Bioactive glass-based nanocomposites for personalized dental tissue regeneration

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Bioactive glass nanoparticles (BGNs) have been used over a range of dental tissue engineering. One main reason is possibly that BGNs strongly interact with hard tissues, while forming a stable interface after implantation. Recently, BGNs have been further diversified and ameliorated by incorporating bio-functional ions into BGNs or by functionally modifying the surface of BGNs. A comprehensive overview of the processes and applications of BGNs and their derivatives for the use in dentistry is thus necessary for their step-forward. Therefore, this review focuses on a variety of processes and practical applications of BGNs and their derivatives, which is expected to aid readerships with understanding and employing BGNs and their derivatives for personalized dental treatments.

Keywords: Bioactive glass, Bioactivity, Personalized dentistry, Nanocomposite, Nanoparticle

INTRODUCTION

Bioactive glasses are a group of biomaterials used in the fields of dentistry and orthopedics. In 1969, bioactive glasses were firstly introduced by Hench who implanted them in the human body¹. Those days, the implantable materials (e.g. metals and polymers) initiated fibrous encapsulation despite their bioinert property after implantation. To deal with this, Hench attempted to make a degradable silica-based glass in the SiO₂-Na₂O-CaO-P₂O₅ system. Silicate-based glasses composed of calcium and phosphorus similar to the component of natural bone can strongly interact with bone tissue without an intervening fibrous tissue¹. Finally, he and his coworkers discovered specialized bioactive glasses composed of 46.1 mol% SiO₂, 24.4 mol% Na₂O, 26.9 mol% CaO and 2.6 mol% P₂O₅, termed 45S5 and Bioglass[®], which was followed by optimizing composition of SiO₂ and CaO^{2,3}. It was also found that bioactive glasses were chemically bound with bone and rapidly formed the hydroxyapatite (HA, Ca₅(PO₄)₃(OH)) layer on their surface, following initial bioactive glass degradation⁴. As for bioactivity, bioactive glasses are known to be biocompatible without toxicity, inflammation, and foreign-body response⁵. A histological result showed good interaction of bioactive glasses with bone tissue while forming an HA layer, which can interact with collagen fibrils of damaged bone tissue⁶. Since then, bioactive glasses for hard tissue regeneration have been developed in medical field. Formation of HA layer between bioactive glasses and hard tissue is well accepted to facilitate protein adsorption, attachment of progenitor cells, cell differentiation, incorporation of collagen fibrils, the

excretion of extracellular matrix and its mineralization, which is crucial for not only osteogenesis but also dentinogenesis and cementumgenesis⁷. Therefore, bioactive glasses and their derivatives have been highlighted for dentin, cementum or enamel regeneration in dentistry.

With the development of nanotechnology, the application of bioactive glasses has been diversified to overall application beyond hard tissue regeneration in dentistry. Nanoparticles offer more surface area to combine with other dental materials and better biological and mechanical properties for substrate materials per weight of particle, as compared with conventional micro-sized particles⁸. Along with the advantages of nanoparticles, therapeutic ions (*i.e.* Ag, Cu, Sr and so on) doped bioactive glass nanoparticles (BGNs) and their nanocomposites have been applied in dentistry. By virtue of above therapeutic ions released from BGNs, BGNs and their nanocomposites are able to be used as a bone or dentin substitute, which showed antibacterial, angiogenesis effects, self-healing ability or less cure shrinkage with hard tissue regenerative potential^{9–11}. Recently, these biological effects of ions doped into BGNs and the intrinsic properties of BGNs have rendered the personalized treatment facilitated for particular patients who are susceptible of tooth caries or infection and are insufficient in regenerative potential^{12–14}.

Children and the elderly who have bad brushing habits and other potential patients with poor oral conditions from systemic diseases may have a lot of infection chances, such as lack of self-purification against bacteria or regenerative potential, resulting in secondary dental caries, infection of dental pulp tissues and finally tissue damage. Without additional or particular managements, it may be far from the

Color figures can be viewed in the online issue, which is available at J-STAGE.

