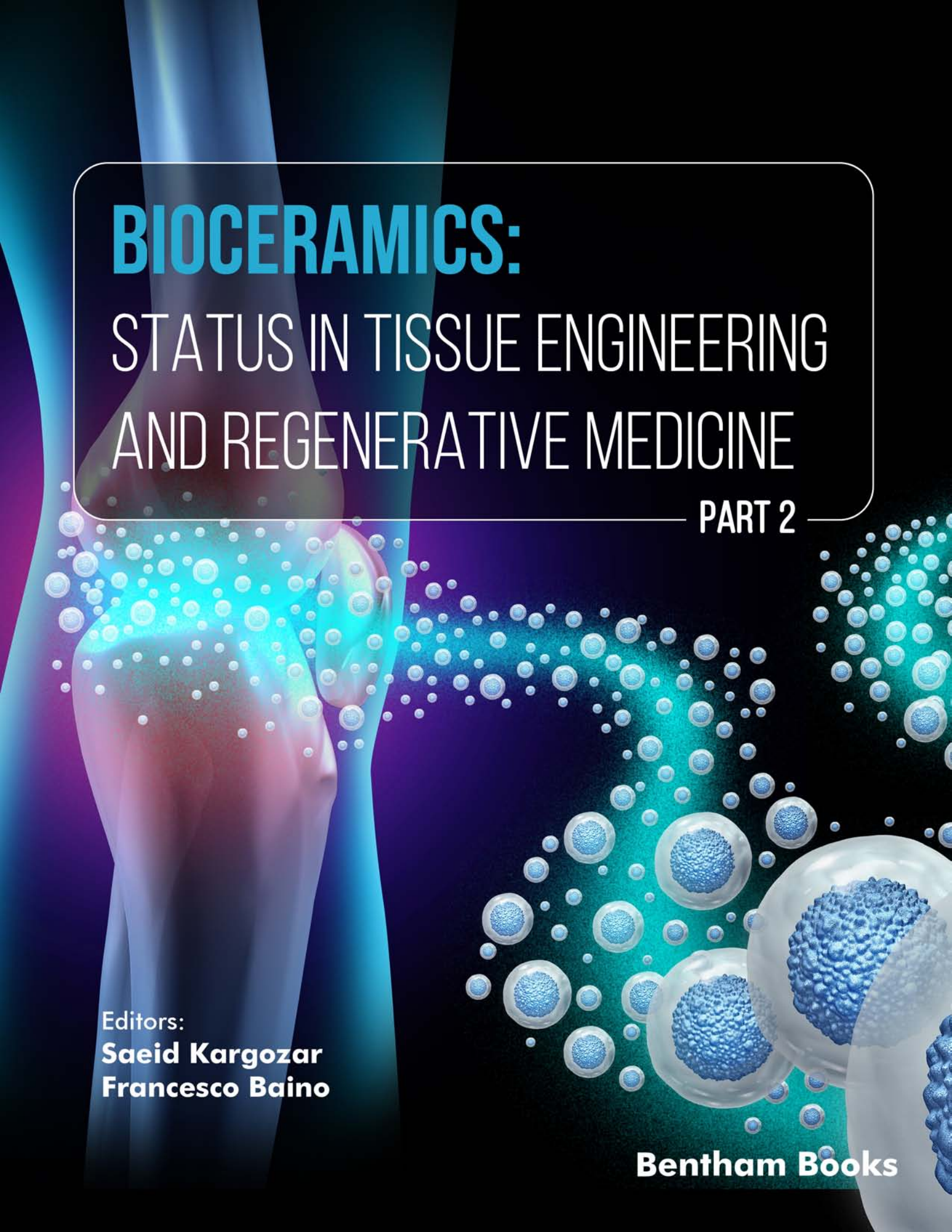
BIOCERAMICS:

STATUS IN TISSUE ENGINEERING AND REGENERATIVE MEDICINE

PART 2



Editors:
Saeid Kargozar
Francesco Baino

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Bioceramics: Status in Tissue Engineering and Regenerative Medicine

(Part 2)

Edited by

Saeid Kargozar
Department of Radiation Oncology
Simmons Comprehensive Cancer Center
UT Southwestern Medical Center
Harry Hines Blvd, Dallas
TX75390, USA

&

Francesco Baino
Department of Applied Science and Technology (DISAT)
Institute of Materials Physics and Engineering
Politecnico di Torino
Torino, Italy

Bioceramics: Status in Tissue Engineering and Regenerative Medicine *(Part 2)*

Editors: Saeid Kargozar and Francesco Baino

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FOREWORD

The use of bioceramics for tissue engineering and regenerative medicine extends over two centuries. Dorozhkin provided a detailed review of the history of bioceramics [1]. He noted that Johan Gottlieb Gahn and Carl Wilhelm Scheele first described the presence of calcium and phosphorus in bone in the second half of the eighteenth century [1, 2]. The first use of bioceramics in medicine occurred in the late nineteenth century when Junius E. Cravens distributed a calcium orthophosphate powder called "Lacto-Phosphate of Lime" for capping the dental pulp during dental restorations [1, 3, 4]. Larry Hench's discovery in 1969 that a sodium-calcium-phosphorous-–silicate glass possesses bone bonding functionality gave rise to the clinical use of "bioactive glass" materials for bone repair [5, 6]. The term "bioceramics" was first used shortly thereafter in 1971 [7]. The bioceramics field is now truly global in nature and includes research, pre-clinical, and clinical activities involving various types of bioactive and bioinert inorganic materials.

This is the second part of a couple of books edited by Saeid Kargozar, a senior assistant professor in the Tissue Engineering Research Group of the Department of Anatomy and Cell Biology at Mashhad University of Medical Sciences, and Francesco Baino, an associate professor in the Department of Applied Science and Technology at the Politecnico di Torino. This second volume provides a comprehensive overview of the use of bioceramics for tissue engineering and regenerative medicine, with focus on applications. In Chapter 1, Girija *et al*. consider the use of hydroxyapatite derived from biogenic sources for biomedical and environmental applications. Rodríguez-González *et al*. describe the use of three-dimensionally printed bioceramics scaffolds for tissue reconstruction in Chapter 2. Chapter 3, by Kargozar *et al*., reviews the additive manufacturing of bioactive glasses. In Chapter 4, Kargozar *et al*. consider the use of additive manufacturing to process bioactive glasses for bone tissue engineering. Crovace and Souza describe the use of bioactive glass and glass ceramics for treating microbial infections in Chapter 5. In Chapter 6, Kargozar *et al*. review the use of bioactive ceramics and glasses with improved angiogenesis functionality. Pourshahrestani *et al*. consider the potent hemostatic activity of bioactive glass and its composites in Chapter 7. Zheng and Xu describe the use of a combination of bioactive glass nanoparticles and natural polymer-based hydrogels for bone tissue regeneration in Chapter 8. In Chapter 9, Borges *et al*. consider the use of bioceramics and bioactive glasses for dental regeneration and repair. Chapter 10, by Bhattacharya *et al*., reviews the use of bioceramics and bioactive glasses for skin wound healing applications.

In this volume, Professors Kargozar and Baino as well as the chapter contributors have provided the bioceramics community with a comprehensive consideration of the bioceramics field. I anticipate that their volume will be beneficial to students as well as researchers in academia, government, and industry as they continue efforts to improve our understanding of the use of bioceramic materials for tissue engineering and regenerative medicine applications.

Prof. Roger Narayan
Joint Department of Biomedical Engineering
North Carolina and North Carolina State University
Raleigh, USA

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List of Contributors

Ahmed El-Fiqi	Glass Research Department, National Research Centre, Cairo 12622, Egypt
Agatha M. Pelosini	Center for Natural and Human Sciences, Federal University of ABC, Santo André, Brazil
D. Muthu	Department of Physics, Periyar University, Salem 636 011, India
E.K. Girija	Department of Physics, Periyar University, Salem 636 011, India
Emilio Castro	Bioengineering Institute of Technology (BIT), Universitat Internacional de Catalunya (UIC), Barcelona, 08017, Spain
Ehsan Zeimaran	Department of Biomedical Engineering, Faculty of Engineering, University of Malaya, Kuala Lumpur-50603, Malaysia
Emanuela P. Ferraz	Department of Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil
Frazad Kermani	Tissue Engineering Research Group (TERG), Department of Anatomy and Cell Biology, School of Medicine, Mashhad University of Medical Sciences, Mashhad 917794-8564, Iran
Francesco Baino	Department of Applied Science and Technology (DISAT), Institute of Materials Physics and Engineering, Politecnico di Torino, 10129 Torino, Italy
Juliana Marchi	Center for Natural and Human Sciences, Federal University of ABC, Santo André, Brazil
Jui Chakraborty	Bioceramics and Coating Division, CSIR–Central Glass and Ceramics Research Institute, Jadavpur, Kolkata-700 032, India
Kai Zheng	Jiangsu Province Engineering Research Center of Stomatological Translation Medicine, Nanjing Medical University, Nanjing 210029, China Jiangsu Key Laboratory of Oral Diseases, Nanjing Medical University, Nanjing 210029, China
Karina F. Santos	Department of Biomaterials and Oral Biology, School of Dentistry, University of São Paulo, São Paulo, Brazil
Luis M. Delgado	Bioengineering Institute of Technology (BIT), Universitat Internacional de Catalunya (UIC), Barcelona, 08017, Spain
Miguel Ángel Mateos-Timoneda	Bioengineering Institute of Technology (BIT), Universitat Internacional de Catalunya (UIC), Barcelona, 08017, Spain
Masoud Mozafari	Research Unit of Health Sciences and Technology, Faculty of Medicine, University of Oulu, Oulu, Finland
Murilo C. Crovace	Bioactive Materials Laboratory (LMBio), Department of Materials Engineering, Federal University of São Carlos (DEMa/UFSCar), São Carlos-SP, Brazil
Marina T. Souza	VETRA – High-Tech Biomaterials, Ribeirão Preto-SP, Brazil

Mh Busra Fauzi	Centre for Tissue Engineering and Regenerative Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur-56000, Malaysia
Nahrizul Adib Kadri	Department of Biomedical Engineering, Faculty of Engineering, University of Malaya, Kuala Lumpur-50603, Malaysia
Peiman Brouki Milan	Department of Tissue Engineering and Regenerative Medicine, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences, Tehran, Iran Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran, Iran Institute of Regenerative Medicine, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences, Tehran, Iran
Paulo F. Cesar	Department of Biomaterials and Oral Biology, School of Dentistry, University of São Paulo, São Paulo, Brazil
Payal Roy	Bioceramics and Coating Division, CSIR–Central Glass and Ceramics Research Institute, Jadavpur, Kolkata-700 032, India
R. Govindan	Department of Physics, Periyar University, Salem 636 011, India
Raquel Rodríguez-González	Bioengineering Institute of Technology (BIT), Universitat Internacional de Catalunya (UIC), Barcelona, 08017, Spain
Raquel Rojas-Márquez	Bioengineering Institute of Technology (BIT), Universitat Internacional de Catalunya (UIC), Barcelona, 08017, Spain
Román A. Pérez	Bioengineering Institute of Technology (BIT), Universitat Internacional de Catalunya (UIC), Barcelona, 08017, Spain
Rongyao Xu	Jiangsu Province Engineering Research Center of Stomatological Translation Medicine, Nanjing Medical University, Nanjing 210029, China Jiangsu Key Laboratory of Oral Diseases, Nanjing Medical University, Nanjing 210029, China
Roger Borges	Center for Natural and Human Sciences, Federal University of ABC, Santo André, Brazil School of Biomedical Engineering, Faculdade Israelita de Ciências da Saúde Albert Einstein, Hospital Israelita Albert Einstein, São Paulo, Brazil
Rupam Saha	Bioceramics and Coating Division, CSIR–Central Glass and Ceramics Research Institute, Jadavpur, Kolkata-700 032, India Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India
Saeid Kargozar	Department of Radiation Oncology, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, United States
Sara Gorgani	Tissue Engineering Research Group (TERG), Department of Anatomy and Cell Biology, School of Medicine, Mashhad University of Medical Sciences, Mashhad 917794-8564, Iran

