Bioglass and bioactive glasses and their impact on healthcare

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Abstract

Glass caused a revolution in healthcare when Bioglass was discovered by Larry Hench. It was the first material to bond with bone, rather than be encapsulated by fibrous tissue, launching the field of bioactive ceramics. Bioglass is also biodegradable. Almost 50 years on from its discovery that revolution continues. Bioactive glasses stimulate more bone regeneration than other bioactive ceramics, which is attributed to their dissolution products stimulating cells at the genetic level. This second discovery has changed the way clinicians, scientists and regulatory bodies think about medical devices and the concept of bioactivity. The original 45S5 Bioglass has only recently found really widespread use in orthopaedics, having regenerated the bones of more than 1.5 million patients. Its full potential is still yet to be fulfilled. This article takes the reader from Hench's Bioglass 45S5 to its clinical uses and products, before giving examples of non-surgical products that now use Bioglass, from consumer products, such as toothpaste, to cosmetics. Other glasses have also found important healthcare applications, such as borate based glasses that heal chronic wounds. The revolution looks set to continue as new healthcare applications are being found for bioactive glasses, contributing to extending the glass age.

Keywords: Bioactive glass; Bioglass; wound healing; synthetic bone grafts; bone regeneration.

1. Introduction and scope

The discovery of Bioglass® was not quite an accident, but it was not far off. Prior to its discovery, all implants designed to repair body parts used materials were selected primarily for their corrosion resistance. The problem is that these implants stimulated a response from the immune system, which recognised them as foreign, isolating from the host tissue through fibrous encapsulation. In orthopaedics, this capsule of soft tissue meant that an implant would not integrate with the host bone and therefore would undergo micromotion and eventually cause the bone to fail. In some cases, the material interaction with the body caused mechanical failure of the implants. Bioglass was different, it was the first synthetic material found to form a chemical bond with bone. The results caused clinicians and medical device companies to change the way they thought about synthetic implant materials. Not only did it form a bond with bone, creating a stable implant, but it (and the bone defect site) was also remodelled over time, restoring healthy bone.

Bioglass was invented by Larry Hench at the University of Florida following a serendipitous bus ride conversation with a US Army Colonel [1]. The colonel challenged Hench to develop a material that could survive the aggressive environment of the human body. Hench made a degradable glass in the Na_2O-CaO-SiO_2-P_2O_5 system, with a composition close a ternary eutectic in the Na_2O-CaO-SiO_2 diagram [2]. The first composition he tried (46.1 mol% SiO_2, 24.4 mol% Na_2O, 26.9 mol% CaO and 2.6 mol% P_2O_5), which was later termed 45S5 Bioglass, formed such a strong bond with bone that it could not be removed without breaking the bone [3]. This discovery launched the field of bioactive inorganic materials, and soon bioactive glass-ceramics [4] and calcium phosphate ceramics were also developed [5] as synthetic bone graft materials. Originally, the term “bioactive” referred to forming a bond with bone, and that

definition is still used in the context of synthetic bone grafts[6]. Applications for bioactive glass now stretch far wider than bone repair[7] so a wider definition may be more appropriate, such as "stimulation of a beneficial biological response".

Bioglass offers two modes of bioactivity in orthopaedics. Bone bonding is attributed to hydroxycarbonate apatite (HCA) layer on the glass that forms following dissolution of the glass surface and reprecipitation of the ions released from the glass surface[3]. HCA is similar to bone mineral and is thought to interact with collagen fibrils to integrate (bond) with the host bone. Comparative *in vivo* studies between 45S5 Bioglass and similar sized particles of synthetic hydroxyapatite (HA) and apatite/wollastonite (A/W) glass ceramics showed Bioglass could produce more rapid and higher quality bone regeneration [8]. After one week, there was 17 times more bone in defects filled with Bioglass, and twice as much bone after 24 weeks, compared to defects filled with HA (Figure 1a) [8-11]. The superior osteogenic properties (later termed osteostimulation) of the glass is 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. [12, 13] Other studies have shown that a significant number of genes were up-regulated within 48 h which supported osteogenic behaviour [14]. Transcription of at least five extracellular matrix (the matrix that cells produce to form the basis of a tissue) components was also induced (Figure 1b). Extracellular matrix secretion increased, which mineralised without addition of supplements [15, 16]. The gene expression was dose dependent, with the highest gene expression observed at ~ 20 μg ml^{-1} of soluble silica, accompanied by 60-90 μgml^{-1} of calcium ions [17]. A similar dose-dependent response was observed to the mature osteoblasts with 15-20 μgml^{-1} of soluble silica promoting highest metabolic activity and enhanced formation of mineralised bone nodules [18]. Osteostimulation is

Biolgass' second mode of bioactivity and has led to bioactive glasses to be made to contain other cations with therapeutic benefits, but they are yet to reach clinical use [19].

