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Recent Advances in Composite Materials for the Treatment of Critical-Size Bone Defects: A narrative review

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ABSTRACT

Critical-sized bone defects (CSBDs) are a significant issue in reconstructive surgery, demanding the development of improved biomaterials to promote bone regeneration. Composite materials have emerged as attractive alternatives because of their ability to approximate native bone's hierarchical structure while also providing specific mechanical and biological qualities. IN this narrative review, a complete discussion of material selection for composite construction including bio ceramics, polymers, and bioactive agents were summarized. this review determines the most recent fabrication techniques used in composite synthesis, such as solvent casting, electrospinning, freeze-drying, and 3D printing, focusing on their effects on structural integrity and bioactivity. Details of the most used composites were also summarized. Additionally, different bone healing assessment approaches were explored to determine the efficacy of these composites in promoting bone regeneration. Over all the composites containing biomaterials like natural bone, such as hydroxyapatite and collagen, are the most widely used composites, due to their excellent osteoconductivity, biocompatibility, and mechanical properties.Fabrication methods are tailored to the desired composite properties, electrospinning is the choice for the precise fabrication of nanofibrous composites with high surface area. While Sol-gel processing was used if high-purity, bioactive ceramic-polymer composites are required. Additionally freeze-drying method was used if a highly porous composite structure was required for rapid vascularization. Micro-CT is the most reliable technique for non-destructively analyzing the structure, degradation, and osseointegration of composites using high-resolution imaging. In conclusion Composites are expected to provide an effective long-term solution for CSBD and offer insight that may inform future human bone regeneration strategies and veterinary regenerative therapies.

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INTRODUCTION

Bone composite is a biomaterial system used in bone healing and tissue engineering, mimicking Host bone tissue's structural and functional characteristics. It provides mechanical strength, osteoconductive, osteoinductive and metabolic cues, stimulating bone remodeling, angiogenesis, and defect healing **(Geng *et al.*, 2021)**. It regulates Bone tissue growth, promotes the healing process and restores function **(Pires *et al.*, 2021)**. These composites contain inorganic and organic components, such as natural or synthetic polymers, ceramics, and metals **(Guo *et al.*, 2023)**. They enhance osteointegration in bone-implant systems **(Fraile-Martínez *et al.*, 2021)**.

Composite biomaterials play a crucial role in bone healing by promoting the differentiation of mesenchymal stem cells through gene-enhancing drugs, such as Bone Morphogenetic Proteins (BMPs) and Vascular Endothelial Growth Factor (VEGF), which stimulate osteogenesis and angiogenesis **(Kudiyarasu**

***et al.*, 2024)**. Also, composites distribute growth factors to injured bone regions, expediting bone regeneration and reducing inflammation **(Nayak *et al.*, 2024)**.

Composites are indicated for animals with metabolic bone illnesses, such as osteoporosis, as they promote cellular migration and mineralization to mend huge defects **(Patel and Wairkar, 2023)**. Using 3D printing technology, composites are made to fit the animal's mechanical and anatomical requirements for the best possible recovery **(Xu *et al.*, 2023)**, They are indicated for non-union fractures and osteomyelitis **(Yin *et al.*, 2024)**. Also, they are used in craniofacial reconstruction **(Atiyah and LM, 2024)**. Composites also support the integration and stabilization of metal implants during orthopedic surgeries (**Abd-Elaziem *et al.*, 2024)**. They are utilized in joint reconstruction to address osteochondral abnormalities **(Xu *et al.*, 2023)**, periodontal disease **(Balaji *et al.*, 2020, Nabeel *et al.*, 2024)**, endodontics **(Talaat *et al.*, 2024)**, spinal fusion, orthopedic surgeries **(Gloria *et al.*, 2017)** and in the healing of tendons and ligaments **(D'Amora *et al.*, 2017)**.

A CSBD is a bone defect larger than the host tissue's regenerative capacity that Lacks ability to heal spontaneously **(Kim *et al.*, 2018; Mohammed *et al.*, 2023)**. CSBD can be caused by high-energy trauma, open fractures that do not heal spontaneously **(Sagi and Patzakis, 2021)**, surgical resection **(Liang *et al.*, 2024),** particularly for malignant bone tumor removal **(Bläsius *et al.*, 2022)**, osteomyelitis **(Bezstarosti *et al.*, 2021)**, congenital defects, bone diseases, bone cysts, metabolic bone diseases, chronic conditions like rheumatoid arthritis, genetic factors, and disuse osteoporosis **(Stahl and Yang , 2021; Wei *et al.*, 2024)**.

Nutritional deficiencies and endocrine disorders, such as hyperparathyroidism, Cushing's syndrome, and hypothyroidism, can weaken bones and increase the risk of CSBDs. Ischemic bone lesions, necrosis, and severe deformities can also lead to CSBDs and post-surgical complications **(Dahl and Morrison, 2021)**. Long-term use of corticosteroids, radiation exposure, improper fixation or rejection, and osteochondrosis can all contribute to bone deformities and osteoporosis **(Chotiyarnwong and McCloskey, 2020)**. Excessive physical activities and overuse in performance animals can lead to traction or tension fractures, which can become serious defects if not addressed promptly **(Xue *et al.*, 2022)**. Biocompatibility is crucial for bone composite materials, preventing immune responses during implantation and promoting safe body integration **(Nabeel *et al.*, 2024).** It prevents adverse effects like inflammation, toxicity, or rejection, promoting natural healing and bone structure restoration **(Abdelaziz *et al.*, 2023)**.

