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Bioceramics: A Potential Biomaterial for Hard Tissue Repair

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Abstract: In the past two decades, significant progress has been made in the biomaterials field aimed at developing calcified tissues and facilitating tissue regeneration. The increasing demand for innovative biomaterials capable of replacing damaged tissues, enhancing the body's regenerative capacity, and promoting efficient calcification in hard tissues is primarily motivated by the rising number of elderly individuals afflicted with age-related ailments. Bioceramics, such as calcium phosphates, bioactive glasses, and glass ceramics, exhibit considerable potential in closely mimicking the structure of original calcified tissues when constructing scaffolds for repairing, restoring, reconstructing, or regenerating diseased body parts. These biomaterials have shown promising applications in calcified tissue engineering in recent years. This review covers the fundamental requirements of bioceramics for biomedical purposes and provides an extensive examination of the latest developments in bioceramics and composites, encompassing tissue engineering and drug delivery. The review concludes by underscoring the need for future research endeavors, particularly in the realm of fabricating scaffolds for tissue engineering utilizing nanotechnology.

Keywords: Biomaterial; Bioceramics; Bioinert ceramics; Bioactive ceramics; Tissue engineering

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1. Introduction

Hard tissue repair refers to the process of healing and regenerating bone and other hard tissues in the body after injury or damage. This process involves a series of complex biological events that aim to restore the structure and function of the affected tissue. During hard tissue repair, specialized cells called osteoblasts are recruited to the site of injury to produce a new bone matrix. This matrix serves as a scaffold for new bone formation. In addition, blood vessels grow into the area to provide oxygen and nutrients necessary for tissue regeneration. Factors such as age, nutrition, and the extent of the injury can influence the speed and success of hard tissue repair. For more severe injuries or in cases of certain medical conditions, additional interventions such as bone grafts or surgical procedures may be necessary to facilitate the healing process. Overall, hard tissue repair is a dynamic and highly regulated process that plays a crucial role in maintaining the structural integrity of the skeletal system and supporting overall mobility and functionality. Researchers continue to explore new technologies and treatment strategies to improve the outcomes of hard tissue repair and enhance patient recovery.

Hard tissue repair, also known as bone repair, refers to the process by which the body restores damaged or fractured bone tissue to its original structure and function. This process involves a series of biological events orchestrated by specialized cells and signaling molecules. The following is a simplified overview of the steps involved in hard tissue repair:

(1) Hematoma formation: When a bone is fractured, blood vessels within the bone and surrounding tissues are damaged, leading to bleeding. This results in the formation of a hematoma (a blood clot) at the site of injury.

(2) Inflammatory phase: The hematoma triggers an inflammatory response, where immune cells, such as neutrophils and macrophages, migrate to the site of injury. These cells remove debris and damaged tissue, creating a clean environment for repair.

(3) Soft callus formation: Within a few days, cells called chondroblasts start to produce a soft callus made of cartilage at the fractured site. This serves as a temporary scaffold to stabilize the fracture.

(4) Hard callus formation: Over the next several weeks, osteoblasts begin to produce new bone tissue, gradually replacing the cartilaginous callus with a harder, woven bone structure. This process is called osteogenesis.

(5) Bone remodeling: The hard callus is eventually remodeled into mature lamellar bone through a process called bone remodeling. Osteoclasts remove excess bone tissue, while osteoblasts deposit new bone, resulting in the restoration of the bone's original shape and strength.

Several factors can influence the rate and success of hard tissue repair, including the extent of the injury, the patient's age and overall health, and the presence of any underlying medical conditions. In some cases, surgical intervention may be required to realign the fractured bone fragments or provide additional support, such as screws, plates, or bone grafts, to facilitate proper healing. Physical therapy and rehabilitation are often recommended following bone repair to restore function and mobility to the affected area.

Hard tissue repair often requires the use of various materials to support and facilitate the healing process. These materials can be synthetic or natural, and they serve different purposes depending on the specific needs of the patient and the type of injury. Some common materials used in hard tissue repair are as follows:

(1) Bone grafts: Bone grafts are perhaps the most common material used in hard tissue repair. They can be sourced from the patient's own body (autograft), a donor (allograft), or synthetic materials (alloplastic grafts). Bone grafts provide a scaffold for new bone growth and can help stimulate bone regeneration in cases of large defects or non-healing fractures.

(2) Bioceramics: Bioceramic materials, such as calcium phosphate ceramics (e.g., hydroxyapatite), are widely used in hard tissue repair due to their biocompatibility and ability to integrate with the surrounding bone tissue. These materials can be used as bone substitutes, coatings for implants, or scaffolds for tissue engineering applications.

(3) Metal implants: Metal implants, such as titanium and its alloys, are commonly used in orthopedic surgeries to stabilize fractures and provide mechanical support to the healing bone. These implants are typically designed to mimic the mechanical properties of bone and can remain in the body permanently or be removed once the bone has healed.

(4) Biodegradable polymers: Biodegradable polymers, such as polylactic acid (PLA) and polyglycolic acid (PGA), are used in the fabrication of scaffolds and implants for hard tissue repair. These materials gradually degrade over time, allowing for the gradual replacement of the implant with new bone tissue.

(5) Collagen matrices: Collagen-based materials, derived from natural sources such as bovine or porcine collagen, are often used in tissue engineering and regenerative medicine applications. Collagen matrices provide a supportive environment for cell attachment, proliferation, and differentiation, promoting the formation of new bone tissue.

(6) Platelet-rich plasma (PRP): PRP is a concentration of platelets derived from the patient's own blood, which contains growth factors that can stimulate tissue repair and regeneration. PRP is sometimes used in conjunction with other materials, such as bone grafts or bioceramics, to enhance their osteogenic properties and accelerate the healing process.

(7) Bioactive glasses: Bioactive glasses, such as silicate-based glasses, have the ability to bond with bone tissue through the formation of a hydroxycarbonate apatite layer, which promotes osseointegration. These materials are often used in bone graft substitutes and dental applications.

These materials can be used alone or in combination with each other, depending on the specific requirements of the patient and the nature of the injury. The choice of material depends on factors such as biocompatibility, mechanical properties, degradation kinetics, and the desired outcome of the treatment.

For hard tissue repair, materials commonly used include:

(1) Ceramics: Ceramics such as hydroxyapatite and tricalcium phosphate, are biocompatible and mimic the mineral composition of bone.

(2) Metals: Metals like titanium and stainless steel, are often used for load-bearing applications due to their strength and durability.

(3) Polymers: Polymers such as poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG), are biodegradable and can provide temporary support during tissue regeneration.

(4) Composite materials: Combining two or more material types, such as ceramic-polymer composites, can offer a balance of mechanical strength and biocompatibility.

(5) Scaffolds: Scaffolds made from natural or synthetic materials provide a framework for cell attachment and tissue growth, aiding in the regeneration of hard tissues.

(6) Biomimetic materials: Biomimetic materials are designed to mimic the structure and function of natural tissues, promoting better integration and regeneration.

(7) Bioactive materials: Bioactive materials incorporate growth factors or other bioactive molecules to stimulate tissue regeneration and promote healing.

These materials play a crucial role in various applications, including bone grafts, dental implants, and orthopedic surgeries, to facilitate the repair and regeneration of hard tissues in the body.

