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REVIEW

Influence of typographic biocomposite scaffold in facilitating biomineralization to progress complex hard tissue repair

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Biomaterial modifications and scaffold fabrication methods in hard tissue engineering applications have seen enormous growth. However, clinical demand in treating and regenerating large bone defects is intricate, as current methods fail to meet requirements such as regenerating bone with optimal physical and mechanical properties in complex bone repair due to poor scaffold design and less bioactivity. To meet such clinical expectations, biomaterials are combined to create a 3D bone composite scaffold to improve the quality of the regenerated bone by improving bioactivity through biomineralization. To advance this process, accelerated and homogenous biomineralization is facilitated by the scaffold with increased surface area and active molecules to progress the repair of large bone defect. This facilitation of biomineralization leads to minerals deposition as a layer on the substrate when 3D-printed porous scaffolds made of biocomposite are exposed to body fluid at the repair site where the substrate degrades and releases active biomolecules. These released molecules crystallized evenly to form an apatite layer on the scaffold surface, where bone-forming cells attach, grow, and regenerate bone. Additionally, the formation of the apatite layer through biomineralization to repair lost structure is also governed by the following factors, which include macromolecules and an active site present between collagen molecules in the bone. In this review, we explore the advantages of biocomposite materials and 3D-printed scaffold design in accelerating biomineralization at the bone defect area to facilitate the formation of an apatite layer to progress complex hard tissue regeneration with optimal properties (1).

Keywords: biocomposite, 3D substrate design, apatite layer, biominerals, collagen and non-collagen molecules, biomineralization, tissue engineering

Introduction

The current focus of researchers in tissue engineering is to learn, understand, and advance the biomineralization process in complex bone regeneration. The attention and importance of biomineralization in tissue engineering are because of the natural control of nucleation, crystallization, and growth of minerals on the organic matrix by an organism during the development of bones and teeth (2). Therefore, the understanding natural phenomenon of biomineralization is imperative to design biocomposite and scaffolds to achieve better results in intricate bone engineering (3). Surface mineralization of three-dimensional bone composite scaffolds is not only escalating bioactivity and osteoinductive properties but also enhancing bonding strength between scaffold and bone surfaces during complex bone regeneration (1). To progress biomineralization in complex hard tissue repairing, the choice of biomaterials for bone composite scaffolds should be based on the composition that supports and improves bioactivity.

Scaffolds constructed with advanced biomaterials with multiple components are capable of promoting a specific biological environment to press forward biomineralization (4). Furthermore, the material of choice for regeneration can also be based on the molecular component's interaction with collagen and non-collagen molecules present in bone. These biocomposites were used to make substrates that release iron molecules in the microenvironment when they come in contact with the bone repair site. In the healing area, macromolecular interaction with biomaterial released iron molecules in the presence of body fluid accelerates nucleation and crystal growth on the surface of scaffold during biomineralization regeneration of complex bone defect is advanced by enhanced biomineralization activity in biocomposite scaffold with 3D structure, which is fabricated using various 3D scaffold manufacturing methods. The advantage of 3D-structured biocomposite scaffold in hard tissue regeneration is fabricating a scaffold that facilitates a perfect structure with optimal physical properties with improved bioactivity that is same like bone present in the healing site. The 3D-structured scaffold provides a large surface area to facilitate mineralization by allowing molecular interaction in an even way in the microenvironment of the complex bone defect regeneration. Following the molecular interaction with the help of body fluid, an iron molecule released due to the degradation of the 3D scaffold is attracted and retained by a negatively charged macromolecule to maintain the integrity of newly formed bone. Additionally, during mineralization process, a 3D substrate support with a newly formed apatite layer is deposited on the surface of the scaffold with adequate physical and mechanical properties to regenerate hard tissue (5).

