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ABOUT COVER

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EDITORIAL

Advances in clinical applications of bioceramics in the new regenerative medicine era

Noha Elshazly, Fayza Eid Nasr, Ayat Hamdy, Safa Saied, Mohamed Elshazly

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Abstract

In this editorial, we comment on the hard and soft tissue applications of different ceramic-based scaffolds prepared by different mechanisms such as 3D printing, sol-gel, and electrospinning. The new concept of regenerative medicine relies on biomaterials that can trigger in situ tissue regeneration and stem cell recruitment at the defect site. A large percentage of these biomaterials is ceramic-based as they provide the essential requirements of biomaterial principles such as tailored multisize porosity, antibacterial properties, and angiogenic properties. All these previously mentioned properties put bioceramics on top of the hierarchy of biomaterials utilized to stimulate tissue regeneration in soft and hard tissue wounds. Multiple clinical applications registered the use of these materials in triggering soft tissue regeneration in healthy and diabetic patients such as bioactive glass nanofibers. The results were promising and opened new frontiers for utilizing these materials on a larger scale. The same results were mentioned when using different forms and formulas of bioceramics in hard defect regeneration. Some bioceramics were used in combination with other polymers and biological scaffolds to improve their regenerative and mechanical properties. All this progress will enable a larger scale of patients to receive such services with ease and decrease the financial burden on the government.

Key Words: Regenerative medicine; Bioceramics; Chronic wounds; Bone defects; Clinical

applications

Core Tip: Some of the most common types of bioceramics used in regenerative medicine are solid prosthesis parts, bone-filling granules, metal prosthesis coatings, injectable bone cement, nanofibers, and porous scaffolds. Bioceramics can be bioactive (like bioactive glass) or resorbable ceramics (like β- and α-tricalcium phosphate, new forms of hydroxyapatite, and bioactive glass). This depends on the tissue's reaction to the grafted biomaterial. Bioactive and bioresorbable scaffolds form a stable bond and are gradually replaced with natural tissues. In this editorial, we discuss some clinical applications of bioceramics and the challenges that need suitable solutions.

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INTRODUCTION

Globally, nonhealing cutaneous wounds are a serious public health obstacle. According to the Global Burden of Disease (GBD) study, which gathered data from over 195 countries and territories, the prevalence of skin and subcutaneous diseases has increased dramatically over the past ten years, with a prevalence of 605036000 in 2015 compared to 492883000 in 2005[1]. An example of the most frequent causes of wounds are mechanical wounds (like persistent/Localized pressure), vascular deficiencies (like venous or arterial incompetence), or metabolic disturbances (like diabetes). In the United States, Chronic wounds affect the quality of life of approximately 2.5% of the population, costing healthcare services over 96 billion dollars with diabetes ulcers and surgical wounds being the costliest to treat[2].

In the same context, it was reported that bone defects resulting from nonunion fractures, trauma, osteomyelitis, surgical operation, segmental bone defects, and tumors are major causes of patient morbidity and impose a crippling financial strain on the healthcare system. An estimated $5 billion is spent annually in the United States on treating bone defects, while even more money is needed for bone grafts to treat tumors, damage to the bone, and other diseases linked to poor fracture repair[3]. Besides, a recent retrospective analytical study which was conducted in the United States reported that 7%–10% of long bone fracture cases that are surgically treated result in non-union with the younger population being at a declined risk when compared to the old population. Complex and shaft fractures were more likely to not unite[4]. It also reported that the estimated cost for treatment of such non-union cases varied from $33–$45K with an increased expense of $16–$34 due to non-union fracture reoperation. Costs were additionally raised due to coexisting infection by $46–86000[4].

The tissue engineering and regenerative medicine field was introduced to improve the quality of life. The new generation of tissue engineering was developed to produce new materials with 3D architecture and chemical characteristics similar to the tissue of interest. These scaffolds stimulate the endogenous body regeneration capacity in which stem cells from all over the body migrate to the site of injury and proliferate to restore the missed tissue[5]. Two accessions of tissue engineering have been introduced; the classic approaches in which a scaffold is used as a supporting structure to allow cell proliferation and the formation of a matrix to be ready for transplantation. The other one uses the scaffold as a 3D structure which provides the tissues with growth factors and required signals, so when it is included in the tissue it stimulates cell recruitment from all over the body to the site of the scaffold to form the required tissue matrix[6].

