biologically derived materials	Exosomes; Cell membrane NPs	Low immunogenicity; Natural targeting	Difficult separation; High cost
Hybrid materials	HAP-chitosan; MSN-liposome; Chitosan-gold	Multifunctional synergy; Optimized performance	Complex preparation processes

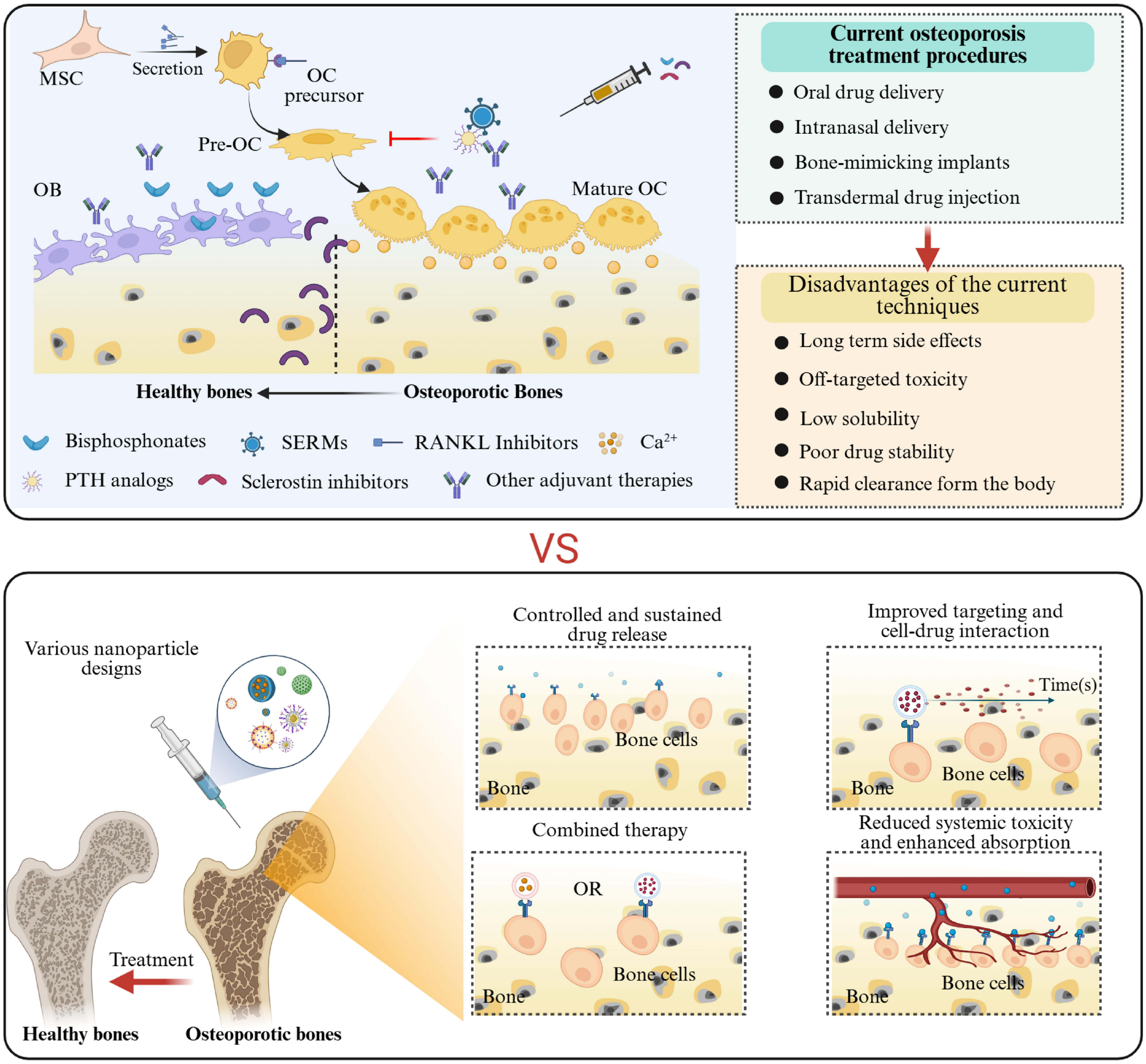


Figure 1 A schematic illustration comparing conventional treatment methods and NDDSs therapies for OP. Traditional treatments, such as bisphosphonates and hormones administered orally or intranasally, have significant drawbacks, including long-term side effects, low solubility, and poor stability. NDDSs offer a promising alternative by enabling controlled and sustained drug release, enhanced targeting, and reduced systemic toxicity.
Abbreviations: MSC, Mesenchymal stem cells; OB, Osteoblast; OC, Osteoclast.

Additionally, polymer brush-modified MHA systems facilitate sustained release of hydrophobic drugs like simvastatin, optimizing therapeutic levels at target sites while promoting osteogenesis. Self-assembled nanomicelles, such as CIT-SO-DOC, further improve bioavailability by enhancing absorption through reduced particle size, significantly benefiting antiosteoporosis therapies. Wu et al found that a polymer brush-modified MHA system offered a sustained release mechanism for hydrophobic SIM to inhibit OP, while MHA nanoparticles promoted osteogenesis. This innovative strategy demonstrated significant potential for enhancing osteogenic capacity and treating local osteoporotic defects.[40] Jiang's research indicated that the increased antiosteoporosis effects and bioavailability of CIT-SO-DOC self-assembled nanomicelles were attributed to enhanced absorption of CIT through reduction in particle size. SO may serve as an effective oral carrier for antiosteoporosis drugs with low bioavailability.[41] In intranasal applications, poly(lactic-co-glycolic) acid (PLGA-based) polymeric nanoparticles for risperidone (RIS) have shown promise in navigating nasal mucosal barriers for systemic effects in OP treatment. Fazil et al successfully prepared polymeric nanoparticles of RIS using a biodegradable polymer PLGA, with intranasal delivery yielding promising results in vivo. Thus, PLGA-NPs hold substantial potential for delivering RIS in the treatment and prevention of OP, pending clinical evaluation in the near future.[42] A nanoemulsion gel formulation of fluvastatin enhances transdermal delivery by improving drug penetration through the skin barrier. Kaur et al developed a nanoemulsion gel formulation of fluvastatin, which showed enhanced potential for transdermal delivery in the treatment of OP[43] (Figure 2 and Table 2). Overall, nanomaterials enhance drug delivery by improving targeting, bioavailability, and sustained release, effectively overcoming biological barriers across various administration routes.

Organic Nanomaterials

Liposomes consist of phospholipid bilayers encapsulating an aqueous core, allowing them to carry both hydrophilic and hydrophobic drugs. Their advantages include high biocompatibility (eg, DOPC, DSPE-PEG) and the ability to achieve prolonged circulation through PEG modification or active targeting using peptide modifications.[44,45] Xu et al concluded that the NLRP3 inflammasome may serve as a novel biomarker for the diagnosis of postmenopausal osteoporosis (PMOP) and plays a critical role in its pathology. The use of CH6-LNPs-siNLRP3 presents potential therapeutic applications for the treatment of PMOP.[46] Nirwan et al demonstrated that aspartic acid conjugate (PAL-DPPE)-based bone-targeted liposomes containing linagliptin show promise for OP treatment. Furthermore, the mechanistic pathways involved in this effect appear to include the Wnt and AMPK signaling pathways.[47] Chitosan, a positively charged polymer, can bind nucleic acids like siRNA and exhibits mucosal adhesion due to its electrostatic interactions with negatively charged mucosal surfaces. This attraction enhances its binding to mucosal tissues, thereby prolonging drug retention time.[48] Sandomierski et al found that newly developed scaffolds (chitosan-calcium zeolite) effectively retain the drug and facilitate its slow release in small doses. The results obtained are promising and indicate significant potential for this material in bone tissue engineering.[49] Snega et al found that polymer-based nanoconjugates like CH-CS-DZ can effectively mitigate OP through targeted delivery and sustained release, offering a potent strategy for bone health restoration.[50] Hyaluronic acid (HA), a polysaccharide found in connective tissues, has been shown to promote osteoblast proliferation, enhance alkaline phosphatase activity, and increase mineral deposition and the expression of bone differentiation markers such as Runx2 and osteocalcin.[51,52] Tenger et al[53] demonstrated that depletion of high-molecular-weight HA (HMW-HA) from culture media, induced by hyaluronidase treatment, led to increased RANKL expression in the ST2 bone marrow stromal cell line. These findings indicate that HMW-HA may mitigate OVX-induced bone loss by downregulating osteoclast formation and/or activity in mice. Nanogels are nanoscale gel particles, typically

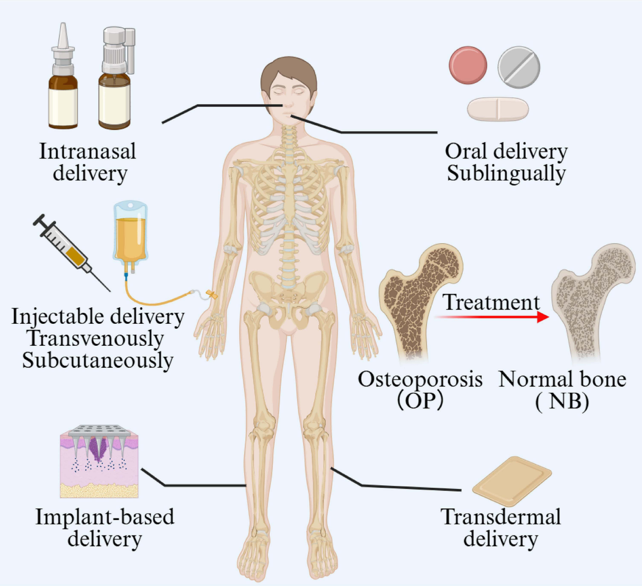


Figure 2 Representative approaches for the delivery of NDDSs in OP.

