Bioceramics

POTENTIAL OF BIOACTIVE GLASS SCAFFOLDS AS IMPLANTS FOR STRUCTURAL BONE REPAIR

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ABSTRACT

The repair of structural bone defects such as segmental defects in the long bones of the limbs is a challenging clinical problem. While many commercial osteogenic filler materials are suitable for repairing contained bone defects, no satisfactory biological solution to reconstituting segmental bone loss is yet available. Bioactive glass has attractive properties as a scaffold material for bone repair but there are concerns about its mechanical reliability in vivo. Recent advances have shown the ability to create porous scaffolds of silicate 13-93 glass with promising mechanical properties such as compressive strength and elastic modulus comparable to human cortical bone. Bone regeneration in osseous defects can be significantly enhanced by loading those strong porous 13-93 scaffolds with bone morphogenetic protein-2 (BMP2) prior to implantation. When implanted in critical-size segmental defects in rat femurs, as-fabricated scaffolds of 13-93 glass showed the capacity to support new bone infiltration and integration with host bone within 12 weeks. The release of metal ions from bioactive glass scaffolds could provide another approach for stimulating osteogenesis and angiogenesis in healing osseous defects. Recent advances in the mechanical and in vivo performance of 13-93 bioactive glass scaffolds are promising for the application of those scaffolds in structural bone repair.

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. While contained bone defects can be repaired using autogenous bone grafts, allografts and biocompatible synthetic materials,[1,2] the reconstitution of structural bone loss, such as segmental defects in the long bones of the limbs, is challenging. Autogenous bone grafts are the gold standard for treatment but they suffer from limited availability, donor site morbidity and increased surgery time. Allografts are the most widely used bone graft but they suffer from high cost, uncertain healing to bone, increased risk of disease transference and undesirable immune host reactions.[3,4] Porous metals cannot be readily shaped prior to surgery to fit the anatomy of the patient, are bioinert and can serve as a surface for long-term bacterial infection. Because of these limitations, the need for synthetic bone grafts continues to increase.

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 bone grafts should be biocompatible, osteoconductive and osteoinductive, and they should have a three-dimensional (3D) microstructure capable of supporting new bone infiltration and angiogenesis to sustain new bone growth.[5,6] An interconnected pore size (diameter or width of the openings between adjoining pores) of ~100 μm has been considered to be the minimum requirement for supporting tissue ingrowth,[7] but

pores of size >300 μm may be required for enhanced bone ingrowth and formation of capillaries.[8] The scaffold should also have the ability to resorb or to convert to hydroxyapatite (HA), the mineral constituent of bone, at a rate that is comparable with the rate of new bone growth. The scaffold should also have sufficient strength to withstand physiological loads.[9] While there are no clear guidelines, it is generally assumed that the as-fabricated scaffold should have mechanical properties at least comparable to the bone to be replaced. As the scaffold resorbs or converts to HA, the reduction in strength should be compensated by an increase in strength due to new bone ingrowth (Fig. 1). Thus, the design of scaffolds for structural bone repair involves an optimization of the mechanical properties of the scaffold and its capacity to integrate with the host bone and support new bone infiltration.

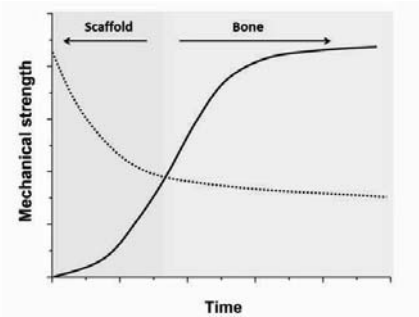

Fig. 1. Schematic diagram showing trends in the strength of a resorbable or bioactive scaffold and in new bone formation as a function of implantation time in vivo. At shorter implantation time, the scaffold provides the main load-bearing function; thereafter, new bone formed in the scaffold should provide an increasing contribution to the implant strength. The cross-over point of the two curves is arbitrary but it should not be longer than 3−6 months for clinical applications.

