



Biomaterials for surgical repair of osteoporotic bone defects

Xu Luo^{a,b,1}, Jinwen Xiao^{a,b,c,1}, Qiming Yang^{a,b,1}, Xiaolong Lu^{a,c}, Qianjun Huang^{a,c},
Xiaojun Ai^{a,c}, Bo Li^{a,b,*}, Li Sun^{a,b,c,*}, Long Chen^{a,b,c,*}

^a Department of Orthopedics, Guizhou Provincial People's Hospital, Guiyang 550000, China

^b Medical College, Guizhou University, Guiyang 550000, China

^c Graduate School, Guizhou University of Traditional Chinese Medicine, Guiyang 550025, China

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ABSTRACT

As the global population ages, osteoporotic bone fractures leading to bone defects are increasingly becoming a significant challenge in the field of public health. Treating this disease faces many challenges, especially in the context of an imbalance between osteoblast and osteoclast activities. Therefore, the development of new biomaterials has become the key. This article reviews various design strategies and their advantages and disadvantages for biomaterials aimed at osteoporotic bone defects. Overall, current research progress indicates that innovative design, functionalization, and targeting of materials can significantly enhance bone regeneration under osteoporotic conditions. By comprehensively considering biocompatibility, mechanical properties, and bioactivity, these biomaterials can be further optimized, offering a range of choices and strategies for the repair of osteoporotic bone defects.

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1. Introduction

With the intensification of population aging, osteoporosis and the fractures it causes have increasingly become a focus of attention. Particularly, the treatment of osteoporotic bone defects has become a key area of orthopedic research. Patients with osteoporosis are prone to fractures from minor traumas or daily activities, often accompanied by osteoporotic bone defects [1]. Statistically, there are approximately 9 million osteoporotic fractures annually worldwide. These fractures have high disability and mortality rates, posing significant challenges to individual health and public health systems [2]. In osteoporotic bone tissue, the bone-forming ability of osteoblasts decreases, while the bone-resorbing activity of osteoclasts increases, leading to continuous loss of bone minerals and ultimately a reduction in bone rebuilding capacity and slow new bone formation. Elderly patients often have other chronic diseases, further complicating the repair of bone defects. Currently, the main treatment for osteoporotic bone defects is bone grafting surgery, including the use of autografts, allografts, and synthetic bone materials. However, due to the imbalance in the activity and differentiation of osteoclasts and osteoblasts in osteoporotic bone tissue, grafts are easily absorbed, which may lead to loosening of

internal fixations, delayed fracture healing, or even nonunion. Although new biomaterials show great potential in repairing osteoporotic bone defects, current research and development still face various challenges, including improving biocompatibility, promoting osteogenesis, and inhibiting osteoclast activity. Additionally, the mechanical strength, degradation rate, and cost-effectiveness ratio of materials are also important factors to consider in research and development [2–4]. Combining the experience in the development of biomaterials for bone defects, a correct understanding and knowledge of the biological processes in the osteoporotic microenvironment are crucial for clinical treatment and the development of new biomaterials. This article aims to comprehensively analyze the current application status and challenges of biomaterials in the repair of osteoporotic bone defects, providing a theoretical basis and practical guidance for further research. We hope that by summarizing and analyzing existing studies, we can offer valuable insights for the future research and clinical application of biomaterials.

2. Composite scaffold materials for osteoporotic bone defects

2.1. Bioceramics

In current biomaterial research, bioceramics, as a crucial material for repairing osteoporotic bone defects, have garnered widespread attention. There are various types of bioceramics, with research mainly focusing on micro/nanostructured calcium phos-

* Corresponding authors.

E-mail addresses: libo8588@hotmail.com (B. Li), lisun@gzu.edu.cn (L. Sun), longchen@gzu.edu.cn (L. Chen).

¹ These authors contributed equally to this work.

phate bioceramics, strontium (Sr) and silicon ion-enhanced bioceramics, akermanite bioceramics, and mesoporous ceramics loaded with bone morphogenetic proteins (BMP). Calcium phosphate bioceramics are particularly valued for their application in bone regeneration. Specifically, micro/nanostructured calcium phosphate bioceramics exhibit excellent biocompatibility and osteoinductivity. Studies have shown that these materials significantly promote bone regeneration in osteoporotic rats. For instance, Wang *et al.* found that a composite material of porous calcium phosphate ceramics with berberine (PCPC/BBR) significantly promotes bone regeneration and increases the expression of alkaline phosphatase (ALP), osteocalcin, BMP-2, and runt-related transcription factor 2 (Runx2) in bone marrow mesenchymal stem cells (BMSCs) [5]. Similarly, micro-/nano-structured calcium phosphate bioceramic composed of a nanoparticle-reinforced micro-whisker backbone (nwCaP), designed by Zhao *et al.*, with its unique sandwich structure, not only offers higher compressive strength and appropriate degradation rate but also improves cell adhesion, thereby facilitating osteoporotic bone regeneration [6]. Moreover, bioceramics incorporating Sr and silicon ions have also shown great potential in the field of bone defect repair. These materials not only promote bone regeneration but also aid in angiogenesis, further enhancing bone formation and mineralization processes [7,8]. Additionally, akermanite bioceramics, with a phosphorus-rich intermediate layer formed on their surface, can directly bond with newly formed bone, significantly stimulating osteogenesis and angiogenesis (Fig. S1 in Supporting information) [9,10]. Bioceramics demonstrate tremendous potential in the treatment of osteoporotic bone defects, offering a variety of choices and combinations for clinical treatment. By comprehensively considering the biocompatibility, mechanical properties, and bioactivity of these materials, their performance can be further optimized to meet diverse clinical needs.