Bone composites' osteoconductivity is crucial for bone regeneration, as it facilitates the adhesion, proliferation, and migration of osteoblasts from the surrounding bone tissue, periosteum, bone marrow, and vascularized regions to the implanted composite material or the bone defect site, accelerating repair and guiding the formation of new bone tissue. Osteoinductivity is a composite material's ability to stimulate stem cell differentiation into osteoblasts **(Kazimierczak and Przekora, 2020)**. Osteointegration is the composite material's ability to bond with native bone tissue, ensuring seamless integration and long-term support for the healing bone, crucial for successful bone injury healing, bone remodeling, and function restoration at the injured site (Aykora **and Uzun, 2024)**. Bone composites' mechanical strength and load-bearing capacity are crucial, especially in weight-bearing regions **(Yang, 2018)**.

Bone composites require controlled degradation and bio-resorption to minimize surgical removal and facilitate natural bone regeneration **(Barbieri *et al.*, 2013)**. Failure or rapid degradation could compromise healing and implant failure **(Kamil, 2022)**. A durable composite material is crucial for successful bone defect repair **(Shen and Qhobosheane, 2020)**. Bone composites' porosity and interconnectivity are crucial for vascularization and cell migration, facilitating the formation of new blood vessels and nutrient-rich bone tissue, especially in large defects where poor vascularization or insufficient cellular infiltration hinders healing **(Abbasi *et al.*, 2020)**. Biodegradability in composite materials keeps foreign materials from accumulating at implant sites; these materials degrade into non-toxic byproducts, which the body can safely absorb or eliminate, resulting in smooth and efficient healing **(Subuki *et al.*, 2018)**.

Bioactive molecules like growth factors, cytokines, or antibiotics as bone composites loaded with antibiotics release medication locally, preserving sterility, controlling excessive inflammation, enhancing osteoblast function, and preventing systemic side effects **(Pountos *et al.*, 2011)**. growth factors and cytokines enhancing bone healing by stimulating cellular responses, accelerating regeneration, reducing infection risks, and enhancing bone tissue repair **(Szwed-Georgiou *et al.*, 2023)**. Bone composites promote angiogenesis, promoting the formation of new blood vessels around implants to ensure adequate oxygen and nutrients for regenerating bone tissue **(Lee *et al.*, 2021)**. Advanced bone composites incorporate multi-functional properties like antimicrobial, electrical conductivity, and drug delivery systems to reduce infection risks, stimulate bone growth, and deliver therapeutic agents directly to injury sites, improving healing and reducing complications **(Todd *et al.*, 2024)**.

Bone composites are designed to support healing in diverse anatomical locations by allowing the material to adapt to different types of bone tissue, such as cortical or cancellous bone **(Zhu *et al.*, 2021)**. Bone composites require cellular compatibility and support to promote osteoblasts, osteoclasts, and mesenchymal stem cells (MSCs) for bone healing **(Ielo *et al.*, 2022)**. Nanostructured materials improve bone composites' mechanical and biological properties by improving cell attachment surface area, mimicking bone microarchitecture **(Lyons *et al.*, 2020)**, and minimizing residual stress during degradation or mechanical loading **(Huang *et al.*, 2023)**.

Classification of bone composites

Bone composites are classified based on their composition, structure, and purpose of applications, especially in bone healing and tissue engineering. Advanced classification includes material design, biological interaction, mechanical properties, and bioactive additives. This detailed classification allows for the selection of optimal materials and methods tailored to specific clinical needs and applications **(Xue *et al.*, 2022)**.

Classification based on material design and functional integration includes multiple composite types. Multi-phase composites integrate various components such as ceramics, polymers, and metals, with each material fulfilling distinct roles **(Bhong *et al.*, 2023)**. Ceramic-polymer composites, for example, utilize ceramics like hydroxyapatite **(Mohammed *et al.*, 2023)** or tricalcium phosphate, Various types of polymers have been created to encourage bone healing and regeneration, such as poly(lactic-co-glycolic acid) (PLGA) or polycaprolactone **(Kumar *et al.*, 2022)**. Another type is polymer-metal composites like polymer-coated titanium alloys and biodegradable magnesium-polymer composites that provide enhanced mechanical qualities and biocompatibility **(Zerankeshi *et al.*, 2022)**. Additionally, polymers are reinforced with nanostructured materials such as hydroxyapatite nanoparticles (hydroxyapatite/polymer composites) to improve structural strength **(Alhussary *et al.*, 2020; Tang *et al.*, 2024)**. Metallic nanocomposites, such as nano-titanium or nano-silver, have been used to improve their antimicrobial properties **(Ghosh and Webster, 2021)**. Lastly, biopolymer-nanoceramic composites combine biopolymers like collagen or chitosan with nanoceramics **(Abdelaziz *et al.*, 2023)**.

