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REVIEW

Zinc Doped Synthetic Polymer Composites for Bone Regeneration: A Promising Strategy to Repair Bone Defects

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Abstract: Zinc-doped synthetic polymer composites are a potential approach for bone regeneration, effectively meeting the urgent requirement for efficient bone repair materials. This review critically examines recent advancements in zinc-doped synthetic polymer composites for bone regeneration, with a focus on their synthesis methods, material properties, biological interactions, and potential clinical applications. The primary findings indicate that adding zinc to synthetic polymers, such as poly (lactic-co-glycolic acid), polycaprolactone, and polyethylene glycol, enhances their mechanical strength, bioactivity, and biocompatibility. Those composite materials enable the regulated release of zinc, which stimulates cellular responses crucial for bone repair. The importance of this technique lies in its ability to give a versatile framework that promotes the regeneration of bone tissue, presenting a new alternative for patients with bone abnormalities and enhancing clinical results. Despite these advantages, Zn-doped polymer composites need to overcome challenges including high Zn concentration toxicity and altered degradation kinetics and changes in mechanical properties for optimized clinical success. Moreover, homogeneous Zn distribution within polymer matrices stands as an essential requirement to accomplish both stable bioactivity properties and uniform mechanical characteristics. The use of advanced fabrication methods will help overcome pelletization issues to improve the therapeutic application of Zn-doped polymer composites in bone tissue regeneration. This review is intended to provide a valuable resource for future research, contributing to the advancement of innovative therapies for bone regeneration. It facilitates the development of innovative solutions in regenerative medicines and bone repair by emphasizing the prospective role of zinc-doped polymers.

Keywords: zinc doping, synthetic polymer composites, bone regeneration, bone defects, biomaterials

Introduction

Bone cancer and osteoporosis, lead to a growing demand for sophisticated bone healing materials appropriate for skeletal reconstruction. Bone is widely recognized as the second most regenerative tissue in the body after blood. The body depends on bones for several essential functions, including the protection of vital organs, support for the body's structure, and enabling movement by serving as levers for muscles. Additionally, bones are crucial for storing minerals like calcium and phosphorus and house the bone marrow, where blood cells are produced.[1] Several causes can lead to bone defects, including congenital deformity, trauma, and infection. These defects cause severe pain and place a considerable strain on the healthcare system.[2] Each year, around $45 billion is spent on the healthcare of 15 million individuals with bone-related issues, including 1.6 million trauma-induced fractures and 2 million osteoporosis-related abnormalities.[3] There

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are almost 2.2 million bone transplant surgeries conducted globally every year, with an approximate annual cost of 2.5 billion dollars.[4]

Bone deficiencies remain a major clinical challenge, with the demand for bone substitutes outpacing the availability of autogenous, allogeneic, and xenogeneic grafts. Autogenous grafts, harvested from the patient's own body, are considered the gold standard due to their low risk of immune rejection and their ability to promote bone formation. However, they are limited by donor site morbidity and the volume of graftable tissue available. Allografts, derived from human donors, offer an alternative with sufficient supply and the ability to support bone regeneration. While they share osteoinductive and osteoconductive properties, their effectiveness is constrained by donor availability, immune rejection risks, and slower integration. Advances in processing techniques are improving their immunocompatibility. Xenografts, sourced from animals such as cows or pigs, can also support bone regeneration but face challenges related to immune response and disease transmission. Recent developments in graft sterilization are enhancing their safety and efficacy for bone repair. While all three types of grafts provide valuable solutions for bone repair, each has limitations that ongoing research aims to address, aiming to improve clinical outcomes and meet the growing demand for bone substitutes.[5]

Consequently, the development of techniques for tissue engineering has met the requirements for new and creative methods to restore and regenerate bone abnormalities. Bone tissue engineering (BTE) seeks to create a bone replacement using cell biology and architecture principles. Bone defects arise from congenital abnormalities, trauma, tumor resection, and infections, which not only result in significant pain but also impose considerable strain on healthcare systems. In recent decades, bone tissue engineering (BTE) has emerged as a promising approach for addressing these defects. BTE involves the combination of biomaterials and stem cells to promote the regeneration of damaged bone. A diverse range of biomaterials, including ceramics, metals, natural and synthetic polymers, and their composites, have been utilized in BTE to repair and replace compromised bone tissue.[6] Recent advancements in bone tissue engineering (BTE) have leveraged various processing techniques, including solvent casting, freeze-drying, and three-dimensional (3D) printing, to develop synthetic polymer scaffolds for bone regeneration. Solvent casting involves dissolving a polymer in a solvent, which is then cast into a mold to form a scaffold. This method allows for precise control over the scaffold's porosity and surface characteristics, which are critical for cell attachment and osteointegration. However, challenges such as solvent toxicity and the potential limitations in mechanical strength can affect the functionality of the resulting scaffold. Freeze-drying, or lyophilization, creates highly porous scaffolds by freezing a polymer solution and subsequently removing water under vacuum. This technique enhances cellular infiltration and nutrient diffusion, promoting bone regeneration. However, the mechanical properties of freeze-dried scaffolds may not always meet the demands of load-bearing applications. Three-dimensional (3D) printing enables the precise fabrication of scaffolds with complex geometries, offering the ability to tailor porosity, mechanical strength, and bioactivity. This method allows for the creation of patient-specific scaffolds that closely match the defect site, potentially improving the efficiency of bone regeneration. 3D printing also facilitates the integration of multiple materials, further enhancing scaffold functionality. Each of these techniques offers distinct advantages, and ongoing research aims to optimize their use in the development of more effective bone repair scaffolds.[7]

Synthetic polymers used in bone tissue engineering can be tailored in terms of their composition, architecture, and physical properties, providing flexibility in their design and function. These materials are also highly reproducible, allowing for consistent manufacturing of scaffolds with desired characteristics. Additionally, synthetic polymers possess the unique ability to degrade over time, offering initial mechanical support to the defect site while gradually breaking down to accommodate the growth of newly formed tissue. However, while these polymers may exhibit osteoconductive properties, they often fail to achieve complete bone regeneration when used alone. To overcome this limitation, the incorporation of zinc (Zn) is emerging as a promising strategy. The release of Zn^{2+} ions from these polymers has been shown to stimulate the proliferation of bone-forming cells, thereby accelerating the bone regeneration process and enhancing the overall efficacy of the scaffold.[8] Zn-doped synthetic polymer composites receive attention because Zn^{2+} ions serve dual functions in the bone metabolic process. During osteogenesis Zn functions as a vital stimulant for osteoblasts to multiply and differentiate and simultaneously suppresses osteoclast activity. Zn-doped synthetic polymers demonstrate dual antibacterial properties together with angiogenesis promotion which increases their potential application as bioactive components for bone scaffolds.[9–12] Nanocomposite biomaterials are advanced materials designed for biomedical applications, combining a matrix made of biopolymers and biodegradable materials with small-sized,

bioactive fillers. Biopolymers, such as collagen or chitosan, are naturally derived and biocompatible, offering a supportive scaffold for tissue regeneration. Biodegradable materials, like polylactic acid (PLA) or polycaprolactone (PCL), gradually break down within the body, eliminating the need for surgical removal as new tissue forms. Bioactive fillers, often at the nanometer scale, include substances like hydroxyapatite or growth factors that enhance the material's biological activity, promoting cell proliferation and tissue regeneration. The integration of these components creates a synergistic effect, where the matrix provides structural support, the fillers stimulate biological responses, and the biodegradability ensures the material gradually disappears, making nanocomposite biomaterials ideal for applications in bone regeneration and other areas of tissue engineering.[13] The incorporation of nano-fillers into the polymer matrix enhances both the mechanical and biological properties of the scaffold, making it more suitable for bone regeneration applications. This is crucial for ensuring compatibility with tissue regeneration.[14]

Zinc ions integrated into bone tissue engineering scaffolds has gained significant attention because of their fundamental importance in osteogenic processes.[15]