BIOACTIVE GLASS AS A SCAFFOLD MATERIAL FOR BONE REPAIR

Bioactive glasses have several attractive characteristics as a scaffold material for bone repair.[10–12] 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 promote osteogenesis and activate osteogenic gene expression.[11] 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.[13–17]. As the glass degrades in vivo these elements are released at a biologically acceptable rate. Another advantage is the flexibility of preparing 3D scaffolds with a wide range of architectures that could provide the requisite mechanical properties for load bearing and an optimum physical and chemical environment for bone infiltration.[10]

The composition and microstructure of a bioactive glass scaffold have a marked effect on its mechanical properties and capacity to regenerate bone. Silicate 45S5 glass and glasses based on the 45S5 composition, such as 13-93 and S53P4, have been widely studied but borate and phosphate bioactive glass have also been receiving expanding interest in recent years.[10] A borate glass composition that has been used in several recent studies is the composition designated 13-93B3, which is obtained by replacing all the SiO_2 in 13-93 glass with B_2O_3.[18] Because of the higher strength of the Si−O bond when compared to the B−O bond and the higher coordination of Si when compared to B, scaffolds of some silicate bioactive glasses often show a lower reactivity and a higher strength than scaffolds of borate bioactive glass with a similar

microstructure.[18,19] 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.[19,20] The higher reactivity of borate glass means that the strength of 13-93B3 scaffolds degrades much faster than 13-93 scaffolds.[20] Consequently, according to Fig. 1, a higher rate of now bone formation might be required for the 13-93B3 scaffolds to support the physiological loads in vivo.

Even for some silicate bioactive glass compositions, the composition of the glass can have a strong effect on the strength of the scaffold due to differences in the ease of processing. Typically, porous scaffolds formed from melt-derived glass are created by sintering glass particles into the desired 3D architecture. Commonly, the sintering process is carried out at a temperature between the glass transition temperature (T_g) and the crystallization temperature (T_x). Because of the narrow window between T_g and T_x, 45S5 glass is prone to crystallization during sintering which limits its ability to be sintered to high density and, thus, the strength of the fabricated scaffold. In comparison, because of the broader window between T_g and T_x, 13-93 glass can be sintered to high density without crystallization which leads to higher strength.

Because they typically have better mechanical properties when compared to the glass with the same starting composition, glass–ceramics have received interest for structural bone repair.[5] The creation of a 3D glass–ceramic scaffold typically requires a procedure in which the starting material consists of the glass particles that are sintered to form a dense glass phase and subsequently treated thermally to achieve the glass–ceramic. An issue with glass–ceramic scaffolds is that the ceramic phase often degrades much more slowly than the glass phase, resulting in unpredictable degradation rates and the long-term presence of the implant in vivo.

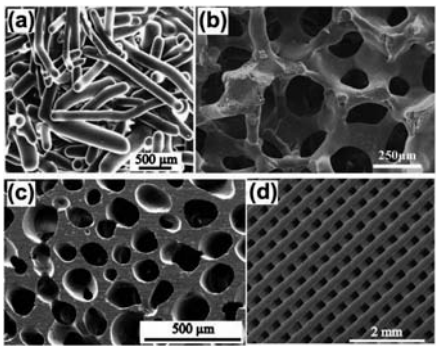

Fig. 2. Images of bioactive glass scaffolds with (a) fibrous, (b) trabecular, (c) oriented and (d) grid-like microstructure.[10]

CREATION OF BIOACTIVE GLASS SCAFFOLDS

A variety of techniques have been used to create bioactive glass scaffolds for bone repair, 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 solid freeform fabrication.[5,10,21] The microstructures produced by those methods cover a wide range. Selected examples are shown in Fig. 2. A fibrous microstructure (Fig. 2a) 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, produced by a foam replication method, has a nearly ideal

microstructure for bone ingrowth (Fig. 2b). Both the fibrous and trabecular microstructure suffer from low strength (typically in the range reported for human trabecular bone) and, consequently, they are unsuitable for structural bone repair. An oriented microstructure, formed by unidirectional freezing of suspensions, has 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 (Fig. 2c). In general, solid freeform fabrication (or robotic deposition) 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 (Fig. 2d).