The classification based on biological interaction includes osteoconductive, osteoinductive, osteogenic, and osteointegrative composites **(Khan *et al.*, 2012)**. Osteoconductive bone composites provide a scaffold for new bone tissue growth and attachment by allowing osteoblasts and osteoprogenitor cells to adhere and disseminate from the periosteum and bone marrow to the ward composite (Agrawal **and Srivastava, 2020)**. Examples include synthetic ceramics, such as hydroxyapatite and tricalcium phosphate **(Yuan *et al.*, 2010)**. Natural polymers, such as collagen or chitosan, are combined with inorganic fillers like bioactive glass **(Guo *et al.*, 2021)**. Osteoinductive bone composites stimulate progenitor cells to differentiate into osteoblasts, thus enhancing bone formation **(García-Gareta *et al.*, 2015)**. These include composites with bone morphogenetic proteins (BMPs), such as BMP-2 and BMP-7 **(Liu *et al.*, 2023)** and gene-activated matrices, which use polymers combined with gene delivery systems (e.g., plasmid DNA encoding osteogenic factors) **(Nedorubova *et al.*, 2022)**. Osteogenic bone composites deliver biological molecules, such as stem cells or growth factors **(Safari *et al.*, 2021)**. Examples include cell-laden composites, which are composites preloaded with mesenchymal stem cells (MSCs) or osteoblasts **(Salerno *et al.*, 2019)**. Growth factor-coated composites incorporate surface-bound growth factors like vascular endothelial growth factor (VEGF) for angiogenesis or BMPs for osteogenesis **(Oliveira *et al.*, 2021)**. Osseointegration bone composites are capable of forming a direct bond with the surrounding bone tissue, ensuring long-term stability **(Shah *et al.*, 2019)**. Examples of these include titanium/hydroxyapatite composites, which combine osteoconductive hydroxyapatite with titanium for superior osteointegration **(Oliver-Urrutia *et al.*, 2025)** and bioactive glass-based composites, which are highly bioactive materials that bond with bone while promoting osteogenesis **(Li *et al.*, 2025)**.

Classification based on mechanical properties and load-bearing capacity categorizes composites into low-strength and high-strength types. Low-strength composites are designed for non-load-bearing applications **(Cheng *et al.*, 2021)**. Examples include polymer-ceramic composites **(Monia and Ridha, 2024)** and natural polymer-based composites, which are appropriate for small defects or tissue engineering where strength is less critical **(Sathiya *et al.*, 2024)**. High-strength composites are engineered for weight-bearing bones like the femur, tibia, or spine **(Heimbach *et al.*, 2018)**. Which include ceramic-metallic composites that combine bioactive ceramics with durable metals like titanium or magnesium **(Khorashadizade *et al.*, 2021)** and titanium-based bone implants, which provide mechanical strength and stability in load-bearing applications **(Abd-Elaziem *et al.*, 2024)**. The family of materials known as smart composites or intelligent composites has shown great promise due to its capacity to recognize structural and environmental changes **(Kontiza and Kartsonakis, 2024)**. Reactive materials were used to define smart materials, meaning that their properties can be altered in response to changes in the environment and returned to their initial conditions (Xing ***et al.*, 2023)**. Smart polymeric biomaterials are examples of a viable substitute that promotes endogenous bone healing **(Wei *et al.*, 2022).**

Classification based on degradability and bioresorption rate focuses on the temporal support provided by the composites during bone healing. Fast-degradable composites include polymeric-ceramic composites, which utilize fast-degrading polymers like Poly Lactic Acid (PLA) and Polyglycolic acid (PGA) combined with beta-tricalcium phosphate (β-TCP), and magnesium alloy composites **(Dachasa *et al.*, 2024)**. Slow-degradable composites offer extended support for long-term healing, such as titanium-based bone composites and bioactive glass composites, and non-degradable composites, such as metallic materials like titanium, stainless steel, and tantalum (Abd-Elaziem ***et al.*, 2024)**.

Classification based on synthesis and fabrication techniques distinguishes between conventional and advanced methods. Conventional composite synthesis includes methods like sol-gel, precipitation, casting, or melt blending **(Sumithra *et al.*, 2023)**. An example is polymer casting, where ceramic powders are combined with polymer matrices to create composite structures **(Parida *et al.*, 2024)**. Advanced fabrication techniques allow for precise control of composite properties and include 3D bioprinting, which is used to design custom composites with variable porosity based on imaging data; electrospinning, which produces a nanofiber composite that mimics bone's extracellular matrix; and additive manufacturing, which builds composite structures layer by layer and enables tailored mechanical as well as biological properties **(Maresca *et al.*, 2023).**

Classification based on functionalization and bioactive additives involves enhancing composites with bioactive agents to improve healing outcomes. Growth factor-loaded composites incorporate molecules like BMPs, VEGF, or TGF-β **(Safari *et al.*, 2021)**. Antibiotic-loaded composites are infused with antibiotics such as gentamicin or vancomycin **(Bistolfi *et al.*, 2011)**. Drug-delivery composites are designed to gradually release therapeutic agents, such as anti-inflammatory or anti-cancer drugs **(Chen *et al.*, 2020).**