Received Dec 14, 2015; Accepted Mar 30, 2016

doi:10.4012/dmj.2015-428 JOI JST.JSTAGE/dmj/2015-428

Fig. 1 Beneficial effects of therapeutic ion-doped BGNs and their nanocomposites on the personalized dental treatment.

success of tissue regeneration. Therefore, customized preparation of dental materials and the treatment of patients are imperative, which is called 'personalized dental treatment'.

Here, the usage of BGNs and their nanocomposites for dental tissue regeneration is reviewed with highlighting personalized dental treatments. Beneficial properties of bioactive glass-based nanocomposites for personalized dental treatments are depicted with representative processing methods (Fig. 1).

PROCESS

Sol-gel techniques

Advantages and disadvantages of processes for fabricating bioactive glass nanoparticles were summarized in Table 1. The sol-gel process is one of the powerful fabricating methods for synthesis of silicate-based glasses and has been widely spread due to the easy but facile preparation of BGNs^{2,15}. Sol-gel involves the use of metal-organic precursors which are converted to inorganic materials in either water or organic solution. The synthesis of specific silicate bioactive glasses by the sol-gel technique at low temperatures using metal alkoxides as a precursor was shown in 1991 by Li *et al.*². Tetraethyl orthosilicate (TEOS), calcium nitrate

and triethylphosphate are used as typical precursors. Gel is formed after hydrolysis and polycondensation, which subsequently is calcined at 600–700°C to form the bioactive glass. The morphology of bioactive glasses in terms of porosity and surface area could be tailored by varying preparations¹⁶.

A recent work on fabricating BGN by sol-gel process reported by Hong *et al.*¹⁵ showed that BGNs were obtained by following two steps; sol-gel process and coprecipitation method, wherein the mixture of precursors was hydrolyzed in acidic condition and condensed in alkaline environment separately and then followed by a freeze-drying process. Mixture solution of TEOS and $\text{Ca}(\text{NO}_3)_2$ in ethanol and water was adjusted at pH 1–2 with an addition of citric acid and vigorously agitated for hydrolysis. Transparent acidic mixture dropped into $(\text{NH}_4)_2\text{HPO}_4$ solution under vigorous agitation. Continuously, ammonia water was added into the solution to set the pH of solution to 10–11. After incubation for certain periods, formed gel and its precipitation was separated by centrifugation and freeze-dried. Finally, freeze dried gel was calcinated at 700°C and BGNs were gathered. The porosity, surface area, general shape and size of BGNs could be tailored by varying the production conditions and the feeding ratio of reagents¹⁷. For example, various shapes of BGNs such

Table 1 Advantages and disadvantages of processes for fabricating bioactive glass nanoparticles

Process	Advantages	Disadvantages
Sol-gel	Simple process	Time consuming process
	Low cost	Residual solvent leading cytotoxicity
	Controlled porosity, pore size and surface area	High calcination temperature
Microemulsion	Homogeneity with high purity	Relatively low production yield
	Easy to add another metal precursors	
Flame spray	Low processing temperature	Low production yield
	Minimum aggregation	Large quantity of oil and surfactant
	Fast process	High technical sensitivity
Flame spray	High production yield	High processing temperature
	No need of additional energy	Limitation of metal precursors
	High chemical homogeneity	High cost
	More bioactive due to amorphous structure	Safety issue during process

as spherical or elliptical shapes could be fabricated¹⁸⁾. It is important to control the characteristics of BGNs in order to obtain the desired bioactivity or biological properties.

Lactic acid was involved in the sol-gel process of CaO–P₂O₅–SiO₂-based BGNs, which was able to control size of BGNs from 20 to 200 nm¹⁹⁾. With a contribution to a silane coupling agent, dispersibility of BGNs was improved and size of BGNs was changeable between 20 and 70 nm²⁰⁾. Recently, different ions have been added to BGNs, such as zirconium, zinc (Zn), magnesium (Mg), titanium, boron, copper (Cu), cobalt (Co) and silver (Ag) in order to improve functionality and bioactivity of BGNs²¹⁾. However, it is not easy to prepare bioactive glasses in nano-size scale after addition of those ions. Delben *et al.* have developed sol-gel-derived silver-doped BGNs (~100 nm) to induce antibacterial effects by releasing silver ions²²⁾. In addition, the development of BGNs releasing various therapeutic ions to induce hard or nerve tissue regeneration, angiogenesis and antibacterial effects was introduced.

