REVIEW ARTICLE

Bioactive Materials for Bone Tissue Engineering

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ABSTRACT

Many surgical procedures are performed each day to treat or replace organic human tissues that have been damaged. In the clinic, trauma, bone defects, surgical resection, and genetic malformations are significantly challenging to heal. Three-dimensional scaffolds constructed with biomaterials are promising for the treatment of bone defects. The papers were reviewed some bioactive materials for bone tissue engineering. The main results of this study showed that the release of calcium and phosphorus ions from biomaterials controls osteoblasts and osteoclasts activation to ease bone regeneration. Some biomaterials such as nano-hydroxyapatite (nano-HA) can provide a good environment for bone regeneration due to its biological and mechanical properties. However, nano-HA also has some disadvantages that limit its clinical applications. Bioactive glasses have a widely known ability to develop the expansion of bone cells and to bond powerfully with onerous and soft tissue.

Key words: Bioactive glass, biomaterial, calcium phosphate, calcium sulfate, nano-hydroxyapatite, scaffolds, tissue engineering

INTRODUCTION

Calcium phosphate (CaP) is used for bone regeneration, for it has appreciable osteoconductive and osteoinductive attributes. For the purpose of easing bone regeneration, calcium and phosphorus ions are diffused so that activity of osteoclasts and osteoblasts is regulated, leading to facilitated bone regeneration. Impact brought upon by different CaPs has a broad-spectrum (due to their differences in ion release, stability, solubility, and mechanical strength capacities) on bioactivity. To utilize different potentials mentioned a forehand, one must grasp the concept that each can be used as a mixture or with other substances so that the optimal characteristics, positive synergies are obtained, and disadvantageous assets are diminished as much as possible.[1] CaP is viewed as "Biocompatible" thanks to its solubility in biofluids and abundance in solid form.[2] These calcium ions engender bone formation and maturation by calcification and trigger bone regeneration by inducing cellular signals.[3] Phosphorus is abundant in human body. Over 80% of phosphorus ions can be found in bone as CaPs alongside calcium ion.[4] Regulation of osteoblasts differentiation and growth as well as osteoclasts differentiation and bone reabsorption inhibition are a couple of phosphorus influence on bone structure.[5]

Hydroxyapatite (HA) $Ca_{10}(PO_2)_6(OH)_2$ with 1.67 calcium to phosphate (Ca/p) molar ratio is highly utilized in medicine thanks to its biocompatibility, bioactivity, and for being applicable on human body. With the production OSTEOSET and its exploitation of calcium sulfate as bone graft, a new era of scientific and clinical brilliance is achieved.

Recent surveys clearly suggest that mesoporous bioactive glass offers superb bone-forming bioactivity assets as well as degradation and drug delivery attributes thanks to its extremely defined surface, large pore size, and mesoporous structure that it contains in addition bioactive glass has an alkalescent degradation product and slow resorption rate. Bioactive glasses are capable of taking on the proliferation

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of osteocytes and bond strongly with the surrounding tissue.

CAP

Degradation and bioactivity action generally depend on the Ca/P ratio, phase purity, and crystallinity. Between different CaPs, HA, and β-tricalcium phosphates (β-TCP) are the most commonly used phases because of their osteogenic property and the capability to make strong bonds with host bone tissues. The solubility of β-TCP is the highest amount between a different kind of HA.[6]

Ramay *et al*.[7] fabricated a biodegradable proliferous nanocomposite scaffold consists of a β-TCP matrix and HAP nanofibers. β-TCP/HAP scaffolds are predicted to improve mechanical features in load-bearing bone tissue engineering. The biphasic CaP scaffolds have microporous structures that affect cell growth and vascularization. Whitlockite (WH) is a ceramic based on CaP that has a magnesium ion. WH induced expression of osteogenic genes more than HAP and β-TCP.[8]

In addition, OCTA CaP in human teeth[9] has an important role in the initial phase of HAP formation in bone tissue[10] and is a precursor of bone mineralization[11] and showed great biocompatibility.[12] Therefore, it has been widely examined in bone implantation and coating.[13]

Studies on CaP coatings are mostly conducted for metal implant applications to inhibit implant corrosion and improve bioactivity.[14] CaP cements are used to fill and heal bone defects.[15]

CaP has been used with scaffolds. Scaffolds of CaP provide stability and allow porosity control and biocompatibility. Scaffold's pores size enhances bone regeneration and revascularization, improves the growth of cells and proteins, and increases biocompatibility, make them good choices for implant use.[16]

Nanostructured CaP diameter is about 100 nm,[17] cells such as human umbilical cord mesenchymal stem cells (hUCMSCs), human bone marrow MSCs (hBMSCs), osteoblasts, human embryonic stem cell-derived MSCs (hESC-MSCs), and human-induced pluripotent stem cell-derived MSCs (hiPSC-MSCs) responded to nanostructured CaP bioactive favorably.