Scientific interest in zinc-based materials has witnessed dramatic changes as research activity and focus developed from 2000 through 2025. A bibliometric analysis of zinc-based biodegradable metallic materials for publication research between 2000 and 2022 has revealed 632 results including 553 research articles and 50 reviews.[16] Throughout 2007 to 2013 the number of publications remained rare. Research interest in this field experienced a dramatic yearly rise starting from 2014 according to publication records. The increased attention toward zinc applications in biomedical research corresponds to general scientific acknowledgment of its biomedical potential. The research community investigates zinc-based biomaterials since they provide multiple advantages that include their biological relevance and both compatibility and degradability features alongside tissue regeneration properties. The breakdown of metallic zinc implants supports healing processes through a rate that matches tissue regeneration rates while triggering tissue rearrangement mechanisms.[17]

The method through which Zn^{2+} leaves scaffolds determines both bone tissue growth outcomes and influences cellular behavior and degradation.[17] The controlled and extended release of Zn^{2+} activates osteoblasts along with promoting angiogenesis and enabling extracellular matrix formation which are necessary elements for successful bone healing.[18] The rapid release of Zn^{2+} will generate toxicity that can harm cellular functions and cause damage to tissue regenerative processes. Different initiatives have been used to maximize Zn^{2+} release patterns through material structure modification and surface treatment developments.[15] Zn-based biodegradable metals along with Zn-Mg and Zn-Cu alloys provide the ability to customize degradation speeds and regulate Zn^{2+} ion discharge thus enhancing mechanical performance while improving biocompatibility.[19,20] Understanding and regulating Zn^{2+} release kinetics is crucial for maximizing the benefits of zinc in bone tissue engineering while minimizing potential cytotoxic risks associated with uncontrolled ion release. The tuning of these specific parameters allows Zn^{2+}-incorporated biomaterials to become highly effective for improving bone healing together with scaffold integration.

This review examines zinc-doped synthetic polymer composites used in bone tissue engineering by investigating their potential upshots on mechanical properties and bioactivity and biocompatibility. Moreover, it examines the methods of synthesis and structural features and biological interactions of materials to understand their capability in bone regeneration. Studies were selected based on their relevance to the topic, methodological rigor, and the significance of their experimental or clinical findings. Preference was given to more recent studies that contribute to understanding key developments in the field. This review starts with a section that explains synthesis techniques of zinc-doped polymer composites before detailing their physicochemical properties, biological interactions and their function in bone regeneration. The review evaluates current challenges alongside prospects in this field after investigating their utilization challenges. Moreover, it focuses on building knowledge that promotes the development of innovative materials to enhance bone repair and regeneration.

Zinc Oxide (ZnO)-Doped Polymers in Bone Tissue Engineering

The combination of zinc oxide (ZnO) with polymer-based scaffolds and nanofibers and nanoparticles has become prominent because ZnO serves simultaneously as a structural support material and biological functional component. The core advantage of ZnO stems from its antimicrobial effects alongside its biological compatibility together with its

capability to support osteogenesis by steady Zn^{2+} ion release.[21] ZnO induces the gradual release of Zn^{2+} ions which modulates cellular pathways towards differentiation of osteoblasts and stimulates new blood vessel formation.[22] The controlled release mechanism of ZnO-functionalized scaffolds permits the scaffolds to sustain a proper equilibrium between their bioactive properties and their mechanical support capabilities. The inclusion of Zn^{2+} directly into matrix polymers leads to rapid cellular responses yet demands exact control of the release rates to prevent toxicity.[23,24]

Doping involves incorporating small quantities of filler materials, or dopants, into a host polymer to modify its physical properties. However, large filler particles that do not chemically interact with the polymer are not considered true dopants. Nanomaterials, due to their high surface-to-volume ratio and enhanced surface reactivity, are particularly effective as polymer dopants. These materials, often exhibiting quantum confinement effects, interact uniquely with polymers, offering significant potential for performance enhancement. When a non-polymeric nanomaterial is incorporated into a polymer matrix, it forms a nanomaterial-doped polymer, and when the dopant is inorganic, the resulting structure is referred to as a "hybrid nanocomposite", which combines both inorganic and organic components (Figure 1).[10] This section focuses on the impact of doping polymers with zinc oxide (ZnO) in the form of scaffolds, nanofibers, and nanoparticles. The doping of ZnO into polymers can achieve three primary objectives: (1) modification of the ZnO itself, (2) modification of the polymer matrix, or (3) creation of a hybrid nanocomposite with enhanced or novel properties,[25] as illustrated in Figure 1.

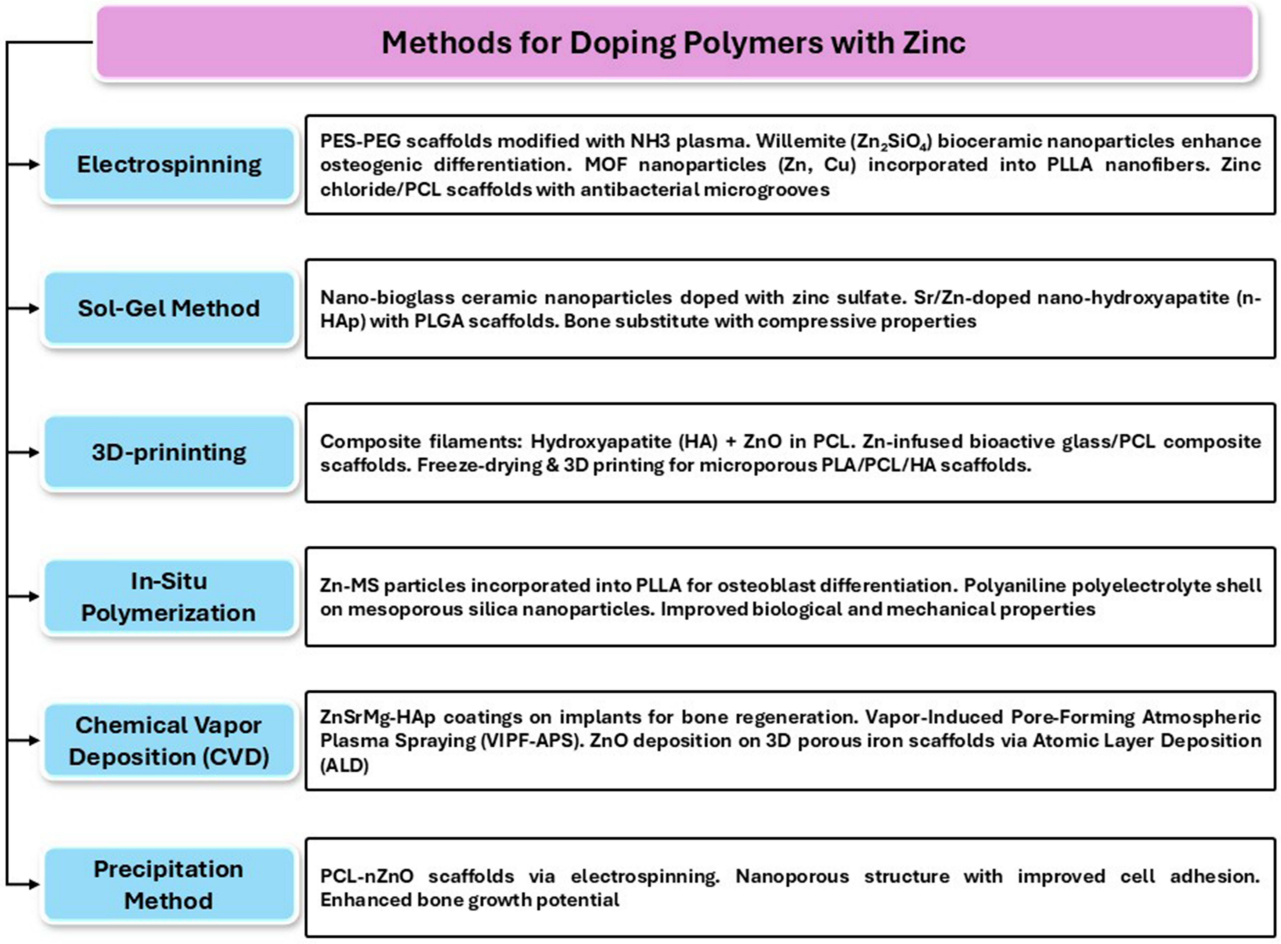

Figure 1 The flowchart illustrates six major techniques used to incorporate zinc into polymeric scaffolds for biomedical applications. Each approach enhances the biological, mechanical, and osteogenic properties of the scaffolds, making them suitable for bone tissue engineering and regenerative medicine.

