Ceramic Materials for Biomedical Applications

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The word “biomaterial” refers to a substance or a mix of materials of synthetic or natural origin interacting with biological systems. The main purpose of biomaterials is to support the healing or replacement of an organ in a human body that has been altered by a disease or an accidental event and to successfully restore function and sometimes aesthetic features without endangering human life. Biomaterials can be classified according to their chemical nature as metallic, polymeric, ceramic, and composite, and can also be biologically derived. The term “ceramic” (from the Greek word κεραμικό: “keramikò,” which means “burnt stuff”), a word that is also found in ancient texts, indicates any heat-treated material derived from clayey raw materials through a process called firing. Generally speaking, ceramics are inorganic materials consisting of metallic and non-metallic components chemically bonded together by means of ionic or prevalently ionic bonds with a variable degree of covalent character.

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1. Bioceramics for General Applications

The science of ceramics is developing rapidly, as ceramics can be porous or glassy and hence can have many applications in medicine and biotechnology. They are widely used in dental and orthopedic applications for wound healing and tissue engineering when non-metallic inorganic materials are required. Bioceramics can be designed to mimic the mechanical properties of the surrounding tissues, and this can improve the long-term stability of the implant. For biomedical applications, these materials can also be used for the fabrication of all-ceramic prosthetic components and can be distinguished according to their glass-content structure in (i) mainly glass, (ii) glass mass filled with other particles, and (iii) polycrystalline [1][2][3]. These biomaterials can be crystalline (sapphire), polycrystalline (alumina, hydroxyapatite), glass–ceramic (Ceravital), and composite. As described in the following sections, bioactive and bioresorbable ceramic materials are currently employed to repair and reconstruct diseased or damaged parts of the musculoskeletal system by inserting customized supporting structures called biomimetic scaffolds” in the fracture site [2][4]. Obviously, the choice of the correct bioceramic depends on the site of application.

Alumina (Al_2O_3) and zirconia (ZrO_2) are the two most important ceramic oxides for biomedical purposes, which are used for damaged bone tissue and joint repair and replacement, as in the case of total-hip and -knee arthroplasty, due to their excellent wear resistance and biocompatibility. They are inert materials but can be used in combination with other materials, such as biodegradable polymers, to deliver drugs and promote tissue regeneration. The

biocompatibility of these materials is related to the chemical stability of the crystal lattice, a symmetrical three-dimensional structural arrangement of the constituent ions inside a crystalline solid, which gives alumina and zirconia high anticorrosive performance and reliable in vivo behavior. Free hydroxyl radicals (-OH) are commonly found on the surfaces of implants realized with these materials, which interact with body fluids, providing a lubricating layer around the implants. The mechanical strength, fatigue strength, and brittleness of Al_2O_3 depend on the purity, size, and distribution of its crystals, as well as its density. Due to the high mechanical strength, it is used to produce endosseous implants both in orthopedics and in maxillofacial surgery [5]. Implants made of Al_2O_3 combine small average grain size (<4 μm) and low surface roughness (Ra ≤ 0.02 μm), showing excellent tribological properties [6]. Pure zirconia has a single crystal structure at room temperature and transitions to a tetragonal and cubic structure at higher temperatures. To stabilize the grid of the square and the cubic structure of zirconia, various oxides are added, among which are magnesium oxide, yttrium oxide, calcium oxide, and cerium oxide (Ce_2O_3) [7]. Pure zirconia occurs in three main crystalline-phase structures: cubic (c), tetragonal (t), and monoclinic (m). Microcracks in the crystal-mesh structure of zirconia are self-limiting if the transformation from a tetragonal to a monoclinic crystal structure is controlled. Zirconium oxide exhibits more than twice the strength of polycrystalline aluminum oxide, a lower modulus of elasticity, and greater brittleness [8]. A huge number of zirconia femoral ball heads have been implanted with good results in terms of biocompatibility and mechanical behavior, as well as immovable prosthetic works and dental implants [9]. By adding CaO, MgO, and Y_2O_3 oxides, which stabilize the zirconia lattice, it is possible to control the transformation of the phases, thus obtaining multiphase materials such as the stabilized zirconia. The addition of 2–3% mole yttrium oxide (Y_2O_3) produces a partially stabilized zirconia consisting of fine square zirconia crystals. During the propagation of a crack in the mass of this material around the crack tip, a transformation of the crystals from a cubic to a monoclinic crystal system takes place [10].