Composites fabrication techniques

Fabrication techniques used to create bone composites for medical and veterinary applications are influenced by material qualities like porosity, biocompatibility, degradation rate, and mechanical strength. One widely used method is the sol-gel process commonly used for creating bioactive ceramic-based composites in bone regeneration applications **(Murugan and Parcha, 2021)**. Another important method is electrospinning, which creates a nanofiber composite by applying an electric field to a polymer melt or solution, pulling it into thin threads **(Abdulhussain *et al.*, 2023)**. These nanofibers mimic the bone's extracellular matrix (ECM) and can promote cell attachment and growth factor release **(Dhand *et al.*, 2016)**. 3D printing, also known as additive manufacturing, has gained popularity in bone composite fabrication which builds three-dimensional items layer by layer based on digital models, allowing for exact control over composite shape, porosity, and structure **(Girón *et al.*, 2021; Zhang *et al.*, 2023)**.

Freeze-drying or lyophilization is another conventional method that produces highly porous materials with precise pore diameters to create biodegradable composites **(Jain *et al.*, 2015)**. Melt blending is a relatively simple and cost-effective technique this method combines the biomechanical properties of ceramics with the flexibility and degradability of polymer **(Biglari and Zare, 2024).** Solvent casting and particulate leaching are other effective techniques for creating porous bone composites. Solvent casting and particulate leaching involve pouring a polymer solution into a mold, which evaporates to form a solid composite. Particulate leaching, on the other hand, incorporates salt particles into the polymer solution, and these particles are removed after the casting process, creating a porous structure **(Joseph *et al.*, 2023)**. Gas foaming is a technique where a gas, typically CO_2, is introduced into a polymer melt, causing it to foam and produce a porous structure with controlled porosity and homogeneous pore sizes **(Wubneh *et al.*, 2018)**.

Hot pressing is a process that uses heat and pressure to solidify a polymer-ceramic composite material and is commonly used to create high-density scaffolds capable of withstanding mechanical loads **(Miranda *et al.*, 2016)**. Thermally Induced Phase Separation (TIPS) is a process where a polymer solution separates into phases when cooled below the solvent freezing point **(Murugan and Parcha, 2021)**. TIPS allows for precise control over porosity, mechanical strength, and degradation rates, making it suitable for bone tissue engineering **(Rowlands *et al.*, 2007)**.

Biomaterials in composite formation

Biomaterials play a crucial role in forming bone composite materials, each contributing unique properties to enhance the regenerative potential of bone composites and implants. These materials, from natural substances like hydroxyapatite (HA) to synthetic polymers and ceramics, form the backbone of composite systems designed for bone tissue engineering and fracture healing. Hydroxyapatite (HA) is one of the most commonly used biomaterials. It is a natural mineral form of calcium apatite that closely resembles the mineral composition of bone. Its primary function is osteoconductivity, as it promotes osteoblast attachment, proliferation, and differentiation, aiding bone mineralization and osseointegration. HA is widely used in bone fillers, composites, and coatings for implants **(Pires *et al.,* 2021)**. Collagen, another important biomaterial, is a fibrous protein that makes up the majority of the bone extracellular matrix. It mimics the natural bone matrix and helps bone regeneration in composites and scaffolds by providing structural support, encouraging cellular infiltration, and promoting angiogenesis **(Zang *et al.,* 2017)**.

Chitosan, a biopolymer derived from chitin, offers antimicrobial properties while enhancing osteoblast adhesion, mineralization, and cell proliferation **(Abbas *et al.,* 2020).** It is commonly used in hydrogels, scaffolds, and composites for bone tissue engineering **(Shi *et al.,* 2016)**. Polylactic acid (PLA) and polyglycolic acid (PGA) are biodegradable polymers that provide structural support in scaffolds and composites **(Girón *et al.,* 2021; Khosronejad *et al.,* 2025)**. Tricalcium phosphate (TCP), a ceramic biomaterial similar to bone mineral, is widely used for critical defect repairs due to its ability to support bone regeneration and promote osseointegration and osteogenesis **(Bohner *et al.,* 2020)**. Biphasic calcium phosphate (BCP), a combination of HA and β-TCP, takes advantage of HA's mechanical strength and β-TCP's resorbability, offering a balanced solution for bone grafts and composites **(Girón *et al.,* 2021; Ferbert *et al.,* 2023**). Silk fibroin, a protein from silk, is used in composites for tissue engineering to promote osteogenesis. Similarly, fibrin, a protein involved in blood clotting, is used to form hydrogels that support cell adhesion, migration, and neovascularization **(Noori *et al.,* 2017)**. On the other hand, gelatin, derived from collagen, also plays a crucial role in composites and hydrogels, supporting osteoblast growth and bone regeneration **(Echave *et al.,* 2017)**.