Table 2 Representative Approaches for the Delivery of NDDSs in OP

Authors	**Treatment Method**	**Main Characteristics of Nanomaterial**	**Main Results**	**Reference**
Fouand-Elhady et al, 2020	Intravenously	nHA, nCh/HA and nAg/HA (25.5, 28.85 and 22.73 nm)	↓SOST, BALP, BSP, RANKL, CtsK and ↑calcification in all groups vs OVX only	[37]
Kotak et al, 2020	Injected sublingually or subcutaneously	HA-NPs (100 nm) loaded with SCT	↓serum ALP, Ca, P, erosions, porosity, resorption pits and ↑bone density and strength in all groups vs saline	[38]
Qayoom et al, 2020	Implanted in a femur defect	NC functionalized with BMP-2, ZOL or EXO	↑mineralization, BV/TV, Tb.N, ↓Tb.Sp in all groups vs NC. ↑peak fracture force in NC-BMP-2-ZOL vs all groups	[39]
Wu et al, 2020	Loaded with SIM (MHA-SIM-P) on femur defects	MHA-P NPs (4 nm pores) loaded with SIM	↑BV/TV, Tb.N, OPN, BSP and ↓Tb.Sp, OCs number in MHA-SIM-P vs all groups	[40]
Jiang et al, 2015	Administrated orally	CIT-SO-DOC nanomicelles (204.77 ± 6.81 nm and 100.80 ± 7.21 nm)	↑BMD, BMC, TMC, TMD, VOB, Tb.Th, BV/TV, Tb.N, energy to failure, stiffness, ultimate load, OPG, OCN, OPG and ↓Tb.Sp, BS/BV, CalibTbSp3D, HOP, ALP, TRACP-5b and RANKL in EV, CIT (40, 20 mg/kg) and CIT-SO (40, 20 mg/kg) vs OVX only, and in CIT-SO vs CIT	[41]
Fazil et al, 2016	Delivered intranasally	PLGA-NPs loaded with RIS (184.87 ± 4.33 to 77.86 ± 8.67 nm)	↓ALP, creatinine, ALT, AST and ↑Ca in all groups vs OP only	[42]
Kaur et al, 2019	Transdermally	NE gel (11–123 nm) loaded with LNG	↓ALP, BALP, CTx, TRACP-5b, ↑Ca, P, OCN, PINP, Young's modulus, peak load in LNG5 and LNG10 groups vs OP only. ↑BV/TV, Tb.Th, Tb.N and ↓Tb.Sp in all groups vs OP only	[43]

Notes: ↑, upgraded; ↓, downgraded.

https://doi.org/10.2147/IJN.S539879

1 to 100 nm in size, formed from a cross-linked polymer network. They combine the high water content of hydrogels with the benefits of nanomaterials, making them suitable for diverse applications in biomedical fields, drug delivery, cosmetics, and beyond.[54] Ansari et al demonstrated that the transdermal administration of RLX-spanlastic nanogel significantly enhanced drug bioavailability—approximately double that of oral administration—without any toxic effects observed in treated rats. This suggests that spanlastic nanogel may represent a superior approach for transdermal delivery of RLX in the management of OP.[55] Cui et al[56] reported that PNG@mRandC exhibited satisfactory therapeutic effects in an OVX mouse model. This study introduces a new paradigm for re-establishing bone metabolic homeostasis through multiple targets, showing great promise for the treatment of PMOP. Gelatin is a natural polymer derived from the partial hydrolysis of collagen, widely utilized in food, pharmaceuticals, cosmetics, and tissue engineering.[57] Li et al concluded that their findings indicate the strontium ranelate loaded gelatin nanoparticle/silk fibroin aerogel (S/G-Sr-MT) scaffold could effectively stimulate the osteogenic differentiation of OBs while inhibiting osteoclast activity in vivo. In vivo studies demonstrated that S/G-Sr-MT exhibits significant osteogenic capacity in calvarial defects of ovariectomized rats, with elevated Runx2 expression and reduced TRAP activity. These findings highlight the potential osteogenic properties and clinical applicability of the strontium (Sr)-incorporated enzyme-cross-linked scaffold for healing OVX bone.[58] Mg^{2+} (magnesium ion) influences bone tissue metabolism by modulating signaling pathways associated with bone metabolism.[59] Huang et al concluded that this innovative strategy effectively addresses the issue of precise controlled release of Mg^{2+}, ultimately facilitating in situ bone tissue regeneration.[60] PLGA, an FDA-approved synthetic polymer, enables controlled degradation over 2 to 6 months, making it ideal for long-acting sustained release applications, such as microspheres for teriparatide delivery.[61] Guan et al conducted in vivo and in vitro experiments that demonstrated that ZOL-PLGA@Yoda1/SPIO can activate Piezo1 in the bone defect areas of osteoporotic mice. This activation enhances osteogenesis through the YAP/β-catenin signaling axis, promotes a well-coordinated coupling of osteogenesis and angiogenesis, and significantly accelerates the reconstruction of bone within the defects, all without noticeable side effects. Overall, this innovative dual-targeting nanocarrier presents a potentially effective strategy for the clinical treatment of osteoporotic bone defects.[62] Lee et al reported that, based on the observed synergistic effects, OP can be suppressed, and bone regeneration can be achieved by inhibiting the RANKL pathway in both in vitro and in vivo settings, which is a well-established mechanism in bone physiology. Consequently, this study offers a promising approach for developing multifunctional regenerative materials aimed at sophisticated osteoporotic bone regeneration.[63] PEG-PCL is a block copolymer of polyethylene glycol (PEG) and polycaprolactone (PCL) that combines the advantageous properties of both components, making it suitable for various biomedical applications.[64] Wang et al indicated that NOB-PEG-PCL micelles effectively inhibit the rapid release of NOB from the micelles, thereby extending its circulation time. This delivery system has potential as a promising strategy for the prevention and treatment of OP.[65] Polyurethane nanomicelles are nanoscale colloidal structures formed through the self-assembly of polyurethane block copolymers in a solvent. These nanomicelles typically feature a hydrophobic core and a hydrophilic shell, enabling them to encapsulate hydrophobic drugs while maintaining stability in aqueous environments.[66] Cai et al demonstrated that this delivery system can encapsulate and selectively deliver miRNAs to OSCAR+ OCs at the bone-resorption surface in vivo, without causing overt toxicity or eliciting an immune response. Utilizing the Asp8-PU delivery system, anti-miR214 was effectively delivered to OCs, resulting in improvements in bone microarchitecture and bone mass in OVX OP mice. Consequently, Asp8-PU may serve as a valuable targeting delivery system for addressing osteoclast-induced bone diseases and age-related OP.[67]

Inorganic Nanomaterials

Hydroxyapatite (HAP) is a biomaterial extensively utilized in clinical applications and pharmaceuticals. Research on HAP-based materials primarily focuses on their chemical characterization and biocompatibility.[68] Yu et al concluded that in vivo experiments indicated that the ALN-PEG-PSI-HAP formulation (with an ALN-PEG/PSI molar ratio of 1:20) was the most effective preparation due to its superior distribution in bone (120 hours) and reduced distribution in other tissues. The formulated nanoparticles were characterized as uniformly spherical or sphere-like with a negative zeta potential. Furthermore, they demonstrated pH-sensitive drug release in phosphate-buffered saline (PBS) as determined by in vitro drug release tests. Polysuccinimide-hydroxyapatite (PSI-HAP) was prepared in an aqueous solution using a simple method that avoids ultrasound, heating, and other conditions that could compromise drug stability.[69] Mesoporous silica nanoparticles (MSNs) have a high drug loading capacity, making them ideal for delivering agents like estrogen or raloxifene. They can also be surface-modified with targeting ligands, such as RGD peptides, which interact with integrin's RGD-binding sites to help alleviate osteoporosis.[70–73] Cerium oxide (CeO_2) is a recognized catalyst in the petrochemical industry and one of the earliest antioxidant nanoparticles proposed for medical use. Despite its toxicity, it is now regarded as a promising therapeutic alternative.[74,75] Li et al found that CeO_2-incorporated HAP coatings effectively reversed the reduction in superoxide dismutase (SOD) activity, diminished ROS generation, and suppressed malondialdehyde (MDA) formation. These findings suggest that CeO_2-modified HAP coatings may serve as promising materials for osteoporotic bone regeneration.[76]

Biologically Derived Materials

Exosomes can be derived from various cell types, including mesenchymal stem cells (MSCs) and OBs. They possess a natural targeting capability, such as the homing effect to bone marrow, and are capable of carrying bioactive molecules, including proteins and microRNAs. Zhan et al found that Pueraria lobata-derived exosome-like nanovesicles (PELNs) show promise as a therapeutic approach for OP, with trimethylamine N-oxide (TMAO) identified as a potential target for OP treatment[77] (Figure 3). Bionic nanoparticles, coated with membranes derived from OCs or osteoblasts OBs,