Simin Nazarnezhad	Tissue Engineering Research Group (TERG), Department of Anatomy and Cell Biology, School of Medicine, Mashhad University of Medical Sciences, Mashhad 917794-8564, Iran
Sara Pourshahrestani	Centre for Tissue Engineering and Regenerative Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur-56000, Malaysia
Soumalya Bhattacharya	Bioceramics and Coating Division, CSIR–Central Glass and Ceramics Research Institute, Jadavpur, Kolkata-700 032, India
Thomas J. Webster	UFPI - Universidade Federal do Piauí, Teresina, Brazil CBCMT, Vellore Institute of Technology, Vellore, 632014, India Hebei University of Technology, Hebei, China
V.S. Kattimani	Department of Oral and Maxillofacial Surgery, Sibar Institute of Dental Sciences, Guntur, 522 509, India

CHAPTER 1

Hydroxyapatite Derived from Biogenic Sources for Biomedical and Environmental Applications

E.K. Girija[1,*], V.S. Kattimani[2], D. Muthu[1] and **R. Govindan[1]**

[1] *Department of Physics, Periyar University, Salem 636 011, India*

[2] *Department of Oral and Maxillofacial Surgery, Sibar Institute of Dental Sciences, Guntur, 522 509, India*

Abstract: Hydroxyapatite (HAp), one of the calcium phosphate minerals, has been widely used for biomedical applications because of its similarity to bone mineral content. Synthetic nano HAp, despite being made from chemical precursors, differs in composition from that of natural hard tissues such as bone and teeth. The properties of synthetic HAp solely depend on the precursors and production processes employed. Biogenic calcium resources such as fish scales, bones of animals and fish, and shells from land, freshwater, and marine origin can be used to synthesise HAp, which has trace elements that mimic the constituents of bone. Also, we have emphasised that HAp can be synthesised economically from one of the abundantly available low-cost biowastes, namely eggshells. There are numerous biomedical uses like bone substitute material, scaffold for bone tissue engineering, drug delivery agent, *etc*., and environmental uses, notably as an adsorbent for heavy metal removal, dye degradation, *etc*. This chapter will help readers understand the significance of natural resources and methods for producing HAp from biogenic sources.

Keywords: Biomedical applications, Calcination, Calcium phosphates, Hydroxyapatite.

INTRODUCTION

Bone being the regularly repaired and transplanted tissue, the annual demand for bone grafts and substitute materials is constantly rising [1, 2]. Moreover, when skeletal muscles get damaged due to accidents, ageing, diseases, trauma, *etc*., the ability to self-repair the body is limited and there is a need for graft materials. There are various bone grafting procedures based on the available native bone sources like from self, from the donor of the same species, or from different species and these procedures are termed autograft, allograft, and xenograft, respectively [3].

[*] **Corresponding author E.K. Girija:** Department of Physics, Periyar University, Salem 636 011, India; E-mail: girijaeaswaradas@gmail.com

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Though autograft remains a gold standard method for the reconstruction of large bone lesions, it has several drawbacks including limited availability, donor site issues such as pain, discomfort and the need for repeated surgery [4]. Despite the fact that allografts are osteoconductive, they have some limitations such as disease transmission, donor site morbidity, cost and donor availability [5]. In 2021, the allograft sector, which includes demineralized bone matrix and others commanded over 55% of the market for bone graft and substitutes, thus accounting for the greatest revenue share of the bone graft market [6]. For bone defect repair, a variety of xenografts are used, including bovine, porcine, coral, and others [7, 8]. Although it has some advantages, such as high availability, superior porosity for bone tissue ingrowth, and less cost, the risk of immunological rejection makes it less desirable [9]. Because of the limits of native graft methods, synthetic graft materials are in high demand [9 - 12].

Recent progress in functional materials research and development for various biomedical applications has also led to advancements in orthopaedic care. Many alloplastic bone graft materials have been developed that are functional, aesthetically attractive, non-inflammatory, non-carcinogenic and lower the chance of implant failure [13]. Synthetic bone grafts of ceramics, polymers, and composites are available [4]. The ceramic segment is further divided into hydroxyapatite (HAp), biphasic calcium phosphates (BCP) and other phases of calcium phosphate which dominated the market in 2021.

Bone is composed of 69 wt. % of mineral phase, 22 wt. % of organic matrix and 9 wt. % of water [14]. The predominant inorganic mineral component of the bone is HAp which is nothing but a non-stoichiometric, ion-substituted calcium deficient biological apatite. In bone and teeth, HAp is found in the nanocrystalline form. Trace elements such as Zn^{2+}, Na^{+}, Mg^{2+}, K^{+}, Ba^{2+}, F^{-} and CO^{2-} are also found in the bone [15]. Because of the fact that calcium phosphates like HAp, beta-tricalcium phosphate (β-TCP) and various combinations of these are chemically similar to bone composition and specifically, the structural resemblance of HAp to biological apatite, synthetic HAp has excellent osteoconductive and osteointegration properties making it a popular biomedical material [14]. Alloplastic materials are being investigated extensively as alternatives to bone grafts, and calcium phosphate based biomaterials, particularly HAp have a sizable market as bone substitutes.

The high cost of synthetic HAp from commercial calcium and phosphate sources is a serious concern [16, 17]. In recent decades, calcium rich natural biogenic sources such as bovine and porcine bones, fishbone and scale, corals, seashells, snail shells, oyster shells, eggshells and so on have been studied for HAp synthesis. The non-stoichiometric chemical composition of HAp synthesized from

natural sources is similar to that of the human bone since they contain trace elements such as Na^{+}, Zn^{2+}, Mg^{2+}, K^{+}, Si^{2+}, Ba^{2+}, F^{-}, and CO_3^{2-} [18, 19]. Being biogenic that is materials derived from living organisms, superior cell-material interaction and abundance at zero or low cost, HAp derived from natural sources might be considered a prospective and economic biomedical material.

This book chapter focuses on HAp obtained from biogenic sources such as animal bones, scales and shells. The extraction or synthesis of HAp from these sources using various methods, as well as its crucial physicochemical and biological properties and the intended biomedical and environmental applications are covered.

BIOGENIC SOURCES

The schematic presentation in Fig. (**1**) depicts various calcium rich biogenic sources used for HAp extraction or synthesis, as well as the various biomedical applications of HAp. Calcium phosphate is found in the bones of vertebrates and fish scales, whereas calcium carbonate is found in calcified structures of invertebrates such as seashells, snail shells, coral, and sea urchins, as well as other structures like eggshells. The mode of deriving HAp from various biogenic sources can be separated into two approaches, one is extraction as HAp from the biogenic source and the other is the synthesis of HAp using the biogenic source as a calcium precursor.

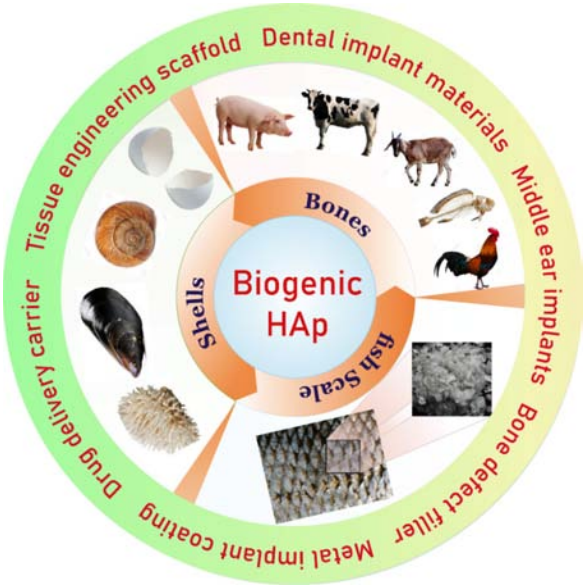

Fig. (1). Various biogenic resources used for deriving HAp and their applications.

CHAPTER 2

Three-Dimensionally (3D) Printed Bioceramic Scaffolds for Tissue Reconstruction

Raquel Rodríguez-González[1], Raquel Rojas-Márquez[1], Emilio Castro[1], Miguel Ángel Mateos-Timoneda[1], Luis M. Delgado[1,*] and **Román A. Pérez[1,*]**

[1] *Bioengineering Institute of Technology (BIT), Universitat Internacional de Catalunya (UIC), Barcelona, 08017, Spain*

Abstract: 3D printing technologies have changed the manufacturing of tissue engineering scaffolds upside down, giving new possibilities to obtain complex shapes that perfectly resemble patient defects using old bioceramics or new materials especially developed as inks for 3D printing.

Bioceramics have been commonly used in tissue regeneration, mainly bone, due to their high biocompatibility and in some cases, bioactivity. Moreover, they can have different compositions and proportions, which give rise to a wide variety of properties. The main types of bioceramics are calcium phosphates and bioactive glasses, but there are other ceramics such as zirconia and alumina.

The 3D printing of bioceramics is usually performed by mixing particles or powders of ceramics with a polymer to obtain proper viscosity, and they can be printed through DIW, SLA or SLS. After printing, they can be sintered to obtain a pure ceramic body, or left as a composite. Additionally, there is a direct ceramic printing method based on SLS that does not need a polymer for printing.

These results indicated that 3D printing of bioceramics has the potential to produce large-scale tissue engineering scaffolds with accurate structure and functionality; however, further studies are needed to improve the biological response to the 3D printed scaffolds.

Keywords: Aluminia, Bioglass, Bone regeneration, Bioceramics, Composites, Calcium phosphates, DIW, FDM, SLA, SLS, Silica, Sol-gel, Zirconia, 3D printing.

[*] **Corresponding authors Román A. Pérez and Luis M. Delgado:** Bioengineering Institute of Technology (BIT), Universitat Internacional de Catalunya (UIC), Barcelona, Spain; Tel: +34 504 20 00;
E-mails: rperezan@uic.es; lmdelgado@uic.es

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INTRODUCTION

Tissue Engineering (TE), is defined as the discipline that seeks to repair, replace or regenerate tissues or organs by translating fundamental knowledge of physics, chemistry, and biology into practical and effective materials, devices, and clinical strategies [1]; mainly relying on three different and interconnected pillars, *i.e.* cells, biomaterials and their 3D structures, and signals. Recent advances in cellular and molecular biology, especially in stem cell technologies and growth-stimulating factors, have expanded our ability to fabricate tissues *ex vivo* and then transplant them back into the patient, the final goal of TE [2, 3].