Polycaprolactone (PCL) is a biodegradable polyester with high mechanical stability, often used in composites for long bone and defect repair **(Dewey *et al.,* 2021).** Carbon-based nanomaterials such as graphene and carbon nanotubes (CNTs) are incorporated into bone composites **(Liu *et al.,* 2021)**. Hydrogels, water-swollen, cross-linked polymers, create a moist environment that promotes cell migration, growth, and the localized delivery of growth factors **(van Houdt *et al.,* 2021)**. Titanium (Ti), a biocompatible and bioinert metal, is commonly used in implants and prosthetics due to its strong mechanical support and ability to promote osseointegration **(Kaur and Singh, 2019).** The bioglass, which is a bioactive glass material, also supports bone-like mineral formation and osteoblast activity **(Girón *et al.,* 2021)**.

Calcium sulfate, a biodegradable and osteoconductive material, is a temporary composite supporting bone growth. Polyhydroxyalkanoates (PHA) are biodegradable polymers with adjustable mechanical properties. Polyvinyl alcohol (PVA) and polyethylene glycol (PEG) are hydrophilic synthetic polymers that are used in bone regeneration **(Pulingam *et al.,* 2022)**. Polyurethane (PU), a versatile polymer, mimics the elasticity of bone tissue. Titanium dioxide (TiO_2) nanoparticles are included in bone composites **(Cooke *et al.,* 2020)**. Hydroxypropyl methylcellulose (HPMC), which is a cellulose derivative, supports osteoblast growth. Fibrinogen, a plasma protein, is used in fibrin hydrogels, which enhance tissue regeneration and support cell adhesion in bone healing **(Seifi *et al.,* 2024).** Zinc oxide (ZnO), a biocompatible ceramic material, is incorporated into bone composites to promote osteogenesis, improve bone mineralization, and stimulate osteoblast differentiation **(Li *et al.,* 2020; Feroz and Dias, 2021)**. Ceramic composites, composed of materials like alumina, zirconia, or silica, offer high mechanical strength, osteoconductivity and bioactivity **(Zhao *et al.,* 2021)**.

Poly (lactic-co-glycolic acid) (PLGA), a biodegradable copolymer, promotes cellular adhesion and provides mechanical support **(Basutkar *et al.,* 2015)**. Alginate, a naturally occurring polysaccharide, forms hydrogels that mimic the ECM and promote cellular infiltration and osteogenesis. BMPs, a family of growth factors essential for bone development and regeneration, are often used in bone grafts and composites **(Liu *et al.,* 2024; Ribeiro *et al.,* 2024)**. Mineral trioxide aggregate (MTA) is a powdered mixture of mineral oxides with strong biological activity and non-cytotoxic properties **(Tay, 2014)**. Nano graphene oxide (nGO) has emerged as a promising additive for bone tissue engineering due to its ability to mimic the stiffness of bone **(Xing and Liu, 2024).**

Advanced types of composites

Over the past years, significant advancements in biomaterials have led to the development of a wide range of composites for healing CSBDs. Magnesium-based alloys combined with HA provide a biodegradable composite. Similarly, magnesium alloy-collagen composites enhance biodegradability and osteogenesis **(Shi *et al.,* 2023)**. Whereas polycaprolactone (PCL)-HA composites integrate PCL’s mechanical stability with HA’s regenerative capabilities **(Podgorbunsky *et al.,* 2025)**, polyurethane-HA composites enhance flexibility and support bone mineralization **(Sultan, 2018)**.

In the domain of metal-based composites, magnesium-based composites (Mg/HA), zinc-based composites, and titanium dioxide nanotubes are leading the way in improving osteointegration. Additionally, magnesium/polymer hybrid composites and metal-organic frameworks (MOFs) have unique qualities such as high porosity and tunable properties, making them ideal for biological applications. Recently, researchers have focused their attention on incorporating MOFs into composites for bone tissue regeneration (BTE) **(Mi *et al.,* 2024)**. The many uses of MOF-integrated composites in BTE are studied, including antibacterial characteristics, osteogenic differentiation, angiogenesis, and immunomodulation **(Imtiaz *et al.,* 2025)**. In the realm of metal-based composites, bio-inspired magnesium-polymer composites are used for bone repair **(Omidian and Babanejad, 2024)**. Further innovations include graphene-HA and carbon nanotubes-hydroxyapatite (CNT-HA) composites, improving mechanical strength and osteoconductivity **(Abubakre *et al.,* 2023)**.

Additionally, biodegradable silk fibroin-collagen composites mimic natural bone environments, while polyvinyl alcohol (PVA)-HA composites combine elasticity with mineralization for enhanced healing **(Wei *et al.,* 2023)**. Moreover, nanoscale HA-chondroitin sulfate composites enable osteogenesis and cartilage repair **(Li *et al.,* 2018)**. Additionally, chitosan-HA composites offer antimicrobial properties alongside osteoconductivity. While fibrinogen-PCL composites encourage angiogenesis and provide a controlled degradation profile. Similarly, chondroitin sulfate-collagen composites promote osteogenesis, and alginate-HA composites offer biodegradable hydrogels that support cell adhesion and bone mineralization **(Khodaverdi *et al.,* 2024; Cao *et al.,* 2024)**. While calcium sulfate-HA composites are resorbable fillers to support bone regeneration **(Nilsson *et al.,* 2013)**. Similarly, gelatin-alginate hybrids provide a composite that combines biodegradability with enhanced cellular activity **(El-Bahrawy *et al.,* 2024)**. Additionally, chitosan-HA-gelatin composites optimize adhesion **(Peter *et al.,* 2010)**. While silk fibroin-HA composites improve osteoconductivity and mechanical flexibility **(Du *et al.,* 2009)**.