2.2. β -Tricalcium phosphate (β -TCP)

In the field of bone tissue engineering, β -TCP based composite ceramics have attracted widespread attention due to their excellent biocompatibility and bone regeneration capabilities. Recent studies have focused on enhancing the functionality of these ceramics by adding various bioactive substances to improve their effectiveness in bone defect repair. Tian *et al.* introduced Sr phosphate-based glass (SPG; $45\text{P}_2\text{O}_5\text{-}32\text{SrO-}23\text{Na}_2\text{O}$) as a sintering additive in β -TCP composite ceramics (TCP/SPGs). Research indicates that TCP/SPG containing a certain amount of SPG possesses high biocompatibility and can significantly promote osteoblast activity while inhibiting osteoclast activity [11]. Tang *et al.* proposed an innovative approach using self-assembled polyelectrolyte multilayer (PEM) membrane coatings to locally fix calcitriol (Cal) in biphasic calcium phosphate (BCP) scaffolds, thereby promoting bone regeneration [12]. This novel coating technique offers a new avenue for precise drug release and bone repair. Another study by Tao *et al.* investigated the effects of Sr-doped β -TCP (Sr/ β -TCP) modified with aspirin (Asp-Sr/ β -TCP). Results showed that this scaffold significantly increased bone regeneration and mineralization, suggesting that the β -TCP scaffold combined with aspirin and Sr promotes bone regeneration, although further research in this area is still needed [13]. Additionally, absorbable collagen sponges (ACS) and medical grade polycaprolactone-tricalcium phosphate (mPCL-TCP) scaffolds have shown potential in enhancing cranial bone regeneration in rats [14]. Zhang *et al.* used low-temperature rapid prototyping technology (LT-RP) combined with polylactic-co-glycolic acid (PLGA) and β -TCP to prepare scaffolds with a porous structure. Experiments on animal models indicated that this novel scaffold effectively promotes bone defect repair in osteoporosis models, especially the best bone regeneration observed in the P/T/I/S combination. Overall, by incorporating various bone regeneration-

promoting materials, composite scaffolds of calcium phosphate ceramics have shown enhanced bone regeneration capabilities [15]. These composite materials not only promote the proliferation, adhesion, and osteogenesis of BMSCs but also demonstrate significant potential in promoting the regeneration of defective bones [13,16,17].

2.3. Hydroxyapatite (HA)

HA has become a research focus as a biomaterial due to its good biocompatibility and osteoconductivity. Recent studies have shown that the effectiveness of HA in bone regeneration can be significantly enhanced by modifying and functionalizing it. The research by Chandran *et al.* focused on Sr-doped HA. They found that Sr-containing HA implants demonstrated higher efficiency *in vivo* bone regeneration [18]. This finding highlights that loading different types of bone-promoting materials into HA can improve its osteogenic capability to varying degrees. Furthermore, Ignjatovic *et al.* focused on the impact of cobalt ion content on the bioactivity of HA. They observed that HA nanoparticles with a higher content of cobalt ions showed superior performance in promoting bone formation [19]. Quan *et al.* introduced a new multifunctional HA combining alendronate (ALN) and Fe_3O_4 . This composite material not only inhibits osteoclast activity but also promotes the proliferation and differentiation of osteoblasts. Under conditions of osteoporosis, this material can enhance the osteogenic capacity of the graft, accelerate bone remodeling, and thus promote bone regeneration [20]. Additionally, Raina *et al.* designed a calcium sulfate/HA (CaS/HA) biomaterial combined with zoledronic acid (ZOL). This material promotes bone formation by slowly releasing ZOL locally. Studies indicate that CaS/HA loaded with ZOL can provide a high concentration of ZOL at the site of bone defects, promoting the regeneration of cancellous bone in the femoral marrow cavity. Meanwhile, the local high concentration of ZOL has minimal systemic impact on the organism [21]. Therefore, chemical modification and structural design of HA can significantly enhance its potential applications in the treatment of osteoporotic bone defects and bone regeneration.