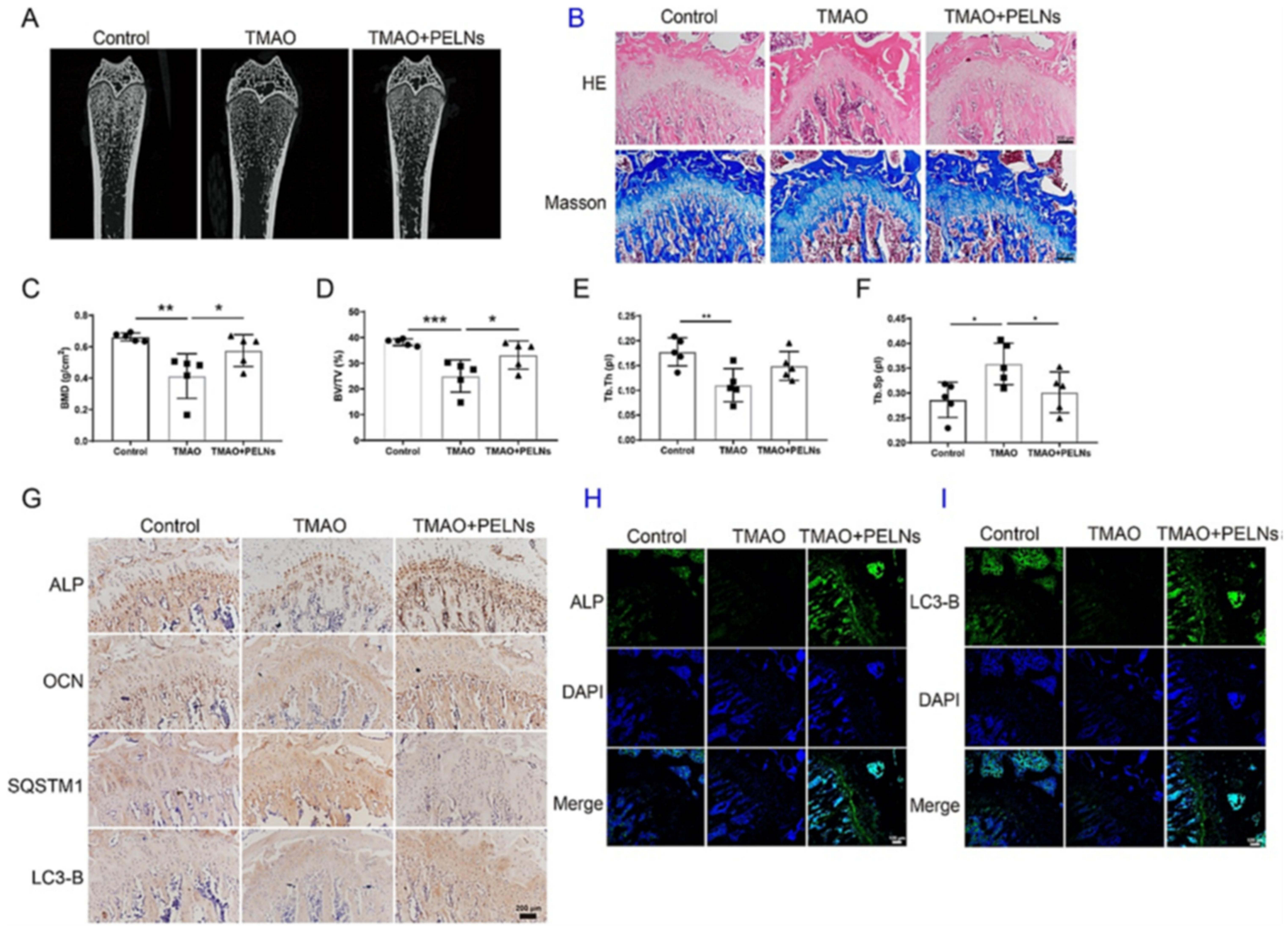


Figure 3 Pueraria lobata-derived exosome-like nanovesicles (PELNs) promote osteogenesis in TMAO-induced SD rat. (**A**) Micro CT pictures of the distal femur in SD rat by treatment with TMAO and PELNs. (**B**) Representative photographs of H&E and Masson's trichrome staining of osteocalcin in femurs treated with TMAO and PELNs (**C**–**F**) Quantification of BMD, BV/TV, Tb.Th and Tb.Sp in femur tissues (n = 5). (**G**) IHC staining of ALP, OCN, SQSTM1 and LC3B in rat femur paraffin sections. (**H**) IF staining of ALP in rat femur paraffin sections. (**I**) IF staining of LC3B in rat femur paraffin sections. Scale bars represent 200 μm. Data represent means ± SD at least 3 separate experiments. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. Figure 3 is reproduced with permission from Zhan W, Deng M, Huang X et al. Pueraria lobata-derived exosome-like nanovesicles alleviate osteoporosis by enhacning autophagy. J Control Release. 2023; 364:644–653. © *2023 The Authors. Published by Elsevier B.V.* CC BY-NC 4.0.[77]

demonstrate immune evasion through macrophage membrane camouflage and enable homologous targeting, such as osteoclast membrane targeting of bone resorption sites.[78] Su et al demonstrated that MSC-derived cell membrane (MSCM) coating promotes macrophage polarization toward a regenerative phenotype, induces apoptosis in CD8+ T cells, and enhances regulatory T cell differentiation both in vitro and in vivo. When combined with a low dosage of bone morphogenetic protein-2 (BMP-2), MSCM coating further accelerates bone regeneration and suppresses inflammation. These findings establish cell membrane-coated microribbon scaffolds as a promising strategy for the treatment of critical-size bone defects through immunomodulation. This platform may be broadly applicable to various cell membranes and scaffolds to enhance the regeneration of multiple tissue types.[79]

Hybrid Materials

Inorganic-organic composites, such as hydroxyapatite (HAP)-chitosan microspheres, leverage HAP's bone-binding capabilities and chitosan's ability to enhance drug loading efficiency.[80] MSN-liposomes combine MSNs for drug loading with a lipid layer that improves biocompatibility. Rasool et al explored the application of MSNs in bone tissue engineering and OP treatment as a composite system that incorporates metals such as gold and cerium, or as nanocarriers loaded with growth factors or active drugs. This study presents a straightforward and cost-effective method to enhance the properties of MSNs and introduce new functionalities through a single-step surface modification. The findings suggest that MSN-SH may serve as a complementary and alternative treatment for OP alongside standard therapies.[71] Nah et al investigated chitosan-gold nanoparticles (Ch-GNPs) and found that the fabricated gold nanoparticles (VGNPs) significantly enhanced the osteogenic differentiation of human adipose-derived stem cells (hADSCs) in vitro. These findings suggest that VGNPs are promising functional nanomaterials for bone regeneration in tissue engineering.[81] Takanche et al reported that c-myb delivered via Ch-GNPs supports the osseointegration of dental implants, even under osteoporotic conditions. This suggests that c-myb may be a viable option for enhancing dental implant integration and treating age-related bone degradation diseases[82] (Table 3 and Figure 4).

Table 3 Representative NDDSs in Treatment of OP

Author	Material	Drug	Effects	Reference
Xu et al	Liposome nanoparticles	–	CH6-LNPs-siNLRP3 show potential for treating PMOP.	[46]
Nirwan et al	Liposome nanoparticles	Linagliptin	The findings demonstrate that aspartic acid conjugate (PAL-DPPE)-based bone-targeted liposomes of linagliptin hold promise for the treatment of osteoporosis.	[47]
Sandomierski et al	Chitosan	Risedronate	The results are promising, highlighting the material's potential in bone tissue engineering.	[49]
Snega Priya et al	Chitosan (CH), chondroitin sulfate (CS), and daidzein (DZ)	Antiosteporotic drugs	CH-CS-DZ can effectively address osteoporosis through targeted delivery and sustained release, providing a robust strategy for bone health restoration.	[50]
Tenger et al	Hyaluronic Acid	Hyaluronic Acid	HMW-HA is a potential novel therapeutic agent for osteoporosis.	[53]
Ansari et al	Nanogel	Raloxifene	Spanlastic nanogels may offer an improved transdermal delivery method for RLX in osteoporosis management.	[55]
Cui et al	Nanogel	-	PNG@mRandC exhibits satisfactory therapeutic effects in the ovariectomized (OVX) mouse model.	[56]
Li et al	Enzyme-cross-linked gelatin	Strontium ranelate	These findings underscore the osteogenic potential and clinical applicability of enzyme-cross-linked SR scaffolds in bone healing post-ovariectomy (OVX).	[58]
Huang et al	Gelatin	Bisphosphonate	This innovative strategy effectively addresses the precise controlled release of Mg^{2+}, promoting in situ bone tissue regeneration.	[60]
Guan et al	PLGA	-	This novel dual-targeting nanocarrier provides a potentially effective strategy for the clinical treatment of osteoporotic bone defects	[62]

(*Continued*)

Table 3 (Continued).

Author	Material	Drug	Effects	Reference
Lee et al	PLGA	-	The study presents a promising approach for developing a multifunctional regenerative material for sophisticated osteoporotic bone regeneration.	[63]
Wang et al	NOB-PEG-PCL micelles	Nobiletin	The NOB-PEG-PCL delivery system may be a promising way to prevent and treat osteoporosis.	[65]
Cai et al	Polyurethane (PU) nanomicelles	Acidic peptide Asp^8	Asp^8-PU could be a useful bone-resorption surface-targeting delivery system for treatment of osteoclast-induced bone diseases and aging-related osteoporosis.	[67]
Yu et al	HAPs	Tanshinol	The proposed PSI-HAP preparations were developed in aqueous solution using a simple process that avoids ultrasound, heating, and other conditions that could compromise drug stability.	[69]
Rasool et al	MSN	Thiol	MSN-SH holds promise as a complementary and alternate treatment for osteoporosis along with the standardized therapy.	[71]
Li et al	CeO_2-incorporated HA	CeO_2	The findings suggested that CeO_2-modified HA coatings may be promising coating materials for osteoporotic bone regeneration[66]	[76]
Zhan et al	Exosome	Pueraria lobata	PELNs demonstrate promise as a therapeutic approach for OP, with TMAO emerging as a potential target of OP treatment.	[77]
Su et al	Cell membrane-coated NPs	-	It is demonstrated that MSCM coating promotes macrophage (Mφ) polarization toward regenerative phenotype, induces CD8+ T cell apoptosis, and enhances regulatory T cell differentiation in vitro and in vivo.	[79]
Nah et al	Gold nanoparticles	Vitamin D	VGNPs can be utilized as functional nanomaterials for bone regeneration in the tissue engineering field.	[81]
Takanche et al	Chitosan-gold	c-myb	The c-myb may be applicable to support dental implant integration and treatment in age-dependent bone destruction disease.	[82]

Future Development Directions

Smart responsive systems employ multiple mechanisms to target specific conditions in osteoporotic lesions. These include a pH response that targets the acidic environment (pH 4.5–5.5) characteristic of osteoclast resorption areas, an enzyme response that activates in regions with elevated matrix metalloproteinase (MMP-2/9) expression, and a redox response that reacts to high levels of ROS present in these lesions.[83–85] The system also incorporates external triggers for drug release, including near-infrared (NIR) controlled release, which employs gold nanorods for targeted drug delivery, and ultrasound-activated microbubble carriers that utilize lipid microbubbles loaded with bone morphogenetic protein-2 (BMP-2).[86,87] Yu et al developed nanoparticles responsive to the osteoclast microenvironment by incorporating Oroxylin A with amorphous calcium carbonate (ACC) and coating them with glutamic acid hexapeptide-modified phospholipids. These smart nanoparticles, designated as OAPLG, are capable of instantly neutralizing acidity and releasing Oroxylin A in the extracellular microenvironment. The combination of Oroxylin A and ACC works synergistically to inhibit osteoclast formation and activity, resulting in a significant reversal of systemic bone loss in an ovariectomized mouse model[88] (Figure 5). Chen et al demonstrated that smart implants featuring controlled release of bioactive agents provide a comprehensive solution for enhancing bone-implant integration, particularly under conditions of oxidative stress.[89] Multimodal therapy aims to overcome the limitations of single-drug approaches by integrating drug combinations, gene therapy, and immunoregulation. This strategy often involves pairing anti-resorptive agents like bisphosphonates with osteogenic agents such as bone morphogenetic protein-2 (BMP-2).[90] Gene-drug co-delivery strategies may include concurrent delivery of small interfering RNA (siRNA) targeting RANK with small molecule drugs like raloxifene.[91,92] Additionally, nanoparticles loaded with interleukin-4 (IL-4) can promote M2 macrophage polarization, inhibiting osteoclast activity.[93] Lee et al demonstrated that nanoparticles containing bioactive agents, including zinc oxide (ZO), alendronate, and BMP-2, can be integrated into a biomimetic scaffold. This scaffold imparts multifunctionality, offering anti-inflammatory properties, promoting angiogenesis, inhibiting osteoclastogenesis, and facilitating bone regeneration.