PCL-bioactive glass composites provide excellent structural support for load-bearing applications. Additionally, ceramic-polymer hybrids, incorporating alumina or zirconia with polymers like PCL or PLGA, offer a balance between mechanical strength and controlled degradation **(Palmero *et al.,* 2016)**. Moreover, gelatin-PCL composites improve cell attachment and bone mineralization **(Shahin-Shamsabadi *et al.,* 2018)**. Bioactive glass-collagen composites stimulate bone formation and improve cellular adhesion; moreover, graphene and CNTs have been incorporated into polymers and ceramics to reinforce mechanical strength, conductivity, and bioactivity (Kumar ***et al.,* 2020)**. Additionally**,** bioactive ceramics with silicon further enhance bone mineralization and cellular response **(Francis, 2018)**.

Recent advancements in bone regeneration materials have explored various composite strategies that combine multiple biomaterials to enhance bone healing, particularly for CSBDs. Calcium-based composites have played a pivotal role in bone regeneration, with materials like HA, TCP, BCP, and Calcium Phosphate Cement (CPC) being extensively researched for their osteoconductive properties **(Min *et al.,* 2024)**. Innovations such as strontium-doped calcium phosphate (Sr-CP) and fluorapatite-based composites further improve biological performance by promoting cell adhesion and osteogenesis **(Tavoni *et al.,* 2021**). Newer composites incorporating calcium sulfate hemihydrate (CSH), calcium silicate-based composites, and hybrid systems such as α-tricalcium phosphate/chitosan and calcium phosphate/polymer composites with antibiotics also enhance healing while addressing infection risks **(Kjalarsdóttir *et al.,* 2019)**. Other calcium-based composites, such as hydroxyapatite/strontium substitution and calcium phosphate/polymer nano-hybrids, and the development of magnesium-substituted bioactive glass/HA and calcium silicate/graphene hybrid composites further enhance the material's ability to regenerate bone tissue effectively **(Du *et al.,* 2020; Daneshmandi *et al.,* 2021)**.

Bioactive glass-based composites such as mesoporous bioactive glass (MBG) have been engineered to improve the bioactivity and osteoinductivity of the composite **(He *et al.,* 2023).** Materials like zinc-doped bioactive glass and strontium-doped bioactive glass are showing the potential to accelerate bone regeneration **(Balu *et al.,* 2021)**. The addition of functional components like bioactive glass/chitosan composite and bioactive glass/silk fibroin provides additional support for cellular growth and mineralization **(Liang *et al.,*** 2021). Advancements in 3D-printed bioactive glass composites and bioactive glass with micro/nanoporous structures are opening new possibilities for customized composite fabrication **(Golniya *et al.,*** 2024). Bioactive glass-based composites such as zirconium-doped bioactive glass and aluminum-substituted bioactive glass composites, are providing solutions to overcome challenges in traditional bone grafts **(Hammami *et al.,* 2023; Sreena *et al.,* 2024)**.

Polymer-based composites like poly(lactic-co-glycolic acid) (PLGA)/HA, PCL/TCP, and polyethylene glycol (PEG)/Nano-HA combine the flexibility of polymers with the regenerative power of calcium phosphates or ceramics **(Gentile *et al.,* 2014)**.

Other innovations such as PLA/chitosan, PU/bioactive glass, and alginate-based hydrogels are emerging to promote cellular infiltration and differentiation **(Motameni *et al.*, 2024)**. Gelatin methacryloyl (GelMA)/HA and silk fibroin/polylactic acid composites also show the potential to provide mechanical strength and biocompatibility **(Guo *et al.*, 2021)**. In polymer-based composites, innovations like polymeric composite scaffolds with controlled drug release for bone healing similarly polylactic acid-co-ethylene glycol (PLAEG) with bioactive glass demonstrate the importance of combining polymers and bioactive materials to enhance healing at the site of the bone defect **(Filippi *et al.*, 2020; Souza *et al.*, 2024)**. PCL-bioactive glass composites provide excellent structural support for load-bearing applications **(Dziadek *et al.*, 2021)**. Additionally, ceramic-polymer hybrids, incorporating alumina or zirconia with polymers like PCL or PLGA, offer a balance between mechanical strength and controlled degradation **(Palmero *et al.*, 201**6). Moreover, gelatin-PCL composites improve cell attachment and bone mineralization **(Shahin-Shamsabadi *et al.*, 2018)**.