2.4. Mesoporous bioactive glass scaffolds (MBG)

In current research, MBG have been proven to be effective osteogenic material carriers. Particularly, the study of Sr-doped MBG (Sr-MBG) has shown its potential application in bone tissue engineering. Zhang *et al.* conducted a systematic study on Sr-MBG and found that incorporating Sr into MBG significantly enhances the proliferation of BMSCs and stimulates the expression of osteoblastic differentiation markers, such as ALP, collagen I (Col I), and Runx2. These findings suggest the potential of Sr-MBG scaffolds in promoting new bone formation in osteoporotic bone defects [22]. Additionally, the research by Zhang *et al.* further emphasized the significant reduction in the number of osteoclasts at the site of bone defects following implantation of Sr-containing bioactive glass [17]. Wei *et al.* also supported the role of Sr-containing bioactive glass in bone fracture repair, where local release of Sr promotes fracture healing [23]. Building upon this, Wu *et al.* developed Sr-containing bioactive glass scaffolds by creating modified amino-functional MBG. Their results showed that this Sr-containing amino-functional MBG scaffold not only possesses good biocompatibility but also significantly enhances *in vitro* osteogenesis and angiogenesis through the addition of Sr. In *in vivo* experiments, this scaffold demonstrated better performance in bone regeneration and vascular formation. Notably, bioinformatics analysis revealed that the scaffold could reduce the levels of reactive oxygen species in BMSCs in osteoporosis models

by activating the cyclic adenosine monophosphate-dependent protein kinase A (cAMP/PKA) signaling pathway, thereby exerting anti-osteoporotic functions while promoting osteogenesis [24]. In summary, Sr-containing bioactive glass scaffolds, especially modified amino-functional MBG scaffolds, show great potential in the treatment of osteoporotic bone defects, offering valuable directions for future research and applications.

2.5. Other biomaterials

In the field of osteoporotic bone defect repair, various biomaterials have demonstrated outstanding performance. For instance, the research team led by Kao incorporated Xuduan into Sr-doped calcium silicate/poly(ϵ -caprolactone) scaffolds (SRCS/PCL), and their results indicated that the scaffold stimulated bone regeneration in osteoporotic animal models. A synergistic effect between the released Sr ions and Xuduan promotes new bone formation [25]. The study by Chu and colleagues showed that lanthanum (La) doped layered double hydroxide (La-LDH) scaffolds not only enhanced the proliferation and osteogenic differentiation of BMSCs from ovariectomized rats but also significantly inhibited the generation of osteoclasts induced by receptor activator of nuclear factor- κ B ligand (RANKL) through suppressing the nuclear factor- κ B signaling pathway, demonstrating a dual regulatory role in bone formation and osteoclastogenesis inhibition [26]. In terms of design, Yang's research group developed a novel porous titanium scaffold combined with ZOL-loaded gelatin nanoparticles, which exhibited superior biocompatibility and bone regeneration capacity [27]. Research by Ray and team showed that foam iron implants coated with Sr or bisphosphonates (BPS) demonstrated significant bone formation on their surface when implanted in osteoporotic bone defects [28]. Wu and colleagues incorporated Sr into calcium silicate-based bioceramics (Sr-MSCs), finding that Sr-MSC scaffolds showed a trend towards promoting angiogenesis, indicating a positive osteogenic capacity in bone regeneration [29]. In other research, Yu's team observed the repair of bone defects using PLGA/collagen Type I (Col) microspheres in combination with BMSCs, revealing that the combined application of PLGA/Col microspheres and BMSCs repaired bone defects more rapidly, promoting trabecular reconstruction and improving bone quality in osteoporotic rats [30]. The research group led by AJDUKOVIC designed and synthesized a novel composite scaffold (BCP/PLGA), which demonstrated high osteogenic regeneration capability and increased osteoblastic cell activity [31]. Zheng *et al.* designed a new type of poly(ether-etherketone) (PEEK) material composed of PLGA and ALN-loaded nHA (nHA-ALN), with a coating grafted with the anti-inflammatory cytokine interleukin-4 on the outer surface. This modified PEEK material exhibited excellent bone regeneration and bone immune regulation effects in osteoporosis model rats [32]. On the other hand, Mengen Zhao and team developed a PEEK based bioactive composite scaffold containing Sr²⁺-doped bioactive glasses (SrBG) and ALN-SrBG (A-SrBG). In osteoporotic animal models, this composite scaffold exhibited good biocompatibility and bone regeneration capability, especially the ASP40 group, which showed the best osteogenic activity and osteoclast inhibition effect [33]. Another study conducted by Jun-Kyu Lee and colleagues developed a nitric oxide-releasing, bioinspired scaffold made of PLGA, combined with organic/inorganic extracellular matrix (ECM) and magnesium hydroxide. The scaffold also contained nanoparticles of zinc oxide (ZO), ALN, and BMP-2. The results showed that the nitric oxide produced by ZO stimulated the activity of cGMP and protein kinase G, and by inhibiting the Wnt/ β -catenin signaling pathway, it reduced the RANKL/osteoprotegerin ratio, regulating bone homeostasis in osteoporotic rat models, demonstrating superior new bone formation [34]. Addressing the issue of dysfunctional and aging mesenchymal stem cells in osteoporotic environ-