MECHANICAL PROPERTIES AND RELIABILITY OF BIOACTIVE GLASS SCAFFOLDS

The mechanical reliability of porous 3D bioactive glass scaffolds is a major concern for structural bone repair. Glass has low fracture toughness and the ability to improve its fracture toughness significantly is limited. One approach that has been shown to improve the toughness of porous bioactive glass or bioceramic scaffolds involves coating or infiltrating the scaffold with a biodegradable synthetic polymer.[22–24] However, a polymer coating might reduce the bioactivity of the scaffolds, particularly at early implantation times when the coating limits the interaction of the scaffold surface with cells and tissues. Another approach is the use of a bioactive glass−ceramic. A glass−ceramic typically has better mechanical properties when compared to the glass with the same starting composition but the improvement in fracture toughness achieved with a glass−ceramic is often limited. Furthermore, when compared to the glass scaffold with the same composition, the glass−ceramic scaffold often suffers from a lower bioactivity and less predictable degradation rate.

Another approach is to use engineering principles and design to drastically reduce the probability of failure of the bioactive glass implant in vivo. 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 3 shows a comparison of the Weibull plot for the compressive strength of 13-93 bioactive glass scaffolds prepared by robotic deposition (Fig. 2d) with plots for calcium phosphate scaffolds with a similar microstructure tested in compression.[22,25,26] Under the same allowable failure probabilities, the bioactive glass scaffolds showed a compressive failure strength and Weibull modulus that were higher than HA scaffolds, and far higher than beta-tricalcium phosphate (β-TCP) scaffolds. Based on the strength and the Weibull modulus data, when subjected to a compressive stress of 50 MPa, the failure probability of the bioactive glass scaffolds, P_f, is equal to 10^{-3} (1 in 1000 scaffolds is predicted to fail). In comparison, the average stress on a hip stem is reported as 3−11 MPa,[27,28] well below the stress (50 MPa) for a failure probability of 10^{-3}.

As fabricated, 13-93 bioactive glass scaffolds with a grid-like microstructure (Fig. 2d) have shown a compressive strength and elastic modulus comparable to human cortical bone.[20,25,29,30] In flexure (bending), the modulus of those 13-93 scaffolds were comparable to cortical bone but the flexural strength was much lower than cortical bone. As flexure is an important loading mode in structural bone, an improvement in the flexural strength of bioactive glass scaffolds should form an important consideration. The fatigue resistance of bioactive glass scaffolds intended for structural bone repair is also relevant because the long bones of the limbs undergo cyclic loading. A recent study has shown promising fatigue resistance in compression for strong porous 13-93 scaffolds created by robotic deposition[25]. Under a peak cyclic stress of 10 MPa, all six bioactive glass scaffolds tested in air survived the 10^6 cycles of loading. The fatigue life of the scaffolds decreased as the peak cyclic stress increased to 30 MPa but the

decrease was not significant. When tested in phosphate buffered saline (PBS), the fatigue life of the scaffolds decreased from $10^{5.9}$ cycles to $10^{4.2}$cycles as the peak cyclic increased from 10 MPa to 30 MPa. In comparison, the stress on the human femur during normal walking is less than 5−10 MPa, indicating that the scaffolds have excellent fatigue resistance under normal physiologic stresses.

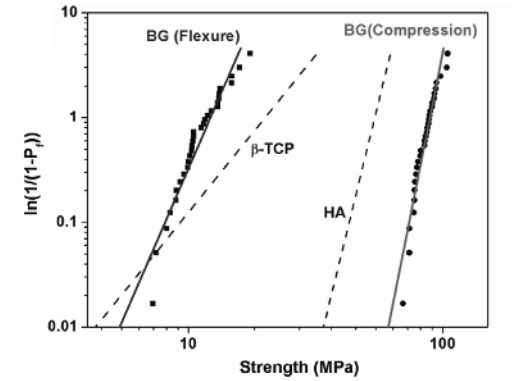

Fig. 3. Weibull plots of the compressive and flexural strength data for 13-93 bioactive glass scaffolds with a grid-like microstructure created by robotic deposition.[25] For comparison, plots of the compressive strength data for β -TCP and HA scaffolds created by the same method are also shown.[22,25,26]

The mechanical properties of bioactive glass scaffolds change markedly as the glass degrades and converts to HA. A rapid decrease in strength and modulus relative to the rate of new bone infiltration into the scaffold could lead to failure of the bioactive glass implant in vivo, as discussed earlier. Figure 4 shows the compressive strength of silicate 13-93 and borate 13-93B3 bioactive glass scaffolds with a grid-like microstructure as a function of immersion time in SBF in vitro.[20] As-fabricated, the 13-93B3 scaffold has a strength that was approximately half that of the 13-93 scaffold and the strength decreased more rapidly with immersion time. While the 13-93B3 scaffolds have shown a better capacity to regenerate than silicate 13-93 scaffolds (described later), their rapid loss in strength could be a challenge in structural bone repair.

