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Review Article

History and trends of bioactive glass-ceramics

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Abstract: The interest around bioactive glass-ceramics (GCs) has grown significantly over the last two decades due to their appropriate biochemical and mechanical properties. The intense research effort in this field has led to some new commercial products for biomedical applications. This review article begins with the basic concepts of GC processing and development via controlled heat treatments of monolithic pieces or sinter-crystallization of powdered glasses. We then go on to describe the processing, properties, and applications of some commercial bioactive GCs and discuss selected valuable reported researches on several promising types of bioactive GCs. The article finishes with a section on open relevant research directions for bioactive GC development. © 2016 Wiley Periodicals, Inc. J Biomed Mater Res Part A: 104A: 1231–1249, 2016.

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INTRODUCTION

Glass-ceramics (GCs) are polycrystalline materials that contain one or more crystal phases embedded into a residual glass and are produced by the controlled heat treatment of certain glasses. The heat treatment is usually (but not always) performed in two stages: first, at relatively low temperatures, not far from the glass transition, T_g, to induce internal nucleation, followed by a second stage at a higher temperature to promote the growth of different phases. Another, less frequent, process is sometimes used in which glass powders are shaped with some binder and then sintered and simultaneously crystallized. Sintering and crystallization usually proceed concurrently, where the free surfaces of the glass frits encourage crystallization.[1–3] Recently, a third method, the synthesis of GCs via the sol-gel method has been thoroughly investigated. This method allows for low-temperature chemistry-based synthesis, where a solution of chemical precursors or a dispersion of colloidal particles gelifies under certain pH and chemical concentrations near room temperature. Gels are wet inorganic networks of silica that can then be dried and heated, for example, at 400–700°C, and are finally converted into glass. Through a controlled (normally very slow) heat treatment of a gel, a powder or monolith glassy or crystalline material may result. Internally nucleated and crystallized monoliths or sinter-crystallized glass powder compacts can be called GCs. In the latter case, each particle of the GC powder is a conglomerated piece of many individual finer particles, which have been crystallized from their surfaces. Figure 1 shows the main stages in the synthesis of bioactive GCs.

GCs always contain a residual glassy phase and one or more embedded crystalline phases. Their crystallinity varies between 0.5% and 99.5%, most frequently between 30% and 70%. Controlled crystallization yields a group of materials with interesting, sometimes unusual, combinations of properties such as biological, electrical, thermal, and mechanical.[1–3]

A bioactive glass or GC is one that elicits a particular biological reaction at the interface of the material, which stimulates cell proliferation, gene response and the formation of a bond between living tissues and the material. A common characteristic of bioactive GCs is that their surface develops a biologically active hydroxycarbonate apatite (HCA) layer that bonds to bone. The HCA phase that forms on bioactive GCs is chemically and structurally equivalent to the mineral phase of bone. This similarity is key for interfacial bonding.[4–10] Figure 2 shows an example of HCA growth on a GCs surface. Bonelike HCA developed on the sample

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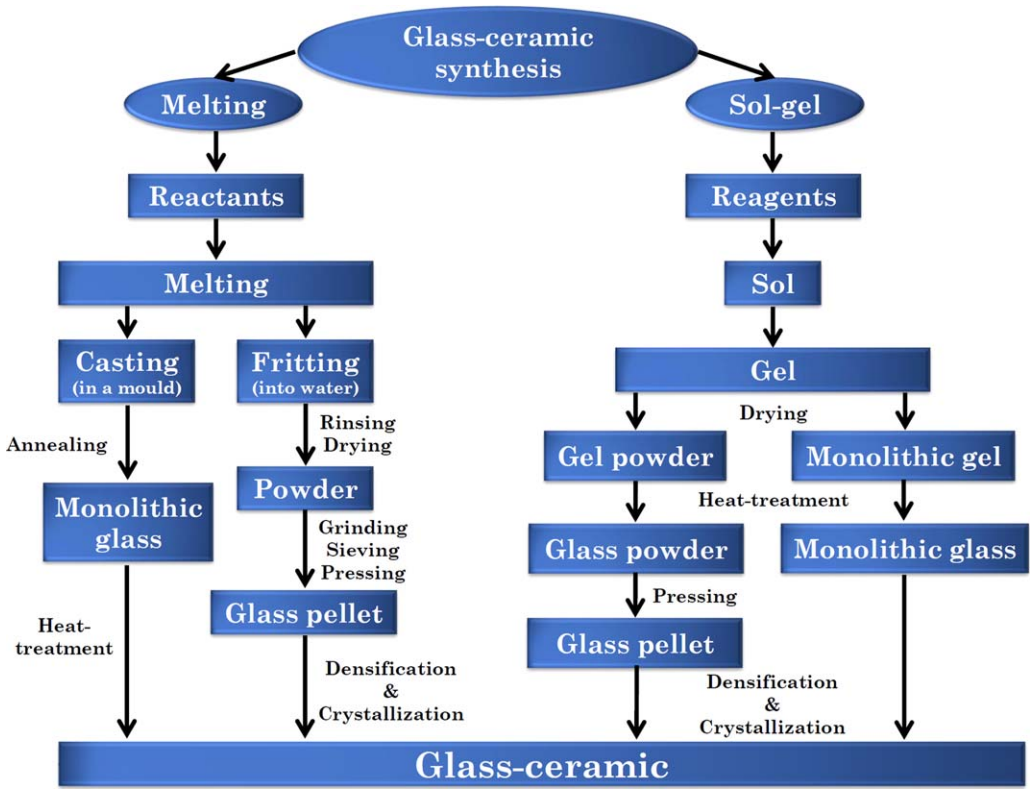

FIGURE 1. Schematic diagram of the main stages in the synthesis of GCs.

surface after immersion in simulated body fluid (SBF). The details of HCA formation could be identified by scanning electron microscopy (SEM) when the rate of HCA growth was reduced by ZrO_2 addition to the gel-derived SiO_2-CaO-P_2O_5 bioactive GCs.[11]

Figure 3 shows the number of scientific publications (papers, books, and conference papers) per year in the field of bio GCs. We searched the Scopus database using the keywords "bio* + glass-ceramic*" only in the publication title (blue line) and in the title, abstract and keywords (maroon line). It should be noted that the actual number of publications per year related to bio GCs falls between these two extremes. The number of publications shows some fluctuations over the years; however, an exponential increase over the past four decades is observed. The same graph for "bioactive + glass-ceramic*" keywords is shown in Figure 4. This figure definitely shows an increasing trend for research related to bioactive GCs, which indicates that the field of bio and bioactive GCs has been a "hot" research topic in the past 4 decades. Furthermore, a comparison between these two graphs reveals that almost 50% of research related to bio GCs is actually related to bioactive GCs. The other half is connected to inert (biocompatible) dental GCs.

In this article, we review the fabrication method, properties and applications of biologically active GCs. First, we summarize their history. We then discuss their properties

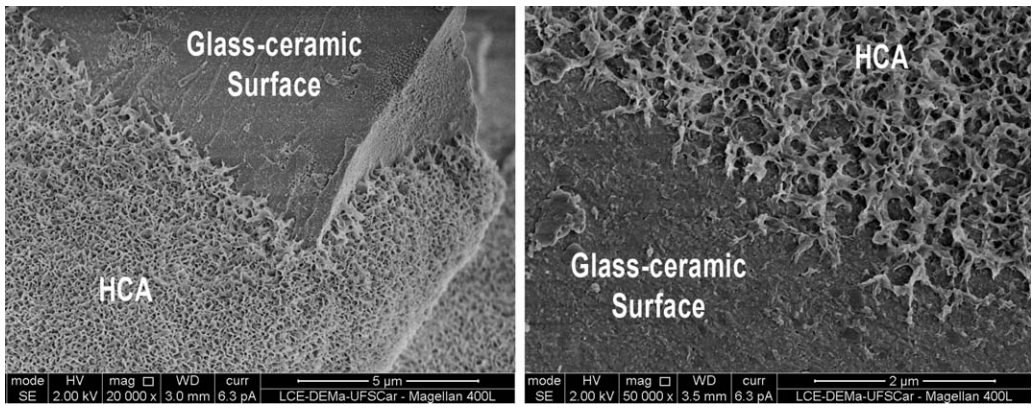

FIGURE 2. Hydroxycarbonate apatite (HCA) formation on the GC surface after 24 h exposure to simulated body fluid (SBF).[11]

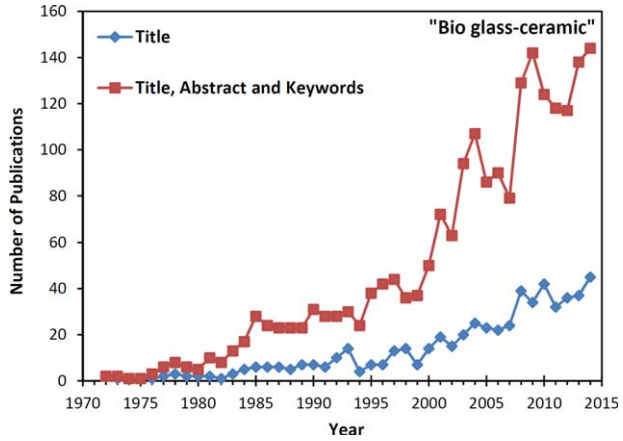

FIGURE 3. Number of publications (papers, books and conference papers) per year extracted from the Scopus database by searching the keywords ("sittal" OR "vitroceramic*" OR "glass-ceramic*" OR "glass ceramic*") AND (bio*) in the publication title (blue) and also in the title, abstract and keywords (maroon) during the period of 1972–2014.

and applications, and we provide a summary of most common fabrication methods of the most famous and commercially available bioactive GCs. Finally, we highlight recent relevant research and possible developments in this field.

BACKGROUND

Bioactive glasses have been widely investigated for diverse clinical applications for >4 decades. Several families can be distinguished in the historical evolution of bioactive glasses. The first melt-derived bioactive glass, *Bioglass 45S5*, was discovered by Hench in 1969,[4] followed by bioactive gel-derived glasses, also proposed by Hench in 1991.[5] Most recently, bioactive glasses with ordered mesoporosity were designed by Vallet-Regi et al.[6]

Bioactive glasses show both osteoconduction and osteoinduction properties and can be used in a variety of applications, such as bone grafting, scaffolding, drug delivery, coatings, and soft tissue engineering. However, despite their excellent bioactive properties, the major disadvantages of bioactive glasses are their low mechanical strength and low fracture toughness, K_{IC} (a bending strength of approximately 70 MPa and K_{IC} of 0.5 MPa·$m^{1/2}$). These characteristics restrict their use to only a few applications that do not demand significant loads. To improve their mechanical strength, various types of glasses that undergo the precipitation of different crystalline phases under heat treatment, known as bioactive GCs, have been developed. The most famous and commercially available bioactive GCs are Cerabone®, Biosilicate®, Ceravital®, and Bioverit®.[5–10]

Ceravital® has apatite ($CaO–P_2O_5$) precipitates in a $Na_2O–K_2O–MgO–CaO–SiO_2–P_2O_5$ glass matrix and was first developed by Brömer et al. in 1973.[9] Kokubo et al. developed A-W GC in the late 1980s, commercially known as Cerabone®, in which apatite and wollastonite crystallize in a $MgO–CaO–SiO_2–P_2O_5$ glass.[10] Bioverit®, with apatite and mica dispersed in a $Na_2O–MgO–CaO–Al_2O_3–SiO_2–P_2O_5–F$ glass, was developed by Höland et al. in 1985.[12] All these GCs are composed of an apatite-like crystalline phase and are much less soluble than Bioglass® 45S5. In 1996, Peitl et al.[13] developed an apatite-free GC based on the crystallization of (a somewhat modified) Bioglass®. They called their product Biosilicate® and demonstrated that controlled crystallization that led to a well-designed microstructure of a $Na_2O–CaO–SiO_2–P_2O_5$ glass could increase its average 4-point bending strength from 75 to 210 MPa. This value is similar to that found for the A-W GC (215 MPa), which exhibits the best mechanical performance of all commercial bioactive GCs.[13,14]

We will provide more details on the properties, applications and fabrication methods of the above-cited bioactive GCs in Cerabone®, Bioverit®, Biosilicate®, and Ceravital® sections. In addition to these commercially available bioactive GCs, there are less investigated GCs based on canasite, apatite-mullite, chain silicate, oriented apatite, chlorapatite, calcium pyrophosphate, rhenanite, and alkali-free which will be discussed in Miscellaneous Bioactive Glass-Ceramics section.

Recent developments associated to gel-derived GCs, scaffold fabrication, GCs for soft-tissue engineering, GCs for hyperthermia, and GCs as composites or coatings will be explained in Coatings and Composites, Bioactive GC Scaffolds, Gel-Derived Bioactive GCs sections. Finally, possible developments and trends will be highlighted in Future Research Directions section.

CERABONE®

Definition

Apatite-wollastonite GC, commercially available with the brand name Cerabone®, is the most extensively and successfully used bioactive GC for bone replacement. It was developed by Kokubo[10]and commercially produced under license by Nippon Electric Glass Co., Japan.[3,5]

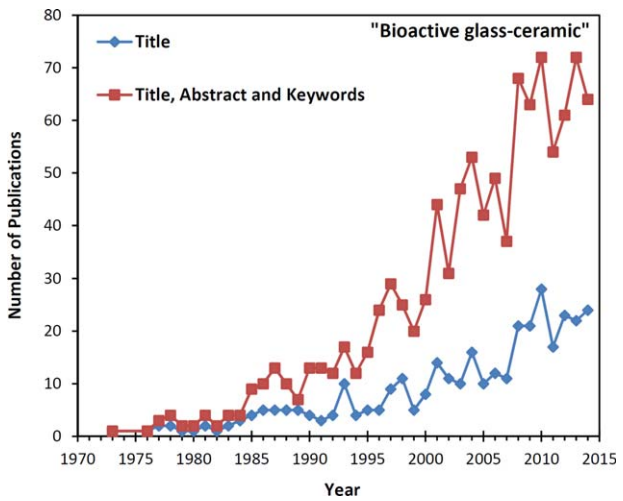

FIGURE 4. Number of publications (papers, books and conference papers) per year extracted from the Scopus database by searching the keywords ("sittal" OR "vitroceramic*" OR "glass-ceramic*" OR "glass ceramic*") AND (bioactive) in the publication title (blue) and also in the title, abstract and keywords (maroon) during the period of 1973-2014.