Collagen-based composites have been optimized for bone healing with materials such as mineralized collagen/polycaprolactone (mCol/PCL) and collagen/chitosan/bioactive glass composites **(Li *et al.*, 2021)**. Additionally, composites like collagen/nano-silver composites, collagen/CNTs hybrids, and collagen/HA/chitosan hybrid composites offer further enhancements in antibacterial properties and mechanical strength **(Vijayalekha *et al.*, 2023)**.

Hybrid composites that combine multiple components such as chitosan/bioactive glass/nano-HA, GelMA/bioactive glass/nano-silica, and silk fibroin/HA/graphene oxide are at the forefront of bone tissue engineering **(Nwuzor *et al.*, 2025; Sousa *et al.*, 2025).** Advanced hybrid composites such as chitosan/HA/graphene oxide for bone repair and GelMA/graphene oxide/bioactive glass composite scaffolds are facilitating the development of multifunctional materials for bone regeneration **(Liu *et al.*, 2021)**. Nano-silver/bioactive glass/polymer composites for antibacterial bone healing combine the healing properties of bioactive glass with antibacterial agents **(Zhang *et al.*, 2024)**.

Graphene and carbon-based composites like graphene oxide/HA (GO/HA) and CNTs/collagen-based composites have gained attention due to their unique mechanical strength and conductivity **(Chen and Li, 2022; Amiryaghoubi *et al.*, 2022)**. The inclusion of graphene-polymer composite for bone tissue engineering and graphene-based nanocomposite hydrogels for bone regeneration represents a shift towards incorporating carbon nanomaterials for improving mechanical properties and promoting cell adhesion and differentiation **(Liu and Wang, 2023; Lv *et al.*, 2025)**.

Advanced functional composites such as fibronectin-coated composites, growth factor-embedded hydrogels, and stimuli-responsive composites (e.g., pH- or temperature-sensitive) are being developed to allow controlled drug release, optimize healing, and adapt to the physiological conditions of the site **(Canciani *et al.*, 2023)**. The integration of antimicrobial polymer/ceramic composites ensures that infections do not compromise bone healing, especially in CSBDs **(He *et al.*, 2025)**. The advent of 3D-printed composites has revolutionized the design of composites with the ability to precisely control the composite's structure, porosity, and mechanical properties. 3D-printed ceramic/bioactive glass composites and 3D-printed graphene oxide/HA composites show great promise for replicating the native bone structure and improving tissue integration **(Belaid *et al.*, 2020; Alonso-Fernández *et al.*, 2023)**.

Nanotechnology-inspired composites like nano-hydroxyapatite embedded in polymeric matrices, nano-silica-reinforced polymer/HA composites, and nano-bioactive glass/nano-graphene oxide hybrids are taking center stage in bone regeneration research **(Kumari *et al.*, 2022; Mo *et al.*, 2023)**. New approaches in nanotechnology and bifunctional materials, such as nano-structured calcium phosphate/bioactive glass composites and injectable nanocomposites for bone healing, are advancing the ability to treat larger bone defects with minimal invasiveness, ensuring better integration with bone tissue **(Abdolahinia *et al.*, 2024; Pablos *et al.*, 2024).** Similarly, the injectable thermo-responsive hydrogel for bone tissue engineering provides a minimally invasive approach with great potential for bone regeneration **(Romagnoli *et al.*, 2014)**. Miscellaneous innovative composites, including silk fibroin/nano-HA/chitosan and thermo-responsive hydrogels with osteogenic additives, are being explored for unique approaches to bone repair **(Miranda *et al.*, 2016)**.

Injectable composites have also seen remarkable progress, with injectable hydrogel/calcium phosphate nanocomposites and polymeric composites being developed for more effective bone regeneration **(Omidian and Chowdhury, 2023)**. These injectable bioactive glass/chitosan hydrogels offer efficient healing and have been combined with nano-hydroxyapatite/polymer composites for bone repair. Additionally, injectable hydroxyapatite/graphene oxide composites are emerging as a potential solution for addressing critical bone defects, while injectable PCL/HA nanocomposite hydrogels and gelatin-alginate hybrid composites demonstrate promising results in tissue engineering applications **(Yao *et al.*, 2019; Ye *et al.*, 2023)**.

The development of antibacterial and osteogenic hybrid composites, including chitosan/silver nanoparticles for antibacterial bone repair and antibiotic-loaded bioactive glass composites for bone defect healing, addresses both infection control and bone healing **(Wang *et al.*, 2023)**. 3D-printing innovations for bone regeneration continue to evolve with 3D-printed multi-material bone composite scaffolds offering the ability to tailor the material properties to specific clinical needs **(Ai *et al.*, 2020*).***

Significant strides have been made in surface modification techniques for enhanced biocompatibility. These include plasma-treated hydroxyapatite/polymer composites and surface-functionalized bioactive glass scaffolds, which promise improved bone integration. Polymers with bioactive peptide coatings and surface-modified graphene/bioactive glass composites are gaining attention for their ability to support bone healing and integration **(Qi *et al.*, 2023; Subramaniyan *et al.*, 2024)**.