There was wide agreement with using a sol-gel technique to synthesize BGNs, as discussed in this section. However, the method showed limitations in terms of compositions. Moreover, remaining water or organic solvent could result in undesirable effects for the intended biomedical applications of BGNs. A high temperature calcination step made possible to eliminate organic solvent. In addition, batch-to-batch variations of BGN's characteristics may occur because of sensitivity and multiple steps of the sol-gel process.

Microemulsion techniques

The technique of microemulsion has been introduced as an appropriate method to obtain inorganic materials at the nanoscale with minimum aggregation²³⁾. Microemulsion refers to dispersion in water, oil, and surfactant(s) that are an isotropic and thermodynamically stable system with dispersed domain diameter varying in approximate size from 10 to 50 nm according to IUPAC

definition. In water-in-oil microemulsions, there are nanosized water droplets dispersed in the continuous hydrocarbon phase and surrounded by the monolayer of surfactant molecules²⁴⁾. These aqueous droplets act as a nanoreactor in which designed reactions can take place when droplets containing the suitable reactants collide with each other. After drying and calcination of the precursor powder at an appropriate temperature, the desired ceramic particles can be obtained.

Microemulsion techniques are capable of processing nano-sized particles of organic and inorganic composition with minimal aggregation. However, low production yield despite the usage of a large amount of oil and surfactant has remained as a main disadvantage of the microemulsion techniques. Therefore, although microemulsion techniques provide an alternative way to produce nanosized inorganic and organic particles, only few reports are available on the synthesis of nano-sized bioactive glass particles using this method to prepare spherical BGNs^{25–27)}.

Flame spray synthesis (Gas phase synthesis)

Flame spray synthesis needs metal-organic precursor compounds to produce nanoparticles above 1,000°C. The principle of all flame spray synthesis is the formation of molecular nuclei which is followed by condensing and merging of precursor droplets, inducing the subsequent growth of nanoparticles in high temperature flame regions without requiring additional energy source²⁸⁾. The most critical factor to determine the particle size is the mean residence time of particles in the high temperature regions. Short residence time (1 ms) with high cooling rates (>1,000 K/s) enables the nanoparticle preparation. In contrast to above two wet phase processes, gas phase synthesis relatively gives higher production rates.

Several investigations have performed the flame spray process, which noted that key factors how they can be controlled to obtain designed nanoparticles with desired size range and chemical composition^{29,30)}. It has

been shown that the liquid metal carboxylate precursor is a convenient source replacing the gaseous precursor because any composition of liquid precursor could be used²⁹. In this process, the liquid precursor is dispersed by oxygen gas over a nozzle thereby forming a flame spray after being ignited. As the flame spray is formed, the organic constituents of the liquid precursor completely combust, and water and carbon dioxide and metal constituents oxidize remain to form the nanoparticles.

In addition, liquid metal-carboxylate precursors are highly stable in air and humidity condition as being miscible among each other. This process allows the production of any kind of nanoparticulates with higher chemical homogeneity. Moreover fast quenching after synthesis of nanoparticles can preserve the amorphous state of the material, which is important for bioactivity of BGNs^{31,32}. By using flame spray synthesis, therefore, the preparation of nanoparticles of different bioactive glass compositions has made possible to use 2-ethylhexanoic acid salts of calcium and sodium, hexamethyldisiloxane, tributyl phosphate^{33,34}

APPLICATIONS

Intrinsic properties

Bioactive glasses have bioactivity and antibacterial effects and thus have been used as a carrier for drugs or ions^{35,36}. In terms of structural integrity, bioactive glasses could not be an optimal carrier due to their intrinsic brittleness³⁷. To achieve mechanically stable bioactive glasses, new sintering protocols including temperature and time must be optimized³⁷. SiO₂ in the bioactive glasses is crucial for tailoring mechanical properties, bioactivity and antibacterial effects, since less than 60 wt.% of SiO₂ could be bioactive but more could be biologically inert³⁸. Increase in SiO₂ is able to increase in their mechanical properties such as hardness, compressive strength. Therefore, increase in SiO₂ was suggested to increase in the surface area to higher percentages while maintaining bioactivity and improving mechanical properties³⁹.