To diminish the dependence on tissue and organ transplants, novel materials have been engineered to function as implants or scaffolds for damaged organs, promoting the regeneration of various tissues. These advancements have emerged in response to the treatment of organ or tissue injuries stemming from diseases or various forms of physical, chemical, or biological harm. A global concern is the development of novel biomaterials to enhance human life standards through the replacement of malfunctioning organs or the regeneration of tissue using scaffolds. The need for biomaterials that can replace, regenerate, and restore soft and hard tissues including skin, bones, cartilage, blood vessels, and even organs has grown dramatically as the population has grown exponentially. Many materials are now being employed in regenerative medicine, including materials for bioimaging to track the progression of illness, drug delivery vehicles, and porous scaffolds for tissue engineering structures. Several organic and inorganic materials have been specifically developed and used as scaffolds for tissue regeneration and medication administration [1].

Biomaterials for hard tissue repair play a crucial role in regenerative medicine, as they provide structural support and promote tissue regeneration in damaged or diseased tissues such as bones and teeth. These biomaterials can be synthetic or natural in origin, and they are designed to mimic the properties of the native tissue to enhance healing and integration. Some commonly used biomaterials for hard tissue repair include:

(1) Calcium phosphate ceramics: These biomaterials, such as hydroxyapatite and tricalcium phosphate, are biocompatible and bioactive, making them ideal for bone regeneration. They can be used as bone graft substitutes or coatings for implants to promote osseointegration.

(2) Collagen-based materials: Collagen, a naturally occurring protein present in connective tissues, is frequently utilized in tissue engineering owing to its biocompatible nature and capacity to facilitate cell proliferation and tissue rejuvenation. Collagen scaffolds are applicable in the restoration of bone and cartilage, as well as in various dental procedures.

(3) Polymers: Synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) are commonly used for hard tissue repair due to their tunable properties, biodegradability, and biocompatibility. These materials can be used for drug delivery, scaffolds, and implants in bone and cartilage regeneration.

(4) Bioglass: Bioglass is a bioactive glass material that can stimulate bone formation and integrate with surrounding tissues. It is often used in dental applications, as well as in bone grafts and implants for repairing bone defects.

(5) Composite materials: Composite biomaterials combine different materials to enhance their properties for hard tissue repair. For example, calcium phosphate nanoparticles can be incorporated into polymer scaffolds to improve mechanical strength and bioactivity for bone regeneration.

Overall, biomaterials for hard tissue repair play a critical role in regenerative medicine by providing support and promoting tissue regeneration in damaged or diseased tissues. Researchers continue to explore new biomaterials and combinations to improve outcomes for patients in need of hard tissue repair.

Many definitions for biomaterial have been proposed and endorsed. The term biomaterial could be defined as "a systemically, pharmacologically inert substance designed for implantation within or incorporation with a living system" [2] or "a nonviable material used in a medical device, intended to interact with biological system" [3]. In this definition, the word "medical" would be removed, and the term becomes more applicable and broader suggested above. According to the National Institute of Health, USA, the biomaterial is defined as "any substance or combination of substances, other than drugs, synthetic or natural in origin, which can be used for any period of time, which augments or replaces partially or totally any tissue, organ or function of the body, in order to maintain or improve the quality of life of the individual" [3]. A complementary definition is necessary while dealing with the understanding of biomaterials is "biocompatibility." It is defined as "the ability of a material to perform with an appropriate host response in a specific application" [3]. Furthermore, biomaterials should exhibit an acceptable host response, which in tissue engineering applications translates to strong resistance to bacterial colonization, blood clotting, and biofilm formation while promoting the natural healing process. Without a doubt, biomaterials improve human life quality and prolong the lives of many individuals annually. There are countless and unparalleled uses for biomaterials in the treatment of human illnesses when compared to alternative therapies and treatments. It comprises prosthetic limbs and arteries, skin replacements, scaffolds for ocular tissue engineering and contact lenses, and bone substitutes. Therefore, as the world's population grows faster than ever, there is a growing need for biomaterials. By 2021, the value of the global biomaterials market is expected to reach USD 149.17 million. At a compound annual growth rate of 16.0%, this market is projected to grow from USD 70.90 billion in 2016 to USD 149.17 million in 2021. The expansion is dependent upon a number of factors, including the global increase in hip and knee replacement surgeries, the market for implants, the prevalence of growing illnesses, advances in tissue engineering, and the quick aging of the population. Additionally, the biomaterial types—such as polymers, metals, or ceramics—as well as the area and use of the material in treatment determine the market's growth [4]. The demand for ceramic biomaterials, such as orthopedic implants, which are now on the market, is enormous and accounts for over 1.5 million units annually globally at a cost of $10 billion.

Bioceramics are a class of biomaterials that have shown great promise for hard tissue repair, particularly in bone and dental applications. These materials are biocompatible, bioactive, and have similar mechanical properties to natural bone, making them ideal for use in repairing and regenerating damaged or diseased hard tissues. One of the most well-known bioceramics used for hard tissue repair is hydroxyapatite (HA), which is the main mineral component of natural bone. HA is osteoconductive, meaning it promotes the growth of new bone tissue, and is often used in bone grafts and dental implants. Another commonly used bioceramic is calcium phosphate, which can also promote bone formation and has been used in bone cement and coatings for orthopedic implants. Bioceramics can be used in a variety of forms, including powders, granules, scaffolds, and coatings, and can be tailored to have specific properties depending on the application. For example, bioceramic scaffolds can be designed to have a porous structure that mimics the natural architecture of bone, allowing for better integration with surrounding tissue and promoting new bone growth. Overall, bioceramics have shown great potential for hard tissue repair and have been used successfully in a wide range of clinical applications. Continued research and development in this field are likely to lead to further advancements in the use of bioceramics for repairing and regenerating hard tissues. This paper reveals the overview of bioceramics and its classification and application for hard tissue repair.

2. Overall classification of biomaterials

Biomaterials can be classified in various ways based on their composition, properties, and intended applications. An overall classification of biomaterials is presented as follows:

(1) Natural biomaterials:
- (a) Biological: Derived from living organisms, such as collagen, alginate, chitosan, silk, and hyaluronic acid.
- (b) Mineral: Naturally occurring minerals used in biomedical applications, such as hydroxyapatite and calcium phosphate.

(2) Synthetic biomaterials:
- (a) Polymers: Synthetic polymers designed for biomedical use, including polyethylene glycol (PEG), poly(lactic-co-glycolic acid) (PLGA), polyethylene terephthalate (PET), and polyvinyl alcohol (PVA).
- (b) Ceramics: Inorganic, non-metallic materials like alumina, zirconia, and bioglass.
- (c) Metals: Metallic biomaterials like titanium, stainless steel, cobalt-chromium alloys, and nickel-titanium alloys.
- (d) Composites: Combination of two or more materials, such as polymer-ceramic composites or metal-polymer composites.

2.1. Functional biomaterials

Bioactive materials are materials that elicit a specific biological response at the interface of the material and biological system, such as bioactive glasses and ceramics. Bioinert materials are materials that do not elicit a significant immune response or biological reaction, often used in applications where long-term stability and compatibility are critical, such as certain metals like titanium and some polymers like PTFE (polytetrafluoroethylene). Bioresorbable materials are materials that degrade and are absorbed by the body over time, such as certain polymers (e.g., PLGA) and ceramics (e.g., tricalcium phosphate).

Derived biomaterials:

(1) Decellularized extracellular matrices (ECMs): ECMs obtained by removing cellular components from tissues or organs, leaving behind the extracellular matrix, which can serve as a scaffold for tissue regeneration.

