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Review

Current State of Bioceramics

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Abstract

In the late 1960s, strong interest grew in studying various types of ceramics as potential bone grafts thanks to their suitable biomechanical properties. A bit later, such synthetic biomaterials were termed bioceramics. Since then, there has been a number of important achievements in this field. Namely, after the initial development of bioceramics that were just tolerated in the physiological environment, emphasis was shifted towards those able to form direct chemical bonds with the adjacent bones and tissues. Afterwards, based on selection of the appropriate chemical composition coupled with structural and compositional controls, it became possible to choose whether the bioceramic implants remained biologically stable once incorporated into the skeletal structure or whether they should be resorbed over time. At the turn of the millennium, a new concept of regenerative bioceramics was developed and such formulations became an integrated part of the tissue engineering approach. Now bioceramic scaffolds are designed to induce bone formation and vascularization. These scaffolds are usually porous and often harbor various biomolecules and/or cells. This review describes the major types and properties of bioceramics suitable for tissue engineering.

Keywords: Bioceramics, biomaterials, grafts, biomedical applications, tissue engineering

I. Introduction

The field of biomaterials requires the input of knowledge from very different areas of science and technology so that the implanted material performs adequately in a living body. This discipline was founded in the knowledge of materials science and biological clinical science with the final aim of achieving the correct biological interaction between the implanted material and the living body. Therefore, biomaterials appear to be an excellent example of a truly multi-disciplinary field, in which the material, developed by materials scientists and engineers, has to be validated and must perform its task inside the human body under the expertise of physicians and biologists, while the final outcome must be analyzed and coordinated by all the intervening research. A procedure starts after a specific need has been identified. Afterwards, an idea for a potential implant is created with the final insertion of the implant into a patient's body. The whole process appears to be very long because several stages have to be verified: material synthesis, design and manufacturing of the prosthesis, combined with multiple material tests, followed by biomedical evaluation. Finally, a potential biomaterial must also pass all necessary regulatory requirements [1].

The physical character of the majority of the available biomaterials is solid. Depending on their nature and composition, they are divided into four major groups: biometals, biopolymers, bioceramics and various blends thereof, called biocomposites. All of them play very important roles in both replacement and regeneration of various human tissues; however, setting biometals, biopolymers and biocomposites aside, this paper is focused on bioceramics only. The bioceramic materials are designed to be in contact with living tissues and have experienced great development in the last 50 years. The medical needs of an increasingly aging population have driven a great deal of research work looking for new bioceramic materials to regenerate and repair living bones damaged by disease or trauma. For those specific clinical applications, mainly in orthopedics and dentistry, bioceramics are playing a key role.

The use of ceramic materials represents an evolution of many aspects of human history. Namely, many millennia ago, the possibility to store grains in ceramic receptacles allowed man to become a settler instead of a nomad hunter. Some centuries ago, the use of structural ceramics also brought great advances in the quality of life of people with the possibility of making clay bricks and tiles. Decades ago, ceramics generated a new revolution in the human way of life, with development of the functional ceramics as dielectrics, semiconductors, magnets, piezoelectrics, high-temperature superconductors and so on. In addition, ceramics plays an important role in improving the quality and length of human life through their use as biomaterials and in medical devices [1].

In general, ceramics are inorganic materials with a combination of ionic and covalent bonding. Therefore, they have high melting temperatures, low electricity and heat conduction, as well as relatively high hardness. Regarding their mechanical behavior, ceramic materials exhibit

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high compressive strengths, but very much lower tensile strengths. In addition, they are stiff materials, with a high Young's modulus, and brittle because failure takes place without plastic deformation. With regard to their surface properties, ceramics usually possess high wetting degrees and surface tensions, which favor adhesion of proteins, cells and other biological moieties. Furthermore, the ceramic surfaces can be treated to reach very high polish limits. Currently, many research efforts are devoted to ceramics with interconnected porosity.

Regarding their composition, the vast majority of inorganic compounds (metal haloids, metal oxides, metal chalcogenides, metal nitrides, metal phosphides, metal carbides, as well as various oxygen-containing salts of metals (sulfates, phosphates, nitrates, acetates, carbonates, silicates, etc.)) are classed as ceramics. However, the chemical elements used to manufacture bioceramics form just a small set in the Periodic Table. Namely, bioceramics might be prepared from alumina, zirconia, magnesia, carbon, silica-contained and calcium-contained compounds, as well as from a limited number of other chemicals. Therefore, all these compounds plus calcium phosphates, calcium sulfates, certain glasses and glass-ceramics appear to be genuine examples of bioceramics. Although carbon is not a compound but an element and conducts electricity in its graphite form, it is also considered as a ceramic owing to its many ceramic-like properties. Nowadays, new advanced bioceramics are under study, including ordered mesoporous silica materials or specific compositions of organic-inorganic hybrids. All these compounds might be manufactured in both dense and porous forms in bulk, as well as in the forms of crystals, powders, particles, granules, scaffolds and/or coatings [1].

II. General Knowledge and Definitions

Several definitions have been developed for the term "biomaterials". For example, by the end of the 20th century, the consensus developed by the experts was the following: biomaterials were defined as synthetic or natural materials to be used to replace parts of a living system or to function in intimate contact with living tissues [2]. However, in September 2009, a more advanced definition was introduced: "A biomaterial is a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure, in human or veterinary medicine" [3]. Changes to the definition were accompanied by a shift in both the conceptual ideas and the expectations of biological performance, which mutually changed over time [4].

In general, the biomaterials discipline is founded in the knowledge of the synergistic interaction of material science, biology, chemistry, medicine and mechanical science and it requires the input of comprehension from all these areas so that potential implants perform adequately in a living body and interrupt normal body functions as little as possible [5]. As biomaterials deal with all aspects of the material synthesis and processing, knowledge of chemistry, material science and engineering appear to be essential. On the other hand, since clinical implantology is the main purpose of biomaterials, biomedical sciences become the key part of the research. These include cell and molecular biology, histology, anatomy and physiology. The final aim is to achieve the correct biological interaction of the artificial grafts with living tissues of a host. Thus, to achieve the goals, several stages must be performed, such as: material synthesis, design and manufacturing of prostheses, followed by various types of tests. Furthermore, before clinical applications, any potential biomaterial must also pass all regulatory requirements [6].