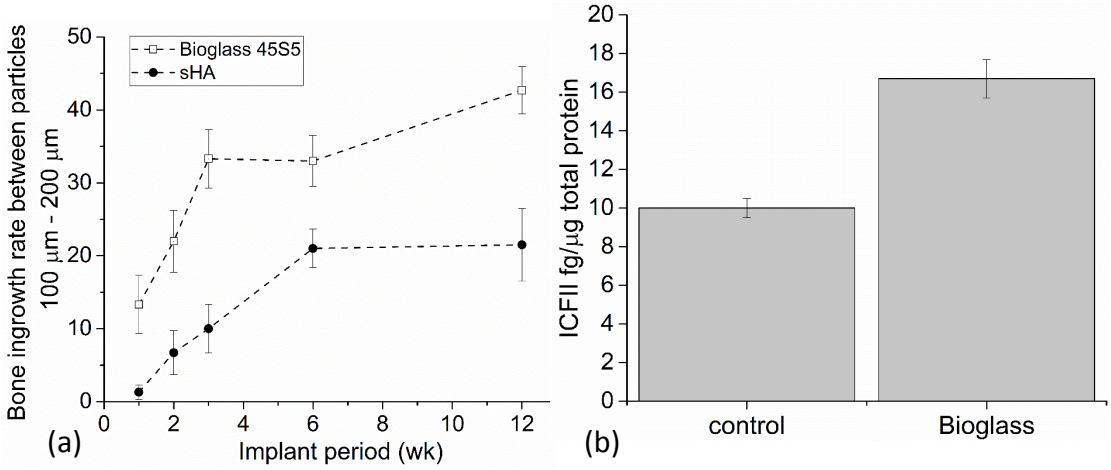

Figure 1. (a) Comparison of % bone ingrowth between particles of 45S5 Bioglass and synthethic HA (sHA) in a bone effect (rabbit femoral chondyle) from 1 to 12 weeks. Particle sizes were 100-300 μm. Data replotted from Oonishi *et al.*[10]; (b) Concentration of unbound insulin-like growth factor IGFII protein in culture media, produced from osteoblasts, comparing control medium to media containing Bioglass dissolution products. Data replotted from Xynos *et al.* [15]

Recently interest has increased in borate glasses [20], largely due to very encouraging clinical results of healing of chronic wounds, such as diabetic ulcers that would not heal under conventional treatment [21]. Phosphate glasses give the benefit of controllable total dissolution, but have not yet reached the clinic[22]. This article aims to summarise the currently available medical devices and products, for which the principle material is bioactive glass and then it discusses some applications that are likely to follow in the near future.

2. Synthetic bone graft granules

Synthetic bone grafts are designed to reduce use of autografts, where clinicians move bone from one part of a patient, usually the pelvis, to the defect site [23]. Problems are that unnecessary bone is in limited supply and patients can experience pain and/or infection at the donor site, which then also needs to be repaired.

The original Bioglass 45S5 has been used in more than 1.5 million patients[24] in the form or a particulate, marketed under the name NovaBone® (NovaBone Products LLC, Jacksonville, FL), to repair bone defects in orthopaedics and maxillofacial reconstruction [25]. However other products exist, based on 45S5 and also on other compositions.

The first clinical use of Bioglass was actually in the form of a monolith, in the form of cones that were used to replace the small bones in the middle ear of a patient. Infection had caused the bones to degrade, causing deafness. The Bioglass implant restored the patient's hearing [26]. The Bioglass middle ear prosthesis (MEP®) was cast into shape from the melt. Ten year follow up studies showed 17 out of 21 retained function (the other four fractured), improving on polymeric, metallic and ceramic implants [26]. The product (DOUEK MED™ , USBiomaterials, Alachua, FL, Figure 2) contained several glass cones of different sizes to enable the clinician to choose appropriately for the patient.

