Review

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Review - bioactive glass implants for potential application in structural bone repair

Abstract: Bioactive glass particles and weak scaffolds have been used to heal small contained bone defects but an unmet challenge is the development of bioactive glass implants with the requisite mechanical reliability and in vivo performance to heal structural bone defects. Inadequate mechanical strength and a brittle mechanical response have been key concerns in the use of bioactive glass scaffolds in structural bone repair. Recent research has shown the capacity to create strong porous bioactive glass scaffolds and the ability of these scaffolds to heal segmental bone defects in small and large rodents at a rate comparable to autogenous bone grafts. Loading these strong porous scaffolds with bone morphogenetic protein-2 can significantly enhance their ability to regenerate bone. Recent work has also shown that coating the external surface of strong porous scaffolds with an adherent biodegradable polymer can dramatically improve their load-bearing capacity in flexural loading and their work of fracture (a measure of toughness). These tough and strong bioactive glass-polymer composites with an internal architecture conducive to bone infiltration could provide optimal synthetic implants for structural bone repair.

Keywords: Bioactive glass for structural bone repair; bioactive glass composites; mechanical and in vivo evaluation of bioactive glass scaffolds

1 Introduction

Bone defects are a common occurrence in orthopedic practice, resulting from trauma, malignancy, infection and congenital disease. Clinically, these defects can be reconstructed through the use of various bone grafts. Whereas small contained bone defects are repairable with a wide variety of commercially-available, osteoconductive and osteoinductive filler materials [1, 2], the repair of segmental defects in structural (load-bearing) bone is a challenging clinical problem. The available treatments such as bone allografts, autografts and porous metals are limited by costs, availability, durability, infection risk, donor site morbidity, and uncertain healing. Consequently, there is a clinical need for synthetic biomaterials that can reliably repair intercalary skeletal tissue loss in load-bearing bones.

Scaffolds made of synthetic and natural polymers degrade in vivo and are replaced by new bone matrix synthesized by tissue-forming cells [3, 4]. These materials have proven useful for filling small contained bone defects, but their use in structural bone repair is challenging because of their inherently low strength and elastic modulus [5, 6]. Calcium phosphate bioceramics such as hydroxyapatite (HA), beta-tricalcium phosphate (β-TCP), and biphasic calcium phosphate (BCP) are logical bone repair materials since they are composed of the same ions as the mineral constituent of bone. However, synthetic HA degrades too slowly to allow osseous repair while porous β-TCP scaffolds are typically not strong enough to survive physiologic loading.

Bioactive glasses have several attractive characteristics as a scaffold material for bone repair [7–9]. Bioactive glasses degrade chemically and convert to HA which bonds firmly to host bone. Calcium ions and soluble silicon released from the silicate bioactive glass designated 45S5 have been shown to promote osteogenesis and activate osteogenic gene expression. The compositional flexibility of glass can be used so that it is a source of many of the trace elements, such as boron, copper and zinc that are known to favor bone growth [10–14]. As the glass degrades in vivo these elements are released at a biologically accept-
able rate. Another advantage is the flexibility of preparing three-dimensional (3D) scaffolds with a wide range of anatomically relevant shapes and architectures to provide an optimal physical and chemical environment for bone infiltration.

In the form of particles and weak scaffolds, bioactive glasses such as silicate 4S55 and 13-93 glasses are used clinically to heal small contained (non-loaded) bone defects. However, they are just one of several bone graft substitutes available commercially to reconstitute non-loaded bone defects [1, 2]. An unmet challenge is the development of bioactive glass scaffolds with the requisite mechanical properties and in vivo performance to heal structural bone defects. Most bioactive glass scaffolds created to date are weak, with compressive strength in the range of human trabecular bone (2-12 MPa) and even lower flexural strength [15, 16]. This low strength and the brittleness of glass have largely served to diminish interest in the development of bioactive glass scaffolds for repairing structural bone defects.