The other pillar of TE is biomaterials and their 3D structures, *i.e.* scaffolds. These 3D structures play a crucial role because they need to act as a temporary extracellular matrix to support cell activity and ingrowth of the newly formed tissue [4]. The scaffolds should mimic the architecture of the targeted native tissue, thus, they should match the pore architecture, size and volume percentage in order to promote tissue ingrowth and vascularization. Among the different scaffolding biomaterials, bioceramics have been traditionally a favorable candidate, especially for bone tissue engineering, due to their inherent biocompatibility and bioactivity. Some are derived from biological sources such as demineralized bone matrix, and others are synthetic such as, bioactive glasses, calcium phosphate family (hydroxyapatite, β-tricalcium phosphate, and α-tricalcium phosphate), and others [5].

Traditionally, bioceramic based-scaffolds have been made by techniques such as gas foaming, salt leaching, freeze-drying, and the polymer template method [6]. Even though, many of these methods are relatively simple and inexpensive, they suffer from several drawbacks such as inflexibility and a lack of reproducibility. More importantly, the internal structural features (*e.g.*, pore size, shape, and interconnectivity between pores) and the overall shape of the scaffold cannot be precisely controlled. This main drawback has been related to a heterogeneous distribution of cells and non-uniform tissue ingrowth [7]. The application of additive manufacturing technologies in tissue engineering has the power to overcome these limitations of the classical scaffold fabrication methods. Thus, it has emerged with a promise of manufacturing patient-specific scaffolds to repair the damaged tissue. In recent years, the application of additive manufacturing in tissue engineering has been growing exponentially [8]. These set of technologies are based on layer by layer construction of 3D structures. Thus, they have allowed to construct bioceramic scaffolds with highly sophisticated and precise structures, which would not have been possible by using traditional methods. These methods allow to have an absolute control over the physical attributes of scaffolds, such as pore size, pore shape, interconnectivity between pores and porosity. Moreover,

the overall shape of the scaffold can be designed as a 3D model and fabricated. Among the various types of additive manufacturing techniques, stereolithography (SLA), selective laser sintering (SLS), 3D printing (3DP), and direct-ink writing (DIW) are the most commonly used ones for printing bioceramic scaffold, and they will be further explained in this chapter. These techniques can be generally classified as slurry-based and powdered-based. This chapter will give a brief overview of the different classes of bioceramics that can be processed by additive manufacturing (AM) techniques. Afterward, the different technologies that can be used in TE will be described, paying particular attention to the better suited to process bioceramics. And finally, several examples of 3D-printed bioceramic scaffolds will be discussed.

BIOCERAMICS FOR TISSUE ENGINEERING

Calcium Phosphates

Calcium phosphates (CaPs) are one of the most commonly used biomaterials in bone regeneration, namely because of their chemical similarity to the mineral part of mammalian teeth and bones [9]. Human bones are predominantly constituted by calcium orthophosphates (approximately 60 wt %), specifically carbonate hydroxyapatite (HA), while the other main components are collagen (30 wt %) and water (10 wt %) [9, 10]. In addition to this chemical similarity, which renders CaPs as biocompatible materials, implants made of CaPs are also bioactive, meaning that they can form stable bonds with the bone [11, 12]. Moreover, these biomaterials are also osteoconductive [13] (they allow bone growth on the scaffold's surface or pores) and some of them are osteoinductive [14, 15] (they stimulate host pluripotent cells to develop into the osteogenic lineage).

The term "calcium phosphates" encompasses a family of materials made up of calcium (Ca), phosphorous (P) and oxygen (O), the latter two elements being part of phosphate anions. Some CaPs also include hydrogen as an acidic phosphate anion (like $H_2PO_4^-$), water ($CaHPO_4 \cdot 2H_2O$) and/or hydroxide [$Ca_{10}(PO_4)_6(OH)_2$] [16]. CaPs can be classified according to the type of phosphate anion incorporated: polyphosphates [$(PO_3)_n^{n-}$], pyrophosphates ($P_2O_7^{4-}$), metaphoshates (PO_3^-) and orthophosphates (PO_4^{3-}). Additionally, ortho and pyrophosphates can be further distinguished by the amount of hydrogen ions replaced by calcium, giving rise to mono- [$Ca(H_2PO_4)_2$], di- ($CaHPO_4$) (BCP), tri- [$Ca_3(PO_4)_2$] (TCP) and tetra- ($Ca_2P_2O_7$) calcium phosphates [9, 17]. This section is mainly focused on calcium orthophosphates, as they are the main inorganic component of hard tissues in vertebrates [18 - 20].

The properties of different calcium orthophosphates depend on their chemical composition. The name, chemical composition and solubility values can be found

CHAPTER 3

Additive Manufacturing of Bioactive Glasses: Focus on Bone Tissue Engineering

Saeid Kargozar[1], Masoud Mozafari[2,*], Frazad Kermani[3], Peiman Brouki Milan[4,5,6] and **Francesco Baino[7]**

[1] Department of Radiation Oncology, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, United States

[2] Research Unit of Health Sciences and Technology, Faculty of Medicine, University of Oulu, Oulu, Finland

[3] Tissue Engineering Research Group (TERG), Department of Anatomy and Cell Biology, School of Medicine, Mashhad University of Medical Sciences, Mashhad 917794-8564, Iran

[4] Department of Tissue Engineering and Regenerative Medicine, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences, Tehran, Iran

[5] Cellular and Molecular Research Center, Iran University of Medical Sciences, Tehran, Iran

[6] Institute of Regenerative Medicine, Faculty of Advanced Technologies in Medicine, Iran University of Medical Sciences, Tehran, Iran

[7] Department of Applied Science and Technology (DISAT), Institute of Materials Physics and Engineering, Politecnico di Torino, 10129 Torino, Italy

Abstract: In tissue engineering and regenerative medicine, bioactive glasses (BGs) offer many potential advantages. These inorganic substances belong to the bioceramics family and are traditionally produced in powder and granular formats *via* the sol-gel and melt-quenching synthesis routes. In order to mimic the native structure of human tissues, BGs should be fabricated into three-dimensional (3D) constructs (*i.e.*, scaffolds). There are specific conventional fabrication methods for producing BG-based scaffolds (*e.g.*, foam replication); however, they suffer from some critical limitations such as the lack of exact control on the pore dimension and distribution. In this regard, additive manufacturing (AM), also known as 3D printing, has emerged for the generation of precise and high-resolution BG-based scaffolds. Currently, 3D printing of BG-based scaffolds is performed by using a series of well-developed AM techniques, including direct 3D printing, selective laser sintering (SLS), robocasting, and stereolithography (SLA). In some methods, BGs are added to polymeric matrices and then introduced into the 3D printing machine as a raw material. In general, 3D-printed constructs exhibit important advantages over conventionally-fabricated tissue-engineering scaffolds in terms of reproducibility, scalability, architecture (*e.g.*,

[*] **Corresponding author Masoud Mozafari:** Research Unit of Health Sciences and Technology, Faculty of Medicine, University of Oulu, Oulu, Finland; E-mail: mozafari.masoud@gmail.com

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controllable strut thickness, pore shape and size), and biomechanical properties. It is of significance that BGs can be simultaneously printed with mammalian cells (*e.g.*, stem cells), known as 3D bioprinting. Still, some challenges (*e.g.*, decreased cell viability) remain that should be addressed by conducting further research and proposing innovative solutions.

Keywords: Additive manufacturing, Bioactive glasses (BGs), Bioprinting, Bone regeneration, Direct ink writing (DIW), Mesoporous bioactive glasses (MBGs), Melt quenching, Osteogenesis, Powder technology, Regenerative medicine, Robocasting, Scaffold, Selective Laser Sintering (SLS), Sol-gel method, Stereolithography (SLA), Tissue engineering, Wound healing.

INTRODUCTION

There is a growing demand for suitable bone substitutes over the world due to increased injuries and skeletal disorders, congenital genetic abnormalities, and obesity [1]. In this regard, autografts and allografts are considered the main sources and golden standards for replacing large bone defects [2]. However, limited availability and donor site morbidity as well as immune rejection and disease transmission risks are mentioned the major remaining challenges ahead of autografts and allografts, respectively [3, 4]. Moreover, it is difficult to process these grafts in the shape and architecture of bone defects. Accordingly, synthetic biomaterials are increasingly used for fabricating tissue-engineered (TE) constructs. In contrast to autografts and allografts, synthetic biomaterials are easily capable of generating three-dimensional (3D) scaffolds with varying sizes and shapes. Until now, many biocompatible synthetic materials have been developed and used as bone reconstruction materials. Among them, bioactive glasses (BGs) have a unique position in research and clinical studies.

BGs are inorganic substances that are classified as bioactive members of the bioceramics superfamily. Melt-quenching and sol-gel synthesis are both common methods for producing them. Their invention history originates with Professor Larry Hench's research at Florida University in 1969 [5]. The first developed BGs is named 45S5 Bioglass® composed of $45SiO_2$–$24.5CaO$–$24.5NaO$–$6P_2O_5$ (wt.%). This composition is known as the parent of silicate-based glasses in which silicon oxide is the glass network former. In the course of time, other types of BGs were successfully developed including phosphate- and borate-based glasses, in which phosphorus oxide and boron oxide act as the glass network formers, respectively. In 2004, a subgroup of BGs has been introduced under name of mesoporous BGs (MBGs). This kind of porous glasses has an ordered nano-texture due to the presence of pores (size -2-50 nm) inside their particles. The size and shape of pores are controlled by structure-directing agents (*e.g.*, Pluronic 123) used during the sol-gel synthesis process. It is well known that BG formulations readily react

with physiological fluids (*e.g.*, blood plasma) to form hydroxyapatite, which is a constituent of bone and binds to both hard and soft tissues. A number of studies have demonstrated that BGs can improve healing [6 - 8]. This improvement is due to ions (*e.g.*, Si^{4+} and Ca^{2+}) released from BG structures into the biological environment, which influence osteogenesis and angiogenesis [9 - 11]. It is of importance that different formulations of BGs show appropriate antibacterial activities against both Gram-positive and Gram-negative species, which can inhibit bone infections [12]. To improve the biological properties of glasses, therapeutic elements (such as strontium (Sr) having an anti-osteoporotic effect) are commonly incorporated into their basic composition [13 - 16].

It is necessary to do further processing steps on BG fine powders in order to generate 3D porous constructs capable of mimicking the natural architecture of bone tissue. Traditionally, BG-based scaffolds were made by using a series of fabrication methods, including polymeric sponge replication [17]. Nevertheless, traditional approaches are not able to control the scaffold structure (shape, pore size, *etc*.). Therefore, additive manufacturing techniques can be used to manufacture 3D-printed BG scaffolds. Over the last 30 years, we have witnessed the growth of additive manufacturing in different areas like biomaterials science. During the past 5 years, applications of this technology, which is also referred to as 3D printing, have grown significantly [18]. 3D printing is a manufacturing method that can provide scalable and robust fabrication of BG-based scaffolds [19]. This procedure would also enable the fabrication process to be controlled precisely by creating constructs that are specific to each patient through computer simulations [20, 21].