In any case, biomaterials are intended to interface with biological systems in vivo to evaluate, treat, augment or replace any tissue, organ or function of the body and are now used in several different applications throughout the body. Thus, biomaterials are solely associated with the health care domain and must have an interface with tissues or tissue components. One should stress that any artificial materials that are simply in contact with skin, such as hearing aids and wearable artificial limbs, are not included in the definition of biomaterials since the skin acts as a protective barrier between the body and the external world [7, 8].

The major difference between biomaterials and other classes of materials lies in their ability to remain in a biological environment without damaging their surroundings nor being damaged in the process. Therefore, biomaterials must be distinguished from biological materials because the former are the materials that are accepted by living tissues and, therefore, they might be used for tissue replacements, while the latter are just the materials being produced by various biological systems (wood, cotton, bones, chitin, etc.) [9]. Furthermore, there are biomimetic materials, which are not made by living organisms but have the composition, structure and properties similar to those of biological materials. Concerning the subject of the current review, bioceramics (or biomedical ceramics) are defined as biomaterials having a ceramic origin. Now it is important to define the meaning of ceramics. According to Wikipedia, the free encyclopedia: "The word ceramic comes from the Greek word κεραμικός (keramikos), "of pottery" or "for pottery", from κέραμος (keramos), "potter's clay, tile, pottery". The earliest known mention of the root "ceram-" is the Mycenaean Greek ke-ra-me-we, "workers of ceramics", written in Linear B syllabic script. The word "ceramic" may be used as an adjective to describe a material, product or process, or it may be used as a noun, either singular, or, more commonly, as the plural noun "ceramics". A ceramic material is an inorganic, non-metallic, often crystalline oxide, nitride or carbide material. Some elements, such as carbon or silicon, may be considered as ceramics. Ceramic materials are brittle, hard, strong in compression, weak in shearing and tension. They withstand chemical erosion that occurs in other materials subjected to acidic or caustic environments. Ceramics can generally withstand very high temperatures, such as temperatures that range from 1000 °C to 1600 °C (1800 °F to 3000 °F). Glass is often not considered a ceramic because of its amorphous (non-crystalline) character. However, glassmaking involves several steps of the ceramic process and the mechanical properties of glass are similar to those of ceramic materials." [10]. Similar to any other type of biomaterial, bioceramics can have structural functions as joint or tissue replacements, be used as coatings to improve biocompatibility, as well as function as resorbable lattices, providing temporary structures and frameworks that are dissolved and/or replaced as the body rebuilds the damaged tissues [11–14]. Some types of bioceramics feature a drug-delivery capability [15–18].

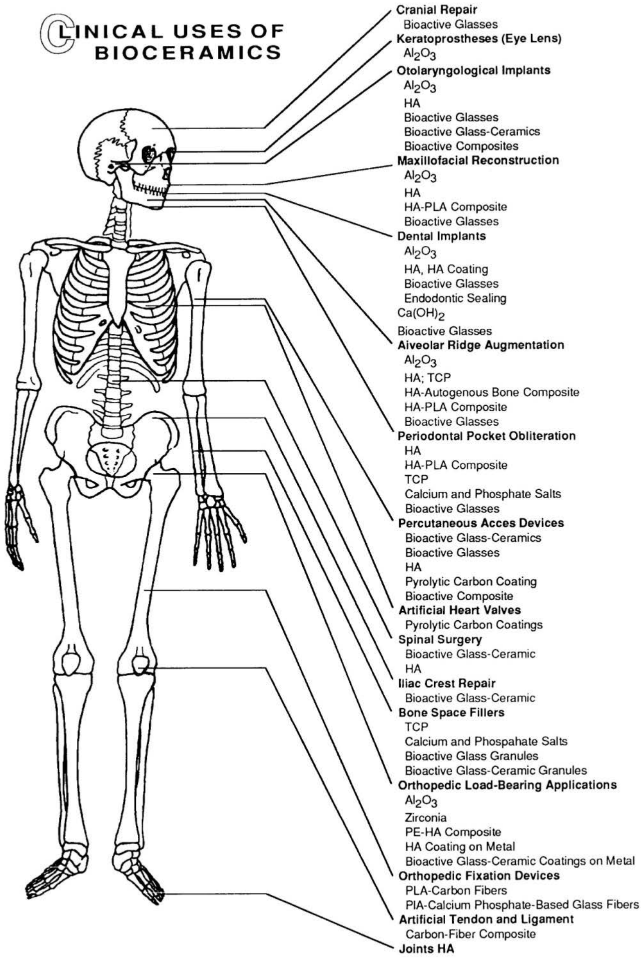

Fig. 1: Clinical uses of bioceramics. Reprinted from Ref. [19] with permission.

Bioceramics are produced in a variety of forms and phases and serve many different functions in the repair of the body. Fig. 1 presents a graphical sketch of clinical uses of bioceramics within the human body [19]. In biomedical applications, bioceramics are used in the form of bulk materials of a specific shape, called implants, prostheses or prosthetic devices. A great challenge facing its medical application is, first, to replace and, second, to regenerate old and deteriorating bones with a biomaterial that can be replaced by a new mature bone without transient loss of mechanical support [8, 20]. Since the average lifespan of humans is now 80+ years and the major need for spare parts begins at about 60 years of age, the after-effects of the implanted bioceramics need to last, at least, for 20+ years. This demanding requirement of survivability is under conditions of use that are especially harsh to implanted biomaterials: corrosive saline solutions at 37 °C under variable, multiaxial and cyclical mechanical loads. The excellent performance of the specially designed bioceramics that have survived these clinical conditions represented one of the most remarkable accomplishments of research, development, production and quality assurance by the end of the past century [11].

III. Brief Historical Overview

In medicine, bioceramics have been used for millennia to alleviate pain and restore functions of diseased or damaged calcified tissues (bones and teeth) of the body. For example, in 1972, Amadeo Bobbio discovered Mayan skulls, some of them more than 4000 years old, in which missing teeth had been replaced by nacre substitutes [21]. In addition, according to Wikipedia, literature dating back to 975 AD notes that calcium sulfate was useful for setting broken bones. However, those were ex vivo applications. According to the available literature, by the end of the 19th century, surgeons were already using plaster of Paris as a bone-filling substitute [22]. Nevertheless, it was a famous German surgeon Themistocles Gluck (1853 – 1942), who, amongst his range of contributions, on 20 May 1890 performed the first well-documented ivory (virtually pure biological apatite) knee replacement bedded in a calcium-sulfate-based cement, which was followed by a total wrist replacement in another patient three weeks later [23]. Later in 1890, Gluck presented a further case of a total knee replacement to the Berlin Medical Society: at only 35 days after operation, the patient was free of pain with active knee flexion and extension. All the joint arthroplasties performed by Gluck were remarkably successful in the short term; however, all ultimately failed because of chronic infections [24, 25]. With regard to other types of bioceramics, the first attempt to implant laboratory-produced calcium phosphate as an artificial material to repair surgically created defects in rabbit bones was performed in 1920 [26] by the US surgeon Fred Houdlette Albee (1876 – 1945), who invented bone grafting [27] and some other advances in orthopedic surgery. Extensive studies of plaster of Paris to repair bone defects continued through the first half of 1900s [28, 29], while the first application of alumina as a biomaterial was suggested in 1933 by Rock [30].

