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Review

Bioglasses Versus Bioactive Calcium Phosphate Derivatives as Advanced Ceramics in Tissue Engineering: Comparative and Comprehensive Study, Current Trends and Innovative Solutions

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Abstract: *Tissue engineering represents a revolutionary approach to regenerating damaged bones and tissues.* The most promising materials for this purpose are calcium phosphate-based bioactive ceramics (CaPs) and bioglasses, due to their excellent biocompatibility, osteoconductivity, and bioactivity. This review aims to provide a comprehensive and comparative analysis of different bioactive calcium phosphate derivatives and bioglasses, highlighting their roles and potential in both bone and soft tissue engineering as well as in drug delivery systems. *We explore their applications as composites with natural and synthetic biopolymers, which can enhance their mechanical and bioactive properties. The review critically examines the advantages and limitations of each material, their preparation methods, biological efficacy, biodegradability, and practical applications.* By summarizing recent research from scientific literature, this paper offers a detailed analysis of the current state of the art. The novelty of this work lies in its systematic comparison of bioactive ceramics and bioglasses, providing insights into their suitability for specific tissue engineering applications. The expected primary outcomes include a deeper understanding how each material interacts with biological systems, their suitability for specific applications, and the implications for future research directions.

Keywords: Bioceramics; Bioglasses; Tissue Engineering; Calcium Phosphates; Biocompatibility; Biodegradibility; Scaffolds; Injectable Hydrogels

1. Introduction

Bioactive materials (glasses and ceramics) are commonly employed to restore and replace unhealthy and damaged hard and soft tissues [1]. Two major classes of bioactive materials are bioactive ceramics **and** bioglasses. They have gained widespread attention due to their ability to connect with biological tissues, promote cellular interactions, and regenerate tissue **[2]**. Thus, these novel materials are pivotal in a wide range of biomedical applications. According to the host tissue interactions, bioceramics can be classified as nearly bioinert, bioactive, and bioresorbable [3]. Among these, calcium phosphate-based ceramics are highly bioactive materials, and they are particularly significant due to their compositional similarity to natural bone minerals. Overall, the damaged tissues and bones can be restored or replaced using these types of biomaterials and other bioactive molecules. Theoretically, the bioceramics and bioactive glasses bond to bone through a bone-like carbonated hydroxyapatite layer, facilitating effective biological interaction [4]. Similarly, bioglasses are also recognised for their high bioactivity and potential stimulation of osteogenesis [1]. Advantages of bioactive ceramics include their various chemical composition and controlled degradation rates, whereas bioglasses excel in forming strong bonds with hard tissues and have enhanced versatility in composition. However, both materials present challenges such as limited flexibility, fragile texture, and low mechanical properties [5-7]. It is well-known that the most bone-like bioactive ceramics are the different calcium phosphate phases, such as hydroxyapatite (HAp),

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dicalcium phosphate (DCP), and tricalcium phosphate (TCP), that are widely used in bone tissue engineering since they can support osteointegration and osteoconduction**.** On the other hand, bioglasses, such as 45S5 Bioglass, are known for their ability to bond with soft and hard tissues, making them versatile for widespread applications such as bone grafts, scaffolds, coatings for implants and even in dentistry as bone fillers**.** However, their brittleness (in ceramics) and rapid degradation (in bioglasses) limit their standalone use or their applications in load-bearing conditions. Recent advancements have focused on combining these materials with biopolymers to overcome these limitations [8,9].

In addition, the demand for biomaterials in regenerative medicine has also significantly increased due to the growing need for functional tissue replacements. Consequently, recent research has expanded their use in soft tissue repair [10], wound healing [11,12], and drug delivery [13-15]**.** Despite extensive research on both material types, a detailed comparative analysis **of** calcium phosphate-based ceramics vs. bioglasses in tissue engineering is still missing. This review systematically compares their biological interactions, material properties, applications, and limitations to provide a clear understanding of their respective advantages and potential improvements. The review also explores composites with biopolymers, which offer enhanced mechanical and biological properties, making them attractive alternatives for clinical applications. Figure 1 illustrates the differences between the two materials in composition and main constituents.

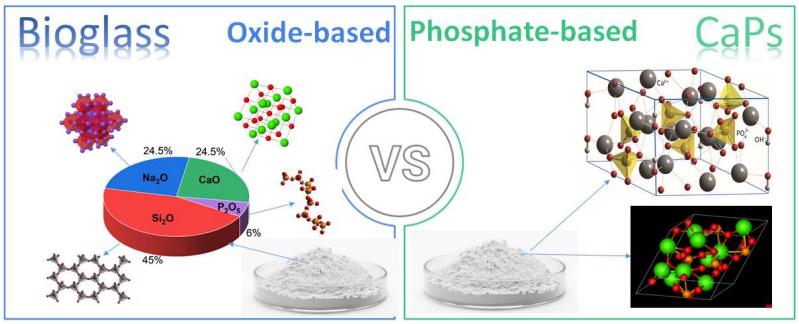

Figure 1. Schematic illustration the differences in compositions of bioglasses and CaP-based ceramics.

2. Calcium Phosphate-Based Bioactive Ceramics

Calcium phosphate (CaPs) based ceramics constitute a group of biomaterials which includes many different calcium phosphate phases with varying Ca to P molar ratio (from 0.5 to 2) that causes different morphology, particle size, and form, thus diverse biological performance [16]. These materials have a chemical composition and structure like the mineral phase of bone. The properly manufactured CaP ceramics have an interconnected porous structure, and they are well-known for their excellent osteoconductive properties. However, they do not have proper osteoinductivity, moderating the attachment and the differentiation of osteogenic cells [17]. As CaP ceramic particles are poorly moldable, they cannot be used to fill bone defects with a complex geometry. Porous CaP ceramics possess a compressive strength corresponding to 10–25% of the compressive strength of long bones [18]. Thus, porous CaP ceramics need more mechanical support via osteosynthesis when used in weight-bearing bone parts [19].

Owing to their unique structures, CaP ceramics facilitate the growth of bones on their surface and into their three-dimensional structure, which means osseointegration. It has been shown that osseointegration depends on the pore size of the materials. The optimal osteoconductivity of biomaterials can be achieved with pore sizes ranging from 300 to 400 μm, while the minimum pore size that is required to generate mineralized bone is considered to be 50 μm [20].

The different calcium phosphate phases can be synthesized by mixing calcium and phosphate solution under acid or alkaline conditions. The used preparation parameters and conditions strongly determine the formed phases [21]. Only particular CaP compounds are beneficial for implantation in

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the body, as those with a calcium-to-phosphorus ratio lower than 1 are not fit for biological use because they are highly soluble [22]. The high osteoinductive and bone regenerative capability of these materials mainly linked to their chemical and physical properties, such as surface roughness and porosity [23,24]. It is also reported [25,26] that the presence of calcium ions and inorganic phosphate activates specific signaling routes that facilitate bone generation. The calcium phosphate powder particles can be prepared in many ways, either at low or high temperatures and in dry or wet conditions. The main technologies are summarized in Figure 2.

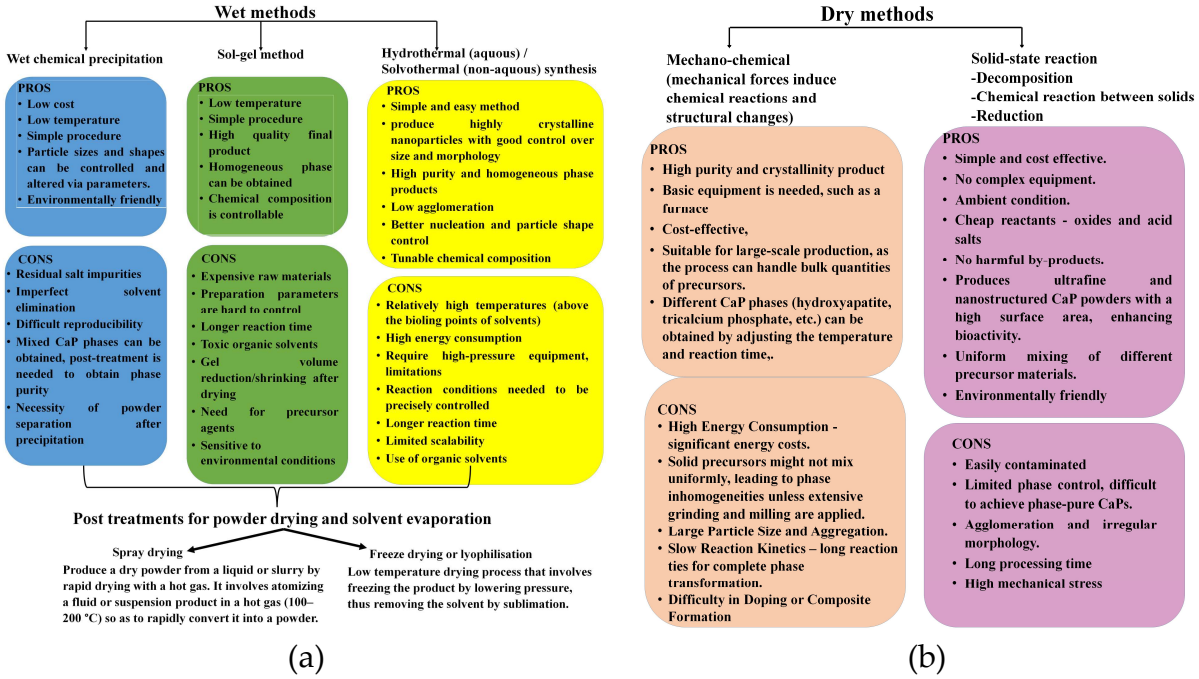

Figure 2. Most commonly used preparation methods for CaPs, classified as wet chemical methods (a) and dry methods (b).

All the above-discussed methods can include doping and composite formation capability: Facilitates easy incorporation of dopants (e.g., Sr, Zn, Mg) or composite formation with polymers or other bioceramics [27].

Figure 3 demonstrates a comprehensive SWOT assessment of the uses of calcium phosphate materials, considering their primary benefits and the challenges they present to society.

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Figure 3. SWOT analysis of CaP-based ceramics.