In the last five to ten years, a few studies have been showing promise in developing bioactive glass scaffolds with the requisite mechanical properties and microstructure which could be applied to structural bone repair. Glass-ceramic scaffolds (porosity \(\sim\) 56%; pore size \(\sim\) 240 \(\mu\)m) created using a foam replication technique from a glass of composition 57SiO\(_2\), 34CaO, 6Na\(_2\)O, 3Al\(_2\)O\(_3\) (mol. %) were found to have a compressive strength of 18 \pm 5 MPa, which was higher than the strength reported in the literature for most scaffolds with a comparable microstructure [17]. The Weibull modulus of these scaffolds (m = 4) was within the range (3-9) reported for HA and \(\beta\)-TCP scaffolds created by solid freeform fabrication techniques. Scaffolds of bioactive glass (13-93) with an oriented microstructure of columnar pores (porosity = 50%; pore width = 50-150 \(\mu\)m), created by unidirectional freezing of suspensions, showed a compressive strength in the orientation direction of 50-70 MPa and a microstructure capable of supporting bone infiltration [18, 19]. When normalized to the available pore area (volume) of the scaffolds, new bone formation in rat calvarial defects implanted with these “columnar” scaffolds for 12 and 24 weeks was higher than that for defects implanted with “foam-replicated” scaffolds of the same glass (porosity = 80%; pore size = 100-500 \(\mu\)m) [19].

Bioactive glass (13-93 or S53P4) scaffolds created with a grid-like microstructure (porosity \(\sim\) 50%; pore width \(\sim\) 300 \(\mu\)m) by additive manufacturing (3D printing) techniques have shown even higher compressive strength, comparable to human cortical bone (100-150 MPa) [20-25]. These scaffolds were shown to have a microstructure conducive to infiltration with new bone [26, 27], elicited no adverse biological reaction over a long-term period in vivo (6 months) [26, 28], and healed critical-size segmental defects in small and large rodents [29, 30]. Loading these strong porous scaffolds with an osteogenic growth factor significantly enhanced the rate of bone healing [26]. Bonding a layer of biodegradable polymer such as polylactic acid (PLA) to the external surface of these strong porous scaffolds improved their mechanical response considerably [31]. The load-bearing capacity of the scaffolds increased by over 2 times and their work of fracture (a measure of toughness) increased dramatically, resulting in a “non-brittle” mechanical response.

This article will review recent advances in the development of tough and strong porous bioactive glass scaffolds and the performance of these scaffolds in vitro and in vivo. Current issues and future potential for the use of these scaffolds for healing structural bone defects are discussed.

### 2 Creation of bioactive glass scaffolds

Synthetic bone grafts can be the ideal implants for bone repair provided that they can replicate the structure and function of bone and have the requisite mechanical properties for long-term load bearing. Synthetic scaffolds for bone repair should be biocompatible, osteoconductive and osteoinductive, and they should have a 3D microstructure capable of supporting new bone infiltration and angiogenesis to sustain new bone growth [32, 33]. An interconnected pore size (diameter or width of the openings between adjoining pores) of \(\sim\) 100 \(\mu\)m has been considered to be the minimum requirement for supporting tissue ingrowth [34]. However, pores of size >300 \(\mu\)m may be required for enhanced bone ingrowth and formation of capillaries [35]. The scaffold should also be bioactive, with the ability to degrade or convert to HA at a rate comparable to new bone ingrowth. While there are no clear guidelines, it is generally assumed that the scaffold should, at least initially, have mechanical properties comparable to the bone to be replaced [36]. As the scaffold degrades or converts to HA, the reduction in strength should be compensated by an increase in strength due to new bone ingrowth.