The purpose of this chapter is to discuss the suitability of BGs to fabricate 3D-printed scaffolds for bone tissue engineering. In order to achieve this goal, we discuss and introduce additive manufacturing processes for the development of BG-based 3D scaffolds.

ADDITIVE MANUFACTURING OF BGS AND GLASS/POLYMER COMPOSITES

General 3D Printing of BG Powder

In tissue engineering applications, BGs are extremely useful due to their osteogenesis, angiogenesis, and antibacterial properties [22 - 25]. It is recognized that doping specific elements to BGs networks boosts their therapeutic capacity in medical settings. Doped elements mostly include strontium (Sr), copper (Cu), silver (Ag), zinc (Zn), magnesium (Mg), and cobalt (Co) [26]. However, the low fracture toughness and high brittleness of BGs limit their use in treating defects of load-bearing bones. This restriction is more serious in the case of porous glasses

CHAPTER 4

Mesoporous Bioactive Glasses: Effective Biocompatible Materials for Drug Delivery and Tissue Engineering

Saeid Kargozar[1,*], **Sara Gorgani**[2] and **Ahmed El-Fiqi**[3]

[1] *Department of Radiation Oncology, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, United States*

[2] *Tissue Engineering Research Group (TERG), Department of Anatomy and Cell Biology, School of Medicine, Mashhad University of Medical Sciences, Mashhad 917794-8564, Iran*

[3] *Glass Research Department, National Research Centre, Cairo 12622, Egypt*

Abstract: Mesoporous bioactive glasses (MBGs) are a special subclass of bioactive glasses (BGs), which have held great promise in biomedicine. Compared to melt-derived BGs, MBGs exhibit higher bioactivity (apatite-forming capability) due to highly ordered nanoscale pores (2 to 50 nm) in their structure. The size and shape of well-ordered pores of MBGs depend on structure-directing agents (*e.g.*, CTAB, Pluronic F-123, and Pluronic F-127) used during their sol-gel synthesis process. Having a mesoporous structure, MBGs provide great opportunities in tissue engineering and drug delivery applications. Although MBGs have been mainly explored for managing hard tissue injuries (*e.g.*, bone defects), recent studies indicate their usefulness in soft tissue healing as well. In this regard, MBGs can be utilized for tissue reconstruction in different forms, including fine powders, granules, and scaffolds. In addition, MBGs have been found suitable vehicles for the delivery of a wide range of chemicals, bioactive molecules, and pharmaceutical drugs. Loading and delivery of antibacterial (*e.g.*, antibiotics), pro-angiogenic, and anti-inflammatory substances are commonly being performed using MBGs for improved and accelerated tissue repair and regeneration. Furthermore, MBGs are regarded as promising DDSs for localized delivery of anticancer drugs. Currently, it is feasible to make MBGs as smart drug delivery systems (DDSs) with the help of chemical engineering approaches; for example, opening and closing MBGs' pores are achievable by stimuli-responsive molecular gates. With the invention of three-dimensional (3D) printing technology, MBGs were successfully incorporated into polymeric inks to generate potent tissue substitutes capable of simultaneous tissue engineering and drug delivery.

[*] **Corresponding author Saeid Kargozar:** Department of Radiation Oncology, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, United States; Tel: 214-648-3111; E-mail: Saeid.kargozar@utsouthwestern.edu

Saeid Kargozar and Francesco Baino (Eds.)

Keywords: Antibacterial activity, Anticancer effects, Bioactive glasses (BGs), Bioactivity, Biocompatibility, Bone tissue engineering (BTE), Cetyltrimethylammonium bromide (CTAB), Drug delivery systems, Pluronic F-123, Pluronic F-127, Polymeric foam replication, Pro-angiogenesis, Mesoporous bioactive glasses (MBGs), Scaffolds, Mesoporous silica nanoparticles (MSNs), Soft tissue engineering, Structure-directing agents, Tissue repair, Tissue engineering, Three-dimensional (3D) printing, Wound healing.

INTRODUCTION

Along with the increase of human diseases and disorders and the shortage of donors, there is an urge for developing tissue substitutions in the lab and the utilization in the clinic. On this matter, tissue engineering has emerged as a multidisciplinary approach for generating tissue and organ replacements using the principles of materials science, biology, and medicine. Three main building blocks of tissue engineering include biomaterials, cells, and bioactive molecules. From a biomaterial point of view, numerous types of organic and inorganic substances have been examined and used for the repair and regeneration of injured tissues. Among them, bioactive glasses (BGs) have achieved a significant position in the treatment of both hard and soft tissue complications.

Bioactive glasses (BGs), as the second generation of biomaterials, have shown great therapeutic potential for managing different tissue damages and diseases. BGs represent biocompatible materials with the ability to bind with both hard and soft tissues. These man-made materials were initially developed by Professor Larry L. Hench at Florida University in 1969 and introduced to the world by the name of 45S5 Bioglass$^{@}$ with the composition of $45SiO_2$–24.5CaO–24.5NaO–$6P_2O_5$ (wt%). After the invention of silicate-based BGs (45S5 bioglass$^{@}$), researchers and scientists could synthesize other categories of BGs, including phosphate- and borate-based BGs. Currently, BGs are being prepared in diverse formats (*e.g.*, fine powders, granules, fibers, *etc*.) to meet the requirements of tissue defects. Mechanically, BGs seem suitable materials for treating hard tissue (bone and teeth) lesions; however, recent studies have emphasized their usefulness in managing soft tissue injuries as well. Experimental studies have demonstrated the capability of BGs for improving cell proliferation, migration, and differentiation. In addition, they can inhibit bacterial infections and promote neovascularization, leading to accelerated tissue healing. Still, the most distinctive feature of BGs is associated with their bioactive nature; a hydroxycarbonate apatite (HCA) layer forms on their surface after incubation in physiological fluids (*e.g.*, human plasma and simulated body fluid (SBF)).

Two main approaches for the production of BGs are the melt-quenching and sol-gel methods. From a biomedical engineering perspective, each synthesis route has its pros and cons; for example, sol-gel BGs show higher bioactivity due to their porous structure. Over the years, materials scientists, physicists, and chemical engineers in collaboration with biologists and medical experts have tried to develop novel BGs with optimal structural properties in terms of tissue engineering and drug delivery. On this matter, mesoporous bioactive glasses (MBGs) were developed as a new class of BGs with controlled and reproducible textural features. These substances were firstly produced by Yan *et al*. [1] and then by López-Noriega *et al*. [2] using the sol-gel method combined with the principles of supramolecular chemistry. In order to produce MBGs, structure-directing agents (surfactants) should be added to the sol during the sol-gel process. Indeed, surfactant molecules can self-organize and generate the mesoporous texture *via* the evaporation-induced self-assembly (EISA) process under specific and controlled pH and temperature conditions. Cetyl trimethyl ammonium bromide (CTAB), $EO_{20}PO_{70}EO_{20}$ (P123), and $EO_{100}PO_{65}EO_{100}$ (F127) and among the most frequently used organic templates for obtaining MBGs with highly-ordered pores [3, 4]. The surfactants are amphiphilic molecules that exhibit self-assembling capability in aqueous solutions at a certain concentration (*i.e.*, critical micellar concentration). It is well-demonstrated that the chain length of surfactant and solution chemistry determine the pore dimensions and structures of MBGs.

Structurally, MBGs have highly ordered nanoscale pores with diameters of 2 to 50 nm. This mesoporous structure enables MBGs to have higher bioactivity in comparison with other types of BGs and plays a major role in promoting their apatite-forming ability. In addition, the mesoporous nature of MBGs provides an outstanding opportunity for loading and delivering a broad range of bioactive molecules (*e.g.*, growth factors) and drugs (*e.g.*, antibiotics) [5]. Accordingly, the use of drug-loaded MBGs can potentially result in accelerated tissue healing *in vivo*. In this chapter, we firstly introduce the structure and characteristics of MBGs and then discuss their capacity in drug delivery and tissue engineering applications.

Ordered Mesoporous Materials: A Brief History

The history of silica-based ordered mesoporous nanomaterials dates back to the first report published in the 1990s by the oil industry [6]. Indeed, mesoporous materials represent a specific type of nano-scaled materials that have ordered arrays of uniform nano-channels. This kind of material has attracted much attention in different areas of science (*e.g.*, biomedicine) due to its excellent structural features, including large pore volume (~ 1 cm^3/g) and high surface area

CHAPTER 5

Bioactive Glass and Glass-Ceramics for Managing Microbial Infections

Murilo C. Crovace[1,*] and **Marina T. Souza**[2]

[1] *Bioactive Materials Laboratory (LMBio), Department of Materials Engineering, Federal University of São Carlos (DEMa/UFSCar), São Carlos-SP, Brazil*

[2] *VETRA – High-Tech Biomaterials, Ribeirão Preto-SP, Brazil*

Abstract: Bioactive glasses and glass-ceramics are promising materials for both hard and soft tissue regeneration through gene activation mechanisms triggered by their dissolution products. This chapter presents a key property of bioactive glasses and glass-ceramics of growing interest in materials science *i.e* their antibacterial activity. The main compositions, including composites, with proven bactericidal action, were gathered. The current understanding of compositional effects on the bacteria-killing mechanisms is summarized as well as the main dopants used to enhance the antibacterial activity. Finally, examples of bioactive glass-based products that have being developed for many important applications in orthopedics are presented, such as the treatment of osteomyelitis, coating in metallic implants, the treatment of infected skin wounds, and also in dentistry, in the treatment of oral ailments.

Keywords: Anti-biofilm, Antibiotics, Bacteria, Bactericide material, Bioactive glass, Bioactivity, Bactericidal activity, Bioglass, Bone, Chronic infection, Diabetes, Glass-ceramic, Implant failure, Osteomyelitis, Skin burn, *Staphylococcus aureus*, Tissue regeneration, Wound healing.

INTRODUCTION

The year 2021 marked the 50th anniversary of the invention of 45S5 bioactive glass by Larry Hench, which was the first known synthetic material to exhibit an unusual property: the ability to form a strong chemical bond with the bone. Until the early 1980s, it was believed that bioglasses were only capable of binding to hard calcified tissues such as bone. In the following years, it was discovered that these materials were also able to bind to connective tissues, muscles, nerves and even the skin, promoting their regeneration. Currently, bioactive glasses, or just

* **Corresponding author Murilo C. Crovace:** Bioactive Materials Laboratory (LMBio), Department of Materials Engineering, Federal University of São Carlos (DEMa/UFSCar), São Carlos-SP, Brazil; E-mail: mcc@ufscar.br

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"bioglasses", are considered third-generation biomaterials. Third-generation biomaterials are capable of forming not only a direct link with living tissues, but also releasing ions that stimulate specific cellular responses at the molecular level, through the activation of certain types of genes.

Although the involved mechanisms are not yet fully understood, some bioactive glasses can promote *in situ* regeneration of both hard tissues (bone, dentin, *etc*.) and soft tissues (skin, cartilage and nerves). For this reason, these materials are gaining more and more relevance within tissue engineering. Currently, there is a vast literature proving numerous positive properties of bioactive glasses and glass-ceramics, among which, the following are highlighted:

• Osteoconduction and osteoinduction [1-3], that is, the ability to be colonized by bone cells and stimulate their proliferation;

• Angiogenic potential [4, 5], that is, *i.e.* material can stimulate the formation of new blood vessels;

• Ability to stimulate fibroblast cell proliferation and collagen production [6];

• Hemostatic properties (decreases local bleeding) [7].