As written in the literature, the "modern" era of bioceramics can be traced to Smith's successful study of 1963 on a ceramic bone substitute material Cerosium®, composed of a porous aluminate ceramic impregnated with an epoxy resin. The porosity of that bioceramic was controlled at 48 % in analogy to a comparable value for natural bone and in order to produce net physical properties very close to those of bone [31]. In 1960s, several other publications on the application of the ceramic materials as prostheses were published as well [32–35]. In 1969, the first scientific study of the outstanding biomedical properties of zirconia emerged [36]. In 1971, bioactive glasses were prepared [37]. In 1972, a famous paper by Boutin was published [38]; since then alumina took off on its worldwide triumphal course as a suitable bioceramic for femoral balls of hip endoprostheses. Concerning the earliest appearance of term "bioceramics" in the scientific literature, according to the available databases, the first paper with this term in the abstract was published in 1971 [39], while the earliest papers with the term in the title were published in 1972 [40, 41]. On 26 April 1988, the first international symposium on bioceramics was held in Kyoto, Japan. The historical development of bioceramics is schematically shown in Fig. 2 [42].

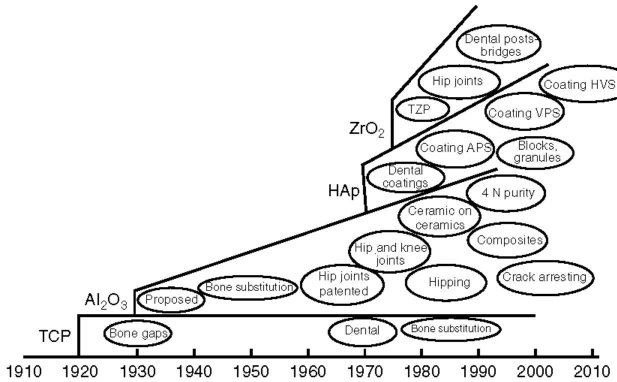

Fig. 2: Application of bioceramics in medical devices: 100 years of history. Reprinted from Ref. [42] with permission.

IV. The First, Second and Third Generations of Bioceramics

Both conceptually and historically, the study of biomaterials (therefore, bioceramics as well) can be divided into the first [43], second [44] and third [45] generations (Fig. 3) [1]. The first generation of biomaterials started in the 1960s, when the goal was to minimize reactivity. Briefly, when synthetic materials were first used in biomedical applications, the requirements for use were suitable physical properties to match those of the replaced tissue with a minimal toxic response of the host, so biologically inert or nearly inert materials were used in order to reduce the corrosion and the releasing ions and particles after implantation to minimize the immune response and foreign body reaction. Mechanical properties and toxicity also played a leading role in the selection of materials for implant manufacture. Therefore, the first generation of biomaterials was used solely for tissue replacement. When inert biomaterials (strictly speaking, a material should never be considered as totally inert; such materials just do not create a direct interface with the adjacent tissues) are placed inside the body, they would elicit a foreign fibrous capsule around the material which isolates it from the surrounding tissue. This biological shielding leads to mechanical (stress) shielding, known to promote micro-motion and subsequent aseptic implant loosening. The representative examples of this type of bioceramics are alumina (Al_2O_3) and zirconia (ZrO_2). Owing to their high strength, excellent corrosion and wear resistances, stability, non-toxicity and in vivo biocompatibility, they are widely used to fabricate femoral heads [43]. Non-oxide almost inert bioceramics such as silicon nitride (Si_3N_4) [46,47] and silicon carbide (SiC) [48] are being developed as well.

In addition, there are certain compositions of ceramics that are able to form a mechanically strong bond to bones. These materials have become known as bioactive bioceramics. All of them represent the second generation of biomaterials, which uses the materials' ability to interact with the biological environment to enhance the biological response and provide the tissue/surface bonding. Among them, there is a group of bioresorbable biomaterials that possess an ability to degrade when tissues are regenerated and healed. Thus, around the 1980s, the objective changed to obtain favorable interactions with the living body, namely a bioactive response or degradation [44]. Therefore, the second generation of biomaterials is used for tissue regeneration. A common characteristic of this generation of biomaterials is a time-dependent, kinetic modification of the surface that occurs upon implantation as the result of interactions with the physiological fluids. Namely, in the case of bone grafts, a biologically active layer of carbonated apatite is formed on the surface of such biomaterials and this layer provides the bonding interface with adjacent bones and surrounding tissues. This carbonated apatite phase appears to be chemically and structurally equivalent to the mineral phase of bones which is responsible for the interfacial bonding [11]. Moreover, owing to the actions of living cells, this apatite can form new bones. Specific compositions of calcium phosphates and/or sulfates, bioactive glasses and glass-ceramics are examples of the second-generation bioceramics used clinically for bone tissue augmentation. For biomedical applications, these materials are provided as powders, both porous and dense pieces, injectable mixtures, self-setting formulations and coatings. All of them have excellent features in terms of biocompatibility and bioactivity, but their mechanical properties are poor [1].

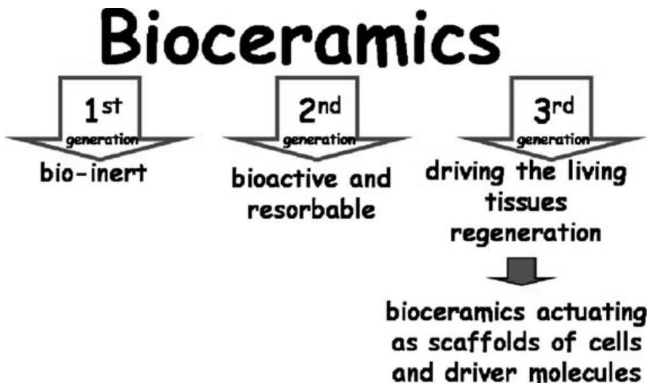

Fig. 3: A schematic layout of the three generations of bioceramics. Reprinted from Ref. [1] with permission.