Another important class of bioceramics includes calcium orthophosphates, such as hydroxyapatite (HA, $Ca_{10}(P0_4)_6(OH)_2$) and tricalcium phosphate (TCP, $Ca_3(PO_4)_2$). In general, apatites are inorganic compounds with the general formula $Ca_5(PO_4)_3X_2$, where X can be fluorine ions (such as fluorapatites (FAp)), chloride ions (chloroapatites (ClAp)), or hydroxyl ions (hydroxyapatites (OHAp)). $Ca_{10}(PO_4)_6(OH)_2$ hydroxyapatite is the main structural mineral component of bones and teeth and has typically low crystallinity. The stoichiometric composition consists of 39.68% Ca and 18.45% P. As the Ca/P ratio increases, the resistance increases, reaching a maximum value for a ratio of ~1.67, and after this value it decreases [11][12]. The bone substance, although similar to hydroxyapatite, contains sodium, chlorine, and magnesium, plus other additional ionic units, and is stable at pH 9–12. The key property of hydroxyapatite lays in its high biocompatibility, thus promoting osseointegration and making it one of the most suitable materials for bone-repair and -replacement applications. For the same reasons, hydroxyapatite is commonly selected as an optimal material for dental implants. Furthermore, the advantage of this material is its ability to incorporate different chemicals and gradually attribute them to their microenvironment. It can be used as a drug-delivery platform to release therapeutic agents over a controlled period of time. In addition, it promotes bone synthesis and the regeneration of bone tissue, but its major drawback is the relatively low mechanical strength [13]. The strength decreases exponentially with increasing porosity. The Weibull's modulus belongs to the value range of 5–18, which indicates that hydroxyapatite behaves like a typical brittle ceramic, and the Young's modulus ranges between 35–120 MPa. The low strengths combined with the susceptibility to slow

crack growth (especially in wet conditions) confirm the low-load reliability of dense hydroxyapatite implants [14]. As porosity increases, fracture toughness decreases dramatically. Noteworthy is the fact that porous hydroxyapatite ceramics are less fatigue resistant than dense hydroxyapatite. Mechanical properties can be modified by changing the percentage content of the components or the grain size of the solid phase [15]. Porous hydroxyapatite ceramics have been widely used as bone substitutes, as the porous hydroxyapatite allows contact with the bone and the pores provide a stable matrix for cell attachment and osteogenic factors. Osseous tissue develops within the pores, increasing the strength of the implant. The usual preparation method of porous hydroxyapatite ceramics (pore sizes of 100–600 µm) is through the powder-sintering process with suitable additives such as paraffin, naphthalene, and hydrogen peroxide, which allow pores to form through the gases they release at elevated temperatures [16][17]. Tricalcium phosphate has several uses, such as in maxillofacial surgery, otolaryngology, orthopedic prosthesis, neurosurgery (spinal-cord surgery), dental implants, percutaneous appliances, periodontal therapy, and alveolar incrementations [18][19]. The biochemical behavior of calcium phosphates interacting with body fluids depends on temperature and pH variations. In fact, the non-hydrated phases of calcium phosphate in a high-temperature environment interact with body fluids at 37 °C to form hydroxyapatite, which are outlined on the exposed surfaces of tricalcium phosphate [20][21]. However, calcium-phosphate cements also have some disadvantages, mainly related to poor mechanical performance, which has limited or no application in relation to pure ceramic materials [22][23].