Addition of positively charged ions, such as Zn²⁺, Cu²⁺, Ag⁺, Al³⁺, Ti⁴⁺ or Ta⁵⁺, to the bioactive glass has been performed to control intrinsic properties of bioactive glass⁴⁰. For instance, metal ions can render mechanical properties of bioactive glasses sustained or decreased⁴¹. Therefore, one main reason of addition of these ions to bioactive glasses may make possible to modulated bioactivity and other biological effects. In another example, Ca²⁺ and Si⁴⁺ released from implanted bioactive glasses can be a precursor of HA and increase in pH, inducing antibacterial effects. Released Mg, Sr, Cu, Co, Ag and Ga ions as metal precursors from bioactive glasses could facilitate odontogenesis, osteogenesis, angiogenesis and antibacterial effects²¹.

Applicable forms of bioactive glasses in dentistry can be diversified to particles, porous scaffolds, or dense constructs. Dentists prefer to use a form of particles or granules rather than a bulk style, as they can be easily pressed to fill a defect. In 1993, Perio-Glas® (NovaBone

Products, Alachua, FL, USA) was introduced as the first particulate bioactive glass with the size range of 90–710 µm for the repair of bony defects of the jaw and bone loss by periodontal disease. Other bioactive glass products, which have been used as a grafting material in dentistry, include Biogran® (BIOMET 3i, Palm Beach Gardens, FL, USA) and BonAlive® (BonAlive Biomaterials, Turku, Finland)^{35,42}. *In vivo* and clinical studies showed a success of bone synthesis with Perio-Glas® compared to controls. Perio-Glas® has been used in “guided tissue regeneration” as a polymer membrane as well as sterilizing material for root canal therapy prior to inserting dental implants, raising pH to bactericidal levels in addition to its bioactive properties^{43–47}.

BGNs have gained attention due to their promising bioactivity and nanosize effects. They have larger surface area to release ions than micro-sized bioactive glass particles. By controlling the particle size to nanoscale, properties like osteoconductive, dissolution, drug loading capacity and other vital characteristics can be greatly improved. The nanostructured surface enhances cell adhesion, enhances proliferation, promotes differentiation, and increases bioactivity (biomineralization)⁴⁸. It was also reported that they have different intrinsic characteristics depending on the shape (*i.e.* wire, fiber and tube).

Also BGNs with mesoporosity have been developed to efficiently deliver biological molecules such as siRNA, growth factors and therapeutic drugs due to their ability of endocytosis and biocompatibility⁴⁹. Pore diameter of mesoporous BGNs usually ranges between 2 and 50 nm according to IUPAC notation compared to microporous and macroporous materials with diameters of less than 2 nm and greater than 50 nm respectively^{4,50}. As an approach to locally deliver the drugs in implanted site⁵¹ mesoporous BGNs have shown high delivery efficiency, continuous action, biocompatibility and bioactivity due to higher surface areas and larger pore volumes than conventional bioactive glasses^{52–54}. Therefore, BGNs are able to be employed as a graft materials replacing dentin and cementum or for jaw and alveolar bone in periodontology and endodontology^{55,56}.

Beneficial effects of bioactive glass nanocomposites on dental hard tissues

BGNs have an advantage as for superior apatite-mineralization ability in biological solution, expecting excellent hard tissue regeneration. In the past, many studies focused on the *in vitro* bioactivity of BGNs with different forms, including particles and composite scaffolds. Yan *et al.* found that apatite mineralization of BGNs was formed only after incubation with SBF for 4 h⁵⁷. In particular, apatite mineralization of nano-sized particles superior to that of other-sized particles, due possibly to the highly specific surface area of nanoparticles, enhancing ion releasing and bioactive behavior⁵⁷. According to the nuclear magnetic resonance spectroscopy study regarding mechanism of apatite mineralization of BGNs, conventional bioactive glass particles require typical ‘first three stages’ but

BGNs do not^{7,58}. In the first three stages, conventional bioactive glass particles release silicate ions and form Si–OH groups, and then Si–OH groups form networks by repolymerization. By contrast, the surface of BGNs is inherently able to accelerate these first three stages⁵⁸. These findings indicate that BGNs and their composites are appropriate to hard tissue engineering.

