Journal of Clinical and Nursing Research, 2024, Volume 8, Issue 6
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Nanobioceramics for Tissue Engineering Application

Kirubanandan Shanmugam*

Independent Research Scholar, Chennai, India

Corresponding author: Kirubanandan Shanmugam, Ksh1005@yahoo.com

Copyright: © 2024 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

Abstract: Nanobiomaterials demonstrate great potential in bone and dental tissue regeneration. These materials mimic the natural extracellular matrix in the human body, promoting the controlled release of growth factors and other bioactive molecules to enhance tissue regeneration and integration. Nanobioceramics mimic the structure and composition of natural bone. A major challenge in hard tissue healing is creating scaffolds that incorporate stem cells for bone tissue engineering. Scaffolds and implants for regenerative medicine should be designed using computer-aided design (CAD) and three-dimensional (3D) printing to replicate the tissue's anatomical structure. Future studies should examine the relationship between the size of bioceramics and biological reactions. The more interacting nature of nanoceramics better triggers the cellular processes, facilitating the regeneration of calcified tissue. Osteoblasts and osteoclasts are crucial in the development and maintenance of calcified tissue *in vivo*, and nanoceramics enhance the functionality of orthopedic and dental implants.

Keywords: Nanobioceramics; Bone repair; Orthopedic and dental application

Online publication: July 18, 2024

1. Introduction

Nanobiomaterials have shown great potential in hard tissue repair, such as bone and dental tissue regeneration. These materials are designed to mimic the natural extracellular matrix found in the body, providing a suitable environment for cell attachment, growth, and differentiation. One of the key advantages of nanobiomaterials is their ability to promote the controlled release of growth factors and other bioactive molecules, which can enhance the regeneration process. Nanoparticles can also be functionalized with specific ligands to target specific cell types, further enhancing their regenerative potential. In addition, nanobiomaterials can be engineered to have mechanical properties that closely match those of natural tissues, providing support and stability during the healing process. They can also be designed to degrade over time, allowing for new tissue formation without the need for additional surgical interventions. Overall, nanobiomaterials offer a versatile and customizable approach to regenerative medicine. Further research and development in this field will continue to advance our understanding of how these materials can be used to improve patient outcomes in a variety of clinical applications.

Nanobiomaterials provide unique properties that can enhance bone regeneration and promote tissue integration. Some examples of nanomaterials used for hard tissue repair include nanohydroxyapatite (nHA), nanofibrous scaffolds, nanoparticles, and nanocomposites. (1) nHA is a synthetic form of hydroxyapatite, which is the main mineral component of bone. nHA has been shown to enhance bone regeneration by mimicking the structure and composition of natural bone. It can be used in bone grafts, scaffolds, and coatings for implants. (2) Electrospun nanofibrous scaffolds have been developed for bone tissue engineering. These scaffolds have a high surface area and porosity, which can promote cell attachment, proliferation, and differentiation. They can be loaded with growth factors or drugs to enhance tissue regeneration. (3) Nanoparticles can be used to deliver bioactive molecules, such as growth factors or drugs, directly to the site of tissue repair. They can also be functionalized with ligands to target specific cells or tissues. Nanoparticles can be incorporated into scaffolds or coatings for implants. (4) Nanocomposites are materials that combine nanoparticles with polymers or ceramics to create materials with enhanced mechanical properties and bioactivity. These materials can be used in bone implants, dental restorations, and drug delivery systems. Overall, nanomaterials hold great promise for hard tissue repair by providing unique properties that can enhance tissue regeneration and promote successful outcomes in bone and dental applications. However, further research and development in this field are needed to fully realize this potential.

Nanoceramics are a type of ceramic material that has been engineered at the nanoscale level. These materials have unique properties that make them well-suited for use in hard tissue repair, such as in orthopedic and dental applications. One key advantage of nanoceramics for hard tissue repair is their strength and durability. This makes them ideal for use in load-bearing applications, such as bone grafts or implants. The small size of the nanoparticles also allows for better integration with the surrounding tissue, promoting faster healing and reducing the risk of rejection. Nanoceramics also have a high surface area to volume ratio, which can enhance their bioactivity and promote cell adhesion and proliferation. This can help to stimulate the growth of new bone tissue and accelerate the healing process. Additionally, nanoceramics can be tailored to release bioactive molecules, such as growth factors or antibiotics, in a controlled manner. This can further enhance their therapeutic potential and improve the outcome of hard tissue repair procedures. Overall, nanoceramics show great promise for use in hard tissue repair and have the potential to revolutionize the field of orthopedics and dentistry in the future.

Nanobioceramics are a class of biomaterials that have gained significant interest in the field of bone tissue engineering. These materials are composed of nano-sized particles that exhibit unique properties, such as high surface area-to-volume ratio, enhanced mechanical strength, and the ability to mimic the structure of natural bone. One of the key advantages of using nanobioceramics for bone tissue engineering applications is their ability to promote bone regeneration and repair. These materials can act as scaffolds for cell attachment, proliferation, and differentiation, ultimately leading to the formation of new bone tissue. Additionally, nanobioceramics have been shown to have excellent biocompatibility and bioactivity, making them suitable for use in a variety of biomedical applications. Furthermore, nanobioceramics can be tailored to have specific properties, such as controlled porosity, surface roughness, and degradation rates, which can further enhance their performance in bone tissue engineering. These materials can also be functionalized with bioactive molecules, growth factors, or drugs to promote specific cellular responses and improve the overall success of bone regeneration. Overall, nanobioceramics show great promise for use in bone tissue engineering applications due to their unique properties, biocompatibility, and ability to promote bone regeneration. Further research and development in this area are needed to fully understand the potential of these materials and their impact on the field of regenerative medicine.