Bioactive glasses are a unique group of synthetic bioresorbable ceramics that react in the presence of biological fluids, improving and enhancing the healing ability of human bodies. Bioactive glasses can be used in tissue engineering as scaffold materials to support tissue regeneration in several applications, including wound healing and nerve regeneration. Regarding the chemical composition, they mainly contain silica but also small quantities of some components such as Na_2O, P_2O_5, and CaO. These components are very important because they determine their bioactive activity and bioabsorbability. A remarkable advantage is their mechanical strength and the possibility of being used as veneering materials [24]. Bioactive glasses are prepared either by the method of rapid cooling of a molten glass at room temperature (melt-derived glasses) to avoid crystallization or by the sol-gel method, which provides the formation of a three-dimensional porous gel network from a colloidal solution by controlling the pH value [25].

In the class of non-oxide ceramic materials, silicon nitride (Si_3N_4) is the most excellent, particularly for its high reliability in environments characterized by high temperatures. It has superior mechanical strength and hardness compared to alumina and is typically produced by the hot-isostatic-pressing (HIP) method [10][18]. Hardened silicon nitride, with a tensile strength of approximately 1 GPa and a stress-intensity factor of 10–12 $MPa \cdot m^{1/2}$, has been used in the production of femoral heads with extremely low levels of wear.

Another non-oxide ceramic is silicon carbide (SiC), which is also produced through the HIP process. This material has greater hardness and strength than alumina and a similar stress-intensity factor. The tensile strength of this material reaches 650 MPa and a stress-intensity factor of 9–10 $MPa \cdot m^{1/2}$. This material is particularly useful in the orthopedic field. In its preparation, the silicon-carbide bulk is covered with a layer of silicon oxide a few nanometers

thick as the product of surface oxidation [19]. The main properties of the bioceramic materials presented in the current section are synthesized in **Table 1**.

Table 1. Properties and biomedical applications of the main bioceramic materials [26][27][28][29][30][31][32][33][34][35].

Material	Young's Modulus (GPa)	Compressive Strength (MPa)	Density (g/cm^3)	Bioactivity	Applications
Alumina	380	4000	>3.9	Inert	Orthopedics, load-bearing applications, dentistry
Zirconia	150–200	2000	6.0	Inert	Orthopedics, load-bearing applications, dentistry
Porous hydroxyapatite	70–120	600	3.1	Bioresorbable	Dentistry, coatings, scaffolds
Tricalcium phosphate	120–160	540	3.1	Bioresorbable	Dentistry, scaffolds
Bioactive glasses	75	1000	2.5	Bioactive	Dentistry, spinal surgery

2. Advanced Bioceramics

Over time, engineers have tried to improve ceramic materials in order to give them ultra-specialized properties through the development of composite micro- and nano-systems [36][37]. A composite material is defined as a heterogeneous combination of two or more distinct materials presenting a finite interface between them. Ceramic nanocomposites constitute an emerging research field aiming to further improve specific properties of bioceramics and to offer new opportunities for the treatment of a wide range of biomedical issues [38][39][40][41][42]. Nanocomposites are a class of composites in which one or more dimensions of the reinforcing phase is in the nanometer range (1 nm = 10 Å), typically up to 100 nm [43]. The characteristic trait of nanocomposite materials is their ability to combine properties and functionalities that are out of reach for traditional materials. By incorporating nanoparticles into a ceramic matrix (e.g., by adding organic molecules, carbon nanotubes, graphene, nanoscale ceramics, proteins, or even DNA to bioceramics or bioglasses), it is possible to create materials with improved mechanical strength, biocompatibility, and osteoconductivity [44]. Ceramic nanocomposites have been developed for a wide range of biomedical applications, including bone replacement or repair and drug delivery. In dentistry and tissue engineering, the architecture of a custom-built nanocomposite material should allow the tissues to self-organize within the organism [45]. In clinical applications, nanocomposite ceramic materials must exhibit adequate mechanical properties, including compressive strength, stiffness, fracture toughness, and fatigue resistance, as well as biocompatibility [46].