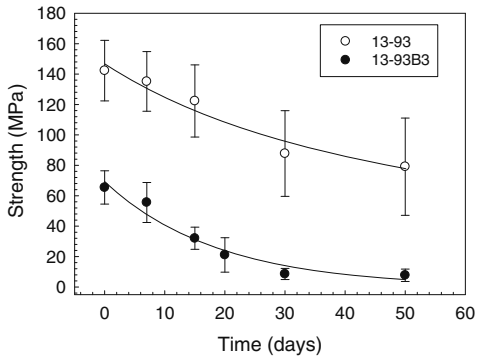

Fig. 4. Compressive strength of silicate 13-93 and borate 13-93B3 scaffolds with a similar grid-like microstructure as a function of immersion time in SBF.[20]

As fabricated, bioactive glass scaffolds typically show an elastic response in which the stress increases almost linearly with strain until fracture occurs in a brittle manner. When immersed in a phosphate solution (such as SBF) in vitro, the strength of the scaffold decreases with time (due to the conversion to HA) but the mechanical response remains essentially elastic. However, upon implantation in osseous defects in vivo, conversion of the scaffold to HA coupled with infiltration of new bone results in a composite. The scaffold–bone composite has been reported to show an elasto–plastic response.[31] For strong porous 13-93 bioactive glass scaffolds implanted in rat calvarial defects, the transition from brittle failure to an elasto–plastic response has been observed to occur within 3–4 weeks.[31] Consequently, for reliability in structural bone defects, concerns about the brittleness of bioactive glass scaffolds might be important mainly during the first 3–4 weeks of implantation only. A low probability of failure in the first 3–4 weeks coupled with the subsequent transition to an elasto–plastic response are factors that could ensure the mechanical reliability of bioactive glass scaffolds in vivo.

CAPACITY OF BIOACTIVE GLASS SCAFFOLDS TO REGENERATE BONE IN VIVO

The rat calvarial defect model, a non-loaded osseous defect model, has been widely used to test the response of biomaterials in osseous defects. For a similar 3D microstructure consisting of bonded short fibers, scaffolds of borate 13-93B3 glass have shown a significantly better capacity to regenerate bone in rat calvarial defects at 12 weeks post-implantation when compared to silicate 13-93 scaffolds.[32] However, the amount of new bone in the defects implanted with the scaffolds was small (15% for the 13-93B3 scaffolds vs. 9% for the 13-93 scaffolds as a fraction of the total defect area).

The capacity to regenerate bone has also been found to depend strongly on the microstructure of the bioactive glass scaffold. In one study, scaffolds of borate 13-93B3 glass with a fibrous, trabecular and oriented microstructure (see Fig. 2) were implanted for 12 weeks in rat calvarial defects and evaluated for their ability to regenerate bone.[33] The amount of new bone in the defects implanted with the trabecular scaffolds (33% of the total defect area) was significantly higher than that in the defects implanted with the fibrous scaffolds (15%). Table I shows the effect of the microstructure on the capacity of silicate 13-93 scaffolds to regenerate bone in rat calvarial defects (4.0–4.6 mm in diameter × 1.5 mm) at 12 weeks post-implantation.[34] Scaffolds with a grid-like microstructure showed the best capacity to regenerate bone in the defects. Based on their high as-fabricated strength, slow reactivity and reduction in strength in SBF, and their and capacity to regenerate bone, scaffolds of silicate 13-93 glass with an optimal microstructure could be promising as implants for structural bone repair.