In 1988, a simple cone of Bioglass®, termed the Endosseous Ridge Maintenance Implant (ERMI®), was commercially available in dentistry. To repair the tooth roots and to provide a stable alveolar bone ridge for dentures and dental implants, such micro-sized bioactive glasses were inserted into fresh tooth extraction or bony defects area. They showed high stability and much better efficacy than that of HA-based hard tissue substitutes. However, they failed to gain a commercial attention, since dental surgeons preferred the customized graft rather than the ready-made one.

In tooth extraction sites, BGNs have been used not only to preserve the height of the alveolar ridge⁵⁹ but also to reconstruct the mandible or maxilla bone following autograft harvesting, and to fill bony defects as well. These clinical applications confirmed the benefits of BGNs as a highly compatible graft in dentistry⁶⁰. More recent applications of BGNs include several exemplar studies on doping therapeutic ions for accelerating hard tissue regeneration or coatings of hard tissue substitute with these nanocomposites^{55,61}.

Mg or Sr is an important trace element in human bone. Mg ions play a critical role in bone remodeling and skeletal tissue development and for nucleation in biological apatites⁶². Sr²⁺ ions are able to impact bone-related cells and induce osteoblast activity by stimulating bone formation and reducing bone resorption⁶³. For this reason, Mg and Sr have been incorporated into biomaterials to further improve their bioactivity for bone-regeneration applications^{64,65}. They can be substituted instead of calcium in BGNs for better bone remodeling and osseointegration stimulation and ion-doped BGNs promoted osteoblast proliferation while also decreasing in the osteoclast activity^{66,67}.

Scaffolds are still needed in dentistry for oral environment regeneration. For hard tissue regeneration in dentistry, there has been widespread use of bioceramic scaffolds, such as HA, tri-calcium phosphate and those composites. However, their clinical applications have been limited because of their brittleness, difficulty of shaping, and absence of other functionality⁶⁸. Therefore, BGN-added nanocomposite bioceramic scaffold was introduced to overcome above the drawbacks. In addition, numerous synthetic polymers including polycaprolactone, polyethylene glycol (PEG), poly-L-lactic acid (PLLA), polyglycolic acid (PGA) and poly-DL-lactic-co-glycolic acid (PLGA) with nanocomposites have been used in the attempt to produce scaffolds in dentistry. Because these materials can be fabricated with a tailored architecture, their degradable characteristics can be controllable and replaced by host hard tissue^{69,70}. Without BGNs, the synthetic polymer itself has drawbacks due to reduced

bioactivity, low mechanical properties and lowering the local pH due to byproducts after hydrolysis⁷¹. Therefore, various BGNs have been fabricated with bioceramic cement and synthetic polymers for osteogenic or odontogenic properties^{12–14,72,73}. Owing to mesoporosity of BGNs, therapeutic drugs could be loaded and accelerate biological effects of these nanocomposite-based BGNs^{49,74–77}.

Use of BGNs for treatment of hypersensitivity in the tooth restoration has led to a form of very fine Bioglass® particulates called NovaMin® (NovaMin Technology, GlaxoSmithKline, London, UK) and sol-gel derived BGNs as an active repair additive in toothpaste. This material makes tiny holes in the dentine filled with minerals so as to reduce sensitivity of the tooth. Dentin hypersensitivity is caused by dentin exposure in root surface due to periodontal disease, toothbrush abrasion or cyclic loading fatigue of the thin enamel near the cemento-enamel junction⁷⁸. The hydrodynamic theory about dentin hypersensitivity mechanisms explains how BGNs reduce hypersensitivity. When external stimuli such as contact to cold or hot materials, and osmotic pressure are applied to the exposed dentin, they cause fluid movement within the open-dentinal tubules, which may result in pressure changes in the dental pulp nerve endings⁷⁹. When BGN-included toothpastes are used, BGNs adhere to the open-dentinal tube and form an apatite-like layer; therefore, blocking the dentinal tubules halts pressure changes in the dental pulp nerve endings and relieves the pain for longer periods. An *in vitro* study, showed a good attachment of BGNs to the lightly etched human dentin and an apatite-like layer was covered with the surface within 24 h. This showed that BGNs stimulated the deposition of calcium phosphate over the dentine tubules *via* bioactivity⁵³. In a clinical trial, volunteers who brushed with a NovaMin®-containing toothpaste over 2–6 weeks experienced pain relief compared to users of a normal toothpaste as a control group.