(2) Extracellular vesicles (EVs): Small membrane-bound vesicles secreted by cells that contain bioactive molecules, such as proteins, nucleic acids, and lipids, which can be used for therapeutic purposes.

Nanostructured biomaterials:

(1) Nanoparticles: Nanoscale materials with unique properties, such as enhanced surface area and reactivity, used for drug delivery, imaging, and tissue engineering.

(2) Nanofibers: Fibrous materials with diameters on the nanometer scale, often used as scaffolds for cell growth and tissue regeneration.

This classification system helps in organizing biomaterials based on their characteristics and functions, aiding researchers and clinicians in selecting the most appropriate materials for specific biomedical applications.

The biocompatibility of the materials is the basis for the first classification of biomaterials. The ability of a substance to be recognized by or accepted by the surrounding tissues and organs in the human body is known as biocompatibility. Biocompatibility refers to the ability of a material to perform its desired function within a specific application without eliciting an adverse biological response in the body. In other words, a biocompatible material is one that is compatible with living tissues and does not cause harm or induce a significant immune reaction when in contact with biological systems. Biocompatibility is a critical consideration in the design and development of biomaterials for medical devices, implants, drug delivery systems, and tissue engineering scaffolds.

Several factors influence the biocompatibility of a material:

(1) Chemical composition: The chemical composition of a material plays a significant role in determining its biocompatibility. Materials that closely mimic the composition of natural tissues are often more biocompatible. For example, biodegradable polymers derived from natural sources like collagen or hyaluronic acid are generally well-tolerated by the body.

(2) Physical properties: Physical properties such as surface roughness, porosity, stiffness, and mechanical strength can affect how a material interacts with biological tissues. For instance, a rough surface may promote better cell adhesion and tissue integration, while excessive stiffness or flexibility may cause tissue irritation or failure.

(3) Degradation kinetics: For bioresorbable materials, the rate of degradation and the by-products formed during degradation are critical factors in determining biocompatibility. Ideally, degradation should occur at a controlled rate, allowing for tissue regeneration without causing inflammation or toxicity.

(4) Surface characteristics: Surface properties such as wettability, charge, and the presence of functional groups can influence protein adsorption, cell adhesion, and tissue response. Modifying the surface of a material through techniques like surface coating, plasma treatment, or biomolecule conjugation can improve its biocompatibility.

(5) Immunogenicity: Some materials may trigger an immune response when implanted in the body, leading to inflammation, foreign body reactions, or rejection. Minimizing the immunogenicity of biomaterials through appropriate surface modifications or using materials with low immunogenicity, such as

biocompatible polymers, is essential for long-term implant success.

(6) Bioactivity: Bioactive materials have the ability to interact with biological systems and promote specific cellular responses, such as cell attachment, proliferation, and differentiation. Bioactive materials can enhance tissue integration and regeneration, improving overall biocompatibility.

(7) Sterility: Ensuring the sterility of biomaterials is crucial to prevent infection and adverse reactions when implanted or used in contact with biological fluids or tissues.

Overall, achieving biocompatibility requires a thorough understanding of the interactions between biomaterials and biological systems, as well as careful consideration of material properties, design, and fabrication techniques. Biocompatibility testing, including *in vitro* assays, animal studies, and clinical trials, is often conducted to evaluate the safety and performance of biomaterials before their use in medical applications. Stated differently, implants made of natural or synthetic materials should not cause negative tissue reactions or immune system responses in humans. Using a categorization system based on biocompatibility, the materials can be classified as follows.

2.2. Bioinert materials

Any substance that, when in touch with physiological systems, causes little unfavorable reaction to the host tissue or organs in the human body is referred to as a bioinert biomaterial. Dental implants made of stainless steel, titanium, alumina, partly stabilized zirconia, polyethylene, and bioinert alumina are examples of this category. Tissue integration occurs via the implant because the biomaterial is functionally wrapped in a fibrous capsule.

Bioinert materials for hard tissue repair are those that do not elicit a significant immune response or adverse reactions when implanted in the body. These materials are often used in applications where long-term stability and compatibility are critical. While they may not actively promote tissue regeneration, they provide mechanical support and stability to facilitate the natural healing process. Some examples of bioinert materials commonly used in hard tissue repair are described below:

(1) Titanium and titanium alloys: Titanium and its alloys, such as Ti-6Al-4V, are widely used in orthopedic and dental implants due to their excellent biocompatibility, corrosion resistance, and mechanical properties. Titanium implants provide structural support for bone fixation and can integrate with the surrounding bone tissue through osseointegration.

(2) Stainless steel: Stainless steel alloys, such as 316L stainless steel, are commonly used in orthopedic implants, fracture fixation devices, and dental instruments. Stainless steel implants provide mechanical strength and stability while minimizing the risk of corrosion and adverse tissue reactions.

(3) Cobalt-chromium alloys: Cobalt-chromium alloys, such as Co-Cr-Mo, are used in orthopedic implants, including hip and knee prostheses, due to their high strength, wear resistance, and biocompatibility. These alloys provide durable and long-lasting support for hard tissue repair.

(4) Polyethylene (PE): Ultra-high molecular weight polyethylene (UHMWPE) is often used as a bearing surface in joint replacement implants, such as hip and knee prostheses. While not completely bioinert, UHMWPE has been extensively studied and modified to improve its wear resistance and biocompatibility *in vivo*.

(5) Polytetrafluoroethylene (PTFE): PTFE, commonly known as Teflon, is a fluoropolymer with low friction and excellent chemical resistance. PTFE coatings are sometimes applied to orthopedic implants to reduce friction and wear, although their use in direct contact with bone tissue is limited.

(6) Alumina (Al_2O_3) and Zirconia (ZrO_2): Ceramic materials such as alumina and zirconia are used in hard

tissue implants, particularly in dental applications. These materials are biocompatible, wear-resistant, and can be fabricated into highly precise components for dental crowns, bridges, and dental implants.

While bioinert materials play a crucial role in hard tissue repair by providing mechanical stability and support, they may not actively participate in the regeneration process. In some cases, bioactive or bioresorbable materials may be used in conjunction with bioinert materials to enhance tissue integration and promote long-term healing.

Bioinert materials are substances that do not elicit a significant immune response when implanted into the body. They are often used in hard tissue repair procedures due to their compatibility with the human body. Some common bioinert materials used for hard tissue repair include titanium, stainless steel, and certain ceramics like alumina and zirconia. These materials are chosen for their excellent mechanical properties, biocompatibility, and resistance to corrosion. Titanium and stainless steel are frequently used in orthopedic implants due to their strength and durability. Ceramics like alumina and zirconia are favored for dental implants and joint replacements because of their biocompatibility and wear resistance. Bioinert materials play a crucial role in promoting successful hard tissue repair by providing support and stability to damaged bones and joints. Their ability to integrate seamlessly with the surrounding tissues helps in reducing the risk of rejection and complications post-surgery. Overall, bioinert materials are essential in the field of hard tissue repair as they offer a reliable and effective solution for patients in need of bone and joint treatments.

2.3. Bioactive materials

Bioactive biomaterials are found in implant materials, which engage with soft tissue via a stimulation process, leading to a regeneration and healing process. One example is the formation of a physiologically active carbonate apatite (CHAp) layer on the implant through an anion-exchange interaction with bodily fluids, mimicking the chemical and crystallographic properties of bone's mineral component. The greatest examples in this area include synthetic hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], glass ceramic A-W, bioglass, and bioactive hydroxyapatite coating on a metallic dental implant, surface active bioglass, and bioresorbable tricalcium phosphate implant.