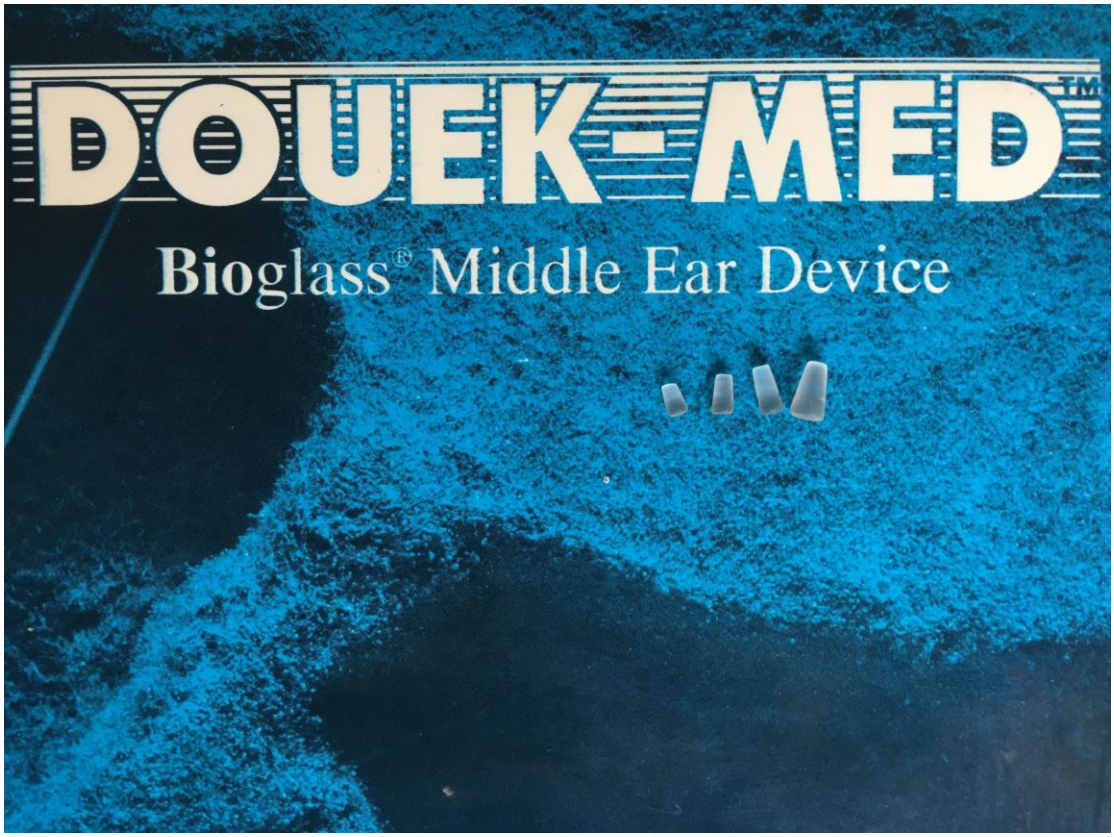

Figure 2. The four sizes of Bioglass cone shaped grafts, photographed (inset) on the packaging of the DOUEK-MED Bioglass Middle Ear device. Scale bar = 1 cm.

The second commercial Bioglass 45S5 device was also cones. The Endosseous Ridge Maintainence Implant [ERMI®] launched in 1988 were inserted into fresh tooth extraction sites (where the root would have been) to provide a stable platform for dentures. Five year follow up showed quantified improvements over synthetic HA implants [27].

These products are no longer in clinical use as surgeons want to be able to mould or cut bone grafts to shape. Providing the glass in the form of particles or granules meant that the glass could be pressed into a defect. Surgeons tend to mix the particles with blood from the patient to create a putty-like material (as the blood begins to clot), which is

pressed into the defect. The blood improves handling of the material and also contains natural growth factors and cells that can accelerate bone regeneration.

PerioGlas® was the first Bioglass particulate (90-710 µm), launched in 1993 by USBiomaterials, now sold by NovaBone Products LLC) as a synthetic bone graft for repair of bone defects in the jaw that resulted from periodontal disease, e.g. to regenerate bone around the root of a healthy tooth to save the tooth, or to repair bone in the jaw to allow the anchoring of titanium implants. Figure 3 shows its packaging and an SEM image of the particles. Clinical studies [28-40] showed that defects treated with PerioGlas were ~70% filled with new bone compared to ~35% for controls. The product has also been used with polymeric membranes, termed guided tissue regeneration [41].

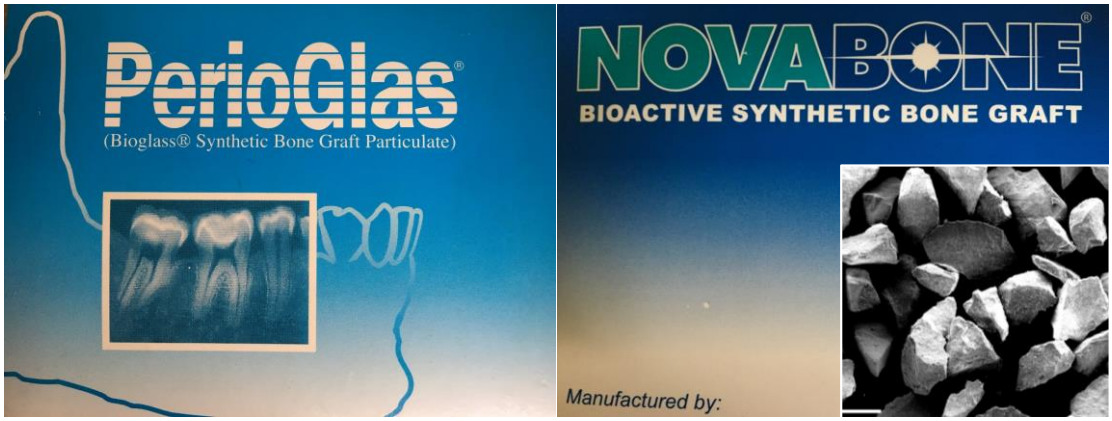

Figure 3. PerioGlas® and NovaBone® packaging. Inset is an SEM image of Bioglass particles of the equivalent particle size range of both products. Scale bar is 200 µm.