However, periodontal tissue regeneration still remains a big challenge in periodontics, mainly when large defects are concerned. Guided tissue regeneration is by far the best studies in the dental field and has contributed to regeneration⁷⁹. In this regard, BGNs have been considered promising for regenerative applications including cementoblast compatibility, cementum regeneration, filling of bone defects, the reduction of probing depth and clinical attachment gain^{80–83}. Incorporation of Sr into BGNs accelerated the biological response to periodontal ligament cells due to releasing effects of Sr²⁺ ions⁷⁹. Therefore, combination of ion doped BGNs with guided tissue regeneration technique seems like to be applied in periodontal tissue regeneration.

Other applications in dentistry

Antibacterial effect of BGNs has been used in dentistry. During dissolution of BGNs, pH rises up by various released cations and such high pH condition can kill microbes¹. For instance, an *in vitro* study showed that S53P4 BGNs can kill pathogens attached to enamel caries

(*Streptococcus mutans*), root caries (e.g. *Enterococcus faecalis*, *Actinomyces naeslundii* and *Streptococcus mutans*) and periodontitis (e.g. *Actinobacillus actinomycetemcomitans* and *Pseudomonas aeruginosa*)⁸⁴. Also S53P4 BGNs and other nanocomposite-based BGNs with higher than 50 mg/mL in the broth cultures of 16 different bacteria showed antibacterial properties due to the high pH⁸⁴. It is evidenced that ideal BGNs include antibacterial elements which prevent infections. The possible elements for this purpose are antibacterial metal ions²⁰. Ag is one of representative elements known as antimicrobial, which is induced by destruction of essential enzymes for homeostasis of bacteria, inhibition of cell division and interaction with nucleic acids⁸⁵. Ag precursors can be easily introduced into BGNs and then Ag ions can be released during their dissolution. The sol-gel derived BGN composition of 76% SiO₂, 19% CaO, 3% Ag₂O and 2% P₂O₅ (by weight) affected antibacterial treatments, particularly due to Ag ions²². Less than 1 mg/mL is enough to kill oral pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* while 50 mg/mL of silver-free glasses is needed to be bactericidal. It is promising that low concentrations of the sol-gel derived BGNs that can be bactericidal were not cytotoxic to human osteoblasts⁸⁶. Cu, Co Ni, and its alloys can also be used in antimicrobial precursor for BGNs^{87,88}.

In addition, other biological effects are gaining attention for adding functional ions to BGNs. For example, Cu, an excellent antimicrobial agent, plays an essential role in forming bone tissue, triggering wound healing, and improving angiogenesis with elastin matrix deposition around implanted sites⁸⁹⁻⁹¹. Previous studies suggested that insufficient level of oxygen, a condition known as hypoxia, plays a critical role in endothelial recruitment, differentiation and blood vessel formation, linking to angiogenesis. Hypoxia can be artificially induced by treating Cu ions and, consequently, Cu can induce angiogenesis further by replacing the calcium element⁹².

Zn also improves bone bonding with BGNs, inhibits bone resorption, controls osteoblastic cell growth, differentiation, and development, and stimulates apatite formation⁹³. Zn acts as nucleation for apatite formation and accelerates biological activities of osteoblast cells associated with BGNs⁹⁴. In addition, Zn, another metal precursor in bioactive glass, is thought to have antibacterial properties, but it can cause cytotoxicity in higher concentrations⁹⁵. Ga has diverse therapeutic activities such as suppressing osteoclast activity, immunomodulating activities, and antibacterial effects. Mechanisms for Ga's antimicrobial activity is likely to similarities of Ga and Fe ions in a view of bacteria. Ga ions enter microbes through Fe ion transport, disrupt Fe metabolism and interfere with DNA and protein synthesis^{96,97}.