Characteristic examples of nanocomposite reinforcements include fullerenes, carbon nanotubes, layered silicates, metal nanoparticles, and dendrimers. In most cases, the necessity is to increase the bending strength, reduce the modulus of elasticity, and avoid material failure. Regarding mechanical bone reconstruction, the solid part of the bone exhibits anisotropic deformation and specific fracture resistance, characteristics that result from its complex composition (collagen fibrils and brittle hydroxyapatite-carbonate crystals). A variety of bioceramics possesses greater hardness than bone, yet several exhibit lower fracture toughness [47]. Therefore, one method of ensuring biomimetic properties occurs by developing biocompatible composites by inserting polymers such as polyethylene within a ceramic matrix of higher mechanical strength, such as sintered hydroxyapatite powder, as a second phase. A transition from ductile to brittle behavior occurs for a volume fraction of hydroxyapatite that ranges between 0.4 and 0.45. In addition, the bioceramic composite acquires a tensile strength of 22–26 MPa and increased fracture toughness for a hydroxyapatite volume fraction < 0.4 due to the deformation associated with crack propagation [48] [49]. The hydroxyapatite–polyethylene composite exhibits properties close to those of bone, and when increasing the volume fraction of hydroxyapatite to 0.5 it acquires an increased modulus of elasticity of 1–8 GPa and a greatly reduced probability of failure from >90% to 3% [50]. Bioceramic nanocomposites reinforced with carbon nanotubes were shown to improve mechanical properties of ceramic matrices for scaffolds and enhance cellular proliferation and differentiation in vitro [51]. Other studies demonstrated that bioceramic nanocomposites based on hydroxyapatite matrices can be used for releasing drugs over a controlled period of time, thus promoting tissue regeneration [52]. In dentistry, nanocomposites are now being exploited as functional rather than simply structural materials through the exploitation of their biochemical properties [53][54]. Finally, the contact of dental prostheses with a biofilm from dysbiosis oral micro-biota has a strong impact on the possibility of developing periimplantitis and the infection and failure of an implant. Furthermore, even teeth with local dysbiosis adjacent to the implant could be detrimental to the survival of the implant itself [55]. The micro-surface of the implant affects the ability of the biofilm to adhere to the implant area. For this reason, scientific research must protect dental implants from this condition by developing new materials that can inhibit the adhesion of the bacterial load on the prosthesis with material that has antibacterial properties and is an inert bioceramic [56]. An optimal biomaterial would be the ceramic nanocomposite Al_2O_3/Ce-TZP, which has all the properties necessary for osseointegration but at the same time guarantees a reduced accumulation of bacteria near the implant in the oral cavity. In a study concerning the adhesion of standard bacteria that are very common in the oral cavity (i.e., Actinomyces naeslundii, Aggregatibacter actino-mycetemcomitans, Fusobacterium nucleatum, Porphyromonas gingivalis, Streptococcus oralis, and Veillonella parvula), several biomaterials for implants were compared: calcium hydroxyapatite, Al_2O_3/Ce-TZP with sterile sandblasted nanocomposites and with glassy coating, and another type of Al_2O_3/Ce-TZP (enriched with ZnO). The analysis showed that the adhesion of bacteria was reduced in the groups in which the coatings with antimicrobial glass materials were present. Furthermore, the one enriched with ZnO had a significant antimicrobial effect [57].

Another outstanding development in the bioceramics field is the creation of bioactive coatings. The surfaces of metal or ceramic implants can be coated with ceramic layers, bioactive molecules, or antimicrobial agents to prevent the risk of infection and promote tissue regeneration, wound healing, and osteointegration with the surrounding tissues, thus making them an effective functional material [58]. Bioceramic coatings can significantly