2. Bioceramics at a nanoscale

Examining the nature of materials helps make regenerative medicine based on nanotechnology more comprehensible. Bone is a nanocomposite made of hard inorganic components like hydroxyapatite (HA) or $Ca_{10}(PO_4)_6(OH)_2$, and a protein-based soft hydrogel template made of collagen, non-collagenous proteins including laminin, fibronectin, and vitronectin, and water [1]. Particularly, 70% of the bone is made up of nanocrystalline HA, which ranges in size from 2 to 5 nm thick and 20 to 80 nm long. Most protein components of bone are at a nanoscale, which promotes an efficient cell fate determination for bone regeneration. Prior studies have validated the significance of nanoscale bioceramics development in improving bone mineralization and osteointegration. The osteoblast's cell fate processes, including adhesion, proliferation, and differentiation, are enhanced by the ceramic material's nanograin sizes and a large surface fraction of grain boundaries in nanoceramics [1-3].

Nanoceramics exhibit promising behavior for biomedical applications. Additionally, nanoceramics present a promising avenue for further investigation into ceramic biomaterials. Because of their superplastic nature, nanoceramics may be elongated to 300% of their original length. The unique properties of nanoceramics are described below.

(1) Good machinability and formability

(2) Excellent mechanical, chemical, and physical properties

(3) Malleable at much lower temperatures by pressing and sintering

Nanoceramics with specific chemical compositions, surface topographies, and grain size distribution can be created to resemble the physiological structure of bones. Bones typically have a weight percentage of 70% HA and grain sizes smaller than 100 nm.

Conventional materials like titanium and titanium alloys cannot mimic the chemical, mechanical, surface, and grain size distribution characteristics of bones. Research on nanophase ceramics, such as nanoalumina, titania, and HA, has shown increased osteoblast adhesion, which is beneficial for bone formation. These nanophase ceramics also demonstrated decreased fibroblast adhesion, reducing the risk of fibrous encapsulation and implant loosening, and decreased endothelial adhesion, which minimizes vascular complications. the performance of orthopedic and dental implants was enhanced by the improved functions of osteoblasts and osteoclasts provided by nanobioceramics at the site of bone damage. Recently, commercialized nanoceramics have entered the market as novel materials for implants or bone grafts. Examples include nano-HA paste (Ostim® from Obernburg, Germany) and nano-beta-tricalcium phosphate (Vitoss from Orthovita, USA) [4].

3. *In vitro* performance of nanoceramics

Nanoceramics have gained significant interest in various industries due to their unique properties such as high strength, hardness, and wear resistance. *In vitro* performance testing of nanoceramics involves evaluating their mechanical, physical, and chemical properties in laboratory settings. Some common *in vitro* performance tests for nanoceramics include mechanical properties, wear resistance, chemical stability, and biocompatibility tests. (1) Mechanical properties test involves evaluating the hardness, strength, and fracture toughness of nanoceramics using techniques such as Vickers hardness testing, nanoindentation, and flexural strength test. (2) The wear resistance test involves subjecting the material to wear tests such as pin-on-disc or abrasive wear tests to evaluate its resistance to wear and friction. (3) Chemical stability: Nanoceramics are often used in harsh environments, so it is important to evaluate their chemical stability. *In vitro* testing may involve exposing the material to various chemicals and solutions to assess its resistance to corrosion and chemical attack. (4) Biocompatibility testing involves assessing the material's biocompatibility by exposing it to cell cultures to evaluate cell

adhesion, proliferation, and toxicity. Overall, *in vitro* performance testing of nanoceramics plays a crucial role in understanding their properties and identifying potential applications in various industries. These tests help researchers and engineers determine the suitability of nanoceramics for specific applications and optimize their performance for practical use.

The applicability of nanoceramics for biomaterial and tissue engineering in the regeneration of bone or any other hard tissue type is determined by their *in vitro* performance. Compared to uncoated or standard millime-ter-size HA-coated tantalum, monocrystalline HA employed in the coating provides osteoconductive properties and promotes the production of new bone on tantalum scaffolds. After six weeks of implantation, histological data showed that nanocrystalline HA coatings stimulated new bone development in the rat calvaria more than uncoated or standard HA-coated tantalum [5].

The nanoscale surface characteristics of nanoceramics such as titania, zinc oxide, and alumina, encourage the formation of new bone. In comparison to micro-size zinc oxide (4.9 μm) and titania (4.1 μm), osteoblast adhesion was enhanced by 146% and 200% of the nanophase zinc oxide (23 nm) and titania (32 nm), respectively. Comparing nanoceramics to conventional materials, researchers [6] found that these materials improved collagen synthesis, alkaline phosphatase activity, and mineralization via calcium mineral deposition by osteoblasts [3].

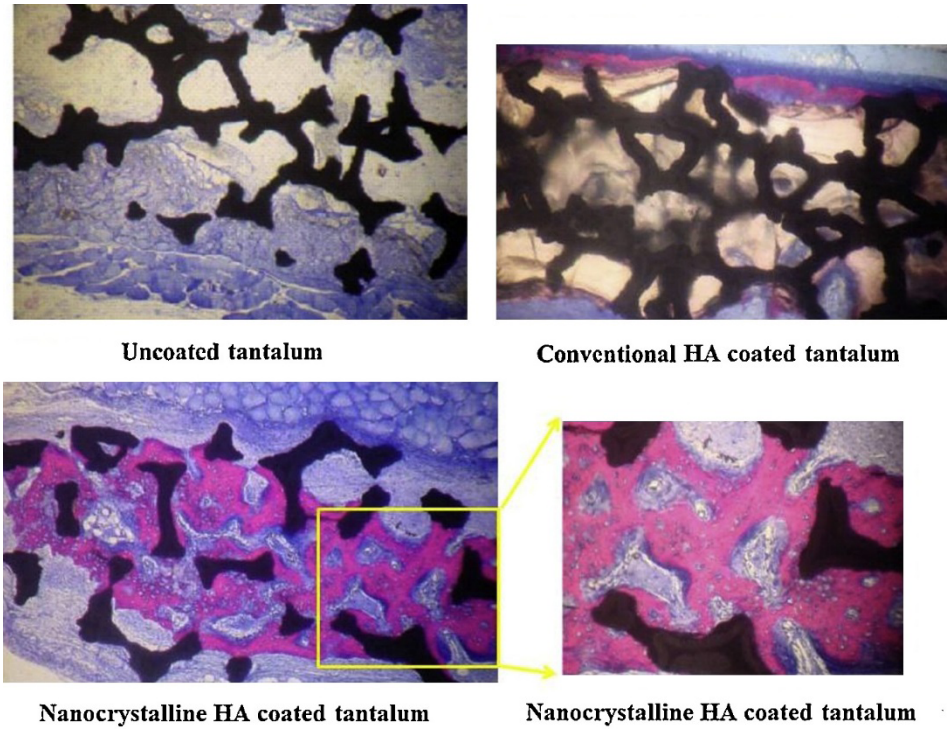

Figure 1. Rat calvaria histology following six weeks of tantalum implantation: untreated, conventionally HA-coated, and nanocrystalline HA-coated. When nanocrystalline HA-coated tantalum was implanted in rat calvaria, more new bone was formed than with uncoated or traditional HA-coated tantalum. Blue denotes collagen, while red indicates new bone [7].