Scaffolds in tissue engineering have passed through various improvements. The first generation of tissue engineering scaffolds started as matrices that transfer cells and growth factors to the site of the defect and allow mechanical support until complete tissue formation. The next generation was developed to improve the performance of these materials and produce specific materials that can simulate the microenvironment of different tissue types with which the material interacts and produces intimate integration and communication with the surrounding tissue besides controlling the dynamics of cells. This includes the use of more complex biomaterials with a 3D architecture to mimic the ECM and affect cell behavior through distinct techniques. Scaffolds may be built from a wide range of natural and synthetic materials some of them bioresorbable or permanent, thanks to research and engineering efforts. Of these, bioceramics have received a lot of attention since, in general, their tissue reactions are advanced to those of metals and polymers[6,7].

Bioceramics possess lots of advantages that put them on top of the hierarchy of biomaterials utilized to stimulate tissue regeneration in soft and hard tissue wounds. Different types of bioceramics have been utilized to induce in-situ tissue regeneration due to their biocompatibility, multi-scale porosity, angiogenic, antibacterial, and mechanical properties[8,9]. In addition to that they could be designed using different techniques such as sol-gel, electrospinning, and 3D printing, which make them able to simulate any hard or soft ECM ultrastructure. For that reason, these scaffolds allow *in vivo* stem cell recruitment to the site of the defect, helping in building the cell niche which restores tissue integrity and function within a short frame of time[8,9]. The following sections will review different kinds of bioceramics and their clinical applications in hard and soft tissue engineering.

BIOCERAMICS IN HARD TISSUE REGENERATION

Bioceramics are categorized according to their bioactivity when implanted in a physiological environment into bioinert, bioactive, and bioresorbable[10]. Bioactive glasses, hydroxyapatite (HA), as well as tricalcium phosphate (TCP α and β), are the most studied bioceramics through the last 5 decades till the present. These bioceramics are the cornerstone of bioceramics that have regenerative potential concerning hard and soft tissues.

Recent investigations have demonstrated a wide range of advanced bioceramics that have been created by combining these three bioceramics with other biomaterials to enhance their regenerative properties for hard tissue applications[11]. Bioactive glasses attract interest in bone regeneration as they bind intimately with mineralized tissue. During the last 50 years, various types of bioactive glasses have been developed by altering their ions' composition, ratio, ultrastructure, and mechanism of action. Furthermore, some bioglasses are commercially available and FDA-approved[12].

Anesi and his research group investigated the osteogenic capacity of two novel bioglasses, BGMS10 and Bio-MS when implanted in a rabbit's femur in comparisoncompared to 45S5 BG[13]. Histomorphometric and histological observations of the implanted sites demonstrated that the neo trabeculae were thicker and uniformly distributed in the BGMS10/Bio-MS treated group when compared withthan in the 45S5 BG group. However, the quantitative amount of new bone was the same in all groups during 30- and 60-d post-grafting. Moreover, BGMS10 and Bio-MS showed preference over 45S5 BG as they possess slower dissolution rates, permitting the occurrence of two cascades of osteogenesis during the long-term implantation. Another study conducted by Liao *et al*[14] investigated the fast healing of rabbits' long bone segmental defects (radius and ulna) within 4 and 12 weeks after implanting Cu/Mg BGs. The group reported that Cu/Mg BGs appended advantages on the mechanical strength and porosity assessed in decreasing its degradation rate. As a result-Consequently, they sustained the released ions to maintain osteogenesis. Further, Cu/Mg BGs extract encourages the function of osteoclasts concurrently with upregulating the expression of osteopontin that is diminished in the late stage of ossification[14]. Gravina *et al*[15] demonstrated a case report of a 27 years old male with distal forearm laceration and loss of soft tissues where the ulna fracture was damaged by pseudoarthrosis six months post-surgery. Bioglass A bioglass spacer was implanted in the defect site after biological activation. Three and six months post-implantation, the defect spontaneously healed without the need for a bone graft[15].