Modification of dental adhesive or glass ionomer cement with therapeutic ions doped into BGNs is one of the most attractive approaches in future dentistry. Microleakage of dental materials is one of the

representative reasons for failure of restoration with functional dental materials, which released therapeutic drugs or biomolecules leading to vacancy in restorative material. With BGNs-added dental materials, gaps could be healed due to self-sealing properties of bioactive behavior of BGNs, which decrease gap-oriented secondary caries and micropenetration of oral bacteria. Along with the self-sealing effects, other functionalities, such as antibacterial effect and angiogenesis, from doped therapeutic ions are able to prevent the failure of hard tissue restorations in oral cavity by killing oral bacteria and increasing blood supply. Biological and mechanical characteristics of ion doped BGNs have been investigated so far, applications in currently used dental materials (i.e. dental adhesive and restorative material) have been less tried, which is needed further.

Biocompatibility of bioactive glass-based nanocomposites

Bioactive glass has been considered as one of the outstanding biocompatible materials, and the use of their nanocomposites has been suggested as a promising strategy to enhance cell-biomaterial interaction. Currently, there exist many types of bioactive glasses approved by Food and Drug Administration (FDA) in the market and termed 'Bioactive glass', which reveals biocompatibility of bioactive glass particles. However, their nanoparticulate forms still include safety issues due to the concern of toxicity attributed to high reactivity and easy endocytic property⁹⁸. According to the revealed results, cytotoxicity could be dependent on the cell type and the ratio of cell number to nanoparticle concentration. Toxicity of BGNs in dental tissue-derived cells such as dental pulp stem cells, odontoblasts, periodontal ligament cells, cementoblasts and gingival fibroblasts was not detected in the low concentration (≤ 100 $\mu\text{g/mL}$) and the *in vivo* study⁹⁹⁻¹⁰² including several clinical cases^{5,13,69,74}. However, further detailed researches of BGNs including the long-term study are needed for their safe use^{9,13,14}.

Personalized dental treatment using ion-doped BGNs

Personalized treatments performed on the basis of CAD/CAM process have been suited for each dental patient, which fabricates customized restorative tooth structure¹⁰³. Despite their promise, there have been limits on dental materials and technologies used for personalized dental treatment, which could not deal with oral poor condition or infection in certain types of patients¹⁰⁴. This infection could be due to poor dental treatment procedures or patients' particular conditions¹⁰⁵. Poor oral conditions can induce dental tissue degeneration. This could be initiated by bad brushing habits or invasion of germs by external injury. Especially, the symptoms of the elderly who have relatively less amounts of saliva secretion and less angiogenesis potential could be severe than the young.

In this respect, BGNs or therapeutic ion-doped BGNs have been suggested as an emerging implant for the personalized dental treatment¹⁰⁶. For instance, they can be suitable for the patients suffering from

Table 2 Functional property from therapeutic ions of BGNs and personalized dental treatment

Therapeutic ions released from BGNs	Functional property	Personalized dental treatment
Sr ²⁺ Mg ²⁺ Fe ²⁺ B ³⁺ Zn ²⁺ Li ⁺ Zr ⁴⁺	Hard tissue regeneration	People lack of hard tissue regenerative potential (dental pulp tissue, bone, cementum)
Ag ⁺ Cu ²⁺ Co ²⁺ Ga ³⁺	Antibacterial activity	Children and the elderly who have bad brushing habits Other potential patients who have poor oral conditions from systemic diseases
Cu ²⁺ Co ²⁺	Angiogenesis	Children who need blood supply for further tooth development The elderly who need blood supply for proper regeneration

hypersensitivity, which requires dentin tissue formation for blocking dentinal tube^{33,53}, since they are able to be controllably prepared and treated. Functional property from therapeutic ions from BGNs or BGNs-based nanocomposite and its personalized dental treatment were summarized in Table 2.