The composition and microstructure of bioactive glass scaffolds have a strong effect on their mechanical properties and capacity to regenerate bone. Silicate 4S55 glass and glasses based on the 4S55 composition, such as 13-93 and S53P4, have been widely studied but bioactive borate
glasses, such as the compositions designated 13-93B3 and 2B6Sr have also been receiving interest in recent years (Table 1). Because of the lower three-dimensional connectivity of the borate glass structure and the greater susceptibility of the B-O bond to attack by water molecules, scaffolds of 13-93B3 and 2B6Sr show a higher reactivity (conversion rate to HA) and a lower strength than 13-93 scaffolds with a similar microstructure [37, 38]. As fabricated, scaffolds of 13-93 bioactive glass have shown a compressive strength that is approximately twice the value for 13-93B3 scaffolds with a similar microstructure and a degradation rate that is up to ten times slower in vitro and in vivo [24, 38]. The higher reactivity of borate glass means that the strength of 13-93B3 scaffolds degrades much faster than 13-93 scaffolds in an aqueous medium [38]. Rapid degradation without sufficient bone infiltration in vivo reduces the capacity of the implant to support physiological loads.

Table 1: Nominal composition (in wt. %) of 45S5 glass and some bioactive glasses studied for bone repair.

<table>
<thead>
<tr>
<th>Composition</th>
<th>45S5</th>
<th>13-93</th>
<th>S53P4</th>
<th>13-93B3</th>
<th>2B6Sr</th>
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<tr>
<td>Na2O</td>
<td>24.5</td>
<td>6.0</td>
<td>23.0</td>
<td>5.5</td>
<td>5.4</td>
</tr>
<tr>
<td>K2O</td>
<td>0</td>
<td>12.0</td>
<td>0</td>
<td>11.1</td>
<td>10.9</td>
</tr>
<tr>
<td>MgO</td>
<td>0</td>
<td>5.0</td>
<td>0</td>
<td>4.6</td>
<td>1.2</td>
</tr>
<tr>
<td>CaO</td>
<td>24.5</td>
<td>20.0</td>
<td>20.0</td>
<td>18.5</td>
<td>17.8</td>
</tr>
<tr>
<td>SrO</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9.0</td>
</tr>
<tr>
<td>SiO2</td>
<td>45</td>
<td>53</td>
<td>53.0</td>
<td>0</td>
<td>15.6</td>
</tr>
<tr>
<td>P2O5</td>
<td>6.0</td>
<td>4.0</td>
<td>4.0</td>
<td>3.7</td>
<td>4.1</td>
</tr>
<tr>
<td>B2O3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>56.6</td>
<td>36.1</td>
</tr>
</tbody>
</table>

A variety of techniques have been used to create bioactive glass scaffolds with a variety of microstructures (or architectures) from particles of melt-derived glass, including thermal bonding of particles, spheres or short fibers; consolidation of particles with a pore-producing fugitive phase; sol-gel methods; polymer foam replication; foaming of suspensions; freezing of suspensions; and additive manufacturing techniques [8, 32, 39]. The microstructures produced by these methods cover a wide range. Selected examples of scaffolds created from 13-93 bioactive glass are shown in Figure 1. A “fibrous” microstructure (Figure 1a) has been formed by thermally bonding a random arrangement of short glass fibers (100-300 µm in diameter × 3-5 mm) into a 3D network. A “trabecular” microstructure similar to dry human trabecular bone, created by a foam replication method, has a nearly ideal microstructure for bone ingrowth (Figure 1b). However, scaffolds with the fibrous or trabecular microstructure commonly suffer from low strength, typically in the range reported for human trabecular bone (Table 2). Consequently, they are unsuitable for structural bone repair. Scaffolds with an oriented microstructure of columnar pores, formed by unidirectional freezing of suspensions, have a higher strength in the direction of the pore orientation but the range of pore widths is often limited to less than 100-150 µm (Figure 1c). In general, additive manufacturing techniques can provide unprecedented control in creating pre-designed scaffold architectures which can result in an optimal combination of strength for load bearing and pore architecture for bone infiltration (Figure 1d). Scaffolds of bioactive silicate glasses (such as 13-93 and S53P4) created with a grid-like architecture by robotic deposition techniques have shown compressive strengths comparable to human cortical bone (100-150 MPa). These strong porous bioactive glass scaffolds have better potential for use in structural bone repair.