Kresakova *et al*[16] have demonstrated HA implants in 12 female sheep with critical size defects in the load-bearing bone. During 6 months of follow-up, there was were no clinical signs of infection, inflammation, or pathological wound damage. At the histomorphological analysis level, the defect area showed no fibrous tissue formation and islets of osteoblasts and osseous tissue that indicate bone remodeling. In addition, the neo-bone showed similar organization of to the cortical and trabecular bone. On the other hand, one case showed no degraded and noor resorbed HA with a thin layer of cortical bone on its surface, which is evident that the shape and structure of the implant significantly influence significantly the biodegradability and resorbability of the implant. Histological analysis showed revealed tight connection and integration of the new bone inside the HA implant. Meanwhile, the new bone showed incomplete mineralization comparable to the physiological bone as well as the density of the neo-bone is was lower. Another study investigated the regenerative potential of a 3D printed brushite scaffold in an equine model with tuber coxae defect. In this study, the wounds of five horses were healed without complications, except for one that was infected at 3 days post-operation. The hHistomorphometric and histological analysis at 6 months post-operatively showed that, the newly formed bone fully grew inside the microporous brushite implant with tight contact with the host bone. As well a high amount of collagen and mineralized tissues were deposited inside and on the surface of the scaffold[17].

The osteoconduction and osseointegration capabilities of a novel constructed 3D porous hydroxyapatite (3DP-HA) were evaluated by Kijartorn *et al*[18]. In this clinical trial, 3DP-HA was grafted around dental implants after teeth extraction from 30 patients to enhance ridge preservation. The regenerative ability of the HA scaffold was compared with that of a commercially available bone graft[18]. Histological/ histomorphometric results showed the apical and coronal distribution of the new bone in the sockets. Furthermore, 3DP HA3DP-HA minimized the ridge resorption and increased the stability of the implant. Another study used a mixture of biphasic tricalcium phosphate and HA in the Maxilla for sinus lifting in elderly patients. Bone biopsies showed the formation of lamellar bone with the presence of osteoblast in the peripheral and woven bone after 6 months post-after material implantation. High expression of osteocalcin protein in the areas of grafting was also observed[19]. It is important to mention that the ionic portion of bioceramics influences various osteogenic and angiogenic genes such as HIF-1α and TNF-α for bone regeneration and PI3K/AKT and MAPK/ERK cascades for vascularization[14]. Conversely, the porosity of the material is considered a critical characteristic which has to be controlled for inadequate nutrient delivery and determining the mechanical strain required for cellular attachment and proliferation[20]. One of the obstacles to use clinically the bioceramics is the complexity of matching patient–specific destruction besides the alteration in the degradability behavior of some bioceramics *in vitro* or *in vivo*. The formation of the HA layer may decrease the rate of implant resorption and decrease its solubility[17]. Recently this obstacle has been resolved by constructing of implants *via* 3D printing technology[21]. Another significant impediment is bacterial infection transmission after-surgical implantation. Zhao *et al*[22] summarized recent strategies of providing the antibacterial ability tobioceramics with preservation of bone healing encouraging.

BIOCERAMICS IN SOFT TISSUE REGENERATION

Soft tissues represent an extensive part of the human body. Injuries to soft tissues are common as they are exposed organs [23]. ECM of soft tissues is mainly composed of fibrous proteins (*i.e.*, collagen, elastin), glycosaminoglycans (GAGs: *i.e.*, hyaluronic acid, chondroitin sulfate), and proteogly-cans (*i.e.*, aggrecan, versican), which contribute to the elasticity of

these tissues[24]. Regeneration of the skin, orbit, cardiac, nerves, lung, and many other examples of soft tissues requires the introduction of several biomaterials that meet the required criteria, especially in immunocompromised models and critical-sized defects[23]. Tissue engineering scaffolds proposed for soft tissue applications must acquire general criteria including biocompatibility, biodegradation, and proper mechanical properties; in addition to specific criteria according to the site of application as angiogenesis and electrical stimuli transmission. Bioceramic scaffolds offered promising results in that area[25].