ments due to elevated levels of reactive oxygen species (ROS), Chen *et al.* developed a bone microenvironment-sensitive biofunctional metal-organic framework (MOF) coating on titanium surfaces using a hydrothermal method. This coating, formed by the coordination of pxyllylenebisphosphonate (PXBP) and Ce/Sr ions, with the anchoring of Ce and Sr ions, exhibited superoxide dismutase and catalase-like catalytic activities, degrading ROS in MSCs and restoring their mitochondrial function. *In vivo* studies showed that this bio-MOF coated titanium implant could restore the function of mesenchymal stem cells at the implant site, promote new bone formation, thereby improving bone integration in osteoporotic rats [35]. And these MOFs have multiple functions to adapt to special applications. Li *et al.* have also suggested that MOFs can load Ca²⁺, ALN, ZOL, ketoprofen and other drugs, which play an important role in the treatment of osteoporosis, and can significantly reduce the side effects caused by the use of BPS. Its good drug loading rate and controlled release make it an ideal drug system for the treatment of osteoporosis [36]. Related studies have shown that Wnt signaling pathway is closely related to the osteogenic differentiation of cells and the maintenance of adequate bone mass and density, and plays an active role in the process of osteoporotic fracture healing. Wang *et al.* reported a novel approach combining the synthesis of MOFs and protein encapsulation in a one-pot process based on zeolitic imidazolate framework-8 (ZIF-8) and Wnt3a protein, with improved biomechanical behavior and enhanced protein biological response. The results showed that the Wnt3a protein-loaded ZIF-8 crystals served as efficient drug delivery vehicles to promote osteogenesis, preventing protein denaturation. In particular, Wnt3a-loaded ZIF-8 nanoparticles (Wnt3a@ZIF-8 NPs) had higher efficacy on BMSCs than ZIF-8 NPs or Wnt3a proteins, contributing to the osteogenesis through ZIF-8 crystals and intracellular Wnt3a proteins released from Wnt3a@ZIF-8 NPs [37]. Current research on various biomaterials in osteoporotic bone defect repair demonstrates superior performance, and future studies can focus on the design and optimization of multifunctional biomaterials. Exploring the introduction of new bioactive components in existing scaffolds to enhance osteogenesis and achieve better therapeutic effects through more precise release mechanisms.

3. Modified calcium phosphate bone cement (CPC) for osteoporotic bone defects

In the field of osteoporotic bone defect repair, the application of CPC has become a significant advancement. CPC is highly regarded for its excellent biocompatibility, bone generation-promoting ability, and outstanding osteoconductivity. Recent research trends indicate that by incorporating metal ions into CPC, its application potential can be significantly enhanced, especially in the treatment of osteoporotic bone defects.

3.1. Selenium (Se)

Se is a trace element that plays a crucial role in bone formation and metabolism. Studies have shown that Se can inhibit the differentiation and formation of mature osteoclasts *in vitro* and promote osteogenic differentiation of BMSCs, offering a new perspective for bone defect treatment [38,39]. Additionally, Se significantly protects against oxidative stress and cell apoptosis *via* the mitochondrial pathway, which is particularly important in the context of bone regeneration [40]. Based on these findings, some research teams have combined Se with CPC, creating a Se-CPC composite material. Once implanted in bone defect areas, this material absorbs surrounding tissue fluid and gradually releases selenium ions. This localized release of Se not only activates the OPG/RANKL pathway related to bone regeneration but also effectively inhibits local oxidative stress, thus promoting the process of

defective bone regeneration and bone formation in ovariectomized rat models [41]. Notably, the high affinity between Se and CPC ensures that the Se released from the Se-CPC scaffold effectively binds with bone tissue in and around the defect area, exerting its biological function [42]. In this context, researchers like Zhou *et al.* have developed a new type of Se-modified bone cement based on silk fibroin and CPC (SF/CPC). When this Se-modified bone cement was implanted in ovariectomized rats for 8 weeks, it significantly promoted the repair of bone defects, increased new bone tissue formation, and enhanced the expression of GPx1 [43]. These findings not only demonstrate the potential of Se-CPC in bone regeneration but also provide important references for the design of future bone defect repair materials.