Table I. Comparison of new bone formed in rat calvarial defects implanted with silicate 13-93 bioactive glass scaffolds with four different microstructures at 12 weeks post-implantation.[34]

Microstructure	Porosity (%)	Pore size (μm)	% new bone (total defect area)	% new bone (available pore area)	Reference
Grid-like	47	300 × 300 × 150	24 ± 3	50 ± 5	35
Trabecular	80	100–500	19 ± 9	25 ± 12	32
Oriented	50	100–150	18 ± 3	37 ± 8	32
Fibrous	50	50–500	9 ± 2	17 ± 4	33

HEALING OF STRUCTURAL BONE DEFECTS USING BIOACTIVE GLASS SCAFFOLDS

Healing of structural bone defects such as segmental defects in the long bones of the limbs is challenging. The implant should have not only the requisite porosity to support bone infiltration and integration with host bone but also the requisite mechanical properties for reliable

load bearing. The method used to stabilize the implant in the defect is also relevant for bone infiltration and integration. The two main internal fixation methods that have been used in animal models are (1) plates and screws and (2) intramedullary nail fixation (Fig. 5). The plate fixation method results in the scaffold supporting only a small portion of the physiologic load and it suffers from stress sheilding and the risk of fatigue failure of the metal plate. Consequently, the plate fixation is not a clinically-relevant implant stabilization method in sgmental bone repair. 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 make bone infiltration and integration diffcult. The use of a locked intramedullary nail fixation technique can serve to reduce rotational motion and compression of the implant.[35]

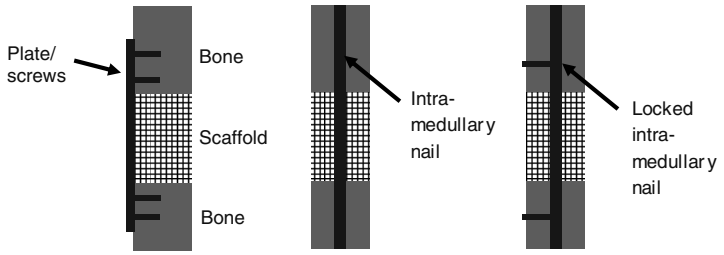

Fig. 5. Fixation methods for stabilizing implants in segmental bone defects in animal models in vivo..

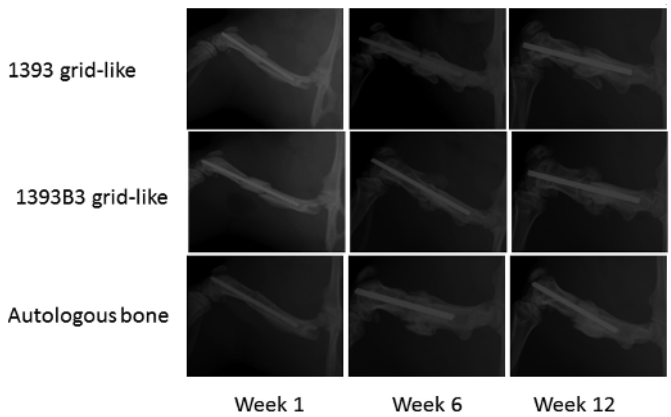

Fig. 6. Radiographs of rat femoral segmental defects implanted with 13-93 and 13-93B3 scaffolds and autologous bone.[36]

Strong porous scaffolds of silicate 13-93 glass with a grid-like microstructure created by robotic deposition (compressive strength = 86 ± 9 MPa) have been recently evaluated for their capacity to heal critical size segmental defects in rat femurs.[36] For comparison, borate 13-93B3 scaffolds with a similar microstructure (compressive strength = 32 MPa) and autogenous bone grafts were used as the control groups. 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 intramdeullary nail fixation using a Kirchner wire. Microcomputed tomography (microCT) at 6 and 12 weeks post-implantation showed integration of the implants with the host bone but the autogeneous bone grafts and 13-93B3 scaffolds appeared to show better integration than the 13-93 scaffolds (Fig. 6). Interestingly, the 13-93B3 scaffolds survived the twelve-week implantation despite their lower strength.

Histomorphometric analysis of hematoxylin and eosin (H&E) stained sections of the defects implanted for 12 weeks with the three groups of implants 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 and 13-93B3 scaffolds (25–28% based on the total defect area) was lower than that in the defects implanted with the autografts (38%), the difference was not statistically significant ($p>0.05$) (Fig. 7a). Blood vessel area in the defects implanted with the bioactive glass scaffolds (4–8%) was not significantly different from that in the defects implanted with the autografts (5%) (Fig. 7b).