Electrospinning Method

Polyethylene glycol (PES-PEG) scaffolds modified with NH3 plasma to improve hydrophilicity and promote cell adhesion, proliferation, and osteogenic differentiation.[26] Incorporating Willemite (Zn2SiO4) bioceramic nanoparticles into electrospun fibers significantly enhanced the proliferation and osteogenic differentiation of human mesenchymal stem cells (hMSCs), as evidenced by increased alkaline phosphatase (ALP) activity, calcium deposition, and upregulation of osteogenic genes and proteins. This Zn2SiO4-loaded PES-PEG scaffold offered a promising matrix for bone tissue engineering.[27]

Another study involved the incorporation of metal-organic framework (MOF) nanoparticles (using zinc and copper as metal ions) into electrospun PLLA nanofibers, with air plasma treatment improving scaffold hydrophilicity. This modification enhanced osteogenic activity, reducing the water contact angle and promoting better cell proliferation. While the tensile strength of the scaffold was not significantly improved by the MOF addition, the improved osteogenic properties made it a valuable candidate for bone regeneration.[28] Zinc chloride/polycaprolactone (PCL) electrospun scaffolds with antibacterial microgrooves were shown to enhance mesenchymal stem cell proliferation, highlighting their potential for nerve regeneration.[29]

Sol-Gel Method

Nano-bioglass ceramic nanoparticles were synthesized using the sol-gel method with a SiO2:CaO:P2O5 ratio of 55:40:5 (Mol %) and doped with zinc sulfate.[30] These nanoparticles were evaluated for their chemical, physical, and biological properties, showing potential for reducing post-surgical infections and enhancing bone tissue engineering applications.[30] Water-based sol-gel method to create strontium- and zinc-doped nano-hydroxyapatite (n-HAp), which was incorporated into composite scaffolds with PLGA using supercritical carbon dioxide. These Sr/Zn n-HAp-PLGA scaffolds exhibited compressive properties similar to cancellous bone, suggesting their potential as a bone substitute in tissue engineering.[31]

In-Situ Polymerization

In-situ polymerization is a technique used to create polymer nanocomposites by chemically reacting nanoparticles within the polymerization medium, ensuring a homogeneous dispersion of nanoparticles within the matrix. This method has been applied to enhance poly (L-lactic acid) (PLLA), which lacks inherent osteogenic activity, by incorporating zinc (Zn) to stimulate bone regeneration. Zinc-doped mesoporous silica (Zn-MS) particles were synthesized and integrated into PLLA scaffolds, promoting osteoblast differentiation and improving compressive strength through micromechanical coupling with the PLLA matrix.[32] Additionally, polyaniline was used to create a polyelectrolyte shell on mesoporous silica nanoparticles, with zinc cations incorporated during in-situ polymerization to improve surface properties and enhance osteogenic potential.[33] These approaches demonstrate the efficacy of in-situ polymerization for improving the biological and mechanical properties of polymer-based scaffolds for bone tissue engineering.

3D Printing

Composite filaments were developed by incorporating hydroxyapatite (HA) and zinc oxide (ZnO) nanoparticles into poly(caprolactone) (PCL), enabling the fabrication of scaffolds with enhanced osteoconductive properties. The use of PCL allowed for low-temperature printing, preventing thermal damage to surrounding tissues during scaffold fabrication.[34] The in situ-printed scaffolds demonstrated good adhesion to moist bone tissue, reducing the risk of scaffold displacement. These scaffolds promoted osteodifferentiation of mesenchymal stem cells, showing potential for bone regeneration. Further studies have explored zinc-infused bioactive glass/PCL composite scaffolds for bone regeneration, produced through both direct and indirect 3D printing techniques. These scaffolds released Zn^{2+} ions, which not only supported bone formation but also helped reduce inflammation, enhancing their overall effectiveness for bone defect healing.[35] Additionally, research is ongoing into the combination of freeze-drying and 3D-printing methods to create microporous PLA/PCL/HA scaffolds, which are expected to improve the mechanical and biological properties for bone tissue engineering applications.[36]

Chemical Vapor Deposition (CVD)

Chemical Vapor Deposition (CVD) techniques have been employed to enhance the properties of biomaterial coatings for tissue engineering. A study involving ZnSrMg-HAp coatings on implants demonstrated significant bone tissue

production and growth, suggesting their potential for bone regeneration. The use of Vapor-Induced Pore-Forming Atmospheric Plasma Spraying (VIPF-APS) on titanium implants also showed promise in preventing bacterial infection due to its porous nature.[37] In another study, zinc oxide (ZnO) was deposited on 3D porous iron scaffolds using Atomic Layer Deposition (ALD).[38] The ZnO coating improved cell adhesion, exhibited antibacterial activity, and maintained scaffold degradability, making it a promising strategy for enhancing the performance of metal scaffolds in bone tissue engineering.[39]

Precipitation Method

The precipitation method was used to create PCL-nZnO scaffolds by incorporating zinc oxide nanoparticles into PCL via electrospinning.[40] The resulting scaffolds were nanoporous, with fibers that exhibited random alignment and expanded diameter. Characterization through SEM, EDX, ATR-FTIR, XRD, and contact angle measurements confirmed their composition.[41] Cell culture studies with MG63 cells showed enhanced cell growth and improved cell adhesion on the PCL-nZnO scaffolds. The presence of ZnO particles promoted bone growth, indicating their potential for bone tissue regeneration.[42]

Significance of Zinc in Bone Regeneration

Zinc (Zn) is a vital micronutrient with a significant concentration in bone tissue, accounting for about 30% of the body's total zinc. It plays an essential role in bone formation, mineralization, and maintenance, as zinc is crucial for the function and differentiation of osteoblasts, which are responsible for bone synthesis.[43] Zinc also influences collagen production, a key component of the bone matrix. Zinc deficiency can lead to skeletal disorders, such as osteoporosis and impaired bone growth.[44] Recent studies suggest that incorporating zinc into synthetic polymer scaffolds for bone tissue engineering can enhance osteoblast differentiation and accelerate bone regeneration by releasing Zn^{2+} ions.[45] This approach holds promise for improving the efficacy of biomaterials in bone repair and regeneration.[8] In addition to hydroxyapatite (HAp)-based scaffolds, studies have demonstrated that Zn^{2+} ions contribute to osteogenesis through their interactions with polymeric scaffolds, facilitating enhanced mineralization, stem cell differentiation, and mechanical reinforcement of biomaterials.[46,47]

Numerous studies have demonstrated that Zn^{2+} ions play a crucial role in enhancing stem cell osteogenesis and promoting mineral deposition in bone tissue. Zinc is known to stimulate the differentiation of mesenchymal stem cells (MSCs) into osteoblasts, the cells responsible for bone formation (Figure 2).[48] This process is essential for the

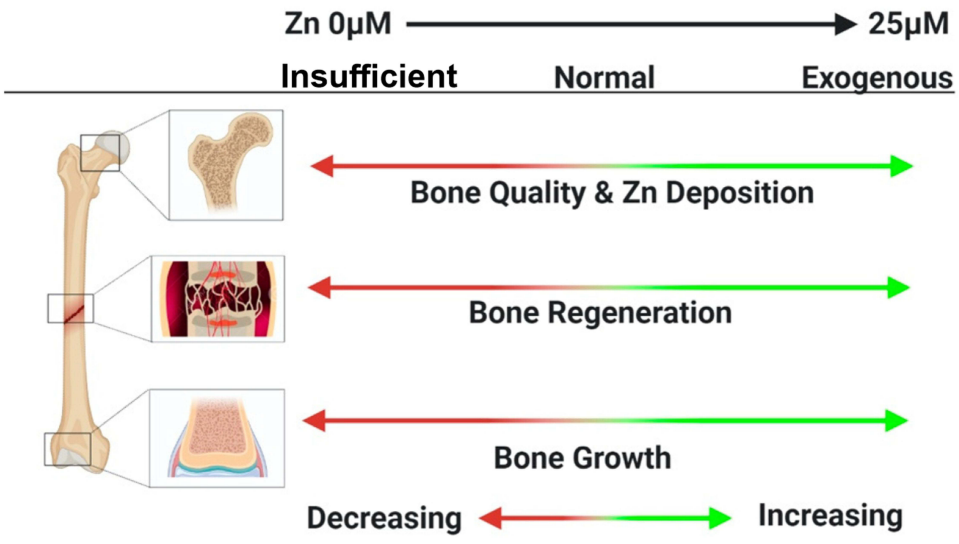

Figure 2 Role of zinc in bone regeneration. Adapted from O'Connor JP, Kanjilal D, Teitelbaum M, et al. Zinc as a therapeutic agent in bone regeneration. Materials. 2020;13(10):2211. © 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).[11]