TABLE I. Crystalline phases, bending strength and fracture toughness of parent glass, apatite GC, apatite-wollastonite GC and human cortical bone.[5]

Samples	Phases (wt %)	Bending strength (MPa)	Fracture toughness ($MPa \cdot m^{1/2}$)
Parent glass	100% glass	70	0.8
Apatite GC	38% apatite + 62% glass	90	1.2
Apatite-wollastonite GC	38% apatite + 34% wollastonite + 28% glass	220	2.0
Human bone	Mainly apatite and collagen	160	2–12

Kokubo et al.[10] envisaged that they should develop a biomaterial with a microstructure and biomedical properties similar to those of natural bone. Bone is a composite material consisting of nanosized apatite particles reinforced by collagen fibers. Those authors, therefore, expected that a composite containing apatite and a fibrous mineral could exhibit mechanical properties analogous to those of bone. They have thus selected β-wollastonite (a fibrous mineral of $CaO \cdot SiO_2$ composition) for its inherent bioactivity and reinforcing ability as a sister phase for apatite.[5,10]

They designed a glass composition based on apatite-wollastonite. The phase diagram of the $3CaO \cdot P_2O_5$–$CaO \cdot SiO_2$ system shows an eutectic at 36 wt % ($3CaO \cdot P_2O_5$)−64 wt % ($CaO \cdot SiO_2$) at 1420°C. Additionally, the partial replacement of $CaO \cdot SiO_2$ by $CaO \cdot MgO \cdot 2SiO_2$ could decrease the liquidus temperature. Therefore, a composition containing 36 wt % ($3CaO \cdot P_2O_5$), 40 wt % ($CaO \cdot SiO_2$), and 24 wt % ($CaO \cdot MgO \cdot 2SiO_2$), that is, $4.6MgO–44.9CaO–34.2SiO_2-16.3P_2O_5$ in wt %, was chosen as the base glass composition in Kokubo's study.[5,10]

To produce this GC, a batch mixture of reagent grade MgO, $CaCO_3$, SiO_2, and $CaHPO_5 \cdot 2H_2O$ was melted in a Pt–10% Rh crucible at 1450°C for 2 h in an electrical furnace. Then, the melt was poured onto a stainless steel plate, and then pressed into a plate approximately 2 mm thick. This glass plate was heated to 1050°C at a heating rate of 5°C/min. Fine-grained apatite and fibrous β-wollastonite normally precipitate in the parent glass using this heat treatment. However, large cracks were formed in the interior of the crystallized product because the fibrous wollastonite precipitated perpendicularly to the outer surface of the glass specimen.[5,10] To suppress the preferred orientation of wollastonite, those authors crushed the glass plate into a powder with a particle size below 44 μm, pressed it uniaxially and subsequently isostatically into a disc, and then subjected it to the same heat treatment described above. As a result, fine-grained apatite and wollastonite crystallized from the glass particles surfaces. However, the crystallized product contained 3.5% residual porosity because the glass powder compact began to crystallize before full densification. The addition of 0.5 wt % CaF_2 to the composition provided a fully densified crystallized product because it decreased the softening temperature of the glass powder and increased the crystallization temperature of the wollastonite. This polycrystalline material was denominated A-W GC after the names of the crystalline phases it contains. The apatite phase was identified to be oxyfluorapatite. The apatite, β-wollastonite, and glassy phase content were calculated to be 38, 34, and 28 wt %, respectively. The density of the A-W GC was approximately 3.1 g/cm^3. A-W GC can be machined into various shapes to be used as a bone substitute.[3,5,9,10]

Mechanical properties

The bending strength and fracture toughness of the A-W GC are shown in Table I, which compares the values for the parent glass, apatite GC, containing only apatite, and human cortical bone.[5]

The average bending strength of 220 MPa of A-W GC is higher than that of human cortical bone. Comparing the bending strength of A-W GC with that of parent glass and apatite GC, it is obvious that the high bending strength of the A-W GC is conferred by the precipitation of the wollastonite crystals in addition to apatite. A-W GC exhibits a fracture toughness of 2.0 $MPa \cdot m^{1/2}$, whereas parent glass and apatite GC show fracture toughnesses of 0.8 and 1.2 $MPa \cdot m^{1/2}$, respectively. Other mechanical properties of the A-W GC, such as compressive strength, Young's modulus and Vickers hardness were approximately 1080 MPa, 118 GPa, and 680 HV, respectively.[5]

To evaluate the fatigue resistance of this GC as a bone substitute under load-bearing conditions, it was subjected to a cyclic load at 36.5°C in a simulated body fluid (SBF) with ion concentrations nearly equal to those of the human blood plasma. The test results suggested that A-W GC is able to withstand >10 years in a living body, even under the constant loading of a bending stress of 65 MPa.[5]

Biological properties

The interaction of bone with A-W GC was investigated by Kokubo's team, which implanted $10 \times 15 \times 2$ mm^3 samples into the tibial metaphyses of a rabbit. The cross-section of an interface between A-W GC and bone after 25 weeks of implantation revealed that the GC directly adhered to the bone without the formation of any fibrous tissue. When a tensile stress was applied perpendicularly to the interface, the bone did not break at the interface, and GC was tightly bonded to the bone. After the implantation of 200–325 μm granular particles of this GC into a hole drilled at a rat's tibia, they were covered with newly grown bone on up to 90% of their surface in 4 weeks.[5] Figure 5 shows the bonding mechanism of A-W GC to bone.[5]

Applications

Apatite-wollastonite GC has been used to fabricate various types of prostheses and spacers used in spinal and tumor

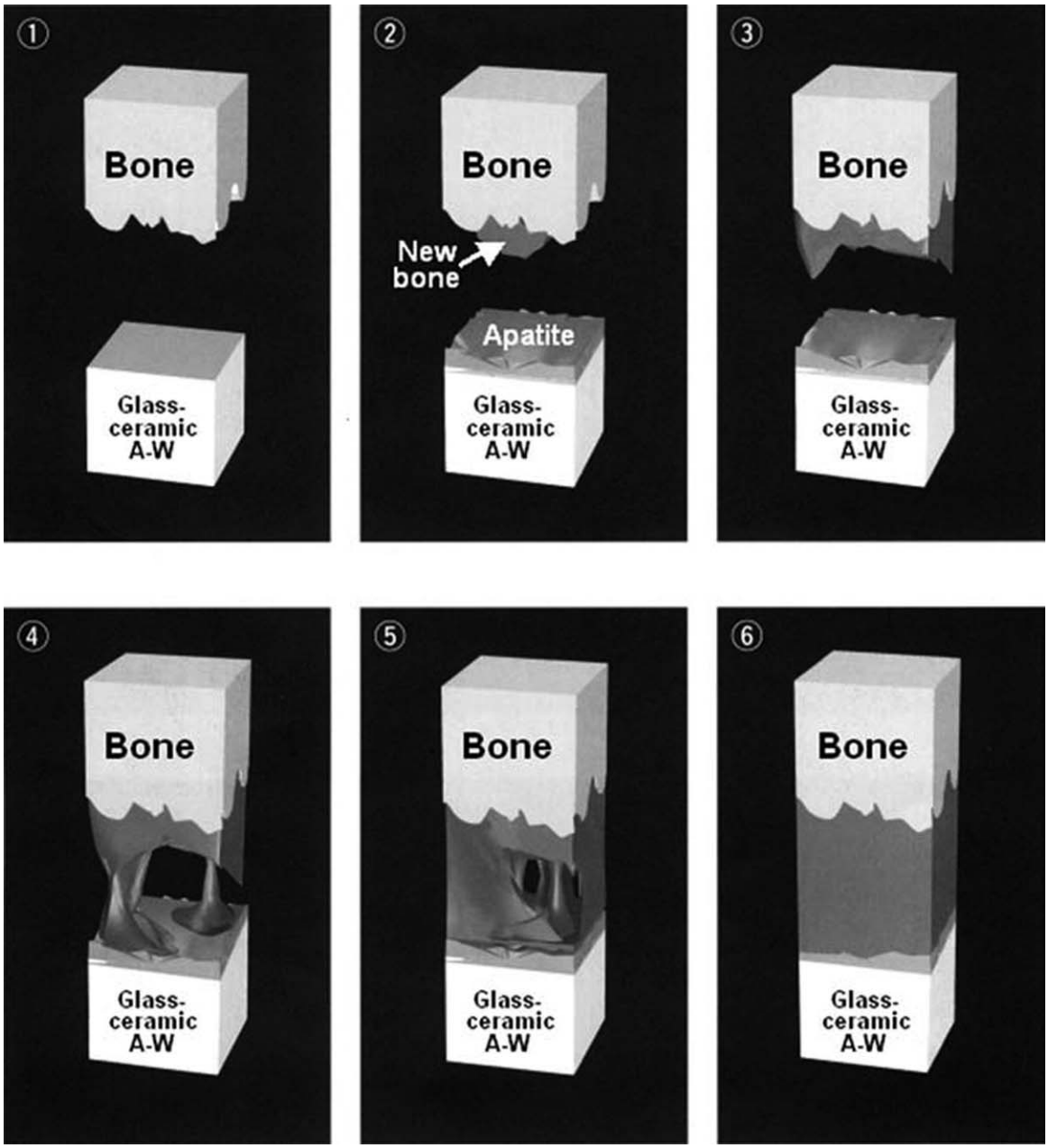

FIGURE 5. Bone-bonding mechanism for A-W GC: (1) just after implantation; (2) formation of bonelike apatite; (3) growth of new bone; (4) bonding of new bone with apatite layer; (5) and (6) increase in density of new bone.[5]

surgeries. In particular, lumbar intervertebral spacers and cervical laminoplastic spacers have been used in thousands of clinical cases with excellent clinical, radiological, and biomechanical results. A-W GC has also been used as a coating material of hip prostheses by the technique of coating on the porous surface. A mid-term follow-up study of several thousands of clinical cases of hip replacement demonstrated a significantly earlier osseointegration at the A-W GC bottom-coated area of the implant compared with a hydroxyapatite-coated implant.[5]

It has been clinically shown that the A-W GC is useful as a bone substitute and as a coating material. For further details about clinical applications of the A-W GC, readers are encouraged to refer to chapter 26 of Ref. [5].

BIOVERIT®

Definition

Bioverit® is the commercial name of two different types of GCs that contain mica-apatite and mica crystals. They are produced and distributed under the brand names of Bioverit® I and Bioverit® II by Vitron Spezialwerkstoffe, Germany. Bioverit® I and II are machinable. They can be easily cut, drilled and shaped by standard metal tools and instruments. Their workability depends on the mica content and

TABLE II. Bioverit® I and II (mica and mica-apatite GCs) compositions.[3]

	Bioverit® I	Bioverit® II
SiO_2	29.5–50	43–50
MgO	6–28	11–15
CaO	13–28	0.1–3
Na_2O/K_2O	5.5–9.5	7–10.5
Al_2O_3	0–19.5	26–30
F	2.5–7	3.3–4.8
P_2O_5	8–18	0.1–5
TiO_2	some	–

on the morphology of the GCs; for example, a GC with high mica content shows excellent machinability.[3]

The base glass compositions of Bioverit® I and II, which are produced via casting the melt in a metallic mold, are summarized in Table II.

Höland and Beall found that through the addition of Na_2O, K_2O and F to the SiO_2–Al_2O_3–MgO base glass, controlled crystallization takes place when the glasses are heated to form mica crystals. Interlocked, elongated, and plane mica crystals precipitate after liquid-liquid phase separation and the precipitation of other crystal phases, such as chondrodite ($Mg_2SiO_4{\cdot}2MgF_2$) and norbergite ($Mg_2SiO_4{\cdot}MgF_2$).[3]

However, if Na_2O, K_2O, F, and further additions < 3 wt % of CaO and P_2O_5 are introduced (Bioverit® II in Table II), then phase separation is greatly reduced, preventing the nucleation of the primary phase. As a result, a new curved mica crystal, which is called cabbage-head mica, develops in this Bioverit® II-type GC.[3] The SEM images in Figure 6 show the microstructure of elongated and cabbage-head mica GCs.

In this eight-component glass, if the CaO and P_2O_5 contents are considerably increased, a new mica-apatite GC, Bioverit® I, develops. This type of base glass shows the phase separation of two droplet-like phases. One phase is alkali-fluorine rich, and the other is rich in Ca, P, and F. After a twofold heat treatment of the glass between 750°C and 1100°C, mica and fluorapatite crystals precipitate. The formation of fluorapatite follows a homogeneous nucleation mechanism within the CaO-, P_2O_5-, and F-rich droplet phase at a lower temperature than mica nucleation.[3]

TABLE III. Mechanical properties of Bioverit® I and II.[3]

Properties	Bioverit® I	Bioverit® II
Density (g/cm^3)	2.8	2.5
Bending strength (MPa)	140–180	90–140
Compressive strength (MPa)	500	450
Young's modulus (GPa)	70–88	70
Hardness Vickers (GPa)	5	~8
Fracture toughness ($MPa{\cdot}m^{1/2}$)	1.2–2.1	1.2–1.8

Properties

Some mechanical properties of Bioverit® I and II are shown in Table III. The bonding strength of Bioverit® I to bone was measured by Höland et al. A value of approximately 2.3 MPa found for GC implants is eight times greater than that for Al_2O_3 implants. Bioverit® II is a biocompatible GC but with lower reactivity than Bioverit® I. An *in vivo* test has shown that bone intergrowth occurs without causing any adverse effects. Intergrowth takes place as if the implant were part of the body.[3]

Applications

After being approved in *in vivo* tests, Bioverit® I and II were accepted for application as bone substitutes in humans. More than 850 implants were successfully applied by 1992 in different orthopedic surgeries, particularly spacers and middle ear implants.[3,7] It has been reported that implanted Bioverit® II in the middle ear tends to be coated with an epithelial layer that exhibits not only the absence of inflammation but also a minimal osteogenic response and an antibacterial effect against gram-negative bacteria.[3,15] In 2009, to improve the bone-bonding ability of Bioverit® II, the coating of the implant with a nanostructured silica layer was proposed, and promising results in animal middle ear models (mice and rabbits) were reported.[16]

BIOSILICATE®

Definition

A recent comprehensive review of the literature on Biosilicate® is available.[17] In the mid-1990s, a great challenge was the development of a new material that could combine

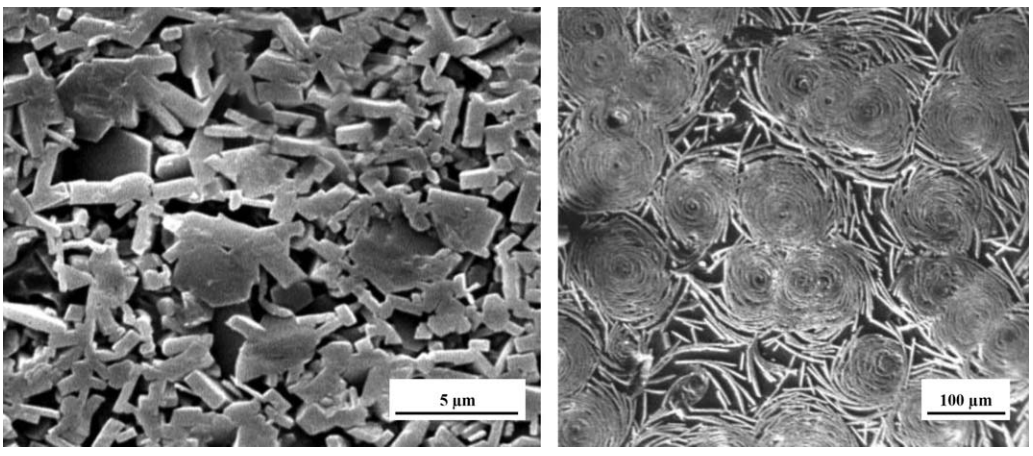

FIGURE 6. Microstructures of elongated and cabbage-head mica GCs. Reproduced from Ref. 3, with permission from John Wiley and Sons.