3.2. Sr

The systemic use of Sr has been proven to increase bone mass by simultaneously stimulating osteoblasts and inhibiting osteoclasts, offering a new strategy for treating osteoporotic bone defects [44,45]. Hence, Sr demonstrates significant potential in enhancing the bioactivity and biocompatibility of biomaterials. Further research indicates that incorporating Sr into CPC can stimulate bone formation both within and around the bone cement. Notably, the local release of Sr does not lead to an increase in its systemic concentration, thereby effectively reducing the potential for adverse reactions [46]. Moreover, Sr modification enhances the strength and radiographic contrast of the cured cement, showing unique advantages in kyphoplasty, especially in minimally invasive spinal surgeries [44]. Tao *et al.* further added BMP-2 to Sr-modified bone cement. Their findings reveal that lower doses of BMP-2 combined with locally applied Sr-modified CPC can promote the healing of bone defects in ovariectomized (OVX) rats. Compared to using CPC and Sr-modified CPC alone, the combination of a single dose of BMP-2 and Sr-CPC showed a more potent effect in promoting local bone formation. This suggests a synergistic effect of BMP-2 and Sr-CPC in promoting local bone formation in osteoporotic rats [47]. To improve the utilization and efficacy of Sr, Miao *et al.* prepared chitosan-coated Sr-containing calcium sulfate hemihydrate (CS-SrCSH). Studies show that CS-SrCSH microspheres degrade slower than SrCSH microspheres both *in vitro* and *in vivo*, with a more stable release rate of Sr²⁺, achieving a sustained-release effect. *In vivo* experiments further demonstrate that CS-SrCSH microspheres have long-term abilities in osteogenesis, angiogenesis, and bone metabolism inhibition [48]. Building on the research of Sr and selenium ions, Lu *et al.* explored the incorporation of lithium (Li) into CPC, forming a CPC@Li composite material. Compared to regular CPC, CPC@Li shows enhanced abilities to promote the adhesion, proliferation, and osteogenic differentiation of rat bone marrow stem cells. In osteoporotic mouse models, the implantation of CPC@Li led to the formation of more new bone around it, displaying superior osteogenic and bone integration abilities [49]. These studies not only demonstrate the potential of various metal ion-modified CPCs in bone defect repair but also provide valuable references for the design and application of future biomaterials.

3.3. Other ingredient

In addition to loading metal ions, the research and application of CPC composite systems have received widespread attention. The composite system formed by the combination of PLGA particles with CPC, represented by CPC/PLGA, marks an important advancement in this research area. This composite system not only achieves controlled degradation of CPC but also can load and release a variety of bioactive substances, such as bone inductive growth factors, which has been well-documented and supported

in the literature [50]. Studies by Gunnellaa and Bungartz *et al.* focused on integrating the growth/differentiation factor-5 (GDF-5), also known as BMP-14, into the CPC/PLGA composite system. Their experimental results showed that GDF-5 significantly promoted bone formation in the lumbar osteoporotic sheep model. Notably, low doses of GDF-5 (≤ 100 micrograms) were sufficient to effectively enhance mid-to-long-term bone formation [51,52]. These findings provide an experimental basis for a novel combination of CPC+GDF-5, suggesting its potential as an alternative to the biologically inert, supra-physiologically rigid polymethylmethacrylate (PMMA) bone cement currently used for treating osteoporotic vertebral fractures. Research by Gunnellaa *et al.* on integrating BMP-2 into the CPC/PLGA composite system also supports this conclusion. Their results further confirmed the effectiveness of the CPC/PLGA composite system in promoting new bone formation and increasing bone volume at bone defect sites [53]. These findings emphasize the improved repair effects on osteoporotic bone defects through rational design of composite materials to effectively load and release key bioactive factors. Additionally, research by Li *et al.* developed a recombinant human BMP-2-loaded gelatin microsphere calcium phosphate bone cement (rhBMP-2/GM/CPC) composite material. This novel bone graft composite material can effectively release loaded factors, thereby repairing osteoporotic bone defects more effectively and demonstrating the innovative potential of materials science in medical applications [54]. On the other hand, traditional drug treatment for osteoporosis mainly relies on the systemic application of BPS. Although these drugs are significant in increasing bone density, preventing bone loss, and reducing fracture risk, their systemic application has certain limitations, such as gastrointestinal disturbances, high fever, and other severe adverse reactions, as well as the potential risk of jawbone osteonecrosis. Against this backdrop, research by Verron *et al.* explored the possibility of increasing new bone formation on the surface of CPC by locally releasing BPS from CPC. The study showed that local release could effectively alleviate adverse reactions of systemic application, but also pointed out the urgent need to optimize the radiopacity and injectability of CPC [55]. In addressing the injectability and biocompatibility of CPC, research by Hu *et al.* provided valuable insights. They studied alkali-treated SF/CPC, and the results showed that this material has good injectability, anti-washout properties, and biocompatibility [56]. This finding positively contributes to enhancing the clinical application potential of CPC-based composite materials.

4. Hydrogel for osteoporotic bone defects

In recent years, hydrogels have attracted researchers' attention due to their potential applications in tissue engineering and drug delivery, particularly in the field of bone regeneration. Hydrogels are commonly fashioned into scaffolds and then implanted in the body to regulate the behavior of bone marrow stem cells [57,58]. To date, numerous hydrogel scaffolds have been developed to promote bone mineralization and integration in bone defect areas, including engineered gels made from natural components and 3D printed dual-network hydrogels [57,59]. Current hydrogel scaffolds often swell in physiological aqueous environments, significantly reducing their mechanical stability and shape compatibility. Additional swelling caused by hydrogel degradation can also induce severe adverse reactions in surrounding tissues [57,60]. This severely limits their use as load-bearing implants in the treatment of osteoporosis. Despite growing interest in hydrogel bone scaffolds, designing a biocompatible and stable hydrogel for treating osteoporotic bone defects remains crucially necessary.