regeneration of bone tissue, as zinc supports the synthesis of osteogenic proteins and the deposition of mineralized matrix components, such as hydroxyapatite.[49] Moreover, zinc's influence on key signaling pathways, such as the Wnt/β-catenin (for example, the C17.2 neural stem cells were used as a subject, low zinc concentration produced both reduced GSK-3β phosphorylation and diminished β-catenin levels. The data shows that appropriate levels of zinc must exist for Wnt/β-catenin pathway maintenance since it controls GSK-3β phosphorylation states that stabilize β-catenin and promote its transport into the nucleus for activating proliferation and differentiation control genes.[50] Research on osteosarcoma cells demonstrates that zinc treatment turns on the Wnt-3a/β-catenin signaling pathway which results in elevated Wnt-3a and β-catenin protein levels.[51] The pathway activation resulted in restrained cell proliferation together with cell invasion suppression and cellular apoptosis promotion of osteosarcoma cells. The results suggest zinc works through Wnt/β-catenin pathway components but researchers have not yet determined the complete molecular actions of zinc[51]), Mitogen-Activated Protein Kinase (MAPK pathway (Several studies show modified titanium surfaces release zinc ions that activate MAPK/ERK pathway to enhance osteogenesis and angiogenesis through osteoblast behavior activation[52]) and Bone Morphogenetic Protein-2 (BMP-2) signaling pathway (The activation of BMP-2 pathway causes transcription factors Runx2 and Osterix (Sp7) to become active for osteoblast generation[53,54]), further enhances osteogenic differentiation and mineralization.[55,56] As a result, the incorporation of zinc into biomaterials and scaffolds used in bone tissue engineering has been shown to significantly accelerate bone healing and improve the mechanical strength of the regenerated bone, making it a promising strategy for enhancing bone regeneration therapies. Several experimental studies prove that adding zinc to biomaterials leads to rapid bone healing and it enhances the mechanical properties of repaired tissue.[57,58] The discussion of Zn's cell adhesion functions and proliferative effects on osteogenesis expands in detail in Role of Zinc Ions in Cell Adhesion, Proliferation, and Osteogenesis where the scaffold-polymer relationships and material composition interactions are presented.

The Impact of Zn Ions on Inflammation Behaviors and Bone Scaffold Degradation

Recent studies have shown that incorporating Zn^{2+} ions into polymeric scaffolds can significantly influence their swelling behavior, which is essential for facilitating nutrient and oxygen transport to encapsulated cells during the early stages of bone healing.[59] Zinc ions enhance the hydrophilicity of scaffolds, promoting water absorption and improving the scaffold's capacity to support cellular infiltration and growth, crucial for osteoblast proliferation and extracellular matrix (ECM) formation.[60]

In addition to modulating swelling, Zn^{2+} ions play a pivotal role in the degradation of bone scaffolds. Zinc accelerates the hydrolytic breakdown of biodegradable polymers such as polylactic acid (PLA) and polycaprolactone (PCL), thereby regulating the scaffold's degradation rate.[45] Zn^{2+} incorporation facilitated the controlled degradation of these materials, allowing scaffolds to provide temporary mechanical support while being gradually replaced by newly formed bone tissue.[61] Furthermore, studies have shown that the release kinetics of Zn^{2+} ions from scaffolds significantly influence the rate of bone regeneration. Zn^{2+} ions stimulate osteoblast differentiation and mineralization, promoting more efficient bone formation.[45] However, research emphasized that an imbalanced release rate—either too rapid or too slow—can hinder bone healing and scaffold performance.[62] Thus, understanding and optimizing the release profile of Zn^{2+} ions is crucial for enhancing both the degradation behavior and therapeutic efficacy of bone scaffolds.

Impact of Zn Ions on the Physical Characteristics of Bone Scaffold

Zinc (Zn) ions have been shown to significantly influence the physical and mechanical properties of bone scaffolds, primarily by enhancing their compressive strength, porosity, and degradation rate.[63] Zinc incorporation into bone scaffold materials, such as hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), and polymer-based composites, alters their microstructure, leading to an increase in crystallinity and stability, which in turn improves mechanical properties.[64] Recent studies have demonstrated that the optimal concentration of zinc (typically in the range of 1–5 wt%) results in enhanced compressive strength and elasticity without compromising the scaffold's biodegradability.[65] Zinc incorporation also modulates scaffold porosity, enhancing pore connectivity, which facilitates better cell infiltration and nutrient exchange—key factors for tissue regeneration.[66] Furthermore, zinc ions promote accelerated scaffold degradation by increasing the dissolution rate of calcium phosphate materials, facilitating the timely replacement of the scaffold by

newly formed bone tissue.[67] The ion release rate, however, must be carefully controlled, as excessive zinc may induce cytotoxicity, while inadequate release could impair osteogenesis. Advanced release systems, such as mesoporous silica or polymeric carriers, are being explored to regulate the controlled release of zinc ions, ensuring sustained biological effects and minimizing adverse reactions.[68] Moreover, zinc ions are known to promote osteoblast differentiation via the Wnt/β-catenin and MAPK signaling pathways, while also enhancing angiogenesis, which is critical for bone regeneration in vivo.[18]

Role of Zinc Ions in Cell Adhesion, Proliferation, and Osteogenesis

Cell adhesion and proliferation can be aided by zinc ions as Zinc could improve MBG scaffold colonization by mesenchymal stem cells of human bone marrow.[69] According to Mangaraj et al, MG-63 cells showed enhanced adhesion and proliferation when grown on β-TCP scaffolds that contained 2.5 wt % ZnO.[70] Ghorbani et al discovered that incorporating 5% of nano zinc hydroxyapatite (nZnHA) into nanocomposites made of polycaprolactone (PCL), chitosan, and nZnHA can greatly improve and speed up their proliferation and development; stem cells derived from human adipose tissue.[71] Xiong et al discovered that bone marrow stem cells (BMSCs) from mice proliferated faster when zinc was released from calcium phosphate cement (CPC) at concentrations varying from 10.91 μM to 27.15 μM. In addition, they found that the effect was dose-dependent, with the opposite effect of decreased proliferation occurring when the dosage of zinc exceeded 128.58 μM.[72]

Recent research has shown that Zn ions play a role in osteogenesis, the process by which new bone tissue is produced. Researchers found that nano bioglass ceramic particles with zinc ions added had better osteoconductive properties than those without the metal.[73] Research also suggests that zinc, an important ALP cofactor, can modulate ALP activity to a considerable degree.[74] The discipline of bone tissue engineering is currently very interested in immunomodulated osteogenesis. Zinc enhances the process of osteogenic differentiation by controlling the polarisation of macrophages.[23] During the initial stage (1–3 days) of bone regeneration, Bai et al found that macrophages were polarised into an inflammation-related phenotype (M1 subtype) when exposed to a dose of 1.39 ppm of zinc.[75] Another hypothesis is that zinc has insulin-like properties that aid in osteochondral tissue regeneration.[74] It reduces the development of bone-destroying cells called osteoclasts by blocking the production of RANKL in bone-forming cells known as osteoblasts.

Impact of Zinc Ions on Antibacterial Properties

Surgical infection is a complication that often arises after surgery and has significant detrimental effects on bone healing, including the need for additional surgical procedures, prolonged hospitalization, increased mortality, and other related consequences.[76] Zn ions possess notable antibacterial properties,[77] as depicted in Figure 3 and Table 1. The antibacterial efficacy of hydrogels was improved by including zinc ions, leading to increased efficiency against both Gram-negative and Gram-positive bacteria.[78] Furthermore, Heras et al identified that the concurrent use of zinc and antibiotics can provide synergistic effects, resulting in comparable therapeutic effectiveness with a lower antibiotic dosage.[76]

Synthetic Polymer Composites for the Regeneration of Bone

Synthetic polymers (have been widely employed as scaffolding materials in bone tissue engineering. The functionality of these materials receives added enhancement through Zn^{2+} incorporation due to its ability to stimulate osteogenesis and angiogenesis processes as well as promote scaffold breakdown. Polymeric composites that contain Zn^{2+} ions deliver specific ion levels which enable long-term bioactivity without producing harmful effects to cells. The results from various studies showed that Zn^{2+} functionalized polymer scaffolds improve cellular response outcomes and enhance mechanical strength and integration potential in host tissue[10] (Table 2).