Figure 1 reveals In a histological study of rat calvaria following six weeks of tantalum implantation, three different types of coatings were compared: untreated tantalum, conventionally hydroxyapatite (HA)-coated tantalum, and nanocrystalline HA-coated tantalum. The results showed that the nanocrystalline HA-coated tantalum led to a greater formation of new bone compared to both the uncoated and traditionally HA-coated tantalum. In the histological images, collagen is stained blue, and new bone is stained red. The increased amount of red staining in the samples with nanocrystalline HA-coated tantalum indicates enhanced bone formation,

suggesting that this type of coating provides a more favorable environment for bone growth compared to the other two types of coatings. This could be due to the improved surface properties and higher bioactivity of the nanocrystalline HA, which may better support osteoblast attachment, proliferation, and differentiation.When compared to micro-sized ceramics, the surface area, roughness, and surface energy of nanoceramics increased rapidly due to the materials' decreasing pore diameters and grain sizes. A study showed that nanoalumina, HA, and titania, for instance, enhanced the wettability of ceramic materials [2]. Another noteworthy example is that compared to alumina with a grain size of 177 nm, nano-alumina with a 23 nm grain size, which was created by compressing nano ceramic particles, has almost 50% more surface area for cell attachment. Similarly, according to Lück *et al*. [8], titania with a particle size of 32 nm has around 35% larger surface area than one with a 2.12 μm grain size. Because of their enormous surface area, nanoceramics may promote cell adhesion. Additionally, their unique surface features, such as surface energy, are strongly linked to their superior biocompatibility and osseointegration qualities. For instance, compared to standard HA scaffolds, the 67 nm grain size of nano-HA considerably improved osteoblast adhesion with suppression of fibroblast cell proliferation [2]. The most common explanation for this phenomenon is that the adsorption of certain proteins required for bone cell activities, including fibronectin, by nano-HA preferentially increases osteoblast adherence over fibroblasts. Interestingly, when compared to conventional ceramics, nano-ceramics exhibit a lag in antibacterial effects. For instance, nano ZnO and TiO_2 can inhibit *Staphylococcus epidermis*, a common pathogen that contributes to the formation of undesired biofilms around the functions of orthopedic implants. They can also enhance the synthesis of collagen in bone cells, the activity of alkaline phosphatase, and the deposition of calcium minerals [9].

In a similar vein, *in vivo* investigations have demonstrated that nanoscale materials, unlike microscale ceramics, promote new bone formation. Histological evidence shows that tantalum scaffolds coated with nano-HA achieve full osseointegration after just four weeks, a significant improvement over uncoated or conventionally coated tantalum. Animal studies have also shown that using nano-HA pastes as a bone replacement for bone deficiencies results in improved tissue incorporation and quick osseointegration [10]. When used for acetabular bone grafting, bio-resorbable nano-HA did not cause any adverse biological reactions and maintained the integrity of the acetabular cup better than pure allografts [11].

HA is a commonly utilized regenerative biomaterial in tissue engineering and biomedical applications. It is a naturally occurring mineral found in teeth, bones, and other calcified vertebrate tissues. With its exceptional osteoconductivity and biocompatibility, synthetic HA is crucial for human implant coatings and scaffolds, promoting attachment to and regeneration of human hard tissue. In physiological settings, HA acts as a substrate for the efficient adhesion of proteins, peptides, lipids, bacteria, and strains. Because nano-HA resembles the natural nanostructure of human bone, it offers a promising option for enhancing the functionality of bone implants.

Although nanoceramics are on the path to successful commercialization, their intrinsic brittleness, difficulty in forming specific defect shapes, and poor mechanical properties limit their ability to withstand the mechanical loading required to replace large bone defects. As a result, their use in large bone defect applications is still restricted. Additionally, there are inherent issues such as potential coating delamination and greater coating stiffness than bone, even when these ceramics are used as coatings on conventional metals. Consequently, a different class of materials called nanocomposites (polymers/ceramics) is being investigated for use in orthopedics.

4. Ceramic nanofibers as biomaterials

Ceramic nanofibers are a promising class of biomaterials that have gained significant attention in recent years due to their unique properties and potential applications in the biomedical field. These nanofibers are typically

made from ceramic materials such as hydroxyapatite, alumina, and titania, and are characterized by their high surface area, porosity, and mechanical strength. One of the key advantages of ceramic nanofibers as biomaterials is their ability to mimic the structure and composition of natural bone tissue, making them highly biocompatible and suitable for use in bone tissue engineering and regeneration. These nanofibers can provide a scaffold for the growth and differentiation of bone cells, promote mineralization, and enhance bone formation. In addition to bone tissue engineering, ceramic nanofibers have also shown promise in other biomedical applications, such as drug delivery, wound healing, and tissue repair. Their high surface area and porosity allow for efficient drug loading and release, while their mechanical strength and biocompatibility make them suitable for use in wound dressings and tissue scaffolds. Overall, ceramic nanofibers hold great potential as biomaterials for a wide range of biomedical applications, and ongoing research is focused on further improving their properties and exploring new ways to harness their unique characteristics for therapeutic purposes.