3. Bioglasses

Bioglasses are a type of bioactive material that exhibit excellent biocompatibility and the ability to bond directly to bone tissue and have the function of enhancing the regeneration of bone tissues while gradually degrading. [28]. The commercial composition of bioglasses is mainly an amorphous mix of oxides, such as silicon dioxide, sodium oxide, calcium oxide, and phosphorus pentoxide in different ratios. The most used composition is 45 Wt.% SiO_2-24.5 Wt.% Na_2O-24.5 Wt.% CaO-6 Wt.% P_2O_5, but many other variations are available which is widely elaborated in detail in numerous reviews [29-31].

Generally, these materials can be considered as amorphous silicate glass made either by the melting method [32,33] or the sol-gel method [34]. In addition, researchers [35] compared the mechanical and physical properties of bioglass scaffolds made in two different ways. They found that the sol–gel-synthesized bioactive glasses are superior to melt-produced glasses because of their greater porosity and better bioactivity. According to the main constituent, there are three main types of bioglasses, such as silica-based glasses [36], borate-based glasses [12,37,38], and phosphate-based glasses [39,40]. Each type has its unique chemical composition, mechanical and structural properties, therefore, they can be utilized in various for in biomedical fields. Their main and widespread applications are as bone grafts and fillers. Recent studies have demonstrated their effectiveness in promoting osteogenesis and angiogenesis [41]. The bioglasses can be prepared alkali-free, especially Na-free. Sodium is regarded as an essential component for bioactivity, since it effectively disintegrates the glass network. However, bioglasses without sodium revealed similar dissolution characteristics and bioactivity as traditional bioglasses with sodium [42-44]. In addition, some in vitro biocompatibility studies have proven that the glasses with higher Na2O content can be linked to cytotoxic effects [45].

It has also been investigated that the apatite formation and the degradation rate are significantly affected by the glass network porosity and the amount of phosphate. The CaO, Na_2O, and P_2O_5 components are network modifiers, and they can be integrated into the original SiO_2-CaO-Na_2O composition to obtain a more reactive surface [46,47]. The P2O5 content as a phosphate derivative is also necessary for bioactivity [48,49]. The different types of bioglass powders can be prepared in many ways, the most widely used ones are illustrated in Figure 4.

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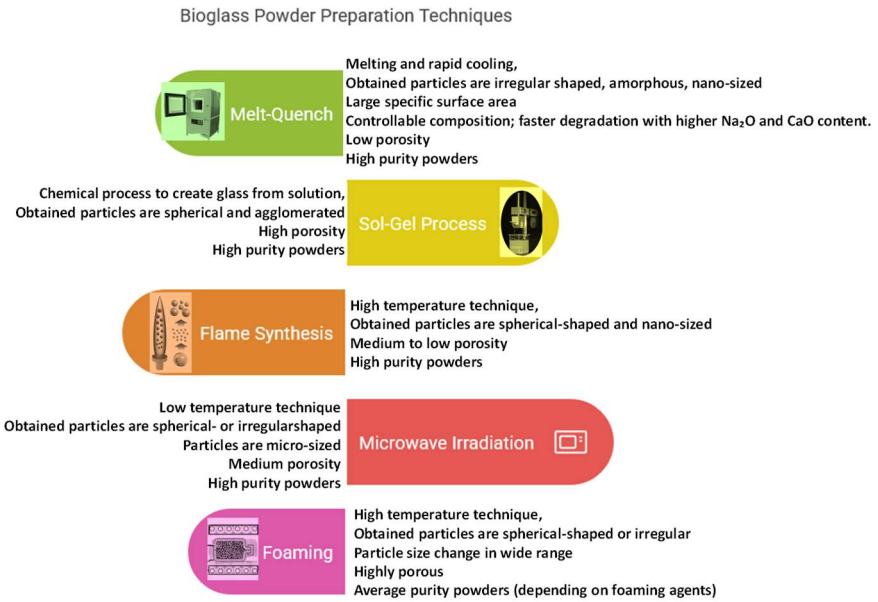

Figure 4. Schematic illustration of bioglass preparation methods an their properties.

An analysis of the strengths, weaknesses, opportunities, and threats associated with bioglass powder applications, highlighting their significant societal benefits and drawbacks is shown in Figure 5.

Figure 5. SWOT analysis of bioglass powders.

4. Applications of Bioactive Ceramics

The main application areas of bioactive ceramics (CaPs and bioglasses alike) are very versatile, and we will discuss the most important ones above.

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4.1. Bioglasses and Calcium Phosphates in Bone Tissue Engineering (BTE)

The most important applications are depicted in Figure 6.

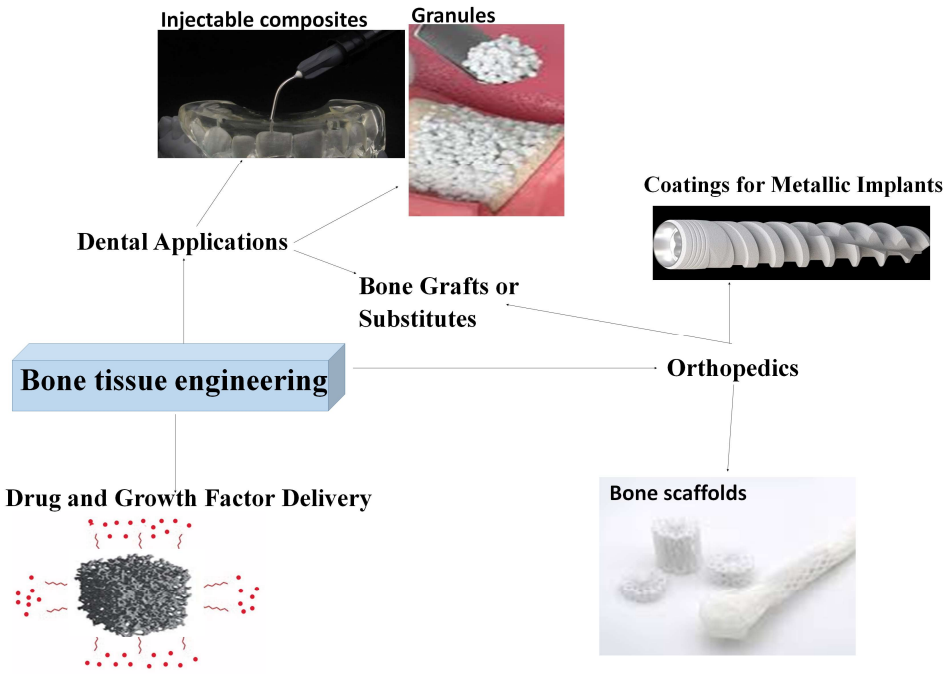

Figure 6. Bioactive ceramic utilization in bone tissue engineering.

4.1.1. Scaffold Materials and Bone Substitutes

In clinical practice, bone irregularities are prevalent and impose a considerable burden on the families of patients, as well as on society and healthcare infrastructures. Scaffolds made from calcium phosphate with complex nano- and micro-level structures have proven to be highly effective in facilitating bone regeneration. These materials can be fabricated into porous scaffolds that support cell attachment, proliferation, and differentiation [50-53].

Calcium phosphate cements (CPCs), as unique forms of CPs, are synthetic, self-assembling bone substitute materials. The main benefit of CPCs is that they are injectable, moldable and hardened in situ, so the contact between the tissue and the implant will be optimal, even when the defect dimensions are irregular [49]. Calcium phosphate scaffolds provide stable properties and allow the control of porosity and biocompatibility. The pore size of the scaffold improves revascularization and bone remodeling, enabling the ingrowth of cells and proteins and enhancing biocompatibility, making them suitable for implant use [54].

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As Figure 7 clearly illustrates, many techniques are employed to prepare porous ceramic scaffolds, each one differently influences the final products' mechanical properties and suitability for specific applications [55, 56].

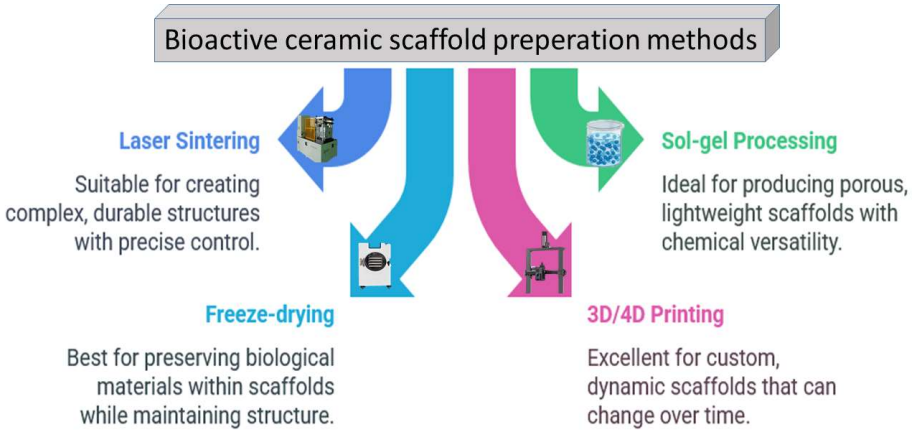

Figure 7. The most utilized ceramic scaffold preparation methods so far.

However, numerous other methods and additives can be utilized to modify the porous characteristics of ceramic scaffolds. For example, adding a pore-forming agent [57], applying foam technology [58], or extrusion molding method [59]. Nonetheless, the connectivity of pores plays a crucial role in determining the biological performances, and at the same time, a three-dimensional arrangement of connected pores has been found to be more susceptible to a decrease in the mechanical properties of ceramic materials [60,61].

Bioglasses and CaPs have a similar role in bone tissue engineering thanks to their ability to directly adhere to bones. They function effectively as bone grafts, fillers, and restorative materials, promoting rapid integration and regeneration. Preparation methods like melt-quenching and sol-gel facilitate the development of porous structures with adjustable characteristics. Specifically, the ideal method for bioactive glass preparation is the sol-gel technique [62]. It helps to customize the properties of materials for bone tissue regeneration, because they can degrade at a controlled rate, transform into bone-like material, and connect well with tissues while promoting bone-forming cell growth. Adding bioactive elements or drugs into these glasses can further enhance their ability to heal bone and prevent infections. One of the most ideal structures for scaffold materials is the mesoporous system [63,64] that can be prepared by 3D printing as hierarchically porous scaffolds. However, there are still existing challenges regarding their applicability due to insufficient mechanical strength, especially for load-bearing bones [31,65]. Another key challenge in the field of bone tissue engineering is the imitation of the extracellular matrix's composition. But scaffolds derived from bioglass particles and hydroxyapatite feature a naturally porous architecture that enhances cell attachment and development. In addition, it can enable vascularity, migration of nutrients, and metabolic by-products. The unique structures of these materials ensure better adherence of osteoblast cells, promoting their faster proliferation, differentiation, and mineralization into bone [66,67]. This was a huge achievement in the development and optimization of different bone filler materials [68].