Zinc-Doped Synthetic Polymer Composites

Zinc-doped synthetic polymer composites are gaining attention for their ability to enhance bone tissue regeneration. Zinc (Zn) plays a vital role in osteogenesis by promoting osteoblast differentiation and mineralization. Incorporating Zn into polymers such as PCL, PLGA, and PLA improves mechanical properties, degradation rates, and cell interactions,

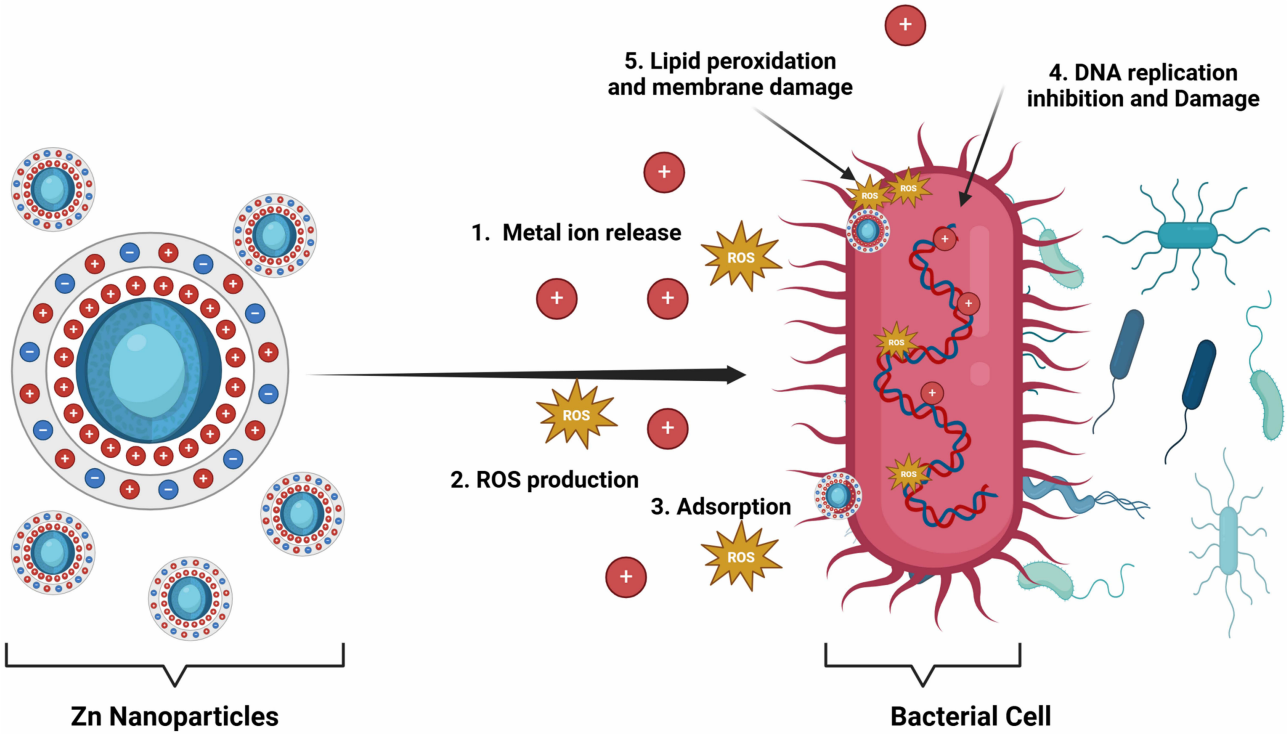

Figure 3 Schematic representation of the antibacterial mechanism of zinc ions. The schematic shows how zinc-based nanomaterials trigger the release of Zn^{2+} ions and ROS reactive oxygen species. Bacterial cell membranes become more permeable when Zn^{2+} encounters them. The penetration of Zn^{2+} inside bacterial cells cause enzymatic failure and creates oxidative stress through ROS production. The bacterial cell death occurs because of DNA damage along with protein dysfunction while lipid peroxidation happens simultaneously. These antimicrobial effects result in bacterial lysis and prevent bacterial proliferation while being captured through the image representation.

facilitating better bone integration.[102] Recent studies have shown that Zn-doped scaffolds improve cell adhesion, proliferation, and osteogenic differentiation of mesenchymal stem cells, while also enhancing the swelling behavior and hydrophilicity of the scaffolds.[103] However, challenges remain in optimizing Zn ion concentrations, as higher doses can lead to cytotoxicity and reduce biocompatibility. Therefore, careful control of Zn doping levels is essential for balancing osteogenic benefits with scaffold safety.[104] Additionally, variability in study results highlights the need for standardized fabrication methods and long-term in vivo studies to assess the reproducibility and effectiveness of Zn-doped scaffolds in clinical applications.[105] Despite these challenges, Zn-doped composites hold significant potential for advancing bone tissue engineering.

In vitro and in vivo Experiments of Zinc-Doped Synthetic Polymer

The incorporation of degradable polymers combined with bioactive inorganic glasses, such as zinc-doped bioactive glass (ZnBG), offers a promising strategy for enhancing bone regeneration, as illustrated in Figure 4. In a laboratory study, rat bone marrow mesenchymal stem cells (rBMSCs) were cultured on various membrane substrates, including pure PLA (polylactic acid), PLA–BG (bioactive glass), and PLA–ZnBG (zinc-doped bioactive glass), to investigate the synthesis of osteogenic phenotypes and cellular mineralization.[106] There was significant increase in the synthesis of osteocalcin and alkaline phosphatase at days 7 and 21 in the presence of bioactive glass and ZnBG, with the highest levels observed in the ZnBG-incorporated samples. Immunostaining analysis revealed that ZnBG significantly upregulated the expression of bone sialoprotein in rBMSCs.[107]

In addition to bioactive glass, pro-osteogenic components, such as those found in bone graft replacements, play a crucial role in accelerating bone healing. In one study, scaffolds made from calcium phosphate cement were enhanced with PLGA microspheres and a Si-Zn dual component to promote bone regeneration.[67] The incorporation of Si/Zn PLGA microspheres significantly improved the assembly and compressive strength of the CPC scaffolds. These scaffolds exhibited a gradual release

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Table 1 Zinc-Doped Composites, Their Properties, and Mechanical Property Enhancements

Sr. No.	Zinc Composite	Properties	Mechanical Property Enhancement	Ref.
1	Zinc-Doped Poly (lactic-co-glycolic acid) (PLGA)	1. Improves biocompatibility and osteogenesis. 2. Enhances the hydrophilicity of the polymer. 3. Stimulates osteoblast proliferation and differentiation.	Zinc-doped PLGA composites exhibit enhanced mechanical strength and elasticity due to better hydrophilic interactions, improving scaffold stability.	[79]
2	Zinc-Doped Polycaprolactone (PCL)	1. Increases bone mineralization. 2. Reduces osteoclast activity and promotes osteoblast differentiation. 3. Provides antimicrobial properties	Zinc incorporation into PCL scaffolds improves their mechanical properties by increasing their tensile strength and enhancing their load-bearing capabilities.	[80]
3	Zinc-Doped Hydroxyapatite (Zn-HA)	1. Enhances bone formation and mineralization. 2. Improves cellular adhesion. 3. Demonstrates osteoconductive properties	Zinc-doped Zn-HA composites enhance the mechanical strength of scaffolds by increasing their compressive strength and stiffness, making them suitable for load-bearing applications.	[81]
4	Zinc-Doped Polyethylene Glycol (Zn-PEG)	1. Improves cell adhesion and differentiation. 2. Enhances hydrophilicity and biocompatibility. 3. Exhibits osteogenic properties.	Zn-PEG composites improve the flexibility and mechanical durability of scaffolds, particularly in high-stress applications like bone repair.	[82]
5	Zinc-Doped Calcium Phosphate Cement (Zn-CPC)	1. Promotes bone mineralization and osteogenesis. 2. Enhances scaffold bioactivity and osteoconductivity. 3. Reduces inflammation.	Zinc-doped CPC scaffolds improve mechanical strength and are more resistant to cracking, making them suitable for repairing large bone defects	[83]
6	Zinc-Doped Silk Fibroin (Zn-SF)	1. Biodegradable and biocompatible. 2. Enhances bone cell proliferation. 3. Increases collagen deposition.	Zinc-doped silk fibroin scaffolds show improved tensile strength and toughness, providing enhanced mechanical stability for bone regeneration.	[84]