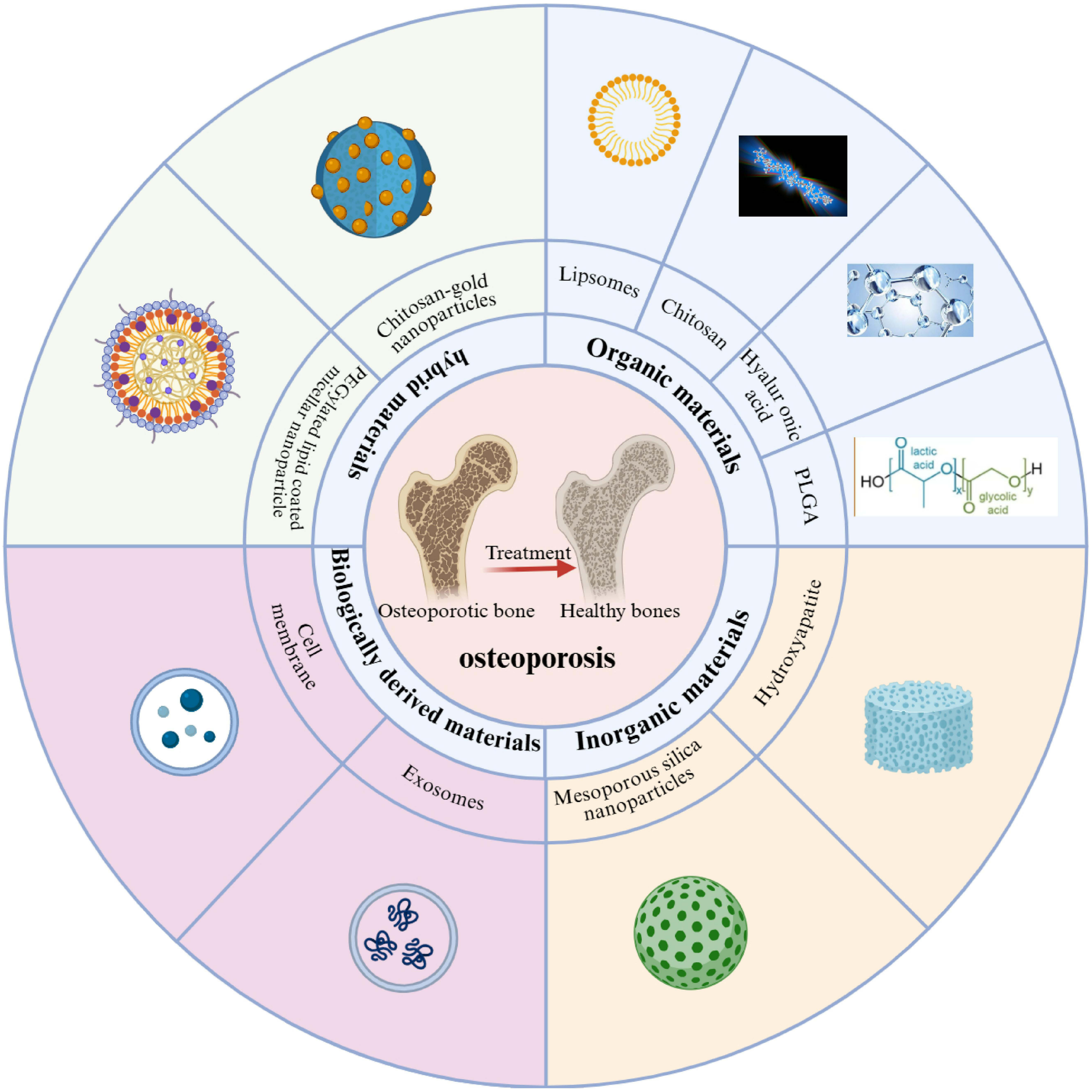


Figure 4 Main materials used as NDDSs against OP in this review, including chitosan, hyaluronic acid, and PLGA, which are macromolecules that can be engineered into various forms—such as microspheres, nanogels, dendrimers, polymeric micelles, and hydrogels—for biomedical applications. Hydroxyapatite, a small molecule or particle, is typically utilized in the form of sponges or porous scaffolds.

Notably, nitric oxide (NO) generated from ZO stimulates cyclic guanosine monophosphate (cGMP) and protein kinase G activity, while ZO also downregulates the RANKL/osteoprotegerin ratio by inhibiting the Wnt/β-catenin signaling pathway. In osteoporotic rat models, the formation of new bone was significantly enhanced compared to normal models, indicating the scaffold's effectiveness in regulating bone homeostasis. These synergistic effects suggest that such bioinspired scaffolds could provide a comprehensive strategy for exceptional bone regeneration[90] (Figure 6).

Bioinspired delivery and cell membrane camouflage technologies. The primary aim is to utilize natural carriers to enhance targeting efficiency and biocompatibility in therapeutic applications. Exosomes derived from mesenchymal stem cells (MSCs) are known to transport osteogenesis-related microRNAs, such as miR-29b.[94,95] Cell membrane-coated nanoparticles are designed with osteoclast membranes to specifically target bone resorption areas, while red blood cell membranes are used to prolong circulation half-life.[96] Zhang et al demonstrated that the formulation ALN@BMSCM@PLGA-TK-PEG-SS31 exhibited dual effects on bone tissue in vitro, significantly inhibiting RANKL-induced osteoclastogenesis in the presence of hydrogen peroxide (H_2O_2) and promoting osteogenic differentiation in bone marrow-derived stem cells (BMSCs). In a mouse model of ovariectomy-induced OP, this formulation significantly

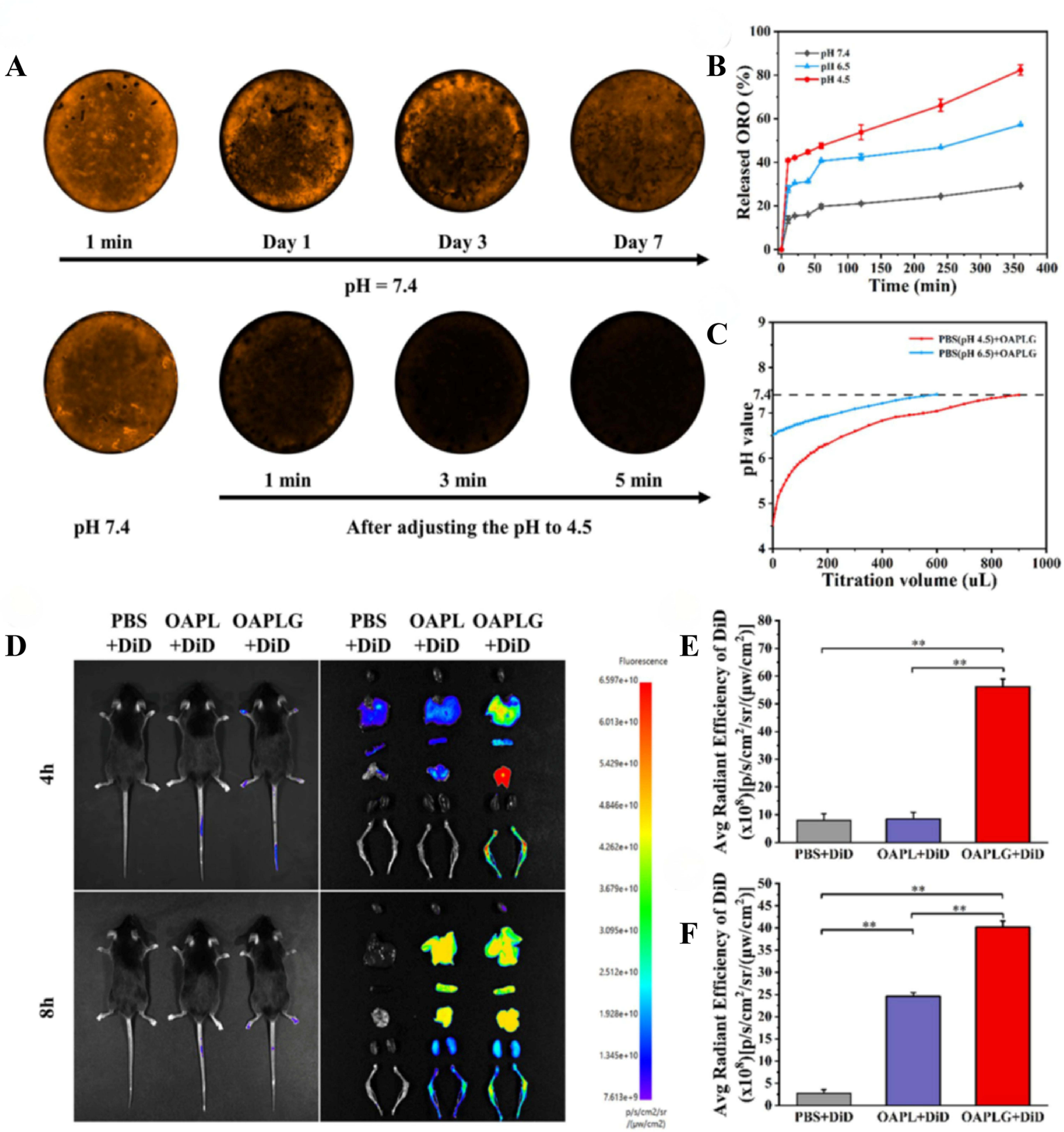


Figure 5 pH responsiveness and bone targeting properties of the nanoplatform OAPLG. (**A**) Following incubation with DiD-labeled OAPLG at pH 7.4, the fluorescence signal of DiD on the surface of the bone slice was assessed at time intervals of 1 min, 1 day, 3 days, and 7 days. Subsequently, the pH was rapidly adjusted to 4.5, and the DiD fluorescence signal was measured at intervals of 1 min, 3 min, and 5 min. (**B**) Drug release curves of OAPLG in different pH buffer solutions over time. (**C**) Detection of pH value in OAPLG titration of different pH buffer solutions. (**D**) Fluorescence signals in live as well as isolated organs and femur and tibia of mice 4 and 8 h after intravenous injection of DiD-labeled OAPLG. (**E**) Quantification of fluorescence signals in femur and tibia 4 h after intravenous injection of DiD-labeled OAPLG. (**F**) Quantification of fluorescence signals in femur and tibia 8 h after intravenous injection of DiD-labeled OAPLG. n=3. **P<0.001. Figure 5 is reproduced with permission from Yu B, Gao Q, Sheng S et al. Smart osteoclasts targeted nanomedicine based on amorphous $CaCO_3$ for effective osteoporosis reversal. J Nanobiotechnology. 2024; 5; 22(1):153. Creative Commons Attribution 4.0 International License Copyright (2024), BMC. Creative Commons Attribution 4.0 International License.[88]

reduced oxidative stress and increased bone mass without notable systemic side effects. These findings suggest that ALN@BMSCM@PLGA-TK-PEG-SS31 holds promise as a treatment for OP.[97]