Due to the success of PerioGlas, a particulate for grafting of non-load bearing bone defects was released in 1999 named NovaBone (now distributed by NovaBone Products LLC). The particles have a similar distribution to PerioGlas (90-710 µm). FDA approval was granted for orthopaedic use in 2005. In clinical trials, NovaBone was

compared to autograft in posterior spinal fusion operations for treatment of adolescent idiopathic scoliosis (curvature of the spine). The NovaBone was mixed with the patient's blood and fixed in place by compressing the neighbouring vertebrae with metal screws and hooks [42]. NovaBone performed as well as autograft over the follow-up period of 4 years but with fewer infections (2% versus 5%) and fewer mechanical failures (2 versus 7.5%), with the main benefit that a donor site was not needed with NovaBone. The term "osteostimulation" was approved by the FDA in 2015.

Biogran® (Biomet 3i, Palm Beach Gardens, FL) is another 45S5 glass product used in jaw bone defect regeneration. It has a more narrow (300-350 μm) particle size range, which was chosen based on *in vivo* studies that indicated particles with diameters in that particle size range hollowed out within four weeks of implantation. The HCA layer formed and the silica dissolved. [43] The silica dissolution is attributed to the action of phagocytes. Clinical trials on 87 patients, where Biogran was compared to synthetic HA for bone defects in the jaw (alveolar ridge) left by cystic defects, extraction sites, and defects left by surgery, showed that Biogran outperformed HA[44]. After 6 months, little difference could be seen between glass particles and bone by X-ray.

A variation of the 45S5 composition is the S53P4 composition (53.8 mol% SiO_2, 21.8 mol% CaO, 22.7 mol% Na_2O, 1.7 mol% P_2O_5 but usually quoted as 53 wt% SiO_2, 23 wt% CaO, 20 wt% Na_2O, 4 wt% P_2O_5), which is now known as BonAlive® (BonAlive Biomaterials, Turku, Finland). BonAlive (Figure 4) received European approval as a bone graft substitute for orthopaedic use in 2006 and FDA 510k approval in 2008. The BonAlive brand name was introduced in 2007. Small enterprises in Turku, first Abmin Technologies (1996) and then Vivoxid Ltd. (2002) started to produce S53P4 for clinical trials in University Hospitals in Finland, such as the Turku University and Helsinki University. BonAlive Biomaterials began trading in 2010 and BonAlive products are

now available in more than 50 countries and it is estimated to be used in >6000 procedures in 2016.

The S53P4 composition evolved in 1990 from studies investigating the relationship between the incorporation of alumina and borate in silicate glasses and their bioactivity [45]. A rabbit tibia model showed that alumina was detrimental to bioactivity (it increases network connectivity) but good bone bonding was seen for the alumina (and borate) free S53P4 [45]. In addition, *in vitro* studies demonstrated that this composition possessed anti-microbial properties[46]. Preclinical studies for spinal fusion [47], grafting [48] and sinus obliteration [49] followed in the 1990's. Key orthopaedic clinical indications for which BonAlive are now used are for synthetic bone grafting following tumour removal, trauma and to treat chronic osteomyelitis (bone infection, usually caused by bacteria). The published data (in terms of journal articles) on clinical trials of S53P4 is extensive compared to that of the original 45S5 Bioglass.

Figure 4. BonAlive (S53P4 granules) packaging and application demonstration of BonAlive putty (biodegradable polymer containing S53P4 glass particles) into a simulated bone defect. Inset: photograph of BonAlive granules. Photographs obtained with permission from bonalive.com.

Removal of benign bone tumors: S53P4 granules (1-4 mm, 14 patients) were compared with autograft (11 patients), for bone defects (1-30 cm^3) left by benign bone-tumour surgery in hands, tibia (shin) and humerus (arm), with 14 year follow up [50]. Following S53P4 treatment, the cortical bone thickness was twice as thick as it was when autograft was used. However, some of the glass remained in the bone, even after 14 years. The glass was observed to begin to decrease in size (degrade) between 12-36 months and stimulated remodelling of the bone [51] but remodelling was slower than for autograft (at 12 months) [52]. The glass did not disturb the growth of bone in children (which is often problematic with synthetic bone grafts, as seen following a trial on a three year old child (two year follow up) that had a cyst removed [53].

Bone defects from trauma: S53P4 particles (0.83–3.15 mm) were compared to autograft in tibial fractures [54] that required joint realignment. The grafts were placed inside the subchondral bone defects (in the crushed porous bone), supported by metal condylar plates and casts. Full weight bearing was allowed when radiographs indicated healing had occurred, so the implants were loaded. Eleven year follow-up showed similar bone regeneration and no difference in articular depression. Some glass particles were still present, even at 11 years post-operation [55]. The lack of resorption of S53P4 may be due to glass composition, which has higher silica content, and therefore higher network connectivity than 45S5.

Osteomyelitis: 11 patients with chronic osteomyelitis in the spine, where quality of the vertebrae was reduced due to bacterial infection [56], were treated with S53P4 by filling cavity bone defects, with metallic stabilisation of the vertebrae. The most common pathogen was Staphylococcus aureus. Follow up was 10–38 months. Nine patients healed without complications, while the other two had unrelated complications.