Different generations of bioactive glasses were introduced for skin regeneration and showed promising results. An example of this was a mixture of different types of bioactive glass prepared in an ointment form[26]. Another form was borosilicate bioactive glass nanofibers, which were applied in full-thickness skin defects in rabbit animal models, where the very early ion release since the first day enhanced the cascade toward cutaneous regeneration[27]. The results were in agreement with those of an earlier study conducted on dogs[28] where 13–93Borate-based bioglass promoted full-thickness wound healing. A recent study also evaluated the incorporation of gold nanoparticles into bioactive glass on skin wounds in rats to accelerate its healing cascade[29].

In the ocular regeneration field; glass ceramics were proposed as orbital implants in rabbits as early as 1999s, showing an accelerated fibrovascular effect. Trials were made to add bioactive glass particles to polyethylene implants to produce MedporR Plusr spheres. In human clinical trials, these implants showed satisfying results with no conjunctival inflammation or thinning. Biosilicate®-derived implants were first introduced in 2010, and since then animal and early clinical trials have shown favorable biointegration, biocompatibility, and antibacterial effect[30].

Bioceramics showed interesting results in the nervous system regeneration. Phosphate glass microfibers showed improvement in different functions when applied to transacted spinal cords in a rat model[31]. Beta-tricalcium phosphate allowed nerve regeneration and restoration of functions among a swine model with a 35 cm long nerve injury[32]. Hydroxyapatite nanoparticles were reported to remarkably accelerate nerve regeneration in an induced experimental model[33].

Bioactive glass repaired induced ulcerative colitis wounds in rats through significant upregulation of some inflammatory pathways[34]. Despite the wide range of applications of bioceramics in soft tissue regeneration, the introduction of bioceramics in lung and cardiac tissue regeneration research is still uncommon[24].

Bioceramics have been proven to be good candidates for soft tissue regeneration through the byproducts resulting from biodegradation. Calcium ions for example; increase the pH of the site resulting in antibacterial activity. Silica and calcium target many cellular behaviors, whereas copper and boron enhance angiogenesis and anti-inflammatory effects. whereas silver ions play a crucial antibacterial role[23].

The promising results of bioceramics in soft tissue regeneration have encouraged their use in immunocompromised models as those reported by Elshazly *et al*[35]; in testing the regenerative capacity of borosilicate bioactive glass nanofibers in oral mucosal defects in diabetic-induced rabbits. The mucosal wounds grafted with BGnf showed inflammation-free wound closure, increased cellular activity, and neo-vascularization since the first week opposite to what happened in the wounds that were left empty, where infection and open wounds persisted. These exciting results introduced a new soft tissue scaffold in a wet area borne with microorganisms as the oral cavity and in a diabetic model [35]. Fibrous 13-93B3 borate bioactive glass having the trade as “Dermafuse” [Mo-Sci Corporation (United States)], “ReadiHeal TM” and Mirragen®(ETS Wound Care, MO, United States) with “cotton candy” like appearance have also achieved promising results in wound healing applications with interesting results in chronic wounds in diabetic patients [24].

Introducing hard bioceramics for soft tissue regeneration was faced with many challenges. From the physico-mechanical point of view, the inconsistency between the bioceramics and the delicate nature of these tissues; in this context, they were produced in fibrous forms as the cotton-like 13-93B3 borate bioactive glass used in wound healing applications, or they were used as composites with other polymeric scaffolds. Another aspect is that there is a structural variation between different types of soft tissues that makes one type of bioceramic that is suitable for all soft tissue applications a very difficult choice[24]. For example, in cardiac tissue applications concerns were reported about using bioactive glasses, claiming that they are electrical insulators as well as promote calcifications in the cardiac apparatus[24].

BIOCERAMICS FROM BENCH TO CLINICAL APPROVAL

In the last five years, bioceramics have shown promising results in hard and soft tissue repair; *in vitro* and *in vivo*. However, evaluation of its impact on humans is insufficient compared to the abundance of preclinical studies and the diversity of the bioceramic products. Even though clinical trials of bioceramics applications in diseases implying tissue loss; excluding oral diseases, are few, the results demonstrated a well-tolerated capability of governing tissue regeneration with and without autologous cells.