Composite used to modify mechanical attributes of nanostructured CaP in load-bearing area. Combining nanostructured CaP with natural or synthetic polymers is an encouraging strategy because bone tissue is made of nanocomposite of HA and collagen. Different polymers used for this aim such as collagen fibers,[18] gelatin,[19] chitosan,[20] silk fibroin,[21] poly-L-lactide,[22] poly-DL-lactide-co-glycolide (PLGA),[23] and poly (vinyl alcohol).[24]

The most numerous polymer in bone tissue is collagen. When collagen combined with composite it obtains more cell recognition sites and makes biomaterials decadence faster, therefore allows new bone replace faster. The use of collagen polymers has its own limitations such as high cost and antigenic potential and transmission of pathogen.[25] Denatured form of collagen is the gelatin that has not immunogenic concerns.[19] Chitosan and silk have excellent mechanical properties.[20] Synthetic polymers advantage is evading immunogenicity and pathogen transferring and possessing flexibility in property controls.[24] Homogeneously spread the nanoparticles into a polymer matrix is the most important difficulty in developing polymer/CaP nanocomposites.[26] Multiple methods have been suggested to dominate that problem such as HA modification.

Some studies test the result of different kinds of stem cells, adding to nanostructured calcium phosphate cements (CPCs) with various compositions. Stem cell that used were rat[27] stem cell and hBMSCs,[28] hUCMSCs,[29] hESC-MSCs,[30] and hiPSC-MSCs[31] attached to CPC including apatite nanocrystals. SEM observation showed that the cells anchored to nano-apatite crystals create a polygonal morphology via cytoplasmic processes.

Size of composite particle effect on alveolar bone reconstruction examined in the osteoporotic alveolar bone of rat.[23] Micro and nanoparticulate CaP/PLGA composites used to treat defects of bone (1.8 mm deep and 1.6 mm diameter). The amount of regenerated bone by the nanoparticulate CaP/PLGA cluster was more than the microparticulate CaP/PLGA group. Adding autologous plasma additional improved the bone regeneration, with the best bone regeneration by the nanoparticulate CaP/PLGA/plasma composite.[23]

Fricain *et al*. compared the potential of bone regeneration of natural hydrophilic polysaccharides scaffolds composing such as dextran and pullulan, supplemented with or while not nHA in 5 animals.[32] This examination has three orthotopic models of critical-size defects in 3 different bony sites (femoral rat condyle, a tibial osteotomy in goats, and a transversal mandibular defect) and 2 heterotopic implantations (intramuscularly in goat and subcutaneously in mice). The outcome shows that solely the nHA-incorporated scaffold in mice makes a layer of biological apatite and dense mineralized tissue formation subcutaneously. Osseous tissues after intramuscular implantation in goats had the same result of rat subcutaneously experiment. nHA makes early bone regeneration in 3 orthotopic bone models without matter of implant location.[32] These facts indicate that new bone organization by Nano-sized CaP composites is better than another conventional-sized peer *in vivo*.

When scaffold of a nHA/collagen I was riched with seeded hMSCs by CaPs for subcutaneous implantation, period of a bone matrix development was decreased from 2 weeks