Sponpondylolisthesis (displacement of the vertebral column): S53P4 granules of 1-2 mm were compared to autograft and held in position between vertebrae by compression of the vertebrae using metal screws. After 11 years, the fusion rate for the glass was 88% compared to 100% for autograft [57].

Dental/maxillofacial: While the mandible (lower jaw), consists mainly of compact cortical bone that can be easily grafted, the maxilla (upper jaw) consists of porous cancellous bone that resorbs rapidly in periodontitis and is therefore more difficult to graft. Treatment is usually maxillary sinus floor lifting, where bone grows partially into the sinus cavity. Implantation of a mixture of S53P4 granules in combination with autograft allowed the implantation of titanium roots in the porous maxilla and showed more rapid bone repair with thicker trabeculae compared to autograft alone [58].

Craniofacial: Sinus obliteration is a procedure that eliminates the frontal sinuses in order to prevent chronic infection or in response to trauma or tumour removal. Traditionally, the defect is filled with fat, but this lead to up to 25% of patients experiencing complications. Trials with S53P4 (0.5-1 mm size range) showed improved bone repair, in terms of quantity and quality, compared to synthetic HA [59].

BonAlive has also successfully been used in trials for filling cavities in the middle ear created by surgeons removing mastoid air cells and mucous membranes that were damaged by chronic infection [60].

Clinical results are good for the BonAlive (S53P4) and Bioglass 45S5 particulates. The two compositions been compared in very few *in vivo* studies. Bioglass 45S5 reacts more rapidly than S53P4, so when cones were implanted in rat bone defects, the HCA layer was thicker for 45S5 than for S53P4 [61]. The original Bioglass degrades more rapidly due to its lower silica content and therefore lower network connectivity.

Clinicians would prefer to use a bioactive glass that is in the form of a putty and/or that has the porous structure of autograft (cancellous bone). NovaBone have produced porous constructs that they term NovaBone OS-Si^{+} Morsels (Figure 5a). The morsels (scaffolds) have interconnected pores and are 1-5 mm in diameter. However these morsels are no longer totally amorphous, as sintering the Bioglass particles causes crystallisation[62], so they are glass-ceramics. Partial crystallisation can lead to instability as the residual amorphous regions degrade preferentially[63] but the morsels still biodegrade within 12 months.

More recently, other 45S5 particulates have reached market, such as Unigraft® (Unicare Biomedical, Laguna Hills, CA), which is available in particle size ranges of 200-400 µm and 200-600 µm and used mainly for periodontal bone regeneration. GlassBone (Noraker, Lyon, France, Figure 5a) is a 45S5 particulate for orthopaedic and cranio-maxilo-facial surgeries (Figure 5b). GlassBone is available in particle size ranges of 90–500 µm, 500–1000 µm and 1000–3150 µm. Having been launched in 2008, GlassBone has sold in excess of 25 000 units and is available in the European Union (EU), Mexico, Turkey, Iran and Taiwan.

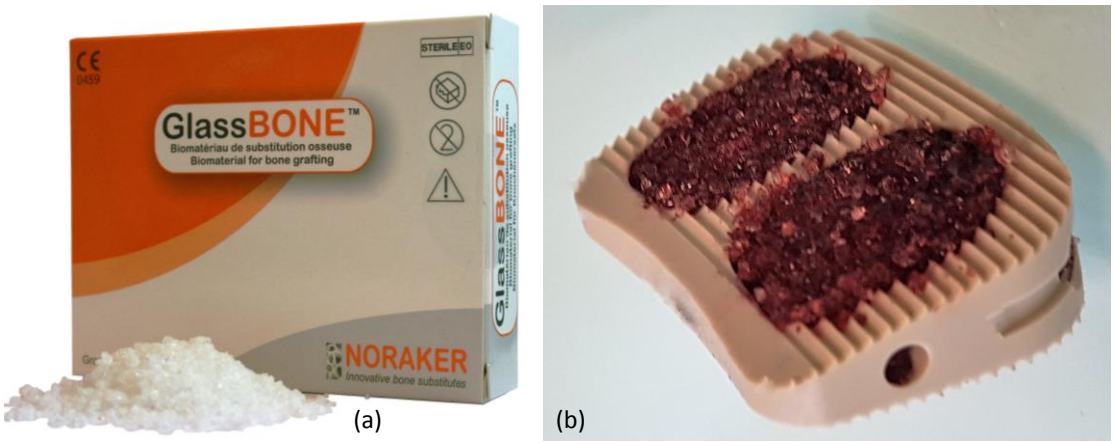

Figure 5. (a) GlassBone® particles and packaging and (b) demonstration of use of

GlassBone, mixed with blood and inserted in a spinal fusion cage. Photographs courtesy of Noraker.

3. Composites and putties for bone repair

Both NovaBone (45S5) and BonAlive (S53P4) glasses are available in bioresorbable putties (Figure 4 and Figure 6b).[64] NovaBone putties consist of a carrier matrix of polyethylene glycol (PEG) and glycerine, with 69 wt% Bioglass 45S5 (32 μm-710 μm, NovaBone Putty®) or a combination of 25 wt % macroporous morsels (500-700 μm) and 44 wt% Bioglass 45S5 (32 μm-710 μm), termed NovaBone Macroporous Putty (Figure 6b).