4.1.2. Bioactive Ceramic-Polymer Composites

In tissue engineering, another interesting area is the development of composite materials that combine bioglasses and calcium phosphates with different biopolymers to enhance their suitability and adjustability.

As Figure 8 shows, composite scaffolds can be prepared in many ways. Each has its advantages and disadvantages. These unique composite materials (both bioglasses and calcium phosphate

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derivatives) can be prepared as solid scaffolds, injectable composite hydrogels, fiber mats, thin films, or even matrices [69]. Among the various types of these composites, the injectable form is very attractive and useful [70-73]. The most commonly used biopolymers to form these composites can be classified into two main categories. One is the natural biopolymers, such as cellulose, cellulose acetate, alginates, chitosan, collagen, gelatin, and the other is the synthetic polymers like polylactic acid (PLA), polyvinyl pyrrolidone (PVP), polycaprolactone (PCL), and polyethylene glycol (PEG). A wide array of materials has been explored for the fabrication of these polymer-based scaffolds, each offering unique properties and functionalities tailored to specific applications. Chiu et al. [74] prepared injectable implants in the form of calcium sulfate and self-setting calcium phosphate composite. The developed injectable pastes were easy to handle, had excellent biocompatibility, and sufficient mechanical properties. These pastes also had great potential in minimally invasive surgery, and they can be utilized to treat maxillofacial defects or even in reconstructive rhinoplasty. In other interesting work, Cai et al. [75] prepared injectable chitosan oligosaccharide (COS) and bovine-derived hydroxyapatite (BHAp) composites. The intended use of this material was as a dental pulp cap. The developed biocomposite was slightly soluble in physiological solutions, however, the solubility rate can be changed by applying certain cross-linking agents. Regarding bone regeneration, a promising composite can also be a dextran-based injectable hydrogel [76] which can be utilized as scaffolds and drug-release systems simultaneously.

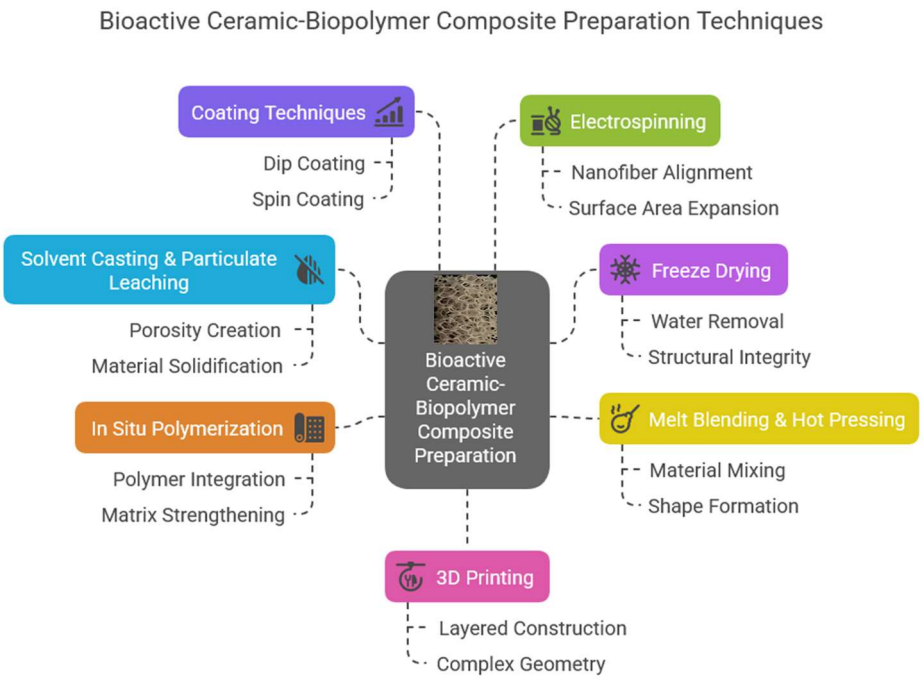

Figure 8. Bioactive ceramic and biopolymer composite preparation possibilities and their forms.

The alginate-, chitosan-, collagen-, and gelatine-based composites are similarly ideal choices to prepare injectable materials. For example, Xu et al. [77] prepared bioactive glass containing sodium alginate hydrogel that had immunomodulatory and angiogenic properties to heal tendon tissues. According to their results of the biomechanical tests, the BG/SA hydrogel noticeably enhanced the load, failure stress, and tensile modulus of the repaired tendon. Therefore, applying injectable BG/SA hydrogel can be a novel and promising therapeutic approach to heal Achilles tendons along with surgical intervention. On the other hand, in a very recent study, Estevez et al [78] developed calcium phosphate containing sodium alginate and gelatin hydrogels as bone replacement injectable composites. They proved that the developed hydrogel composites had mineralization ability with slight antimicrobial properties and a slow-to-moderate degradation rate. Wu et al [79] recently

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reported their work on the preparation of porous composites microspheres based on hydroxyapatite (HAp), di-calcium phosphate dihydrate (DCPD), and chitosan. They prepared the composites via the hydrothermal method, in which chitosan had an important role as a chelating agent to promote the calcium phosphate particles' growth. They found that the formed microspheres comprised of $Ca_2P_2O_7$, β-TCP, and HAp, and they can be utilized as injectable bone graft materials. Chitosan is also an important matrix for injectable hydrogel preparation. Ciotek et al. [80] examined chitosan and sodium hyaluronate hydrogels with bioglass particle addition under different conditions and found that these bioglass and polysaccharide hydrogels were microstructurally stable and bioactive. Besides the above-mentioned works, numerous other researches are exploring these kinds of important injectable composite materials [81-84]

In the form of solid and stable scaffold materials, these novel composites can be utilized in cases of larger bone deficiency as filler materials. In this case, the main preparation methods are molding and additive manufacturing, such as 3D or 4D printing [85-87].

For instance, PLA polymer with embedded calcium phosphate particles has been evaluated for its bioactivity [88]. In vitro studies have shown that human mesenchymal stromal cells (hMSCs) proliferate on these composites, indicating potential for tissue engineering applications. In other research, Zhang et al. [89] investigated the effect of different amounts (5%, 10%, and 20% in wt%) of 63s bioglass on the properties of bioglass-PCL composites as scaffolds. They shaped the scaffold with 3D printing. The results revealed that the performance of the composites improved by increasing the 63s BG content. However, despite their advancements, they did not successfully reproduce the complex mechanical characteristics of cortical bone, which limits their application in load-bearing orthopedic settings, but they are appropriate for addressing minor bone or cartilage repairs. Rajzer et al. [90] prepared bioglass and zinc-doped bioglass containing PCL composite filaments by injection molding. They studied the mechanical and biological properties of the composites. In vitro mineralization studies revealed apatite formation on the surface of bioglass-added scaffolds after 7 days of immersion in SBF, however, in the case of Zn-doped bioglass, slower apatite formation was observed. An interesting work [91] reported a 3D preparation of biphasic calcium phosphate-PCL scaffolds with high and interconnected porosity as well as chemical degradability. They found that the PCL content improved the strength and toughness of composites, that is important to withstand mechanical loading in bone tissue engineering.

Hajiali et al [92] compiled a thorough review paper on the PCL-bioglass and PCL-CP composites and studied their mechanical and biological performances as well as their biodegradability. In their paper, they focused on the preparation methods of scaffolds with ideal mechanical and structural properties, however, they did not discuss or draw any conclusion about the differences between the bioglass and CP containing PCL matrices. They concluded that the conventional preparation methods cannot produce scaffolds with controllable pore sizes, interconnectivity and reliable internal as well as external structures. Thus, their mechanical characteristics do not meet the requirements. However, the most ideal preparation method, according to their paper, is the FDM 3D printing process, which *deposits melted composite filaments over a build platform layer by layer. This provides excellent mechanical and biological properties for the entire scaffold.*

A very recent paper [93] reports that the PCL polymer has no inherent antibacterial characteristic; therefore, can be subject to bacterial attachment and biofilm generation. They tried to make the composite bactericidal by CaP nanoparticle incorporation into the polymer matrix. They stated that the flake-like morphology of the prepared CaP particles could disrupt bacteria's membranes, thus impeding bacterial growth.

Another paper [94] described the preparation of novel, three-layer calcium phosphate/polycaprolactone scaffolds. These scaffolds had a graded increased porosity fraction from the inner to the outer layer. In addition, they were bioresorbable at a gradual rate. The scaffolds are composed of a dense hydroxyapatite (HAp)/β-tricalcium phosphate inner layer, a macroporous HAp/β-TCP intermediate layer, and lastly a macroporous PCL/(HA/β-TCP) outer layer. The preparation methods were gel-casting for the inner layers, while the outer composite layer was

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formed by a solvent casting and particle leaching technique. They carried out in vitro dissolution tests in TRIS solution, and the results showed that the dissolution happened in a differentiated mechanism within the different layers. They concluded that a targeted multi-functionality can be reached with this layered structure.

In earlier research, Ródenas-Rochina et al. [95] compared the properties of hydroxyapatite and bioglass (BG) nanoparticles in a polycaprolactone composite scaffold. They found that pre-osteoblast cells proliferated well on all scaffolds. However, in their study, the addition of bioactive particles did not cause noticeably more positive effects on cell differentiation than that of a pure PCL scaffold.

Besides the widely investigated HAp and TCP calcium phosphate phases, another promising filler material can be the octacalcium phosphate (OCP), which has been combined with various polymers to create composites for tissue regeneration. For example, gelatin-OCP composites have been studied for their ability to support osteointegration due to their inherent porosity. In vivo preclinical studies have demonstrated that these composites can regenerate substantial amounts of bone within months of implantation, suggesting potential applications in both bone and soft tissue engineering [96].