Sr, Mg, Fe, B, Zn Li or Zr ions are well known for accelerating hard tissue regeneration and these ion-doped BGNs and nanocomposites could be used for the special dental patient deficient in tissue regeneration force. The *in vitro* studies using B ion-doped implants showed no cytotoxic effects in bone-marrow mesenchymal stem cells, and ions were gradually released into the culture medium, resulting in enhanced cell proliferation and alkaline phosphatase (ALP) activity and mineralization¹⁰⁷. Sr, Fe, Mg, Zn or Zr-doped BGNs and their nanocomposite enhanced cell proliferative activity and apatite formation ability as well as the expression of bone-related genes (osteocalcin and ALP) and dentin-related genes (DSPP and DMP) in human bone-marrow mesenchymal stem cells and pulp stem cells^{108,109}. Li-doped BGNs and their nanocomposites in the use of human periodontal ligament-derived cells improved cementum formation of the cells and thereby mineralization during periodontal regeneration, which is responsible for linking the roots and surrounding alveolar bone¹¹⁰.

In addition to studies of specific effects of BGNs in hard regeneration, several reports have focused on the antibacterial properties, resulting from release of antibacterial ions in surrounding area, for the treatment or prevention of infections in dental pulp or periodontal tissues. Ag, Cu, Co and Ga ions are known to induce antibacterial effects like a broad spectrum of antibiotics, and these ion-doped BGNs and nanocomposites could be used for patients having periodontal diseases infected by bacteria in the treatment area. For example, Ag-doped BGNs and their nanocomposites can be used for not only

bacteriostatic but also bactericidal materials against *Streptococcus mutans*, *Staphylococcus aureus* and *E. coli* growth which are responsible for dental tissue infection and dental careis^{55,111,112}. These antibacterial properties are likely due to leaching of silver ions which interfere with several cellular mechanisms and induce dysfunction in a not yet fully understood way¹¹³. By virtue of silver ion release, antibacterial effects in the treatment site were positive in terms of tissue regeneration.

Cu and Co ions have shown a promising potential of angiogenesis, and these ion-doped BGNs and nanocomposites could be used for children and the elderly who need blood supply for further tooth development and proper regeneration respectively. Recently, Co-doped BGNs and their nanocomposites induced a hypoxic environment for enhancing angiogenesis, as estimated by confirming the expression of hypoxia-inducible factor-1 α as well as dentin-related gene expression of dental pulp stem cells^{56,114}. Similar results can be achieved by incorporating Cu in BGNs and their nanocomposites^{92,115}. Above angiogenesis potential BGNs-based nanocomposites can be applied for the elderly or genetically modified patients who need an increase in blood supply, or children who need angiogenesis for root formation.

CONCLUSION

A comprehensive overview of the processes and applications of BGNs and their derivatives for the use in dentistry was presented in this article. BGNs can be produced *via* three methods, sol-gel processing, microemulsion techniques and flame spray synthesis method. Among these techniques, sol-gel processing has been widely used to make BGNs due to their simple operation, low cost and controllable properties of BGNs. Taking into account beneficial effects of BGNs on binding to oral hard tissue and promoting the hard

tissue growth, BGNs and their derivatives have been customized for the purpose of hard tissue regeneration as well as hypersensitivity treatments. BGNs have been further beneficial for hard tissue regeneration by incorporating variable doping materials, which can show improvement of dentin, cementum and bone regeneration in pulp or periodontal tissue. These beneficial effects include an antibacterial or angiogenesis activity, which creates a bacteria-free environment in implanted sites while healing and regenerating the soft or hard tissue with enough blood supply. The addition of therapeutic elements, such as Ag, Cu, Co, Zn or Ga precursors to BGNs have shown more promoted therapeutic effects than when using primitive BGNs, and it is possible to use for personalized dental treatments. However, there remains further detailed research *e.g.*, of long-term study for their safe use in the clinical application.

CONFLICTS OF INTEREST

The author has no financial relationship with the organization that sponsored this research.

ACKNOWLEDGMENTS

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2015R1C1A1A01052127) and Research Fellowship Program (NRF-2013R1A1A2062694) funded by the NRF of Korea.

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