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Review

# Reprint of: Review of bioactive glass: From Hench to hybrids

Julian R. Jones *

*Department of Materials, Imperial College London, South Kensington Campus, London SW7 2AZ, UK*

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ABSTRACT

Bioactive glasses are reported to be able to stimulate more bone regeneration than other bioactive ceramics but they lag behind other bioactive ceramics in terms of commercial success. Bioactive glass has not yet reached its potential but research activity is growing. This paper reviews the current state of the art, starting with current products and moving onto recent developments. Larry Hench's 45S5 Bioglass® was the first artificial material that was found to form a chemical bond with bone, launching the field of bioactive ceramics. In vivo studies have shown that bioactive glasses bond with bone more rapidly than other bioceramics, and in vitro studies indicate that their osteogenic properties are due to their dissolution products stimulating osteoprogenitor cells at the genetic level. However, calcium phosphates such as tricalcium phosphate and synthetic hydroxyapatite are more widely used in the clinic. Some of the reasons are commercial, but others are due to the scientific limitations of the original Bioglass 45S5. An example is that it is difficult to produce porous bioactive glass templates (scaffolds) for bone regeneration from Bioglass 45S5 because it crystallizes during sintering. Recently, this has been overcome by understanding how the glass composition can be tailored to prevent crystallization. The sintering problems can also be avoided by synthesizing sol–gel glass, where the silica network is assembled at room temperature. Process developments in foaming, solid freeform fabrication and nanofibre spinning have now allowed the production of porous bioactive glass scaffolds from both melt- and sol–gel-derived glasses. An ideal scaffold for bone regeneration would share load with bone. Bioceramics cannot do this when the bone defect is subjected to cyclic loads, as they are brittle. To overcome this, bioactive glass polymer hybrids are being synthesized that have the potential to be tough, with congruent degradation of the bioactive inorganic and the polymer components. Key to this is creating nanoscale interpenetrating networks, the organic and inorganic components of which have covalent coupling between them, which involves careful control of the chemistry of the sol–gel process. Bioactive nanoparticles can also now be synthesized and their fate tracked as they are internalized in cells. This paper reviews the main developments in the field of bioactive glass and its variants, covering the importance of control of hierarchical structure, synthesis, processing and cellular response in the quest for new regenerative synthetic bone grafts. The paper takes the reader from Hench's Bioglass 45S5 to new hybrid materials that have tailorable mechanical properties and degradation rates.



## 1. Introduction and scope

Many of the best inventions have been made by accident. That was not quite the case for bioactive glass, but it was nonetheless a curious set of events. The first bioactive glass was invented by Larry Hench at the University of Florida in 1969. Professor Hench began his work on finding a material that could bond to bone following a bus ride conversation with a US Army colonel. The colonel, having just returned from the Vietnam war, asked him if materials could be developed that could survive the aggressive environment of the human body. The problem was that all implant materials available at the time, e.g. metals and polymers that were designed to be bioinert, triggered fibrous encapsulation after implantation, rather than forming a stable interface or bond with tissues. Professor Hench decided to make a degradable glass in the $Na_2O$–CaO–$SiO_2$–$P_2O_5$ system, high in calcium content and with a composition close to a ternary eutectic in the $Na_2O$–CaO–$SiO_2$ diagram [1]. The main discovery was that a glass of the composition 46.1 mol.% $SiO_2$, 24.4 mol.% $Na_2O$, 26.9 mol.% CaO and 2.6 mol.% $P_2O_5$, later termed 45S5 and Bioglass®, formed a bond with bone so strong that it could not be removed without breaking the bone [2]. This launched the field of bioactive ceramics, with many new materials and products being formed from

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* Tel.: +44 2075946749.
*E-mail address:* julian.r.jones@imperial.ac.uk

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variations on bioactive glasses [1] and also glass–ceramics [3] and ceramics such as synthetic hydroxyapatite (HA) and other calcium phosphates [4]. Herein, a bioactive material is defined as a material that stimulates a beneficial response from the body, particularly bonding to host tissue (usually bone). The term "bioceramic" is a general term used to cover glasses, glass–ceramics and ceramics that are used as implant materials. The name "Bioglass®" was trademarked by the University of Florida as a name for the original 45S5 composition. It should therefore only be used in reference to the 45S5 composition and not as a general term for bioactive glasses.

Bioglass 45S5 bonds with bone rapidly and also stimulates bone growth away from the bone–implant interface. The mechanism for bone bonding is attributed to a hydroxycarbonate apatite (HCA) layer on the surface of the glass, following initial glass dissolution [2]. HCA is similar to bone mineral and is thought to interact with collagen fibrils to integrate (bond) with the host bone. Section 6.1 describes the mechanism of HCA formation. The osteogenic properties (often termed osteoinduction) of the glass are thought to be due to the dissolution products of the glass, i.e. soluble silica and calcium ions, that stimulate osteogenic cells to produce bone matrix [5]. Section 6.2 provides more detail.