4.2. Bioglasses and Calcium Phosphate Derivatives in Soft Tissue Engineering (STE)

While primarily associated with hard tissue repair, bioglasses and calcium phosphate derivatives can also find applications in soft tissue engineering. Unfortunately, their use in soft tissue regeneration is less common and requires further research. On the other hand, they can be prepared in ideally porous structures that can support cell attachment and proliferation; thus, they can modulate cell behavior. This makes them suitable for cartilage, tendon, and ligament repair [97-99]. Techniques like freeze-drying, hydrogel incorporation, and electrospinning are employed to tailor these materials for soft tissue applications. Hence, nanostructured calcium phosphate is an essential biomaterial for hard tissue repair, but also has potential in some soft tissues, as reported by a recent review [10].

In Figure 9, the possible fields of applications in soft tissue repair are summarized briefly.

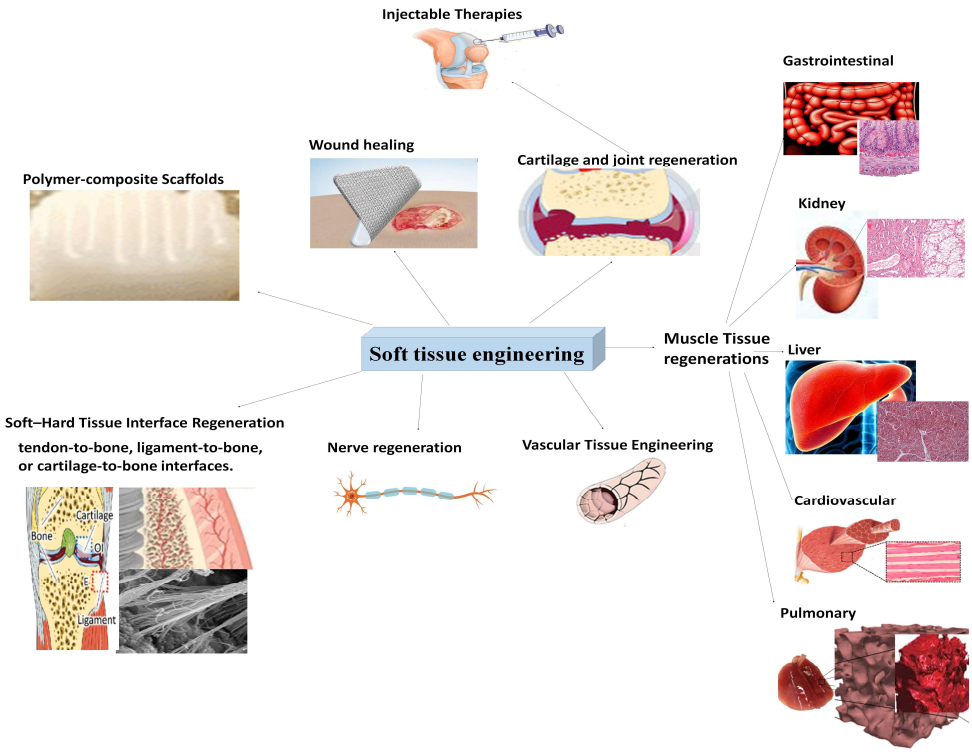

Figure 9. Schematic illustration of the most important fields of bioceramic-biopolimer composites use in STE.

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The main goal in soft tissue engineering is to repair and restore damaged or diseased tissues and get rid of the disadvantageous properties of both allografts and autografts. These materials can be prepared with optimized flexibility, biocompatibility, and biodegradability. These novel materials can initiate neovascularization, which is important for host tissue integration with the implanted structure [100]. Some reports describe their ability to aid the healing process of acute and chronic wounds [101-104]. Besides, bioglasses and calcium phosphate derivatives can be used to regenerate heart and lung tissues that are commonly known for their poor renewal capacity, as well as to repair peripheral nerve and musculoskeletal tissues [10, 100, 105-108]

The extensive research revealed that the incorporation of ceramic nanoparticles has a significant role in the improvement of mechanical strength and biological characteristics and alters the degradation kinetics of polymers. In addition, it can noticeably improve flexibility, which is crucial for soft tissue applications [109]. Furthermore, bioactive glasses have also proven their capacity to promote skin healing by improving blood vessel formation and collagen production during the proliferation phase, along with beneficial impacts on all other critical phases of the wound healing process [38].

It is noteworthy that since the bioactive calcium phosphate-based ceramics are primarily used in association with bones, the number of reported data utilizing them in the field of wound healing is very limited. For example, Eliaz et al. [110] discussed in a review paper that calcium phosphates have also shown potential as wound dressings since the cellular reaction is different for hydrophilic and hydrophobic implants, particularly in the initial stages of wound healing. CaPs can provide sufficient hydrophilicity to the surfaces with higher surface energy, resulting in faster cell activation and differentiation than those with lower surface energy.

Wang et al. [111] also mentioned in their mini review that traditional phosphate-based ($Ca_3(PO_4)_2$, $Ca_5(PO_4)_3(OH)$) and silicate-based ($CaSiO_3$, $MgSiO_3$) powders can be changed into black bioceramics by the addition of magnesium and thermal reduction causing structural defects and oxygen vacancies. These black bioceramics could efficiently and controllably release Ca, Si, and Mg ions that were reportedly beneficial in the cases of skin-tumor-bearing mice [112]. Furthermore, black bioceramic-based materials have the potential to substantially boost the healing process of skin injuries in mice through improved tissue regeneration. In another review [103], the calcium phosphate ceramics were also mentioned regarding their applications in wound treatment.

4.3. Bioglasses and Calcium Phosphate Derivatives as Drug Delivery Matrices

Nanostructured CaPs and mesoporous bioglasses with large surface areas are suitable for drug/gene delivery systems. These matrices are suitable architectures for incorporating and releasing drugs, growth factors, therapeutic agents, and even genes in a controlled way. Common preparation methods can be co-precipitation [113] and layer-by-layer assembly [114,115], which can control release kinetics and enhance efficacy. In addition, they have a moderate and gradual degradation rate in different biological conditions, as well as a large surface area. The CaP derivatives dissolve faster at a slightly acidic pH, which enables a controlled drug release into cells [116]. It is also discussed that the drug delivery ability of bioceramics (CaPs) is dependent on their crystalline rate, relative surface area, microstructure, micro- and nano-morphology, as well as particle sizes and forms [117]. Structures with low crystallinity or amorphous phases with high surface areas can incorporate more drugs and have lower release rates compared to crystalline structures, such as HAp [118]. The higher the solubility of the CaP phases, the faster the drug release rate [119]. For example, Uskoković et al. [120] reported that spheroid CaP particles had more effective drug loading and release capacity than flaky, brick-like, or elongated orthogonal-shaped particles. A large number of therapeutic agents can be delivered by bioactive ceramic nanoparticles, including antibiotics, anti-inflammatory drugs, and growth factors for bone healing [117].

Bioglasses can also serve as versatile platforms for drug delivery, capable of releasing therapeutic agents in a controlled manner. Their composition can be adjusted to achieve desired release profiles, utilizing techniques such as ion exchange and nanoparticle embedding. Their porous

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structure is an ideal matrix for drug inclusion, delivery, and controlled release [121]. The other unique structure of BGs is the mesoporous (MBGs) [122]. The mesoporous channels in MBGs improve textural properties and bioactivity compared to sol-gel BGs, while their large pore volume allows simultaneous loading of drugs, growth factors, or other bioactive molecules [123]. Additionally, the silanol groups at the surface of MBGs enable further modification strategies with different functional groups for the controlled release of therapeutic compounds [124,125].

Yao et al [126] developed a mesoporous bioactive glass (MBG) modified with alginate. They reported that by mixing MBGs with the polymer, the otherwise immediate and fast release of incorporated drug molecules can be better controlled. They have used simvastatin (SIM) as a model drug. Generally, any antibiotic incorporation is useful to prevent or cure infections at the implanted sites. For example, Huang et al. [127] prepared boron-doped bioactive glass (BG) scaffolds using the sol-gel method. Boron content aimed to enhance the bioactivity. The microstructural analyses showed mesoporous structures. They further revealed that the boron-doped BG had nano-sized pores and rougher microstructures than those of pure BGs, which is beneficial for drug delivery. In their case, the incorporated drug was teicoplanin. Teicoplanin and vancomycin are the last generation of antibiotics against infections caused mainly by Gram-positive bacteria. Teicoplanin is a better choice for use since it has a lower toxicity and longer half-life. According to the drug-release tests, the release rate gradually slowed down during immersion for 7 days.

The other important agents are the different growth factors, such as bone morphogenetic proteins (BMPs), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor-beta (TGF-β) are all critical factors in bone healing [128]. Hence, the addition of growth factors can further enhance the osteogenic ability of bioactive ceramics. For instance, BMP-2 connects with CaPs through the functional groups, such as -OH, -NH2, and -COO [129]. However, it is important to denaturalize the protein during its incorporation into the ceramic matrix, otherwise, it would lose its main functionality. The addition of different genes into the system also promotes and facilitates bone regeneration [130].

Bioactive element doping also alters the drug-encapsulation capacity of BGs. In a very recent study [131], therapeutic element-added mesoporous bioactive glass nanoparticles (MBGNs) were reported as unique multifunctional systems. These ions were strontium and magnesium (SrMg-MBGNs). According to their results, the Sr and Mg-doping increased pore volume, thus higher solubility rate. In addition, the original mesoporous structure changed from worm-like to radial–dendritic, which caused a little faster drug release compared to undoped MBGNs. They used ibuprofen for the drug-release experiments. The experiments showed that the drug loading capacity slightly decreased while the release rate increased due to the open dendritic pores at the external surface, which resulted in accelerated ibuprofen emission. Additionally, several studies have been actively carried out to improve the efficacy of bioactive ceramics in combination with various healing agents [132-138]. The most important preparation techniques are described briefly in Table 1.

Table 1. Preparation methods of drug-loaded bioactive ceramics.