to 1 week.[33] Another experiment on ectopic implantation, scaffolds of nHA/chitosan (CS)/PLGA mixed with pre-osteogenic hUCMSCs gained the most bone formation.[34] Chai *et al*. seeded human periosteum-derived cells onto Three-dimensional (3D)-functionalized porous nCaP-Ti6Al4V hybrids.[35] These hybrids induced ectopic bone degeneration that mostly related on the physicochemical confidants of the CaP coating in a cell density-dependent method. Amount of new regenerated bone spicules around the hybrids when 1 million cells were seeded was small, whereas considerable bone regeneration was observed when 3 million cells were seeded.[35] Besides that, seeding stem cells, the effect of growth factors in nano-CaP scaffolds can increase bone regeneration. For example, bone defect in a rabbit calvaria model, the triple application of MSC/nHA/platelet-rich growth factor yielded 29.45% and 44.55% of new bone area at 6 and 12 weeks, severally.[36] In distinction, bone formation in nHA, nHA/MS, and nHA/platelet-rich growth factor nHA/MSC at 6 and 12 weeks were 11.35%, 29.10%, 32.53%, and 39.74%, 39.11%, 25.82%, respectively. Thus, mixing stem cells with nano-CaP scaffolds can considerably improve bone regeneration. Concerning the kind of stem cells, hBMSCs are the gold standard in stem cell-based bone regeneration and have been successfully utilized in clinics.[37]

HA

HA [$Ca_{10}(PO_4)_6(OH)_2$] has 1.67 Ca/P molar ratio. Due to its biocompatibility, bioactivity, and reliability for use in the body, it is widely used for medical, dental, pharmaceutical, and sanitary applications.

As of recent time application of HA-based biomaterial is utilized the most.[38-41] Despite its superior biocompatibility CaP is used as an alternative to HA-based material. HA obtainment is done by either organic extraction (e.g., coral or animal bone) or by a synthetic one. Methods by which the extraction of HA is made possible are numerous (e.g., wet, dry, flux, and sol-gel reactions), but the most prominent one is the wet method.[42-44] Specific methods are put in to use to facilitate the acquisition of appropriate material morphometry, crystal structure, and proper molar ratio Ca/P as well as insertion of foreign ions into a crystalline structure.

There is not a method capable of recreating the ideal microstructure of HA for bone grafting.[45] To achieve fast resorption, the nano-HA was utilized in bone defect regeneration. As a result, the newly formed (combination of collagen as the organic part and nano-HA particle as the inorganic-composite) is a biocomposite. The advantage of using Nano-HA over HA is the close resemblance of crystals to natural bone and thus the bioactivity is enhanced. In addition to the afore mentioned edge application of nano-HA as the following benefits: Enhanced protein adhesion, cell adhesion, and proliferation.[46]

In addition to achieving highly specific surfaces, use of nanohydroxyapatite has the following benefits:

In addition to achieving highly specific surfaces, use of nanohydroxyapatite has the following benefits for teeth bone; reduction of dental sensitivity, reconstruction of enamel, having biocompatibility with soft and hard tissues and osteoconductivity.

Nano-HA particles exhibit distinctive assets and also furnish an improved environment for bone regeneration to take place.[47] Low clinical application of nano-HAp is due to its low plasticity and low fracture toughness that limit its clinical applications.

In addition to superior biological assets, HAP/CS composite also possesses sufficient mechanical support for tissue growth.[48]

The biomimetic nano-HAP has the ability to protect the teeth by creating a fresh layer of enamel around the tooth, nano-HAP preserves teeth instead of hardening the old layer with fluoride. Several studies on nano-HAP as a biomimetic material showed the capability of remineralizing initial enamel lesions under pH cycling model.[49]

The newly introduced nano-HAP paste is a bioactive agent that contains calcium nano-phosphate organized in a crystalline form of HA incorporated with highly concentrated sodium fluoride of 9000 ppm fluoride ion. This paste is indicated for desensitization and/or remineralization of the enamel and is commercially available for professional use. According to the manufacturer, the maximum remineralizing effect can be observed by two professional applications of the paste, but the estimated number of sessions may vary according to the clinical judgment.

As a result of superior osteoblast adhesion, differentiation, and proliferation, employing nano-HA leads to faster osteointegration and escalated formation of fresh bone tissue. Because of its hydrophilic nature ceramic particle which has been implanted in polymer matrix surface, improvement in biocompatibility and higher tissue integration is observed as opposed to more hydrophobic polymer.[50-55]

BIOACTIVE GLASS

Clinical trials are available to repair large bone defects in displacement or implantation. However, there are a limited number of participants for relocation, long waiting lists, and the possibility of eliminating or transmitting of the disease. Artificial implantation, such as complete hip replacement, is successful for a short time, but not all orthopedic implants have three of the most important features of living tissue: The ability to repair itself;[56] ability to support blood flow;[57] and

the possibility of changing their system; and properties in answer to environmental factors such as mechanical stress.[58]

