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 reactivities 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 Al2O3 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 SiO2-containing bioactive glasses to be able to bond with the soft tissue is that the SiO2 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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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...
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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4. Hench LL, Greenspan D (2013) Interactions between bioactive glass and pharmaceutical molecules. However, this next stage of improvement to locally deliver, in addition to certain cells to the tissue, certain soft tissues. Moreover, new BG-based composites will be constructed containing the microparticles

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

| Glass particles | Polymeric matrix | Glass matrix | Osteo-odontokeratoplasty surgery efficiency | The cumulative dissolution of SiO2 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. | 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. | 50 |
| BG microparticles (20 µm) | Polymeric membranes | 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 neo-vascularization 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 |

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