Integration of 3D printing and tissue engineering. The goal is to combine bone repair scaffolds with NDDSS to effectively treat osteoporotic fractures. Hydroxyapatite (HAP)/PLGA scaffolds can be loaded with BMP-2 and anti-

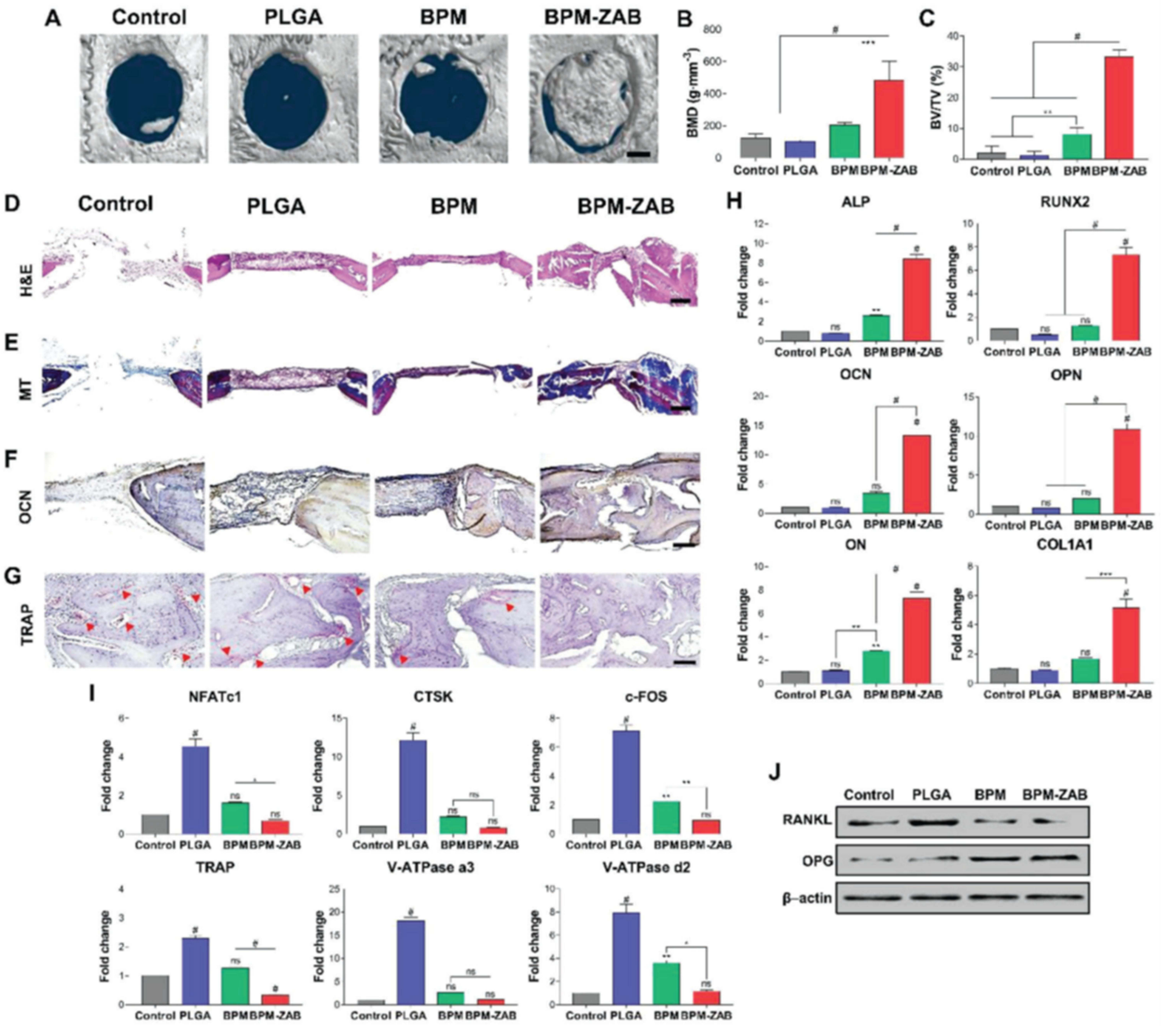


Figure 6 In vivo new bone formation ability of the BPM-ZAB in osteoporotic rat Model 2. (**A**) Representative micro-CT images of ovariectomy-induced rats with OP and calvarial defects showing mineralized new bone at 8 weeks post-implantation (scale bar, 1000 µm). (**B**) Quantification of BMD (n = 4). (**C**) Bone volume density (BV/TV) quantification (n = 4). Histological analysis with (**D**) Hematoxylin and Eosin (H&E), (**E**) Masson's Trichrome (MT), (**F**) osteocalcin (OCN; IHC), and (**G**) tartrate resistant acid phosphatase (TRAP, red arrow). (**H**) Gene expression related to osteogenesis in rats with OP at week 8 after implantation: ALP, RUNX2, OCN, OPN, ON, and COL1A1 (n = 3). (**I**) Gene expressions related to osteoclast activation: NFATc1, CTSK, c-FOS, TRAP, and V-ATPase a3 and d2 (n = 3). (**J**) The protein expression of RANKL and OPG was determined using Western blotting. #p < 0.0001, ***p < 0.001, **p < 0.01, and *p < 0.05 indicate statistically significant differences, respectively. Figure 6 is reproduced with permission from Lee JK, Kim DS, Park SY, Baek SW, Jung JW, Kim TH, Han DK. Nitric Oxide-Releasing Bioinspired Scaffold for Exquisite Regeneration of Osteoporotic Bone via Regulation of Homeostasis. Adv Sci (Weinh). 2023;10(6): e2205336. © 2022 The Authors. Advanced Science published by Wiley-VCH GmbH. CCBY License.[90]

resorptive agents to enhance therapeutic efficacy. Polypyrrole is utilized to facilitate osteogenesis through electrical stimulation. Scaffolds can be custom-designed using patient-specific CT data to ensure optimal fit and functionality.[98–101] Kong et al introduced a 3D-printed polycaprolactone scaffold embedded with strontium-substituted mesoporous bioactive glass nanoparticles (Sr-MBGNPs) and icariin for targeted regeneration of osteoporotic bone. Their findings indicate that this novel scaffold platform offers a promising localized treatment strategy, minimizing systemic side effects while enhancing fixation stability. The innovative combination of Sr-MBGNPs and ICN underscores its potential to transform OP therapy by promoting bone regeneration and reducing bone resorption.[99]

AI-driven design. The aim is to accelerate the optimization of nanomaterials and facilitate their clinical translation. This involves assessing the relationship between nanoparticle size and charge with respect to bone targeting efficiency, as

Table 4 Summary of Future Perspectives

Direction	Representative Technology	Potential Breakthroughs
Smart responsive materials	pH/enzyme dual-responsive nanoparticles	Achieve "on-demand drug release" to reduce side effects
Multimodal therapy	Gene-drug co-delivery systems	Synchronously regulate bidirectional targets in bone metabolism
Bioinspired delivery	Exosome/cell membrane-coated nanoparticles	Enhance targeting and biocompatibility
3D printing integration	Drug-loaded bone repair scaffolds	Treat osteoporotic fractures
AI-assisted design	Machine learning for nanomaterial optimization	Accelerate clinical translation

well as simulating drug release kinetics. AI-assisted methods are employed to identify optimal material combinations, such as suitable polymer-drug pairs, thereby enhancing the efficiency of the design process[102–104] (Table 4).

Key Challenges and Solutions

Biosafety concerns arise from the long-term accumulation of inorganic nanomaterials like silica, which pose toxicity risks, and from cationic polymers such as polyethylenimine, which can damage cell membranes. To address these challenges, the adoption of biodegradable cationic polymers like poly (β-amino esters) can mitigate toxicity. Additionally, surface modifications such as PEGylation can reduce immune clearance, while incorporating targeting ligands may allow for lower dosages.[32,105,106]

Manufacturing challenges include batch-to-batch variability in liposomes and exosomes, as well as difficulties in reproducing processes for complex nanosystems like hybrid materials. To address these issues, microfluidic technology enables continuous and standardized production of nanoparticles, while process analytical technology (PAT) allows for online monitoring of critical parameters, such as particle size and zeta potential, thereby enhancing the reproducibility of manufacturing processes.[107–109]

Clinical translation faces barriers due to discrepancies between animal models, particularly OVX rats, and human diseases, along with a lack of standardized efficacy evaluation systems. To overcome these challenges, employing large animal models such as osteoporotic sheep or non-human primates can provide more relevant data for human applications. Furthermore, dynamic efficacy assessment can be enhanced by concurrently monitoring biomarkers like CTX-1, a bone resorption marker, and P1NP, a bone formation marker.[110–112]

Personalized medicine for OP faces challenges due to variability among patient subtypes, such as postmenopausal and senile osteoporosis, and the absence of individualized dosing regimens. Solutions include companion diagnostics that match nanoparticles based on genetic testing for LRP5 mutations, enabling more tailored therapies. Furthermore, smart delivery systems that adjust drug release rates according to real-time monitoring of bone density can improve treatment efficacy and safety.[113,114]

Conclusions

This review systematically explores recent applications of NDDSs—comprising inorganic, organic, biogenic, and hybrid materials—in the treatment of OP. It focuses on targeting design strategies, efficacy validation, and clinical translation challenges. To combat drug resistance, improvements in targeting specificity, combination therapies, and sustained release profiles are crucial. Moreover, advancements in gene editing, immunotherapy, and biomarker-driven approaches can enhance therapeutic efficacy. Biosafety concerns related to toxicity and membrane damage can be addressed using biodegradable polymers and surface modifications. Manufacturing challenges may be mitigated through microfluidic technology and process monitoring. Finally, the use of large animal models and companion diagnostics can support clinical translation and personalized medicine.