Method	Description
Impregnation	Loading drugs into pre-formed CaP scaffolds by soaking them in a drug-containing solution.
Co-precipitation	Simultaneous precipitation of CaP and the drug from a solution, leading to homogeneous distribution of the drug within the matrix.
Encapsulation	Enclosing drugs within CaP microspheres or nanoparticles providing controlled release profiles.

4.4. Coatings on Metallic Implants to Improve Osseointegration

So far, enormous work has been undertaken to create coatings that improve the biocompatibility of commercially used metallic implant materials, such as titanium, Ti6Al4V, CoCrMo, and stainless steel, while also aiding in the prevention of implant-assisted infections. Coating materials such as

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bioactive glasses and phosphate-based ceramics are favored for bone implants due to their ability to promote integration with host tissues and enhance biological functionality, as it is widely discussed in many review papers [139-142]. At the junction of the bone implant and surrounding bone tissue, an apatite-like layer develops that simulates natural bones, due to the excellent bioactivity of these coatings. These layers form a robust and direct bond, ensuring the long-lasting stability of the implant within the human body [143]. In the research work of Nezami et al., [144] 58S tape bioactive glass powders were prepared via the sol-gel technique with subsequent calcination. The coatings were deposited electrophoretically. They studied the dissolution characteristics of the coatings by immersion tests. The results revealed excellent bioactivity and corrosion resistance of the coatings. While Zanca et al. [145] prepared CaP-bioglass composite coatings onto stainless steel substrates by the galvanic co-deposition of calcium phosphate and bioglass particles. According to their results, these coatings also had excellent biocompatibility and a low corrosion rate. In another recent paper, Farjam et al [146] deposited CaP coatings onto polycarbonate-urethane (PCU) foils. In this case, the PCU samples were immersed in supersaturated SBFs, which resulted in a semi-crystalline CaP coating formation on the flexible foil over time. Such prepared CaP coatings were stable and intact when the foil was bent. The *in vitro* cell viability tests revealed that these coatings did not affect the cell viability and proliferation compared to the uncoated PCU substrate. Moreover, the CaP coatings promoted cell-mediated calcium deposition.

In other work [147], the preparation of double-layered porous CaP coatings onto Ti6Al4V was reported. The inner coating was deposited by plasma electrolytic oxidation (PEO), while the outer one was by radio frequency magnetron sputtering (RFMS). They used different CaP targets, such as β-tricalcium phosphate, hydroxyapatite, Mg-added β-tricalcium phosphate, Mg-added hydroxyapatite, Sr-added β-tricalcium phosphate, and Sr-substituted hydroxyapatite. They revealed that the RFMS treatment of PEO inner coating caused multileveled roughness, increased the Ca/P ratio and Young's modulus, and also helped to alter the crystallinity of the coating. Duta et al. [148], on the other hand, investigated the differences between the synthetic and naturally derived hydroxyapatite coatings. They reported that natural HAps contain a wide variety of trace elements (such as Na, Mg, Sr, and K) compared to synthetic ones. Therefore, they can have a more dynamic connection with the surrounding biological area.

Gao et al. [149] applied CaP coatings onto magnesium alloy to enhance its biocompatibility and to decelerate the degradation rate of bare magnesium implant material. The most common methods are depicted in Figure 10 and categorized as high and low temperature methods.

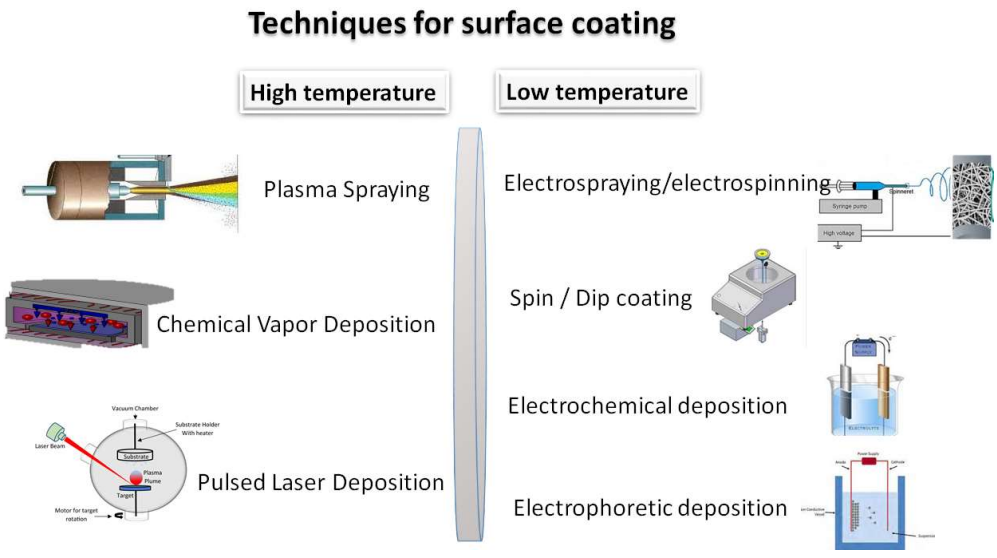

Figure 10. Schematic illustration of the most commonly utilized coating techniques.

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These deposition techniques and their main characteristics are discussed in detail in many review papers [150].

Table 2 demonstrates the main characteristics (strengths and deficiencies) of coatings prepared by the described methods [150].

Table 2. Preparation methods of ceramic coatings onto implant materials and coating properties.

Technique	Coating Characteristics
Plasma Spray Chemical Vapor Deposition Pulsed Laser Deposition	Homogeneous and dense layer; fast deposition rate; coating thickness and deposition parameters are easy to control; good coating adherence to substrate; improved corrosion and wear resistance. But: expensive equipment; high temperature; crack development; complex-shaped substrates are difficult to coat.
Electrospraying/electrospinning	Nanofibrous; porous structure; high specific surface area; mimics ECM. But: poor adhesion; limited thickness; poor mechanical properties.
Spin / Dip coating	Smooth, thin film, good adhesion, moderate mechanical properties. But: low porosity; limited thickness
Electrochemical deposition	Compact, crystalline coating, good adherence, tailored thickness, scalable coats on complex shapes But: requires conductive substrate; limited polymer use; poor porosity and mechanical properties.
Electrophoretic deposition	Uniform and dense coating, good adhesion, moderate porosity, and scalable coats on complex shapes. But: cracking risk; requires stable suspension; poor mechanical properties.

4.5. Effect of Bioactive Element Doping of Bioglasses and CaP Derivatives

It has been widely elaborated that the mechanical, chemical, and morphological properties of both bioglasses and calcium phosphate-based bioceramics can be altered and tailored by different bioactive minerals or metallic ions' incorporation. These elements can be Si, Sr, Mg, Zn, Fe, Cu, Co, F, and Ag in the form of either organic or inorganic salts [151-154]. They reportedly affect the crystal structure, nano- and micromorphology, surface topography, thus the biological performances of bioceramic substrates, and have been extensively discussed and evaluated in scientific literature [156-160]. Here, the most commonly used and investigated substituting elements and their biological role are discussed further. Theoretically, the doping elements are entrapped into the interconnected pores of scaffolds and coatings. Upon interaction with adjacent tissues in human body, body fluids can enter the pores and dissolve the doping components depending on their solubility levels. Yet, in the fluctuating environment of the human body, these rates of dissolution might increase to a certain extent. In Figure 11, a porous scaffold material infused with ions is depicted as it interacts with tissue, along with the suggested mechanism for leaching.

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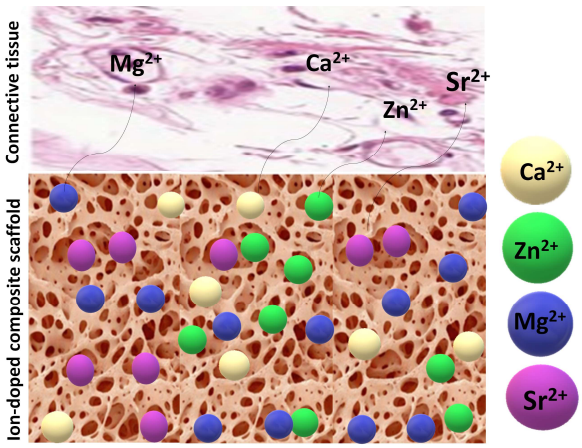

Figure 11. Illustration of ion-doped porous scaffold in contact with tissues and the doping ions' dissolution pathway.

In Table 3, we listed the most useful doping elements (along with their roles) that can enhance the effectiveness and bioactivity of the base bioglasses and CaP ceramics or composites.

Table 3. Different bioactive ion dopants and their effects on the base materials.

Element	Effect
Sr^{2+}	Influence both osteoblast (bone-forming cells) and osteoclast (bone-resorbing cells) activity. Repair bone defects and promote osseointegration Mimic calcium ion (Ca^{2+}) and modulate key signaling pathways involved in bone formation and resorption. Enhanced bone formation due to osteoblast stimulation. Reduced bone resorption by inhibiting osteoclastogenesis. Improved bone mineral density (BMD) and fracture healing. Favorable effects on metabolic energy balance, supporting bone tissue homeostasis.
Mg^{2+}	Enhance immunomodulation, angiogenesis, and vascularized osteogenesis in bone defect areas. Promote osteoblast proliferation and differentiation. Facilitate osteoblast adhesion and matrix mineralization. Accelerate HAp nucleation kinetics Regulates calcium homeostasis, essential for hydroxyapatite formation. Inhibits osteoclast activity Essential cofactor for ATP production, supporting osteoblast energy demands
Zn^{2+}	Enhance bone metabolism, cell proliferation, and tissue regeneration. Significant role in bone tissue's normal development and maintaining homeostasis. Enhance ossification in stem cells. Promote osteogenesis and mineralization and confer antibacterial properties. Key transcription factor in osteoblast differentiation. Increasing osteogenic gene expression. Inhibits osteoclast differentiation Boosts protein synthesis.
Si^{4+}	Facilitate human cell adhesion and differentiation. Induce angiogenesis, collagen type I, and osteocalcin expression. Enhance bone matrix quality Promote osteoblast differentiation Support hydroxyapatite crystallization and mineralization. Improve mitochondrial respiration in osteoblasts

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	Enhance nutrient transport via silicon-mediated ion exchange
	Essential for collagen cross-linking, aiding in bone matrix stability Promote vascularization in bone healing. Affecting osteoblast proliferation. Excess iron ions can increase oxidative stress, inducing osteoclastogenesis.
	Promote angiogenesis. Improve vascularization in bone grafts. Stimulate osteogenic differentiation. Excess Co can cause oxidative stress, leading to cytotoxicity at high concentrations
	Stimulate angiogenesis Increase collagen synthesis and cross-linking, improving bone matrix crucial for bone stability. Excess Cu can generate reducing oxidative stress (ROS), potentially leading to cytotoxic effects. Slight antibacterial effect
	Exhibit antimicrobial properties, preventing infection in bone implants. Stimulates osteoblast proliferation at low concentrations. Inhibit osteoclast differentiation, balancing bone resorption. Disrupt bacterial metabolism without significantly affecting osteoblasts at low doses Alter mitochondrial function, potentially inducing apoptosis at high concentrations.