Table 2 Summary of Synthetic Polymer Composites for Bone Tissue Engineering (BTE)

Sr. No.	Polymer/ Composite	Key Features Properties	Benefits in Bone Tissue Engineering (BTE)	Challenges / Limitations	Recent Studies / Examples
1	Poly(ε-caprolactone) (PCL)	Aliphatic, semi-crystalline, cost-effective, flexible, tough, biocompatible.	Strong cell adhesion, proliferation, and mechanical strength.	Slow degradation rate, hydrophobic nature hindering cell attachment.	PCL/alginate composite scaffold enhanced osteogenic differentiation, cell survival, calcium accumulation, and water absorption after 14 days.[85] PCL scaffolds with hydroxyapatite nanoparticles improved osteoblast attachment and differentiation in vitro.[86]
2	Polylactic Acid (PLA)	Thermal stability, non-toxic degradation products, cytocompatible.	Encourages bone regeneration, suitable for scaffold creation.	Needs enhancement with other materials for improved mechanical properties.	PLA/hydroxyapatite scaffolds exhibited enhanced osteo-differentiation and cell proliferation in human mesenchymal stem cells.[87] PLA/chitosan composite scaffold improved osteogenesis and vascularization in vivo.[88]

(*Continued*)

Table 2 (Continued).

Sr. No.	Polymer/ Composite	Key Features Properties	Benefits in Bone Tissue Engineering (BTE)	Challenges / Limitations	Recent Studies / Examples
3	Poly(lactic-co-glycolic acid) (PLGA)	Degradable, can control breakdown rate by adjusting monomer ratio.	Useful for controlled degradation over weeks to months for bone regeneration.	Limited bioactivity, hydrophilicity, and antibacterial properties.	PLGA/nano-hydroxyapatite composite scaffolds showed increased osteoblast proliferation and mineralization in vitro.[89] PLGA/graphene oxide scaffolds enhanced mechanical properties and bone regeneration[90]
4	Polyurethane (PU)	Good physical, mechanical, and biocompatible properties. Block copolymeric structure.	Increased mechanical properties, retains toughness, and biocompatibility.	Can suffer from poor surface modification or bioactivity.	PU nanocomposite scaffolds incorporated with nanohydroxyapatite exhibited better osteogenesis and improved mechanical properties[91]-
5	Poly(L-lactic acid) (PLLA)	Biocompatible, non-toxic, used in various polymer blends.	High potential for bone tissue regeneration and scaffolding.	Mechanical properties may need enhancement with other materials like hydroxyapatite.	PLLA-gelatin nano-fibrous meshes supported mesenchymal stem cell differentiation into bone tissue in vivo.[92]
6	PLA/PVA Nanofibers	Enhanced mechanical properties, increased breaking strain and tensile strength.	Improved ductility and mechanical properties for scaffold formation.	Stability of PVA-only fibers is an issue.	PLA/PVA fibers incorporated with bone morphogenic proteins (BMPs) promoted osteogenesis in vitro[93]
7	Poly(glycolic acid) (PGA)	Degradable and biocompatible.	Promotes cellular adhesion, scaffold formation, and bone regeneration.	Limited mechanical properties without reinforcement.	PGA-based scaffolds with nanocellulose improved mechanical strength and osteogenic potential in vitro[94]
8	Bioglass (BG)	Bioactive, enhances mineralization.	Stimulates mineralization and increases ALP and osteocalcin production on scaffolds.	Breakdown may generate inflammatory chemicals, although beneficial in suppressing acidic conditions.	BG added to PCL scaffolds enhanced bioactivity, mineralization, and suppressed inflammation[95]
9	Polycaprolactone/ Chitosan (PCL/CS)	Biodegradable, non-toxic, antimicrobial properties.	Enhanced biocompatibility, antibacterial properties, and osteogenesis.	Limited mechanical properties without reinforcement.	PCL/Chitosan scaffolds with added hydroxyapatite promoted bone tissue regeneration and improved cell adhesion[96]
10	Poly(ether-ether-ketone) (PEEK)	High mechanical strength, excellent chemical resistance, biocompatible.	Highly durable, suitable for load-bearing bone implants.	Degrades slowly; poor osteoinductive properties.	PEEK scaffolds combined with bioactive glass exhibited enhanced mechanical properties and osteogenic differentiation in mesenchymal stem cells.[97]

(*Continued*)

Table 2 (Continued).

Sr. No.	Polymer/ Composite	Key Features Properties	Benefits in Bone Tissue Engineering (BTE)	Challenges / Limitations	Recent Studies / Examples
11	Polyvinyl Alcohol (PVA)	Hydrophilic, biodegradable, good mechanical properties, non-toxic.	Improves scaffold flexibility, cell compatibility, and hydration.	Limited biodegradability, poor osteoinductive properties.	PVA scaffolds combined with collagen or HA showed enhanced bone formation in animal models[98]
12	Poly acrylic acid (PAA)	Hydrophilic, pH-responsive, capable of ionic interactions with metal ions like Zn^{2+}.	Facilitates controlled Zn^{2+} release, enhances mineralization, and improves scaffold stability.	Can exhibit excessive swelling, requiring crosslinking for structural integrity.	PAA-based hydrogels functionalized with Zn^{2+} demonstrated controlled ion release, promoting osteogenic differentiation and mineral deposition in vitro[99,100]
13	Gelatin Methacrylate (GelMA)	Photocrosslinkable, biocompatible, bioactive.	Supports cell adhesion, proliferation, and osteogenic differentiation.	Low mechanical strength without reinforcement.	GelMA-based scaffolds combined with mesenchymal stem cells and hydroxyapatite demonstrated enhanced bone regeneration.[101]

of Si and Zn ions, which, in turn, facilitated the production of anti-inflammatory cytokines by M2 RAW 264.7 cells in vitro.[108] Furthermore, when grown on PLGA/CPC-Si/Zn scaffolds, rat bone marrow stem cells (rBMSCs) demonstrated improved bone formation.[108] In a femur defect model, rats treated with these scaffolds exhibited new bone formation after 4 weeks, with the PLGA microspheres promoting further bone development over 12 weeks.[109] By 24 weeks, the microspheres had degraded, and the defect was almost completely filled with newly formed bone. The synergistic effects of PLGA/CPC-Si/Zn scaffolds, enhancing both immunological responses and biodegradability, significantly promoted bone formation and repair.[109]

Zinc, widely known for its anti-inflammatory properties, plays an essential role in the regulation of the immune response during bone healing. Zinc's anti-inflammatory mechanism involves the suppression of the NF-kB pathway, inhibition of COX-2 enzyme activity, and downregulation of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. As a result, zinc reduces inflammation, creating a favorable immunological environment for early bone defect repair.[110] Moreover, the regulated release of zinc and silicon ions from scaffolds can accelerate bone remodeling in the intermediate and advanced stages of healing. In a study by Qian et al, CPC, when combined with zinc silicate (ZS) and PLGA microspheres, demonstrated improved osteogenic and anti-inflammatory properties.[111] The presence of zinc ions upregulated the anti-inflammatory cytokine IL-10 while suppressing pro-inflammatory cytokines, facilitating an optimal immune response conducive to bone regeneration.[55]