The innovative materials utilized to create scaffolds for tissue engineering are ceramic nanofibers. Because nanofibrous three-dimensional scaffolds replicate the structure of extracellular matrix at the site of damage, they have great potential for superior tissue integration and regeneration. Ceramic fibers have a high surface-to-volume and aspect ratio, and they may be produced using a variety of methods, including electrospinning, self-assembly, and template-assisted synthesis. The most popular method for creating porous 3D nanofibrous ceramic scaffolds for bone and dental tissue engineering as well as its regenerative medicine is electrospinning. Electrospinning is used to create ceramic fibers that could be used in making biomedical implants. Ceramic precursors or nanoparticles combined with polymer are used in the electrospinning process to create ceramic fibers. The polymer residue is then removed using high-temperature calcination. Ceramic fibers made without the use of polymers are made using ceramic sols. The electrospinning process yields extremely thin fibers with excellent mechanical qualities, a high aspect ratio, and ease of functionalization. These characteristics open up a wide range of applications for the fibers, including tissue engineering and drug delivery.

The steps for creating ceramic nanofibers by electrospinning are described below.

(1) A polymer solution suitable for electrospinning is made using a sol-gel precursor.

(2) Under regulated conditions, the solution is electrospun to produce precursor nanofibers using inorganic precursor and polymer helper materials.

(3) Precursor nanofibers are calcined at a high temperature to extract polymers and produce ceramic phases.

The electrospinning method can be used to create a range of metal oxide nanofibers. According to Wu *et al.* [12], notable examples include ZnO, CuO, NiO, TiO_2, SiO_2, Co_3O_4, Al_2O_3, SnO_2, Fe_2O_3, $LiCoO_2$, $BaTiO_3$, $LaMnO_3$, $NiFe_2O_4$, and $LiFePO_4$. In the study, using apatite as a precursor, HA and fluor-hydroxyapatite (FHA) nanofibers were created using electrospinning. By varying the concentration of the sols, fibers with sizes ranging from a few micrometers to hundreds of nanometers (1.55 μm – 240 nm) were generated. The apatite nanofibers were polycrystalline and their sizes ranged from 30 to 40 nm. These fibers may find application in the field of bone and calcified tissue engineering [13]. Recent advancements in the field include the electrospinning of nHAp-bioglass, PAN-bioglass hybrids, and ceramic-based composites incorporating novel bioceramics such as willemite (Zn_2SiO_4), dicalcium phosphate anhydrate (DCPA), dicalcium silicate (C_2S), among others, which are considered promising candidates for bone tissue regeneration. **Figure 2** shows a schematic diagram illustrating the steps involved in producing HA (Hydroxyapatite) and FHA (Fluorinated Hydroxyapatite) nanofibers with the electrospinning laboratory setup shown in the inset, a macroscale morphology of the electrospun nanofibers, and a macroscale morphology of the heat-treated nanofibers.

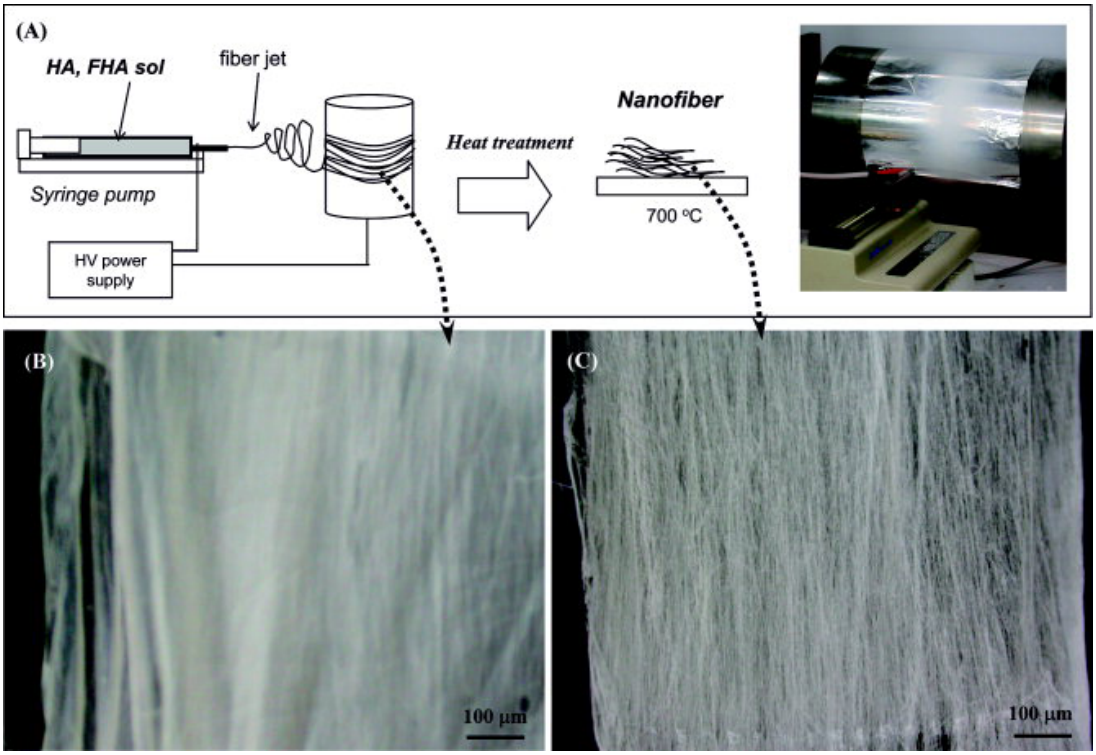

Figure 2. (A) Schematic diagram of the steps involved in producing HA and FHA nanofibers. The electrospinning laboratory setup is seen in the inset. The macroscale morphologies of the electrospun **(B)** and heat-treated **(C)** nanofibers are shown [13].

5. Bioceramics scaffolds for tissue engineering

Bioceramics scaffolds are a type of material that is used in tissue engineering to support the growth and regeneration of new tissue. These scaffolds are made from biocompatible ceramic materials. One of the key advantages of bioceramics scaffolds is their ability to mimic the structure and properties of natural bone tissue. This allows them to provide a suitable environment for cells to grow and differentiate into bone tissue. In addition, bioceramics scaffolds have high porosity and interconnected pore structures, which allows for the efficient exchange of nutrients and waste products within the scaffold. Bioceramics scaffolds can also be customized to have different mechanical properties, degradation rates, and surface characteristics to suit the specific needs of the tissue being regenerated. This customization allows for the scaffolds to be tailored to promote the growth of different types of tissue, such as bone, cartilage, or skin. Overall, bioceramics scaffolds are a versatile and effective tool in tissue engineering, with the potential to revolutionize the field by enabling the regeneration of damaged or diseased tissues.