The third generation of biomaterials uses both the bioactive and the bioresorbable materials as temporary three-dimensional porous structures (scaffolds) which are able to activate genes that stimulate regeneration of living tissue. For these biomaterials, concepts of bioactivity and biodegradability are combined, and this combination of both concepts appears to be the key feature for the third generation of biomaterials. Thus, the major purpose of the third generation of bioceramics is basically to provide an adequate scaffolding system which helps living cells to perform their natural processes [45]. In addition, a concept of porosity and its range of order appears to be of paramount importance. Namely, bioceramics with mesoporosity between 2 and 50 nm are of interest for applications where drugs and/or biologically active molecules are loaded and later released to help in the bone regeneration process. Macroporous materials with pore dimensions exceeding several microns appear to be suitable as scaffolds for tissue engineering. The studies in third-generation bioceramics are based more on biology and follow the purpose of tissue regeneration (rather than tissue replacement) with attempts to develop artificial materials able to restore damaged biological tissues in situations when the human body cannot perform this by itself. One attempt consists of designing biomimetic materials that combine synthetic materials with cellular recognizing positions. Generally, this category is based on the second-generation bioceramics with porosity, loaded with biologically active substances. The examples comprise mesoporous silica, mesoporous ordered glasses, porous calcium phosphate scaffolds and organic-inorganic hybrids with cellular recognizing positions [1].

To finalize this section, one should stress that the first generation of inert bioceramics was aimed at serving as artificial bone grafts, the second generation of bioactive and bioresorbable bioceramics was developed to mimic some biomineralization-related functions, while the purpose of the third generation of bioceramics is basically to provide an adequate scaffolding system that helps bone cells to perform their restorative functions. In addition, one should mention that the fourth generation of biomaterials was announced in 2016. According to the authors, it should be designed to both manipulate and monitor cellular bioelectrical signals [49]. Currently, it has nothing in common with bioceramics.

V. Various Types of the Bioceramic/Issue Interfaces

In general, no implanted material appears to be totally inert for the surrounding tissues; thus, all implants elicit a response from the host tissues. This response occurs at the tissue/implant interface and depends on many factors. According to the literature [19], all factors affecting this interfacial response may be divided into two groups: factors from the tissue side and those from the implant side. The first group of the factors comprises the type of tissue, the health of the tissue, the age of the tissue, blood circulation in both the tissue and at the interface, as well as motion at the interface, while the second group of the factors includes the implant composition, phases in the implant, phase boundaries, surface morphology, surface porosity and chemical reactions. Factors such as closeness of fit and a mechanical load appear to have an influence from the both sides of the tissue/implant interfaces [19].

A combination of all the aforesaid factors creates the overall tissue response. According to the available knowledge on the subject, there are four possible types of tissue responses to the implanted materials: biotoxic, biologically nearly inert, bioactive and bioresorbable. A biotoxic response causes cell death in the surrounding tissues owing to release of dangerous chemicals that are able to migrate within tissue fluids and cause systemic damage to the patient. Since a lack of toxicity appears to be critical, biotoxic materials are excluded from any type of biomedical applications. Therefore, in the case of bioceramics, just three types of the implant/tissue responses – biologically nearly inert, bioactive and bioresorbable – are considered. It is important to note that these three types of responses correlate fully with the aforementioned three generations of bioceramics (Fig. 3). Thus, each generation of bioceramics appears to possess an implant/tissue response of its own.

VI. The Major Properties of Bioceramics

(1) *Mechanical properties*

The modern generation of bioceramics is designed to stimulate the body's own self-repairing abilities [45]. Therefore, during healing, a mature bone should replace the modern grafts and this process must occur without transient loss of mechanical support. Unluckily for material scientists, a human body provides one of the most inhospitable environments for implanted biomaterials. It is warm, wet and both chemically and biologically active. For example, a diversity of body fluids in various tissues might have a solution pH varying from 1 to 9. In addition, a body is capable of generating quite massive force concentrations and the variance in such characteristics among individuals might be enormous. Typically, bones are subjected to ~ 4 MPa loads, whereas tendons and ligaments experience peak stresses in the range of 40 – 80 MPa. The hip joints are subjected to an average load up to three times body weight (3000 N) and peak loads experienced during jumping can be as high as ten times body weight. These stresses are repetitive and fluctuate depending on the nature of the activities, which can include standing, sitting, jogging, stretching and climbing. Therefore, all types of implants must sustain attacks of a great variety of aggressive conditions [50]. Regrettably, there is presently no artificial material fulfilling all these requirements.

For dense bioceramics, the strength is a function of the grain sizes. Namely, finer grain size bioceramics have smaller flaws at the grain boundaries and thus are stronger than those with larger grain sizes. Thus, in general, the strength for ceramics is proportional to the inverse square root of the grain sizes [51]. In addition, the mechanical properties decrease significantly with increasing content of an amorphous phase, microporosity and grain sizes, while a high crystallinity, a low porosity and small grain sizes tend to give higher stiffness, higher compressive and tensile strength and greater fracture toughness. Furthermore, ceramic strength appears to be very sensitive to slow crack growth [52]. Accordingly, from the mechanical point of view, bioceramics appear to be brittle polycrystalline materials for which the mechanical properties are governed by crystallinity, grain size, grain boundaries, porosity and composition [53]. Thus, they possess poor mechanical properties (for instance, low impact and fracture resistances) that do not allow bioceramics to be used in load-bearing areas, such as artificial teeth or bones [11 – 14]. For example, fracture toughness (this is a property that describes the ability of a material containing a crack to resist fracture and is one of the most important properties of any material for virtually all design applications) of hydroxyapatite bioceramics does not exceed the value of ~ 1.2 MPa·m$^{1/2}$ [54] (human bone: 2 – 12 MPa·m$^{1/2}$). It decreases exponentially with increasing porosity [55].

Furthermore, strength decreases almost exponentially with increasing porosity [56, 57]. However, by changing the pore geometry, it is possible to influence the strength of porous bioceramics. It is also worth mentioning that porous bioceramics are considerably less fatigue-resistant than dense bioceramics (in materials science, fatigue is the progressive and localized structural damage that occurs when a material is subjected to cyclic loading). Both grain sizes and porosity have been reported to influence the fracture path, which itself has little effect on the fracture toughness [53, 58]. However, no obvious decrease in mechanical properties was found after the bioceramics had been aged in the various solutions during the different periods of time [59].