Bioactive materials for hard tissue repair are designed to interact with the biological environment and actively promote tissue regeneration and integration. These materials have properties that facilitate cell adhesion, proliferation, differentiation, and extracellular matrix formation, leading to enhanced healing and functional restoration. Bioactive materials for hard tissue repair are designed to interact with the biological environment and actively promote tissue regeneration and integration. These materials have properties that facilitate cell adhesion, proliferation, differentiation, and extracellular matrix formation, leading to enhanced healing and functional restoration. Bioactive materials commonly used in hard tissue repair include:

(1) Hydroxyapatite (HA): Hydroxyapatite is a naturally occurring mineral form of calcium apatite, which is the main component of bone tissue. Synthetic hydroxyapatite is widely used in orthopedic and dental applications due to its excellent biocompatibility and similarity to natural bone minerals. HA coatings and scaffolds provide a bioactive surface for cell attachment and promote osseointegration with surrounding bone tissue.

(2) Tricalcium phosphate (TCP): Tricalcium phosphate is another calcium phosphate ceramic commonly used in hard tissue repair. TCP is biocompatible, bioresorbable, and osteoconductive, meaning it promotes new bone formation. It can be used as a bone graft substitute, scaffold material, or coating for implants to enhance bone regeneration.

(3) Calcium phosphate ceramics: Calcium phosphate ceramics, such as hydroxyapatite (HA) and tricalcium

phosphate (TCP), mimic the mineral composition of natural bone. They are widely used in bone graft substitutes, bone fillers, and coatings for orthopedic implants. These materials provide a scaffold for new bone formation and promote osseointegration with the surrounding tissue.

(4) Bioactive glass: Bioactive glasses, composed of silica-based or borate-based compositions, have the ability to bond with bone tissue through the formation of a hydroxycarbonate apatite layer. This bioactive interaction stimulates bone growth and facilitates the repair of bone defects. Bioactive glass is used in bone grafts, scaffolds, and coatings for orthopedic and dental applications.

(5) Calcium sulfate: Calcium sulfate, in the form of synthetic gypsum (calcium sulfate hemihydrate), is used as a bone void filler and scaffold for bone regeneration. When implanted in the body, calcium sulfate dissolves and is gradually replaced by new bone tissue. It provides temporary support and stimulates bone healing in defects and fractures.

(6) Polymers with bioactive moieties: Some synthetic polymers are modified with bioactive moieties, such as peptides or growth factors, to enhance their interaction with cells and tissues. These polymers can be used as scaffolds for tissue engineering or as drug delivery vehicles to promote tissue regeneration and repair.

(7) Collagen-based materials: Collagen is a natural protein found in connective tissues and is an essential component of the extracellular matrix. Collagen-based materials, such as collagen sponges, sheets, and hydrogels, are used as scaffolds for tissue regeneration in various applications, including bone repair. Collagen provides a bioactive environment that supports cell adhesion, migration, and tissue remodeling.

(8) Platelet-rich plasma (PRP): Platelet-rich plasma (PRP) is a concentrated form of platelets derived from the patient's own blood. PRP contains growth factors and cytokines that promote tissue repair and regeneration. It is used in conjunction with other biomaterials or as a standalone treatment to enhance the healing of bone fractures, tendon injuries, and soft tissue wounds.

These bioactive materials play a crucial role in promoting the regeneration and repair of hard tissues, such as bone, by providing a conducive environment for cellular activities and tissue growth.

2.4. Bioresorbable biomaterials

Bioresorbable biomaterials for hard tissue repair are designed to degrade over time within the body, gradually being replaced by native tissue as the healing process progresses. These materials offer several advantages, including eliminating the need for implant removal surgeries, reducing the risk of long-term complications, and providing temporary structural support during the healing phase. Some examples of bioresorbable biomaterials commonly used in hard tissue repair are as follows:

(1) Poly(lactic-co-glycolic acid) (PLGA): PLGA is a biodegradable copolymer composed of lactic acid and glycolic acid monomers. It is widely used in orthopedic and dental applications for bone fixation devices, such as screws, pins, and plates. PLGA degrades via hydrolysis into biocompatible by-products (lactic acid and glycolic acid) that are metabolized and excreted by the body.

(2) Polylactic acid (PLA): PLA is a biodegradable polymer derived from lactic acid. It is used in bone fixation devices, scaffolds for tissue engineering, and drug delivery systems. PLA degrades into lactic acid, a naturally occurring compound that can be metabolized and eliminated by the body.

(3) Polyglycolic acid (PGA): PGA is a biodegradable polymer commonly used in absorbable sutures and tissue scaffolds. It degrades rapidly *in vivo* via hydrolysis into glycolic acid, which is metabolized and eliminated by the body. PGA is often combined with other polymers, such as PLA, to modify its

degradation rate and mechanical properties.

(4) Calcium phosphate-based ceramics: Some calcium phosphate ceramics, such as α-tricalcium phosphate (α-TCP) and β-tricalcium phosphate (β-TCP), exhibit bioresorbable properties. These ceramics provide a scaffold for new bone formation and gradually degrade over time as they are replaced by native bone tissue. They are used in bone graft substitutes, scaffolds for tissue engineering, and coatings for orthopedic implants.

(5) Polydioxanone (PDO): PDO is a synthetic bioresorbable polymer used in orthopedic surgery for sutures, anchors, and fixation devices. It degrades via hydrolysis into non-toxic by-products that are metabolized and eliminated by the body. PDO maintains its strength for an extended period before gradually losing mechanical integrity as it degrades.

(6) Bioresorbable magnesium alloys: Magnesium alloys, such as magnesium-calcium (Mg-Ca) and magnesium-zinc (Mg-Zn) alloys, exhibit bioresorbable properties and are being investigated for orthopedic and cardiovascular applications. These alloys degrade *in vivo* via corrosion reactions, releasing magnesium ions that can be utilized by cells for tissue regeneration. However, controlling the degradation rate and addressing potential biocompatibility issues are ongoing challenges in the development of magnesium-based implants.

These bioresorbable biomaterials offer versatile solutions for hard tissue repair, providing temporary support while facilitating natural tissue healing and regeneration. The choice of material depends on factors such as the specific application, required mechanical properties, degradation kinetics, and biocompatibility considerations.

Common applications for bioresorbable materials include implanting them into the body, where they interact with biological fluids, dissolve in the physiological medium, and reabsorb into the body through a variety of metabolic processes, eventually being replaced by newly formed tissue like skin and bone. Appropriate examples are polylactic–polyglycolic acid copolymers and tricalcium phosphate [$Ca_3(PO_4)_2$]. Calcium carbonate, gypsum, and calcium oxide are regarded as bioresorbable biomaterials.

2.5. Natural biomaterials

The biomaterials are divided into natural and synthetic categories according to their source. Additionally, there are two categories of natural biomaterials: those based on proteins and those based on carbohydrates. Composites, metals, ceramics, and polymers make up the categories of synthetic materials.

Natural biomaterials for bone repair are gaining significant attention due to their biocompatibility, bioactivity, and ability to promote tissue regeneration. Several commonly used natural biomaterials for bone repair are described as follows:

(1) Collagen: Collagen is the main protein component of the extracellular matrix in bone tissue. It provides structural support and serves as a scaffold for cell attachment and growth. Collagen-based scaffolds can mimic the natural bone environment, promoting cell adhesion, proliferation, and differentiation.