Table 2: Comparison of as-fabricated compressive strength of four groups of bioactive glass (13-93) scaffolds and amount of new bone formed in rat calvarial defects implanted with the scaffolds at 12 weeks post-implantation. The new bone is given as a percentage of the available pore area of the scaffolds.

<table>
<thead>
<tr>
<th>Microstructure</th>
<th>Porosity (%)</th>
<th>Pore size (µm)</th>
<th>Compressive strength (MPa)</th>
<th>% new bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous</td>
<td>50</td>
<td>50-500</td>
<td>5 ± 2</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>Trabecular</td>
<td>80</td>
<td>100-500</td>
<td>11 ± 1</td>
<td>25 ± 12</td>
</tr>
<tr>
<td>Oriented</td>
<td>50</td>
<td>100-150</td>
<td>47 ± 5</td>
<td>37 ± 8</td>
</tr>
<tr>
<td>Grid-like</td>
<td>47</td>
<td>300 × 300 × 150</td>
<td>86 ± 9</td>
<td>50 ± 5</td>
</tr>
</tbody>
</table>

Figure 1: Examples of bioactive glass microstructures that have been studied for bone repair: (a) fibrous; (b) trabecular; (c) oriented; (d) grid-like.
3 Mechanical properties and reliability of bioactive glass scaffolds

As bioactive glasses are brittle, their mechanical reliability in vivo is a major concern for structural bone repair. Two approaches have been used to alleviate this concern. One approach has been to use engineering principles and design to create scaffolds with high strength such that the probability of failure under physiological loads is low. The probability of failure of brittle materials is often treated in terms of statistical methods such as Weibull statistics. The probability of failure can be lowered if the failure stress of the implant is much larger than the physiologic stress on the implant and the Weibull modulus of the implant is high (equivalent to a low variability in the implant strength).

Figure 2 shows a comparison of the Weibull plots for the compressive and flexural strength of bioactive glass (13-93) scaffolds with a grid-like microstructure (see Figure 1d) prepared by robotic deposition [25] with plots for calcium phosphate scaffolds with a similar microstructure [40, 41]. Under the same allowable failure probabilities, the bioactive glass scaffolds showed a compressive strength comparable to human cortical bone, the flexural strength of the scaffolds (12 ± 3 MPa) was far lower than cortical bone (100-150 MPa). As flexure is an important loading mode in structural bone, an improvement in the flexural strength of the scaffolds is desirable. Unlike the uniform grid-like microstructure (Figure 1d), the long bones of the limbs in humans are composed of two types of bone that differ in porosity. Cortical bone, found primarily in the shaft of the long bones, has a porosity of 5-10%. Trabecular bone found in the inside region of the long bones, has a porosity of 50-90%. Re-designing the uniform grid-like microstructure to mimic the structure of human long bone was studied as an approach to improve the flexural strength of bioactive glass scaffolds.

For a model with a grid-like structure (Figure 1d), composed of alternating layers of orthogonal filaments, a large number of structures can be studied. Instead of using a trial-and-error experimental approach, finite element modeling (FEM) was used to simulate the mechanical response of a variety of relevant structures [27]. Using a uniform grid-like structure as a reference, the glass filaments were redistributed within the model to form different structures. Each model had the same external shape (a beam that is relevant to mechanical testing in four-point bending) and was composed of 13 alternating orthogonal layers of parallel glass filaments made up of 7 layers of short filaments (designated S) and 6 layers of long (L) filaments (Figure 3). The glass filaments had a diameter of 330 µm, equal to the diameter of the scaffolds created previously by robotic deposition.