TABLE IV. A summary of the *in vivo* and clinical tests performed with Biosilicate®.[17]

Analysis		Applications and material form
In vivo	**Animal model**	
	Rat tibia	Solid particles, scaffolds and scaffolds + laser irradiation
	Rat calvaria	Monolithic discs
	Rabbit femur	Monolithic rod implants
	Rabbit eviscerated sockets	Orbital implants
	Dog mandibular socket	Coarse particles
	Guinea pig middle ear	Ossicle implants
Clinical	**Specialty**	
	Dentistry	Dentin hypersensitivity (fine powder)
	Ophthalmology	Orbital implants (monolithic)
	Otorhinolaryngology	Middle-ear ossicle implants (monolithic)

both high bioactivity, as shown by Bioglass® 45S5, and the good mechanical strength and toughness of GCs such as Cerabone®. A straightforward strategy to achieve this goal was to improve the mechanical strength of Bioglass® 45S5 or any other bioactive glass through controlled crystallization. However, two questions arose: (1) Does crystallization impair bioactivity? (2) Can the crystallization of such bioactive glasses significantly improve their mechanical properties?

In 1996, Peitl et al.[13] published a groundbreaking report that revealed that the crystallization of Bioglass® 45S5 slightly decreased the kinetics of HCA formation but did not inhibit its formation, even in the case of "full" crystallization. Later on, Peitl et al.[14] tested the *in vitro* bioactivity of GCs with different compositions and crystallized fractions within the Na_2O–CaO–SiO_2–P_2O_5 system. The result was similar: Crystallization did not hinder HCA formation for glasses of this system. The HCA layer forms fast on these GCs surface due to the presence of a soluble nonphosphate crystal phase with phosphorus ions in solid solution that are rapidly released to the medium, in a similar way to Bioglass® 45S5.[13,14] However, even the stoichiometric composition $1Na_2O$–$2CaO$–$3SiO_2$ without P_2O_5 was bioactive when fully crystallized. Peitl and Zanotto[13,14] gave their product the brand name Biosilicate®.

Biosilicate® is the designation of the composition $23.75Na_2O$–$23.75CaO$–$48.5SiO_2-4P_2O_5$ (wt %) and other compositions with minor modifications. Under controlled double-stage heat treatments, the microstructure of the material can be engineered to be composed of one or two crystalline phases: a sodium-calcium silicate phase ($Na_2CaSi_2O_6$) plus a sodium-calcium phosphate ($NaCaPO_4$) phase.[17]

Properties

Peitl et al.[14] showed that the controlled crystallization of glasses of the above system could increase their average 4-point bending strength by a factor of 2.8 compared with that of the parent glass (from 75 to 210 MPa). This value is similar to that found for the A-W GC (215 MPa), which exhibits the best mechanical performance among the commercial bioactive GCs. The elastic modulus also increased slightly, from 60 to 80 GPa, but it is still the closest value to that of human cortical bone (~20 GPa) among the commercial bioactive GCs. This characteristic is important to minimize "stress-shielding" effects. In addition, the fracture toughness increased by 60% to $\sim$ 1.0 $MPa{\cdot}m^{1/2}$ due to a crack deflection mechanism. Finally, Biosilicate® has the highest bioactivity index ($I_B > 8$) among all the commercial GCs.[17] Biosilicate® was also found to exhibit fair machinability. It is relatively easy to cut and drill, which is an important feature that allows for the fabrication of implants with different shapes for specific purposes and last-minute adaptations that are performed *in situ* by surgeons during surgical procedures.[17]

Applications

Several *in vitro* bioactivity tests using SBF have shown that the crystallization of the Biosilicate® parent glass, whether in solid or scaffold form, does not significantly affect the formation of HCA when soaked in SBF. Instead, it can even be improved, depending on the crystalline phases present. This result makes Biosilicate® a potential candidate for applications in which bone bonding or bone regeneration is desired. After 20 years of research, Biosilicate® was evaluated in different situations and by various *in vitro*, *in vivo*, and clinical tests, as shown in Table IV.[17] After successful *in vivo* tests on rabbits, 12 patients who had undergone enucleation or evisceration procedures were implanted with Biosilicate® orbitals (Fig. 7).[17]

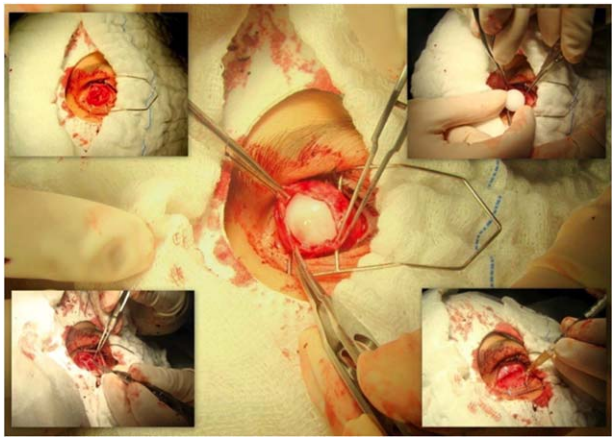

FIGURE 7. Implantation of a Biosilicate® orbital implant in a patient after an evisceration procedure. Courtesy of Drs. Simone M. Brandão and Suzana Matayoshi (Medical School, São Paulo State University, Botucatu, SP, Brazil).

CERAVITAL®

Definition

Ceravital is another osteoconductive GC that contains only apatite as the crystalline phase. Various GCs of the SiO_2–CaO–MgO–Na_2O–K_2O–P_2O_5 base system containing the main crystal phase of apatite were developed by Brömer et al. at the beginning of the 1970s, immediately following the development of Bioglass®. Later on, they were produced by the Leitz Wetzlar Company under the brand name Ceravital®.[9]

The composition range of Ceravital® GCs selected by Brömer et al. was (40–50)SiO_2–(30–35)CaO–(2.5-5.0)MgO–(5–10)Na_2O–(0.5-3)K_2O–(10–15)P_2O_5 in wt %. The GCs were fabricated by the melting-casting method followed by controlled heat-treatments. Nucleation was encouraged at 600°C for 24 h, and apatite crystallization took place after 24 h soaking at 750°C. Components such as 5–15 wt % Al_2O_3, 0–5 wt % Ta_2O_5 and 5–15 wt % TiO_2 were added to the base composition. Ceravital® contains apatite crystals with an average size of 40–50 nm.[9]

Properties and applications

The bioactivity of Ceravital is comparable to that of Bioglass® and higher than that of Cerabone®. However, it has much lower mechanical strength than human cortical bone. Its bending and compressive strengths are 100–150 and 500 MPa, respectively. Therefore, it has not been recommended for load-bearing conditions or orthopedic surgery. Commercial prosthetic ossicles are currently the unique clinical application of Ceravital® GC.[9]

MISCELLANEOUS BIOACTIVE GCs

In addition to those well-known 4 types of GCs, numerous studies have been published on, for example, apatite-mullite, canasite, oriented fluorapatite, chain silicate, chlorapatite, calcium pyrophosphate, rhenanite, and other GCs for biomedical applications.

Apatite-mullite GCs

In the mid-1990s, Hill et al.[18] introduced apatite-mullite GC as a potential bioactive GC with a good fracture toughness and mechanical properties. They prepared two series of glasses based on the (2-x)SiO_2–xP_2O_5–Al_2O_3–CaO–yCaF_2 composition: In the first series of glasses, y was fixed at 1, and x varied from 0 to 1; there was thus a systematic substitution of one silicon ion by two phosphorous. In the second series of glasses, x was kept constant at 0.5, and y was varied from 0 to 1. Glasses in which $x = 0.5$ and y was greater than 0.5 crystallized to fluorapatite and mullite. Crystallization occurred by a bulk nucleation mechanism involving prior amorphous phase separation. The glass with $x = 0.5$ and $y = 0.5$ was converted into a GC consisting of elongated fluorapatite crystals that had a relatively high fracture toughness. They have reported fracture toughness values of 1.0 to 3.3 MPa·$m^{1/2}$, a bending strength of 90–330 MPa and a Young's modulus of 70–90 GPa.[18–20]

Later, Goodridge et al.[21] reported on the biological properties of apatite-mullite GCs produced via laser sintering for use as tissue-engineered scaffolds. Some apatite-mullite GCs did not form HCA *in vitro* after immersion in SBF. There were no pH changes following immersion and no significant ion release into the SBF solution. However, they show osseointegration *in vivo* with no sign of fibrous capsule formation. On the contrary, some glasses are degradable and form HCA in SBF but do not osseointegrate *in vivo*. The *in vitro* and *in vivo* responses of this GC depend on the presence of the crystalline and residual glass phases. The GC, which crystallized to apatite but had not crystallized to mullite, osseointegrated poorly. The sample crystallized to both apatite and mullite exhibited better osseointegration and evidence of osteoconduction. Increasing the apatite volume fraction in the glass appears to increase the osseointegration ability. The residual glass phase may add to osseointegration by promoting apatite formation or may hinder osseointegration if the glass phase degrades and releases ions such as Al^{3+}, which are known to inhibit biological mineralization. In the case of aluminum-containing GC compositions, it is important that all the aluminum ions be either locked away in a chemically inert glass phase or in a chemically inert crystalline phase (Even trace amounts of the order of 1 ppm of aluminum are known to inhibit the mineralization of a newly forming osteoid). The SBF test developed by Kokubo is widely used as a predictor of bioactivity and the ability of a bioceramic to osseointegrate. Although Hill says that this test is applicable for bioactive glasses and A-W GC, its value with regard to aluminum-containing glasses and GCs should be questioned. It seems that extensive research is still being conducted on these GCs as bioactive bone substitutes or implant under the supervision of Profs. Hill, Wood, and Stanton in the UK and Ireland.[18–22]

Canasite-based GCs

G. Beall and his team at Corning developed glasses based on a fluorocanasite ($Ca_5Na_4K_2Si_{12}O_{30}F_4$) composition that was made by the melting-casting method and then crystallized into a GC. They managed to produce materials with a high content of fluorocanasite crystals that displayed significant fracture toughness up to 4 MPa·$m^{1/2}$.[5,6] Then, in 1994, Wolcott[23] managed to develop apatite-canasite GC by the controlled crystallization of two phases from a (42–70)SiO_2–(6–12)Na_2O–(3–10)K_2O–(20–30)CaO–(3–11)F–(2–13)P_2O_5 (wt %) base glass composition with additions of B_2O_3, Al_2O_3, and ZrO_2 up to 6 wt %. Controlled crystallization was carried out in a temperature range of ~580°C–640°C for nucleation and 900°C–950°C for crystallization. Canasite was formed by heterogeneous nucleation on the CaF_2 primary crystals. The crystallization of apatite, however, takes place during the nucleation of the droplet glass phase rich in Ca and P. Apatite-canasite GCs have high fracture toughness, up to 3.9 MPa·$m^{1/2}$, combined with bioactive properties. Therefore, the material has been suggested for use as a biomaterial for replacing bone tissue.[23]

In 2002, Miller et al.[24] and Barros et al.[25] investigated the *in vitro* and *in vivo* properties of canasite-based GC. Miller et al.[24] modified the composition by either increasing

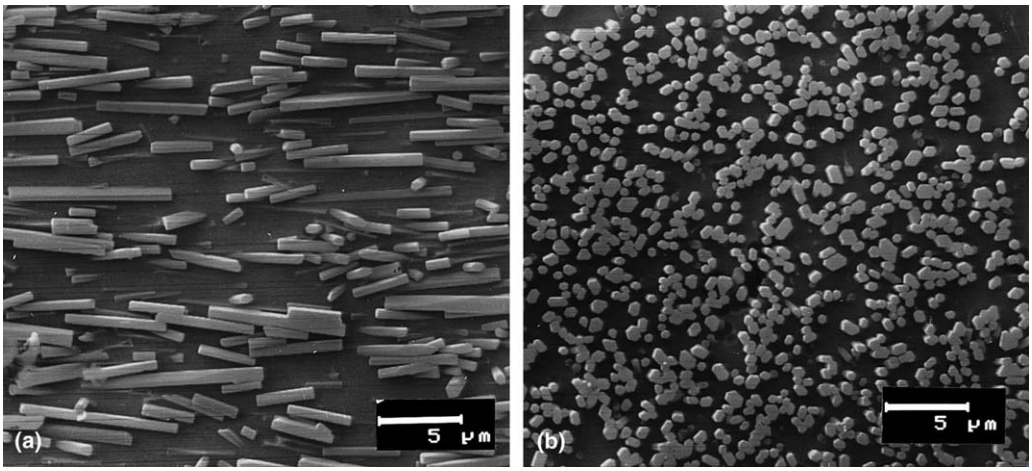

FIGURE 8. SEM-micrograph of an oriented fluorapatite GC prepared by extruding of the GC (previously crystallized at 1200°C). (a): cut parallel to the extrusion direction; (b): cut perpendicularly to the extrusion direction.[31]

the concentration of calcium in the glass or by adding P_2O_5. Samples of these novel materials were placed in simulated body fluid (SBF), along with a control material (commercial canasite GC), for periods ranging from 12 h to 28 days. No apatite was detected on the surface of commercial canasite, even after 28 days of immersion in SBF. A crystalline apatite layer was formed on the surface of a P_2O_5-containing canasite after 5 days and after 3 days for calcium-enriched canasite.[24] However, *in vivo* bone tissue response to canasite GC evaluated by Barros et al.[25] revealed that the canasite formulation is not osteoconductive and degrades in the biological environment. They therefore concluded that the canasite formulation was inappropriate for use as implants.[25] Further work is required to improve the biocompatibility of these materials with bone tissue. It is possible that this could be achieved by reducing the solubility of the glass and GC[25] because there should be an optimum level of solubility. High soluble materials will not remain in the body after implantation.