Owing to a high brittleness (associated with low crack resistance), the biomedical applications of bioceramics are limited. Therefore, ways are continuously sought to improve their reliability. Namely, diverse reinforcements (ceramics, metals or polymers) have been applied to manufacture various biocomposites and hybrid biomaterials [60]. Another approach to improve the mechanical properties of bioceramics is to cover the items with polymeric coatings [61–63] or infiltrate porous structures with polymers [64–66].

(2) Electric/dielectric and piezoelectric properties

Occasionally, an interest in both electric/dielectric [67–80] and piezoelectric [81, 82] properties of bioceramics is expressed. For example, a surface ionic conductivity of both porous and dense hydroxyapatite bioceramics was examined for humidity sensor applications, since the room temperature conductivity was influenced by relative humidity [68]. Namely, the ionic conductivity of solid hydroxyapatite was a subject of research for its possible use as a gas sensor for alcohol [69], carbon dioxide [67, 76] or carbon monoxide [72]. Electric measurements were also used as a characterization tool to study the evolution of microstructure [70].

The electric properties of bioceramics appear to influence their biomedical applications. For example, there is interest in polarization of hydroxyapatite bioceramics to generate a surface charge by the application of electric fields at elevated temperatures [83, 84]. The presence of surface charges was shown to have a significant effect on both in vitro and in vivo crystallization of biological apatite [85–91]. Furthermore, growth of both biomimetic calcium orthophosphates and bones was found to be accelerated on negatively charged surfaces and decelerated at positively charged surfaces [89–102]. A similar effect was found for adsorption of bovine serum albumin [103]. In addition, the electric polarization was found to accelerate a cytoskeleton reorganization of osteoblast-like cells [104–107], extend bioactivity [108], enhance bone ingrowth through the pores of porous implants [109] and influence cell activity [110, 111].

(3) Possible transparency

Single crystals of many ceramic materials are optically transparent to visible light. Since bioceramics have a polycrystalline nature with a random orientation of large amounts of small crystals, it is opaque and white in color, unless colored dopants are added. However, in some cases, a transparency is convenient to provide some essential advantages (e.g. to enable direct viewing of living cells, their attachment, spreading, proliferation, and osteogenic differentiation cascade in a transmitted light). Thus, transparent bioceramics (Fig. 4) [112] have been prepared and investigated [112–121]. They can exhibit an optical transmittance of ~ 66 % at a wavelength of 645 nm [118]. The preparation techniques include hot isostatic pressing [120], ambient-pressure sintering [113], gel casting coupled with low-temperature sintering [114, 117], pulse electric current sintering [115], as well as spark plasma sintering [122–128]. Fully dense, transparent bioceramics are obtained at temperatures above ~ 800 °C. Depending on the preparation technique, the transparent bioceramics have a uniform grain size and always are pore-free. Furthermore, translucent bioceramics are also known [129–131]. Concerning possible biomedical applications, the ceramics that are optically transparent to visible light can be useful for direct viewing of other objects, such as cells, in some specific experiments [116]. In addition, bioceramics with transparency to laser light may appear to be convenient for minimal invasive surgery by allowing the laser beam to pass through it to treat the injured tissues located underneath. However, owing to a lack of both porosity and the great necessity to have see-through implants inside the body, the transparent and translucent forms of bioceramics will hardly be extensively used in medicine except the aforementioned cases and possible eye implants.

Fig. 4: Transparent hydroxyapatite bioceramics prepared by spark plasma sintering at 900 °C from nano-sized HA single crystals. Reprinted from Ref. [112] with permission.

(4) Porosity

Porosity is defined as a percentage of voids in solids and this morphological property is independent of the material. The surface area of porous bodies is much higher, which guarantees good mechanical fixation in addition to providing sites on the surface that allow chemical bonding between the bioceramics and bones [132]. Furthermore, a porous material may have both closed (isolated) pores and open (interconnected) pores. The latter look like tunnels and are accessible by gases, liquids and particulate suspensions [133]. The open-cell nature of porous materials (also known as reticulated materials) is a unique characteristic essential in many applications. In addition, pore dimensions are also important. Namely, the dimensions of open pores are directly related to bone formation, since such pores grant both the surface and space for cell adhesion and bone ingrowth [134–136]. On the other hand, pore interconnection provides the ways for cell distribution and migration, as well as allowing efficient in vivo blood vessel formation suitable for sustaining bone tissue neo-formation and possibly remodeling [109, 137–143]. Thus, porous bioceramics is colonized easily by cells and bone tissues [137, 143, 144–151]. Therefore, interconnecting macroporosity (pore size > 100 μm) [132, 137, 152, 153] is intentionally introduced in solid bioceramics (Fig. 5). In addition, macroporosity might be formed artificially due to a release of various easily removable compounds and, for that reason, incorporation of pore-creating additives (porogens) is the most popular technique to create macroporosity. The porogens are crystals, particles or fibers of either volatile (they evolve gases at elevated temperatures) or soluble substances. The popular examples comprise paraffin [154–156], naphthalene [157–159], sucrose [160, 161], $NaHCO_3$ [162–164], NaCl [165, 166], polymethylmethacrylate [167–169], hydrogen peroxide [170–175]. Several other compounds [176–187] might be used as porogens as well. The ideal porogen should be nontoxic and be removed at ambient temperature, thereby allowing the bioceramic/porogen mixture to be injected directly into a defect site and allowing the scaffold to fit the defect [188]. Sintering particles, preferably spheres of equal size, is a similar way to generate porous 3D bioceramics. However, pores resulting from this method are often irregular in size and shape and not fully interconnected with one another. Schematic drawings of various types of the ceramic porosity are shown in Fig. 6 [189].

Many other techniques, such as replication of polymer foams by means of impregnation [190–194] (Fig. 5), various types of casting [175, 195–203], surfactant washing [204], microemulsions [205, 206], ice templating [207–210], as well as many other approaches [211–246] have been applied to fabricate porous bioceramics. In addition, both natural porous materials, such as coral skeletons [247, 248] or shells [248, 249], and artificially prepared ones [250] can be converted into porous bioceramics under the hydrothermal conditions (250 °C, 24–48 h) with the microstructure undamaged. Besides, porous bioceramics might be prepared by hardening of the self-setting formulations [155, 156, 163, 164, 166, 176, 177, 235]. In addition, porous bioceramics might be prepared by using different starting powders of the same compound and sintering at various temperatures by means of pressureless sintering [213]. Porous bioceramics with improved strength might be fabricated from fibers or whiskers. In general, fibrous porous materials are known to exhibit improved strength owing to fiber interlocking, crack deflection and/or pullout [251]. Namely, porous bioceramics with well-controlled open pores were processed by sintering of fibrous particles [212]. Finally, superporous (~ 85 % porosity) bioceramics were developed, too [231–233]. Additional information on the processing routes to produce porous ceramics can be found in the literature [252].