Abbreviations

OP, osteoporosis; NDDSs, nano drug delivery systems; OCs, osteoclasts; OBs, osteoblasts; PMOP, postmenopausal osteoporosis; ROS, reactive oxygen species; OVX, ovariectomized; PLGA, poly(lactic-co-glycolic) acid; RIS, risperidone; HA, hyaluronic acid; BMP-2, bone morphogenetic protein-2; PELNs, pueraria lobata-derived exosome-like nanovesicles; PEG, polyethylene glycol; PCL, polycaprolactone; HAP, hydroxyapatite; MSNs, mesoporous silica nanoparticles; CeO_2, cerium oxide; MSCs, mesenchymal stem cells; MSCM, MSC-derived cell membrane; BMSCs, bone marrow-derived stem cells; PAT, process analytical technology.

Data Sharing Statement

All data analyzed was included in this study, further request could be consulted and obtained from correspondent author Pro. Yunxiang Hu.

Ethics Approval and Consent to Participate

This is a review study, then ethic approval is waived.

Acknowledgments

We highly appreciated Pro. Yunxiang Hu in writing and revising this paper. Yin Peng, Shilin Dong, and Jiaoyang Yu contributed equally to this work and therefore should be defined as co-first authors.

Funding

This study was funded by the Liaoning Provincial Natural Science Foundation-Joint Fund(2024-MSLH-090).

Disclosure

The authors declare no competing interests.

References

1. Reid IR, Billington EO. Drug therapy for osteoporosis in older adults. *Lancet*. 2022;399(10329):1080–1092. doi:10.1016/S0140-6736(21)02646-5
2. Hu Y, Han J, Ding S, Liu S, Wang H. Identification of ferroptosis-associated biomarkers for the potential diagnosis and treatment of postmenopausal osteoporosis. *Front Endocrinol*. 2022;13:986384. doi:10.3389/fendo.2022.986384
3. Zhao Y, Wang HL, Li TT, Yang F, Tzeng CM. Baicalin ameliorates dexamethasone-induced osteoporosis by regulation of the RANK/RANKL/OPG signaling pathway. *Drug Des Devel Ther*. 2020;14:195–206. doi:10.2147/DDDT.S225516
4. Huang X, Li S, Lu W, Xiong L. Metformin activates Wnt/β-catenin for the treatment of diabetic osteoporosis. *BMC Endocr Disord*. 2022;22(1):189. doi:10.1186/s12902-022-01103-6
5. Xia X, Fang Z, Qian Y, et al. Role of oxidative stress in the concurrent development of osteoporosis and tendinopathy: emerging challenges and prospects for treatment modalities. *J Cell Mol Med*. 2024;28(13):e18508. doi:10.1111/jcmm.18508
6. LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2022;33(10):2049–2102.
7. Amin U, McPartland A, O'Sullivan M, Silke C. An overview of the management of osteoporosis in the aging female population. *Womens Health*. 2023;19:17455057231176655.
8. Ramchand SK, Leder BZ. Sequential therapy for the long-term treatment of postmenopausal osteoporosis. *J Clin Endocrinol Metab*. 2024;109(2):303–311. doi:10.1210/clinem/dgad496
9. Tambe S, Kesari KK, Mishra YK, Amin P, Das SS. Long-acting biodegradable implants for osteoporosis management: transforming the landscape of bisphosphonates delivery. *Future Med Chem*. 2023;15(9):731–734. doi:10.4155/fmc-2023-0097
10. Yan R, Guo Y, Wang X, Liang G, Yang A, Li J. Near-infrared light-controlled and real-time detection of osteogenic differentiation in mesenchymal stem cells by upconversion nanoparticles for osteoporosis therapy. *ACS Nano*. 2022;16(5):8399–8418. doi:10.1021/acsnano.2c02900
11. Cui Y, Guo Y, Kong L, et al. A bone-targeted engineered exosome platform delivering siRNA to treat osteoporosis. *Bioact Mater*. 2022;10:207–221. doi:10.1016/j.bioactmat.2021.09.015
12. García-García P, Reyes R, Segredo-Morales E, Pérez-Herrero E, Delgado A, Évora C. PLGA-BMP-2 and PLA-17β-estradiol microspheres reinforcing a composite hydrogel for bone regeneration in osteoporosis. *Pharmaceutics*. 2019;11(12):648. doi:10.3390/pharmaceutics11120648
13. Hejazi F, Ebrahimi V, Asgary M, et al. Improved healing of critical-size femoral defect in osteoporosis rat models using 3D elastin/polycaprolactone/nHA scaffold in combination with mesenchymal stem cells. *J Mater Sci Mater Med*. 2021;32(3):27. doi:10.1007/s10856-021-06495-w
14. Sezlev Bilecen D, Rodriguez-Cabello JC, Uludag H, Hasirci V. Construction of a PLGA based, targeted siRNA delivery system for treatment of osteoporosis. *J Biomater Sci Polym Ed*. 2017;28(16):1859–1873. doi:10.1080/09205063.2017.1354675
15. Hosny KM, Bahmdan RH, Alhakamy NA, Alfaleh MA, Ahmed OA, Elkomy MH. Physically optimized nano-lipid carriers augment raloxifene and vitamin D oral bioavailability in healthy humans for management of osteoporosis. *J Pharm Sci*. 2020;109(7):2145–2155. doi:10.1016/j.xphs.2020.03.009
16. Song S, Guo Y, Yang Y, Fu D. Advances in pathogenesis and therapeutic strategies for osteoporosis. *Pharmacol Ther*. 2022;237:108168. doi:10.1016/j.pharmthera.2022.108168
17. Gehrke B, Alves Coelho MC, Brasil d'Alva C, Madeira M. Long-term consequences of osteoporosis therapy with bisphosphonates. *Arch Endocrinol Metab*. 2023;68:e220334. doi:10.20945/2359-4292-2022-0334

18. Yuan F, Peng W, Yang C, Zheng J. Teriparatide versus bisphosphonates for treatment of postmenopausal osteoporosis: a meta-analysis. *Int J Surg*. 2019;66:1–11. doi:10.1016/j.ijsu.2019.03.004
19. Moshi MR, Nicolopoulos K, Stringer D, Ma N, Jenal M, Vreugdenburg T. The clinical effectiveness of denosumab (Prolia®) for the treatment of osteoporosis in postmenopausal women, compared to bisphosphonates, selective estrogen receptor modulators (SERM), and placebo: a systematic review and network meta-analysis. *Calcif Tissue Int*. 2023;112(6):631–646. doi:10.1007/s00223-023-01078-z
20. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the Phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol*. 2017;5(7):513–523. doi:10.1016/S2213-8587(17)30138-9
21. Zhang JY, Zhong YH, Chen LM, Zhuo XL, Zhao LJ, Wang YT. Recent advance of small-molecule drugs for clinical treatment of osteoporosis: a review. *Eur J Med Chem*. 2023;259:115654. doi:10.1016/j.ejmech.2023.115654
22. Ayers C, Kansagara D, Lazur B, Fu R, Kwon A, Harrod C. Effectiveness and safety of treatments to prevent fractures in people with low bone mass or primary osteoporosis: a living systematic review and network meta-analysis for the American college of physicians. *Ann Intern Med*. 2023;176(2):182–195. doi:10.7326/M22-0684
23. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375(16):1532–1543. doi:10.1056/NEJMoa1607948
24. Capozzi A, Scambia G, Lello S. Calcium, vitamin D, vitamin K2, and magnesium supplementation and skeletal health. *Maturitas*. 2020;140:55–63. doi:10.1016/j.maturitas.2020.05.020
25. Reginster JY, Brandi ML, Cannata-Andía J, et al. The position of strontium ranelate in today’s management of osteoporosis. *Osteoporos Int*. 2015;26(6):1667–1671. doi:10.1007/s00198-015-3109-y
26. Dayanandan AP, Cho WJ, Kang H, et al. Emerging nano-scale delivery systems for the treatment of osteoporosis. *Biomater Res*. 2023;27(1):68. doi:10.1186/s40824-023-00413-7
27. Li J, Wei G, Liu G, et al. Regulating type H vessel formation and bone metabolism via bone-targeting oral micro/nano-hydrogel microspheres to prevent bone loss. *Adv Sci*. 2023;10(15):e2207381. doi:10.1002/advs.202207381
28. Hu Y, Yang R, Liu S, Song Z, Wang H. The emerging roles of nanocarrier drug delivery system in treatment of intervertebral disc degeneration-current knowledge, hot spots, challenges and future perspectives. *Drug Des Devel Ther*. 2024;18:1007–1022. doi:10.2147/DDDT.S448807
29. Saeedi M, Vahidi O, Moghbeli MR, et al. Customizing nano-chitosan for sustainable drug delivery. *J Control Release*. 2022;350:175–192. doi:10.1016/j.jconrel.2022.07.038
30. Rai S, Singh N, Bhattacharya S. Concepts on smart nano-based drug delivery system. *Recent Pat Nanotechnol*. 2022;16(1):67–89. doi:10.2174/1872210515666210120113738
31. Nikezić AV, Novaković JG. Nano/microcarriers in drug delivery: moving the timeline to contemporary. *Curr Med Chem*. 2023;30(26):2996–3023. doi:10.2174/0929867329666220821193938
32. Wu Y, Sun B, Tang Y, et al. Bone targeted nano-drug and nano-delivery. *Bone Res*. 2024;12(1):51. doi:10.1038/s41413-024-00356-2
33. Lv Y, Li W, Liao W, et al. Nano-drug delivery systems based on natural products. *Int J Nanomed*. 2024;19:541–569. doi:10.2147/IJN.S443692
34. Khosla S, Hofbauer LC. Osteoporosis treatment: recent developments and ongoing challenges. *Lancet Diabetes Endocrinol*. 2017;5(11):898–907. doi:10.1016/S2213-8587(17)30188-2
35. Pant A, Singh J, Barnwal RP, Singh G, Singh B. Theranostic approach for the management of osteoporosis. *Crit Rev Ther Drug Carrier Syst*. 2023;40(3):95–121. doi:10.1615/CritRevTherDrugCarrierSyst.2022043413
36. Ma M, Zeng H, Yang P, Xu J, Zhang X, He W. Drug delivery and therapy strategies for osteoporosis intervention. *Molecules*. 2023;28(18):6652. doi:10.3390/molecules28186652
37. Fouad-Elhady EA, Aglan HA, Hassan RE, Ahmed HH, Sabry GM. Modulation of bone turnover aberration: a target for management of primary osteoporosis in experimental rat model. *Heliyon*. 2020;6(2):e03341. doi:10.1016/j.heliyon.2020.e03341
38. Kotak DJ, Devarajan PV. Bone targeted delivery of salmon calcitonin hydroxyapatite nanoparticles for sublingual osteoporosis therapy (SLOT). *Nanomedicine*. 2020;24:102153. doi:10.1016/j.nano.2020.102153
39. Qayoom I, Teotia AK, Kumar A. Nanohydroxyapatite based ceramic carrier promotes bone formation in a femoral neck canal defect in osteoporotic rats. *Biomacromolecules*. 2020;21(2):328–337. doi:10.1021/acs.biomac.9b01327
40. Wu T, Sun J, Tan L, et al. Enhanced osteogenesis and therapy of osteoporosis using simvastatin loaded hybrid system. *Bioact Mater*. 2020;5(2):348–357. doi:10.1016/j.bioactmat.2020.03.004
41. Jiang J, Li J, Zhang Z, Sun E, Feng L, Jia X. Mechanism of enhanced antiosteoporosis effect of circinal-icaritin by self-assembled nanomicelles in vivo with suet oil and sodium deoxycholate. *Int J Nanomed*. 2015;10:2377–2389. doi:10.2147/IJN.S76191
42. Fazil M, Hassan MQ, Baboota S, Ali J. Biodegradable intranasal nanoparticulate drug delivery system of risedronate sodium for osteoporosis. *Drug Deliv*. 2016;23(7):2428–2438. doi:10.3109/10717544.2014.1002947
43. Kaur R, Ajitha M. Transdermal delivery of fluvastatin loaded nanoemulsion gel: preparation, characterization and in vivo anti-osteoporosis activity. *Eur J Pharm Sci*. 2019;136:104956. doi:10.1016/j.ejps.2019.104956
44. Chen Y, Chen QW, Fu FS, Gu HY, Yu A, Zhang XZ. Bone destruction-chemotactic osteoprogenitor cells deliver liposome nanomedicines for the treatment of osteosarcoma and osteoporosis. *ACS Nano*. 2024;18(43):29864–29879. doi:10.1021/acsnano.4c10053
45. Xia D, Qian Q, Wang S, Dong X, Liu Y. Alendronate functionalized bone-targeting pomolic acid liposomes restore bone homeostasis for osteoporosis treatment. *Int J Nanomed*. 2024;19:7983–7996. doi:10.2147/IJN.S462514
46. Xu L, Zhu J, Rong L, et al. Osteoblast-specific down-regulation of NLRP3 inflammasome by aptamer-functionalized liposome nanoparticles improves bone quality in postmenopausal osteoporosis rats. *Theranostics*. 2024;14(10):3945–3962. doi:10.7150/thno.95423
47. Nirwan N, Anjaneyulu YP, Sultana Y, Vohora D. Development of linagliptin-loaded liposomes using aspartic acid conjugate for bone-targeted delivery to combat osteoporosis. *J Drug Target*. 2025;33:1–12.
48. Wang YM, Shen JT. Chitosan-based promising scaffolds for the construction of tailored nanosystems against osteoporosis: current status and future prospects. *J Appl Biomater Funct Mater*. 2024;22:22808000241266487. doi:10.1177/22808000241266487
49. Sandomierski M, Adamska K, Ratajczak M, Voelkel A. Chitosan - zeolite scaffold as a potential biomaterial in the controlled release of drugs for osteoporosis. *Int J Biol Macromol*. 2022;223(Pt A):812–820. doi:10.1016/j.ijbiomac.2022.11.071
50. Snega Priya P, Surisetti R, Gopi S, et al. Chitosan-chondroitin sulfate-daidzein nanoconjugate ameliorates glucocorticoid induced osteoporosis in vivo. *Int J Biol Macromol*. 2024;280(Pt 1):135662. doi:10.1016/j.ijbiomac.2024.135662