The predictions of the FEM simulations showed that redistributing some long (L) filaments from the interior of the structure to the surface layers but keeping the same arrangement of the short (S) layers produced an increase in flexural strength. Figure 3 compares the structure of two models with a gradient in porosity (designated L3S1 and L4S1) with the uniform grid-like model (L1S1). The L3S1 model had the same porosity (43%) as the L1S1 model. It was obtained from the L1S1 model by keeping the total number of filaments constant but redistributing some long filaments from the interior to the outermost layer at the top and bottom of the structure. In comparison, the L4S1 model (porosity 33%) was obtained from the L3S1 model by adding long filaments to the second layer from the top and bottom to achieve the same number of long filaments.
as the outermost layer at the top and bottom of the structure.

Creation of bioactive glass (13-93) scaffolds with microstructures approximating the structures in the FEM models by robotic deposition and testing them in four-point bending provided data that validated the predictions of the finite element simulations. The flexural strength increased from $15 \pm 5$ MPa for the L1S1 scaffolds to $22 \pm 3$ MPa for the L3S1 model and to $34 \pm 5$ MPa for the L4S1 scaffolds (Table 3). Although the flexural strength of these L4S1 scaffolds was still lower than that of human cortical bone, it showed a considerable improvement over the values reported for porous bioactive glass scaffolds reported in the literature ($0.4$ to $25$ MPa for the porosity range $50$ to $88\%$) [15, 16]. The compressive strength of the L4S1 scaffolds ($88 \pm 20$ MPa) was also $\sim 20\%$ higher than the L1S1 scaffolds ($72 \pm 10$ MPa). In general, the FEM simulations and mechanical testing showed that bioactive glass scaffolds with a designed gradient in porosity could be created with a combination of high compressive strength and high flexural strength which is appropriate for potential use in structural bone repair.

### 4 Tough and strong bioactive glass composite scaffolds

Another approach to improve the mechanical reliability of bioactive glass implants is to modify their brittle mechanical response through the use of composites. Loading a bioadgradable polymer matrix with bioactive glass particles or short fibers is limited by the low strength of the polymer matrix and, thus, the composite itself has low strength. In comparison, several studies have shown that coating or infiltrating porous bioactive glass and bioceramic scaffolds with a biodegradable polymer can drastically modify their mechanical response and increase their work of fracture (toughness) considerably [40, 44, 45]. Complete infiltration of the pore space can limit the bioactivity of bioactive glass scaffolds and the rate of bone infiltration, particularly at early implantation times. In comparison, coating only the external surface of the bioactive glass scaffold (but not the internal surface area of the pores) has the potential for providing a combination of bioactivity and improved toughness.

Addition of an adherent layer of polylactic acid (PLA), $\sim 500$ µm thick, to the external surface of cylindrical scaffolds (diameter $\sim 4.2$ mm; porosity $\sim 20\%$) composed of thermally-bonded unidirectional bioactive glass (13-93) fibers was found to produce a significant improvement in the load-bearing capacity and a dramatic improvement in the work of fracture of the scaffolds [46]. In a recent study [31], the effect of an adherent PLA surface layer of varying thickness on the flexural strength of strong porous bioactive glass (13-93) scaffolds was investigated.
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Figure 4: (a) Schematic diagram illustrating the structure of bioactive glass-polymer composite; (b) as-fabricated composite composed of a bioactive glass (13-93) scaffold with the L1S1 structure and adherent layers of polylactic acid (PLA) of thickness 400 µm on the top and bottom surface of the scaffold.

Bioactive glass scaffolds (L1S1 structure) without the PLA layer showed the typical response of a brittle material, as observed previously [27]. The load increased with strain and, after reaching a peak value, decreased rapidly (Figure 5). For a PLA layer thickness of 200 µm, the peak load to failure increased but the load vs. strain response still showed a single peak and a typical brittle failure mode. In comparison, a PLA layer thickness of 400 µm or 800 µm produced a marked change in the response. The composite did not fail in a brittle manner. Instead, there was a dramatic increase in the work of fracture or toughness (area under the load vs. displacement curve). When the experiments were terminated at a flexural strain of 2.5-3%, the composite continued to support a load that was up to three times the failure load of the scaffold without the PLA layer. The load at the first peak when macrocracks started to appear was over two times higher for a PLA layer thickness of 400 µm or 800 µm. For a given thickness of the PLA layer, the load vs. strain response for scaffolds with a gradient in porosity (L3S1 and L4S1 structures) showed the same trends but the load at the first peak, referred to as the load bearing capacity, was in the order L4S1 > L3S1 > L1S1.