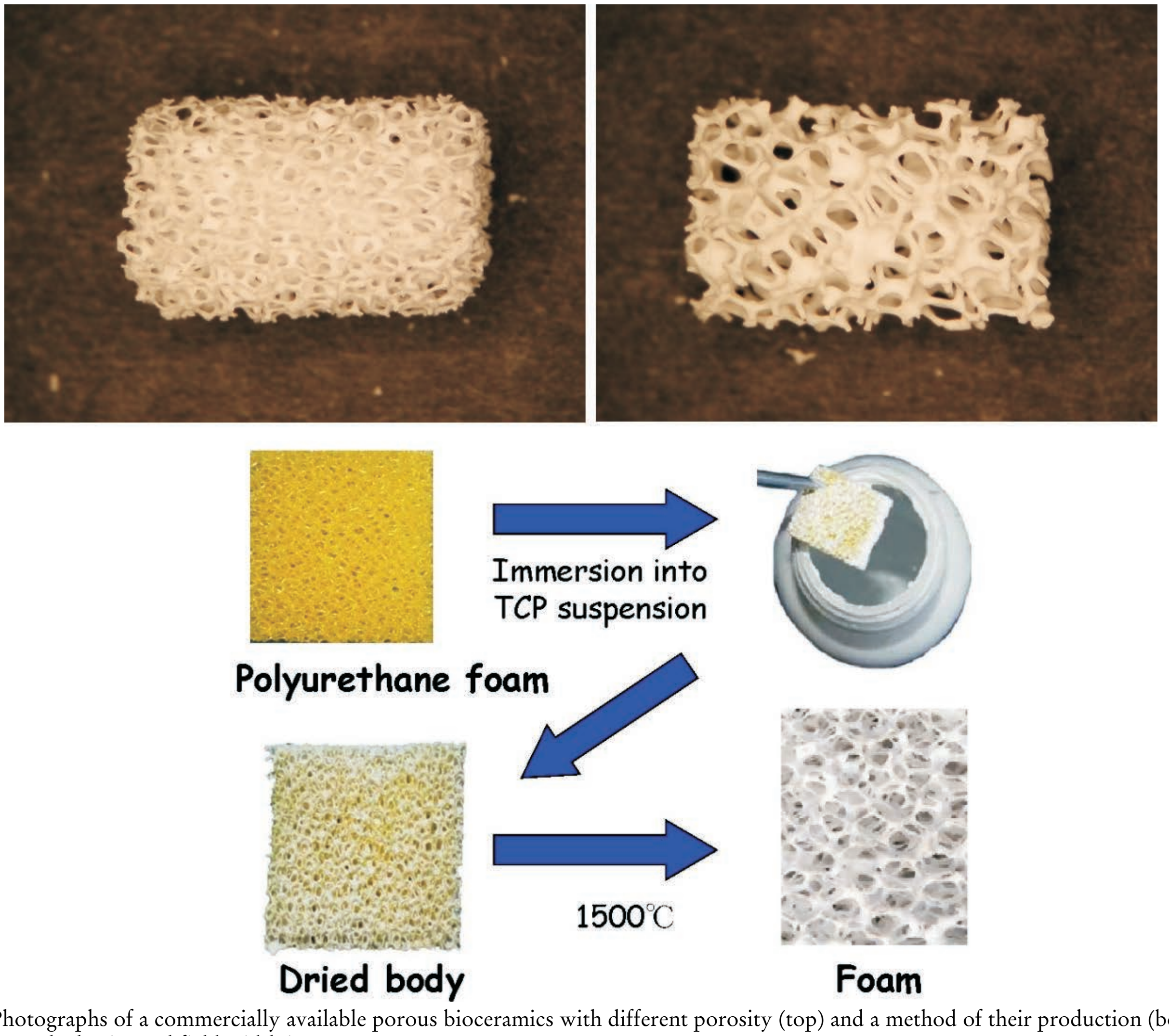

Fig. 5: Photographs of a commercially available porous bioceramics with different porosity (top) and a method of their production (bottom). For photos, the horizontal field width is 20 mm.

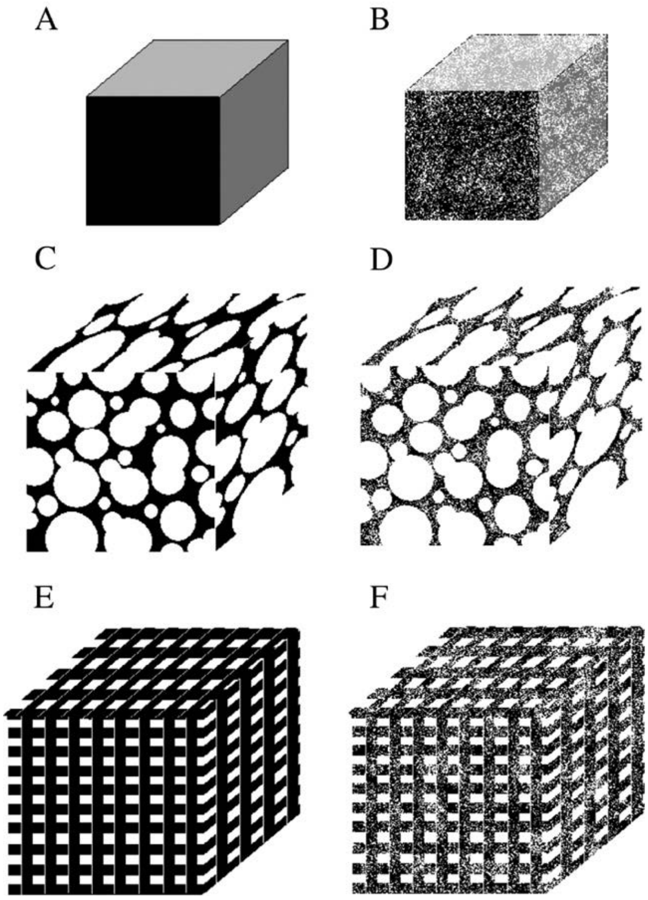

Fig. 6: Schematic drawings of various types of the ceramic porosity: A – non-porous, B – microporous, C – macroporous (spherical), D – macroporous (spherical) + micropores, E – macroporous (3D-printing), F – macroporous (3D-printing) + micropores. Reprinted from Ref. [189] with permission.