Zhao *et al.* developed a unique mineralized hydrogel scaffold designed to promote the expression of osteogenic markers and repair osteoporotic bone defects. This scaffold, formed through

the supramolecular assembly of nano-HA (n-HAp), sodium carbonate (Na_2CO_3), and polyacrylic acid (PAA), is known as CHAP-PAA. Under physiological conditions, CHAP-PAA demonstrates excellent shape and mechanical property retention, along with good primary stability, biocompatibility, bioactivity, and osteoconductivity. Studies have shown that CHAP-PAA significantly enhances the proliferation, differentiation, and extracellular matrix production of BMSCs, effectively promoting bone regeneration in the complex pathological environment of osteoporosis [61]. Further research by Yuan *et al.* explored the effects of Sr-doped HA gel was modified by integrating branched poly(ϵ -lysine) dendrons with third-generation branches exposing phosphoserine (SrHA/G3-K PS). Their experimental results indicated that SrHA/G3-K PS effectively downregulated the gene expression of inflammatory factors such as IL-1b, TNF- α , and MCP-1. *In vivo* experiments showed that adding G3-K PS to HA significantly promoted new bone regeneration [62]. Yang *et al.* prepared a alginate–chitosan/trace elements-multidoped octacalcium phosphate–bioglass (AT-CS)/teOCP-BG hydrogel composite as an injectable biomaterial. *In vivo* experiments demonstrated that this injectable biomaterial significantly enhanced bone regeneration in osteoporotic rats [63]. Lastly, Zhao *et al.* introduced a multifunctional scaffold aimed at improving the physiological microenvironment of osteoporosis and promoting the regeneration of vascularized bone defects. This scaffold, composed of gel-coated hollow mesoporous silica nanoparticles (HMSNs/GM) containing pro-osteogenic parathyroid (PTH) and anti-osteoclastogenic ALN, is combined with magnesium calcium phosphate cement (MCPC). The results showed that this approach significantly promoted the proliferation, migration, and tubular structure formation of endothelial progenitor cells in the osteoporotic pathological environment, supporting its effectiveness in promoting the repair of vascularized bone defects and improving the microenvironment of osteoporosis [64]. These studies provide a new perspective on composite hydrogels in repairing osteoporotic bone defects, and future research may continue to explore more functionalized hydrogels, as well as different combinations and mechanisms for promoting the repair of osteoporotic bone defects.

5. Molecular and drug delivery for osteoporotic bone defects

5.1. Protein delivery

Protein delivery has garnered significant attention for repairing osteoporotic bone defects. Commonly used proteins include BMP-2, BMP-6, BMP-7, GDF-5, and related peptides, among which the research on BMP-2, BMP-7, and GDF-5 is more mature [51,52,65–70]. Studies have shown that biomaterials loaded with BMP-2 significantly promote new bone formation in osteoporotic bone defects (Fig. S2 in Supporting information) [53,54,65,66,71,72]. Sun *et al.* developed a heparinized mineralized small intestinal submucosa (mSIS) loaded with BMP2-related peptide P28 (mSIS/P28), as a novel guided bone regeneration (GBR) membrane. The *in vitro* results indicated that mSIS-Heparin-P28 promotes the cell proliferation activity, ALP activity, and mRNA expression of osteogenic-related genes in rBMSCs OVX without additional osteogenic components; *in vivo* experiments suggested that mSIS-heparin-P28 significantly stimulates osteoporotic bone regeneration [70]. However, some studies have noted that BMP-2 does not show significant positive effects in the repair of osteoporotic bone defects [21]. Other research confirmed that ovariectomy and corticosteroid-induced osteoporosis significantly weakened the activity of BMP-2, reducing its bone repair promoting ability [67]. There is controversy regarding the role of BMP-2 in the repair of osteoporotic bone defects, although most researchers believe it plays a positive role. BMP-7, a subclass of BMP, was proven by Zhang *et al.* to promote new bone formation at osteoporotic bone defect

sites [69]. Additionally, the combination of BMP-7 with platelet-derived growth factor (PDGF) significantly promotes bone regeneration. Recent studies show that GDF-5 promotes medium to long-term bone formation by altering bone structure, formation, absorption, and compressive strength, demonstrating good results in a live sheep lumbar vertebra bone loss model [52]. GDF-5 significantly stimulates angiogenesis at bone defect sites, although its bone formation capability may be slightly inferior compared to BMP-2 [73]. To enhance the bone formation capability of GDF-5, a mutant GDF-5 protein named BB-1 was recently produced [74]. Compared to wild-type GDF-5, BB-1 exhibits stronger bone formation ability, even comparable or superior to BMP-2. At the same time, BB-1 maintains its angiogenesis-promoting characteristics [75]. Gunnella *et al.* found that a single local dose of BB-1 as low as 100 μg is sufficient to enhance medium to long-term bone formation, a conclusion also reached by Bungartz *et al.* [51,52]. These findings suggest that the mutant GDF-5 protein BB-1, as a biomaterial, has great potential to promote bone formation.