To summarize at this stage, bioactive glass (13-93) scaffolds created with a gradient in porosity (L4S1 structure) to mimic the structure of human long bones showed a combination of high compressive strength (88 ± 20 MPa), high flexural strength (34 ± 5 MPa) and a Weibull modulus of 8. With the addition of an adherent surface layer of PLA (400 or 800 µm), the load-bearing capacity of the scaffolds in flexure increased by ~ 2.5 times and the work of fracture increased dramatically, resulting in a non-brittle mechanical response.

Figure 5: Measured load vs. strain curves for (a) 13-93 bioactive glass scaffold with L1S1 structure; (b) composite composed of 13-93 bioactive glass scaffold with L1S1 structure and PLA layer thickness of 200 µm; (c) composite composed of 13-93 bioactive glass scaffold with L3S1 structure and PLA layer thickness of 400 µm; (d) composite composed of 13-93 bioactive glass scaffold with L4S1 structure and PLA layer thickness of 400 µm.
5 Bone regeneration in strong porous bioactive glass scaffolds

The capacity of synthetic implants to stimulate bone regeneration and angiogenesis is critical to their effectiveness in healing large (critical size) bone defects. Blood vessels provide a means for tissues to receive oxygen and nutrients, and they are essential for bone growth and bone defect repair. The vasculature penetrates into the scaffolds and allows cells and tissues to receive nourishment. Most synthetic biomaterials are osteoconductive but they lack the osteoinductivity and osteogenicity present in autogenous bone grafts (the gold standard for bone healing). Consequently, synthetic biomaterials often cannot by themselves produce the requisite bone formation within a clinically relevant time. A variety of approaches have been used to improve the osteogenic and angiogenic capacity of synthetic biomaterials. They include the use of engineered blood vessels, seeding cells within the implants or loading the implant with a growth factor [47, 48]. More recently, the release of inorganic ions from bioactive glass and bioactive ceramics has been receiving interest for stimulating osteogenesis and angiogenesis in vivo [11, 12, 49].

Scaffolds for bone regeneration should stimulate sufficient bone healing within a clinically relevant time. In general, the scaffold should completely integrate with host bone and the available pore space in the scaffolds should be sufficiently infiltrated with new bone within 6 to 12 weeks. When strong porous bioactive glass (13-93) scaffolds with a uniform grid-like microstructure (L1S1 structure) were implanted in rat calvarial defects, 50 ± 5% of the available pore space was infiltrated with new bone at 12 weeks [26]. Pre-treating these bioactive glass scaffolds in an aqueous phosphate solution to convert a thin surface layer (~ 5 µm) of the glass to HA significantly enhanced their ability to regenerate bone at 6 weeks but not at 12 weeks post-implantation.

Loading the pre-treated scaffolds with an osteogenic growth factor, bone morphogenetic protein-2 (BMP2), further enhanced their ability to support new bone formation. The pore space of the scaffolds was almost completely infiltrated with new bone at 6 to 12 weeks. The converted surface layer provided a favorable porous substrate for loading the scaffolds with BMP2 and for local release of the BMP2 but it had little effect on the strength of the scaffold because its thickness (5 µm) was much smaller than the diameter of the glass filaments in the scaffold (330 µm). The amount of BMP2 used (60 ng/mm³) was well below the value (>120 ng/mm³) required for bridging 5 mm defects using poly(lactic-co-glycolic acid) scaffolds [50] and the value (250 ng/mm³) observed to cause adverse biological effects in the same animal model [51]. The use of implantation times up to 6 months did not show any adverse biological effects of the BMP2 addition on bone regeneration [28]. These BMP2-loaded scaffolds could provide attractive implants for accelerating bone healing.