There are now several types of bioactive glass: the conventional silicates, such as Bioglass 45S5; phosphate-based glasses; and borate-based glasses. Recently, interest has increased in borate glasses [6], largely due to very encouraging clinical results of healing of chronic wounds, such as diabetic ulcers, that would not heal under conventional treatment [7]. The soft tissue response may be due to their fast dissolution, which is more rapid than that for silica-based glasses. The benefits of phosphate glasses are also likely to be related to their very rapid solubility rather than bioactivity [8]. This review will focus on silicates made by both the conventional melt-quenching route, and on glasses and hybrids made by the low-temperature chemistry-based sol–gel process.

Surprisingly, after 40 years of research on bioactive glasses by numerous research groups, no other bioactive glass composition has been found to have better biological properties than the original Bioglass 45S5 composition. While reviewing the literature on bioactive glasses, this paper will explain the reasons why. Answers to the question of why calcium phosphates are the market leaders for artificial bone graft materials will also be sought, considering the apparent potential benefits of Bioglass 45S5 over synthetic HA and other calcium phosphates. The paper will explain why the original Bioglass 45S5 is so difficult to process into fibres, scaffolds and coatings, and why it has not been such a commercial success as perhaps it should have been. It will then review the recent developments in bioactive glasses and processing methods, such as: the first amorphous bioactive glass scaffolds with pore sizes suitable for bone regeneration; bioactive glass nanoparticles and nanofibres; and bioactive inorganic–organic hybrids that impart toughness to bioactive glasses while maintaining their bioactive properties. The paper focuses on the most recent developments.

## 2. Synthetic bone grafts, scaffolds and bone regeneration

The most important applications for bioactive bioceramics is the healing of bone defects, which can arise due to trauma, congenital defects or disease, e.g. osteoporosis or tumour removal. Another common procedure is spinal fusion, where the cartilage intervertebral disc has badly herniated (slipped disc). The disc is replaced with a titanium or poly(ether ether ketone) (PEEK) cage filled with bone graft. The bone grows through the cage and bone, fusing the vertebrae. Currently, autografts are favoured by surgeons for defect repair and spinal fusion. Autografting involves transplanting bone from another part of the patient, usually the pelvis, to the defect site [9]. Bone is one of the most commonly transplanted tissues, second only to blood. The disadvantages of autografts are that the bone is limited in supply, and a large proportion of patients suffer severe pain at the donor site. A synthetic alternative is needed for the one million bone graft operations that are carried out worldwide each year. When not enough autograft is available, granules of a bone graft extender material, usually a calcium phosphate, are mixed with the autograft. Surgeons tend to mix graft granules with blood from the patient to create a putty-like material, which is pressed into the defect. The blood improves handling of the material and the hope is that the natural growth factors and cells that it contains will help bone repair.

The concept of bone regeneration is to use a scaffold that can act as a three-dimensional (3-D) temporary template to guide bone repair. Ideally the scaffold will stimulate the natural regenerative mechanisms of the human body. The scaffold must therefore recruit cells, such as bone marrow stem cells, and stimulate them to form new bone. Blood vessels must also penetrate if the new bone is to survive. Over time, the scaffold should degrade, leaving the bone to remodel naturally. Another way to look at it is that a scaffold that mimics autograft cancellous bone is needed. Fig. 1 shows a photograph of a femur with a piece of bone removed and an X-ray microtomography (μCT) image of the removed cancellous bone. From a materials science perspective, bone is a

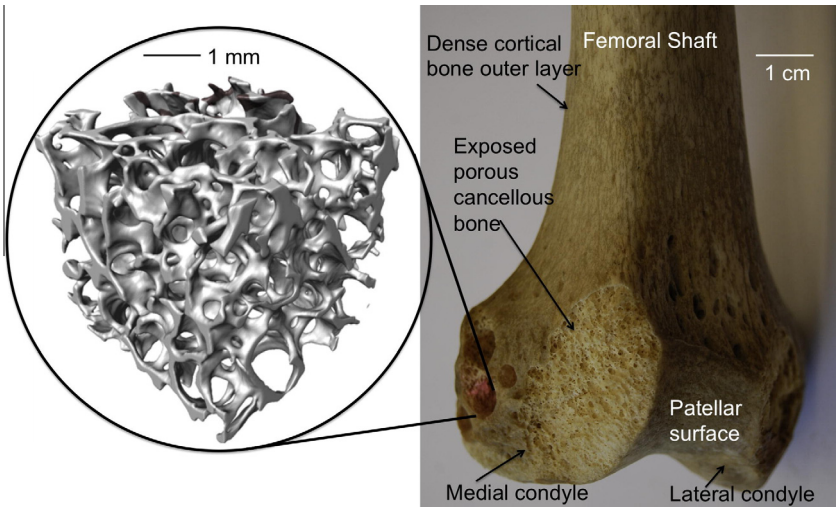


**Fig. 1.** Photograph of a human femur with a core-drilled piece removed. Inset: X-ray microtomography (μCT) image of the cancellous bone removed from the femur proximal to the knee joint.