Proliferation and Viability of Cells

Recent studies on zinc-doped synthetic polymer composites for bone regeneration have shown promising results in enhancing cell proliferation and osteogenesis (Figure 5). Zinc-containing polymers, such as polyacrylic acid (PAA), exhibit low cytotoxicity at moderate concentrations, promoting cell viability and supporting bone regeneration.[18] Specifically, PAA at concentrations of 0.025 and 0.05 mol/L has been found to enhance cell proliferation, while higher concentrations lead to toxicity and reduced cell viability.[112] The addition of zinc further improves the osteogenic properties of these polymers, stimulating osteoblast differentiation and enhancing scaffold integration. However, excessive zinc concentrations can disrupt cellular functions and impair tissue repair. Therefore, optimizing the concentration of both zinc and the polymer is crucial to achieving a balance between promoting bone regeneration and ensuring biocompatibility, making zinc-doped polymer composites a promising strategy for repairing bone defects.[97]

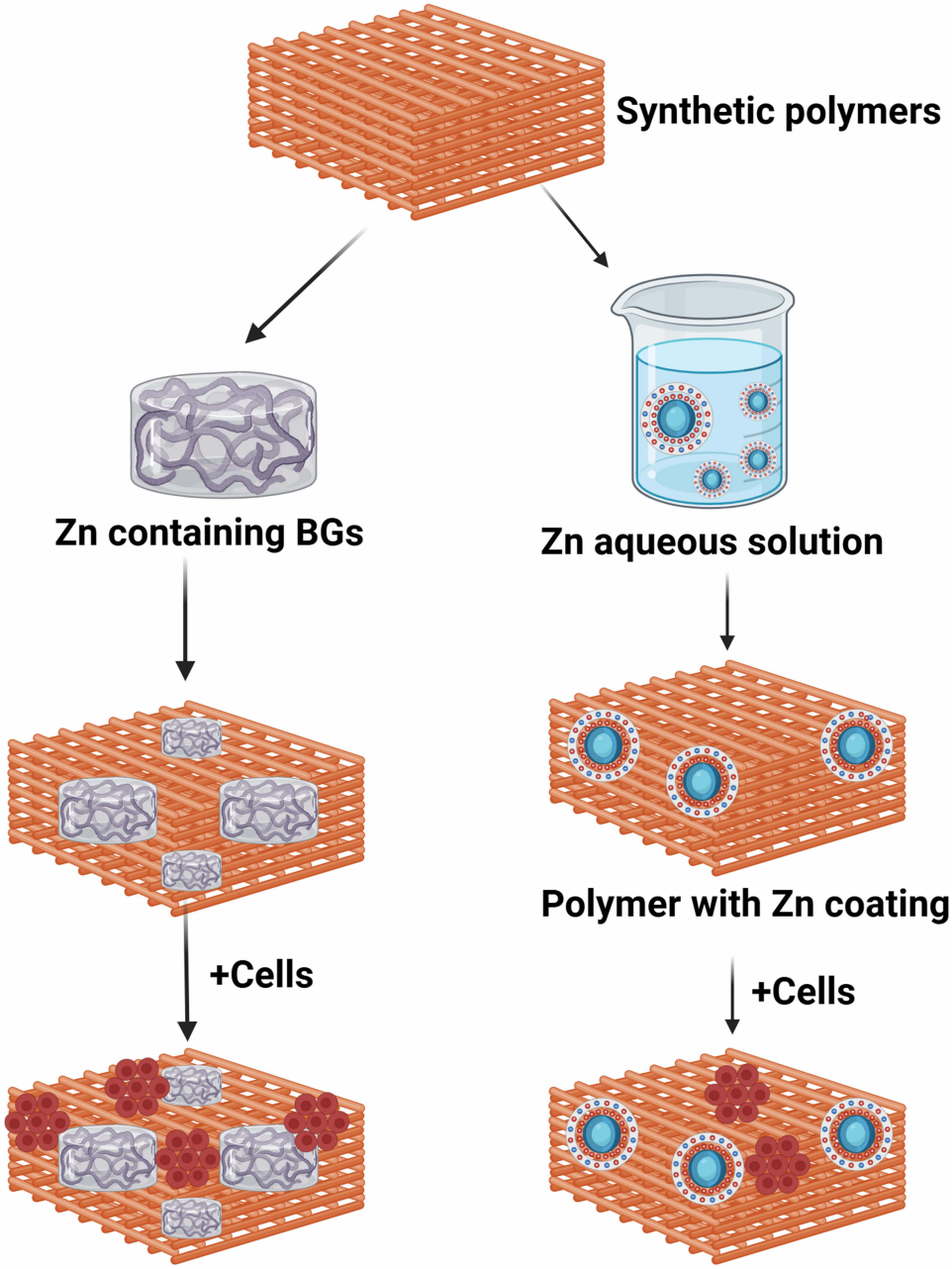

Figure 4 Schematic representation of the fabrication and biological response of zinc-doped bioactive scaffolds for bone regeneration.

Prior research has examined the potential cytotoxic impact of Zn on cellular structures. Several researchers have noted that cytotoxicity occurs when the concentration of Zn doping in BGs exceeds approximately 5 mol%. In addition, it was shown that only the elution extracts with the greatest concentration (5 mg/L) were able to suppress the proliferation of fibroblasts of mouse embryonic (MEFs). Neščáková et al[113] demonstrated that Zn-doped bioactive glasses (containing approximately 8% ZnO) did not exhibit harmful effects on MEF or MG-63 cells. Utilizing a solution provides a more precise measure than the amount of zinc in materials.[114] Studies have demonstrated that Zn^{2+} enhances the attachment, expansion, growth, and movement of vascular smooth muscle cells. This effect is observed at concentrations ranging from 60–80 μM. However, at higher concentrations of Zn^{2+} (80–120 μM), the reversible are observed.[115] Aina et al[116] found that a dosage of 1.1 mg/L of Zn^{2+} stimulated endothelial cell proliferation, whereas a dose of 2.7 mg/L led to cell death. Yamaguchi et al discovered that MC3T3-E1 osteoblasts synthesized more regucalcin mRNA, Runx-2, and

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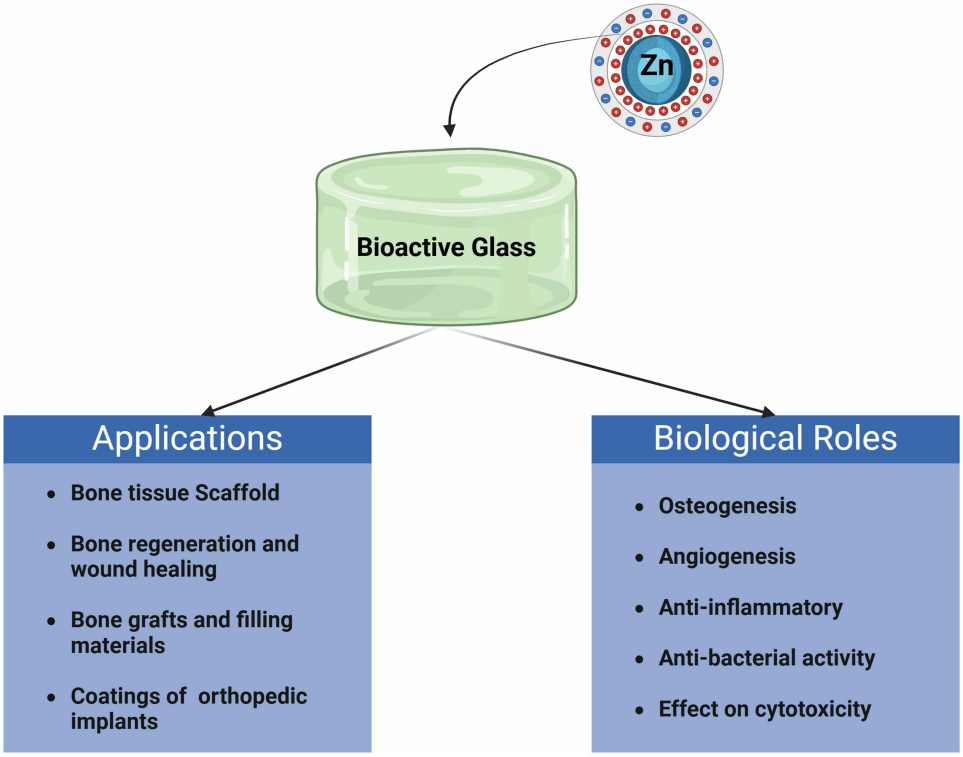

Figure 5 Schematic representation of the applications and biological roles of zinc-doped bioactive glass. Zinc incorporation enhances the bioactivity of bioactive glass, making it a promising material for bone tissue engineering.

osteoprotegerin when Zn was present at quantities ranging from 10−6 to 65 μg/L–6.5 mg/L.[117] The author's results showed that the concentration of Zn^{2+} ranging from 10 to 250 μM (equal to 0.65 and 16.25 mg/L) hindered the production of osteoclasts in RAW264.7 cells. The zinc amount had an impact on the activity of SaOS-2, a cell line that resembles human osteoblasts.