Later on, the canasite glass composition was further modified by Mirsaneh et al.[26] at Sheffield University when they tried to develop a new GC based on another chain-silicate mineral, K-fluorrichterite ($KNaCaMg_5Si_8O_{22}F_2$, KFR). The authors knew that excess CaO in canasite-based GCs enhances their bioactivity. Therefore, two new GC compositions were fabricated with 5 mol % CaF_2 (glass A) and 5 mol % CaO (glass B) substituted for MgO in the KFR formula. For glass A, the fracture toughness (2.7 $MPa{\cdot}m^{1/2}$) and biaxial flexural strength (227 MPa) were optimized for samples crystallized at 900°C for 4 h. In glass B, however, the best toughness (2.1 $MPa{\cdot}m^{1/2}$) and strength (217 MPa) were obtained after treatment at 950°C. In view of their excellent mechanical properties and castability, these GCs were considered potential candidates for the fabrication of custom medical devices in restorative dentistry and moderate load-bearing reconstructive bone surgery.[26]

Bhakta et al.[27–29] investigated some *in vitro* and *in vivo* characteristics of modified K-fluorrichterite GCs. They modified the composition by either increasing the concentration of calcium or by addition of P_2O_5 and suggested that an apatite forming ability of the materials (seen in SBF tests) is responsible for osteoconductivity.[27] *In vitro* biocompatibility assessment, including investigation of solubility, ion release, and cell culture indicated that potassium fluorrichterite GCs appear to be biocompatible.[28] Osteoconductivity was investigated by implantation into defects in the midshaft of rabbit femora. All samples showed direct bone tissue contact with evidence of new bone formation and cell proliferation along the implant surface into the medullary space. There was no evidence of bone necrosis or fibrous tissue encapsulation around the test specimens. A P_2O_5-containing K-fluorrichterite GC showed the greatest promise as a bone substitute for load-bearing conditions due to its osteoconductive potential and good mechanical properties ($K_{IC} = 2.7$ $MPa{\cdot}m^{1/2}$ and MOR = 250 MPa), but further investigations, for example, clinical tests are still required.[29,30]

Oriented fluorapatite GCs

At Friedrich Schiller University in Jena, Germany, Moisescu et al.[31] tried to improve the mechanical properties of apatite GCs by developing orientated needle-like apatite crystals within the glass matrix. They selected GCs with bioactive properties in the systems $24.5SiO_2-16.8Al_2O_3-18.3P_2O_5-16.4CaO-16.2Na_2O-7.8F^-$ (wt %) and $26.2SiO_2-17.9Al_2O_3-19.6P_2O_5-17.5CaO-10.5K_2O-8.3F^-$ (wt %) and demonstrated that anisotropic apatite crystals can be oriented in the glassy matrix by extruding the GC at high temperatures.[31] Figure 8 shows the typical microstructure of these GCs.

Oriented mica GCs have also been developed by hot extrusion. Habelitz et al.[32] reported that the fracture toughness varies in direction by approximately 350%, the Knoop-microhardness varies by approximately 30%, and the Young's modulus varies by approximately 15%. Through a comparison with randomly oriented mica GC, an enhancement of the mechanical properties was obtained in the direction perpendicular to the extrusion axis.[32]

Bioactive rhenanite GC

Apel, Höland and Rheinberger[33] have registered a patent for a new bioactive GC. They designed a glass composition of (29.5–70.0)SiO_2–(5.5-23.0)CaO–(6.0-27.5)Na_2O–(2.0-23.5)P_2O_5–(0–1.5)F in wt % (for example, 58SiO_2−12.9CaO–22.9Na_2O–6.0P_2O_5−0.3F in wt %[3,34]) and claimed that their GCs contained rhenanite, β-$NaCaPO_4$, as the main crystal phase.[33] The bioactive residual glass phase contributes to quick apatite formation due to its high solubility in SBF, whereas the osteoconductive-acting rhenanite crystal phase leads to a slower apatite formation but guarantees the improved mechanical stability of an implant. This double mechanism of the reactivity of the GC allows for the control of the bioactivity and is a particular advantage of this material. This GC is preferably free of Al_2O_3 because it reduces the bioactivity and the formation of apatite.[33]

The solubility of this particular GC is lower than that of known bioactive glasses. Its reduced solubility prevents it from being transported away from the implantation site before new bone can form. In addition, the decomposition and conversion rates are not as high as with the glass-free phosphates in which the processing time and storage stability of biocompatible materials are limited by the rapid chemical conversion of materials for apatite formation. As a result of the variation of the crystalline proportion of rhenanite in the GC, control of the kinetics of apatite formation is possible, and GCs with 4–50 wt % rhenanite are preferred.[33,34]

Bioactive calcium pyrophosphate GCs

In 1998, Kasuga et al. developed bioactive calcium phosphate glasses and GCs in the pyrophosphate region. They have published comprehensive reviews on the processing, properties and promising applications of their novel materials.[35,36] Kasuga and his team first synthesized glasses of the system xCaO–(90-x)P_2O_5−10TiO_2 in mol %, where $x \leq 62$. Then, they showed that glasses containing CaO > 55 mol % do not have a long phosphate chain structure; they are invert glasses containing ionic pyrophosphate and orthophosphate groups, which are connected through Ca^{2+} or Ti^{4+}. They reported that the apatite did not form on these phosphate glasses with $x \leq 55$ in SBF. However, bonelike apatite particles were detected on the phosphate invert glass with 60CaO–30P_2O_5−10TiO_2.[35,36]

Later on, Kasuga et al. included Na_2O in the glass composition to enhance its bioactivitiy and sinterability. When 60CaO–30P_2O_5–yTiO_2–(10-y)Na_2O glass powders ($y = 3$, 5) below 10 μm were isostatically pressed at 100 MPa and subsequently heated at 800°C–850°C in air, dense GCs with relative densities >93% were prepared. The resulting GCs contained bioactive crystalline phases such as β-$Ca_3(PO_4)_2$ (β-tricalcium phosphate) and β-$Ca_2P_2O_7$ (β-calcium pyrophosphate). Apatite formed on the 60CaO–30P_2O_5−3TiO_2−7Na_2O GC after soaking in SBF for 14–20 days. However, apatite-forming ability significantly improved to 3–10 days after a hydrothermal treatment in distilled water at 120°C–160°C. Negatively charged, hydrated titania groups and anatase crystals on the surface stimulated the nucleation of apatite after a short time.[35,36]

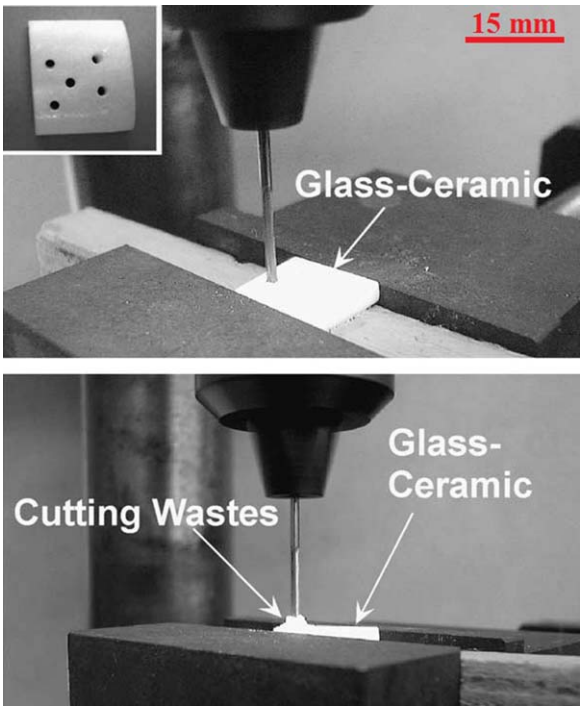

FIGURE 9. Drilling test of the calcium pyrophosphate GC. The diameter of the drilling tool is 1.5 mm and the rotation speed was 1800 rpm. A load of 19.6 N was constantly applied. The insert in the upper photograph is a result of the test. Five holes were easily drilled without chipping. Reproduced from Ref. 35, with permission from Elsevier.

Fracture toughness and bending strength of the 60CaO–30P_2O_5−3TiO_2−7Na_2O GC was estimated to be 1.8 MPa·$m^{1/2}$ and 100 MPa, respectively. However, the bending strength of hot-pressed samples with relative density ≥99% was 160 MPa. We agree with Kasuga that the main advantage of his material or other bioactive GCs over HA or β-TCP bioceramics is that they can be easily machined using conventional tools rather than diamond tips. As shown in Figure 9, both 60CaO–30P_2O_5−3TiO_2−7Na_2O and 60CaO–30P_2O_5−5TiO_2−5Na_2O GCs can be successfully drilled using a conventional carbide tool without chipping.[35] The machinablity is suggested to result from the interlocking platelike microstructure of β-calcium pyrophosphate crystals dispersed in the glassy matrix phase (similar to microstructure of the mica GC in Fig. 6).[35,36]

This GC has been used to coat Ti-based implants and synthesize macroporouse scaffolds.[37,38] It seems that experiments to prepare biomedical material devices for dental and plastic surgery using these calcium pyrophosphate GCs are still in progress.[35,36,39]

Bioactive chlorapatite GCs

Recently, Chen et al.[40] under the supervision of Robert G. Hill reported on the development and characterization of new bioactive GCs based on chlorapatite. They believed that chlorapatite GC would be more interesting than fluorapatite for medical and dental applications, because it is more soluble than fluorapatite and will convert completely to hydroxyapatite in the presence of water.[40] They developed

numerous GCs derived from a wide range of glass compositions of (30.3-38.1)SiO_2–(44.1–55.5)CaO–(5–6.3)P_2O_5–(3–13.2)CaF_2–(1.1-20.6)$CaCl_2$ after adequate heat-treatment at 10°C above crystallization temperature. The GCs contained mixed chlor/fluor-apatite and wollastonite depending on the glass composition and heat-treatment schedule. They concluded that the chloride-containing glasses are very reactive and appear to react with atmospheric water. Therefore, further investigation is required to develop practical chloroapatite and mixed chlor/fluor-apatite GCs and to study their *in vitro* and *in vivo* biocompatibility.[40]

Alkali-free bioactive GCs

In recent years, J.M.F. Ferreira's group has designed and developed a series of alkali-free bioactive CaO–MgO–SiO_2–P_2O_5–CaF_2 glasses and GCs, which is along the diopside ($CaMgSi_2O_6$) – fluorapatite ($Ca_5(PO_4)_3F$) – tricalcium phosphate ($3CaO.P_2O_5$) join.[41–43] The authors were successful in sintering their glasses to appropriate density with good bending strength. They believe the unfavorable effects of alkali ions on the sintering and crystallization behaviors of glasses can be avoided by choosing alkali-free compositions. Additionally, crystallization of a chain silicate mineral, like diopside, with elongated and interlocking morphology, would contribute to the enhancement of mechanical properties. It seems that their materials have proper structure and crystalline phases (diopside and hydroxyapatite) in order to trigger bioactivity and improve the mechanical properties. Preliminary *in vitro* tests and strength measurements are promising, but *in vivo* experiments still need to be performed.[41–43]

COATINGS AND COMPOSITES

Most of the bioactive GCs previously discussed form a mechanically strong interfacial bond with bone. The strength of the bond is generally equivalent to or greater than the strength of the host bone. Therefore, all those bioactive GCs have excellent biochemical compatibility. However, their fracture toughness is typically less than and the elastic modulus is greater than those of bone, indicating that most bioactive GCs have a suboptimal biomechanical compatibility when used in load-bearing applications. Two approaches examined to overcome this problem were the development of bioactive GC composites and the development of coatings.[44]

Bioactive GC coatings

One approach for solving the mechanical restrictions of bioactive GCs for load-bearing applications is to apply them as a coating on a mechanically tough substrate.