After more than 50 years of its discovery, it is possible to find in the literature a wide range of compositions, including silicate, phosphate, and borate-based bioglasses. Glasses are, by nature, very versatile; most elements of the periodic table can be accommodated in its structure [8]. Generally, bioactive glasses are multi-component; the network former oxide elements (SiO_2, P_2O_5, B_2O_3) are usually accompanied by large amounts of network modifier elements, such as alkaline (Li_2O, Na_2O, K_2O) and alkaline earth oxides (MgO, CaO, SrO), as well as intermediate oxides (Al_2O_3, TiO_2, ZnO, ZrO_2) in a lesser extent. Novel bioactive glasses have been developed by introducing small quantities of specific ions with "therapeutic" function [9]. Their incorporation into the glass composition is called doping and can be crucial for the production of functional materials. Doping elements are typically added in low concentrations compared to the main constituents, ranging from a few parts per million (ppm) to a small percentage of the main composition. In many cases, doping elements bring new functionalities to a bioactive glass [10]. The metallic ions that are being incorporated into bioactive glasses to enhance their biological performance include, bismuth (Bi^{+3}), boron (B^{3+}), copper (Cu^{+} and Cu^{2+}), cobalt (Co^{2+}), silver (Ag^{+}), zinc (Zn^{2+}), cerium (Ce^{3+}), gallium (Ga^{3+}), niobium (Nb^{+5}), selenium (Se^{+4}), strontium (Sr^{2+}), tantalum (Ta^{+5}), and vanadium (V^{+5}) [11, 12]. As an example of their impact, we can cite an improved angiogenesis *in vitro* and *in vivo* caused by the incorporation of copper (Cu^{+} and Cu^{2+}) and cobalt (Co^{2+}) ions [11].

The clinical demand for bioactive glass is increasing rapidly; the wide range of applications include bone grafts, repairing or replacing damaged/diseased soft tissues, bone cements, drug carriers and as coatings in implants. In the treatment of bone or soft tissue lesions, there are three main factors that should be considered: (1) bioactivity (in more general terms, the ability to induce tissue regeneration through a chemical stimulus); (2) absorbability (the material should be gradually replaced by the new tissue formed); and (3) prevention of bacterial infection. As we know, the colonization of an implant surface by bacteria can results in failed treatment. Implant infections can have serious consequences and may occasionally require a second surgery, causing significant suffering. In addition to the beneficial properties mentioned above, it was discovered a few decades ago that bioactive glasses also have antibacterial activity. The contact of bioactive glass with biological aqueous fluids results in the release of ions that make the surrounding environment hostile to bacteria growth. Thus, compositional effects, including dopants, have long been investigated in order to unravel the factors involved in this key property.

GLASSES AND GLASS-CERAMICS WITH PROVEN ANTI-MICROBIAL ACTIVITY

Perhaps the first publication showing the interaction of a bioactive glass with bacteria was published by Stoor *et al*. in 1996 [13]. In this study, the S53P4 glass was tested for the first time against periodontal pathogens. In 1999, Stoor *et al*. [14] also studied the interactions both *in vitro* and *in vivo* between S53P4 and the bacteria *Klebsiella ozaenae*, which is associated with atrophic rhinitis. For those tests, the glass was used in the form of granules or discs. Additionally, a 19–74 months clinical follow-up study with ozena patients surgically treated with the S53P4 was performed. Patients exhibited no implant infections, and their symptoms were significantly reduced. This indicates that S53P4 did not promote adhesion and colonization of *Klebsiella ozaenae* (*K. ozaenae*) *in vitro*. These findings were further supported by the absence of bioactive glass-associated infections or reinfections observed *in vivo*. Since then, bioactive glasses have been tested for a wide range of clinically relevant bacteria, aerobic and anaerobic varieties, and for both Gram-negative and Gram-positive species (as summarized in the Table **1**). However, the absence of comparative studies carried out under the same experimental conditions makes it difficult to draw conclusions or establish direct composition-bactericidal activity relationships. In fact, in the published studies, glasses are used with a great variability in terms of chemical composition (*e.g.* different amounts of Na_2O, CaO, SiO_2 and P_2O_5), shapes and particle size distribution, and also surface area. The surface area is particularly important, as the higher its value, the greater the reactivity of the glass will be.

CHAPTER 6

Bioactive Glasses and Ceramics for Improved Angiogenesis

Saeid Kargozar[1,*], Simin Nazarnezhad[2], Thomas J. Webster[3,4,5] and **Francesco Baino[6]**

[1] *Department of Radiation Oncology, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX75390, USA*

[2] *Tissue Engineering Research Group (TERG), Department of Anatomy and Cell Biology, School of Medicine, Mashhad University of Medical Sciences, Mashhad 917794-8564, Iran*

[3] *UFPI - Universidade Federal do Piauí, Teresina, Brazil*

[4] *CBCMT, Vellore Institute of Technology, Vellore, 632014, India*

[5] *Hebei University of Technology, Hebei, China*

[6] *Department of Applied Science and Technology (DISAT), Institute of Materials Physics and Engineering, Politecnico di Torino, 10129 Torino, Italy*

Abstract: Bioceramics form a versatile large family of biocompatible materials with diverse applications in the medical setting. These substances can be classified into distinct groups, including almost bio-inert ceramics (*e.g.*, alumina), bioactive glasses and glass-ceramics, and moderately to quickly bioresorbable ceramics (*e.g.*, hydroxyapatite and tricalcium phosphates, respectively). Bioceramics are conventionally used for healing hard tissue injuries due to their excellent properties, including mechanical performance. From a biological perspective, bioceramics exhibit outstanding features (*e.g.*, inducing osteogenesis) in favor of bone reconstruction. Considering the central role of angiogenesis in tissue healing, different formulations of bioceramics have been demonstrated to have stimulatory effects on neovessel formation. Apart from physical properties (*e.g.*, surface micron and nano topography), the chemical composition of bioceramics greatly affects their angiogenic capacity *in vitro* and *in vivo*. Several additional approaches are now well-established in order to increase the angiogenic activity of bioceramics, including adding pro-angiogenic dopants (*e.g.*, copper and silicon) and loading pro-angiogenic bioactive molecules (*e.g.*, vascular endothelial growth factor (VEGF)). In this sense, the degradation rate of bioceramics is a key property commonly mentioned to effectively promote angiogenesis. Cellular and molecular experiments have revealed the signaling pathways involved in angiogenesis which are activated by ionic dissolution products released from bioceramics. In this manner, this review highlights the new positive role that bioceramics can play in angiogenesis.

[*] **Corresponding author Saeid Kargozar:** Department of Radiation Oncology, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX75390, USA; Tel: 214-648-3111; E-mail: Saeid.Kargozar@utsouthwestern.edu

Keywords: Angiogenesis, Bioactive glasses (BGs), Bioceramics, Calcium phosphates (CaPs), Calcium silicate bioceramics, Calcium sulphate bioceramics, Chorioallantoic membrane (CAM) assay, Endothelial cells (ECs), Hydroxyapatite (HAp), Ion release, *In vitro*, *In vivo*, Mesoporous bioactive glasses (MBGs), Neovascularization, Scaffold, Surface topography, Three-dimensional (3D) printing, Tissue engineering, Scaffold, Vascular endothelial growth factor (VEGF), Wound healing.

INTRODUCTION

Bioceramics represent a versatile class of inorganic biocompatible substances in the field of materials science and engineering with diverse biomedical applications, ranging from dentistry and tissue regeneration towards cancer therapy and diagnostic (*i.e.*, theranostics) [1]. They may be isolated from natural sources (marine sponges) or produced in the laboratory. Bioceramics can be classified into different groups including: (I) almost bio-inert ceramics (*e.g.*, alumina), (II) bioactive glasses (BGs) and glass-ceramics, and (III) bioresorbable ceramics (*e.g.*, calcium phosphates). Currently, they are produced and fabricated in different shapes and forms, including fine powders, granules, three-dimensional (3D) scaffolds, *etc*. [2, 3]. Bioceramics can be synthesized *via* different routes: for example, precipitation, hydrothermal techniques, solution combustion, melt-quenching, sol-gel methods, *etc*. [3 - 5]. It has been well-known that bioceramic synthesis method affects the properties of the final product in terms of morphology, particle size, porous structure, *etc*.

Bioceramics have been historically developed and utilized for managing hard tissue disorders (*e.g.*, bone fractures) due to their inherent bone-like physico-chemical and mechanical properties. In addition, bioceramics exhibit stunning biological features for bone repair and regeneration, including osteoconduction, osteoinduction, osteogenesis, and osteointegration [6 - 8]. Apart from hard tissue engineering, bioceramics in specific formulations can be used for treating soft tissue injuries, such as skin wounds [9]. In fact, specific members of the bioceramics family can support the growth and proliferation, migration, and differentiation of cells from soft tissues, like fibroblasts, keratinocytes, *etc*. In addition, the ability to inhibit bacterial infections and promote neovascularization (angiogenesis) makes bioceramics advantageous materials for soft tissue healing strategies. Regarding the central role of neovascularization in wound healing, a large number of experimental studies have emphasized the use of angiogenesis-inducing materials in order to obtain accelerated tissue reconstruction. In this sense, some bioceramics (mostly BGs) are potent substances for inducing angiogenesis *in vitro* and *in vivo* [10]. Cellular and biomolecular experiments have revealed that the ion release from bioceramics into the surrounding

biological environment is the main reason behind improved angiogenesis. In addition, it is now clear that the surface topography (in particular, nano topography) of bioceramics can influence their angiogenic behavior. Over the years, several innovative approaches have been applied to enhance the pro-angiogenic capacity of bioceramics, including the addition (doping) of specific elements (*e.g.*, silicon, copper, *etc*.) to their basic composition as well as the loading of pro-angiogenic bioactive molecules (*e.g.*, growth factors, phytochemicals, *etc*.) [11]. The degradation rate of bioceramics in physiological environments directly dictates the degree and rate of ion release and, thus, their subsequent pro-angiogenic capacity; therefore, the selection of dopants in bioceramic composition is of great importance for tuning their degradability *in vivo*.

In this chapter, we first describe the angiogenesis process and its importance in tissue engineering strategies and then introduce the pro-angiogenic capability of different classes of bioceramics, including BGs, calcium silicate ceramics, calcium phosphate ceramics (CPCs), and calcium sulphate (CS) ceramics. In each section, the impact of bioceramics is discussed on the behavior of cells involved in angiogenesis, including endothelial cells (ECs) and macrophages. Moreover, the differentiation of stem cells towards endothelial cell lineages as a result of the ionic dissolution products from bioceramics is discussed.