Tissue engineering is the process of repairing, regenerating, and restoring an organ's or tissue's structure and functionality. Biocompatible and bioresorbable scaffolds are required to accomplish these tissue engineering goals, and tissue growth agents are added to these materials to support cellular activity. This scaffold serves as a three-dimensional template for the first cell adhesion and tissue development. Creating a bioactive scaffold that can stimulate cell growth at the site of damage is extremely difficult. It involves creating or designing a scaffold to serve as a template for the freshly produced tissue, supporting and imitating its structure. The target cells proliferate within the scaffold, enabling the formation of fresh regenerated tissue. Creating three-dimensional scaffolds with intricately linked pores is the main goal of tissue engineering. Similar to how human tissue

and the physiological environment multiply, the cultured cells on the scaffolds divide and create new tissue. Selecting an interconnected porosity and pores within the 20–400 μm range is necessary for the design or construction of scaffolds intended for tissue engineering [14].

The porous ceramics function as scaffolds for tissue engineering, encasing cells, growth factors, and signaling molecules to promote the self-regeneration of injured tissue. Bioceramics, which can stimulate the response of the involved cells and cause the regeneration of hard tissues, should be the basis material for building scaffolds. Tissue engineering scaffolds should thus have high mechanical qualities, be porous for the best encapsulation of the cells, and be modifiable so that bioactive compounds like growth factors and signaling molecules may be included. Porosity is crucial when creating scaffolds for tissue engineering. The scaffold can be divided into two categories based on the size of its pores: mesoporous scaffolds, which are used to deliver drugs and biologically active molecules for bone regeneration; and macroporous scaffolds, which pores are in the micron range and are ideal for seeding cells for tissue engineering activities. Maintaining the form and functions of human hard tissue while enhancing its regeneration capability is a difficult job for tissue engineering scaffolds.

The most common substance used to create scaffolds for tissue engineering is calcium phosphate because it demonstrates osteoconductivity, biodegradability, and biocompatibility. HA, a CaP ceramic derived from natural sources such as corals, is particularly employed in addressing orthopedic bone deficiencies. In addition to HA, absorbable inorganic compounds like aragonite ($CaCO_3$), plaster of Paris ($CaSO_4$-$2H_2O$), and beta-whitlockite [$(Ca_3(PO_4)_2$, a form of tricalcium phosphate] have been extensively studied for bone tissue engineering. Among CaP ceramics, tricalcium phosphate (TCP) and HA have been the most researched. These materials are protein-free, do not elicit immunological responses, and are non-toxic to humans. However, they do not possess osteoinductive properties. Various techniques are employed to fabricate ceramic scaffolds, including gas foaming, phase-mixing, processing with soluble or volatile porogens, free-form fabrication (e.g., stereolithography), template coating, and casting. Another approach involves using an active scaffold as a template for tissue engineering by applying a uniform coating of calcium phosphate. Osteo-conversion represents a groundbreaking technique where sterile water is combined with powdered HA sourced from bones to create a paste-like consistency with a microporous structure ranging from 8 to 12 μm, suitable for applications in tissue engineering.

According to Friedman *et al.* [15], bone cells have the special ability to convert directly into new bone without losing implant volume and adhere quickly to existing bone. Similarly, utilizing the freezing behavior of ceramic slurries allows for the creation of a layered microstructure with up to four times the strength of conventional 50% porous HA implants in tissue engineering applications. To stimulate and differentiate bone cells appropriately, it is essential to develop ceramic scaffolds that provide a micromechanical environment conducive to cell fate processes and ensure long-term tissue viability [16]. Additionally, several other technologies have been developed to create intricate ceramic scaffolds for tissue engineering, as summarized in **Table 1**.

Tissue engineering with ceramic scaffolds is an innovative approach in regenerative medicine aimed at repairing or replacing damaged tissues and organs. Ceramic scaffolds, particularly those made from bioceramics like hydroxyapatite (HA) and tricalcium phosphate (TCP), play a crucial role due to their excellent biocompatibility, bioactivity, and osteoconductivity. Here's a detailed key concept of tissue engineering with ceramic scaffolds:

(1) Scaffold design and fabrication:

(a) Porosity and structure: Ceramic scaffolds are designed to mimic the extracellular matrix (ECM) of natural tissues. They possess a highly porous structure to facilitate cell attachment, proliferation, and differentiation. The interconnected pores allow for nutrient and waste exchange, crucial for tissue growth.

(b) Materials: Common materials include hydroxyapatite (HA), tricalcium phosphate (TCP), and bioactive glasses. These materials are chosen for their ability to support bone cell activity and promote new bone formation.

(2) Biocompatibility and bioactivity:

(a) Biocompatibility: Ceramic materials are non-toxic and do not elicit an immune response, making them suitable for implantation in the body.

(b) Bioactivity: Ceramics like HA and TCP can bond with bone tissue, enhancing the integration of the scaffold with the host tissue. They release ions that stimulate cellular activities and bone formation.

(3) Osteoconductivity and osteoinductivity:

(a) Osteoconductivity: Ceramic scaffolds provide a surface that supports the attachment and growth of new bone cells (osteoblasts), guiding the formation of new bone along the scaffold.

(b) Osteoinductivity: Some ceramics can induce the differentiation of progenitor cells into osteogenic cells, promoting bone regeneration.

(4) Mechanical properties: Ceramic scaffolds must possess sufficient mechanical strength to support the load-bearing functions of bones, especially in weight-bearing applications. The mechanical properties are often enhanced by optimizing the scaffold's microstructure and composition.

(5) Functionalization and drug delivery:

(a) Functionalization: Ceramic scaffolds can be functionalized with bioactive molecules, such as growth factors (e.g., BMPs - bone morphogenetic proteins) and peptides, to enhance their regenerative capabilities.

(b) Drug delivery: These scaffolds can also serve as delivery systems for the controlled release of drugs, antibiotics, or anti-inflammatory agents, aiding in the healing process and preventing infections.