Biomineralization

The organism can form hard tissue, such as bones and teeth, by producing and mineralizing organic matrix (6). Likewise, human bone is created by the combination of both organic and inorganic materials. The complex structure of bone is unique where mineralization takes place to maintain the form and function of the bone. The basic structure of bone is collagen fibril, which is made of self-assembled collagen molecules (7). Hydroxyapatite nanoparticles attach and grow to form a mineralized structure that improves the physical and mechanical strength of the bone (1). In this complex, the controlled process is biomineralization, which is regulated by collagen fibrils and non-collagenous protein, which is formed by bone cells. These bone components play major roles in promoting or inhibiting the growth and nucleation of crystals during biomineralization. The importance of bone component's role in biomineralization attracted tissue engineers and influenced their choice of biomaterial for hard tissue engineering. If the components present in the biomaterial are similar to the bone material, like bone, it will enhance biomineralization, which is advantageous in the repair of complex bone damage with improved properties (5).

Additionally, a controlled biomineralization process in tissue engineering is advantageous as it helps develop in- depth knowledge about the factors that influence biomineralization in tissue regeneration. First, factors that help in understanding biomineralization are a characterization of crystal growth, components of biomaterials, and chemical properties of biomaterials. Second, the substrate design allows interaction between scaffold, crystal, and macromolecule in controlling the crystal growth. Finally, the fabrication of biocomposite with organic and inorganic components has similar properties to natural bone and its influence on biomineralization (8).

Biomineralization mechanism (collagen based) (Figure 1) (9)

Native boneform collagenfibril

↓

Collagen peptide assembled to form bundles

↓

Active site present at the gap of the assembled ends

↓

Accumulation of phosphoprotein, glycoprotein at the active site

↓

Attraction of Ca^{+} rich minerals due to charge and structural interaction

↓

Initiation of mineral growth.

↓

Source for mineralization is regulated by calcitonin, PTH, VitD.

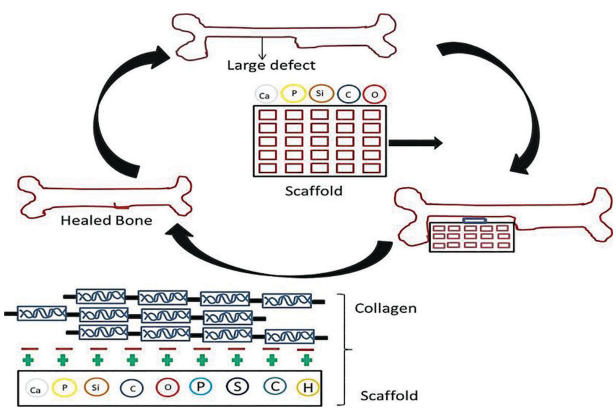

FIGURE 1 | Complex bonding based on charges at collagen bands.

Biomineralization mechanism (non-collagenous protein based) (9)

Proteins→ Osteopontin, osteonectin, osteocalcin, bone sialoprotein
↓
act as a nucleators or inhibiters of mineralization

Bone composite in biomineralization

The basic idea of biocomposite design and fabrication with various bioactive components is to act similarly to the natural extracellular matrix to enhance cellular activity and biodegradation simultaneously to regenerate and repair large complex bone defects (10). Improved bioactivities of biocomposite, such as biomineralization, involve the deposition of minerals as a layer on the outer surface of the substrate scaffolds that could improve the release of iron at the healing area and improve the bonding strength between bone and biocomposite (4). In addition, the apatite layer also allows cells to attach, proliferate, and differentiate into bone-forming cells called osteoblasts. To promote regeneration, biocomposite needs to guide biomineralization to continue apatite layer formation, while biomaterial has to degrade to allow new bone to form in the healing area (11). One of the commonly used biomaterials in tissue engineering is a polymer, which is advantageous as its physical and mechanical properties are similar to those in the natural bone; however, this material has a longer degradation time and is also less bioactive; therefore, the need of combining bioactive material such as bioglass with polymer is necessary to improve the properties of biocomposite.

The composite materials that contain the perfect proposition of bioactive materials are beneficial in boosting bioactivity and the biomineralization process, which helps to progress the complex repair of hard tissue (4). Bioactive molecules present in this composite can increase bioactivity, improve degradation, and enhance chemical properties (12). If the material of choice to make bone com posite is based on bioactivity and physical and mechanical properties, it would impact biomineralization positively to promote large defect healing. In particular, shape, content, and distribution of biomaterial in biocomposite need to be given importance while fabricating a 3D bone composite scaffold (13).