A-W GC (Cerabone®) has been used for this function. Takatsuka et al.,[45] Li et al.,[46] and Kitsugi et al.[47] tried to apply an A-W GC on Ti-6Al-4V and Al_2O_3 implants. Takatsuka et al.[45] modified the A-W GC by removing CaF_2 and adding B_2O_3. A Ti alloy plate coated with this GC was implanted into the tibiae of rabbits for 2, 3, 4, 8, and 25 weeks. Then the detaching failure loads of the coated plates were compared with those of conventional A-W GC plates, hydroxyapatite (HA) plates, and uncoated Ti alloy plates implanted in the same way. The failure load of the coating was as high as that of the A-W GC for all periods, whereas at 3 and 4 weeks it was significantly higher than that of HA. Uncoated Ti alloy showed lower failure loads for all periods, differing significantly from the other materials. Histological examinations by contact microradiographs (CMR), Giemsa surface staining, and SEM showed that the coating bonded directly to bone without any intervening soft tissue layer. Those results indicate that the coating has earlier bone-bonding ability than pure Ti and good mechanical strength, making it a promising veneer material.[45] Li et al.[46] applied the same GC coating on Al_2O_3 implant and performed *in vivo* test in femoral condylus of mongrel dogs. They suggested that A-W GC stimulated bone ingrowth. The bonding behavior of bioinert Al_2O_3 ceramics was, therefore, improved by the coating.[46] Later on, Kitsugi et al.[47] further explored the bone-bonding behavior of plasma spray coatings of A-W GC on Ti-6Al-4V in comparison to Bioglass 45S5 and β-tricalcium phosphate (TCP) coatings. A rectangular specimen was implanted into the tibial bones of mature male rabbits, which were sacrificed 8 or 24 weeks after implantation. Eight weeks after implantation, the failure loads for implants coated with Bioglass, A-W, and TCP were 1 ± 1, 2 ± 1, and 4 ± 2 kg, respectively, and 24 weeks after implantation, the respective failure loads were 3 ± 1, 2 ± 1, and 4 ± 1 kg.[47] It thus appears impossible to obtain a higher failure load using a bioactive-ceramic coating on titanium alloy. Histologically, the coating layer was found to detach from the metal implant and the bone tissue bonded to the coating layer. Those scientists believed that for clinical application, it would be better to use coated metal implants for short-term implantation. However, there is a possibility of breakage of the coating layer because of dissolution of the bioactive ceramic and the mechanical weakness at the interface between the coating and the metal implant.[47]

In another series of experiments, A-W GC particles have been added to a sol made from tetraethyl-orthosilicate (TEOS) and methyl-triethoxysilane (MTES) in order to prepare a hybrid coating. The TEOS–MTES–SiO_2 + bioactive GC coatings on 316 L stainless steel promoted the formation and growth of HCA during *in vitro* tests when the amount of SiO_2 particles was 10 mol %. The stiffness of the newly formed bone *in vivo* seems to be similar to the values for old cortex bone, showing short periods of maturation and mineralization of newly formed bone tissue around the implant.[48]

Similar hybrid coatings of silica sol containing bioactive GC particles ($57.44CaO–35.42SiO_2–7.15P_2O_5$ in mol %) were prepared and applied by Dr. Durán's group on stainless steel, cobalt based alloys and titanium alloys.[49,50] The coating on the metallic alloys triggered bioactivity and improved the corrosion resistance. This improvement could be due to the reaction of the particles with the physiological medium, which encourages the formation of HCA, and blocks the porosity of the coating.[49,50]

Ignatius et al.[51] evaluated the osseointegration of Al_2O_3 coated with Bioverit® I, in a load-bearing implant model in sheep in comparison to uncoated Al_2O_3 and to a minimally

loaded situation. Both types of implants were inserted into the proximal tibia (load-bearing model) and in a drill hole defect into the tibia diaphysis (minimally loaded model). They suggested that the osseointegration of Al_2O_3 could be improved by the coating under load-bearing conditions, under which uncoated Al_2O_3 ceramics cannot directly bind to bone.[51]

An apatite-mullite GC has been tested as coating on Ti-6Al-4V implants.[52–55] Some modified glass compositions have been applied by electrophoretic deposition,[52] sputtering,[53] and enameling.[55] The glasses showed good sinterability and fully crystallized below the $\alpha \rightarrow \beta$ transformation of the Ti-6Al-4V, viz., 970°C. Initial bioactivity tests in SBF showed that these coatings are biologically active and have good adhesion, and evidence for an interfacial reaction between the coating and substrate.[52–55]

Calcium pyrophosphate GC have been also used to coat Ti-based implants.[37,56–58] Kasuga et al.[37,56,57] prepared a fine coating consisting of a bioactive calcium phosphate GC by reaction of the glassy phase with an oxide layer formed on a new β-type titanium alloy, Ti-29Nb-13Ta-4.6Zr (TNTZ), when the metal, on which the mother glass powders with a composition of $60CaO–30P_2O_5–7Na_2O–3TiO_2$ (mol %) were placed, was heated at 800°C in air. A compositionally gradient layer was developed on the titanium alloy. The tensile bonding strength of the coating to the metal (20–25 MPa) was significantly higher than those of the coatings to conventional metals such as Ti-6Al-4V alloy or pure titanium.[56,57] A rod-shape coated TNTZ-alloy of 5 mm diameter $\times$ 10 mm in height was implanted into a femur of a Japanese rabbit. The sample was autoclaved in water at 121°C for 1 h to accelerate bioactivity. Figure 10 shows contact microradiographs (CMR) after 52 weeks of implantation. No significant change in the thickness of the GC coating layer after the implantation was observed. The examination shows new bone formation around the autoclaved GC-coated TNTZ. When the samples after 52 weeks of implantation were sliced and polished for observation, no crack occurred between the coating and bone or between the coating and TNTZ, while crack propagation was seen to have a tendency to occur between the TNTZ (sample without the coating) and bone. Kasuga[57] concluded that the GC coating on TNTZ had excellent bioactivity and could be applicable in surgical implants, such as Kirschner-wires and hip joints, which need to be bioactive.[57] The fatigue endurance limit of the coated alloy was found to be about 15% higher than that of uncoated alloy.[58]

Bream et al.[59,60] have used two novel methods to coat Ti alloy with bioactive GCs. In one research, two sol-gel-derived bioactive glasses were applied by sol impregnation into the open porous network of Ti alloy with a pore throat size of 1–20 μm. The gel-glasses of $60SiO_2–35CaO–5P_2O_5$ (wt %) and $60SiO_2–20CaO–15Na_2O–5P_2O_5$ (wt %) were converted to micrometer thin bioactive GCs by an appropriate heat treatment, while the original porosity and the open pore structure of the Ti coatings were maintained.[59,60] The tensile adhesion strength of coatings was 22–29 MPa.[59,60] In their work, they have deposited a bioactive GC layer by

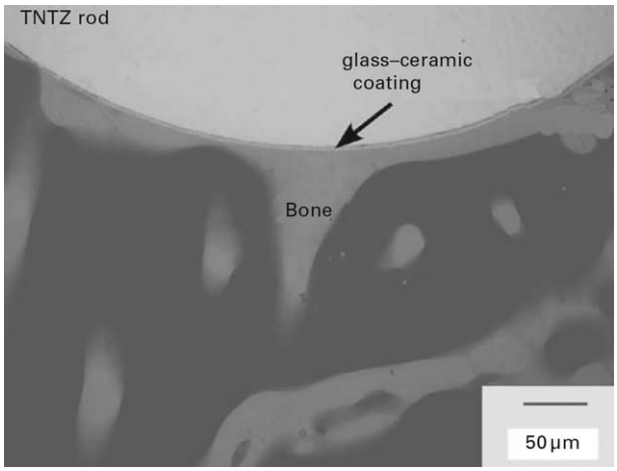

FIGURE 10. CMR image from calcium pyrophosphate GC-coated TNTZ rods after 52 weeks implantation into the femurs of rabbits. Reproduced from Ref. 57, with permission from Elsevier.

electrophoresis on flat Ti alloys. Uniform coatings with thickness of 8 μm were applied by cathodic deposition from nonaqueous suspensions followed by sintering in vacuum, avoiding uncontrolled oxidation of the Ti substrates. The tensile bond strength of the coating was 41 ± 11 MPa.[59,60] These two researches suggested feasible techniques to apply coatings with good mechanical adhesion on commercial implants, which have complex shapes.[59,60]

Mg alloys have been also coated using the dip-coating method and sol-gel-derived 45S5® glass.[61–64] Sol concentration, calcination temperature and the dip-coating cycle have been optimized to prepare compact coatings. The results showed that homogeneous and crack-free coatings with a thickness of 0.50-1.00 μm, consisting of an amorphous phase and $Na_2Ca_2Si_3O_9$ crystals were successfully fabricated on magnesium alloy (AZ31).[61] The coating encouraged bioactivity and showed good adhesion resistance.[61–64]

Good examples of research to develop bioactive GC coatings on metallic alloy, alumina and zirconia implants were reported by Verné and her co-workers.[65–68] Verné et al.[65] prepared double-layer bioactive GC coatings on Ti–6Al–4V substrates by dip coating and firing. A $61.1SiO_2–12.6CaO–10.3Na_2O–7.2MgO–6.0P_2O_5–2.8K_2O$ in wt % based glass was used as the first layer in direct contact with the metallic substrate, and a $26.2SiO_2–17.9Al_2O_3–17.5P_2O_5–10.5K_2O–19.6CaO–8.3F^-$ in wt % based GC was used as the outer bioactive layer. They designed that low-melting intermediate glass composition to be able to work below the $\alpha \rightarrow \beta$ transformation of the Ti alloy and to ensure the adhesion of the outer bioactive layer. The intermediate layer was also chosen to match the thermal expansion coefficient of both the metal and the outer GC. The process used for the coating did not affect the bioactivity of the GC surface and did not modify either the nature of the crystalline phases (needle-like fluorapatite) or their shape. Their method has been recommended to coat Ti–6Al–4V screws for dental applications.[65]

Verné et al.[66] also managed to coat pure and dense Al_2O_3 substrates by a similar GC. Through a careful

optimization of the coating process, they obtained coatings approximately 200 μm thick. The results revealed that to obtain adherent and low-porosity coatings on alumina substrates, the above GC should be used, with very short thermal treatments at a temperature slightly above 1300°C. Lower temperatures did not guarantee a satisfactory degree of adherence between the substrate and the coating and moreover gave the GC coating an excessively high degree of porosity. By optimizing the time and temperature schedule, they could minimize the alumina diffusion through the GC. A further thermal treatment at 1200°C was required to promote the needle-like fluorapatite crystallization.[66]

Ferraris et al.[67] reported that glazing can be successfully used to coat zirconia by bioactive GCs. An intermediate layer often forms between the coating and the substrate, for example, between a glass coating and a zirconia substrate, there is a "composite" layer made of glassy phase and zirconia particles. During the thermal treatment above its liquidus, the glass diffuses within the zirconia substrate; hence, the zirconia granules are surrounded by a glassy matrix, leading to the formation of a "composite" layer, which assures the continuity of the thermal and mechanical properties from the zirconia substrate to the glass coating. The osseointegration of bioactive glass-coated zirconia cylinders has been evaluated in an animal model and compared to uncoated cylinders.[67] After 30 days, the bone bonding was better than that of the uncoated cylinders, but after 60 days, the difference was within statistical uncertainty.[67]

For further reading about the processing, properties, and challenging issues related to bioactive GC-coated implants, readers are encouraged to refer to a book chapter by Verné, which recently reviewed the literature related to bioactive glasses and GCs coatings.[68]

More recently, Marghussian[69] classified nanostructured bioactive GC coatings for biomedical applications. He concluded that "all the coatings that are produced as amorphous or glassy layers in the first stage of their fabrication process, and subsequently are subjected to a controlled heat treatment, in order to transform them into partially crystalline products, can structurally be classified as glass-ceramic coatings."[69] As an example of the development of this type of nanostructured coating, Xiao et al.[70] attempted to deposit bioactive GC coatings on titanium substrates by the liquid precursor plasma spraying (LPPS) process. Tetraethyl orthosilicate, triethyl phosphate, calcium nitrate, and sodium nitrate solutions were mixed together to form a sol after hydrolysis, and the liquid suspension was used as the feedstock for the plasma spraying of P_2O_5–Na_2O–CaO–SiO_2 bioactive GC coatings. Bioactive GC coatings with nanostructures were successfully synthesized, and the coatings showed a quick formation of a nanostructured HCA layer after being soaked in SBF. Overall, their results indicate that the LPPS process is an effective and simple method to synthesize nanostructured bioactive GC coatings with good *in vitro* bioactivity.[70] Wang et al.[71] utilized the same technique to coat a Ti-alloy with nanostructured bioactive hardystonite ($Ca_2ZnSi_2O_7$) and sphene ($CaTiSiO_5$) GC.

Composites

Ceramic and metallic reinforcements. Materials with high fracture toughness, such as metallic or ceramic phases, are utilized to reinforce bioactive glasses or GCs. The reinforced bioactive GCs are usually improved in both the bending strength and the fracture toughness. For example, Kasuga et al.[72,73] reinforced well-known A-W GC with zirconia particles, performed *in vivo* tests, and reported that by using a controlled crystallized glass powder and zirconia powder as raw materials, a sintered body densified to near its theoretical density by hot isostatic pressing (HIP). This bioceramic exhibited an extremely high bending strength of 400–1000 MPa and a fracture toughness of 3–5 $MPa{\cdot}m^{1/2}$ for 30 to 80 vol % of zirconia.[72,73] Montazerian et al.[74,75] also used zirconia to reinforce mica and mica-apatite GCs, and both the bending strength and the fracture toughness were improved. The addition of 15 wt % ZrO_2 to the GCs increased the 3-point bending strength from 50 to 130 MPa, and the fracture toughness was doubled from 0.7 to 1.4 $MPa{\cdot}m^{1/2}$.[74,75] Rawlings[76] reviewed early researches related to metal-reinforced bioactive glasses and GCs in 1993, when there was a growing interest on this topic. He reported on the processing and properties of GC matrix composites reinforced with silver, titanium, Co-Cr alloy, stainless steel, and aluminum. He showed that the strength of the composites was 26–47% greater than that of the monolithic matrix. The *in vitro* and *in vivo* characteristics of such composites have also been investigated; for example, Ag- and Ti-reinforced bioactive GCs showed no adverse effects on the osteointegration or biocompatibility of the composite.[76–78] One disadvantage of GCs reinforced with ceramic or metallic phases is that they are generally denser; they all have elastic moduli much greater than the bone and thus may cause stress shielding of a bone under stress.[76]

GC-reinforced polymers. It has been demonstrated that biopolymers have a closer modulus of elasticity to bone than ceramics and metals. Therefore, stress shielding effects diminish when these polymers are used in the vicinity of bone. However, the lack of mechanical strength and bioactivity are well-known drawbacks of polymers that limit their applications for load-bearing conditions. Therefore, numerous attempts have been made to develop a biopolymer matrix composite reinforced with bioactive GCs.[79]

It has been discussed that Bioglass® is highly bioactive, but its mechanical properties are low. In contrast, for example, Cerabone® and Biosilicate® have much better mechanical properties while still possessing high bioactivity. Particulate Cerabone® can be used as a stiffer reinforcement in the composite while still providing the composite with a much higher bioactivity than hydroxyapatite (HA) particles.[79–81] Therefore, the processing technology established for HA/polyethylene composites (also known as HAPEX® since 1995, when Smith & Nephew Richards Inc. introduced their series of middle ear implants made of the composite) has also been used for producing the Cerabone®/polyethylene composite.[79–81] Young's modulus and the microhardness of the composite also increased with an increase in GC

volume fraction as the tensile strength and fracture strain decreased. Even with 40 vol % of GC particles, the composite exhibited considerable ductility.[79–81]