(6) Applications:

(a) Bone regeneration: Ceramic scaffolds are widely used in orthopedics for bone grafts, fracture repairs, and spinal fusions.

(b) Dental applications: They are used in dental implants and periodontal regeneration.

(c) Cartilage and soft tissue engineering: Emerging research is exploring the use of ceramic scaffolds in cartilage repair and soft tissue engineering, although challenges remain due to differences in mechanical properties and tissue types.

Figure 3 shows a diagram of tissue engineering with ceramic scaffolds: (1) Scaffold fabrication: Illustration of the ceramic scaffold with a porous structure. Steps involved in the fabrication process (e.g., sol-gel, electrospinning, 3D printing); (2) Cell seeding and culture: Diagram showing cells (e.g., stem cells or osteoblasts) being seeded onto the scaffold. Incubation in a bioreactor that provides a controlled environment for cell growth; (3) Implantation: Implantation of the cell-seeded scaffold into the defect site in the body. Interaction of the scaffold with host tissue, showing new tissue formation and integration; (4) Regeneration and healing: Progressive stages of tissue regeneration, highlighting the scaffold's degradation and replacement with natural tissue.

By combining the properties of ceramic materials with advanced tissue engineering techniques, ceramic scaffolds hold great promise for enhancing tissue regeneration and improving patient outcomes in various medical fields.

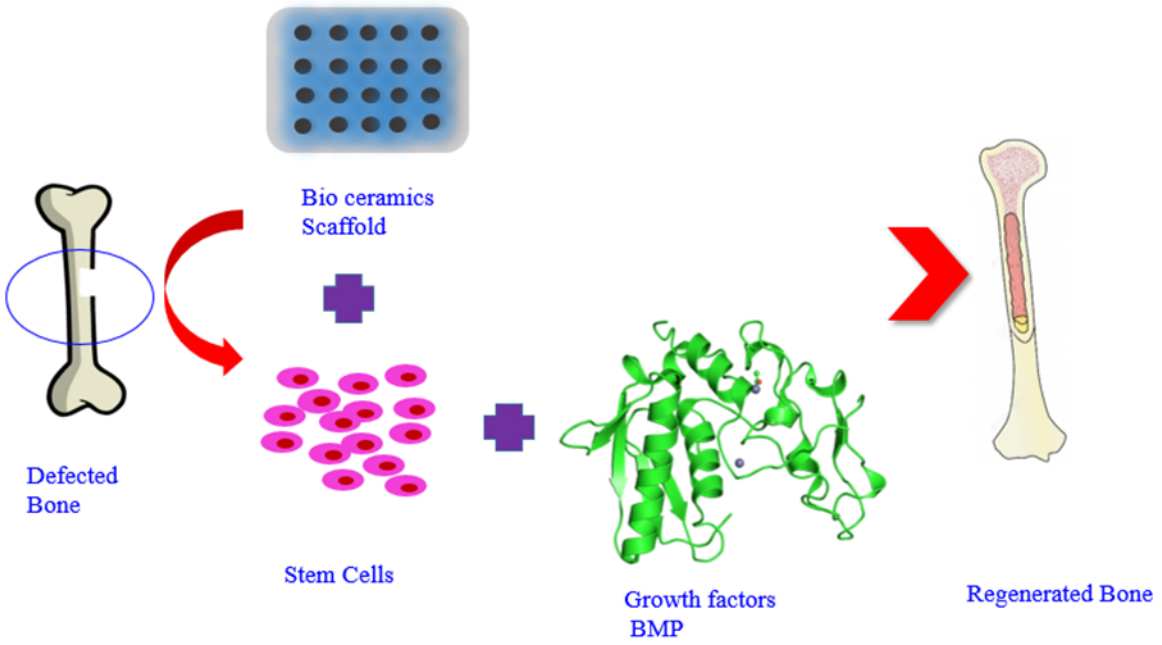

Figure 3. Concept of tissue engineering with ceramics scaffolds

Table 1. Methods for preparing ceramic scaffold [17]

Methods	Properties	Advantages	Disadvantages
3D printing	A scaffold is printed directly from ceramic powder using a 3D printer.	Complex scaffold geometry Controlled pore size Highly interconnected pores High compressive strength	Expensive Complex post-processing
Thermally-induced phase separation	The HA powder dissolved into a dioxane/water mixture to form a stable suspension and the polymer is added. The mixture is then heated to 15–20°C and freeze-dried to create a porous scaffold.	Anisotropic pore structure Tubular morphology High porosity (~95%)	Complex and expensive processing Poor mechanical properties
Solvent casting/ particle leaching	Ceramic powder and NaCl are dissolved in an organic solvent to form a thick paste. The paste is then sintered at a high temperature to obtain a porous scaffold	Simple process Inexpensive Controlled pore size	Poor mechanical properties Presence of porogen in the scaffold
Polymer bead	Ceramics powder is sintered with polymer beads at high a temperature	Simple process Inexpensive	Poor strength and control over distribution Simple geometry
Freeze casting	The ceramic slurry is frozen with dispersant and binder and sintered at a high temperature.	High mechanical strength	Complex process Poor control over pore geometry and distribution
Gas foaming	An in-situ gas-forming agent is mixed with stable HA/β-TCP/Al_2O_3 slurry and cast to a predefined geometry. The gas leaving from the reaction allows the formation of pores in the scaffold.	Inexpensive Good for preparing large samples	Complex process, with poor mechanical properties Poor control over pore size and its distribution
Sacrificial mold	The polymer foam is coated with HA/β-TCP slurry and sintered the scaffold.	Simple process Inexpensive Good control over pore connectivity	Low compressive strength

Table 2 summarizes the use of ceramic scaffolds in tissue engineering. Materials such as bioactive glasses, glass ceramics, and calcium phosphates are deemed most suitable for applications in low- or non-load-bearing

implants or environments with compressive loads, whether in solid or powder form, due to their biomechanical properties. Examples of these applications include bone restoration and augmentation, middle ear repair, vertebral and iliac crest replacements, and tissue regeneration. In clinical settings, the thermal spray method is employed to coat metal joint prostheses with HA. Recently, there has been interest in utilizing bioactive glass-ceramic porous coatings on alumina acetabular cups to improve the osteointegration of prosthetic devices.