Figure 6. (a) NovaBone macroporous morsels; (b) NovaBone Putty® of PEG and glycerine containing Bioglass 45S5 particles; c) MacroFORM™ composite of bovine collagen and Bioglass 45S5 particles. Photographs courtesy of NovaBone LLC.

Comparing putty to particulate in an ovine model, of 10 mm diameter critical sized defects in spine, bone defects filled with the putty filled with 42% bone compared to 20% in the defect filled with NovaBone particulate and 5% bone in the empty control [65]. The putty matrix may separate the particles to allow more new bone to grow between

them than the tightly packed particles allowed. Signafuse® (Biostructures LLC, Newport Beach, CA) is a similar formulation with different particle size ranges. Synergy Biomedical (Collegeville, PA) also have a putty containing 45S5 Bioglass, but the glass is in the form of spheres (BioSphere®, modal diameter ~400 μm), which they hypothesise leave interstices between the spheres during packing, which leaves space for bone ingrowth. Fibergraft® Putty (Prosidyan, Warren, NJ) also contains Bioglass spheres (Fibergraft BG), but the spheres have a unique architecture of a porous shell around a bundle of microfibres. The aim of the microfibres is to increase the surface area the glass and encourage bone ingrowth once the outer shell has degraded.

Bone graft products often combine the bioactive glass with a natural polymeric matrix, in an attempt to mimic natural bone, e.g. demineralised bone matrix (DBM), collagen, such as bovine collagen. An example is a mouldable composite of 90 wt% Bioglass particles (either NovaBone particles or macroporous morsels) in bovine hide collagen (Figure 4c). Other examples of similar products are: Vitoss® Bioactive Bone Graft (Stryker, NJ) and NanoFuse® (Amend Surgical, Alachua, FL). Clinical studies show NanoFuse (approved for orthopaedic and spinal use) improving bone ingrowth into a bone defect compared to the DBM alone[67]. Vitoss Bioactive and BA2X, launched in 2011, are for filling bone defects and have 90% porosity in the DBM matrix. Vitoss BBTrauma (2012) is exclusively sold for trauma surgery and has a greater specific surface area of bioactive glass. Kinex® putty (Globus Medical Inc., Audubon, PA) combines higher concentrations of Bioglass (compared to with collagen with hyaluronic acid. All of these DBM based devices are a mixture of components rather than true composites.

Structural composites are needed that can take cyclic loads that contain bioactive glasses. Cortoss® (Stryker) is a polymethyl methacrylate (non-biodegradable) bone

cement that contains Bioglass particles, that is used to stabilise weakened vertebrae by filling the porous bone with cement. As it is not degradable, it is for bone augmentation, rather than regeneration. Noraker have developed a screw for anterior cruciate ligament reconstruction called LockActiv™, which is a poly(L-lactide)-co-poly(D,L)lactide (PLLA-co-PDLLA) polymer matrix containing 15wt% 45S5 Bioglass. LockActiv™ received its CE in 2015 and clinical trials are in progress. The screw must fix a detached ligament into a hole that the surgeon has drilled into the host bone. Screws that have a combination of the required mechanical properties to hold a ligament in place and that bond with the host bone and then biodegrade, successfully leaving the ligament integrated in the bone would fulfil an unmet clinical need. A future strategy is to produce inorganic/organic hybrids that have molecular level interactions between the glass and the polymer, but their journey to the clinic is likely to take 10 years[66].

4. Wound healing

Bioglass does not only have applications in orthopaedics, but also in soft tissue repair[6]. Exciting clinical results have been reported in human trials and in veterinary practices for treating chronic wounds with a cotton candy like scaffold made of biodegradable borate glasses [20]. Studies included healing diabetic ulcers in human patients, which were not healing under conventional treatment [21]. There are no reports on the mechanism of action for why the scaffolds work so well, but the results are impressive. A product, RediHeal, is available to veterinary practices and FDA approval for the human product is pending.

5. Bioactive glass in toothpaste

Bioactive glass has also had an impact in consumer healthcare. The largest commercial use of bioactive glass, and perhaps any bioactive biomaterial, is in

toothpaste. Enamel and dentine of the tooth are very similar to bone, in that they contain HCA mineral and collagen. Up to 35% of the adult population are affected by dentine hypersensitivity, which is pain associated with chemical (e.g. acid) or thermal (e.g. hot or cold beverages) stimuli. The pain is usually explained by the dentine of the tooth, which is usually covered by enamel, becoming exposed. Dentine contains tubules that lead to the pulp cavity and nerves [68]. Early toothpaste for hypersensitivity delivered anaesthetics during brushing. Recently, occlusion of the dentine tubules has become standard treatment [69] and toothpastes have been developed that can occlude tubules during brushing. Occlusion can be by physical occlusion by particles, stimulation of natural mineral (HCA) formation over and in the tubules, or a combination of the two.