Despite the enormous numbers of studies on bio glass/polymer composites, there are a few studies related to bio GC/polymer composites.[82] It seems that in most cases, the conversion of glasses to GCs reduces the bioactivity as an essential role of these reinforcements. However, highly bioactive glasses or GCs (e.g., Biosilicate®) can be successfully used to develop polymer-based composite or new hybrid materials.[83]

BIOACTIVE GC SCAFFOLDS

Bioactive GCs are very attractive materials for producing scaffolds dedicated to bone regeneration due to their versatile properties, which can be properly designed depending on their composition. Scaffolds should possess 3D interconnected porosity to support vascularization to encourage cells to grow into the required physical structure. A typical porosity of 90% along with a pore diameter of at least 100 μm is required for the proper vascularization of the tissue. For making scaffolds, almost every bioactive glass is sintered to a specific density and shape, which leads to the nucleation and growth of crystalline phases embedded in a residual glass matrix. These crystallized phases must not induce any cytotoxic effect or hinder any bioactive process inside the cell/tissue. An advantage of crystallization is that it improves the mechanical properties.[84]

A comprehensive review of the state of the art in bioactive glasses and GCs scaffolds was authored by Gerhardt and Boccaccini.[85] Furthermore, in their review article, Fu et al.[86] concluded that "use of inorganic scaffolds is still limited by their inherent brittleness (low fracture toughness; in the range of 0.4–0.7 $MPa{\cdot}m^{1/2}$)."[86] They believe one approach to minimize this problem would be the development of bioactive GC scaffolds.[86] Although the fracture toughness values (1–3 $MPa{\cdot}m^{1/2}$) of monolithic bioactive GCs are in the lower range of cortical bone (2–12 $MPa{\cdot}m^{1/2}$), they are much tougher than bioactive glasses (K_{IC} = 0.4-0.7 $MPa{\cdot}m^{1/2}$).[85,86] Therefore, GC scaffolds may have a combination of higher strength and toughness (due to their unique toughening mechanisms) than glass scaffolds.[85,86] For example, the fracture toughness of sintered 45S5® glass is quite low ($K_{IC} \sim 0.5$ $MPa{\cdot}m^{1/2}$) and scaffolds made from this glass have very low mechanical strength, approximately 0.5 MPa.[87–89] On the other hand, relatively stronger scaffolds can be made from bioactive GCs that may be candidates for load-bearing sites.[85,86] Therefore, almost all commercial bioactive GCs and others being developed have been the subject of study for scaffold development using various fabrication techniques, including, for example, foam-replication methods, salt or sugar leaching, thermally induced phase separation, microsphere emulsification sintering, electrospinning to form nanofibrous structures, computer-assisted rapid prototyping techniques and so forth.[85,86,90–93] More recently, Fiocco et al.[94,95] and Elsayed et al.[96] have used novel approach based on the use of preceramic polymers to develop porous bioactive GCs. GCs derive from thermal treatment of preceramic polymers, in the form of silicone resins, containing micro- and nanosized filler powders such as Ca/Mg-carbonate, Na-carbonate, Na-phosphate or even glass particles.[94–96] Shaping, especially in the form of highly porous scaffolds, can be easily obtained using conventional polymer-forming technologies (e.g., direct foaming or extrusion). The synthesis proceeds after the reaction between silica, provided by the thermo-oxidative decomposition of the silicone resins, and the fillers at approximately 1000°C. GCs based on the composition of 45S5 and 58S glasses have been synthesized by this method.[94] GC scaffolds consisting of apatite-wollastonite and diopside crystals were also developed and subjected to biological and mechanical tests.[95,96] The above listed results indicate that glass ceramization is a promising method for stronger scaffold development.

Moreover, there is now a stronger focus on engineered scaffolds from bioactive glass/GC combined with biodegradable polymers. Fracture toughness values within the range reported for cortical bone (2–12 $MPa{\cdot}m^{1/2}$) are required for load-bearing applications, and therefore, toughness must be improved in these types of scaffolds. This improvement can be achieved by producing composites. Polymer-based scaffolds reinforced with bio glasses or GCs represent a suitable option due to the possibility to tailor their various properties (for example, mechanical and structural behavior, degradation kinetics and bioactivity). Polymers exhibit generally high ductility, toughness, favorable formability and processability and plasticity. The glass or GC phase adds stiffness and adequate mechanical strength to the composite. For further reading, comprehensive review papers and book chapters in Refs. 97–100 are recommended.

GEL-DERIVED BIOACTIVE GCs

The main advantages of the gel-derived glasses over melt-derived glasses are[101,102]: lower temperatures are required for their synthesis, easy powder technology production, improved homogeneity, and purity of the powder, wider range of bioactive compositions with increased bioactivity of compositions up to 90 mol % SiO_2, they exhibit mesoporosity and ability to form macroporous structures (scaffolds), sol-gel processing is a versatile technique to develop thin layers of bioactive glasses/GCs on bulk materials with high homogeneity and mechanical and chemical stability.

Upon adequate heat treatment, gel-glasses can be converted to GCs (Fig. 1). Proper heat treatments, which may induce crystallization, are required to stabilize the glass structure or develop mesoporous granules, coatings, and scaffolds with interconnected pore structure. On the other hand, crystallization may reduce the surface area but it is helpful for modulating mechanical properties and bioactivity.

Gel-derived GCs have started to emerge in various applications in medicine and dentistry, including dental tissue and bone regeneration, drug delivery and hybrid materials. For example, Figure 11 shows a good example of scaffold

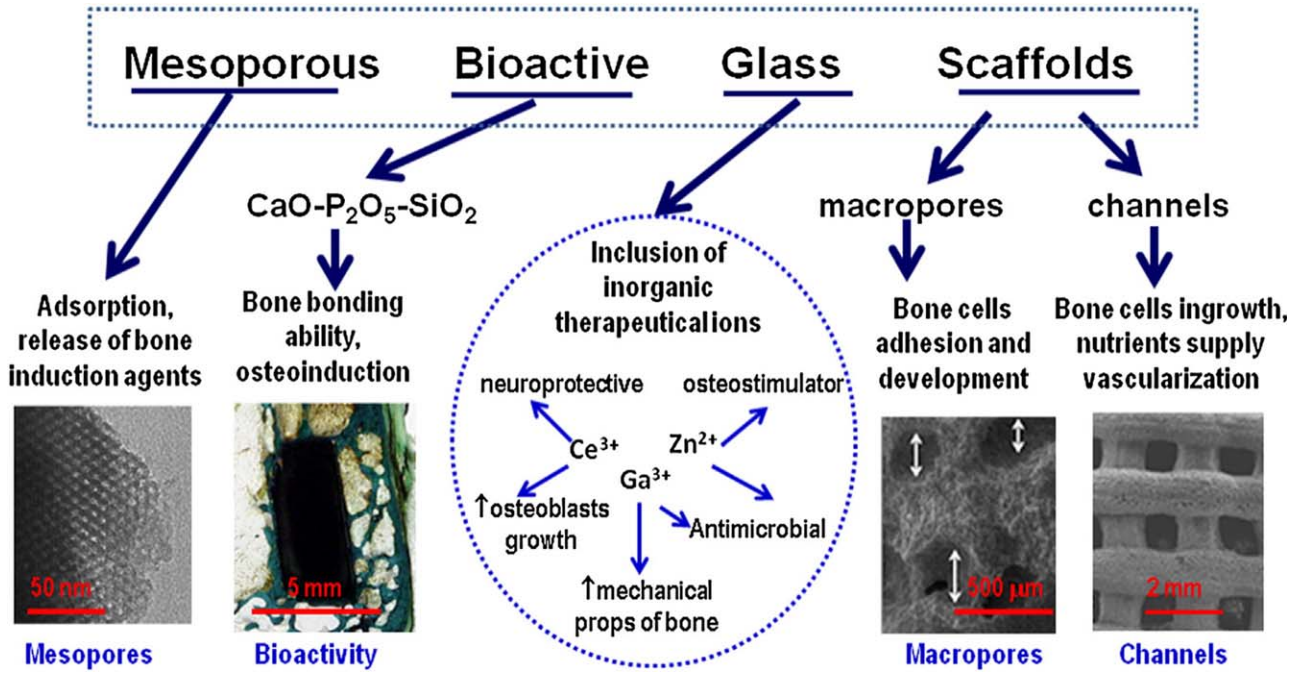

FIGURE 11. Features that make gel-derived bioactive scaffolds optimum candidates for bone tissue engineering. The extra properties coming for the additions of inorganic ions are highlighted.[103]

development based on a mesoporous gel-derived SiO_2–CaO–P_2O_5 GC. This figure also shows that various elements like Ce, Ga, and Zn can be easily included in the glass composition to activate especial biological responses, such as antimicrobial, neuroprotective, and osteoblast growth.[103]

Vallet-Regí's team has demonstrated that controlled heat treatment of mesoporous gel-derived glasses can lead to GCs with improved mechanical properties without deteriorating their bioactive behavior. For instance, in [104, 105], a GC containing pseudo-wollastonite, wollastonite, tricalcium phosphate and cristobalite, was obtained by heating a gel-derived glass ($55SiO_2-41CaO-4P_2O_5$ in mol %) at 1300°C. This GC shows efficient *in vitro* bioactive behavior, i.e. an apatite layer covers the sample surface after 3 days soaking in SBF.[104,105] In order to use this material as a substrate for bone tissue engineering, the authors have synthesized scaffolds with a network of designed three-dimensional interconnected macropores of 400–500 μm in diameter.[106] Further studies revealed that the resulting GC is bioactive, cytocompatible and capable of promoting *in vitro* the differentiation of mesenchymal stem cells into osteoblasts. For that reason, it could be a suitable matrix for bone tissue regeneration.[107] Additionally, *in vivo* evaluation of $70SiO_2-30CaO$, $80SiO_2-17P_2O_5-3CaO$, and $36SiO_2-7P_2O_5$–44CaO–13MgO (mol %) glasses and GCs in New Zealand rabbits showed potential for bone substitute and regeneration.[108,109] Femoral bone diaphyseal critical and smaller size defects were filled with glass/GC cylinders, discs, or scaffolds. An intimate union of the new-formed bone to all materials was observed. A study showed improved mechanical properties for the GC, whereas the gel-glasses showed no differences when compared to the control specimens. The negligible degradation of GC cylinders suggested their application in critical bone defects for moderate load-bearing applications. The performance of the gel-glass samples suggested their usefulness in locations where quick resorption is desirable considering the possibility of serving as drug or cell vehicle. They could also be used as dental cavity fillings and coatings of metal or ceramic implant surfaces.[108,109]

Another example is the gel-derived microporous bioactive GC developed by Chatzistavrou et al.,[110–112] which has potential application in dental restoration. These GCs are able to show bioactive behavior around the margins of fixed restorations and to provide a bioactive surface which can lead to periodontal tissue attachment, providing complete sealing of the marginal gap between teeth and fixed prosthesis.

The sol-gel route was employed for the development of a $60SiO_2-3P_2O_5-14Al_2O_3-6CaO-7Na_2O-10K_2O$ (wt %) GCs and a related composite material combining this GC with a $58SiO_2-33CaO-9P_2O_5$ (wt %) bioactive glass.[110,111] Their method resulted in a homogeneous microporous GC composite which can be applied as a coating on commercial dental ceramic substrates.[110,111] The attachment and proliferation of both periodontal ligament and gingival fibroblast cells confirmed the bioactive behavior of the new materials and their potential ability to be used in dental restorations for soft tissue regeneration and sealing of the marginal gap.[111] Furthermore, an Ag-doped composite showed pulp-cell proliferation and antibacterial properties that may facilitate potential applications in tooth regeneration approaches.[112]

Furthermore, mesoporous magnetic bioactive GCs for hyperthermia treatment of cancer are suggested by Vallet-Regí's team.[113–115] Hyperthermia is a method for destroying

cancer cells by heating them between 41°C and 46°C. Ferro- or ferrimagnetic materials locally generate heat by hysteresis loss under an alternate magnetic field, damaging only tumoral cells and not the healthy tissue. The power loss produced by magnetic materials can be dissipated in the form of heat.[9] For this special application, biphasic materials containing a melt-derived magnetic GC ($45SiO_2-45CaO-10Fe_2O_3$ in mol %) and a gel-derived bioactive glass ($58SiO_2-6P_2O_5-36CaO$ in mol %) were developed.[113–115] The mesoporous gel-glass gives rise to bioactivity and GC, which contains magnetite (Fe_3O_4) crystals, induces the magnetic properties.[113] Generally, iron should remain in the crystal structure, because it would diminish the apatite forming ability of the residual glass. Additionally, the biphasic nature of these materials allows the changing of both magnetic and bioactive properties, depending on the requirements of the patient.[113–115] There are several other publications on this particular subject, but it is clear that further *in vivo* and clinical tests are required before these interesting materials reach the market.

