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A Mini-Review on the Bioactive Glass-Based Composites in Soft Tissue Repair

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Abstract

As a third-generation biomaterial, the bioactive glass (BG) has gained the attention of various research groups who have started to employ it for enhancing tissue regeneration. Most of these applications focus on bone tissue engineering based on either BG alone or BG-based composites, where the properties of the other components can improve those of the BG. Moreover, recently, the BG has become one of the important materials with ability to improve the regeneration of soft tissues. This review highlights the up-to-date advances in the different BG-based composites which have been studied in the treatment of various soft tissue injuries. These include the neuronal, muscle, lung and cardiac tissue regeneration, as well as cornea treatment. In addition, the enhancement in tissue repair due to the composite structure is discussed with comparing to the individual component structures.

Keywords: Bioactive glass; Tissue engineering; Bone; Dentistry; Implants

Introduction

The bioactive glass applications in bone tissue engineering

Since the discovery of the first bioactive glass compound, 45S5 bioglass®, by L. Hench in the 1960s, a series of research activities have started investigating its reaction with the body tissue, and how it can be employed in different biomedical application [1,2]. The primary studies on the 45S5 bioglass® focused on its interactions with the bone tissue, and how they can bond directly in combination with the sequence of reactions which lead to the formation of the bioactive hydroxyl-carbonate apatite layers. The full steps were covered previously [2,3]. Moreover, the interactions between the BG molecules and collagen in both bone and soft tissue were explored [4].

In addition, the bonding between the formed apatite layer crystals and the collagen fibers in bone were further investigated [1,5]. Since that, different BG compositions have been generated with a focal application in bone regeneration, whether in dentistry, as bone implants, bone fillers, or bioactive coating for different implants [6-9]. These currently include three main categories of bioactive glasses based on the main oxide component: silicate, borate, and phosphate-based systems, where each type has its unique properties, bioactivity, degradability rates, mechanical properties and applications [10-12]. However, many glass compositions can be incorporated with certain oxides and elements for getting new properties. For instance, the incorporation of CaO and MgO was found to improve the surface reactivity of different bioactive glasses [10]. The incorporation of Al_2O_3 can improve the mechanical strength the BG [13]. Moreover, Sr was introduced into a BG composition due to its anti-oxidative properties [14]. In addition, Silver ions doping in the bioactive glass impart it certain antimicrobial properties [15,16]. Furthermore, bioactive glasses doped with copper [17,18] and cobalt [19,20] showed improved angiogenesis once implanted in bone.

Literature Review

Bioactive glass in soft tissue repair

In 1981, Wilson and his colleagues discovered for the first time the ability of the 45S5 Bioglass® to extend its interactions through making bonds with soft connective tissues [21]. Moreover, a study by Merwin et al., 1982 showed that the BG, in addition to its bonding abilities to the bone fractions in the ossicle, it could also make attachment with collagen [22]. This was followed by a series of research for investigating a number of issues. The first one focused on understanding the mechanism of this type of bonding; a similar mechanism to bone bonding was discovered, resulting in the formation of a thicker bonding interface [23]. The second issue dealt with the composition of the material which can bond with the soft tissue. It was found that only the bioactive glasses with high surface reactivities can bond with the soft tissues [24]. Greenspan, compared between the suitable compositions of the glasses with a bioactivity towards the hard and soft tissue [25]. However, the most important point in the bioactivity of SiO_2-containing bioactive glasses to be able to bond with the soft tissue is that the SiO_2 content shouldn't exceed 52% [23]. The third issue was to test whether these new compounds have any adverse reactions on becoming in contact with the soft tissue, and that was achieved through a group of *in vitro* and *in vivo* studies as already outlined [26]. The logical forth issue was the synthesis of different BG compositions with more investigating of their soft tissue bonding abilities for further usage in the treatment of different diseases, where the main efforts concentrated on the silicate BG class. This was summarized by Miguez-Pacheco et al., Miguez-Pacheco et al., Baino, et al., [26-28]. Nevertheless, the other types of bioactive glasses have the ability to bond to the soft tissue as well. For instance, borate bioactive glasses have found applications in wound healing [29,30], and nerve injuries [31]. Similarly, phosphate-based BG structures showed a promising ability to promote the regeneration of neurons after nerve injury [32,33].

Bioactive glass-based composites in tissue engineering

As most of the soft and hard tissues are built up of composite structures, the designing of different bioactive composites has gained the attention for mimicking the extracellular matrices. The properties of most of these structures involve those of the composing

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materials, whether made of polymers only, inorganic materials only, or a polymer(s) with inorganic material. Different types of BG-based composite structures were created using different techniques for bone tissue engineering, and proved their abilities to overcome some of the problems related to the brittle characteristics of the glass scaffolds without affecting their bioactivity [34-36]. Depending on the same principle, some efforts have started in designing BG-containing composite structures for further usage in the regeneration of the soft tissue and treatment of their injuries. These designs may compose of different types of BG with a polymer or with other inorganic compounds; however, the final properties involve those of all components.