Studies have shown that 24% of pelvic surgeries require reoperation. Artificial scaffolding is needed to restore a patient's diseased or damaged bone to its normal state and function. One hypothesis for bone tissue testing is the use of stem cells or osteoblasts from the patient, which are then cultured in scaffolding *in vitro*, where conditions are provided to optimize the conditions for bone formation to begin. The tissue/scaffolding composite can then be implanted at the site of the patient's defect, where the tissue must be reconstructed at the rate at which the scaffold is born. Optimal scaffolding must have different criteria for use in bone tissue. First, scaffolding must be biocompatible and use a special 3D pattern in laboratory conditions and growth within the body. To achieve this goal, we need a network of large pores with a diameter of continuous pores connected to at least 100 mm to allow cell migration, internal tissue growth, and eventually vascularity. Scaffolding materials should increase the adhesion and activity of the cell and ideally stimulate osteoporosis at the genetic level[59] so that a bone structure/tissue engineering scaffold can grow in a laboratory, ready for implantation. This structure corresponds to the mechanical properties of the host bone. The scaffold should be able to adhere to the host bone without scarring, create a fixed connection with indirect destruction products, and be easily removed by the body so that the bone eventually returns to its original state. Furthermore, the method of processing scaffolding should be such that it can create irregular shapes to match the bone defect, this makes it possible to sterilize the scaffolding and has the potential to scale to produce profitability with the required international standards. Provide for clinical use. Bioactive glass is a class A bioactive material, meaning that it has the ability to bind to bone and soft tissue and can stimulate bone growth.[59] The ability of bone marrow transplants is attributed to their ability to form a surface layer of hydroxyl-carbonate apatite. Ionic dissolution products released from glasses have been found to regulate seven families of genes in osteoporosis.[60] Bio-glasses derived from Sol-gel gel tend to have simpler compounds than molten biologically activated glasses and indicate increased bioavailability and absorption, due to the presence of a mesenchymal tissue (pores diameter in the range of 2–50 nanometer) natural to sol-gel process.[61]

Although bioactive glass has outstanding properties for bone tissue engineering, the use of glass scaffolding to repair bone defects is often limited due to low mechanical strength and resistance to failure. This study shows that mechanical strength is not a real limiting factor in the use of active glass scaffolding for bone repair. Stress-resistant scaffolds are made in the classroom with samples of fibrous tissue and cortical bones of various sizes. The limitations of bioactive glass scaffolding include high resistance to breakage (low resistance to breakage) and limited mechanical reliability, which has received very little attention to date. Future analysis directions should include biologically active and flexible glass scaffolding events, and their analysis should be performed on unvaccinated and supported bone defects in animal models.

Activated glass scaffolds fragile and synthetic scaffolds of non-mineral minerals such as biochemical ceramics based on CaP and bioactive glass create higher mechanical resistance than polymer scaffolds. Biologically active glasses have a known ability to strengthen bone cells[62] and a strong bond with hard and soft tissue.[63] After implantation, biologically active glass bears specific reactions, resulting in the formation of an amorphous CaP (ACP) or crystalline HA on the surface of the glass, which binds them tightly to the pervasive tissue. Bioactive glasses are also compatible with released ions that activate the expression of purulent genes[60,64] and stimulate vasodilation.[65,66]

The advantage of these glasses is the ease of dominance in the chemical composition, and therefore, the amount of degradation that causes them to be involved as scaffolding. Bones have been shown to be less strong.[18,23,24] Recent work has shown that by optimizing composition, processing, and cooking conditions, glass scaffolding with porous architecture is pre-designed and with strength, fiber textures, and the bones of the cortex form the human brain.[67,68] Another limitation of active glass scaffolding is that it is brittle. Scaffolds made of solid free form have great potential for repairing supported bone defects.[67]