The interested reader is encouraged to refer to comprehensive papers, reviews and book chapters such as [6–9] and [99–103], which are dealing with gel-derived glasses and GCs and their derivative products. They believe that biomimetic regeneration of complex structure of bone and teeth demands 3D porous structure and incorporation of growth factors, therapeutic drugs, and seeded stem cells. Gel-derived bioactive glasses and GCs are promising to meet these requirements.[4,6–9,99–103]

FUTURE RESEARCH DIRECTIONS

Bioactive GCs were originally developed to overcome one marked weakness of bioactive glasses, brittleness. However, a glancing comparison of the fracture toughness of commercial GCs (1–2 $MPa{\cdot}m^{1/2}$) and cortical bone (2–12 $MPa{\cdot}m^{1/2}$) reveals that this property still needs to be significantly improved. Furthermore, highly bioactive glasses and GCs with adequate biological and mechanical properties should be developed for soft-tissue engineering or drug delivery and for preventive treatments to slow down deterioration and maintain tissue health. These two general objectives can be achieved by the efficient engineering of new GC compositions, processing methods and heat treatments. A few key areas for further exploration are summarized below:

- Chemistry-based processes can be used to expand the bioactive GC composition ranges. Recently, it has been demonstrated that new gel-derived glasses with a high ZrO_2 content can be converted to bioactive nano apatite-zirconia GCs with improved mechanical properties.[116,117]
- Adequate matrices can be engineered for the development of hierarchical nanostructured bioactive GCs based on variations in the size, shape, distribution, and composition of nanosized crystals.
- Engineering of porosity is a current research field for the development of hierarchical porous bioactive GCs.
- New or improved crystallization processes, such as microwave heating, the biomimetic assemblage of crystals, textured crystallization, laser crystallization, and electron beam crystallization, should be developed.
- Coating properties should be improved. For example, degradation over time, which leads to detachment of coating, is a noticeable drawback.
- Further investigations are required to improve polymer/GC composites (hybrids). There is a lack of *in vivo* testing in this interesting area. The use of bioactive GC nanoparticles and their combination with bioresorbable polymers is of great interest. However, the toxicity of nanoparticles will have to be investigated.
- Doping bioactive GCs with various elements that provide specific biological responses or cell gene expression should be deeply investigated before being translated into clinical applications.
- Many issues, including sterilization, packaging and international standards for the production of bioactive GCs for clinical applications, need to be resolved to make new GCs commercially viable. For example, conventional sterilization is an issue regarding polymer/glass-based scaffold because it changes the molecular weight of resorbable polymers.
- Not all toughening mechanisms have yet been thoroughly activated in bioactive GCs. There are still several toughening mechanisms, such as transformation toughening, bridging, microcracking, and pull out, that can be stimulated by the controlled crystallization of different crystals with a variety of morphologies and structures.[118]
- Borate and phosphate-based bioactive glasses are promising biodegradable materials for soft-tissue engineering, for example, wound healing.[119,120] However, the effects of crystallization on their biological and mechanical properties are unknown. Controlled crystallization may control their degradation rate and improve their mechanical properties.
- (Expensive, time-consuming) clinical tests have been very limited so far and should be encouraged.
- Finally, we fully agree with an inspiring sentence by Prof. Larry L. Hench: "Previous revolutions in healthcare, prevention of death and replacement of tissues, need to be augmented with two new, innovative revolutions: tissue regeneration and prevention of tissue deterioration."[4,121,122]

REFERENCES

1. Zanotto ED. A bright future for glass–ceramics. Am Ceram Soc Bul 2010;89:19–27.
2. Montazerian M, Singh SP, Zanotto ED. An analysis of glass-ceramic research and commercialization. Am Ceram Soc Bull 2015;94:30–35.
3. Höland W, Beall G. Glass-Ceramic Technology, 2nd ed., USA: The American Ceramic Society & Wiley; 2012.
4. Hench LL. The future of bioactive ceramics. J Mater Sci: Mater Med 2015;26:1–4.
5. Kokubo T, Bioceramics and their clinical applications, USA: Woodhead publishing limited; 2008.
6. Salinas AJ, Vallet-Regí M. Bioactive ceramics: From bone grafts to tissue engineering. RSC Adv 2013;3:11116–11131.

7. Baino F, Novajra G, Miguez-Pacheco V, Boccaccini AR, Vitale-Brovarone C. Bioactive glasses: Special applications outside the skeletal system. J Non-Cryst Solids 2016;432:15–30.
8. Miguez-Pacheco V, Hench LL, Boccaccini AR. Bioactive glasses beyond bone and teeth: Emerging applications in contact with soft tissues. Acta Biomater 2015;13:1–15.
9. Hench LL (Ed.), An Introduction to Bioceramics, 2nd ed., London, UK: Imperial College Press; 2013.
10. Kokubo T. Bioactive glass-ceramics: Properties and applications. Biomaterials 1991;12:155–163.
11. Montazerian M, Effect of ZrO_2 addition on properties of gel-derived bioactive SiO_2-CaO-P_2O_5 glass-ceramics, PhD dissertation, Tehran, Iran: Iran University of Science and Technology; 2015.
12. Höland W, Vogel W, Naumann K, Gummel J. Interface reactions between machinable bioactive glass-ceramics and bone. J Biomed Mater Res 1985;19:303–312.
13. Peitl O, LaTorre GP, Hench LL. Effect of crystallization on apatite-layer formation of bioactive glass 45S5. J Biomed Mater Res 1996;30:509–514.
14. Peitl O, Zanotto ED, Hench LL. Highly bioactive P_2O_5–Na_2O–CaO–SiO_2 glass-ceramics. J Non-Cryst Solids 2001;292:115–126.
15. Turck C, Brandes G, Krueger I, Behrens P, Mojallal H, Lenarz T, Stieve M. Histological evaluation of novel ossicular chain replacement prostheses: An animal study in rabbits. Acta Otolaryngol 2007;127:801–808.
16. Vogt JC, Brandes G, Ehlert N, Behrens P, Nolte I, Mueller PP, Lenarz Y, Stieve M. Free Bioverit® II implants coated with a nanoporous silica layer in a mouse ear model - a histological study. J Biomater Appl 2009;24:175–191.
17. Crovace MC, Souza MT, Chinaglia CR, Peitl O, Zanotto ED. Bio-silicate® - A multipurpose, highly bioactive glass-ceramic. In vitro, in vivo and clinical trials. J Non-Cryst Solids 2016;432:90–110.
18. Hill RG, Bioactive glass–ceramics. In: Ducheyne P, editor. Comprehensive Biomaterials, Volume 1: Metallic, Ceramic and Polymeric Biomaterials, 2011, Netherlands: Elsevier; p 181–186.
19. Hill RG, Wood DJ. Apatite–mullite glass ceramics. J Mater Sci: Mater Med 1995;6:311–318.
20. Clifford A, Hill RG. Apatite–mullite glass-ceramics. J Non-Cryst Solids 1996;196:346–352.
21. Goodridge RD, Wood DJ, Ohtsuki C, Dalgarno KW. Biological evaluation of an apatite-mullite glass-ceramic produced via selective laser sintering. Acta Biomater 2007;3:221–231.
22. Stanton KT, O'Flynn KP, Kiernan S, Menuge J, Hill RG. Spherulitic crystallization of apatite-mullite glass-ceramics: Mechanisms of formation and implications for fracture properties. J Non-Cryst Solids 2010;356:1802–1813.
23. Wolcott CC, Canasite-apatite glass-ceramic, Eur. Patent No. EP 0 641 556, 1994.
24. Miller CA, Kokubo T, Reaney IM, Hatton PV, James PF. Formation of apatite layers on modified canasite glass-ceramics in simulated body fluid. J Biomed Mater Res 2002;59:473–480.
25. Barros VMDR, Salata LA, Sverzut CE, Xavier SP, Van Noort R, Johnson A, Hatton PV. *In vivo* bone tissue response to a canasite glass-ceramic. Biomaterials 2002;23:2895–2900.
26. Mirsaneh M, Reaney IM, James PF, Hatton PV. Effect of CaF_2 and CaO substituted for MgO on the phase evolution and mechanical properties of K-fluorrichterite glass ceramics. J Am Ceram Soc 2006;89:587–595.
27. Bhakta S, Pattanayak DK, Takadama H, Kokubo T, Miller CA, Mirsaneh M, Reaney IM, Brook IM, van Noort R, Hatton PV. Prediction of osteoconductive activity of modified potassium fluorrichterite glass–ceramics by immersion in simulated body fluid. J Mater Sci: Mater Med 2010;89:2979–2988.
28. Bhakta S, Hurrell-Gillingham K, Mirsaneh M, Miller CA, Reaney IM, Brook IM, van Noort R, Hatton PV. *In vitro* biocompatibility of modified potassium fluorrichterite and potassium fluorrichterite–fluorapatite glass–ceramics. J Mater Sci: Mater Med 2011;22:2065–2070.
29. Bhakta S, Faira PE, Salata LA, Neto PJDO, Miller CA, van Noort R, Reaney IM, Brook IM, Hatton PV. Determination of relative *in vivo* osteoconductivity of modified potassium fluorrichterite glass–ceramics compared with 45S5 bioglass. J Mater Sci: Mater Med 2012;23:2521–2529.
30. El-Meliegy E, van Noort R. Glasses and Glass Ceramics for Medical Applications, Chapter 14, New York: Springer; 2011, p 229–238.
31. Moisescu C, Jana C, Habelitz S, Carl G, Rüssel C. Oriented fluoroapatite glass-ceramics. J Non-Cryst Solids 1999;248:176–182.
32. Habelitz S, Carl G, Rüssel C, Thiel S, Gerth U, Schnapp JD, Jordanov A, Knake H. Mechanical properties of oriented mica glass-ceramic. J Non-Cryst Solids 1997;220:291–298.
33. Apel E, Höland W, Rheinberger V. Bioactive rhenanite glass ceramic, United States Patent 7074730, 2006.
34. Höland M, Dommann A, Höland W, Apel E, Rheinberger V. Microstructure formation and surface properties of a rhenanite-type glass-ceramic containing 6.0 wt% P2O5. Glass Sci Technol 2005;78:153–158.
35. Kasuga T. Bioactive calcium pyrophosphate glasses and glass-ceramics. Acta Biomater 2005;1:55–64.
36. Kasuga T. Development of phosphate glass-ceramics for biomedical applications. J Ceram Soc Jpn 2007;115:455–459.
37. Kasuga T, Mizuno T, Watanabe M, Nogami M, Niinomi M. Calcium phosphate invert glass-ceramic coatings joined by self development of compositionally gradient layers on a titanium alloy. Biomaterials 2001;22:577–582.
38. Obata A, Sasaki M, Kasuga T. Control of ß-tricalcium phosphate formation in macroporous phosphate glass-ceramic composites. Mater Trans 2007;48:313–316.
39. Maeda H, Miyajima T, Lee S, Obata A, Ueda K, Narushima T, Kasuga T. Preparation of calcium pyrophosphate glass-ceramics containing Nb_2O_5. J Ceram Soc Jpn 2014;122:122 –124.
40. Chen X, Hill RG, Karpukhina N. Chlorapatite glass-ceramics. Int J Appl Glass Sci 2014;5:207–216.
41. Kapoor S, Goel A, Pascual MJ, Ferreira JMF. Alkali-free bioactive diopside-tricalcium phosphate glass-ceramics for scaffold fabrication: Sintering and crystallization behaviours. J Non-Cryst Solids 2016;432:81–89.
42. Goel A, Kapoor S, Rajagopal RR, Pascual MJ, Kim H, Ferreira JMF. Alkali-free bioactive glasses for bone tissue engineering: A preliminary investigation. Acta Biomater 2012;8:361–372.
43. Kapoor S, Goel A, Pascual MJ, Ferreira JMF. Thermo-mechanical behaviour of alkali free bioactive glass-ceramics co-doped with strontium and zinc. J Non-Cryst Solids 2013;375:74–82.
44. Cao W, Hench LL. Bioactive materials. Ceram Int 1996;22:493–507.
45. Takatsuka K, Yamamuro T, Kitsugi T, Nakamura T, Shibuya T, Goto T. A new bioactive glass–ceramic as a coating material on titanium alloy. J Appl Biomater 1993;4:317–329.
46. Li ZL, Kitsugi T, Yamamuro T, Chang YS, Senaha Y, Takagi H, Nakamura T, Oka M. Bone-bonding behavior under load-bearing conditions of an alumina ceramic implant incorporating beads coated with glass-ceramic containing apatite and wollastonite. J Biomed Mater Res 1995;29:1081–1088.
47. Kitsugi T, Nakamura T, Oka M, Senaha Y, Goto T, Shibuya T. Bone-bonding behavior of plasma-sprayed coatings of bioglass(R), AW-glass ceramic, and tricalcium phosphate on titanium alloy. J Biomed Mater Res 1996;30:261–269.
48. Ballarrea J, Manjubalab I, Schreinerc WH, Orellanod JC, Fratzlb P, Ceréa S. Improving the osteointegration and bone–implant interface by incorporation of bioactive particles in sol–gel coatings of stainless steel implants. Acta Biomater 2010;6:1601–1609.
49. Durán A, Conde A, Gómez Coedo A, Dorado T, García C, Ceré S. Sol-gel coatings for protection and bioactivation of metals used in orthopaedic devices. J Mater Chem 2004;14:2282–2290.
50. García C, Ceré S, Durán A. Bioactive coatings deposited on titanium alloys. J Non-Cryst Solids 2006;352:3488–3495.
51. Ignatius A, Peraus M, Schorlemmer S, Augat P, Burger W, Leyen S, Claes L. Osseointegration of alumina with a bioactive coating under load-bearing and unloaded conditions. Biomaterials 2005;26:2325–2332.
52. Bibby, JK, Mummery, PM, Bubb, N, Wood, DJ. Novel bioactive coatings for biomedical applications deposited by electrophoretic deposition. Glass Tech 2004;45:80–83.