Discussion

This review summarizes the current achievements in the designing of different BG-containing composites with an efficiency to be used in the treatment of certain soft tissue problems. These include their applications in lung tissue repair, cardiac tissue regeneration, skeletal muscle regeneration, intervertebral disc treatment, cornea treatment and nerve regeneration. Although the most prominent application of the BG in soft tissue regeneration was in the field of wound healing and designing of wound dressings, these achievements aren't covered deeply in this review, where they have been reviewed previously in detail [26,28,37]; however, some current examples are highlighted.

Table 1 summarizes the type of the employed BG involving its structure and particle size, the matrix used in the composite structure, the final form of the composite, application and the remarks [38-53].

Conclusion

The advancement in materials science and engineering has paved the way for the creation of different bioactive composite designs in

BG	Matrix	Scaffold form	Application	Remarks	Ref
13-93 B3 borate glass microfiber	Fibrin	Fibrin scaffolds with embedded glass microfibers	Neuronal tissue regeneration	The composite scaffold enhanced the neurite extension from dissociated total dorsal root ganglia cells without any significant differences from that of the control fibrin scaffolds. Moreover, the glass rod and microfibers proved their neuroprotective effects along with the ability to increase the percentage of live neurons.	31
BG nano-particles	Gelatin	Nanocomposite conduits	Peripheral nerve regeneration	The seeded Miapaca-2 cells were still viable after 72 hours of incubation with the conduits referring to their significant non-toxicity. Three months after the implantation of conduits in rats, a near complete degradation was observed with a degree of regeneration similar to the normal state.	39
0.5 SiO_2–0.2 CaO–0.13 ZnO–0.14 Na_2O-0.03 CeO_2 mol%) BG micro-particles (20 wt.%)	PLGA and Pluronic F127 (F127) block copolymer	Nerve guidance conduits as tubular constructs	Peripheral nerve regeneration	The ultimate tensile strength increased from the range (3.2-4 MPa) after one day of incubation in a phosphate buffered saline solution to be within the range (6.2-7 MPa) by the seventh day. These values were higher than those of conduits containing no BG. However, a decrease in the strength was observed after 28 days of incubation using the highest concentration of F127 (5 %). Similarly, the Young's modulus for the composite conduits was higher than that of the BG-free conduits, with a continuous increase by the incubation period to reach its maximum in F127-free structures. After incubation of mouse fibroblasts (L929) in extracts of the conduits, all cells showed more than 85 % viability.	40,41
0.5 P_2O_5–0.4 CaO–0.05 Na_2O–0.05 Fe_2O_3 mol%) BG micro-fibers.	Collagen	Phosphate glass fiber–collagen hydrogel scaffolds	Treatment of nerve injuries	The BG-reinforced hydrogel improved the locomotor and bladder functions after implantation into the gap between the proximal and distal stumps in rats, with some axonal growth from them to the scaffold. There were no significant inflammatory reactions between the effects of the BG-containing scaffolds and the collagen scaffolds alone. The brain derived neurotrophic factor mRNA levels increased in bladder of the rats, implanted by the BG-reinforced scaffolds.	42
45S5® BG micro-particles (5 μm)	PLLA	Composite porous foams	Treatment of the intervertebral discs (IVD)	The foams were able to enhance the proliferation of the seeded bovine annulus fibrosus cells isolated from the coccygeal discs, with providing the suitable local environment for the production of the extracellular matrix. This approach is a promising step towards the repair of human lumbar IVD.	43,44
45S5® BG micro-particles (0.01-1 wt.%)	Polyglycolic acid (PGA)	PGA mesh fibers coated and interpenetrated with BG particles	Soft tissue engineering	The Fibroblasts (208F), seeded in multiwell plates of polystyrene coated with low BG concentrations (0.01% to 0.2%) showed increased proliferation after 24 hours of incubation. At the concentrations higher than 0.2%, a reduction in cell viability was observed. High secretions of the VEGF into the medium were observed within the concentration range (0-0.02%) only. The implanted BG-containing meshes showed increased neovascularization.	45
45S5® BG micro-particles (< 5 μm) (5 and 40 wt.%)	poly(D,L-lactic acid) (PLLA)	Composite porous foams	Lung tissue engineering	The BG-incorporated foams were biocompatible, where the seeded A549 cells (human epithelial lung cells) showed improved proliferation rates than those seeded in the polymer-based foams only. However, this was evident using the BG content of 5%, and the viability decreased with increasing the concentration. This behaviour was in contrast to the results from seeding of MG-63 cells, where the cell proliferation increased with the increase in BG content.	46
45S5® BG nano-particles	poly(glycerol sebacate) (PGS)	PGS-BG elastomeric composite	Treatment of cardiac failure	The elongation at break increased to 550% by the incorporation of the BG instead of 160 for the polymer alone, with the enhancement of the Young's modulus. The modulus decreased in the culture medium, referring to the biodegradability of the composite. The acidity caused by PGS degradation was counteracted with the alkaline products of BG degradation. The compatibility was confirmed through the increased viability of the seeded cardiomyocytes with eliminating the cytotoxic effects of the polymer on cultured mouse fibroblasts after crosslinking with the BG.	47,48
Phosphate-based glass fibre	Collagen	Collagen-coated glass fibres	Skeletal muscle regeneration	The composite enhanced the activity of the seeded muscle precursor cells (MPCs) up to 14 days, followed by a decrease in their metabolic activity. The reinforced scaffolds promoted the expression of MyoD1 and myogenin genes in the MPCs from the first day referring to the activation of their differentiation, with a down-regulation in MyoD1 expression in latter stages. The delay in gene expression relative to that in case of glass fibers refers to the initiation of ECM remodelling within the collagen hydrogel, followed by activation of cell migration and fusion.	49

