



# Bone tissue engineering for osteointegration: Where are we now?

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## Abstract

Bone fracture healing is a challenging process, due to insufficient and slow tissue repair. Sufferers from bone fractures struggle with one-third of nonunion, display graft rejection, high-costed implantation, or chronic pain. Novel advances in tissue engineering presented promising options for this strain. Biomaterials for bone repair allow accelerated regeneration, osteoblastic cell activation, and enhanced bone remodeling. There is a wide range of biomaterials that are biocompatible, bioresorbable, and biodegradable and used for bone tissue regeneration, promoting osteoconductive and osteoinductive properties. The main aim of bone tissue engineering is to generate rapid and optimal functional bone regeneration through a combination of biomaterials, growth factors, cells, and various agents. Recently bone tissue engineering has been attracted to the use of bioactive glass scaffolds incorporated with polymers and patient-specific fabrication of the bone healing material by 3D bioprinting. There are promising future outcomes that were reported by several research. The present review provides an outlook for recent most common biomaterials in bone tissue engineering suggesting bone tissue engineering practices should have been proceeded to clinical application.

**Keywords** Bone healing · Biomaterial · Bone tissue engineering · Bioactive glass scaffold · Polymer

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## Introduction

### Bone and fracture healing biology

Bone tissue has a complicated composite structure that provides resistance against fractures and load lifting. The complex structure of bone involves various layers and a range of different cells to protect the tissue of bone [1]. Bone tissue has the unique ability to regenerate and heal compared to other tissues [2]. However, bone fractures are common pathologies of bone tissue emerging from traumas, tumors, osteoporosis, osteoarthritis, and surgeries [3]. Bone fractures are substantial dysfunctions of mostly elderly people and the whole public having a burden on the health community. High-energy traumas in elderly people and osteoporotic fractures in females account for almost 85% of bone fractures. Treatment of bone fractures requires long periods of immobilization and medical administration. Additionally, fracture treatment comes with several complications (chronic pain, inflammation, nonunion, etc.). These complications vary depending on age and lifestyle giving rise to bone fusion failure [4].

Fracture healing is a complicated and multistage process requiring proper biomechanics and biological conditions. Moreover, fracture healing consists of the release of cytokines (IL-1, IL-6, TNF- $\alpha$ ) [5], chemokines (CCL1, CCL2, CCL3, CCL5) [6], growth factors (TGF- $\beta$ , PDGF, IGF-1/2, FGF) [7], angiogenesis (VEGF, angiopoietin) [8], and supportive basic signaling pathways (BMP/TGF- $\beta$ /SMAD, P38/MAPK, Ca<sup>2+</sup>, Wnt/ $\beta$  catenin) [9] for mesenchymal stem cell migration proliferation and differentiation (Runx2, Osterix) [10]. Withal, the healing process occurs in three phases as follows: inflammation, repair, and remodeling. The perfect fusion of a fracture could only be established in line with these phases so bone regenerates in its original structure [11]—however, inappropriate conditions for fracture healing cause nonunion of the fracture site. Previous studies indicated that systemic or local factors, such as patient, biology, fracture type, surgeon [12], infection, tumor, and disrupted vascular supply [13], and clinical factors account for the nonunion of bone fractures. Nonunion of fractures reduces a patient's life quality by chronic pain, disabilities, and psychological stress and seriously burdens health communities [14].

### The need for advanced methods

Bone fracture healing is still a challenging issue for orthopedics and sufferers. Fracture sites should have been optimized and fixed, and the healing process should have been accelerated. Therefore, there are several current approaches for the treatment of bone injuries. Advanced surgical methods, stabilization, and support of vascularization are initiating improvements for the perfect union of fractures. On the other hand, these methods are still lacking and yet to be effective for the improved conclusion [15]. The recent gold standard method for repair of bone