Bioceramic microporosity (pore size < 10 μm), which is defined by its capacity to be impregnated by biological fluids [253], results from the sintering process, while the pore dimensions mainly depend on the material composition, thermal cycle and sintering time. The microporosity provides both a greater surface area for protein adsorption and increased ionic solubility. For example, embedded osteocytes distributed throughout microporous rods might form a mechanosensory network, which would not be possible in scaffolds without microporosity [254, 255]. Bioceramics with nano-dimensional (< 100 nm) pores might be fabricated as well [256–260]. It is important to stress that differences in porogens usually influence the bioceramics' macroporosity, while differences in sintering temperatures and conditions affect the percentage of microporosity. Usually, the higher the sintering temperature is, the lower both the microporosity content and the specific surface area of bioceramics are. Namely, hydroxyapatite bioceramics sintered at ~ 1200 °C shows significantly less microporosity and a dramatic change in crystal sizes if compared with that sintered at ~ 1050 °C (Fig. 7) [261]. Furthermore, the average shape of pores was found to transform from strongly oblate to round at higher sintering temperatures [262]. The total porosity (macroporosity + microporosity) of bioceramics was reported to be ~ 70 % [263] or even ~ 85 % [231–233] of the entire volume. In the case of coralline hydroxyapatite or bovine-derived apatites, the porosity of the original biologic material (coral or bovine bone) is usually preserved during processing [264]. To finalize the production topic, creation of the desired porosity in bioceramics is a rather complicated engineering task and the interested readers are referred to the additional publications on the subject [57, 136, 234, 265–273].

Regarding the biomedical importance of porosity, studies revealed that increase of both the specific surface area and pore volume of bioceramics might greatly accelerate the in vivo process of apatite deposition and, therefore, enhance the bone-forming bioactivity. More importantly, precise control over the porosity, pore dimensions and internal pore architecture of bioceramics on different length scales is essential for understanding the structure-bioactivity relationship and the rational design of better bone-forming biomaterials [271, 274, 275]. Namely, in antibiotic charging experiments, bioceramics with nano-dimensional (< 100 nm) pores showed a much higher charging capacity (1621 μg/g) than that of a commercially available bioceramic (100 μg/g), which did not contain nano-dimensional porosity [267]. In other experiments, porous blocks were found to be viable carriers with sustained release profiles for drugs [276] and antibiotics over

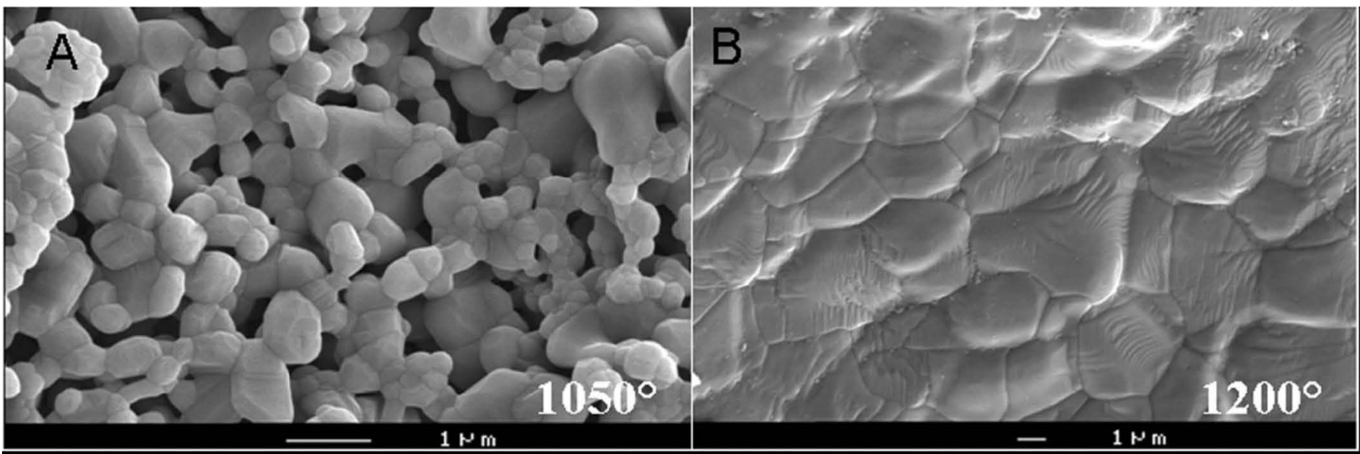

Fig. 7: SEM pictures of hydroxyapatite bioceramics sintered at (A) 1050 °C and (B) 1200 °C. Note the presence of microporosity in A and not in B. Reprinted from Ref. [261] with permission.

12 days [277] and 12 weeks [278], respectively. Unfortunately, porosity significantly reduces the strength of implants [58]. Thus, porous implants cannot be loaded and are used to fill only small bone defects. However, their strength increases gradually when bones ingrow into the porous network of implants [279–282]. For example, bending strengths of 40 – 60 MPa for porous implants filled with 50 – 60 % cortical bone were reported [279], while in another study ingrown bone tissues increased strength of porous bioceramics by a factor of 3 to 4 [281].

(5) Bioceramic scaffolds

Philosophically, the increase in life expectancy requires biological solutions to all biomedical problems, including orthopedic ones, which were previously managed with mechanical solutions. Therefore, since the end of 1990s, biomaterials research focuses on tissue regeneration instead of tissue replacement [283]. The alternatives include use of hierarchical bioactive scaffolds to engineer in vitro living cellular constructs for transplantation or use of bioresorbable bioactive particulates or porous networks to activate in vivo the mechanisms of tissue regeneration [284, 285]. Thus, the aim of bioceramics is to prepare artificial porous scaffolds able to provide the physical and chemical cues to guide cell seeding, differentiation and assembly into 3D tissues of a newly formed bone. Particle sizes, shape and surface roughness of the scaffolds are known to affect cellular adhesion, proliferation and phenotype [286–291]. Additionally, the surface energy might play a role in attracting particular proteins to the bioceramic surface and, in turn, this will affect the cells' affinity to the material. More to the point, cells are exceedingly sensitive to the chemical composition and their bone-forming functions can be dependent on grain morphology of the scaffolds. For example, osteoblast functions were found to increase on nanodimensional fibers compared to nanodimensional spheres because the former more closely approximated the shape of biological apatite in bones [292]. Besides, a significantly higher osteoblast proliferation on hydroxyapatite bioceramics sintered at 1200 °C as compared to bioceramics sintered at 800 °C and 1000 °C was reported [293]. A schematic drawing of the key scaffold properties affecting a cascade of biological processes occurring after implantation of calcium phosphate bioceramics is shown in Fig. 8 [294].