We further analyzed the doping components' influence on a molecular scale and investigated their interactions with tissue or bone cells that can enhance and accelerate the healing process (Table 4).

Ions	Osteoblast Activity	Osteoclast Activity	Energy Metabolism
Sr^{2+}	• Activate Wnt/β-Catenin[1] signaling pathway →bone formation. • Increase Osteoprotegerin (OPG[2]) level • Stimulate of MAPK/ERK[3] pathway • Modulate of Calcium-Sensing Receptor (CaSR[4]) • Activate osteogenic genes such as *RUNX2*[5]	• Inhibit of RANKL[6] pathway →bone resorption • Induce apoptosis in osteoclasts, further limiting bone resorption	• Increase ATP[7] production • Boost collagen and non-collagenous protein synthesis, essential for the formation of new bone.
Mg^{2+}	• Activate Wnt/β-Catenin signaling pathway • Enhance integrin binding, facilitating osteoblast adhesion and matrix mineralization • Regulate calcium homeostasis	• Inhibit of RANKL pathway	• Increase ATP production • Enhance glycolysis and oxidative phosphorylation • Reduce oxidative stress by activating superoxide dismutase (SOD
Zn^{2+}	• Stimulate osteogenic genes such as RUNX2. • Activate the MAPK/ERK pathway, increasing osteogenic gene expression. • Activate the MAPK/ERK pathway, increasing osteogenic gene expression.	• Inhibit osteoclast differentiation by reducing RANKL signalling.	• Boost protein synthesis by upregulating ribosomal function. • Increase antioxiant defenses via metallothioneins. • Enhance insulin-like growth factor (IGF-1)

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			signaling, promoting osteoblast proliferation.
Si^{4+}	• Induce collagen type I and osteocalcin expression, enhancing bone matrix quality • Modulate TGF-β[8] and BMP[9] pathways, promoting osteoblast differentiation • Support hydroxyapatite crystallization and mineralization.	• Minimal effect	• Improve mitochondrial respiration in osteoblasts. • Enhance nutrient transport via silicon-mediated ion exchange. • Modulate reactive oxygen species (ROS) balance, protecting against oxidative damage
Fe^{2+}/Fe^{3+}	• Influence Wnt and BMP pathways, affecting osteoblast proliferation. • Promote vascularization in bone healing. • Essential for collagen cross-linking, aiding in bone matrix stability.	• Cause osteoclastogenesis at high concentrations	• Crucial for ATP production via electron transport chain • Regulate oxygen metabolism, ensuring proper cell function.
Co^{2+}	• Enhance VEGF[10] expression, improving vascularization in bone grafts. • Stimulate osteogenic differentiation via the BMP and MAPK pathways.	• Excess Co can cause oxidative stress, leading to cytotoxicity at high concentrations.	• Increase glycolytic metabolism in osteoblasts. • Affect iron homeostasis, altering mitochondrial function.
Cu^{2+}	• Stimulate angiogenesis by upregulating VEGF. • Increase collagen synthesis and cross-linking, improving bone matrix. • Regulate lysyl oxidase activity which is crucial for bone stability.	• Excess Cu can generate ROS, potentially leading to cytotoxic effects.	• Enhance mitochondrial respiration and ATP production. • Act as a cofactor for superoxide dismutase (SOD), reducing oxidative stress.
Ag	• Exhibit antimicrobial properties, preventing infection in bone implants. • Stimulate osteoblast proliferation at low concentrations	• Can inhibit osteoclast differentiation, balancing bone resorption, osteoclastogenesis.	• Disrupt bacterial metabolism without significantly affecting osteoblasts at low doses. • Alter mitochondrial function, potentially inducing apoptosis at high concentrations.

[1.]The *Wnt/β-catenin pathway* comprises a family of proteins that play critical roles in embryonic development and adult tissue homeostasis. [2.]OPG: Osteoprotegerin. [3.]MAPK: Mitogen-Activated Protein Kinases. [4.]**CaSR:** Calcium-Sensing Receptor. [5]*Runx2: a gene that plays a cell proliferation regulatory role* in cell cycle entry and exit in osteoblasts, as well as endothelial cells. [6]*RANKL: (*Receptor Activator of Nuclear Factor Kappa-B Ligand) an apoptosis regulator gene, a binding partner of osteoprotegerin (OPG), a ligand for the receptor RANK and controls cell proliferation. [7.]ATP: Adenosine triphosphate. [8.] TGF-β: Transforming growth factor beta, a cytokine, which regulates cell adhesion, proliferation, and differentiation, [9.]BMP: Bone morphogenic protein. [10.]*VEGF: Vascular endothelial growth factor* is a potent angiogenic factor. It is a signalling protein that promotes the growth of new blood vessels.

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5. **Biodegradability and Clinical Evaluations of the Different Bioactive Ceramics and Bioglasses as Well as Their Composites**

Generally, both bioglasses and calcium phosphate derivatives are a unique class of bioactive materials that interact with body fluids and generate a biologically active hydroxycarbonate apatite (CHAp) layer on their surfaces. This reaction not only connects the material to bone but also stimulates new bone growth. The biodegradability of these materials is closely related to their ionic dissolution mechanism and rate [162-167], their composition [168,169], and the environmental pH [170]. For example, Gharbi et al. [171] discussed that the high boron concentration in bioglasses increases their degradation rate. The dissolved bioactive ions (as discussed above) can promote osteogenesis and angiogenesis, and in some cases, they provide antibacterial properties too. Surface topography and micromorphology are also very important factors in the biological applications of both bioactive ceramics and glasses. It has also been reported that the rough and porous surface is especially important for cell adherence [172,173]. This structure also enables controlled drug release and better cell adherence, providing useful substrates for numerous medical uses.

It is essential to comprehend the impact of the bioactive ceramics' network structure on the solubility traits of bioactive glasses to develop new materials with customized biological functions and applications. It is well investigated that there is a strong correlation between the structural, morphological properties and biological roles of bioactive ceramics and bioglasses [174,175]

Theoretically, bioglass scaffolds' degradation is initiated by ion exchange when implanted into body fluids [176]. In silicate-based bioglasses, for instance, sodium and calcium ions are leached out and replaced by hydrogen ions. This increases the local pH and leads to the formation of a silica-rich layer. Subsequently, calcium and phosphate ions re-precipitate as an amorphous calcium phosphate layer that eventually crystallizes into CHAp [177]. In borate-based glasses, the network is less dense, resulting in faster degradation and a more complete conversion to CHAp [178]. Phosphate-based glasses, meanwhile, are known for their even higher solubility and complete dissolution in physiological conditions. The degradation rate is crucial as it must be synchronized with the rate of new tissue formation for optimal healing [179].

On the other hand, the biodegradation of calcium phosphate ceramics occurs mainly via a combination of dissolution and cell-mediated resorption [180]. The degradation rate of CaP materials is a critical factor in tissue engineering, as it should match the rate of new tissue formation. In aqueous environments or body fluids, CaP materials dissolve slowly by releasing calcium and phosphate ions. For instance, the hydroxyapatite phase (HAp) is highly stable and degrades very slowly under physiological conditions, making it suitable for load-bearing applications but less ideal when rapid replacement is desired. The β-Tricalcium Phosphate (β-TCP) has relatively higher solubility than HAp, and gradually but slowly dissolves, releasing ions that promote osteogenesis. The other common phase of CaPs is the biphasic calcium phosphate (DCP) or Monetite. This phase can also provide an adjustable degradation rate that can be synchronized with new bone formation. In addition, the degradation rate is influenced by factors such as the material's crystallinity, particle size, porosity, and the presence of ionic dopants. As the material dissolves, released ions may stimulate osteoblast proliferation and differentiation and enhance angiogenesis at the defect site [181].

The degradability is also dependent on the composition and microstructure of bioactive ceramics. Studies have shown that the degradation rate can be tailored to match the tissue regeneration rate [28]. Over the past few decades, both animal studies and clinical trials have proven that bioglasses such as the silicate-based 45S5 Bioglass®, the S53P4 glass, the borate-based formulations as well as the calcium phosphate derivatives are all effective in various clinical applications [182-184].

According to some scientific reports, mixing bioglasses with local autografts resulted in better clinical outcomes without noticeable adverse effects, infections, or immune reactions [185]. For example, Cottrill et al. [186] provided a systematic review of the *meta*-analysis data on bioactive

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glasses in spinal fusion. According to the clinical results, they concluded that this type of bone graft may offer clinical value as an autograft extender in spinal fusion.

Later, Van Vugt et al. [187] reported a mid-term clinical evaluation of results on long bone osteomyelitis treatment utilizing S53P4 bioactive glass. In this clinical trial, 78 patients participated in total, suffering from chronic cavitary long bone osteomyelitis. They reported that the total infection elimination was 85 %; in addition, 89 % were not infected within 1 year. According to the positive results, they concluded that the S53P4 bioactive glass is sufficiently efficient in chronic osteomyelitis treatment performed in a one-stage procedure.

Another clinical trial on the treatment of osteomyelitis with S53P4-type bioactive glasses has also confirmed their efficiency [188]. In this trial, 50 patients participated and were treated with S53P4 BG. In this case, 70.3% of the patients recovered after 6 months, and 83.3% after 12 months without taking any antibiotics, which can be attributed to the thanks to the innate antibacterial trait of this type of bioglass. In another trial, bioactive glass S53P4 has been successfully used as a bone graft substitute in craniofacial reconstructions and the treatment of chronic osteomyelitis [188]. Its antibacterial properties, attributed to the sustained release of alkali ions and the consequent rise in pH, help eradicate infections, while the material gradually degrades to form a new bone matrix. Long-term follow-ups in clinical studies report high fusion rates and satisfactory functional outcomes [189-191].