improve the chemical stability of implants and increase osteogenic activity in vitro and in vivo. For example, a research study showed that bioactive glass coatings on zirconia implants improved osteoconductivity and biocompatibility [59]. The use of hydroxyapatite as a coating on orthopedic and dental metallic implants combines the advantages of metallic materials in terms of mechanical properties with the excellent biocompatibility and bioactivity of hydroxyapatite. In fact, this material coupling is very popular [60]. Pure metal implants do not integrate with bone and, like all bio-inert materials, are surrounded by dense fibrous tissue that prevents the desired stress distribution, with the possible result of implant loosening. However, in the case of coated implants, the bone is fully integrated with the implant even during the first functional-loading phases. Hydroxyapatite coatings perform several functions: they ensure the creation of a stable union of the implant with the bone and minimize adverse reactions of the immune system. In addition, they reduce the release of metal ions into the body and protect the metal surface from the biological environment. In the case of porous metal implants, they encourage bone growth within the pores. Finally, coating an implant with hydroxyapatite also improves its hemocompatibility [61]. During the implantation phase, there is a tendency to adhere to the platelets and a thin layer (film) of proteins is formed, which modifies the surface properties of the biomaterial. Without the addition of hydroxyapatite, this thin film is often incomplete, and when it meets blood and body fluids it leads to clots [62].

The choice of coating technique depends on the specific requirements of the application, such as the desired thickness and uniformity of the coating or the type of bioactive molecule being used. Commonly adopted coating techniques are sol-gel deposition, dip-coating, electrophoretic deposition, and plasma spraying [63][64].

Cyclic-fatigue effects, a topic well described for composite ceramic materials, represent an issue that must be considered in implant design. In most cases, it is necessary to increase the bending strength, reduce elasticity, and avoid material failure. As a positive effect, it was reported that the fracture toughness and flexural strength of bioceramics increased in wet environments [65]. To overcome the above limitation, the usage of bioceramic coatings and the development of nanocomposite ceramics should be considered as appropriate approaches [66][67].

3. Bioceramics for Dentistry Applications

The fundamental property of ceramic materials for dentistry is their compatibility with biological tissues. In recent decades, bioceramics such as alumina, zirconia, SiAlON, bioglasses, and hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) have been studied for dentistry applications. Porcelain, zirconium oxide, and single-crystal sapphire are already being used on a large scale for orthodontic issues [68][69][70]. The main disadvantages of modern osteoplastic devices made of bioceramics are the fragile behavior and the low resistance to tensile or bending forces. They are not osteoinductive except for bioactive glass, and bioabsorption is generally unpredictable. Indeed, TCP and synthetic HA are not bioresorbable in the short term, whereas bioactive glass is rapidly absorbed.

In many dentistry applications, a glass mixture is usually crystallized by employing alumina, zirconia, magnesium spinel ($MgAl_2O_4$), and other compounds in the forms of powders or crystals [68]. By imposing a controlled heat treatment, commonly known as ceramification or devitrification, the final result is obtained. When crystals are used, composite materials known as interpenetrating phase composites (IPC) can be formed. They are constituted by

two phases (crystals and glass) that are interconnected and constantly expand inside each other without generating a chemical bond. The production of these IPCs takes place in two stages. Initially, the ceramic is sintered to form a porous core consisting of alumina- or magnesium-spinel ($MgAl_2O_4$) crystals or alumina and zirconia in a ratio of 70/30 [69]. The molten glass is then filtered through a porous mesh, and after this phase it fills all pores and gaps of a precise shape. In this way, a high-strength frame is created on which a special dental porcelain (i.e., an aesthetic coating) is deposited and fired. In the event that oxides are added in the form of powder, a specific ceramic material called glass–ceramic is formed. Commonly used reinforcing particles are mainly lithium-disilicate crystals [71][72].

Glass-matrix ceramics are based on a ternary-material system consisting of clay/kaolin, quartz (silica), and natural feldspar (a mixture of potassium and sodium aluminosilicate). Potassium feldspar ($K_2A1_2Si_6O_{16}$) forms leucite crystals (crystalline phase) that, depending on the quantity, can increase the intrinsic strength of a restoration. These bioceramic materials are used as a veneering material in metal alloys and ceramic substrates and as an aesthetic monolithic tooth-covering material. As far as the polycrystalline ceramic group is concerned, they have a fine-grained crystalline structure that provides strength and resistance to fracture but tends to have limited translucency. Furthermore, the absence of a glass phase makes polycrystalline ceramics difficult to abrade with hydrofluoric acid, requiring long times or higher temperatures [73].