fractures is now autologous grafts. However, autologous grafts are highly expensive, hard to find proper grafts especially if the fracture site is wider, producing a painful healing process, hematoma, and morbidity. Further donors for autologous grafts are limited and conclude with rejection and nonunion [16]. Allografts are one of the other current treatment methods for bone healing instead of autologous grafts. However, allografts could have evoked immune reactions and transfer pathologies from donors [17]. Beyond those techniques, various implants containing metals and screws are conventional other methods for enhanced fracture healing [18]. Metallic implants solved the fixation issue but could not improve the optimized bone healing due to unnatural structures, maladaptation to physiological conditions, and implant loosened and became useless over a period [19]. So, biomaterials bone tissue engineering is a promising area for improvement of the fracture healing process and presents a range of different and effective options for this challenging issue.

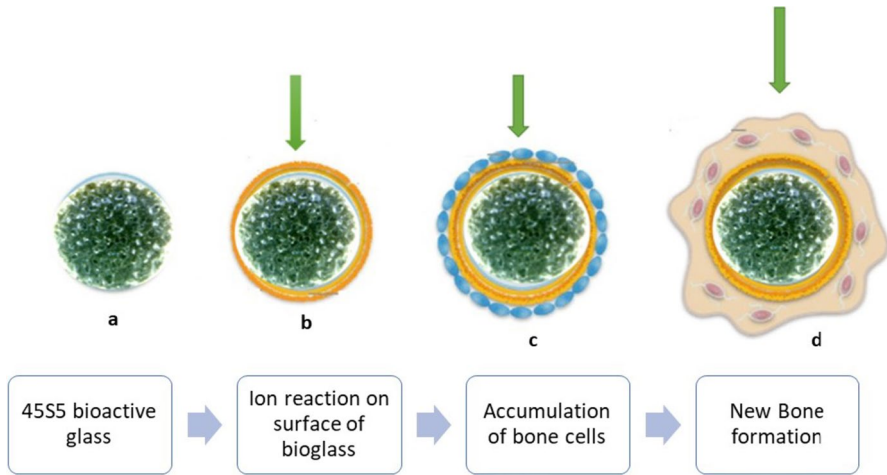
### Novel biomaterials for osteointegration

The term osteointegration was first defined as the fixation of titanium dental implants; however, in recent years by the growing attention to bone tissue engineering, it has been used to describe bone bonding to the surface of osteoinductive and osteoconductive biomaterials [20]. Disadvantages and limitations related to fracture site healing displayed a need for novel clinical options targeted to bone healing. Accordingly, bone tissue engineering has attracted rising attention from researchers to improve optimal bone repair. Bone tissue involves inorganic and organic materials; organic materials consist of 30% and inorganic part is mainly hydroxyapatite crystals 45–58%, sodium 0.7%, carbonate 4%, citrate 0.9%, magnesium 0.5%, and other trace elements, such as  $\text{Cu}^{2+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Sr}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{F}^-$ ,  $\text{K}^+$ , and 10% water [21]. Previous inventory studies aimed to develop novel biomaterials with these substitutes. In addition, those biomaterials should have been biocompatible and biodegradable, and must have osteoconductive and osteoinductive properties to enhance cellular activation and osteointegration in fracture sites [22].

Here are the most recent and commonly studied promising biomaterials for bone tissue engineering to establish optimal bone healing.

### Bioactive glass scaffolds

In recent years, the requirement of the accelerated repair process and bioengineering parallel enhancement indicated an interest in the development of bioactive glass scaffolds used for bone fractures. Since Hench's discovery of 45S5 bioactive, it held a rising attraction for bone tissue engineering [23]. After implantation, bioactive glass scaffolds react with the bone tissue specifically stimulate osteoblastic cell activity, and attach appropriately to bone and soft tissues [24]. First, amorphous calcium and hydroxyapatite crystals aggregate on the surface of bioactive glass; thus, glass material is tightly attached to the tissue as presented in Fig. 1. Afterward, bioactive glass triggers osteogenic gene expression via the release of ions