Additionally, composites containing bioactive glasses and fiber reinforcements are promising materials in maxillofacial surgery and cranial implants [192] and can successfully repair certain bone defects [182].

In another clinical trial, certain bioglass derivatives have confirmed enhanced bone regeneration in animal models and improved implant osseointegration too [193].

Numerous in vivo studies have been conducted to assess both the degradation behavior and the osteogenic potential of bioglasses [193]. For example, studies in small animal models (such as rats and rabbits) have demonstrated that 45S5 Bioglass® degrades gradually and is replaced by newly formed bone within a few months [194-196].

Borate-based glasses have also been shown to promote faster bone healing in vivo due to their higher degradation rates, although concerns about potential toxicity are managed by controlling the ion release in dynamic physiological conditions [12,197]. Regarding phosphate-based BGs, their main benefit is their more similar composition to bone minerals, and their enhanced osteogenic potential [198].

In several animal studies, researchers observed that implanted bioglass scaffolds completely degraded within 3–6 months, being replaced by well-vascularized, mature bone tissue, without adverse inflammatory reactions [199].

Clinical trials using 45S5 Bioglass® (commercial brands: PerioGlas® or BioGran®) have been extensively reported in periodontal therapy [200]. These trials show significant improvements in probing depth reduction and bone defect filling in patients with periodontal osseous defects. For instance, long-term clinical studies have demonstrated that bioglass not only supports new bone formation but also promotes the regeneration of periodontal ligament and cementum, leading to stable and predictable clinical outcomes [201].

In addition, emerging clinical evidence also points to the potential use of borate-based bioglasses in wound healing and soft tissue regeneration. Products such as MIRRAGEN® have been approved for the treatment of chronic wounds, further underscoring the versatility of bioglasses [202].

Clinical studies have also provided strong evidence that bioglass-based treatments can result in significant radiographic and histologic improvements in bone regeneration, with minimal adverse effects reported over long-term follow-up periods [203].

Similarly, the calcium phosphate derivatives were also investigated intensively as bone substitutes. Their advantage is that their degradation rate can be tailored by controlling phase composition, crystallinity, porosity, and doping, enabling gradual replacement by newly formed bone [204-207].

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Both laboratory (in vitro) and animal (in vivo) studies, as well as several clinical investigations revealed positive biological responses when using CaP materials for bone repair and regeneration. The in vitro biological evaluations were based on cellular response and cytocompatibility investigations. These studies have evaluated the interaction between CaP materials and bone cells [208-210]. The surface morphology/roughness and crystalline nature of calcium phosphate-based materials can be detected by osteoclasts, impacting their metabolic processes and bone resorption efficiency. The synergistic effect of these elements results in a favorable micro-environment that stimulates bone formation and influences the overall process of creating bone [211]. For example, osteoblast cultures grown on HAp and β-TCP surfaces typically demonstrate high cell viability, adhesion, and proliferation. In addition, the ionic dissolution products have been shown to increase the expression of osteogenic markers (e.g., alkaline phosphatase, osteocalcin, Runx2) and to support mineralization in culture [212]. Similar ionic dissolution processes can occur in the cases of bioglasses when placed in a biological environment, and the dissolution products promote early-stage mineralization of tissues [213]

In vitro tests in simulated body fluids (SBFs) are also commonly used to assess the bioactivity of CaP materials. When immersed in SBF, CaP-based ceramics reportedly promote the deposition of an apatite layer on their surface. This layer formation, which mimics natural bone mineralization, is indicative of a material's potential to bond with host bone. In several studies, HAp and β-TCP samples immersed in SBF exhibited gradual apatite deposition on their surfaces over 7–14 days, confirming their bioactive nature [214-216].

In Vivo Evaluations were also carried out using various animal models (e.g., rabbits, dogs, and rodents) to evaluate the performance of CaP materials in critical-sized bone defects [183, 217-220].

It is also worth mentioning that studies on HAp have proven its slow degradation rate, therefore, it is often used as a long-term scaffold. Histological analyses in animal models have demonstrated that HAp implants support bone ingrowth and remodeling over periods extending beyond six months [184,221,222]. In contrast, β-TCP has been shown to degrade more rapidly in vivo. Studies indicate that β-TCP can be completely resorbed and replaced by new bone within 3–6 months, particularly in non-load-bearing sites [223-226]. While the Monetite phase (DCP) showed a relatively balanced resorption rate. In vivo, DCP scaffolds exhibit gradual degradation accompanied by the formation of mature bone tissue, with the ratio of HA to β-TCP dictating the pace of new bone formation [227,228]. DCP implants were trialed in rabbit and sheep models alike, with an HA/β-TCP ratio of 60/40 were found to be largely resorbed and replaced by well-vascularized new bone after 12 weeks, with no signs of chronic inflammation [229,230].

In dentistry, HAp and DCP have been applied as bone grafts and coatings for dental implants. Clinical studies have reported improved alveolar bone regeneration, enhanced implant stability, and better long-term outcomes when using CaP-based grafts compared to autografts or allografts [231]. In orthopedics, CaP ceramics are used for fracture repair and reconstructive surgeries. Clinical investigations have shown that β-TCP and DCP granules promote rapid bone healing with minimal adverse reactions. Additionally, CaP coatings on metallic implants improve osseointegration and reduce the risk of implant loosening [232]. Clinical trials with CaP bone graft substitutes have reported high success rates in the treatment of periodontal defects and long-bone fractures. For instance, studies comparing β-TCP with autogenous bone grafts revealed comparable outcomes in terms of new bone formation and defect healing over follow-up periods of 1–2 years [233].

All in all, clinical assessments so far [234,235] have proven successful bone healing using different calcium phosphate-based scaffolds in patients with critical-sized bone defects. In addition, these recent in vivo studies and clinical trials confirmed faster bone regeneration, had better biological performance, and reduced infection rate when bioactive elements were incorporated into calcium phosphate scaffolds. These modifications improve cellular responses, leading to better integration with host tissues [23,46]. For instance, strontium-doped CaPs have shown increased bone formation and mechanical strength both in vitro and in vivo [236-239].

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Table 5 and 6 show a concise overview of the bioactive glass, calcium phosphate ceramics, and their composites that are commercially available and in use today.

Table 5. Commercially available bioglass products and their main application fields.

Brand name	Description	Application	Supplier
Medpor®-Plus™	Standard MEDPOR (biocompatible porous polyethylene particles) combined with bioactive glass (Bioglass®) mixture.	Orbital implants	[240]
NovaBone® Perioglass	100% synthetic and resorbable calcium phosphosilicate dental putty.	Dentistry, Orthopedics	[241]
Smart Healing™	S53P4 bioactive glass. Used for filling defects and replacing damaged bone tissue.	Orthopedics, Bone filler Spine surgeries	[242]
Cortoss®	Injectable, bioactive composite material that mimics the mechanical properties of human cortical bone.	Orthopedics Osteoporosis	[243]
Glassbone™	Bioactive glass 45S5 ceramic composite used in regenerative medicine as a synthetic bioactive bone substitute.	Orthopedics Bone filler	[244]
StronBone™	Strontium containing bioactive ceramics or biomimetic fibrous polymer scaffolds.	Orthopedics Bone Graft Bone substitute, Craniomaxillofacial	[245]
OssiMend®	Osteoconductive, bioactive bone graft matrix. Components: 50% carbonate apatite anorganic bone mineral, 30% 45S5 Bioactive Glass and 20% Type I Collagen	Orthopedics Spine surgery	[246]
Glace™	Fiber-glass material that used in post-traumatic surgery and for surgical bone reconstructions of the cranial and maxilofacial regions, including the orbital floor.	Orthopedics Spine surgery, Orbital implants	[247]
Signafuse®	A composite of biphasic minerals and bioglass. Composition: bioglass and a biphasic mineral (60% hydroxyapatite, 40% β-tricalcium phosphate).	Orthopedics, Spine surgery, Cervical fusion, Lumbar fusion, Bone grafts	[248]
NovaMin®	The original *Bioglass® 45S5*	Orthopedics, Bone filler Bone graft	[249]
RediHeal™ RediHeal Ointment RediHeal Dental	Borate-based bioglass with unique trace elements. As an ointment, it treats topical soft tissue damage, minor abrasions, skin irritations, skin ulceration, burns, and scratches in humans and animals.	Veterinary Wound healing, ointment	[250]
OsteoGlass®	It has been designed with nano- and mesopores to promote osteoblast attachment and to allow blood vessels to grow through the scaffold and gradually	Orthopedic Dental Skin treatment Wound healing	[251]

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	degrade over the same timeframe as the new bone is formed.		

The specific characteristics and possible clinical applications have been extensively reviewed and described in other reviews [252,253].

Similarly, there are numerous commercial CaP-based ceramic compounds, some of which are demonstrated in Table 6.

Table 6. Commercially available calcium phosphate-based ceramic products and their main applications.