Alumina has a high purity that can reach up to 99.5%, a high hardness (between 17–20 GPa), and a relatively high strength, since the elasticity value is 300 GPa which is much higher than all dental ceramics.

Zirconia exhibits more than twice the strength, a lower modulus of elasticity, and more brittleness compared to polycrystalline alumina. Pure zirconia is a very strong material that can accept pressures of more than 700 MPa, and for this reason it is used in permanent restorations. Its hardening process can be based on the stabilization of pure zirconium with specific agents/oxides such as yttrium, magnesium, and calcium [10][74].

To increase the biocompatibility and reduce the toxicity of orthopedic and dental implants, a thin layer of apatites is often used as a coating, as mentioned.

Bioactive glasses exhibit a hemostatic effect, and there is an increasing amount of research data showing that they also have an osteostimulating effect, since they can promote and accelerate bone formation at the cellular level. Bioactive glasses are successfully used to achieve bone regeneration in both maxillofacial and orthopedic surgery.

Resin-matrix ceramics include materials in which ceramic particles are at a huge advantage in terms of mass. They are materials containing mainly inorganic refractory compounds (>50% of their weight), including porcelain, glasses, ceramics, and glass–ceramics. Their development and production aim is (i) to obtain a material that more closely simulates the elastic modulus of dentin than traditional ceramics, (ii) to develop a material that is easier to derail and better suited than glass-matrix ceramics (e.g., synthetic ceramics of the lithium-disilicate family) or polycrystalline ceramics, and (iii) easy to repair with composite resin [75][76]. These materials can be divided into three subcategories, depending on their inorganic composition: (i) nanoceramic resin, highly aged and reinforced

with about 80% in weight of nanoceramic material (combination of discrete nanoparticles of silicon and zirconia), (ii) glass–ceramic in a resin-interpenetrating matrix, and (iii) zirconia–silica ceramic in a resin-interpenetrating matrix adapted to different organic compounds and varying the weight percentage of the ceramic [77].

In addition to tailor-made mechanical properties, ceramics can easily achieve the desired shape and color, and for these reasons they are widely used in dentistry applications. Dental porcelain consists of a vitreous silicate matrix in which crystalline mineral salts are dispersed. The composition of the ceramic contains reduced quantities of metal oxides, which are used both as dyes to reproduce the color of natural teeth and to lower the melting temperature and increase the coefficient of thermal expansion [78][79][80][81]. Dental porcelain is used as a veneering material; to construct immobile frames such as metal–ceramic rims and bridges; to construct indirect aesthetic restorations, e.g., facades and inlays/overlays; and to create artificial teeth. During the last few years, the technology of all-ceramic systems has been developed to avoid the construction of fixed prosthetic devices (bridges and circles) made through a metal frame, e.g., entirely from ceramic biomaterials such as zirconia, alumina, and many others [82][83].

All of the objects created with the all-ceramic technique have significantly expanded the possibilities of their applications, especially in dentistry, making them more popular and allowing classic metal–ceramic restorations to be replaced progressively. This is a recurrent case because they combine high aesthetic performance and remarkable biocompatibility. High-strength glass–ceramic materials have the ability to improve aesthetic performance, as they bio-mimic the optical properties of hard dental tissues (enamel, dentin) in the best possible way. However, due to their low strength, they are used almost exclusively as cladding materials for high-strength ceramic frames. In essence, they do not differ significantly from conventional porcelain for metal–ceramic processing. However, the most appropriate choice of biomaterial for a customized implant must be sought by considering all the aesthetic and functional aspects for each patient. Several examples of bioceramic applications in dentistry are presented in **Table 2**.

Table 2. Examples of bioceramic materials for dental and periodontal surgery.