5.2. Drug delivery

In the treatment of osteoporosis, pharmacotherapy is a common strategy, encompassing a variety of types such as bone-forming agents, bone resorption inhibitors, selective estrogen receptor modulators (SERMs), and RANKL inhibitors [76–79]. Despite this, these therapies face many challenges in practical application, including low bioavailability, gastrointestinal reactions, unstable efficacy, and systemic side effects [80]. Moreover, long-term use may increase the risk of osteonecrosis, non-traumatic fractures, thrombosis, and cardiovascular diseases [80–83].

To overcome these limitations, researchers are working on developing new drug delivery systems. Li and colleagues developed an injectable hydrogel system based on tetramer polyethylene glycol, loaded with ALN. This system not only forms a gel rapidly and has good injectability, but it also achieves long-acting drug release for over 28 days, effectively promoting *in situ* bone regeneration [84]. Similarly, Yang's team coated Ti-6Al-4V alloy scaffolds with polydopamine and successfully combined them with gelatin nanoparticles loaded with ZOL. This strategy significantly improved the integration of the implant with bone, enhanced osteoconductivity, ensured the slow release of ZOL, and effectively regulated osteoblasts and osteoclasts bidirectionally, thus promoting bone regeneration [27]. Additionally, delivery systems containing trace elements have shown broad application potential in the treatment of osteoporosis. For instance, biomaterials rich in Sr, Se, magnesium, and zinc have achieved positive research outcomes in this field [13,85–91]. Miao and other researchers used the electrostatic interaction between chitosan and SrCSH to prepare CS-SrCSH microspheres [48]. This novel material demonstrated sustained osteogenesis, angiogenesis, and inhibition of bone resorption, effectively prolonging the residence time of Sr^{2+} in the body. Considering the issues of low bioavailability and poor solubility of natural compounds or extracts in the body, Li *et al.* designed an injectable composite microsphere of n-HA/resveratrol (Res)/chitosan (CS) that locally released Res in a controlled manner, significantly promoting bone regeneration and effectively reducing inflammatory responses [92].

5.3. Gene delivery

MicroRNAs (miRNAs) are a class of conserved RNA molecules synthesized in organisms, playing a crucial role in regulating various biological processes including the formation of osteoclasts, osteogenic action, and bone formation. Studies have shown that specific miRNAs such as miR-23a, miR-133, miR-335, and miR-3077–5p can inhibit osteogenesis by directly interacting with the 3'

untranslated region of the osteogenic transcription factor Runx2 [93]. Conversely, miR-21 promotes the formation of osteoclasts by targeting the Fas ligand, thereby inhibiting osteogenesis [94]. Focusing on the application of RNA interference therapy in the repair of osteoporotic bone defects, Liu *et al.* constructed small extracellular vesicles (SEVs) derived from human BMSCs with high expression of miR-20a and achieved sustained delivery of SEVs using HA hydrogel. After five weeks, about 80% of SEVs were released, prompting the migration of BM-MSCs around the bone defect to the porous titanium alloy, leading to cell proliferation, differentiation, and extracellular matrix deposition, thus effectively promoting osteogenesis. *In vivo* experiments showed that titanium-hydrogen composite materials had better osteogenic effects than pure titanium, and the group treated with titanium-hydrogen-SEV-20a showed the best performance in terms of bone integration and synergy [95]. Zhang *et al.* designed a hyperbranched polymer (HP) carrier for miRNA delivery, connecting short polyethylene glycol chains and low molecular weight cationic polyethyleneimine (PEI) to the outer shell of a hyperbranched hydrophobic molecular core. The addition of miRNA further assembled it into nano-sized spherical shells sandwiched between the inner and outer hydrophilic polyethylene glycol layers. To address the uncontrolled release issue in miRNA delivery systems, researchers encapsulated stable polymers carrying miR-26a in biodegradable polymer microspheres (MS), allowing controlled release duration and efficient delivery [96]. Li *et al.* constructed hybrid rod-shaped virus vectors expressing miRNA sponges to counteract miR-140 or miR-214, significantly promoting osteogenesis in ovariectomized mouse BMSCs and notably enhancing the ability of OVXBMSCs to inhibit osteoclast maturation, particularly in inhibiting miR-214 expression [97]. Zhang and colleagues developed a targeted drug delivery system based on aspartate, serine, serine (AspSerSer)₆-liposomes, demonstrating innovative applications in the field of drug delivery. The unique structure of the system allows it to effectively position drugs containing siRNA specifically to the surface of bone formation, reducing the impact of siRNA on other non-bone tissues. The study showed that this method significantly promoted bone formation in both healthy and osteoporotic rats, enhancing bone microstructure and increasing bone mass [98]. This research not only provides an efficient drug delivery system but also demonstrates its potential applications in promoting bone formation and treating osteoporosis. Despite the enormous potential of RNA interference (RNAi) therapy in treating osteoporosis, several key challenges need to be overcome for its successful application in clinical treatment. These challenges include achieving effective delivery of RNA molecules, ensuring their biostability, maintaining long-term drug release, and enhancing drug targeting. Solutions to these challenges will significantly impact the clinical application of gene delivery in repairing osteoporotic bone defects.