VII. Clinical Experience

To date, not many publications are known on clinical application of cell-seeded bioceramic scaffolds for bone tissue engineering in humans. Namely, Quarto et al. [295] were the first to report a treatment of large (4 – 7 cm) bone defects of the tibia, ulna and humerus in three patients from 16 to 41 years old, where the conventional surgical therapies had failed. The authors implanted a custom-made unresorbable porous hydroxyapatite bioceramics seeded with in vitro expanded autologous bone marrow stromal cells. In all three patients, radiographs and computed tomographic scans revealed abundant callus formation along the implants and good integration at the interfaces with the host bones by the second month after surgery [295]. In the same year, Vacanti et al. [296] reported the case of a man who had a traumatic avulsion of the distal phalanx of a thumb. The phalanx was replaced with a specially treated natural coral (porous hydroxyapatite; 500-pore ProOsteon) implant that was previously seeded with in vitro expanded autologous periosteal cells. The procedure resulted in the functional restoration of a stable and biomechanically sound thumb of normal length, without the pain and complications that are usually associated with harvesting a bone graft.

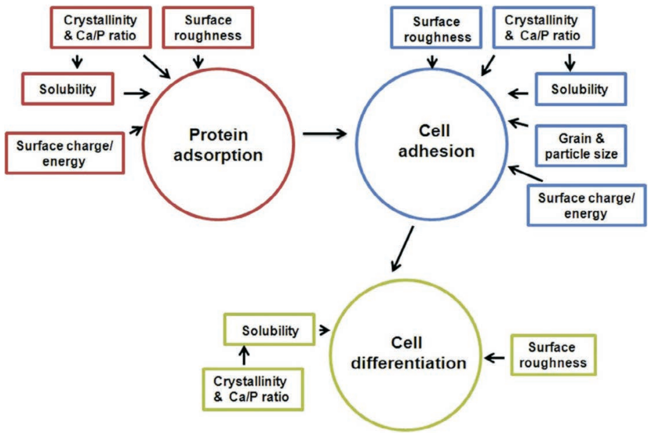

Fig. 8: A schematic drawing of the key scaffold properties affecting a cascade of biological processes occurring after implantation of calcium phosphate bioceramics. Reprinted from Ref. [294] with permission.

Morishita et al. [297] treated a defect resulting from surgery of benign bone tumors in three patients using porous hydroxyapatite bioceramics seeded with in vitro expanded autologous bone marrow stromal cells after osteogenic differentiation of the cells. Two bone defects in a tibia and one defect in a femur were treated. Although ectopic implants in nude mice were mentioned to show the osteogenicity of the cells, details such as the percentage of the implants containing bone and at what quantities were not reported. Furthermore, cell-seeded scaffolds were found to be superior to autograft, allograft or cell-seeded allograft in terms of bone formation at ectopic implantation sites [298].

An innovative appliance named the stem cell screen-enrich-combine(-biomaterials) circulating system (SECCS) was designed in another study [299]. In that study, 42 patients who required bone graft underwent SECCS-based treatment. Their bone marrow samples and calcium phosphate granules were processed in the SECCS for 10 – 15 minutes, to produce composites. These composites were grafted back into bone defect sites. The results showed 85.53 % ± 7.95 % autologous mesenchymal stem cells were successfully screened, enriched, and seeded on the bioceramic scaffolds synchronously. Clinically, all patients obtained satisfactory bone healing [299].

Besides, it has been hypothesized that dental follicle cells combined with calcium phosphate scaffolds might become a novel therapeutic strategy to restore periodontal defects [300]. In yet another study, the behavior of human periodontal ligament stem cells on a hydroxyapatite-coated genipin-chitosan scaffold in vitro was studied followed by evaluation on bone repair in vivo [301]. The study demonstrated the potential of this formulation for bone regeneration.

To conclude this section, one must mention that bioceramic scaffolds are also used in veterinary orthopedics to promote animal bone healing in areas in which bony defects exist [302, 303].

VIII. Conclusions

Bioceramics have already become an integral and vital segment of our modern health care system. Therefore, in this section, the general information on the subject has been collected and summarized. Briefly, among the available types of bioactive and bioresorbable bioceramics, both pure and ion-substituted calcium phosphates and related composites currently are largely used for bone regeneration applications. These materials offer a large variety of compositions and/or structures according to their stoichiometry, the substitution elements' nature and content, the crystallinity and the crystal dimensions with the variable and adjustable osteoconductive and/or osteoinductive properties. At present, calcium phosphates are commercially available in different dimensions and shapes such as powders, granules, porous scaffolds, coatings, injectable and self-setting formulations. In addition, for a long time after their discovery by Hench in 1969, various types of bioactive glasses have also been commercialized for bone grafting purposes, while the recent developments are mainly devoted to sol-gel processing allowing achievement of larger composition ranges at lower temperature treatment and to the performance of coatings on various substrates. The subsequent development of bioactive glass ceramics was carried out to enhance the mechanical properties of bioglasses and led to satisfactory commercial products for small-bone replacements [282].

Regarding bioinert bioceramics, they are currently used as permanent load-bearing parts and comprise inert oxides like alumina, stabilized zirconia, spinel, related micro- or nano-composites and, since recently, non-oxide bioceramics such as silicon nitride and carbide. Many different products prepared from alumina, zirconia and composites are successfully applied for dental restoration and orthopedic devices. The main innovations in progress concern two different aspects: the material and the processing techniques. Concerning the material aspect, research is focused on the development of a particular microstructure favorable for better mechanical properties, the use of new stabilizer ions for tetragonal zirconia and cermet compositions. For the fabrication methods, the novelties concern both additive and subtractive manufacturing techniques recently applied to ceramics materials and a promising reduction in time consumption [282].

Nevertheless, in all known fields of bioceramics, in order to induce higher bioreactivity, improved mechanical properties and/or better localized drug delivery abilities, a general tendency to used nano-scaled particles and/or grains can be observed. Thus, elaboration and manufacturing of the nano-dimensional and nano-crystalline bioceramics appear to be the hot point of current research and development.

Compliance with Ethical Standards

There are no potential conflicts of interest.

There is no research involving human participants and/or animals (this is a review).

There is no informed consent because I am a single author.

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