Table 2. Application of ceramics scaffold in tissue engineering

Material/ Scaffold involved	Application
Porous scaffolds of HA, biphasic calcium phosphates, and bioactive glasses (e.g. 45S5 Bioglass, 13-93)	Bone defect repair
Bioactive glass-ceramic coating with trabecular architecture on bioceramic acetabular cup	Joint prostheses
Porous spheres made of alumina (Known bioceramic implant), HA (examples of coralline HA –Bio-Eye, synthetic HA-FCI3, bovine HA –Molteno M-Sphere), or 45S5 Bioglass/polyethylene composite	Orbital implant
45S5 Bioglass/polymer composite meshes	Wound healing
Ceramic fibrous constructs	Skin tissue engineering
Sol-gel glass foams or PDLLA/45S5 Bioglass porous composites	Lung tissue engineering
Phosphate glass fibrous constructs	Muscle tissue engineering
Bioactive glass fibrous constructs	Peripheral nerve repair

6. Bioceramics coating on implants and drug delivery

Surface modification of standard biomaterials, such as metals, alloys, and polymers, is a valuable technique for enhancing biocompatibility and other biological processes in tissue regeneration. This approach also helps to minimize biological reactions in physiological environments. Additionally, ceramic coatings can improve the wear characteristics of implants. In orthopedic applications, implants must establish stable contact with surrounding tissue, exhibit biocompatibility with hard tissue, and possess strength comparable to bone.

Titanium and its alloys are favored for implant fabrication due to their strength, low stiffness, lightweight, and inertness. However, a challenge with titanium implants is the inadequate bonding with surrounding tissue, leading to the formation of a fibrous, non-adherent tissue layer and potentially causing implant rejection or failure. Consequently, defective implants may require surgical removal from the body. Ceramic coatings on metallic implants mimic the structure of teeth and bone, enhancing biocompatibility with calcified tissue and promoting bone apposition without encouraging fibrous tissue growth. This bone bonding capability, known as bioactivity, has led to extensive research on calcium phosphate ceramic coatings to improve implant fixation in the body. Various methods are employed to coat ceramics on metallic surfaces, including vapor deposition techniques like chemical vapor deposition, plasma spray methods (such as the FDA-approved plasma spraying for calcium phosphate coatings [18]), room-temperature or solution-based coating methods like dipping coating and biomimetic methods, as well as electrophoretic deposition and electrochemical deposition. Surface modification techniques can broadly be categorized into deposited coatings and conversion coatings (surface-modified layers). Deposited coatings involve applying a ceramic film to a metallic surface without altering its substrate, resulting in a distinct coating layer. In contrast, conversion coatings chemically modify the metallic surface, potentially altering its surface properties to enhance substrate interaction and coating adherence [19].

Bioceramics are described as a method of delivering drugs or biological molecules to specific sites of action in a controlled manner, thereby enhancing the bioavailability of the drug in targeted parts of the body. This role makes bioceramics pivotal in targeted drug delivery. Commonly used ceramic-based materials for this pur-

pose include mesoporous silica, calcium carbonate, iron oxide nanoparticles, and gold nanoparticles. These nanoparticles exhibit properties such as antibacterial, anti-inflammatory, and anti-cancer effects, and they are also utilized in gene therapy and radiotherapeutic applications.

Functionalization of these nanoparticles enables them to traverse tissue barriers and cell membranes, facilitating targeted treatment of specific organs. In the realm of bone health, bioceramics serve as effective local drug delivery systems for treating various bone abnormalities such as osteoporotic fractures, infected bones, and bone tumors. Bioceramics with porous structures are particularly valuable for delivering cancer treatments. Mesoporous silica, for instance, releases medications directly into cancer cells, making it a targeted therapy option for certain types of cancer. In practical applications, drugs are integrated into the ceramic production process, resulting in scaffolds that are drug-incorporated and function as efficient drug delivery systems for promoting bone regeneration and treating localized conditions.

Drugs can be physically encapsulated within porous ceramic scaffolds to achieve controlled delivery. The pores within the scaffold act as reservoirs for drug entrapment, typically requiring a diameter of around 10 μm to effectively load medications and facilitate controlled release kinetics. Regulated release of pharmaceuticals from the scaffold is achieved through diffusion mechanisms under controlled conditions. The amount of drug released can be tailored based on the scaffold's pore size, texture characteristics, and the temperature at which the scaffold sinters, affecting its pore volume. Furthermore, the material composition and sintering temperature play crucial roles in determining the dimensions of the pores. Calcium phosphate cement is utilized as a drug delivery system for bones, allowing medications, including anti-osteoporotic drugs, to be impregnated for sustained release over extended periods. This approach ensures targeted and effective delivery of therapeutic agents for bone regeneration and treatment of bone-related conditions.

In the realm of bone regeneration, bioactive glasses have been investigated for their ability to combine with osteogenic substances, forming three-dimensional scaffolds. Biofunctionalization of these glasses facilitates the distribution of osteogenic agents through a drug delivery system, which aids in graft filling and the correction of bone deformities. Biocompatible drug delivery methods are actively researched for calcium phosphate bioceramics and bioactive glasses, which are developed in various forms such as powders, blocks, cement, scaffolds, and coatings. Composite materials comprising ceramics and polymers have been developed as effective matrices for the controlled release of antibiotics and other medications. HA implants are commonly used for administering antibacterial medications. Alpha-tricalcium phosphate (α-TCP) paste has been utilized to impregnate substances like gentamicin sulfate, cefoperazone sodium, and flomoxef sodium, which possess osteoconductive, biocompatible, and antibacterial properties. These approaches aim to enhance therapeutic outcomes in bone repair and orthopedic applications by leveraging the properties of ceramic-based materials for targeted drug delivery and enhanced tissue integration.

Cisplatin is used to treat osteosarcoma and is used with a bioceramic bone transplant to treat bone cancer. Calcium phosphate nanoparticles coated with anti-tumoral medicines are employed in intracellular drug targeting for cancer treatment [20].