51. Chen TY, Lin NY, Wen CH, et al. Development of triamcinolone acetonide-hyaluronic acid conjugates with selective targeting and less osteoporosis effect for rheumatoid arthritis treatments. *Int J Biol Macromol*. 2023;237:124047. doi:10.1016/j.ijbiomac.2023.124047
52. Kawano M, Ariyoshi W, Iwanaga K, et al. Mechanism involved in enhancement of osteoblast differentiation by hyaluronic acid. *Biochem Biophys Res Commun*. 2011;405(4):575–580. doi:10.1016/j.bbrc.2011.01.071
53. Tenger K, Komori K, Maehara A, et al. High molecular weight hyaluronic acid alleviates ovariectomy-induced bone loss in mice. *BMC Musculoskelet Disord*. 2024;25(1):1048. doi:10.1186/s12891-024-08161-y
54. Zhang Q, Chen X, Geng S, et al. Nanogel-based scaffolds fabricated for bone regeneration with mesoporous bioactive glass and strontium: in vitro and in vivo characterization. *J Biomed Mater Res A*. 2017;105(4):1175–1183. doi:10.1002/jbm.a.35980
55. Ansari MD, Shafi S, Pandit J, et al. Raloxifene encapsulated spanlastic nanogel for the prevention of bone fracture risk via transdermal administration: pharmacokinetic and efficacy study in animal model. *Drug Deliv Transl Res*. 2024;14(6):1635–1647. doi:10.1007/s13346-023-01480-y
56. Cui Y, Lv B, Li Z, et al. Bone-targeted biomimetic nanogels re-establish osteoblast/osteoclast balance to treat postmenopausal osteoporosis. *Small*. 2024;20(6):e2303494. doi:10.1002/smll.202303494
57. Huang Y, Chen T, Ren C, et al. High-strength gelatin hydrogel scaffold with drug loading remodels the inflammatory microenvironment to enhance osteoporotic bone repair. *Adv Mater*. 2025;37(13):e2501051. doi:10.1002/adma.202501051
58. Li D, Chen K, Duan L, et al. Strontium ranelate incorporated enzyme-cross-linked gelatin nanoparticle/silk fibroin aerogel for osteogenesis in OVX-induced osteoporosis. *ACS Biomater Sci Eng*. 2019;5(3):1440–1451. doi:10.1021/acsbiomaterials.8b01298
59. Zhao Z, Li G, Ruan H, et al. Capturing magnesium ions via microfluidic hydrogel microspheres for promoting cancellous bone regeneration. *ACS Nano*. 2021;15(8):13041–13054. doi:10.1021/acsnano.1c02147
60. Huang W, Wang X, Zhao Z. Ultrasound-triggered Mg(2+) blasting release hydrogel microspheres for promoting bone reconstruction. *Adv Healthc Mater*. 2025;14(3):e2402935. doi:10.1002/adhm.202402935
61. Huang L, Cai P, Bian M, et al. Injectable and high-strength PLGA/CPC loaded ALN/MgO bone cement for bone regeneration by facilitating osteogenesis and inhibiting osteoclastogenesis in osteoporotic bone defects. *Mater Today Bio*. 2024;26:101092. doi:10.1016/j.mtbio.2024.101092
62. Guan H, Wang W, Jiang Z, et al. Magnetic aggregation-induced bone-targeting nanocarrier with effects of piezo1 activation and osteogenic-angiogenic coupling for osteoporotic bone repair. *Adv Mater*. 2024;36(13):e2312081. doi:10.1002/adma.202312081
63. Lee JK, Kim DS, Park SY, et al. osteoporotic bone regeneration via plenished biomimetic PLGA scaffold with sequential release system. *Small*. 2024;20(23):e2310734. doi:10.1002/smll.202310734
64. Nourany M, Makaremy A, Bazrpash S, Hosseini S. Bimodal macroporous 3D scaffolds based on compatibilized PCL and PLA blend using PCL-PEG-PCL block copolymers and cellulose nanocrystals for osteogenic differentiation of hMSCs. *Int J Biol Macromol*. 2025;299:140149. doi:10.1016/j.ijbiomac.2025.140149
65. Wang Y, Xie J, Ai Z, Su J. Nobiletin-loaded micelles reduce ovariectomy-induced bone loss by suppressing osteoclastogenesis. *Int J Nanomed*. 2019;14:7839–7849. doi:10.2147/IJN.S213724
66. Sun Y, Ye X, Cai M, et al. Osteoblast-targeting-peptide modified nanoparticle for siRNA/microRNA delivery. *ACS Nano*. 2016;10(6):5759–5768. doi:10.1021/acsnano.5b07828
67. Cai M, Yang L, Zhang S, Liu J, Sun Y, Wang X. A bone-resorption surface-targeting nanoparticle to deliver anti-miR214 for osteoporosis therapy. *Int J Nanomed*. 2017;12:7469–7482. doi:10.2147/IJN.S139775
68. de Souza AM, Dantas M, Secundo EL, et al. Are hydroxyapatite-based biomaterials free of genotoxicity? A systematic review. *Chemosphere*. 2024;352:141383. doi:10.1016/j.chemosphere.2024.141383
69. Yu F, Wang H, Wang Q, et al. Studies of a novel bone-targeted nano drug delivery system with a HAP core-PSI coating structure for tanshinol injection. *J Drug Target*. 2023;31(7):762–775. doi:10.1080/1061186X.2023.2230528
70. Mora-Raimundo P, Lozano D, Benito M, Mulero F, Manzano M, Vallet-Regí M. Osteoporosis remission and new bone formation with mesoporous silica nanoparticles. *Adv Sci*. 2021;8(16):e2101107. doi:10.1002/advs.202101107
71. Rasool N, Negi D, Singh Y. Thiol-functionalized, antioxidant, and osteogenic mesoporous silica nanoparticles for osteoporosis. *ACS Biomater Sci Eng*. 2023;9(6):3535–3545. doi:10.1021/acsbiomaterials.3c00479
72. Xu Z, Zhang R, Chen H, et al. Characterization and preparation of food-derived peptides on improving osteoporosis: a review. *Food Chem X*. 2024;23:101530. doi:10.1016/j.fochx.2024.101530
73. Shah P, Rajput SJ. Investigation of in vitro permeability and in vivo pharmacokinetic behavior of bare and functionalized MCM-41 and MCM-48 mesoporous silica nanoparticles: a burst and controlled drug release system for raloxifene. *Drug Dev Ind Pharm*. 2019;45(4):587–602. doi:10.1080/03639045.2019.1569028
74. Casals E, Zeng M, Parra-Robert M, et al. Cerium oxide nanoparticles: advances in biodistribution, toxicity, and preclinical exploration. *Small*. 2020;16(20):e1907322. doi:10.1002/smll.201907322
75. You G, Hou J, Xu Y, Miao L, Ao Y, Xing B. Surface properties and environmental transformations controlling the bioaccumulation and toxicity of cerium oxide nanoparticles: a critical review. *Rev Environ Contam Toxicol*. 2021;253:155–206. doi:10.1007/398_2020_42
76. Li K, Shen Q, Xie Y, You M, Huang L, Zheng X. Incorporation of cerium oxide into hydroxyapatite coating protects bone marrow stromal cells against H(2)O(2)-induced inhibition of osteogenic differentiation. *Biol Trace Elem Res*. 2018;182(1):91–104. doi:10.1007/s12011-017-1066-3
77. Zhan W, Deng M, Huang X, et al. Pueraria lobata-derived exosome-like nanovesicles alleviate osteoporosis by enhacning autophagy. *J Control Release*. 2023;364:644–653. doi:10.1016/j.jconrel.2023.11.020
78. Chen Y, Zhu M, Huang B, Jiang Y, Su J. Advances in cell membrane-coated nanoparticles and their applications for bone therapy. *Biomater Adv*. 2023;144:213232. doi:10.1016/j.bioadv.2022.213232
79. Su N, Villicana C, Barati D, Freeman P, Luo Y, Yang F. Stem cell membrane-coated microribbon scaffolds induce regenerative innate and adaptive immune responses in a critical-size cranial bone defect model. *Adv Mater*. 2023;35(10):e2208781. doi:10.1002/adma.202208781
80. Elkhenany H, Soliman MW, Atta D, El-Badri N. Innovative marine-sourced hydroxyapatite, chitosan, collagen, and gelatin for eco-friendly bone and cartilage regeneration. *J Biomed Mater Res A*. 2025;113(1):e37833. doi:10.1002/jbm.a.37833
81. Nah H, Lee D, Heo M, et al. Vitamin D-conjugated gold nanoparticles as functional carriers to enhancing osteogenic differentiation. *Sci Technol Adv Mater*. 2019;20(1):826–836. doi:10.1080/14686996.2019.1644193
82. Takanche JS, Kim JE, Kim JS, et al. Chitosan-gold nanoparticles mediated gene delivery of c-myb facilitates osseointegration of dental implants in ovariectomized rat. *Artif Cells Nanomed Biotechnol*. 2018;46(sup3):S807–s817. doi:10.1080/21691401.2018.1513940