Since 2004, a fine Bioglass 45S5 particulate, named NovaMin® (NovaMin Technology, FL, owned by GlaxoSmithKline, UK since 2010), has been used in certain toothpastes. NovaMin has a particle size (D_{50} value) of ~18 μm and releases calcium and phosphate species during glass dissolution, which then form HCA on the dentine[70]. NovaMin was first available in the USA in fluoride free toothpastes, but since the 2010 acquisition by GSK, it has been used in Sensodyne Repair and Protect® formulations (Figure 7a) that are "powered by NovaMin", which are available in more than 20 countries. Clinical studies (>100 volunteers) showed improved pain relief when brushing with a NovaMin containing toothpaste compared to a toothpaste containing the anaesthetic potassium nitrate [71]. Figure 7b shows exposed dentine tubules following a brief acid etch. Figure 7c shows the NovaMin immediately after it was brushed onto the dentine in artificial saliva (AS). The particles attached and, within 24 h, the surface was almost completely covered by an HCA (Figure 7c) mineralisation.

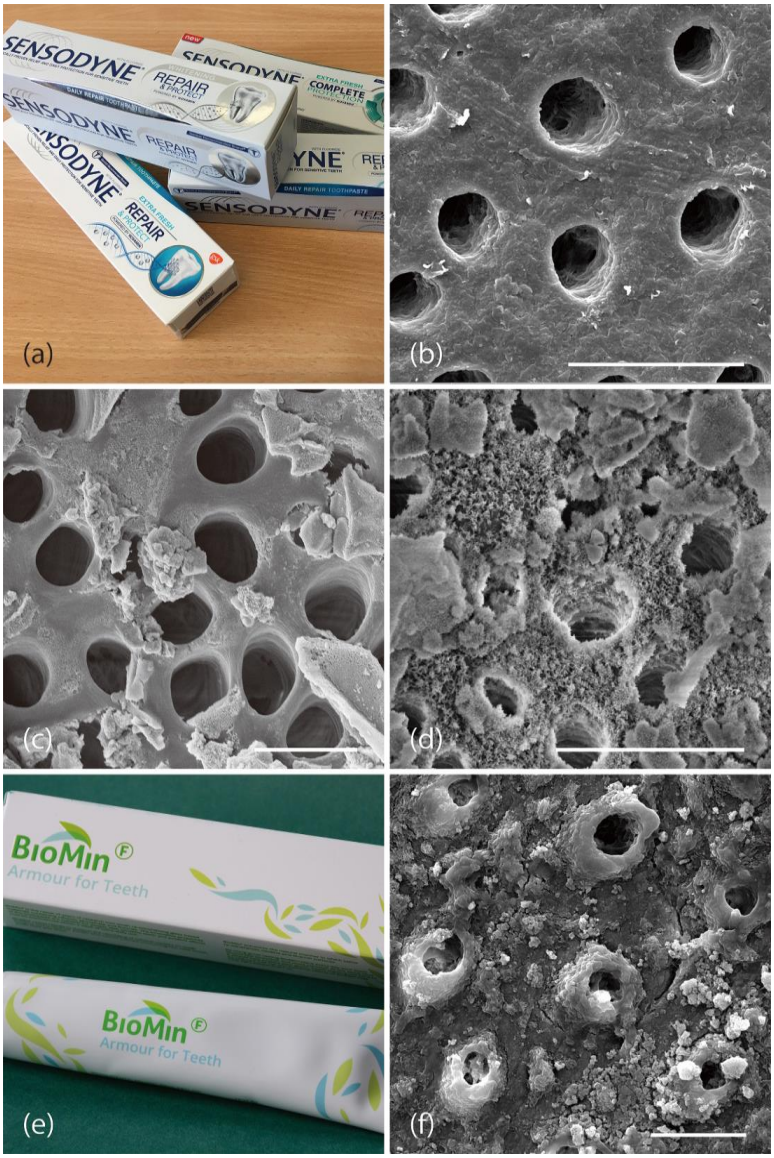

Figure 7. (a) Photograph of Sensodyne Repair and Protect® toothpastes that contain NovaMin (45S5) particles; (b-d) SEMs of human dentin: (b) untreated; (c) immediately after application of NovaMin in artificial saliva (AS); (d) 24 h after application of NovaMin in AS; (e) photograph of BioMinF toothpaste; (f) SEM image of dentine after 2 min brushing with BioMinF toothpaste (c,d) modified with permission from Earl *et al.* [66]; (b, f) provided by Prof. Robert Hill, Queen Mary, University of London/BioMin Technologies Ltd, UK). Scale = 5 μm.

The success of NovaMin led to the development of more complex glass compositions, such as those designed to stimulate the formation of fluorapatite on the dentine, which is more resistant to acid attack than HCA [72, 73]. Fluoride has long been identified as the key agent in preventing caries, as it inhibits tooth demineralisation. It also inhibits the metabolism of bacteria associated with caries, by preventing their metabolic acid production [74]. An example composition that incorporates CaF_2 in the composition is 36.41 mol% SiO_2, 28.28 mol% Na_2O, 24.74 CaO, 6.04 mol% P_2O_5, 4.53 mol% CaF_2 [75]. Fluoride-containing bioactive glasses released fluoride ions during dissolution [76, 77], which resulted in the formation of fluorapatite [75, 78]. Studies showed that substituting CaF_2 at the expense of CaO increased glass dissolution [79]. The ability to form apatite increases with phosphate content, as long as the phosphate remains predominantly as orthophosphate in the glass[80]. 6 mol% P_2O_5 seemed to favour fluoroapatite formation over fluorite [75, 76].