**Fig. 1** Representative scheme of bioactive glass surface reaction and contribution to new bone formation. **a** Tough structure of the bioactive glass. **b** Adhesion of ions to the glass surface to form new bone. **c** The osteogenic cell covers around the glass surface. **d** Colonization of osteogenic cells forming the new bone

and stimulates angiogenesis [25]. The chemical and physical structures of bioactive glasses could be easily diversified for the aim of application options. In this way, glass materials could be designed with different degradation types and applied to the bone repair and remodeling process [26]. There is also a range of reasons for the limitation of bioactive glass application such as the fast degradation profile of the glasses restricted for long time effects, implantation of glasses because of ion content, and change tissue pH [27]. Further, these bioactive glass scaffolds are powerless on themselves to load lifting [28]. Recent studies indicated that improvement of resistance of bioactive glass scaffolds, the material could be developed in mesoporous structure and collaboration of different polymers or metals enhances the durability of the implant [29]. Mesoporous structure improves the efficiency of bioactive glass scaffold adsorption and release of induction agents. The collaboration of polymers such as PLA (polylactic acid) and PLGA (polylactic-co-glycolic acid) with bioactive glass scaffolds improves the regenerative effects of bioactive glass in bone disorders [30]. However, there are a limited number of *in vivo* studies, several *in vitro* developmental studies indicated different options for bioactive glass scaffolds. Sordi et al [31] reported that parathormone-loaded mesoporous bioactive glass scaffolds displayed biocompatible, bioactive, and osteoinductive effects on the SHED cell line. Previous studies also indicated that bioactive glass scaffolds induced IGF, VEGF, and PDGF in bone tissue for fracture site healing [32]. Until now, studies about bioactive glass scaffolds suggested enhancing the structure with different agents, metals [29, 33–35], mesenchymal stem cell coated [36], bone morphogenetic protein2 (BMP2) embedded [37], and PLA, poly-glycolic acid (PGA), polycaprolactone (PCL)-based biomaterials [38, 39]. Further, *in vivo* studies are required to improve the effectiveness of bioactive glass scaffolds in the corporation of therapeutic agents in bone fracture healing.

## Polymers

Bone tissue engineering presented different options for biocompatible natural and synthetic polymeric materials. In addition, similar biology with extracellular matrices and the considerable biodegradability of these polymers became fascinating to researchers [40]. Moreover, polymers highly contribute to bone regeneration with flexible structures and a variety of containing properties and chemicals. There are various fabricating methods have been used for the development of polymeric composites. However, the most common methods are electrospinning and sol–gel methods, fused deposition modeling, laser-assisted bioprinting, freeze drying, and inkjet printing also have been currently used and all have different benefits, limitations, and contributions in tissue engineering [41]. As presented in Fig. 2, electrospinning is a widely used method for bone tissue engineering. Electrospinning has emerged as a leading technique for manufacturing polymeric scaffolds and provides enhanced porosity for polymeric structure patterns.

Most known natural polymers are collagen, gelatine, chitosan, and synthetic polymers such as PLA, PGA, and PCL have been applied and composited with inorganic materials for bone tissue regeneration to optimize tissue repair [42].

Natural polymers have been widely used in bone tissue engineering for their higher biocompatibility and biodegradability and have no toxic effects. Collagen, chitosan, and gelatine alginates are natural polymers that are used in bone tissue engineering. The collaboration of these polymers with bioactive glasses, hydroxyapatite crystals, growth factors, and hydrogels enhances the effectiveness of the polymers for bone repair. Additionally, the vascularization ability of the polymers is appropriate for optimal bone regeneration [43].