In a randomized phase I clinical trial, Deinsberger *et al*[36] reported the effect of topical administration of zeolite-mineral purified clinoptilolite-tuff (PCT) on artificial cutaneous wounds. Improved wound healing without pain stimulation or signs of severe inflammatory response subsequent to the application of PCT was observed. In periodontitis, Bodhare *et al*[37] used 45S5 bioactive glass (BG) morsels to treat intrabony defects in a randomized controlled trial. A decrease in the defects' depth, mesiodistal, and buccolingual width, in addition to the elevation of the alveolar crest level was detected which refers to periodontal restoration. These results were enhanced by the application of BG with autologous platelet-rich fibrin.

Bioceramic products aid in the acceleration of bone healing by providing a matrix that facilitates cell attachment and hence regeneration as in the case of applying MBCP+™, a bone graft prepared of 20% Hydroxyapatite (HA) and 80% beta-

tricalcium phosphate (ß-TCP), coupled with autologous mesenchymal stromal cells to reconstruct long bone fracture in phase I/II clinical trial conducted by Gómez-Barrena *et al*[38]. Healing of tibial, femoral, and humeral non-unions was displayed with no adverse events as a result of the treatment. Herr *et al*[39] found that far-infrared ceramic wraps help in curing lower limb venous ulcers which were represented by a decrease in ulcer dimensions and enhancement of tissue type. It is worth mentioning that some individual cases involve bone defects such as heel osteomyelitis in a Guillain-Barré Syndrome and Charcot foot in a diabetic patient, and sternal cleft showed bone regeneration in the presence of bioactive glass and alumina[40-43].

CAPTURING THE OVERALL IMAGE

Bioceramic scaffolds have a large variety of forms and formulas which consequently results in many applications. Indeed, this opens up new horizons of hard and soft tissue applications, but at the same time results in fewer biomaterial approvals for clinical use. In the past years, testing of bioceramics in large animals was a common scene. Scaffolds such as Hydroxyapatite and bioglass were tested in animal models as goats, sheep, monkeys, and pigs. Over the years this number has declined to a fewer number of studies due to the increased cost of animal welfare and the rise in ethical standards across years. In a recent study, the percentage of bioceramics applications in large animals was estimated at 28% of the studies with the dog animal model representing the highest percentage at 11.11. In the same context, the small animal models occupied the largest percentage with 33.33% of studies conducted in rabbit animal models and 41.27% of studies conducted using rodent animal models[43]. When it comes to clinical studies, they might be categorized more as case studies or case series with a few numbers of clinical trials that were mentioned in the previous section. Each of these clinical studies adopted a different type of bioceramic scaffold according to the required properties.

One of the main challenges in the application of bioceramic materials is adjusting the balance between the mechanical properties and the level of porosity. This enables the scaffold to be used in the load-barring area and large-size defects. Commonly, this goal is difficult when using bioceramics alone; therefore, in most cases, the bioceramic material is combined with a polymeric material to achieve this difficult equation of bioactivity, hardness, and biodegradation. An example of that, is the work conducted by Kim *et al*[44] in which bioactive glass(BGS 7) was incorporated with polycaprolactone as a 3D printed scaffold. This composite was investigated in craniofacial reconstruction in patients with craniofacial defects in load-bearing areas. This composite possesses bioactivity gained from the ionic dissolution of bioactive glass on the surface of the scaffold and sufficient strength thanks to the polymer scaffold[44]. The same was observed in the soft tissue application where researchers reported the disappearance of bioactive glass from the wound surface at day one postoperatively[27,28]. One of the main advantages of bioceramics is the antibacterial effect at the site of application. This allows the use of this material in sites subjected to infection as in the oral cavity or immunocompromised conditions such as diabetic wounds[35]. Indeed, the new technologies used in the fabrication of bioceramics will help improve their properties and as a result their application range[45].

CONCLUSION

Bioceramics has an advanced effect on stimulating in situ tissue regeneration in hard and soft tissues. The variation in ultrastructure and chemical composition gives the bioceramics different degrees of porosity, biodegradation, mechanical, antibacterial, and angiogenic properties. This allows bioceramics to be utilized in different body sites providing the required niche for tissue regeneration and initiating the stem cell recruitment required for wound healing. Despite that, more investigations and studies are required to encourage the use of bioceramics as a substitute for grafts in all suitable applications to reduce the cost of medical services and improve patients' quality of life.

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