ANGIOGENESIS: A CELLULAR AND MOLECULAR PERSPECTIVE

Angiogenesis is referred to as the sprouting of new vasculature from pre-existing capillaries, which penetrate through the underlying vascular basement membrane and constitute tube-like structures. Finally, this can branch, extend, and then create blood vascular networks. Generally speaking, blood vasculature is formed through two distinct biological processes: including vasculogenesis and angiogenesis. Indeed, vascularization plays vital roles in both pre-and post-natal biological phenomena, including organ development (organogenesis) and wound healing, respectively. It should be mentioned that neovascularization is also involved in the progression of some human diseases, specifically cancers [12, 13]. In normal physiological conditions, neovascularization is highly regulated by an intricate network of various cellular and molecular constituents in a spatially and temporally synchronized trend [14]. Angiogenesis is commonly regulated by pro- and anti-angiogenic factors presented in platelets and inflammatory cells, sequestering within the extracellular matrix (ECM) as well. Pro-angiogenic factors are produced in response to hypoxia (*e.g.*, hypoxia-inducible factors (HIF)) and inflammation (*e.g.*, cyclooxygenase-2 (COX-2)) conditions [15, 16]. Immediately following injury, angiogenesis stimulators are released into the wound site and act in favor of vascular growth. Angiogenic GFs and cytokines

CHAPTER 7

Bioactive Glasses and their Composites with Potent Hemostatic Activity

Sara Pourshahrestani[1,*], Ehsan Zeimaran[2], Mh Busra Fauzi[1] and **Nahrizul Adib Kadri[2]**

[1] *Centre for Tissue Engineering and Regenerative Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur-56000, Malaysia*

[2] *Department of Biomedical Engineering, Faculty of Engineering, University of Malaya, Kuala Lumpur-50603, Malaysia*

Abstract: One of the key reasons for death is blood loss or hemorrhage from trauma or surgeries. Management of bleeding by utilizing suitable hemostatic agents is therefore important to diminish related complications and mortality. In recent years, the application of bioactive glasses for hemostasis has shown promising results in both *in vitro* and *in vivo*. In this chapter, we will highlight the mechanism of action of bioactive glasses in accelerating hemostasis, review various forms of bioactive glasses and their composites that have been assessed for potential application in promoting hemostasis and stopping bleeding, and briefly include future perspectives.

Keywords: Activated partial thromboplastin time, Bioactive glasses, Bioactive glasses particles, Bioactive glass microspheres, Bioactive glasses/polymer composites, Biomaterials, Biomedical application, Bleeding, Blood coagulation, Fibers, Hydrogels, Hemorrhage, Hemostasis, Hemostatic application, Mesoporous bioactive glasses, Platelet adhesion, Prothrombin time, Sponges, Thrombin, Thrombus formation.

INTRODUCTION

Uncontrolled bleeding or massive bleeding resulting from surgical procedures and trauma may have life-threatening consequences [1 - 3]. Therefore, immediate management of blood loss is imperative to prevent such related complications and

* **Corresponding author Sara Pourshahrestani:** Centre for Tissue Engineering and Regenerative Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur 56000, Malaysia;
E-mail: sara.pourshahrestani@gmail.com

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reduce mortality. When an injury occurs, hemostasis is the body's inherent function (arrest bleeding) and encompasses three phases: 1) vasoconstriction, 2) platelet plug formation, and 3) blood clotting cascade that leads to sealing off damaged blood vessels and thereby stopping bleeding [4, 5]. However, the body's natural blood clotting process is not capable of managing excessive bleeding effectively, and thus the utilization of hemostatic materials as an external intervention is required to achieve efficient and swift hemostasis [2].

Over the past decades, various hemostatic materials composed of organic and/or inorganic compounds such as chitosan [6 - 10], gelatin [11 - 15], oxidized cellulose [16 - 20], alginate [21 - 25], carrageenan [26 - 29], zeolite [30], kaolin [31 - 34], smectite [35, 36], or bioactive glasses [37 - 39], in forms of powders, sponges, bandages, hydrogels, and adhesives, *etc.*, have been developed and their potential for hemostatic applications have been assessed [40, 41]. The hemostatic biomaterials attain hemostasis *via* various mechanisms including the formation of a physical barrier and /or acceleration of coagulation cascade by coagulation factors' aggregation or releasing therapeutic ions which result in blood cell and platelet adhesion and aggregation. Among the developed materials, bioactive glasses particularly mesoporous bioactive glasses (MBGs), have attracted much attention owing to their excellent textural properties, biocompatibility, and their capability to release therapeutic ions to promote hemostasis, wound healing and prevent infection at wound sites.

Bioactive glasses (BGs) with the composition of SiO_2–Na_2O–CaO–P_2O_5 were first reported by Hench *et al.* over 50 years ago in 1969 and prepared *via* melt quenching technique [42]. These materials are known to have excellent properties and bioactivity and can form a stable and strong bond with hard tissues (*e.g.,* bone and teeth) [43, 44]. Later, porous sol-gel glasses (SGGs) with a high surface area were proposed by Li *et al.* in the 1990s [45]. The glasses with higher contents of SiO_2 and in the system of SiO_2–CaO–P_2O_5 were found to have wider bioactive compositions and bioactivity with respect to the melt bioglass and could exhibit higher rates of bone bonding. However, pore size distribution in sol-gel glasses is wide and insufficient, and may not be suitable for the effective loading and release of drugs and biomolecules [43, 46]. In 2004, with a combination of sol-gel and supramolecular chemistries, MBGs in the composition of SiO_2–CaO–P_2O_5 were developed by Yan *et al*. [47]. The materials with a pore size ranging from 5 to 20 nm are known to have a high surface area, pore volume, and a highly ordered mesoporous structure, and in comparison to conventional non-porous BGs, they display higher bioactivity.

Even though the biomedical applications of porous and nonporous BGs have been primarily aimed for bone tissue engineering and drug delivery [43, 48, 49], they

have recently been proposed for hemostatic and wound healing applications [37, 50]. In this chapter, after summarizing the proposed mechanism of how bioactive glasses accelerate hemostasis, the recent advances in the hemostatic application of porous and nonporous bioactive glasses in different forms of particles, and fibers, as well as composite scaffolds and hydrogels are reviewed (Fig. **1**).

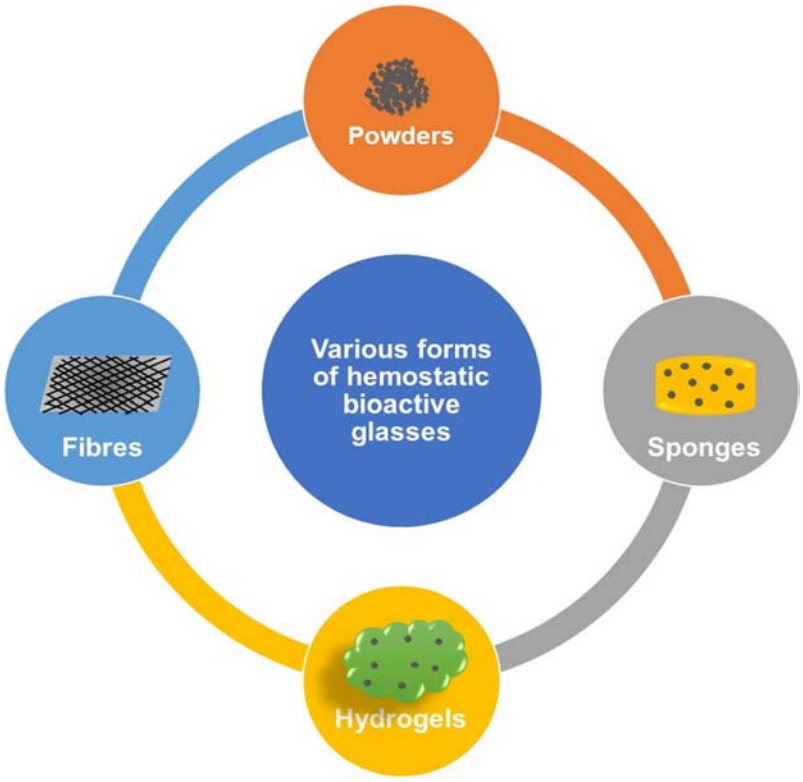

Fig. (1). Various forms of bioactive glasses and their composites for hemostatic applications.

Bioactive Glasses for Hemostatic Applications

Bioactive glasses alone in the form of powders or the combination with polymers to make sponges and hydrogels have shown great promise for hemostatic applications because of their excellent properties. The hemostatic function of bioactive glasses can be ascribed to multiple factors. For instance, it has been described that the high surface area and porosity of the porous bioactive glasses (MBGs), play a vital role in their hemostatic function which allows them to absorb water from the blood and concentrate blood components (*e.g.,* platelets and clotting factors) (Fig. **2**). Importantly, they can release numerous therapeutic ions from their frameworks in contact with biological fluid leading to the acceleration of hemostasis. For example, Ca ions (coagulation factor IV) play a

CHAPTER 8

Combination of Bioactive Glass Nanoparticles and Natural Polymer-Based Hydrogels for Bone Tissue Regeneration

Kai Zheng[1,2,*] and **Rongyao Xu**[1,2]

[1] *Jiangsu Province Engineering Research Center of Stomatological Translation Medicine, Nanjing Medical University, Nanjing 210029, China*

[2] *Jiangsu Key Laboratory of Oral Diseases, Nanjing Medical University, Nanjing 210029, China*

Abstract: Bioactive glass nanoparticles (BGNs) are multifunctional building blocks of tissue engineering scaffolds or drug delivery platforms for bone tissue regeneration owing to their favorable osteogenic, angiogenic, immunomodulatory, and antibacterial activities. Natural polymer-based hydrogels are one of the most promising biomaterials for numerous biomedical applications, considering their extracellular matrix (ECM)-mimic structure, outstanding biocompatibility, and biodegradability. However, these hydrogels are intrinsically mechanically weak and lack biological functionalities, which impede their performance in bone tissue regeneration. Incorporating BGNs as rigid fillers in natural polymer-based hydrogels has been proposed as a feasible strategy to combine the advantages of both components leading to advanced nanocomposite hydrogels. Here the synthesis approaches of BGNs that determine the nanoparticles' morphology and properties are first summarized. The interactions between BGNs and natural polymer-based hydrogels are also emphasized. The key physiochemical and biological properties of BGNs that are related to bone tissue formation are highlighted. Published results are evidence of the fact that the combination of BGNs and natural polymers toward nanocomposite hydrogels is a feasible strategy for successful bone regeneration.

Keywords: Bioactive glasses, Nanoparticles, Natural polymers, Nanocomposites, Tissue regeneration.

INTRODUCTION

Since the development of the first bioactive glasses (BGs) by Dr. Larry Hench in the late 1960s, BGs, and their glass-ceramics derivatives have been recognized as one of the most effective biomaterials for bone repair and regeneration applications [1, 2]. BGs have been widely applied as bone substitutes, bone tissue

* **Corresponding author Kai Zheng:** Jiangsu Province Engineering Research Center of Stomatological Translation Medicine, Nanjing Medical University, Nanjing 210029, China; Email: kaizheng@njmu.edu.cn

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engineering scaffolds, or orthopedic implant coatings. The first developed BGs, 45S5 Bioglass, are silicate glass composed of SiO_2, P_2O_5, CaO, and Na_2O components [2]. After the development of 45S5 Bioglass, numerous BGs compositions with unique properties have been developed for various tissue regeneration applications [3]. According to their type of glass network formers, BGs can be divided into three categories, *i.e.*, silicate, phosphate, and borate BGs [3]. Each composition system has its pros and cons for bone tissue regeneration. Particularly, trace elements can be incorporated into BGs structure as network modifiers and released in ionic form to stimulate specific cellular activities toward enhanced tissue regeneration and therapeutic effects [4]. Recently, due to the favorable effects of released ions, the applications of BGs in soft tissue regeneration and cancer treatment are attracting increasing attention [1, 5, 6]. In addition to controlling chemical composition, the morphology of BGs can also be tailored to modulate BGs' properties [1, 4, 7]. For example, the spheroidization of BGs can improve their flow ability and benefit their performance in injectable formulations [8].