PLA and PLGA are synthetic polymers that are mostly used for bone tissue engineering. Previous studies indicated that due to synthetic polymers being nontoxic, thermostable, and degradation products are nontoxic, these polymers have limited

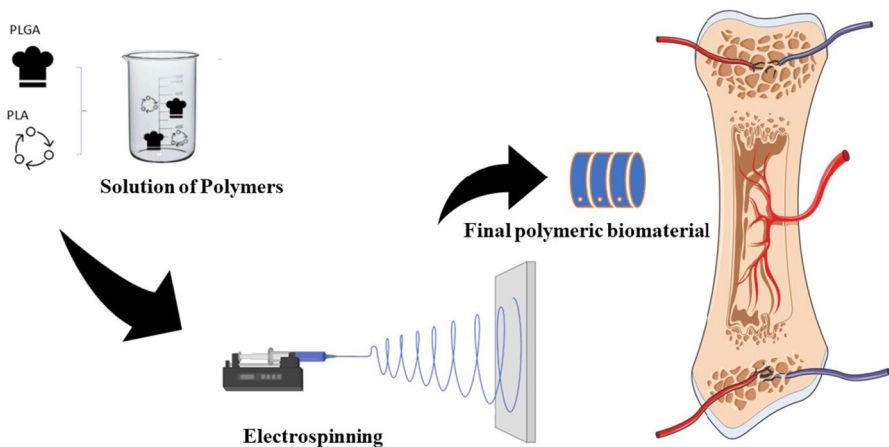


Fig. 2 Fabrication of electrospinning polymer blend composites for bone regeneration

osteoconductive effects and inadequate bone regeneration effects. Related studies have suggested that the improvement of these polymers' effects on osteointegration could be enhanced by coating bioactive molecules and different agents. Coating materials like growth factors, mesenchymal stem cells, osteoinductive agents, or molecules could trigger osteoblastic activation and differentiation [44]. A novel study indicated that the incorporation of bioactive glass scaffolds and PLGA/PLA polymers presents a promising bone repair *in vitro* [45]. Further studies also revealed that embedded agents such as antimicrobial agents, bone morphogenetic proteins [46], gelatin/nanohydroxyapatite cryogel [47], and methylsulfonylmethane [48] into PLGA/PLA polymers alleviate surgical complications, produce less pain, and prevent nonunion. So, the use of PLGA/PLA polymers makes it easy to load osteointegration molecules that could be released in a controlled manner (Ortega-Oller 2015).

### 3D bioprinted poly (lactic acid)/mesoporous bioactive glass-based scaffolds

Bone tissue engineering has been extensively increased over the last few decades, in the field of bioactive scaffolds for bone fracture healing. Three-dimensional printing (3D) is a promising future technology that provides rapid prototyping of a wide range of geometries [49]. 3D printing facilitates a lot of subjects in many fields like food production, auto engineering, biomedical, and tissue engineering [50]. Thus, 3D printing suggests fabricating complicated structures with a computer system and techniques without complex equipment [51]. Over a few decades, 3D bioprinting has been common to produce tissue engineering products successfully with many types of materials like PLA, metals, ceramics, and gels [52]. Previously 3D bioprinting with bioactive glass and polymers indicated stable fixation for bone defect and load bearing [53]. Additionally, it enhanced osteogenic induction displayed good biodegradation with continuous osteogenic induction characteristics, and provided long-term stability via bone integration. The combination of BG and PLA can avoid inflammatory reactions and unfavorable environments for cells by buffering the acidic by-products of polymers with the basic degradation of BG [54].

The biomaterials have been developed with a combination of bioresorbable polymers (due to biocompatibility) and bioactive glass scaffolds (to enhance strength and bioactivity) [55]. However, it was reported that the collaboration of polymers and bioactive glass scaffolds presented slight bioactivity and did not offer adequate strength and load bearing [56]. Further, this type of biomaterials cannot wholly cover the critical size bone defects as shown in Fig. 3. Thus, current studies targeted to advance the mixture of these biomaterials by biobased and patient-specific 3D scaffolds suggest novel strategies for bone tissue engineering to treat critical bone size defects [57]. In a recent study, it was investigated that a composite biomaterial which was fabricated with PLA and 45S5 bioactive glass was used to 3D print scaffolds for bone regeneration. *In vitro* cytotoxicity analysis of this study indicated that the 3D-printed biomaterial displayed an 80% increase in the mechanical strength of the scaffolds [58]. *In vivo* biocompatibility of another study with 3D-printed biomaterial confirmed that the biomaterial had an increased biocompatibility property [59]. A 3D porous scaffold with PCL