BG micro-particles: -1–98 (44 wt.%) -45S5 (40 wt.%) -S53P4 (42 wt.%)	Polymethyl methacrylate (PMMA)	Glass particle–PMMA composite in the form of keratoprosthesis skirt structures	Osteo-odonto-keratoprosthesis (OOKP) surgery	The cumulative dissolution of SiO_2 and CaO in a simulated aqueous humour solution from the composites was in the range (9-13%) and (9-17%), respectively after six weeks of immersion. This was accompanied by the formation of slightly porous surface and a decrease in the compressive strength and Young's modulus.	50
(0.65 P_2O_5-0.15 CaO–0.1 CaF_2–0.1 Na_2O mol%) BG (2.5 wt.%)	Hydroxyapatite (HAP)	Porous BG-reinforced HAP discs	Treatment of cornea	The porosity increased, and density decreased with the increase in percentage of the used porogen, polyvinyl alcohol (PVA). The mass loss was significant under acidic conditions (pH3) with a maximum degradation on using 50% PVA; however, the degradation was weak under the physiological conditions (pH 7.4). The dense composite showed only 13.5% of mass loss after incubation under acidic conditions, with the highest concentration of calcium ions in the physiological solution. The porous composites containing 30 and 50 % PVA illustrated the highest efficiency to enhance the proliferation of the incubated fibroblasts, organization into the pore edges and colonization.	51
$45S5^{®\ BG}$ micro-particles (4 µm)	Poly (D, L-lactide-co-glycolide) (PLGA)	Microporous spheres of the polymer containing the microparticles	Healing of the deep inaccessible wounds.	Comparing with the ability of the neat polymer spheres, the BG-containing spheres stimulated significant increase in VEGF secretion from the cultured myofibroblasts *in vitro,* which was in a direct proportionality with the BG concentration. The BG-containing spheres retained 77% of the original weight after *in vitro* degradation for 16 weeks; while the polymer microspheres retained 82%. The former spheres showed faster integration into the host tissue with neovascularization than the polymer spheres referring to the improvement of cell infiltration.	52
45S5 BG nano-particles (1 wt.%)	poly(3-hydroxy ocatnoate)	Composite films (2D scaffolds)	Wound healing	The bioactive glass nanoparticles showed haemostatic properties, and their incorporation in the polymer films improved the wettability and surface roughness of the films. The increase in the attachment and proliferation of the seeded HaCaT cells to the films proves their biocompatibility.	53
BG microparticles (20 µm)	Polymem-branes	Bioactive skin tissue engineering grafts containing BG-activated fibroblasts	Wound healing	The BG extract could maintain the viability of the incubated cultured human dermal fibroblasts and enhance their ability to secrete the VEGF, EGF and bFGF. Moreover, the secretion of collagen I and fibronectin were enhanced. These results refer to the possible application of such grafts for enhancing the neovascularization with the formation of the new ECM for cell proliferation and migration. The *in vivo* implantation of the BG-loaded grafts in an excisional wound caused accelerating of the healing through the activation of wound contraction, angiogenesis, and collagen deposition.	54

Table 1: A summary of the different BG-based composites with potential applications in soft tissue repair.

which the problems of the composing materials can be overcome with imparting them new unique properties, which can be employed in the repair of different tissues. Among these, the BG has been extensively studied, where different BG-based composites were synthesized, and their different properties, in particular their bioactivity and repairing efficiency were investigated. Although the main focus has been targeting bone repair, currently, there are many advances in the designing of bioactive BG-based composites for soft tissue repair. The future applications of such composites will target, in addition to the improvement of the currently designed ones, the regeneration of other soft tissues. Moreover, new BG-based composites will be constructed to locally deliver, in addition to certain cells to the tissue, certain pharmaceutical molecules. However, this next stage of improvement will not be so long for the improvement of such applications, as this material has already been extensively studied.

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