Among various morphologies, bioactive glass nanoparticles (BGNs) are particularly attractive in fabricating tissue engineering scaffolds or drug delivery platforms thanks to their uniform shape and size, large specific surface area and surface-to-volume ratio as well as controllable size and porosity at the nanoscale [1, 7]. Compared to their microsized counterparts, BGNs possess greater surface reactivity resulting in accelerated mineralization and interactions with cells [7]. Moreover, given their morphological advantages, BGNs are considered more suitable building blocks than microsized BGs for developing bone tissue engineering scaffolds and injectable formulations [9 - 11]. By tuning processing parameters, the pore structure (*e.g.*, pore size, porosity, pore volume) of BGNs can be controlled, which is key to the successful applications of BGNs in regenerative medicine [12, 13]. These desired characteristics of BGNs highlight their potential as multifunctional biomaterials for bone tissue regeneration.

Although BGNs have exhibited numerous advantages favorable for tissue regeneration applications, they still suffer from some limitations impeding successful clinical translation. For example, BGNs are available in the powder form, unsuitable for repairing large bone defects. It is challenging for BGNs to remain in defect sites due to the flowing of biological fluids and therefore BGNs cannot give necessary support to cells for adhesion and proliferation as well as the consequent vascularization and bone tissue growth. In addition, direct interactions between cells and BGNs may result in massive uptake of nanoparticles by cells, which may increase the toxicity of BGNs to cells [14, 15]. To address these challenging issues, BGNs can be used as building blocks to fabricate bone tissue engineering scaffolds or orthopedic implant coatings [16]. For example, BGNs

can be mixed with a suitable solvent or polymer solution leading to extrudable inks for 3D printing. After the construction, the printed structures undertake high-temperature treatment to obtain densified and pure BGs scaffolds [17]. However, the application of high-temperature treatment may counteract the advantages of BGNs over microsized BGs as the porosity and surface reactivity of BGNs could be reduced due to nanoparticle aggregation and the removal of Si-OH groups. Alternatively, BGNs can act as rigid fillers in polymeric matrices to enhance their degradability, and mechanical and biological properties [9]. BGNs have emerged as promising rigid fillers of hydrogels, a type of versatile and multifunctional polymeric material, resulting in various tissue regeneration applications from bone repair to wound healing [8, 11].

Hydrogels are water-swellable polymeric materials with a 3D network structure, generally divided into synthetic polymer-based and natural polymer-based hydrogels. They can mimic the extracellular matrix (ECM) microenvironment and thus facilitate cell adhesion, differentiation, and tissue regeneration [18]. Synthetic polymer-based hydrogels (*e.g.*, polyvinyl alcohol) possess remarkable water absorption capability and outstanding mechanical properties. However, they usually suffer from limited biodegradability and poor cell interactions, negatively affecting their performance in tissue regeneration applications. In comparison, natural polymer-based hydrogels (*e.g.*, collagen, gelatin, chitosan, alginate, starch, polypeptide) show excellent biocompatibility and biodegradability, highlighting their potential in tissue regeneration areas [19]. However, natural polymer-based hydrogels usually exhibit weak mechanical performance, significantly limiting their applications in bone tissue regeneration, particularly in load-bearing defect repair [20, 21]. To address this challenging issue, many strategies have been employed to empower natural polymer-based hydrogels in terms of mechanical properties, including incorporating additional phases toward double-network hydrogels or nanocomposite hydrogels [20]. Inorganic nanobiomaterals such as silica nanoparticles, hydroxyapatite nanoparticles, and calcium phosphate nanoparticles have been successfully combined with natural polymer-based hydrogels as rigid fillers to enhance their mechanical properties [22]. Among these inorganic fillers, BGNs stand out with their advantageous biological properties in addition to their mechanical reinforcement effects. Alternatively, natural polymer-based hydrogels offer BGNs with a 3D structure that can support cell adhesion, growth, and differentiation [22]. Moreover, in this strategy, high-temperature treatment can be avoided, which can retain the porosity and bioactivity of BGNs. A combination of BGNs and natural polymers is thus proposed as a promising strategy for obtaining bioactive nanocomposite hydrogels with enhanced structural, mechanical, and biological cues for tissue regeneration applications.

CHAPTER 9

Bioceramics and Bioactive Glasses for Tooth Repair and Regeneration

Roger Borges[1,4,*], Karina F. Santos[2], Agatha M. Pelosini[1], Emanuela P. Ferraz[3], Paulo F. Cesar[2] and **Juliana Marchi[1]**

[1] *Center for Natural and Human Sciences, Federal University of ABC, Santo André, Brazil*

[2] *Department of Biomaterials and Oral Biology, School of Dentistry, University of São Paulo, São Paulo, Brazil*

[3] *Department of Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil*

[4] *School of Biomedical Engineering, Faculdade Israelita de Ciências da Saúde Albert Einstein, Hospital Israelita Albert Einstein, São Paulo, Brazil*

Abstract: Bioceramics applications in dental materials date back to 1892, and since then, many advances have allowed the development of bioceramics for applications in three main areas of dentistry: restorative, rehabilitative, and regenerative dentistry. This chapter will cover clinical situations in which dental tissues need clinical interventions using bioceramics. The main properties of these ceramics and their main advances and applications in restorative, rehabilitative, and regenerative dentistry will also be addressed. In summary, innovation in bioceramics has allowed the development of implants and restorative materials able to bind to the dentin and enamel, besides showing suitable aesthetics and mechanical properties for applications in load-bearing regions. These bioceramics have also been used as scaffolds in alveolar, mandibular, and maxillary bone regeneration, and recently computer-based technologies like CAD-CAM and 3D-printing have guided their advances. Finally, future perspectives and open questions are discussed at the end of the chapter.

Keywords: Additive manufacture, Alumina, Bioactive glass, Bioinert glass, Bone regeneration, Calcium phosphate, Dental implant, Dental restauration, Dentin hypersensitivity, Drug delivery, Endodontics, Glass-ionomer cement, Hydroxyapatite, Periodontics, Regenerative dentistry, Rehabilitative dentistry, Restorative dentistry, Tricalcium phosphate, Tissue engineering, Titania, Zirconia.

[*] **Corresponding author Roger Borges:** Center for Natural and Humans Sciences, Federal University of ABC, Santo André, Brazil & School of Biomedical Engineering, Faculdade Israelita de Ciências da Saúde Albert Einstein, Hospital Israelita Albert Einstein, São Paulo, Brazil; Tel/Fax +55 11 9 5908 10 57; E-mail: roger.borges@ufabc.edu.br

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INTRODUCTION TO DENTAL TISSUE AND THE NEED FOR CLINICAL INTERVENTIONS

Dental tissue anatomy is divided into two main regions: the crown and the root [1]. Exposed to the oral cavity, the crown is externally composed of enamel, the most mineralized structure in the human body. The enamel is produced by ameloblasts that secrete extracellular matrix but are not found in the tooth when fully developed. The extracellular matrix comprises 96% of the inorganic phase – mainly calcium phosphate phases like hydroxyapatite – 2% water, 1% organic material, and 1% other compounds [2 - 4]. In addition, there is another highly-mineralized structure underneath the enamel, the dentin, which constitutes most of the dental structure. The dentin has a 60% mineral phase, with a tubular structure that confers mechanical strength to the tooth. Also, it mechanically supports the enamel. However, it is not only found in the crown but also in the roots. In the crown, the dentin is covered by the enamel, while in the root, the dentin is covered by the cement – an ectomesenchymal tissue that allows the teeth fixation on the alveolar bone through the periodontal ligament, besides relieving the mechanical stress from masticatory loads [2 - 4]. Inside the dentin, the conjunctive tissue in the pulp cavity comprises dental pulp, odontoblasts, fibroblasts, and dental pulp stem cells (DPSCs), all of which are dispersed in a complex extracellular matrix that also contains blood vessels and nerves. Besides generating neurosensory stimulus, this complex structure is responsible for dental repair [2 - 5]. Fig. (**1**) schematically shows the dental tissue structure and cellular organization [6].

Caries lesions or fractures can cause losses in the dental structure. In this sense, the dental tissue itself triggers a repair response that is dependent on multiple factors: I) the presence of stem cells able to differentiate into specialized cells and replace the lost cells; II) the integrity of the extracellular matrix; III) and stimuli that induce the synthesis of growth factors, chemokines, and cytokines, provoking and regulating the process of repair and regeneration. Altogether, these factors create a favorable environment for repair or regeneration since they regulate cell behavior, differentiation, migration, and proliferation [7 - 9]. Although the dental pulp shows regenerative responses in the pulp-dentin complex, there are certain limitations, such as lesion extension, microorganism presence, operational factors, and patient conditions, which can interfere with the endogenous regeneration mechanism. In this sense, the support of therapeutic approaches is necessary to reestablish tissue homeostasis [10, 11].

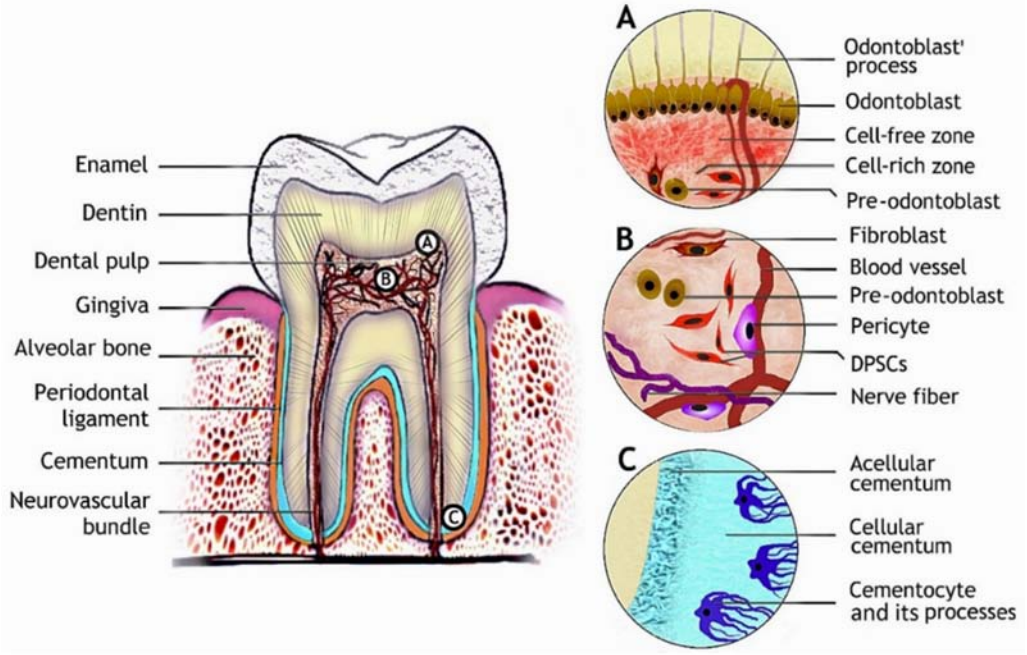

Fig. (1). Dental structure and tissue [6].