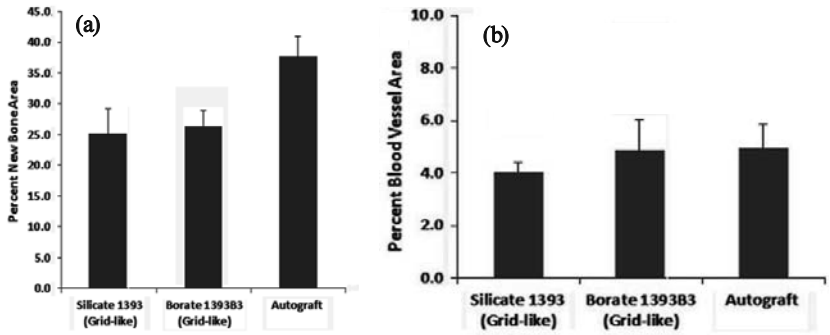

Fig. 7. (a) Percent new bone and (b) percent blood vessel area in rat femoral segmental defects implanted with silicate 13-93 and borate 13-93B3 scaffolds and autologous bone grafts.[37]

ENHANCEMENT OF BONE REGENERATION AND ANGIOGENESIS IN OSSEOUS DEFECTS IMPLANTED WITH BIOACTIVE GLASS SCAFFOLDS

The capacity of synthetic implants to stimulate bone regeneration and angiogenesis is critical to their effectiveness in healing large area (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. Consequently, synthetic biomaterials often cannot by themselves produce the requisite bone formation within a clinically relevant time. A variety of approaches have been used for improving 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.[34,37,38]

In one study,[39] strong porous scaffolds of silicate 13-93 bioactive glass with a grid-like microstructure were pretreated in an aqueous phosphate solution (0.25 M K_2HPO_4) to convert a surface layer of the glass (~5 μm) to HA. Then the pretreated scaffolds were loaded with bone morphogenetic protein-2 (BMP2) and implanted in rat calvarial defects (4.6 mm in diameter) for 6, 12 and 24 weeks to evaluate their capacity to regenerate bone. The amount of BMP2 (60

ng/mm^3) used was well below the value (>120 ng/mm^3) required for bridging 5 mm defects using 3D poly(lactic-co-glycolic acid) scaffolds[40] and the value (250 ng/mm^3) observed to cause adverse biological effects in the same animal model.[41] The as-fabricated 13-93 scaffolds and the pre-treated scaffolds without BMP2 were used as controls. Analysis of hematoxylin and eosin (H&E) stained sections of the calvarial defects implanted with the three groups of scaffolds showed that the BMP2-loaded scaffolds had a significantly better capacity to regenerate bone when compared to the as-fabricated scaffolds and the pretreated scaffolds without BMP2 (Fig. 8a). The pores of the BMP2-loaded scaffolds were almost completely infiltrated with new bone within 12 weeks. The amount of blood vessel area in the defects implanted with the BMP2-loaded scaffolds was also significantly higher at 6 and 12 weeks post-implantation (Fig. 8b).

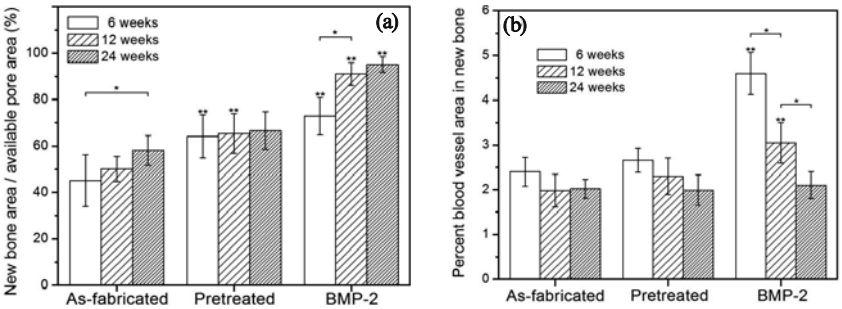

Fig. 8. (a) Percent new bone (as a fraction of the available pore space of the scaffolds) and (b) percent blood vessel area in rat calvarial defects implanted with three groups of 13-93 scaffolds (as-fabricated; pretreated; BMP2-loaded) at 6, 12 and 24 weeks post-implantation. (*significant difference within each group; **significant difference when compared to as-fabricated scaffold at the same implantation time; $p<0.05$).[39]