Grid-like scaffolds with a gradient porosity (L3S1 and L4S1 structures), as mentioned earlier, showed a significantly higher flexural strength than those with a uniform grid-like architecture (L1S1). Implantation of these three groups of scaffolds composed of 13-93 glass (without BMP2) showed no significant difference in their ability to support bone infiltration (Figure 6). These results indicate that the gradient in porosity present in the L3S1 and L4S1 scaffold groups had no significant effect on their ability to support bone infiltration. Thus, composites composed of 13-93 bioactive glass with the L3S1 and L4S1 structures and an adherent PLA surface layer of the requisite thickness, pretreated and loaded with BMP2, should have an optimal combination of mechanical reliability and capacity to enhance bone regeneration.

6 Healing of structural bone defects

Healing of structural bone defects such as segmental defects in the long bones of the limbs is challenging. In addition to the mechanical reliability and in vivo performance of the scaffolds, stable fixation of the implant is also required for optimal bone infiltration and integration because the implant is subjected to complex physiologic loads in the defect. The two main internal fixation methods that have been used in animal models are (1) plates and screws and (2) intramedullary nail fixation (Figure 7). The plate fixation method results in the scaffold supporting only a small portion of the physiologic load and it suffers from stress shielding and the risk of fatigue failure of the metal plate. The intramedullary nail fixation results in the scaffolds supporting a larger portion of the physiologic load. While it is a more relevant clinical model of segmental defect repair, it suffers from easy rotational motion of the implant which can lower the rate of bone infiltration and integration. The use of a locked intramedullary nail fixation technique can serve to reduce rotational motion and compression of the implant [52].

Strong porous scaffolds composed of silicate 13-93 glass and borate 13-93B3 glass with a grid-like microstructure (L1S1) were created by robotic deposition and evaluated for their capacity to heal critical size segmental defects in rat femurs [29]. Autogenous bone grafts were used...
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Figure 6: Optical images of H&E stained sections of rat calvarial defects implanted with bioactive glass (13-93) scaffolds with L1S1, L3S1 and L4S1 structures as fabricated (left) or loaded with BMP2 (1 µg/defect) (right).

Figure 7: Fixation methods for stabilizing an implant in a tibial or femoral segmental bone defect in animal models in vivo.

as the control group. The scaffolds (length = 6 mm) had a tubular shape to match the cross section of the femur and a drill hole (diameter = 1.2 mm) for intramedullary nail fixation using a Kirchner wire (Figure 7b). Microcomputed tomography (microCT) at 6 and 12 weeks post-implantation showed integration of the implants with the host bone but the autogenous bone grafts and 13-93B3 scaffolds appeared to show better integration than the 13-93 scaffolds. Histomorphometric analysis of hematoxylin and eosin (H&E) stained sections of the defects implanted for 12 weeks showed the capacity of the bioactive glass scaffolds and autografts to support bone infiltration and integration. Although the percent new bone in the defects implanted with the 13-93 scaffolds (25 ± 8% based on the total defect area) and 13-93B3 scaffolds (26 ± 6%) was lower than that in the defects implanted with the autografts (38 ± 8%), the difference was not statistically significant (p > 0.05). Blood vessel area in the defects implanted with the bioactive glass scaffolds (4 ± 1%) was not significantly different from that in the defects implanted with the autografts (5 ± 2%).