In recent years, the semaphorin family, as key biological regulatory molecules, has played a crucial role in various physiological and pathological processes, including cardiac development, angiogenesis, tumor metastasis, osteoclastogenesis, and immune regulation. To date, more than 20 different types of semaphorins have been identified [99]. These discoveries have not only enriched our understanding of the functions of semaphorins but also provided new directions for the treatment of related diseases. In the study by Yang *et al.*, a D-Asp8-based position-specific bone-targeting delivery system ((AspSerSer)₆-(STR-R8)+pcDNA3.1(+)-Sema3a-GFP) was successfully developed. Administered *via* intravenous injection, this system allows for *in vivo* treatment of animals in research settings. Due to the unique structure of (AspSerSer)₆ and its chemical affinity for bone surfaces, pcDNA3.1(+)-Sema3a-GFP is specifically transported to bone tissues like the femur. In these tissues, the eukaryotic expression vector pcDNA3.1(+)-Sema3a-GFP induces the expression of Sema3A, which aids in reversing bone loss by

promoting the differentiation of osteoblasts and inhibiting the formation of osteoclasts [100]. Furthermore, the study by Zhang *et al.* revealed the association of overexpression of semaphorin 4d (Sema4d) in bone tissue with osteoporosis. Particularly in animal models of osteoporosis, the expression levels of Sema4d were significantly elevated [101]. This suggests that Sema4d is an important and viable target for gene silencing therapy. In the context of translational medicine, these findings provide new therapeutic approaches, namely, by expressing or silencing specific semaphorin genes at targeted sites, simultaneously inhibiting bone resorption and promoting bone formation to reverse established osteoporosis. Overall, the role of the semaphorin family in regulating cellular biological processes offers new therapeutic strategies, especially in the treatment of osteoporotic bone defects. These studies not only enhance our understanding of the functions of semaphorins but also lay the groundwork for future clinical applications.

6. Conclusion and outlook

This article comprehensively analyzes the current state and challenges of biomaterial research for osteoporotic bone defects. Osteoporosis is a global health issue that has become increasingly prominent due to the growing aging population and the resultant bone defects it causes. The treatment of osteoporotic bone defects primarily relies on bone grafting surgeries, but significant challenges exist due to the unique physiological conditions of osteoporosis patients. In recent years, significant progress has been made in the research and application of synthetic bioactive materials such as bioactive glass, ceramics, polymers, and composites. These biomaterials can be functionalized through surface modification or doping with bioactive factors (such as proteins, drugs, and metal ions), enhancing their ability to promote bone repair. Strategies for protein, gene, and drug delivery in biomaterials have improved their targeting at the site of action, enhanced their structural stability *in vivo*, and controlled release rates. Overall, current research progress indicates that by considering biocompatibility, mechanical properties, and bioactivity comprehensively, these biomaterials can be further optimized, providing diverse options and strategies for the repair of osteoporotic bone defects.

Through a review of literature and combining our own experience in biomaterials, the following considerations should be taken into account for biomaterials aimed at repairing osteoporotic bone defects: (1) Further integration of nanotechnology with biomaterials. The application of nanotechnology in biomaterials can significantly enhance their biocompatibility and osteoinductivity. Future research could focus on developing more efficient nanocomposites that not only provide better support for bone regeneration but also enhance therapeutic effects through improved protein, gene, and drug delivery systems. (2) Advancing the development of smart biomaterials capable of responding to changes in the internal environment, such as pH, temperature, or biochemical signals. Future studies could focus on developing smart materials that actively promote bone regeneration and inhibit osteoclasts in the microenvironment of osteoporosis. (3) Addressing the imbalance between osteoclast and osteoblast activity in the osteoporotic microenvironment by combining biomaterials with drugs, growth factors, or cell therapies to enhance the repair of bone defects. (4) Conducting in-depth research on the interaction mechanisms between biomaterials and bone tissue. This includes studying how material surface characteristics affect cell adhesion, proliferation, and differentiation, and how to optimize these interactions by altering the chemical and physical properties of materials. Future research should focus more on understanding and simulating the biological processes in the osteoporotic microenvironment to develop more effective and targeted treatment strategies. Additionally, with technological advancements, the development of new

biomaterials should pay more attention to the cost-effectiveness ratio, facilitating their widespread application and popularization. Through continuous scientific exploration and technological innovation, there is hope for providing more effective and safer treatment methods for patients with osteoporotic bone defects in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ccl.2024.109684.

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