(2) Hydroxyapatite (HA): Hydroxyapatite is a mineral form of calcium apatite, which is the main inorganic component of bone tissue. It provides strength and rigidity to bones. HA-based biomaterials can enhance bone regeneration by mimicking the mineral composition of natural bone.

(3) Chitosan: Chitosan is derived from chitin, a natural polymer found in the exoskeletons of crustaceans. It has excellent biocompatibility, biodegradability, and antimicrobial properties. Chitosan-based scaffolds can support bone regeneration and have been used in various bone tissue engineering applications.

(4) Alginate: Alginate is a natural polysaccharide derived from brown seaweed. It forms hydrogels in the

presence of divalent cations such as calcium ions. Alginate-based scaffolds can provide a 3D matrix for cell encapsulation and support cell proliferation and differentiation for bone repair.

(5) Gelatin: Gelatin is derived from collagen through hydrolysis and has similar biocompatibility and bioactivity properties. Gelatin-based scaffolds can promote cell adhesion, proliferation, and differentiation, making them suitable for bone tissue engineering applications.

(6) Silk fibroin: Silk fibroin is a natural protein extracted from silkworm cocoons. It possesses excellent mechanical properties and biocompatibility. Silk fibroin-based scaffolds can support bone regeneration by providing a suitable microenvironment for cell growth and tissue formation.

(7) Demineralized bone matrix (DBM): DBM is derived from allograft bone tissue that has been processed to remove minerals while retaining the organic matrix and growth factors. It provides a scaffold for bone regeneration and contains various growth factors that promote osteogenesis.

(8) Decellularized extracellular matrix (ECM): ECM is obtained by decellularizing tissues such as bone, cartilage, or tendon to remove cellular components while preserving the extracellular matrix proteins and growth factors. Decellularized ECM scaffolds can provide a biomimetic microenvironment for cell adhesion, proliferation, and differentiation in bone repair. These natural biomaterials can be used alone or in combination with synthetic materials or growth factors to enhance their properties and tailor them for specific bone repair applications.

Natural biomaterials, also known as allografts from human sources and xenografts from animal sources, are processed and decellularized extracellular matrix of animal tissue. They are utilized as prosthetics. Human dermal allografts are utilized in several organ regeneration processes as well as tissue engineering applications such as biological scaffolds for scar avoidance, dental prostheses, and wound repair. Numerous bioactive ingredients found in these biomaterials promote tissue regeneration and healing, leaving fewer scars behind [5]. Lately, there has been interest in using xenografts made from pig and cow sources as prosthetic heart valves. These grafts or cardiovascular biomaterials have a potential market. It is a transient treatment for tissue regeneration, though, and occasionally it results in serious immunological responses to the host tissue and the spread of illness throughout the host system. Biomaterials called extracellular matrix (ECM) are utilized as scaffolds to repair both soft and hard tissues, including burn injuries and wound healing. The most important component of ECM biomaterials is collagen, which is also obtained from animal tissue, including tendons, and by using recombinant DNA technology. Similar to this, a variety of extracellular proteins, including elastin, fibrin, and fibrinogen, are utilized as a natural biomaterial to create scaffolds for tissue engineering projects. Human hair has recently been shown to contain keratin, and horn meal is the greatest source of protein for use in biomedical applications.

The extracellular matrix's natural protein-based polymers have enormous promise for use in the creation of biomaterials and substrates for tissue engineering, which may repair injured tissue. At the damaged location of an injury, these components may trigger the cell destiny process and cell identification. Collagen, elastin, keratin, and fibrin are the most often utilized materials. Fibrinogen is an extracellular matrix protein that is used to make scaffolds, sponges, hydrogels, and films that are used to treat a variety of connective tissue problems, including those that affect the tendon, ligament, cartilage, bone, and skin. Enzymes such as matrix metal proteinase and serine protease may break down these compounds through tissue healing [6].

Typically, glycosaminoglycan, another essential component of the extracellular matrix of connective tissue, is mimicked by carbohydrate-based biomaterials. In this category, cellulose, chitosan, starch, and alginate are among the most widely used polymers. The structures of these molecules are similar to those of glycosaminoglycan, which is a significant regulator of tissue hydrodynamics [7] and adhesion, migration, proliferation, and differentiation in cells [8]. These biomaterials can be produced as drug-delivery vehicles, scaffolds, sponges, films, and substrates for tissue engineering. Natural biomaterials do have certain drawbacks, though, including lower mechanical properties, difficulty obtaining the necessary quantity for extraction and purification, cross-contamination with other raw material components that could introduce a pathogen or infect host tissue, and high susceptibility to immunological reactions.

2.6. Synthetic biomaterials

Today, the majority of biomedical devices and implants are made with synthetic biomaterials. because it is simple to modify the chemical, surface, and mechanical characteristics to meet biological needs. Nondegradable and biodegradable biomaterials are two major categories into which synthetic biomaterials may be divided. Materials that are biologically inert and do not interact with the physiological milieu of the human body are referred to as non-degradable materials. The most prevalent example of this type, for instance, are implants, which need to be surgically removed from the human body. Materials that can undergo disintegration or resorption of their metabolic pieces under the influence of physiological responses are considered biodegradable materials. The categorization of synthetic biomaterials, together with their uses and justifications in the medical field, are covered in the section that follows. Metals, polymers, composites, and ceramics are the broad categories into which synthetic biomaterials are divided. In **Table 1**, the benefits and drawbacks of different biomaterials are compiled.

Table 1. Advantages and disadvantages of biomaterials

Materials	Advantages	Disadvantages	Applications
Synthetic polymers (nylon, silicone, polyester and biodegradable polymers)	Resilient, simple fabrication, controlled and tailored properties (mechanical strength, biocompatibility, and biodegradation (for biodegradable polymers), reproducible formulation	Lack of good mechanical strength, deform with time, degradable, lack of microenvironment for cell growth, inflammation due to degradation of polymers, lack of balance between polymer degradation and tissue formation	Suture, blood vessels, hip sockets, intraocular lenses.
Natural polymers (collagen, keratin, chitosan and cellulose)	Biocompatible, cell supportive and biodegradable by enzymes mimics extracellular matrix, trigger signaling mechanism (reactive site and growth factors)	Complex decellularization process, poor biomechanical strength, scar formation	Heart valves, Wound dressings
Metals (Ti and its alloys, Ag, Au, and stainless steels)	Strong, tough, and ductile	Corrosion, dense, expensive cost for fabrication of medical device	Joint replacement, dental root implant, pacers, bone plates, and screws.
Ceramics (alumina, zirconia and hydroxyapatite)	Excellent biocompatible	Brittle, not resilient	Dental and orthopedic Implants
Composites (carbon-carbon, bone cement)	Strong, tailor-made	Difficult to prepare	Dental resin and bone cement