Complex bonding based on charges at collagen bands

The advantages of components used in biocomposite mineralization are as follows:

1. Bioglass is used in tissue engineering for hard tissue regeneration because it is capable of enhancing bone formation, supporting tissue growth, guiding bone growth, and also improving bioactivity by increasing the release of iron.
2. Bioglass used in nanoformulation can increase mechanical and biological properties, promote apatite formation, and enhance bonds at the interface between bone and biomaterial.

All of these properties and benefits of bioglass are possible because the nanosized particles have an increased surface area that facilitates faster iron exposure and could accelerate biomineralization (4).

The use of the polymer in biocomposite is beneficial. Because polymers in the composite can improve physical and mechanical strength, apatite formation on the composite can be supported, and the compromised physical properties of bioglass can also be supported.

Biocomposite material model (14)

Chemical property	Crystal structure	Microstructure
Vary concentration, type, rate of iron solubility, and pH.	Provide variable substrate for protein and mineral epitaxy.	Differ in size percentage, distribution of porosity, interfacial areas, and interface.

Scaffold design

To advance bone repair and improve physical and mechanical properties of the newly formed bone at the healing site and to aid scaffold and bone integration, designing and fabrication methods of biocomposite scaffold are important. These methods need to focus on customizing the degradation of the scaffold and also providing a large active surface area to improve biomineralization during bone regeneration to improve the properties of regenerated bone (15).

1. For a desirable result in bone regeneration, such as enhanced quality of the newly formed bone and regenerated hard tissue strength.
2. A composite scaffold needs to be fabricated in a way that encourages controlled degradation of scaffold to release minerals to facilitate apatite layer formation. For example, 3D-printed polymer scaffolds do have a custom-made microporous structure with even size and shape that allows body fluid exposure evenly throughout the 3D porous structured scaffold when implanted at the healing site. This 3D structure allows the mineralization process uniformly in all porous structures that allow bone cells to attach to all surfaces of the substrate simultaneously to form and degrade bone and scaffold, respectively (16).

Scaffolds with a large surface area can provide a more active surface area where tailored mineral deposition and molecular interaction take place in the microenvironment of hard tissue regeneration. This continuous mineral deposition on the scaffold allows crystal formation on the surface of the bone and scaffold. These processes are based on the attraction of the surface electric charge of collagen fibers from natural bone and minerals from a degraded scaffold. The surface mineral deposit can be improved further by various 3D scaffold designs and manufacturing methods. The desirable 3D design could provide more surface area for molecular interaction and mineralization by releasing minerals and improving bioactivity for hard tissue engineering (2).

Conclusion

The importance of biocomposite material used in designing and fabricating 3D typographic substrate for bone tissue engineering to facilitate biomineralization to regenerate bone with desirable properties can be understood by the researchers in tissue engineering if they analyze the formation and arrangement of organic and inorganic components present in the natural bone with a unique physical and mechanical properties. The arrangement of collagen fibrils and bioactive mineral layer in the form of nanocomposite in the bone provide distinctive physical and mechanical properties to perform a function. Therefore, importance should be given for homogenous mineralization to occur while designing biocomposite which releases bioactive minerals, and fabricating a 3D substrate which increased surface area for hard tissue engineering. Furthermore, new methods in fabricating 3D-designed biocomposite substrates in hard tissue engineering can be used to address the current clinical challenges, such as the lack of physical and mechanical properties caused by compromised mineralization at the healing site due to poor design and material combination in the substrate. Applying both of these methods including combining various materials to create biocomposite to improve bioactivity and using various 3D printing methods to develop and advance the availability of more surface area for biomineralization to improve hard tissue regeneration could provide solutions to the current and future demands of complex treatments of bone disorders.

Author contributions

AB: formalanalysis. PK: resources. NK: data curation. All authors reviewed the results and approved the final version of the manuscript.

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