Based on this knowledge, a fluoride-releasing bioactive glass, BioMinF® (BioMin Technologies Ltd, London, UK) for use in toothpaste was developed [81]. It differs from NovaMin by its higher phosphate content, the presence of CaF_2 in the glass and the smaller average particle size (D_{50} of 6 μm). After two minutes of brushing dentine samples with BioMinF toothpaste (Figure 7e), small particles were seen to instantly occlude some of the tubules (Figure 7f) and the tubules remained occluded even after washing with 6% citric acid for 30 s. The BioMinF toothpaste was launched in 2016 in the UK (online only) and in pharmacies in Germany and India. Its efficacy in preventing or treating tooth decay, acid erosion or dentine hypersensitivity still needs to be demonstrated in clinical studies.

Dental care with bioactive glass is not limited to toothpaste. Bleaching teeth, which usually uses hydrogen peroxide, can demineralize enamel. *In vitro* studies indicate that NovaMin can repair the enamel though remineralisation to pre-bleaching levels (5 minute exposure and brushing) [82]. Dentists can use air polishing to whiten teeth, which uses particles (traditionally sodium bicarbonate) as abrasives to remove stains, but the procedure is too painful for patients with hypersensitivity. Replacing the sodium bicarbonate with Bioglass 45S5 powder (Sylc, Denfotex, Ltd, UK) in the polishing procedure can stimulate mineralisation of dentine tubules in a similar mechanism to that of Novamin containing toothpaste [83]. Patients reported the Bioglass 45S5 polishing resulted in a 44% reduction in tooth sensitivity, and enhanced whiteness, according to their subjective scoring.

6. Cosmetics

Bioglass has recently been used in a number of cosmetic creams, particularly as Vitryxx® (Schott AG), a finely ground particulate (D_{50} of 4 μm). Vitryxx is thought to have anti-ageing benefits, such as reducing redness and wrinkles. An example is Visible Youth Professional, a hyaluronic acid based gel that contains Vitryxx.

7. Summary

Bioactive glass is a key contributor to the Glass Age. It has improved the quality of life for millions of patients, regenerating bone faster and in some cases healing defects that would not heal by other means. The near future will see a glass revolution in other tissues, such as wound care, particularly reducing amputations arising from diabetic ulcers and sports injuries, including cruciate ligament damage and cartilage

tears. Applications will then extend to other soft tissues and delivery of therapeutic ions to treat a variety of conditions.

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Captions

Figure 1. (a) Comparison of % bone ingrowth between particles of 45S5 Bioglass and synthethic HA (sHA) in a bone effect (rabbit femoral chondyle) from 1 to 12 weeks. Particle sizes were 100-300 μm. Data replotted from Oonishi *et al.*[10]; (b) Concentration of unbound insulin-like growth factor IGFII protein in culture media, produced from osteoblasts, comparing control medium to media containing Bioglass dissolution products. Data replotted from Xynos *et al.* [15]

Figure 2. The four sizes of Bioglass cone shaped grafts, photographed (inset) on the packaging of the DOUEK-MED Bioglass Middle Ear device. Scale bar = 1 cm.

Figure 3. PerioGlas® and NovaBone® packaging. Inset is an SEM image of Bioglass particles of the equivalent particle size range of both products. Scale bar is 200 μm.

Figure 4. BonAlive (S53P4 granules) packaging and application demonstration of BonAlive putty (biodegradable polymer containing S53P4 glass particles) into a simulated bone defect. Inset: photograph of BonAlive granules. Photographs obtained with permission from bonalive.com.

Figure 5. (a) GlassBone® particles and packaging and (b) demonstration of use of GlassBone, mixed with blood and inserted in a spinal fusion cage. Photographs courtesy of Noraker.

Figure 6. (a) NovaBone macroporous morsels; (b) NovaBone Putty® of PEG and glycerine containing Bioglass 45S5 particles; c) MacroFORM™ composite of bovine collagen and Bioglass 45S5 particles. Photographs courtesy of NovaBone LLC.

Figure 7. (a) Photograph of Sensodyne Repair and Protect® toothpastes that contain NovaMin (45S5) particles; (b-d) SEMs of human dentin: (b) untreated; (c) immediately after application of NovaMin in artificial saliva (AS); (d) 24 h after application of NovaMin in AS; (e) photograph of BioMinF toothpaste; (f) SEM image of dentine after 2 min brushing with BioMinF toothpaste (c,d) modified with permission from Earl *et al.* [66]; (b, f) provided by Prof. Robert Hill, Queen Mary, University of London/BioMin Technologies Ltd, UK). Scale = 5 μm.