7. Conclusion

Bioceramics have significantly advanced biomaterials and implant technologies by aiming to replicate the intricate structure of natural calcified tissues. One of the primary challenges in bioceramics for tissue engineering is the creation of scaffolds that can integrate stem cells effectively for bone regeneration. To mimic the anatomical complexity of tissues, scaffolds, and implants in regenerative medicine are increasingly designed using com-

puter-aided design and three-dimensional printing techniques. Future research should explore how the size of bioceramics influences biological reactions. Nanoceramics, with their highly interactive nature, are particularly effective in triggering cellular processes that promote the regeneration of calcified tissues. *In vivo*, nanoceramics support the active development and maintenance of calcified tissue through interactions with osteoblasts and osteoclasts, thereby enhancing the functionality of orthopedic and dental implants. These advancements underscore the critical role of bioceramics in improving outcomes in hard tissue healing and regenerative medicine.

Disclosure statement

The author declares no conflict of interest.

References

[1] Affatato S, Torrecillas R, Taddei P, et al., 2006 Advanced Nanocomposite Materials for Orthopaedic Applications. I. A Long-Term *In Vitro* Wear Study of Zirconia-Toughened Alumina. Journal of Biomedical Materials Research Part B: Applied Biomaterials, 78(1): 76–82. https://www.doi.org/10.1002/jbm.b.30462

[2] Arcos D, Vallet-Regí M, 2013, Bioceramics for Drug Delivery. Acta Materialia, 61(3): 890–911. http://dx.doi.org/10.1016/j.actamat.2012.10.039

[3] Barralet JE, Grover L, Gaunt T, et al., 2002, Preparation of Macroporous Calcium Phosphate Cement Tissue Engineering Scaffold. Biomaterials, 23(15), 3063-3072. http://dx.doi.org/10.1016/S0142-9612(01)00401-X

[4] Barrère F, Mahmood TA, de Groot K, et al., 2008, Advanced Biomaterials for Skeletal Tissue Regeneration: Instructive and Smart Functions. Materials Science and Engineering: R: Reports, 59(1): 38–71. http://dx.doi.org/10.1016/j.mser.2007.12.001

[5] Ben-Nissan B, 2005, Biomimetics and Bioceramics, in Learning from Nature How to Design New Implantable Biomaterials: From Biomineralization Fundamentals to Biomimetic Materials and Processing Routes. Springer, Netherlands, 89–103.

[6] Billotte WG, 2007, Ceramic Biomaterials, CRC Press, Boca Raton, 2-1–2-34.

[7] Liu H, Webster TJ, 2007, Nanomedicine for Implants: A Review of Studies and Necessary Experimental Tools. Biomaterials, 28(2): 354–369. http://dx.doi.org/10.1016/j.biomaterials.2006.08.049

[8] Campbell AA, 2003, Bioceramics for Implant Coatings. Materials Today, 6(11): 26–30. http://dx.doi.org/10.1016/S1369-7021(03)01128-3

[9] Chris Arts JJ, Verdonschot N, Schreurs BW, et al., 2006, The Use of a Bioresorbable Nano-Crystalline Hydroxyapatite Paste in Acetabular Bone Impaction Grafting. Biomaterials, 27(7): 1110–1118. http://dx.doi.org/10.1016/j.biomaterials.2005.07.024

[10] Colon G, Ward BC, Webster TJ, 2006, Increased Osteoblast and Decreased Staphylococcus Epidermidis Functions on Nanophase ZnO and TiO2. Journal of Biomedical Materials Research Part A, 78(3): 595–604. https://doi.org/10.1002/jbm.a.30789

[11] Dagnija L, Janis L, Kristine S, et al., 2011, Porous Hydroxyapatite Bioceramic Scaffolds for Drug Delivery and Bone Regeneration. IOP Conference Series: Materials Science and Engineering, 18(19): 192019.

[12] Damien E, Hing K, Saeed S, et al., 2003, A Preliminary Study on the Enhancement of the Osteointegration of a Novel Synthetic Hydroxyapatite Scaffold *In Vivo*. Journal of Biomedical Materials Research Part A, 66(2): 241–246. https://doi.org/10.1002/jbm.a.10564

[13] Kim HW, Kim HE, 2006, Nanofiber Generation of Hydroxyapatite and Fluor-Hydroxyapatite Bioceramics. Journal of Biomedical Materials Research Part B: Applied Biomaterials: An Official Journal of The Society for

Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials, 77(2): 323–328.

[14] Dorozhkin SV, 2010, Bioceramics of Calcium Orthophosphates. Biomaterials, 31(7): 1465–1485. https://doi.org/10.1016/j.biomaterials.2009.11.050

[15] Ducheyne P, Mauck RL, Smith DH, 2012, Biomaterials in the Repair of Sports Injuries. Nat Mater, 11(8): 652–654.

[16] Ducheyne P, Radin S, King L, 1993, The Effect of Calcium Phosphate Ceramic Composition and Structure on *In Vitro* Behaviour. I. Dissolution. Journal of Biomedical Materials Research, 27(1): 25–34. https://doi.org/10.1002/jbm.820270105

[17] Eisenbarth E, Velten D, Müller M, et al., 2004, Biocompatibility of β-Stabilizing Elements of Titanium Alloys. Biomaterials, 25(26): 5705–5713. https://doi.org/10.1016/j.biomaterials.2004.01.021

[18] El-Meliegy E, van Noort R, 2012, Selection Criteria of Ceramics for Medical Applications Glasses and Glass Ceramics for Medical Applications, Springer, New York, 19–36.

[19] Friedman CD, Costantino PD, Takagi S, et al., 1998, BoneSource™ Hydroxyapatite Cement: A Novel Biomaterial for Craniofacial Skeletal Tissue Engineering and Reconstruction. Journal of Biomedical Materials Research, 43(4): 428–432. https://doi.org/10.1002/(SICI)1097-4636(199824)43:4<428::AID-JBM10>3.0.CO;2-0

[20] Geetha M, Singh AK, Asokamani R, Gogia AK, 2009, Ti Based Biomaterials, the Ultimate Choice for Orthopaedic Implants – A Review. Progress in Materials Science, 54(3): 397–425. https://doi.org/10.1016/j.pmatsci.2008.06.004

Publisher's note

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.