In these cases - where endogenous dental repair is not enough to repair or regenerate lesions, fractures or loss of dental structure - dental rehabilitation, repair, and regeneration are therapeutic approaches that can be used to reestablish the dental functionality. All these approaches are primarily based on biomaterials that aim to reassemble a functional stomatognathic system. In dentistry, bioceramics have been used in clinical practice and research development field to treat, repair or replace dental structures and tissues. Some of these applications include but are not limited to cement, pulp fillers, implants, and alveolar grafts [1, 11, 12].

The following sections will show how bioceramics are classified according to their biological response in host tissue, besides establishing a relationship between their properties and their application in dental rehabilitation, repair, and regeneration processes.

Bioceramics used in Dental Applications

In 1892, Dr. Dreesman published the first work reporting the use of the plaster of Paris to fill bone defects, which is recognized as the first use of a ceramic material in the repair or regeneration of mineralized tissues. The plaster of Paris is a calcium sulfate hemihydrate ($CaSO_3.½H_2O$), which can be easily placed and

CHAPTER 10

Bioceramics and Bioactive Glasses for Skin Wound Healing

Soumalya Bhattacharya[1], Payal Roy[1], Rupam Saha[1,2] and **Jui Chakraborty[1,*]**

[1] *Bioceramics and Coating Division, CSIR–Central Glass and Ceramics Research Institute, Jadavpur, Kolkata-700 032, India*

[2] *Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India*

Abstract: This chapter provides an overview of wounds, distinguishing between acute and chronic types. It describes the dynamic process of wound healing, involving hemostasis, inflammation, proliferation, and maturation. The role of growth factors and cytokines in the healing process is highlighted, along with the importance of the extracellular matrix. The text emphasizes that chronic wounds, often associated with diseases like diabetes, tumors, or ischemia, have a higher likelihood of recurrence and a prolonged healing period. Additionally, factors such as infections, stress, age, hormonal issues, and medications can compromise the natural wound healing process. The current market offerings for wound dressings, such as gauze and films, often fall short in promoting effective wound healing due to various limitations. In contrast, specific types of bioceramics and bioactive glasses have shown potential for co-delivering therapeutic ions, presenting a smart approach to accelerate the wound healing process. The study emphasizes the need to explore and develop materials with therapeutic efficacy, moving beyond mere wound coverage to actively promoting healing and tissue regeneration.

Keywords: Antibacterial efficacy, Angiogenesis, Bioceramics, Bioactive glass, Cell differentiation, Chronic wounds, Cytokines, Extracellular matrix, Electro spun, Gap junction Cx43, Hageman factor XII, Hemostasis, Hydroxyapatite, Keratinocytes, Micronanofibre, Proliferation, Remodelling, Sol-gel, Woundcare dressings, VEGF.

INTRODUCTION

A wound is generally defined as an injury or damage on the surface of the skin due to any physical, chemical, mechanical, or thermal cause, disrupting the regular functioning or atomic structure of the site [1]. Since the skin is always exposed to the outside, it is most prone to injuries like burns, ulcers, tears, and

* **Corresponding author Jui Chakraborty:** Bioceramics and Coating Division, CSIR–Central Glass and Ceramics Research Institute, Jadavpur, Kolkata-700 032, India; Tel: +91-33-23223233; E-mail: jui@cgcri.res.in

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wounds caused due to accidental trauma, ballistic trauma, or any other cutaneous injuries [2]. Acute wounds are healable within 8 to 12 weeks and do not generally recur on their own [1]. A chronic wound, however, is caused due to diseases like severe physiological contaminations, tumor, diabetes, ischemia, and venous stasis disease, which have a high chance of recurrence and takes more than 12 weeks to cure [1, 3]. The skin is composed of multiple layers as shown in Fig. (**1**).

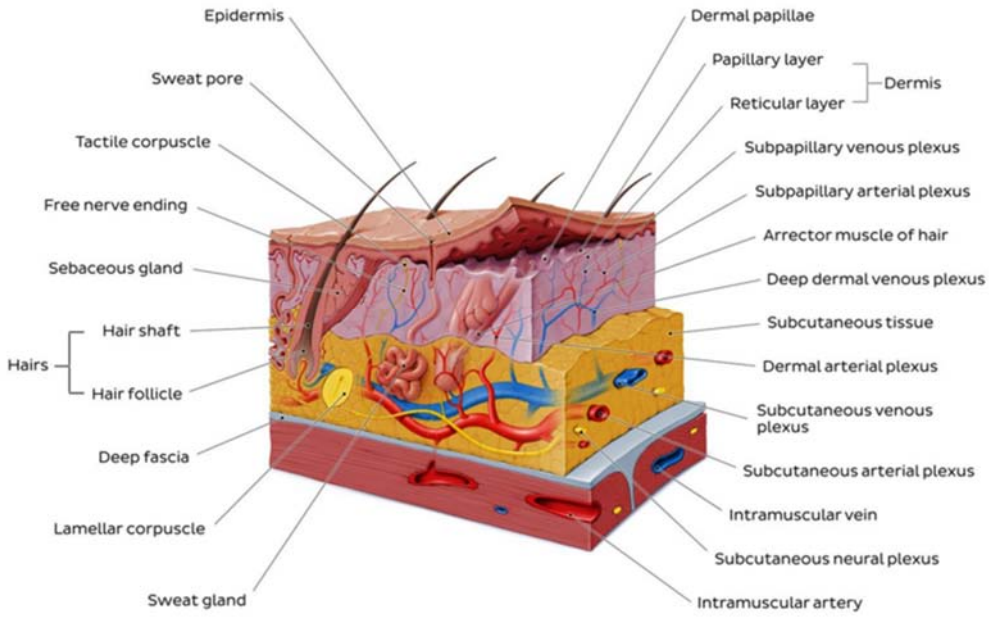

Fig. (1). Structure of the skin.

Wound healing is a dynamic process in which the dermal and epidermal tissues are repaired and regenerated [4] *via* four steps [1, 3 - 6]: the rapid response process of hemostasis initiates immediately [5], followed by inflammation, wherein neutrophils, phagocytes, *etc*. enter the wound medium. In this, various growth factors like transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF), along with cytokines are released at the wound site [1], followed by gradual recruitment of necessary tissues [5]. Next, in the proliferation step, an extracellular matrix (ECM) is formed leading to the contraction of the wound finally [1, 5]. This is the final step called maturation or tissue remodeling. In this step, fibroblasts completely cover the surface of the wound site [1, 5]. Natural wound healing, however, may be compromised due to several factors like infections, ischemia, stress, *etc*. along with other factors like age, hormonal

problems, ongoing medications or disease like diabetes, leading to chronic wounds [3, 5]. The wound healing process is schematically represented below, in Fig. (**2**).

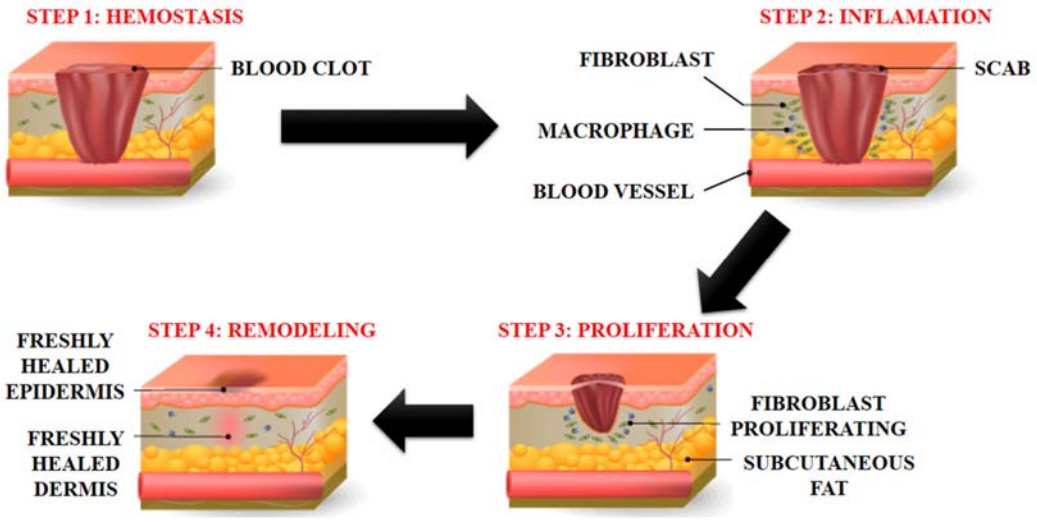

Fig. (2). Schematic diagram of skin wound healing.

There are several wound dressings available in the market, like gauze, films, *etc*. show advantages like being self-adherent, useful for covering the wound, and so on. But these materials have many disadvantages like gauze can stick to the wound bed, causing mechanical pain on removal, also they are dry and cannot control the moisture environment which is very important for healing [7]. Films are so adhesive that during removal, they pose threat to removing the newly developed epidermis, thus losing efficiency and causing pain. Hydrogels are not adhesive but due to their high water content, their absorption capacity is very low, making them unsuitable for wounds with high exudate [7]. The most concerning fact is that these materials may be used for only covering the wound site, protecting the wound from the external atmosphere, and allowing time for self-healing. Most of these market-available materials are unable to trigger the wound healing cascade, which may help in faster closure and recovery of the wound. It is thus highly imperative to develop material with therapeutic efficacy for the healing and regeneration of the skin.

In this regard, bioactive glasses have shown extraordinary angiogenic properties and can be blended with components having antibacterial potency, hemostatic properties, optimum bioactivity, and so on [8 - 10]. Such abilities of bioactive glass can have significant advantages when it comes to wound healing. Various

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Saeid Kargozar

Dr. Saeid Kargozar is a research fellow at the University of Texas Southwestern Medical Centre (UTSW), USA. He holds a master's degree in medical biotechnology and a Ph.D. degree in tissue engineering. His research interests are primarily in the area of bioactive materials applied for treating a broad range of diseases and disorders including non-healing wounds and solid tumors. Having 124 published documents and more that 5,500 citations, he has been ranked among the top 2% of the world's most-cited scientists in 2021 and 2023.

Francesco Baino

Francesco Baino is an associate professor of materials science and technology in the Department of Applied Science and Technology (DISAT), Politecnico di Torino, Italy. He received M.S. in biomedical engineering (summa cum laude) in July 2006 and Ph.D. in materials science and technology in 2010, both from Politecnico di Torino. He has published more than 240 peer-reviewed scientific journal articles, 30 book chapters, 100 abstracts or contributions in congress proceedings and is author of 3 patents. His H-index is 54, with a total number of citations above 10,200 (Scopus database). He is a member of the American Ceramic Society. His current research interests include biomaterials and tissue engineering with special focus on bioceramics and bioactive glasses. Prof. Baino is listed among the 2% top-cited scientists in the world according to a scientometric study performed by Stanford University.