In another study [30], scaffolds with a uniform grid-like microstructure composed of 13-93 glass (porosity = 50%; pore width = 200 µm; compressive strength = 80 MPa) and 2B6Sr glass (porosity = 50%; pore width = 200 µm; compressive strength = 36 MPa) were implanted in rabbit femoral segmental defects (10 mm in length × 6 mm in diameter) for 3 and 9 months. Autogeneous bone grafts and the empty defects were used as the positive and negative control group, respectively. Fixation of the implants was achieved by plates and screws (Figure 7a). All the implants survived the nine-month implantation. MicroCT evaluation showed integration with the host bone at 3 months and complete integration at 12 months post-implantation.
Figure 8: Optical images of H&E stained sections of rabbit femoral segmental defects implanted with scaffolds of 13-93 bioactive glass (a,b), 2B6Sr bioactive glass (c,d), and autogenous bone grafts (e,f) at 3 months (top) and 9 months (bottom) post-implantation. Magnification: ×50. Arrowhead = mature bone; arrow = collagen fiber; star = glass scaffold. [Ref. 30]

Figure 9: (a) Percent new bone and (b) residual glass in rabbit femoral segmental defects implanted with scaffolds composed of 2B6Sr glass and 13-93 glass, and autogenous bone grafts (ABG) (positive control) at 3 and 9 months post-implantation. For comparison, the percent new bone in the empty defects (negative control) are also shown in (a). (*significant difference compared with empty group; †significant difference between three and nine months; ‡significant difference compared with 13-93 group; p < 0.05.) (Ref. 30)

Histologic evaluation of stained sections showed infiltration of new bone into the implants (Figure 8). Gradual degradation of the bioactive glass scaffolds and their conversion to HA was also observed from the stained sections. At 3 months post-implantation, the amount of new bone that infiltrated the 2B6Sr scaffolds (30-35%) was not significantly different from that in the autogenous bone grafts but was significantly higher than that in the 13-93 scaffolds (20-25%) (Figure 9a). A similar trend was observed at 9 months post-implantation. The amount of new bone that infiltrated the 2B6Sr scaffolds (45-50%) was not significantly different from that in the autogenous bone grafts but was significantly higher than in the 13-93 scaffolds (∼ 40%). The number of blood vessels in the new bone that infiltrated the 2B6Sr scaffolds at 3 months was significantly higher than that in the 13-93 scaffolds and autogenous bone grafts but there was no significant difference at 9 months. Due to the faster degradation of the 2B6Sr glass scaffold, the amount of residual 2B6Sr glass in the defects at 9 months (∼ 25%) was significantly lower than that in the defects implanted with the 13-93 scaffolds (∼ 40%) (Figure 9b).
Summary and Future Directions

Two recent studies have shown promising results for the capacity of bioactive glass scaffolds to heal structural bone defects such as segmental defects in the long bones of small and large rodents. Strong porous scaffolds of silicate 13-93 and borate-based 2B6Sr bioactive glass created by robotic deposition have healed large (critical size) segmental defects in the femurs of rats and rabbits in a manner comparable to autogenous bone grafts, the gold standard for bone healing. The scaffolds used in those two studies can be further modified to enhance their mechanical reliability and their ability to regenerate bone at a faster rate. Scaffolds with a porosity gradient to mimic human long bones have higher flexural strength while loading the scaffolds with BMP2 can significantly enhance their ability to regenerate bone in vivo. The addition of an adherent layer of a biodegradable polymer (PLA) to the external surface of the scaffolds can dramatically improve their load-bearing capacity and work of fracture, leading to a non-brittle mechanical response. These bioactive glass composites, combining bioactivity, high compressive strength, high flexural strength, high work of fracture and a internal microstructure conducive to bone infiltration could provide optimal synthetic implants to heal structural bone defects.

Further studies are needed to evaluate the translation of these tough and strong bioactive glass scaffolds to clinical applications. There has been little evaluation of the biomechanical properties of bioactive glass scaffolds as a function of implantation time in vivo. In addition to evaluating their capacity to regenerate bone, the mechanical response of the scaffolds should be evaluated in multiple loading modes as a function of implantation time in large rodents. The compressive strength, flexural strength and fatigue resistance should be evaluated in compression, flexure and torsion. Then implants with promising properties should be evaluated in an appropriate large animal model.

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References