2.6.1. Metals as biomaterials

In orthopedic surgery and dentistry, metals and their alloys are used as load-bearing implants. For load-bearing applications, metallic implants offer excellent tensile strength and fatigue resistance. Metallic implants are employed in the form of wires, screws, fracture fixation plates, and prosthetic joints for the ankles, knees, hips, shoulders, and so on. Furthermore, metallic biomaterials are valuable dental materials and are used in cardiovascular and maxillofacial surgery. The most often utilized metallic implants are made of cobalt-based alloys, pure titanium and its alloys, and stainless steel. According to McGregor *et al.* [9], metallic implants have corroded in physiological fluids and have released metallic cations such as nickel, chromium, and cobalt. These ions have the potential to cause toxic or hypersensitive reactions, including skin-related diseases, or they may even cause carcinogenesis. Peri-implant bone resorption, often referred to as stress-shielding, is caused by a notable mismatch in Young's modulus between metallic implants, such as SUS 316L or Co–Cr, and hard tissue, such as bone [10]. Titanium and its alloys offer a close elastic modulus with bone hardness and produce a layer of titanium dioxide with a physiological environment to solve this issue. This layer offers improved biocompatibility with the biological surface while providing corrosion protection. Titanium implants have a high specific strength, however, when it comes to screws or plates, they have a low shear strength. Furthermore, according to Sumner *et al.* [11], several of the first generation of titanium alloys released aluminum or vanadium ions into the physiological milieu, resulting in harmful effects [12]. Materials that are thought to be bioinert are metals. Nonetheless, certain metals and alloys reacted toxically when they came into touch with the organs' physiological surfaces. Therefore, a number of studies employing various physical, chemical, and biological techniques are being conducted to modify the surface of metal implants in order to improve their biocompatibility and adaptability with the biological surface [13].

2.6.2. Polymers

Polymeric biomaterials are artificial or natural materials designed to interact with biological systems in order to treat, enhance, or repair any kind of tissue found in the human body or its organs. Tissue engineering and regenerative medicine have made substantial use of polymers, a flexible class of biomaterials. The primary characteristic of polymeric biomaterials is their exceptional adaptability in customizing their mechanical, chemical, and physical characteristics by the synthesis or chemical alteration of their functional groups in accordance with the potential for organ or tissue regeneration [14]. Examples of polymeric biomaterials include silicone rubber, polyethylene (PE), acrylic resins, polyurethanes, polypropylene, and polymethylmethacrylate (PMMA) as a cornea replacement. Acrylic bone cement is used in dentistry and orthopedic surgery. The polymer's monomer release, which poisoned the cell, was the constraint. Bioresorbable polymers have potential use as scaffolds for tissue engineering, drug delivery systems, and bioactive scaffolds for tissue regeneration. These break down and are eliminated into the urine since they are biodegradable in the physiological media and participate in the metabolic process. Polyglycolic acid (PGA), polylactide (PLA), and polydioxanone (PDS) are widely utilized as suture materials or resorbable bone fixation devices. Tissue engineering structures made of novel bioactive polymers might replicate several characteristics of the extracellular matrix, including its degradation compatibility. PGA and its copolymers, poly(lactic-co-glycolic acid) (PLGA) and poly-ε-caprolactone (PCL), are examples of common bioactive polymers. Ester bond hydrolysis and bulk erosion are the breakdown mechanisms of these polymers. By adjusting the molecular weight, crystallinity, and copolymer ratio, the rate of degradation may be customized [15].

2.6.3. Composites

The composite can have its mechanical, chemical, biological, and physical characteristics altered to match the tissue's healing processes when it comes to biomaterials. Materials that have two or more different phases separated on a macro scale other than the atomic level are referred to be composites. Fabricating composite for a particular biomedical purpose might change the material's mechanical characteristics. Synthetic composites that are frequently encountered are reinforced plastics and fiberglass. Bone, dentin, cartilage, wood, and extracellular matrix found in connective tissue are examples of natural composites [16].

2.6.4. Ceramics

Tightly packed structures of atoms and ions, ceramics are solid inorganic compounds composed of different proportions via ionic or covalent bonding mechanisms. Open and complicated structures can be created if more needs are needed. These are polycrystalline inorganic non-metallic compounds, which comprise different refractory hydrides and sulfides as well as metallic oxides, silicates, and carbides. Bioceramics, such as bone, teeth, and other calcified tissues, are also found in the human body. Bioceramics, as opposed to other biomaterials, are ceramics that have a remarkable ability to replace or supplement a variety of calcified human body components, particularly bone. In general, ceramics offer materials that are naturally brittle and hard, having a higher Young's modulus than bone. These are extensively employed in biomedical applications, including dental implants, heart valves, and hip prostheses, due to their strong compressive strength, excellent inertness to physiological fluids, and attractive look. In biomedical applications, glasses and glass ceramics are utilized as alternatives to bone. As carbons are compatible with blood in heart valves, they have found applications as biomedical implants. Traditionally, ceramics are quite compressible and have poor tensile strength. Like polymers, the production method affects the mechanical and biological qualities. **Table 2** provides an overview of the use of biomaterials in ceramics.

Table 2. Applications of ceramics biomaterials

Materials used	Application	Materials used	Application
Alumina (Al_2O_3)	Orthopedic load-bearing applications	Trisodium phosphate, calcium and sodium phosphate salts	Temporary bone space fillers
HA, surface-active glasses, and glass ceramics	Coatings for chemical bonding (orthopedic, dental, and maxillary prosthetics)	HA, HA-PLA composites, trisodium phosphate, calcium and phosphate salts, surface-active glasses.	Periodontal pocket obliteration
Al_2O_3, HA, surface-active glasses	Dental implants	Al_2O_3, HA, HA-PLA composites, surface active glasses	Maxillofacial reconstruction
Al_2O_3, HA, HA –autogenous bone composite, HA-PLA composite, surface active glasses	Alveolar ridge augmentations	Bioactive glasses ceramics	Percutaneous access devices
Al_2O_3, HA, surface-active glasses, and glass ceramics	Otolaryngologic applications	PLA-carbon fibers, PLA-calcium/ phosphorus, base glass fibers	Orthopedic fixation devices
PLA-carbon fiber composites	Artificial tendons and ligaments		
Alumina Al_2O_3	Coatings for tissue ingrowth (cardiovascular, orthopedic, dental and Maxillofacial prosthetics)	Zirconia	Femoral heads

The general criteria for the selection of medical applications of ceramics are as follows. When selecting ceramics for medical applications, several criteria need to be considered to ensure their suitability for use in biomedical devices, implants, or other medical purposes.

(1) Biocompatibility: Ceramics must be biocompatible, meaning they should not elicit adverse reactions or toxic responses when in contact with living tissues. They should not cause inflammation, immune responses, or tissue rejection.

(2) Bioactivity: Bioactive ceramics have the ability to form a chemical bond with the surrounding bone tissue, promoting osseointegration and facilitating bone ingrowth. This property is crucial for orthopedic implants and bone substitutes.

(3) Mechanical properties: Ceramics used in medical applications should possess appropriate mechanical properties, including strength, toughness, and elasticity, to withstand physiological loads and stresses. The mechanical properties should match those of the host tissue to prevent implant failure or fracture.
(4) Chemical stability: Ceramics should exhibit chemical stability in the physiological environment, resisting degradation or corrosion over time. This ensures long-term functionality and biocompatibility of the implant or device.
(5) Surface characteristics: The surface of ceramics can influence biological interactions, such as cell adhesion, proliferation, and differentiation. Surface modifications may be necessary to enhance cellular responses and improve the integration of the implant with surrounding tissues.
(6) Wear resistance: For load-bearing applications, ceramics should have high wear resistance to withstand frictional forces and minimize material loss over time. This is particularly important for joint replacements and orthopedic implants.
(7) Radiopacity: Ceramics used in medical imaging or diagnostic applications should have sufficient radiopacity to be visualized on X-rays, CT scans, or other imaging modalities. This enables accurate placement and monitoring of the implant or device.
(8) Manufacturability: Ceramics should be capable of being fabricated into desired shapes and sizes using appropriate manufacturing techniques, such as sintering, machining, or additive manufacturing. The manufacturing process should ensure reproducibility and quality control of the final product.
(9) Cost-effectiveness: The cost of ceramic materials and fabrication processes should be reasonable and justifiable relative to the intended medical application and the benefits provided. Cost-effectiveness considerations are important for the widespread adoption and accessibility of ceramic-based medical devices.
(10) Regulatory compliance: Ceramics used in medical applications must meet regulatory requirements and standards for safety, efficacy, and quality control. Compliance with regulations such as ISO 13485 and FDA regulations in the United States is essential for market approval and commercialization.