53. Bibby JK, Bubb NL, Wood DJ, Mummery PM. Fluorapatite-mullite glass sputter coated Ti6Al4V for biomedical applications. J Mater Sci: Mater Med 2005;16:379–385.
54. Stanton KT, O'Flynn KP, Nakahara S, Vanhumbeeck JF, Delucca JM, Hooghan B. Study of the interfacial reactions between a bioactive apatite-mullite glass-ceramic coating and titanium substrates using high angle annular dark field transmission electron microscopy. J Mater Sci: Mater Med 2009;20:851–857.
55. O'Flynn KP, Stanton KT. Optimisation of the enamelling of an apatite-mullite glass-ceramic coating on Ti6Al4V. J Mater Sci: Mater Med 2011;22:2035–2044.
56. Kasuga T, Nogami M, Niinomi M, Hattori T. Bioactive calcium phosphate invert glass-ceramic coating on β-type Ti-29Nb-13Ta-4.6Zr alloy. Biomaterials 2003;24:283–290.
57. Kasuga T. Coatings for metallic biomaterials. In: Niinomi M, editor. Metals for Biomedical Devices, Cambridge, UK: Woodhead Publishing; 2010, p 260–282.
58. Li SJ, Niinomi M, Akahori T, Kasuga T, Yang R, Hao YL. Fatigue characteristics of bioactive glass-ceramic-coated Ti-29Nb-13Ta-4.6Zr for biomedical application. Biomaterials 2004;25:3369–3378.
59. Braem A, Neirinck B, Schrooten J, Van Der Biest O, Vleugels J. Biofunctionalization of porous titanium coatings through sol-gel impregnation with a bioactive glass-ceramic. Mater Sci Eng C 2012;32:2292–2298.
60. Braem A, Mattheys T, Neirinck B, Čeh M, Novak S, Schrooten J, Van Der Biest O, Vleugels J, Bioactive glass-ceramic coated titanium implants prepared by electrophoretic deposition. Mater Sci Eng C 2012;32:2267–2273.
61. Dou Y, Cai S, Ye X, Xu G, Huang K, Wang X, Ren M. 45S5 bioactive glass-ceramic coated AZ31 magnesium alloy with improved corrosion resistance. Surf Coat Technol 2013;228:154–161.
62. Ye X, Cai S, Dou Y, Xu G, Huang K, Ren M, Wang X. Bioactive glass-ceramic coating for enhancing the in vitro corrosion resistance of biodegradable Mg alloy. Appl Surf Sci 2012;259:799–805.
63. Huang K, Cai S, Xu G, Ye X, Dou Y, Ren M, Wanga X. Preparation and characterization of mesoporous 45S5 bioactive glass-ceramic coatings on magnesium alloy for corrosion protection. J Alloy Compd 2013;580:290–297.
64. Niu S, Cai S, Liu T, Zhao H, Wang X, Ren M, Huang K, Wu X. 45S5 bioactive glass-ceramic coated magnesium alloy with strong interfacial bonding strength by "superplasticity diffusion bonding". Mater Lett 2015;141:96–99.
65. Verné E, Fernández Vallés C, Vitale Brovarone C, Spriano S, Moisescu C. Double-layer glass-ceramic coatings on Ti6Al4V for dental implants. J Eur Ceram Soc 2004;24:2699–2705.
66. Verné E, Vitale brovarone C, Moisescu C, Ghisolfi E, Marmo E. Coatings on Al_2O_3 by bioactive glass-ceramics. Acta Mater 2000;48:4667–4671.
67. Ferraris M, Verné E, Appendino P, Moisescu C, Krajewski A, Ravaglioli A, Piancastelli A. Coatings on zirconia for medical applications. Biomaterials 2000;21:765–773.
68. Verné E. Bioactive glass and glass-ceramic coatings. In: Jones JR, Clare AG, editors. Bio-Glasses: An Introduction, 1st ed., UK: Wiley; 2012, p 107–120.
69. Marghussian V. Nano-Glass Ceramics: Processing, Properties and Applications, 1st ed., Netherlands: Elsevier; 2015.
70. Xiao W, Song L, Liu X, Huang Y, Huang T, Wu Y, Chen Y, Wu F. Nanostructured bioactive glass–ceramic coatings deposited by the liquid precursor plasma spraying process. Appl Surf Sci 2011;257:1898–1905.
71. Wang G, Lu Z, Liu X, Zhou X, Ding C, Zreiqat H. Nanostructured glass-ceramic coatings for orthopaedic applications. J R Soc Interface 2011;8:1192–1203.
72. Kasuga T, Yoshida M, Ikushima AJ, Tuchiya M, Kusakari H. Bioactivity of zirconia-toughened glass-ceramics. J Am Ceram Soc 1992;75:1884–1888.
73. Kasuga T, Nakajima K, Uno T, Yoshida M. Preparation of zirconia-toughened bioactive glass-ceramic composite sinter-hot isostatic pressing. J Am Ceram Soc 1992;75:1103–1107.
74. Montazerian M, Alizadeh P, Eftekhari Yekta B. Pressureless sintering and mechanical properties of mica glass–ceramic/Y-PSZ composite. J Eur Ceram Soc 2008;28:2687–2692.
75. Montazerian M, Alizadeh P, Eftekhari Yekta B. Processing and properties of a mica–apatite glass–ceramic reinforced with Y-PSZ particles. J Eur Ceram Soc 2008;28:2693–2699.
76. Rawlings RD. Bioactive glasses and glass-ceramics. Clin Mater 1993;14:155–179.
77. Müller-Mai C, Schmitz HJ, Strunz V, Fuhrmann G, Fritz T, Gross UM. Tissues at the surface of the new composite material titanium/glass-ceramic for replacement of bone and teeth. J Biomed Mater Res 1989;23:1149–1168.
78. Claxton E, Taylor BA, Rawlings RD. Processing and properties of a bioactive glass-ceramic reinforced with ductile silver particles. J Mater Sci 2002;37:3725–3732.
79. Wang M. Developing bioactive composite materials for tissue replacement. Biomaterials 2003;24:2133–2151.
80. Juhasz JA, Best SM, Kawashita M, Miyata N, Kokubo T, Nakamura T, Bonfield W. Bonding strength of the apatite layer formed on glass-ceramic apatite-wollastonite-polyethylene composites. J Biomed Mater Res A 2003;67:952–959.
81. Juhasz JA, Best SM, Brooks R, Kawashita M, Miyata N, Kokubo T, Nakamura T, Bonfield W. Mechanical properties of glass-ceramic A-W-polyethylene composites: Effect of filler content and particle size. Biomaterials 2004;25:949–955.
82. Zeimaran E, Pourshahrestani S, Djordjevic I, Pingguan-Murphy B, Kadri NA, Towler MR. Bioactive glass reinforced elastomer composites for skeletal regeneration: A review. Mater Sci Eng C 2015;53:175–188.
83. Gabbai-Armelin PR, Cardoso DA, Zanotto ED, Peitl O, Leeuwenburgh SCG, Jansen JA, Renno ACM, Van Den Beucken JJJP. Injectable composites based on biosilicate® and alginate: Handling and in vitro characterization. RSC Adv 2014;4:45778–45785.
84. Kaur G, Pandey OP, Singh K, Homa D, Scott B, Pickrell G. A review of bioactive glasses: Their structure, properties, fabrication, and apatite formation. J Biomed Mater Res A 2014;102:254–274.
85. Gerhardt L, Boccaccini AR. Bioactive glass and glass ceramic scaffolds for bone tissue engineering. Materials 2010;3:3867–3910.
86. Fu Q, Saiz E, Rahaman MN, Tomsia AP. Toward strong and tough glass and ceramic scaffolds for bone repair. Adv Funct Mater 2013;23:5461–5476.
87. Clupper DC, Hench LL, Mecholsky JJ. Strength and toughness of tape cast bioactive glass 45S5 following heat treatment. J Eur Ceram Soc 2004;24:2929–2934.
88. Chen QZ, Thompson ID, Boccaccini AR. 45S5 Bioglass®-derived glass-ceramic scaffolds for bone tissue engineering. Biomaterials 2006;27:2414–2425.
89. Chen QZ, Efthymiou A, Salih V, Boccaccini AR. Bioglass®-derived glass-ceramic scaffolds: Study of cell proliferation and scaffold degradation. J Biomed Mater Res A 2008;84:1049–1060.
90. Baino F, Vitale-Brovarone C. Bioactive glass and glass-ceramic foam scaffolds for bone tissue restoration. In: Netti P, editor. Biomedical Foams for Tissue Engineering Applications, 1st ed., Cambridge, UK: Woodhead Publishing; 2014, p 213–248.
91. Baino F, Vitale-Brovarone C. New trends in bone tissue engineering scaffolds: Hierarchically porous glass and glass-ceramic structures. In: Rimondini L, Bianchi CL, Vernè E, editors. Surface Tailoring of Inorganic Materials for Biomedical Applications, UAE: Bentham Science Publishers; 2012, p 376–391.
92. Roohani-Esfahani SI, Zreiqat HH. Ceramic scaffolds, current issues and future trends. In: Ramalingam M, Haidar Z, Ramakrishna S, Kobayashi H, Haikel Y, editors. Integrated Biomaterials in Tissue Engineering, USA: Wiley; 2012, p 25–46.
93. Desimone D, Li W, Roether JA, Schubert DW, Crovace MC, Rodrigues ACM, Zanotto ED, Boccaccini AR. Biosilicate®-gelatine bone scaffolds by the foam replica technique: Development and characterization. Sci Technol Adv Mater 2013;14:045008.
94. Fiocco L, Bernardo E, Colombo P, Cacciotti I, Bianco A, Bellucci D, Sola A, Cannillo V. Novel processing of bioglass ceramics from silicone resins containing micro- and nano-sized oxide particle fillers. J Biomed Mater Res A 2014;102:2502–2510.
95. Fiocco L, Elsayed H, Ferroni L, Gardin C, Zavan B, Bernardo E. Bioactive wollastonite-diopside foams from preceramic polymers and reactive oxide fillers. Materials 2015;8:2480–2494.

96. Elsayed H, Zocca A, Bernardo E, Gomes CM, Günster J, Colombo P. Development of bioactive silicate-based glass-ceramics from preceramic polymer and fillers. J Eur Ceram Soc 2015;35:731–739.
97. Baino F, Verné E, Vitale-Brovarone C. 3-D high-strength glass-ceramic scaffolds containing fluoroapatite for load-bearing bone portions replacement. Mater Sci Eng C 2009;29:2055–2062.
98. Chatzistavrou X, Newby P, Boccaccini AR. Bioactive glass and glass-ceramic scaffolds for bone tissue engineering. In: Ylänen HO, editor. Bioactive Glasses, Cambridge, UK: Woodhead Publishing; 2011, p 107–128.
99. Miguez-Pacheco V, Misra SK, Boccaccini AR. Biodegradable and bioactive polymer/inorganic phase nanocomposites for bone tissue engineering (BTE). In: Boccaccini AR, Ma PX, editors. Tissue Engineering Using Ceramics and Polymers, 2nd ed., Cambridge, UK: Woodhead Publishing; 2014, p 115–150.
100. Jones JR. Review of bioactive glass: From Hench to hybrids. Acta Biomater 2013;9:4457–4486.
101. Chatzistavrou X, Kontonasaki E, Paraskevopoulos KM, Koidis P, Boccaccini AR. Sol-gel derived bioactive glass ceramics for dental applications. In: Vallittu P, editor. Non-Metallic Biomaterials for Tooth Repair and Replacement, Cambridge, UK: Woodhead Publishing; 2013, p 194–231.
102. Arcos D, Vallet-Regí M, Sol-gel silica-based biomaterials and bone tissue regeneration. Acta Biomater 2010;6:2874–2888.
103. Salinas AJ, Vallet-Regí M. Glasses in bone regeneration: A multiscale issue. J Non-Cryst Solids 2016;432:9–14.
104. Roman J, Padilla S, Vallet-Regí M. Sol-gel glasses as precursors of bioactive glass ceramics. Chem Mater 2003;15:798–806.
105. Vallet-Regí M, Roman J, Padilla S, Doadrio JC, Gil FJ. Bioactivity mechanical properties of SiO_2-CaO-P_2O_5 glass ceramics. J Mater Chem 2005;15:1353–1359.
106. Padilla S, Sanchez-Salcedo S, Vallet-Regí M. Bioactive glass as precursor of designed-architecture scaffolds for tissue engineering. J Biomed Mater Res A 2007;81:224–232.
107. Meseguer-Olmo L, Bernabeu-Esclapez A, Ros-Martinez E, Sánchez-Salcedo S, Padilla S, Martín AI, Vallet-Regí M, Clavel-Sainz M, Lopez-Prats F, Meseguer-Ortiz CL. In vitro behaviour of adult mesenchymal stem cells seeded on a bioactive glass ceramic in the SiO_2-CaO-P_2O_5 system. Acta Biomater 2008;4:1104–1113.
108. Gil-Albarova J, Garrido-Lahiguera R, Salinas AJ, Román J, Bueno-Lozano AL, Gil-Albarova R, Vallet-Regí M. The *in vivo* performance of a sol-gel glass and a glass-ceramic in the treatment of limited bone defects. Biomaterials 2004;25:4639–4645.
109. Gil-Albarova J, Salinas AJ, Bueno-Lozano AL, Román J, Aldini-Nicolo N, García-Barea A, Giavaresi G, Fini M, Giardino R, Vallet-Regí M. The *in vivo* behaviour of a sol-gel glass and a glass-ceramic during critical diaphyseal bone defects healing. Biomaterials 2005;26:4374–4382.
110. Chatzistavrou X, Esteve D, Hatzistavrou E, Kontonasaki E, Paraskevopoulos KM, Boccaccini AR. Sol-gel based fabrication of novel glass-ceramics and composites for dental applications. Mater Sci Eng C 2010;30:730–739.
111. Chatzistavrou X, Tsigkou O, Amin HD, Paraskevopoulos KM, Salih V, Boccaccini AR. Sol-gel based fabrication and characterization of new bioactive glass-ceramic composites for dental applications. J Eur Ceram Soc 2012;32:3051–3061.
112. Chatzistavrou X, Fenno JC, Faulk D, Badylak S, Kasuga T, Boccaccini AR, Papagerakis P. Fabrication and characterization of bioactive and antibacterial composites for dental applications. Acta Biomater 2014;10:3723–3732.
113. Arcos D, Del Real RP, Vallet-Regí M. A novel bioactive and magnetic biphasic material. Biomaterials 2002;23:2151–2158.
114. Arcos D, Del Real RP, Vallet-Regí M. Biphasic materials for bone grafting and hyperthermia treatment of cancer. J Biomed Mater Res A 2003;65:71–78.
115. Serrano M, Portolés MT, Pagani R, De Guinoa JS, Ruiz-Hernández E, Arcos D, Vallet-Regí M. In vitro positive biocompatibility evaluation of glass-glass ceramic thermoseeds for hyperthermic treatment of bone tumors. Tissue Eng 2008;14:617–627.
116. Montazerian M, Schneider JF, Eftekhari Yekta B, Marghussian VK, Rodrigues AM, Zanotto ED. Sol-gel synthesis, structure, sintering and properties of bioactive and inert nano apatite-zirconia glass-ceramics. Ceram Int 2015;41:11024–11045.
117. Montazerian M, Eftekhari Yekta B, Marghussian VK, Bellani CF, Siqueira RL, Zanotto ED. Bioactivity and cell proliferation in radiopaque gel-derived $CaO-P_2O_5-SiO_2-ZrO_2$ glass and glass-ceramic powders. Mater Sci Eng C 2015;55:436–447.
118. Serbena FC, Mathias I, Foerster CE, Zanotto ED. Crystallization toughening of a model glass-ceramic. Acta Mater 2015;86:216–228.
119. Rahaman MN, Day DE, Bal BS, Fu Q, Jung SB, Bonewald LF, Tomsia AP. Bioactive glass in tissue engineering. Acta Biomater 2011;7:2355–2373.
120. Brauer DS. Phosphate glasses. In: Jones JR, Clare AG, editors. Bio-Glasses: An Introduction, UK: Wiley; 2012, p 45–64.
121. Hench LL. Glass and glass-ceramic technologies to transform the world. Int J Appl Glass Sci 2011;2:162–176.
122. Hench LL. Opening paper 2015 - Some comments on Bioglass: Four eras of discovery and development. Biomed Glasses 2015;1:1–11.