Collected from more than 20 studies shows that the amplitude of compressive strengths for bio-glass scaffolding varies depending on their composition. For the same combination of glass and scaffolding microstructure (construction method), the resistance adds to decreasing porosity, which is usually detected for other spongy materials as well. The data show that spongy glass scaffolding can be formed by compressive strength similar to the rates reported for trabecular bones and the human cerebral cortex. The data show that the structure of the scaffold structure is created by the method of construction. For the same porosity, scaffolding with porous architecture showed higher compressive strength than scaffolding with random porosity architecture. Recent studies show that strength is not a limiting factor in the use of active glass scaffolding to repair load-bearing defects. Optimizing the composition of the glass, along with better control of the architecture of the pores using methods such as one-way freezing of the suspension and the construction of solid freezers, has led to scaffolding with federation required for strength and porosity, fracture toughness, and reliability of scaffolding. With the desired compressive strength, support is created to restore bone defects. However, their use in these scrolls may be limited due to their natural fragility or low crack resistance, many studies have been done to

measure the breakdown resistance of glass scaffolding, but a simple method for sizing trimming the fracture toughness of porous scaffolds may be the work of fracture, gwof, that is, the total energy consumed to produce one-unit area of the fracture surface during a complete fracture. Several groups have used fracture work to assess the stiffness of porous glass and ceramic scaffolding. However, fracture work can only be used for comparison in a specific study because it is not a specific material and may be due to different reasons such as differences in sample measurement, sample geometry and test conditions. While the compressive strength and elastic modulus of biologically active glass scaffolds have been extensively studied, the fragile behavior and reliability of these scaffolds have received little attention. Further studies are needed because bioactive glass scaffolding is intended to repair defects in the loaded bone. While the mechanical properties of bioactive glass scaffolding have been extensively reported in the literature, many studies have focused on the mechanical response to compression loading alone, which achieves compressive strength values and sometimes elastic modulus. Scaffolding has a strong effect on the selected deformation rate. Regardless of the composition of the glass, it is on strength.[65,66]

Bioactive glass scaffolds can be built with the specified compressive strength for the reformation of supporting bone defects. However, their use in this function could also be limited by their intrinsic break ableness or low resistance to crack propagation.[69] There have been many studies that, however, gauge the correct strength of glass scaffolding. A simple action to gauge the fracture stiffness of spongy scaffolding may be to break the work. Complete energy consumed to provide the unit space for the fracture surface during a complete fracture. Many groups used fracture work to assess the stamina of porous glass and ceramic scaffolding. However, fracture work is only used to compare in a specific study because the result is not the property of the actual material and must be different for different dimensions, geometries, and test conditions.[70] While the compressive strength and tensile strength of bioactive glass scaffolds have been extensively studied, the fragile behavior and responsibility of those scaffolds have received very little attention. During this period, there is a tendency to study a lot because, as a result, bioactive glass scaffolds have been considered to repair defects in the loaded bone.[71,72] To strengthen, the stiffness of porous glass wood and ceramic scaffolding is paid. One way to cover or penetrate scaffolding with perishable polymer is to prepare an organic part to strengthen the mineral phase. Covering alumina scaffolding with polycaprolactone (PCL), a 7–13-fold growth in fracture has been recorded.[73] In one more research, they found that the breaking work of two-phase CaP scaffolds, up to 10 times the failure of polymer coatings, was attributed to notable growth in the stiffness of these scaffolds, especially composite bridges by PCL fibers.[74] While studies have been conducted to gauge the hardness of biologically active glass scaffolds, these studies did on low-strength scaffolds. It is essential to gauge the hardening of biologically active scaffolds with much higher strength for applications in the repair of load-bearing bone defects[75] *in vitro* and *in vivo* bioactive scaffolds. The laboratory and intracellular response of biologically active glass scaffolding depend primarily on the combination of glass and the architecture of the pores (microstructures) of the scaffolding. The potential of cell proliferation for the scaffolds containing biologically active glass has been reported in various *in vitro* and *in vivo* studies.[76]

CONCLUSION

A 100% recovery of benign bone defects was not observed with calcium sulfate; however, it showed great improvement of the recovery rate through pH-dependent mechanisms or other unknown methods besides its purpose as a filler. The production, mechanical characteristics, and *in vitro* and *in vivo* test results of bioactive glass scaffolds were studied with a focus on the mechanical aspects of the scaffolds for the purpose of treating loaded bone defects. New bioactive glass scaffolds with strengths similar to cortical bone have been produced, and they show great potential for the repair of loaded bone defects. The toughness and mechanical reliability of bioactive glass scaffolds are still the main concern for applications in loaded bone repair; therefore, further study is required to perfect this product.

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COMPETING INTERESTS

The authors state no conflict(s) of interest related to this study.

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