**Fig. 3** Representative image of 3D bioprinted bioactive glass scaffolds with polymers. Bioactive glass and polymeric blend were prepared freshly and 3D bioprinting technique was used for manufacturing the final scaffold. Fracture-specific polymer-based bioactive composite glass scaffolds can be fabricated individually as represented in the above scheme and implanted properly at the fracture site

with 13-93B3 bioactive borate glass was examined for the bioactivity of the material. It was reported that D porous scaffold with PCL with 13-93B3 bioactive borate glass presented a high potential of the solvent-based extrusion process in 3D bioprinting of acellularized scaffold with bioactive properties for tissue engineering applications [60].

Currently, 3D-printed bioactive glass composite scaffolds have been reported as promising in various research and suggested as potential composites with strength and osteogenic properties [61]. Natural and synthetic polymers could be used in combination with bioactive glass. Natural polymers produce higher biocompatibility and biodegradability while synthetic polymers provide enhanced mechanical strength [62]. The preference of which polymer is appropriate to the application area depends on the requirements of the selected bone fracture. The designation and developmental technique of 3D printing also improve the efficiency of the material. Previous studies reported that there are two widely used methods for 3D printing bioactive glass composites [63]. There is a conflict of use in each of these methods. FDM (fused deposition modeling)-based 3D printing method displayed enhanced printability compared to PDM (paste deposition modeling)-based printing [64]. Both methods are proper for bioactive glass combination for bone tissue engineering. In a previous study on PLA-BG composite filament fabricated by FDM of the 3D scaffold, it was observed that *in vitro* bioactivity and cytocompatibility study indicated the beneficial impact of BG effects in increasing osteogenic differentiation of human adipose-derived stem cells (pre-osteoblast MC3T3E1 cells) in comparison with PLA. It was also indicated that there was a decrease in compressive strength with increasing BG loadings [59]. Withal, 3D-printed bioactive glass composites in cooperation with polylactic acid polymers could be a potential target in the field of bone tissue engineering.

## Conclusion and future directions

Bone tissue engineering has a rising popularity among the researchers for enhancement of advanced biomaterials. For the last few decades, there has been significant progress in tissue-engineered bones, and different materials have developed

fascinating bone regenerative abilities. The biomaterials promote bone repair by providing an osteoconductive surface for osteogenic cells. Some of these biomaterials could be incorporated with mesenchymal stem cells and growth factors to enhance the osteogenesis and osteoinductive properties or used alone but have limited effects. Therefore, the initial purpose of bone tissue engineering should be the enhancement of optimal biomaterial development. Bone tissue is unique to regenerate to the original structure, but critical-sized fractures have inadequate repair ability. In addition, autologous grafts or implantation instruments could not wholly repair the defect size. Thus, tissue engineering is a promising option for alleviating nonunion disorders or providing optimal regeneration. The subject is to prefer the most effective biomaterial. Composite materials, such as metal implants, polymers, bioactive glass scaffolds, and additives like stem cells, and growth factors became able to enhance the efficiency of the biomaterials. The ideal option for preferring biomaterial type is that the materials should be well resorbed and placed over time by, and properly, to the bone tissue newly regenerated. Novel and promising biomaterials like polymers and bioactive glass scaffolds are expected to display an osteoconductive and osteoinductive role, increasing the success of bone tissue regeneration. Bone tissue engineering has been emerging as an exciting approach to bone repair. Conversely, to traditional bone repair approaches, tissue engineering targeted to understanding of tissue structure and regeneration and intended new functional biomaterials instead of insufficient implantations.

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## Declarations

**Conflict of interest** The authors have no conflicts of interest to declare related to this article.

**Consent to participate** All authors equally contributed to the literature review and writing.

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