In another study, cylindrical scaffolds of 13-93 glass (porosity = 55−67%; compressive strength = 40 MPa) were created by selective laser sintering and evaluated in rat femoral segmental defects (5 mm long).[42] The scaffolds contained drill holes in the sides of the cylinder which were either filled with dicalcium phosphate dihydrate (DCPD) used as a carrier for BMP2 (10 µg/defect) or left unfilled (control). X-ray radiography and micro-computed tomography showed the formation of bridging calluses around both groups of implants but faster healing and better callus formation were found for the BMP2-loaded scaffolds.

Interest in the use of bioactive ceramics and glasses as delivery systems for inorganic ions that are known to have a positive effect on angiogenesis and osteogenesis has been growing recently.[13–17] When compared to the use of growth factors such as BMP2, the delivery of inorganic ions can have advantages such as lower cost, long-term stability and a lower risk of adverse biological effects. Copper (Cu) ions have been shown to stimulate angiogenesis,[43,44] enhance the proliferation of endothelial and osteoblastic cells,[45,46] and enhance the differentiation of mesenchymal stem cells (MSCs) toward the osteogenic lineage.[47] Copper-loaded brushite bioceramic scaffolds resulted in directional vascularization and enhanced wound healing in mice.[53] Low doses of $CuSO_4$ (~50 µg/ml) in combination with VEGF or FGF-2 improved the vascularization of a fibrin gel in vitro, indicating that low doses of Cu ions might be used as an alternative or complementary approach to the use of growth factors alone.[43]

Cobalt (Co) ions have been shown to be effective in coupling angiogenesis with osteogenesis.[49] Cobalt-containing 13-93 bioactive glass-based scaffolds created using a foam

replication technique were found to bioactive and biocompatible in vitro.[50] The incorporation of <5 wt. % of Co into mesoporous bioactive glass scaffolds enhanced the proliferation, vascular endothelial growth factor (VEGF) secretion, hypoxia inducible factor-1 (HIF-1) expression and bone-related gene expression of bone marrow-derived stem cells.[51]

In a recent study,[52] scaffolds of a borosilicate bioactive glass doped with 0.5–3.0 wt. % CuO were found to be non-toxic to human bone marrow-derived stem cells (hBMSCs) cultured on the scaffolds in vitro. The alkaline phosphatase activity of the hBMSCs and the expression levels of angiogenic and osteogenic genes (such as VEGF and BMP2) increased significantly with increasing amount of Cu in the glass. When implanted in rat calvarial defects in vivo, the scaffolds doped with 3 wt. % CuO significantly enhanced both blood vessel formation and bone regeneration in the defects at 8 weeks post-implantation. The results showed that doping bioactive glass implants with Cu could be a promising approach for enhancing angiogenesis and osteogenesis in the healing of osseous defects.

CONCLUSIONS

Recent studies are showing promising results for the potential use of bioactive glass scaffolds in healing structural bone defects such as segmental defects in the long bones. Porous scaffolds of silicate 13-93 bioactive glass can be created with a compressive strength and elastic modulus comparable to human cortical bone and with excellent fatigue resistance under stresses much higher than normal physiological stresses. However, the flexural strength of the scaffolds was much lower than cortical bone and it remains an area for improvement. Strong porous scaffolds of 13-93 and 13-93B3 glass created by robotic deposition showed the capacity to heal segmental defects in rabbit femora at 12 weeks post-implantation, indicating the potential for their use in structural bone repair. However, the use of borate 13-93B3 bioactive glass scaffolds in structural bone repair could be more challenging because of their lower strength as-fabricated and their higher reactivity (more rapid degradation in strength in vivo). The local delivery of a growth factor (BMP2) from bioactive glass scaffolds or the release of controlled amounts of Cu or Co ions from bioactive glass scaffolds are showing promise for enhancing bone regeneration and angiogenesis in osseous defects in rodent models. Improvement of the flexural strength of bioactive glass scaffolds coupled with the use of clinically safe amounts of a growth factor and/or inorganic ions could provide an approach for enhancing the use of bioactive glass scaffolds in healing structural bone defects.

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