By considering these criteria, researchers and manufacturers can select ceramics that meet the specific requirements of medical applications while ensuring safety, efficacy, and patient well-being.

According to El-Meliegy and van Noort [17], the best ceramic materials for biomedical applications should meet the following specifications.

(1) Biocompatibility is the ability of ceramic biomaterials to integrate and react with tissues, as well as how these materials respond to tissues and the physiological environment. It is the most crucial factor to take into account when using bioceramics for tissue engineering and biomedical applications. Coating inert ceramic materials with biocompatible compounds improves their biocompatibility.
(2) All ceramics and glasses that are intended for use in dentistry and biomedicine should have their radioactivity assessed. According to ISO 13356, the materials' radioactivity content should not be more than 1.0 Bq/g of uranium-238.
(3) When using dental biomaterials to replace tooth structure, aesthetics is the primary factor to be taken into account. Ceramics ought to offer a long-lasting and suitable fix for teeth cosmetic restoration. The three visual characteristics of color, translucency, and surface texture are used to assess the aesthetics of dental ceramics. The amount of crystalline material in the ceramics allows for the customization of these qualities.
(4) The determining factor for the caliber of dental applications is the ceramics' refractive index. This has an impact on the ceramics' translucency for dental applications. Better opacity results in a smaller layer of practically used opaque glass ceramic and better concealing power, making more room for the

more transparent aesthetic ceramic layers. By modifying the two-phase content and particle size of the material, the opacity of the ceramics may be regulated. In a similar vein, the refractive index of the ceramics can change their transparency.

(5) When the ceramics reach the biodegradable or acceptable stage, their chemical solubility should be minimal and their solubility in biological fluids should be regulated. According to ISO standard, if the materials are not degradable, their solubility should be low, less than < 100 m g/cm^2 after 16 hours of soaking in 4% boiling acetic acid. **Figure 1** illustrates the ceramics' solubility order. The dissolution rates of monophasic CaP diminish in the following sequence at physiological pH: OHA > CDHA > HA > TTCP > α-TCP > β-TCP [18].

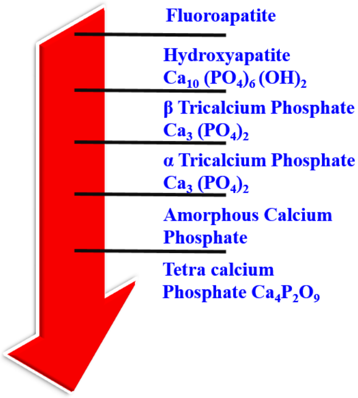

Figure 1. Order of solubility of CaP-based ceramics

(6) Two main aspects influence the mechanical characteristics of ceramics: the magnitude of intrinsic flaws and fracture toughness. To avoid bone loss, osteopenia, or "stress shielding" with the use of bone grafts, the ceramic biomaterial's elastic modulus, tensile strength, fracture toughness, fatigue, and elongation percentage must be as close to the hard tissue as possible, such as bone and other calcified tissue. These characteristics are occasionally linked to ceramic biodegradation. **Figure 2** verifies that porous bioactive ceramics are less potent than cancellous bone and that the bioactive ceramics area is similar to cortical bone's characteristics.

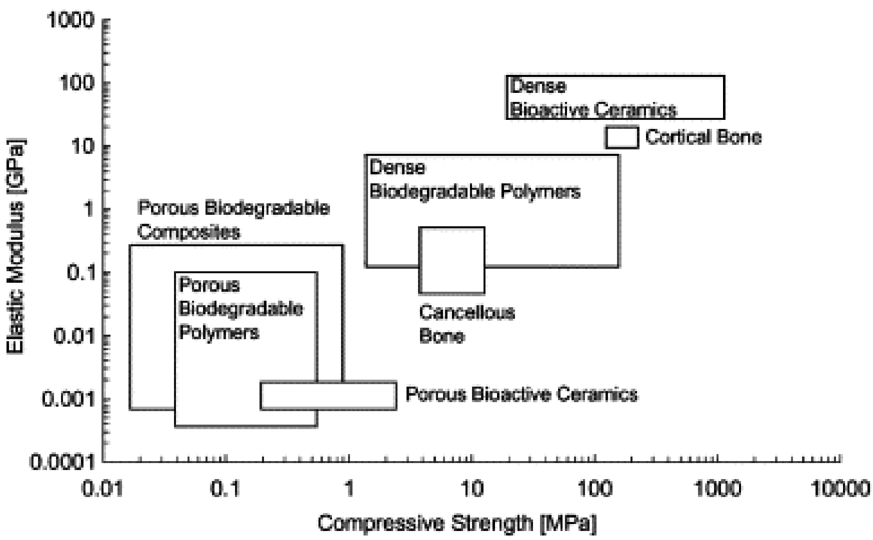

Figure 2. Elastic modulus vs. compressive strength of biodegradable polymers, bioactive ceramics, and composites scaffolds with high porosity (> 75%) and mostly interconnected pore structure [15]

(7) To induce cell fate processes that result in the formation of newly regenerated tissue, the ceramic scaffold's pores and porosity should be optimized. It should also offer a favorable microenvironment for cell proliferation and differentiation, achieving a high mass transfer rate of nutrients, oxygen, and waste metabolic products within the material's structure. For improved cell attachment and proliferation, the ceramic scaffold should also have a wide surface area [19].

(8) Another crucial characteristic in the design of bioceramics is the ceramics' microhardness, which is dependent on the material's surface. The ceramic materials should be easily machined, with little technical difficulty in designing scaffolds with the appropriate dimensions for a given application. The ceramics' other qualities and composition have an impact on this one as well.

(9) The design and production of medical devices, including annealing, covering substrates with glass or glass ceramics, material nucleation, crystallization, etc., depend on the thermal characteristics of the ceramics.

(10) Outstanding osteoconductivity, osteoinductivity, osteogenicity, and osteointegrity are desirable qualities for a bone scaffold composed of ceramic elements.

(11) Another need for ceramic materials is that they should be able to retain their stability throughout storage and function as a medication carrier.

Owing to ceramics' special qualities as biomaterials, treating hard tissue and other calcified tissues using ceramic biomaterials has a significant positive impact on human life and increases lifespan. The many forms of bioceramics, their overview in biomedical and tissue engineering applications, their biological reaction, the benefits of nanofibers and nanoceramics, and some of their processing techniques are all covered in this review paper.