83. Augustine R, Kalva N, Kim HA, Zhang Y, Kim I. pH-responsive polypeptide-based smart nano-carriers for theranostic applications. *Molecules*. 2019;24(16):2961. doi:10.3390/molecules24162961
84. Wang W, Li PF, Xie R, Ju XJ, Liu Z, Chu LY. Designable micro-/nano-structured smart polymeric materials. *Adv Mater*. 2022;34(46):e2107877. doi:10.1002/adma.202107877
85. Rinaldi A, Caraffi R, Grazioli MV, et al. Applications of the ROS-responsive thioketal linker for the production of smart nanomedicines. *Polymers*. 2022;14(4):687. doi:10.3390/polym14040687
86. Zhao Q, Yue X, Miaomiao L, Yanming W, Wu G. Nano-injectable pH/NIR-responsive hydrogel for chemo-photothermal synergistic drug delivery. *J Biomater Appl*. 2023;38(5):614–628. doi:10.1177/08853282231209653
87. Joseph JP, Miglani C, Maulik A, et al. Stereoselective plasmonic interaction in peptide-tethered photopolymerizable diacetylenes doped with chiral gold nanoparticles. *Angew Chem Int Ed Engl*. 2023;62(37):e202306751. doi:10.1002/anie.202306751
88. Yu B, Gao Q, Sheng S, et al. Smart osteoclasts targeted nanomedicine based on amorphous CaCO(3) for effective osteoporosis reversal. *J Nanobiotechnology*. 2024;22(1):153. doi:10.1186/s12951-024-02412-9
89. Chen W, Pan Y, Chu CH, et al. Microenvironment-responsive nanoparticles functionalized titanium implants mediate redox balance and immunomodulation for enhanced osseointegration. *Mater Today Bio*. 2025;31:101628. doi:10.1016/j.mtbio.2025.101628
90. Lee JK, Kim DS, Park SY, et al. Nitric Oxide-releasing bioinspired scaffold for exquisite regeneration of osteoporotic bone via regulation of homeostasis. *Adv Sci*. 2023;10(6):e2205336. doi:10.1002/advs.202205336
91. Zhang Z, Ding P, Meng Y, et al. Rational polyelectrolyte nanoparticles endow preosteoclast-targeted siRNA transfection for anabolic therapy of osteoporosis. *Sci Adv*. 2023;9(10):eade7379. doi:10.1126/sciadv.ade7379
92. Guo Z, Afza R, Moneeb Khan M, et al. Investigation of the treatment potential of Raloxifene-loaded polymeric nanoparticles in osteoporosis: in-vitro and in-vivo analyses. *Heliyon*. 2023;9(9):e20107. doi:10.1016/j.heliyon.2023.e20107
93. Casarrubios L, Cicuéndez M, Vallet-Regí M, Portolés MT, Arcos D, Feito MJ. Osteoimmune properties of mesoporous bioactive nanospheres: a study on T helper lymphocytes. *Nanomaterials*. 2023;13(15):2183. doi:10.3390/nano13152183
94. Tang A, Shu Q, Jia S, Lai Z, Tian J. Adipose mesenchymal stem cell-derived exosomes as nanocarriers for treating musculoskeletal disorders. *Int J Nanomed*. 2024;19:13547–13562. doi:10.2147/IJN.S486622
95. Qin S, Liu D. Long non-coding RNA H19 mediates osteogenic differentiation of bone marrow mesenchymal stem cells through the miR-29b-3p/DKK1 axis. *J Cell Mol Med*. 2024;28(9):e18287. doi:10.1111/jcmm.18287
96. Liao J, Lu L, Chu X, et al. Cell membrane coated nanoparticles: cutting-edge drug delivery systems for osteoporosis therapy. *Nanoscale*. 2024;16(17):8236–8255. doi:10.1039/D3NR06264C
97. Zhang W, Zhang Y, Hao Z, et al. Synthetic nanoparticles functionalized with cell membrane-mimicking, bone-targeting, and ROS-controlled release agents for osteoporosis treatment. *J Control Release*. 2025;378:306–319. doi:10.1016/j.jconrel.2024.12.017
98. Wei D, Jung J, Yang H, Stout DA, Yang L. Nanotechnology treatment options for osteoporosis and its corresponding consequences. *Curr Osteoporos Rep*. 2016;14(5):239–247. doi:10.1007/s11914-016-0324-1
99. Kong CH, Steffi C, Cai Y, Wang W. E-jet printed polycaprolactone with strontium-substituted mesoporous bioactive glass nanoparticles for bone tissue engineering. *Biomater Adv*. 2025;169:214173. doi:10.1016/j.bioadv.2024.214173
100. Li XR, Deng QS, He SH, et al. 3D cryo-printed hierarchical porous scaffolds provide immobilization of surface-functionalized sleep-inspired small extracellular vesicles: synergistic therapeutic strategies for vascularized bone regeneration based on macrophage phenotype modulation and angiogenesis-osteogenesis coupling. *J Nanobiotechnology*. 2024;22(1):764. doi:10.1186/s12951-024-02977-5
101. Lee W, Xu C, Fu H, et al. 3D bioprinting highly elastic PEG-PCL-DA hydrogel for soft tissue fabrication and biomechanical stimulation. *Adv Funct Mater*. 2024;34(28):2313942.
102. Lin Z, Chou WC, Cheng YH, He C, Monteiro-Riviere NA, Riviere JE. Predicting nanoparticle delivery to tumors using machine learning and artificial intelligence approaches. *Int J Nanomed*. 2022;17:1365–1379. doi:10.2147/IJN.S344208
103. Gao XJ, Ciura K, Ma Y, et al. Toward the integration of machine learning and molecular modeling for designing drug delivery nanocarriers. *Adv Mater*. 2024;36(45):e2407793. doi:10.1002/adma.202407793
104. Sun Y, Qin S, Li Y, Hasan N, Li YV, Liu J. Machine learning integrated with in vitro experiments for study of drug release from PLGA nanoparticles. *Sci Rep*. 2025;15(1):4218. doi:10.1038/s41598-024-82728-6
105. Venuta A, Wolfram J, Shen H, Ferrari M. Post-nano strategies for drug delivery: multistage porous silicon microvectors. *J Mater Chem B*. 2017;5(2):207–219. doi:10.1039/C6TB01978A
106. Kozma GT, Shimizu T, Ishida T, Szebeni J. Anti-PEG antibodies: properties, formation, testing and role in adverse immune reactions to PEGylated nano-biopharmaceuticals. *Adv Drug Deliv Rev*. 2020;154-155:163–175. doi:10.1016/j.addr.2020.07.024
107. Sürer Ş, Elçitepe TB, Akçay D, et al. A promising, novel radiosensitizer nanodrug complex for oral cavity cancer: cetuximab and cisplatin-conjugated gold nanoparticles. *Balkan Med J*. 2021;38(5):278–286. doi:10.5152/balkanmedj.2021.21013
108. Zhou D, Zhou F, Sheng S, Wei Y, Chen X, Su J. Intra-articular nanodrug delivery strategies for treating osteoarthritis. *Drug Discov Today*. 2023;28(3):103482. doi:10.1016/j.drudis.2022.103482
109. Malhotra S, Jain N, Rathee J, et al. Nanoneuroscience: cutting-edge approach for disease management. *Recent Pat Nanotechnol*. 2024;18(2):305–320. doi:10.2174/1872210517666230403105152
110. Farjadian F, Ghasemi A, Gohari O, Roointan A, Karimi M, Hamblin MR. Nanopharmaceuticals and nanomedicines currently on the market: challenges and opportunities. *Nanomedicine*. 2019;14(1):93–126. doi:10.2217/nnm-2018-0120
111. Naeem M, Awan UA, Subhan F, et al. Advances in colon-targeted nano-drug delivery systems: challenges and solutions. *Arch Pharm Res*. 2020;43(1):153–169. doi:10.1007/s12272-020-01219-0
112. Roy M, Majid H, Khan P, et al. CTX-1 and TRACP-5b as biomarkers for osteoporosis risk in type 2 diabetes mellitus: a cross-sectional study. *J Diabetes Metab Disord*. 2024;23(2):2055–2064. doi:10.1007/s40200-024-01464-w
113. Gao F, Wu Y, Wang R, et al. Precise nano-system-based drug delivery and synergistic therapy against androgen receptor-positive triple-negative breast cancer. *Acta Pharm Sin B*. 2024;14(6):2685–2697. doi:10.1016/j.apsb.2024.03.012
114. Stringer F, Sims NA, Sachithanandan N, Aleksova J. Severe osteoporosis with pathogenic LRP5 variant. *JCEM Case Rep*. 2024;2(3):luae021. doi:10.1210/jcemcr/luae021