Evaluation of the effectiveness of bone composites in promoting bone healing

High-resolution micro-CT imaging is a non-invasive technique that provides a 3D evaluation of bone healing, allowing detailed analysis of bone formation, mineralization, and composite integration. It tracks bone defects and composite degradation, assessing healing progress and effectiveness **(Su *et al.*, 2024)**. Biomechanical testing *in vivo* measures bone functional recovery by analyzing the load responses of composite materials implanted in living organisms. It assesses strength, stability, and load-bearing capacity, providing important information for treatment response and functional stress tolerance **(Hente *et al.*, 2003)**. Histological and immunohistochemical evaluation examines cellular responses and bone formation at injury sites using H&E staining **(Okasha *et al.*, 2022)**. It helps understand bone remodeling and vascularization during healing, revealing cellular dynamics **(Di Carlo *et al.*, 2018)**.

Advanced biomechanical testing, including micro-mechanical tests at bone-composite interfaces and advanced biomechanical tests, assesses nano-mechanical properties like stiffness and elastic modulus, adhesion strength, and material hardness **(Kong *et al.*, 2020).** These tests help understand the bone-composite system's response to mechanical forces and contribute to regeneration **(Niu *et al.*, 2023)**. Gene expression and osteogenic markers investigate the effects of composite materials on osteogenic differentiation and bone remodeling during healing **(El Ashry *et al.*, 2016).**

RT-PCR or RNA sequencing tracks the expression of key osteogenic markers such as alkaline phosphatase (ALP), osteocalcin, collagen type I, and VEGF. This methodology helps elucidate the molecular mechanisms by which composite materials influence bone healing and regeneration, providing insights into their efficacy as therapeutic agents **(Granéli *et al.*, 2014)**.

Real-time bioluminescence imaging is a non-invasive method for tracking cellular activity via genetically engineered bioluminescent reporters, such as osteoblast differentiation. Light-emitting markers like luciferase are utilized to monitor real-time bone healing, enabling the observation of cellular dynamics *in vivo* **(Conway *et al.*, 2020)**. This technique offers the advantage of continuous monitoring without the need for repeated invasive procedures **(Kimelman *et al.*, 2013)**. X-ray imaging and radiographic scoring are commonly used to monitor bone healing and union. Scoring systems are used to quantify bone consolidation and assess the progress of bone healing **(Gadallah *et al.*, 2022)**. X-ray imaging provides valuable information about the structural integrity of the bone over time, allowing for the assessment of healing at various stages **(Cunningham *et al.*, 2017)**. Fluorescence microscopy is employed to examine bone mineralization and osteogenesis during healing **(Via and Jerele, 2023).** Fluorescent dyes such as calcein and alizarin red are used to label new bone and mineral deposits, allowing for high-resolution imaging of bone regeneration **(Via and Jerele, 2023)**. Magnetic resonance imaging (MRI) is a non-invasive technique used to assess soft tissue and bone composite integration, vascularization, cartilage regeneration, and bone healing without radiation exposure **(Pop *et al.*, 2019)**.

Nano-CT imaging provides ultra-high-resolution imaging for a more detailed analysis of composite microarchitecture and bone remodeling. This method tracks porosity, vascularization, and composite degradation with greater spatial resolution compared to traditional micro-CT **(Salmon and Sasov, 2007)**. Nano-CT is particularly valuable for assessing the microstructure of composites and their interaction with surrounding bone tissue (Salmon **and Sasov, 2007)**. Biochemical markers are non-invasive markers in blood and tissues that are used to assess metabolic activity and osteogenesis during bone healing. Key markers like ALP, osteocalcin, C-terminal telopeptide (CTx-1), and collagen degradation products are measured to evaluate both systemic and local bone remodeling. These markers provide important insights into the biochemical processes that accompany bone healing **(Cox *et al.*, 2010)**.

Cell viability and proliferation assays evaluate composite biocompatibility, osteoblast and MSC growth support, cytotoxicity, and proliferation rates, providing crucial information for the healing process of tissue formation **(van Erk *et al.*, 2024)**. Molecular imaging for bone tissue viability uses molecular imaging methods such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) to assess bone tissue viability, vascularization, and metabolic activity during the healing process. Radiolabeled tracers like fluorodeoxyglucose **(**FDG) for metabolic activity and 99mTc-labeled agents (for bone mineralization) capture detailed, non-invasive images that help monitor bone turnover, vascular growth, and composite integration. Real-time molecular imaging of metabolic and vascular activity offers essential insights into the healing process, providing valuable information that aids in the refinement of bone composite designs for improved treatment outcomes **(Bar *et al.*, 2003)**.

CONCLUSION

In recent years, bone composites have provided substantial distinct advantages over traditional grafting methods for the treatment of CSBDs. Therefore, they are regarded as key challenges in bone tissue engineering and received extensive attention. Bone composites significantly improved the rate and quality of osteogenic differentiation, mechanical strength, and osteogenic conductivity. As research progresses, bone composites are expected to provide an effective long-term solution for large bone defects in animals and improve human bone regeneration strategies as well as veterinary regenerative therapies in the future.

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Declarations

Ethics approval and consent to participate, it is a review article

Conflict of interest

The authors declare that they have no competing interests

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