3. Involvement of nanotechnology in the biofabrication of scaffolds for tissue repair

Biofabrication is a cutting-edge technology that combines biology, engineering, and manufacturing to create functional tissues and organs for regenerative medicine applications. One of the key components in biofabrication is the use of scaffolds, which provide structural support for cells to grow and differentiate into the desired tissue types. Nanotechnology has revolutionized the field of tissue engineering by enabling the fabrication of scaffolds with precise control over their physical and chemical properties at the nanoscale. Nanotechnology allows for the design of scaffolds with biomimetic features that mimic the native extracellular matrix, promoting cell adhesion, proliferation, and differentiation. By incorporating nanomaterials such as nanoparticles, nanofibers, and nanotubes into scaffolds, researchers can enhance their mechanical strength, porosity, and bioactivity. Nanotechnology also enables the controlled release of bioactive molecules, growth factors, and drugs from the scaffolds, which can further stimulate tissue regeneration and repair. Overall, the integration of nanotechnology into biofabrication processes holds great promise for the development of advanced scaffolds for tissue engineering applications, with the potential to revolutionize regenerative medicine and personalized healthcare.

Biofabrication is a cutting-edge technology that combines principles of biology, engineering, and materials science to create scaffolds for tissue repair and regeneration. In the context of hard tissue repairs, such as bone or cartilage, biofabrication techniques can play a crucial role in developing scaffolds that mimic the natural extracellular matrix of the tissue, providing structural support and promoting cell growth and tissue formation. Nanotechnology, which deals with materials and structures on the nanometer scale, has revolutionized the field of biofabrication by enabling the precise control of scaffold properties at the molecular level. By incorporating nanoscale features into the design of scaffolds, researchers can enhance their mechanical strength, bioactivity, and biocompatibility, leading to improved outcomes in tissue repair and regeneration. Some of the key applications of nanotechnology in biofabrication of scaffolds for hard tissue repair include:

(1) Nanofiber scaffolds: Electrospinning techniques can be used to create nanofibrous scaffolds with high surface area and porosity, which are ideal for promoting cell attachment, proliferation, and differentiation. Nanofibers can also be functionalized with bioactive molecules or growth factors to further enhance tissue regeneration.

(2) Nanoparticle-based composites: Nanoparticles can be incorporated into scaffold materials to improve their mechanical properties, bioactivity, and drug delivery capabilities. For example, nanoparticles of hydroxyapatite, a mineral found in natural bone, can be added to scaffold materials to enhance their osteoconductivity and promote bone formation.

(3) Surface modification: Nanotechnology can be used to modify the surface properties of scaffolds, such as roughness, hydrophobicity, and chemical composition, to better mimic the native tissue microenvironment and improve cell-scaffold interactions. Surface modifications with nanoscale features can also help control the release of bioactive molecules and growth factors from the scaffold.

Overall, the integration of nanotechnology into biofabrication processes holds great promise for the development of advanced scaffolds for hard tissue repair. By leveraging the unique properties of nanomaterials, researchers can create scaffolds that closely mimic the structure and function of natural tissues, leading to improved outcomes in regenerative medicine and tissue engineering.

Nanotechnology plays a significant role in the biofabrication of scaffolds for hard tissue repair, particularly in bone tissue engineering. Some key applications of nanotechnology in this field include the following:

(1) Improved mechanical properties: Nanotechnology enables the fabrication of scaffolds with enhanced mechanical properties that closely mimic those of natural bone tissue. By incorporating nanomaterials such as nanofibers, nanoparticles, or nanocomposites into scaffold structures, researchers can strengthen the scaffolds and improve their load-bearing capacity.

(2) Enhanced surface properties: Nanotechnology allows for precise control over the surface properties of scaffolds, such as roughness, porosity, and surface chemistry. Functionalizing scaffold surfaces with nanomaterials or biomolecules can promote cell adhesion, proliferation, and differentiation, leading to improved tissue integration and regeneration.

(3) Drug delivery systems: Nanotechnology-based drug delivery systems can be integrated into scaffolds to provide controlled release of bioactive molecules, growth factors, or drugs at the site of tissue repair. Nanoparticles or nanostructured coatings on scaffold surfaces can release therapeutic agents in a sustained manner, promoting tissue regeneration and reducing inflammation or infection.

(4) Biodegradable nanomaterials: Biodegradable nanomaterials, such as nanofibers or nanoparticles made from polymers or ceramics, can be incorporated into scaffolds to enhance their biocompatibility and degradation kinetics. These nanomaterials can gradually degrade over time, releasing degradation by-products that are non-toxic and easily metabolized by the body.

(5) Nanotopography and nanostructure: Nanotechnology enables the creation of scaffolds with specific nanoscale topographies and structures that mimic the extracellular matrix of natural tissues. Nanotopographic cues can influence cell behavior, including adhesion, migration, and differentiation, leading to improved tissue regeneration and organization.

(6) Bioactive nanoparticles: Nanoparticles loaded with bioactive molecules, growth factors, or signaling molecules can be incorporated into scaffolds to promote specific cellular responses, such as osteogenic differentiation or angiogenesis. These bioactive nanoparticles can enhance the biological functionality of scaffolds and accelerate tissue regeneration.

(7) Nanocomposites: Nanotechnology allows for the development of nanocomposite scaffolds by combining nanomaterials with traditional scaffold materials such as polymers, ceramics, or hydrogels. Nanocomposites can exhibit synergistic properties, including improved mechanical strength, enhanced bioactivity, and controlled release of therapeutic agents, making them ideal for hard tissue repair applications.

(8) 3D printing and nanoscale resolution: Advanced 3D printing techniques, such as stereolithography or direct ink writing, enable the precise deposition of nanomaterials to create scaffolds with complex geometries and nanoscale resolution. This level of precision allows for the fabrication of patient-specific scaffolds tailored to individual anatomies and tissue defects.

Overall, nanotechnology offers versatile tools and techniques for the biofabrication of scaffolds for hard tissue repair, enabling the development of advanced biomaterials with tailored properties and functionalities to promote tissue regeneration and restore function.

4. Conclusion

In conclusion, the development of novel biomaterials plays a crucial role in enhancing human life standards by replacing malfunctioning organs or regenerating tissues. The use of biomaterials for hard tissue repair, such as bioceramics, is essential in promoting tissue regeneration and providing structural support in clinical applications. The classification of biomaterials based on biocompatibility and source, including natural and synthetic materials, highlights the diverse uses and potential for biomaterials in regenerative medicine. New materials have been developed to reduce reliance on tissue and organ transplantation and promote tissue regeneration. These materials, including biomaterials, are used in regenerative medicine to replace, regenerate, and restore soft and hard tissues like skin, bones, cartilage, blood vessels, and organs. Biomaterials for hard tissue repair play a crucial role in regenerative medicine by providing structural support and promoting tissue regeneration in damaged or diseased tissues. Common biomaterials include calcium phosphate ceramics, collagen-based materials, synthetic polymers, bioglass, and composite materials. These materials mimic the properties of native tissue to enhance healing and integration. Researchers continue to explore new biomaterials and combinations to improve outcomes for patients in need of hard tissue repair. These biomaterials are essential for bone regeneration, graft substitutes, and implant applications. Biocompatibility is the basis for the first classification of biomaterials, which is the ability of a substance to be recognized by or accepted by the surrounding tissues and organs in the human body. Bioceramics, a class of biomaterials, have shown great promise for hard tissue repair, particularly in bone and dental applications. They are biocompatible, bioactive, and have similar mechanical properties to natural bone, making them ideal for repairing and regenerating damaged or diseased hard tissues. Bioceramics can be used in various forms, including powders, granules, scaffolds, and coatings, and can be tailored to have specific properties depending on the application.

Disclosure statement

The author declares no conflict of interest.

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