Type of Intervention	Bioceramic Material
Surface coatings (dental and maxillofacial implants)	HA, bioactive glass, bioactive glass–ceramic
Dental implants	Alumina, HA, bioactive glass
Periodontal surgery	HA, HA-PLA, calcium and phosphorous salts, bioactive glass
Implants with alveolar-ridge augmentation	Alumina, HA, HA-PLA, HA–autogenous bone composite, bioactive glass
Coatings for tissue growth	Alumina, HA

4. Bioceramics for Bone-Tissue Engineering

Bone-tissue engineering is a multidisciplinary activity that implements mechanical-design principles in biomedical applications, primarily aiming at realizing volumetric and porous structures commonly known as biomimetic scaffolds. These elements are implanted in patients' bodies to promote and guide bone-tissue regeneration in cases where large bone defects are present that cannot heal spontaneously. From a physiological point of view, it is important to point out the fact that cells can only randomly migrate to form two-dimensional layers, without any control of the shape to reconstruct to regenerate a damaged bone region [84]. Therefore, opportunely designed porous scaffolds act as biocompatible extracellular matrices, since they are engineered to support colonies of undifferentiated stem cells and to promote their differentiation and proliferation in a controlled way.

The general properties required to realize an optimal biomimetic scaffold for bone-tissue regeneration are (a) appropriate mechanical strength and stiffness to support the differentiating cells in load bearing during healing phases; (b) adequate surface properties to enable cell adhesion, differentiation, and osteointegration; (c) optimized topology and interconnectivity between pores to ensure cell migration, vascularization of the structure, and waste-material removal; (d) biocompatibility, intended as the capability of avoiding inflammatory or toxic responses in the implantation sites; (e) biodegradability, consisting of the process of being degraded and absorbed in a precise time period by the physiological environment of the implant; and (f) ease of fabrication into several shapes and dimensional scales [84].

As described in [85], the ceramic materials eligible for bone-tissue replacement can be divided into three main sets: structural ceramics, calcium phospates, and bioactive glasses. The first group includes alumina (Al_2O_3) and zirconia (ZrO_2), which exhibit high hardness and high wear resistance, and this can be considered a problem if the stress-shielding effect is eventually induced in the implant [86]. This phenomenon occurs when a stiff scaffold material does not match the mechanical properties of the tissue to regenerate and, conversely, carries most of the imposed load, thus inhibiting, according to Wolff's law, the natural growth and self-stiffening of bone tissue in the implantation site. Optimal scaffolds, in terms of mechanical properties, should match or be slightly higher than those of the hosting bone [87]. In the second group researchers can find hydroxyapatite (HA, $[Ca_{10}(PO_4)_6(OH)_2]$), which is the primary material constituting human bone, and tricalcium phosphate (TCP, $[Ca_{10}(PO_4)_6]$). The latter is more biodegradable than the former when implanted in vivo and shows higher osteoinductivity [88] and osteoconductivity, which are, respectively, the capability of inducing osteogenesis during a bone-healing process such as a fracture and the tendency of a material to favor bone growth on its surface, which is a typical phase consequent to a bone Implant [89]. It is possible to enhance the bioactivity and biodegradability of synthetic HA by incorporating carbonates and divalent ions such as magnesium and strontium into the bulk material [90]. An innovative and sustainable source of raw biomaterials for highly biocompatible scaffolds, particularly indicated for the chemical synthesis of HA by using phosphorous compounds, is represented by the calcium carbonates that can be extracted from the by-products of the fish industry, in particular from mussel shells [91]. In the third group researchers can find many active compounds [92], such as calcium, sodium, and magnesium oxides, (CaO, Na_2O and MgO, respectively) embedded in a silicon-dioxide (SiO_2) bulk. These are highly biocompatible materials since they can dissolve in biological environments and can even enable chemical bonds with bone substrates. Nevertheless, a major drawback of glass bioceramics is the relatively low toughness of the glass bulk.

In order to reduce the negative effects caused by the brittleness of ceramic and to mimic the natural bone structure, which is essentially a biphasic material, composite scaffolds emerge as a suitable solution. They are obtained as a combination of a ceramic bulk and a natural or synthetic polymeric phase. The first component ensures high compressive strength and low degradation rates, whereas the second enhances the tensile strength and increases the overall toughness of the compound [90].

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