Brand Name	Description	Application	Supplier
Eurobone® 2	Synthetic bone substitute, paste granules with a composition of 75% HA / 25% β-TCP	Orthopedic (Non-load-bearing applications)	
Neobone® Ostibone®	Synthetic bone substitute, putty, is an injectable synthetic bone substitute used to fill defects without mechanical strength.	Orthopedics, Dentistry, Bone grafts Bone substitutes	[254]
NANOGEL®	Synthetic bone substitute. Absorbable bone void filler that provides support for bone ingrowth. Hydroxyapatite particles between 100 nm to 200 nm.	Orthopedic, Dental	
SKUHEAL™ SM-C	Biomimetic mineralized collagen synthetic bone graft material: It contains type I collagen and nano-hydroxyapatite.	Orthopedics Skull surgery Maxillofacial surgery	
HydroSet XT	Injectable, self-setting bone substitute composed of tetra-calcium phosphate that is formulated to convert to hydroxyapatite, the principal mineral component of bone.	Orthopedics Bone filler	
DirectInject	The first and only on-demand, self-setting HAp cement. It is used to repair neurosurgical burr holes, contiguous craniotomy cuts and cranial defects.	Orthopedics neurosurgery Bone filler	[243]
Vitoss®	Beta-tricalcium phosphate and bioactive glass. Available in many forms such as moldable packs, malleable strips, and morsels.	Orthopedic Bone graft	
Osteoset®	Resorbable CaP ceramic that consists of synthetic calcium sulfate beads for bone grafting, calcium sulfate	Bone graft	
Calcigen®	Synthetic calcium sulfate particles for bone grafting, calcium sulfate	Bone Void Filler ()	
ProOsteon®	Porous hydroxyapatite particles that are osteoconductive and have a structure and chemistry similar to human bone	Orthopedics Bone grafts	[255]
BonePlast®	Medical bone void fillers. Calcium sulfate powder, resorbable, extrudable, and moldable bone void fillers		
Norian ®SRS, Norian ®CRS	An injectable, moldable, and biocompatible bone void filler. It contains calcium phosphate powder and sodium phosphate.	Bone graft Bone filler	[256]
ChronOSTM Inject	Synthetic calcium phosphate bone substitute, injectable, osteoconductive, and		

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	resorbable. Irregular bone defects can be completely filled. It consists of a brushite matrix and tricalcium phosphate granules		
Neocement®	Calcium phosphate cement is intended for filling of bone defects of the skeletal system	Orthopedics Traumatology	[257]
Biopex®-R	Calcium phosphate cement which consists of powder and liquid components.		
Apaceram	Synthetic hydroxyapatite that has macro pores and micro pores. Macro pores are effective for new bone formation, while micro pores provide interconnectivity of the pores.		[258]
Superpore	It has a unique "triple pore structure". Contains APACERAM Type-AX to absorbable tricalcium phosphate ceramics.	bone tissue replacement.	
JectOS® TCH TCP Dental HP	Partially biodegradable cement with a composition of 45% TCP and 55% DCPD. Used to fill cancellous bone defects.		[259]
CERAFORM®	Biocompatible synthetic biphasic ceramic made of hydroxyapatite and beta tricalcium phosphate.		[260]
Cerasorb®	Resorbable, pure-phase β-tricalcium phosphate with an interconnecting, open multi-porosity.	Implantology Sinus floor elevation General grafting	[261]
Bonetree®	Octacalcium phosphate (OCP)-based synthetic *bone* substitute material	Ortopedics Dentistry Bone graft	[262]
MBCP®	Bioactive mixture of highly crystalline HAp and β-TCP (Tri Calcium Phosphate)-	Ortopedics Dentistry Bone graft	[263]

These commercial CaP composites are also reviewed and mentioned in other works [264-266].

6. Challenges

One of the main challenges in using bioactive ceramics in tissue engineering is optimizing their dissolution rate. Excessively slow degradation could alter the dynamics of material-bone interactions, while rapid dissolution might compromise new bone formation. Stiller et al. emphasized the need to optimize dissolution rates to enhance bone regeneration without adverse effects [267]. Another critical concern is biocompatibility: minimizing cytotoxic risks and ensuring appropriate biological activity of the material is essential to ensure patients' health post-implantation [268]. To develop safe implant materials—whether bone grafts, substitutes, coatings, or injectable hydrogels—high-quality purified base materials and precisely optimized concentrations of doping elements are imperative.

Bone tissue engineering is highly complex due to the extreme variability in bone injuries (shape, size, location, and origin) across patients. Scaffolds, grafts, and fillers must therefore be personalized to meet specific anatomical and functional needs, even in intricate geometries. This challenge can be addressed through rapidly advancing additive manufacturing (AM) techniques. For scaffolds, the goal is to create highly porous, ordered structures with interconnected pores, homogeneous pore size distribution, and sufficient mechanical strength. AM enables precise mimicry of bone's structural and chemical composition, thereby promoting bone cell ingrowth.

For coatings, surface roughness is critical, as studies suggest rougher topographies enhance bone cell attachment. However, the ideal surface architecture and crystallinity of calcium phosphate-based

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(CaPs) biomaterials—which are detected by osteoclasts and influence their metabolic activity and resorption capacity—require further *in vivo* validation. These materials' particles can penetrate cells, regulating homeostasis and differentiation. Similarly, bioglass performance is highly sensitive to compositional changes. Elements such as lithium, silicon, boron, phosphorus pentoxide, and additives like Mg, Sr, Zn, etc., directly affect bioactivity, degradation rate, and mechanical strength. Tailoring these compositions allows customization for diverse medical needs. Clinical trials and *in vivo* studies have shown varying degrees of bioactivity and biocompatibility across bioactive ceramics (bioglasses and CaPs), underscoring the need for continued optimization to improve clinical outcomes. Additionally, research should prioritize understanding the synergistic mechanisms of multi-element combinations (varying ratios/concentrations) within bioglass and CaP matrices, which could unlock advancements in tissue engineering and wound healing.

Expanding clinical trials to systematically evaluate the long-term performance of bioactive ceramic/bioglass implants is crucial. Reproducible, standardized assessments are needed, particularly for injuries involving both hard and soft tissues, where pathogenic factors and limited self-repair complicate treatment. Despite these hurdles, bioactive ceramics offer promising applications in repairing bone, skin, tendons, cartilage, blood vessels, and myocardium. However, bioceramic-based wound healing materials remain underdeveloped, with challenges including:

- Mechanical, chemical, and biological variability in final products, influenced by bioceramic type, biopolymer matrices, and preparation methods.
- Precise control over scaffold vascularization, degradation rates, and manufacturing standardization.
- Reproducibility in bioceramic distribution within polymer matrices.

Advanced protocols for material production are needed to enhance implant efficacy and quality. In summary, key challenges persist in achieving ideal mechanical performance, controlled degradation, and cost-effective scalability.

7. Future Perspectives

To date, the precise methods for regulating the types, dimensions, and forms of bioactive ceramics, along with their specific interactions with biological responses, remain poorly understood. Thus, future work must continue to refine these materials to optimize their mechanical properties, control degradation kinetics, and enhance biological performance for improved clinical outcomes. The enhancement of mechanical properties is especially critical for load-bearing applications, while optimized composition and interconnected, highly porous morphology are essential for delivering therapeutic ions or drugs incorporated into their network. Standardization of *in vivo* protocols and extended clinical trials will help clarify the long-term safety and efficacy of these versatile biomaterials.

Calcium phosphate-based ceramics (CaPs) are widely used in bone tissue engineering due to their bone-like composition, which confers excellent biocompatibility and osteoconductivity. With optimized chemical compositions, they have demonstrated tunable degradation rates beneficial for bone regeneration. *In vitro* studies consistently confirm their ability to support cell adhesion, proliferation, and osteogenic differentiation, while *in vivo* studies show gradual resorption and replacement by new bone tissue. However, further research is needed to optimize phase composition (e.g., tailoring Ca/P ratios and doping element concentrations), improve mechanical properties through composite formulations, and enhance biological performance via organic/inorganic additives or therapeutic agents.

In contrast, bioglasses—with their complex oxide-based compositions—are versatile for both soft and hard tissue engineering. Their chemical compositions, component ratios, and bioactive dopants can be flexibly adjusted to optimize biological characteristics and degradation rates. However, the molecular dynamics between cells and bioactive particles/bioglasses remain underexplored, yet this knowledge is crucial for maximizing their biological potential.

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Regarding scaffold fabrication, increased adoption of advanced techniques like 3D/4D printing could enable patient-specific, highly porous scaffolds with controlled architectures. Future efforts should prioritize novel fabrication methods and explore synergistic combinations of bioactive ceramics and bioglasses to advance regenerative medicine.

Hybrid scaffolds combining CaPs, bioglasses, and polymers offer a straightforward and efficient strategy. Incorporating bioactive ions in carefully balanced amounts can enhance biological functionality, though further refinement is required. Notably, metallic ions (e.g., Mn^{2+}, Cu^{2+}, Fe^{3+}, Ag^{+}) may trigger unexpected biological responses, necessitating deeper investigation. Understanding the long-term effects of these materials is vital for clinical translation, requiring more *in vivo* studies and clinical trials.

Given existing insights into CaP-based biomaterials, future innovations should focus on customizable designs, including tailored shapes and biodegradation rates [211]. Additionally, studies suggest that scaffold/implant surfaces mimicking native tissue microstructure, texture, and topography can enhance cell adhesion and organization. Future research should investigate cellular responses to nanoscale surface features and the underlying biological mechanisms.

8. Conclusions

This review discussed that bioglasses and calcium phosphate-based ceramics (CaPs) are not only highly biocompatible and osteoconductive but also possess tunable degradation profiles that can be matched to the rate of bone regeneration. Both *in vitro* and *in vivo* studies confirm their potential for diverse clinical applications in hard and soft tissue engineering, with primary uses including scaffolds, grafts, composites, hydrogels, and thin matrices. These materials have been shown to promote osteoconduction, osteoinduction, and antibacterial activity via controlled ion release, while clinical trials validate their efficacy in dentistry, craniofacial and orthopedic surgery (e.g., bone grafts, fillers, injectable composites), wound healing, and drug delivery systems.

The review emphasized that *in vivo* and clinical studies consistently support bioactive ceramics as controllably degradable materials that stimulate bone regeneration and may exhibit antibacterial properties. Advances in fabrication technologies have significantly expanded the diversity of bioactive ceramics, enabling customization of composition, particle size, and morphology to suit specific tissue regeneration needs.

Key findings revealed that bioactive CaPs and bioglasses are promising for tissue engineering due to their unique bioactivity, biocompatibility, and mechanical adaptability. Their capacity to enhance bone regeneration, angiogenesis, and soft tissue repair positions them as versatile tools for clinical use. Notably, CaP-based materials are particularly suited for bone tissue engineering, as their calcium phosphate composition mimics the mineral phase of natural bone. In contrast, bioglasses, owing to their oxide-based structure and adaptable bioactivity, are effective in both soft and hard tissue repair, despite their inherent reactivity in biological systems.

In conclusion, the tunable degradation and biological responses of these materials make them ideal candidates for advancing regenerative medicine. Future efforts should focus on optimizing their design for targeted applications while addressing remaining challenges in scalability and clinical translation.

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