Overextended stimulation, this impact was shown without affecting cell growth.[74] Previous studies have shown that, in laboratory conditions, the released Zn^{2+} may stimulate osteoblast growth, osteogenic mesenchymal cell (MSC) differentiation, and extracellular matrix (ECM) mineralization when present in tiny concentrations,[17] Zn^{2+} may be harmful to cells because it prevents the extracellular matrix (ECM) from mineralizing at high amounts. The research that is now available suggests that adding zinc to a bone scaffold at optimum concentrations and with regulated release characteristics could improve the procedure of bone regeneration.

Cellular Osteogenesis Differentiation

Recent studies investigating the role of zinc in polymeric scaffolds for bone regeneration have consistently shown that the incorporation of zinc enhances osteogenic differentiation and cell proliferation. Additionally, PAA scaffolds with lower zinc concentrations promoted greater calcium deposition and bone differentiation than those with higher zinc levels.[10] Similar findings were observed with zinc-doped polycaprolactone (PCL) scaffolds, which exhibited increased alkaline phosphatase (ALP) expression and apatite formation.[118] Furthermore, the combination of silver and zinc ions in SPEEK polymers resulted in greater cell proliferation and bone differentiation than zinc alone.[119] Other studies, such as those involving PLGA/CPC -Si/Zn composites, also reported improved cell proliferation and bone formation.[120] Zinc-silibinin complexes have additionally been shown to regulate key signaling pathways, promoting osteoblast growth.[121] These findings underscore the significant potential of zinc-doped polymeric scaffolds in enhancing bone regeneration, suggesting that the incorporation of zinc, especially in combination with other metal ions, can optimize the osteogenic properties of biomaterials for bone tissue engineering.[122]

Table 3 This Table Summarizes the Observed Toxic Effects of High-Dose Zinc (Zn^{2+}) Exposure on Systemic Metabolism, Kidney Function, and the Hematological System in Various Animal Models

System Affected	Observed Effects	Study Details	Reference
Systemic Metabolism	Decreased serum triiodothyronine (T3) levels; increased serum cortisol levels	Rats administered 8 mg/kg zinc acetate intraperitoneally every other day for 14 days showed significant reductions in T3 and elevated cortisol, indicating endocrine disruption.	[123]
Kidney Function	Renal tubular dilation, proteinaceous casts, hemosiderin deposits	Sheep ingesting 18 mg/kg/day zinc oxide for 49–72 days exhibited these renal alterations, suggesting nephrotoxicity.	[124]
Hematological System	Decreased red blood cell count, hemoglobin, hematocrit, and platelets; increased mean corpuscular hemoglobin concentration	Albino mice receiving 90 mg/kg zinc chloride daily for 8 weeks experienced significant hematological changes, pointing to potential anemia and impaired blood clotting.	[125]
Oxidative Stress and Hypertension	Elevated superoxide radicals; increased systemic blood pressure	Rats exposed to excessive zinc intake demonstrated renal dysfunction accompanied by oxidative stress and hypertension, implicating superoxide radicals in the pathogenesis.	[126]
Renal Function	Increased serum creatinine and urea levels; histopathological kidney damage	Wistar rats treated with high doses of zinc oxide nanoparticles exhibited elevated markers of renal impairment and kidney tissue damage.	[127]

Potential Drawbacks of Zinc-Doped Synthetic Polymer Composites in Bone Regeneration

Synthetic polymer composites containing zinc ions have gained popularity in bone tissue engineering because zinc shows both improved bone cell growth and antimicrobial properties. Such an approach brings certain unfavorable aspects that need thorough evaluation (Table 3).

The main drawback of elevated Zn^{2+} concentrations emerge as toxic effects on cells. The presence of zinc ions at lower levels stimulates cell growth along with bone-forming cells but excessive amounts result in negative actions against these processes while simultaneously producing toxic effects to cells. For instance, a systematic review highlighted that high-dose Zn^{2+} resulted in cytotoxicity and inhibition of osteogenic differentiation in vitro.[10] The integration of Zn^{2+} ions may modify the apatite formation which represents an essential mineral for bone structure development. Some studies have reported that Zn^{2+} can reduce apatite formation in simulated body fluid, potentially hindering the nucleation process essential for effective bone regeneration.[128] Scaffold-based Zn^{2+} release must be controlled for optimal clinical outcomes. Without proper regulation of Zn^{2+} release an undesirable discrepancy will develop between oxide strength and biological function thus affecting healing success of repaired bones. The studies shows Zn^{2+} has positive effects on bone formation yet high rates of its release could damage the complex mechanisms vital for performing successful bone regeneration.[10]

Zn^{2+} addition during the fabrication of polymer matrices leads to changes in scaffold degradation speed. Prefabricated modifications in scaffold materials can cause early failure of mechanical properties or excessive time delay of scaffold retention and this affects healing negatively.

Moreover, limited research exists on zinc ion doped synthetic polymer composites for human subject use due to their absence in clinical trials. A comprehensive review published in June 2020 revealed 13 suitable studies regarding this subject, but these studies used only in vitro methods and animal experiments without reporting any human clinical trials.[10] Research translation becomes crucial to establish safety parameters and clinical value of Zn^{2+}-doped synthetic polymer composites for human bone regeneration.

Conclusion and Future Perspectives

Zinc-doped synthetic polymer composites have gained attention as a promising solution for bone regeneration, offering potential advancements in the treatment of bone defects. Zinc, an essential element in bone metabolism and healing, plays a crucial role in enhancing both the mechanical and biological properties of bone grafts. Research has demonstrated that zinc stimulates osteoblast activity, improves bone mineral density, and promotes the proliferation and differentiation of osteogenic cells. Additionally, the incorporation of synthetic polymers strengthens the composite, supporting bone regeneration and enhancing the integration of the scaffold with the surrounding bone tissue. Zn composites also exhibits antimicrobial properties which contribute to reducing infection risks during bone repair, aiding in post-operative recovery. A key advantage of zinc-doped composites is their controlled degradation, which ensures the scaffold remains structurally stable as natural bone replaces it. This process promotes seamless integration and minimizes the need for additional surgeries. However, challenges remain, particularly in achieving a uniform distribution of zinc within the polymer matrix to maintain consistent scaffold performance. Furthermore, understanding the interactions between zinc and other biological factors is essential to improve the biocompatibility of these materials and reduce potential negative effects. Future research should focus on optimizing manufacturing techniques to enhance the consistency and mechanical strength of these composites. Additionally, in vivo studies are necessary to validate the safety and effectiveness of these materials in clinical applications. Combining zinc with other bioactive compounds may also enhance the healing process and improve bone regeneration. To facilitate the successful clinical application of zinc-doped composites in bone regeneration, several critical factors must be addressed. Regulatory challenges represent a significant barrier, as these materials must undergo comprehensive preclinical and clinical testing to satisfy stringent safety and efficacy standards. Furthermore, the scalability of production processes is essential for ensuring that zinc-doped composites can be manufactured at a commercial scale without compromising quality or consistency. Recent studies underscore the importance of developing cost-effective, large-scale manufacturing techniques to support the widespread adoption of these materials in clinical practice. In addition, long-term biocompatibility must be thoroughly assessed to ensure that the materials do not provoke adverse immune responses or degrade in a manner that would impede the desired regenerative outcomes over time. Addressing these regulatory, production, and biocompatibility challenges will be crucial for the successful integration of zinc-doped composites into bone regeneration therapies.

Data Sharing Statement

Not Applicable. This is a review article and all relevant information is provided in the article.

Ethical Approval and Consent to Participate

Not Applicable. This is a review paper and do not involve direct research on humans or animals.

Consent for Publication

"Not applicable" as this manuscript does not contain data from any individual person.

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Disclosure

The Authors declare that they have no competing interests financial or non-financial or any other interests that might be perceived to influence the results and/or discussion reported in this paper.

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