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Composites and Hybrid Materials Used for Implants and Bone Reconstruction: a State of the Art

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Abstract

This work presents a review, covering the years 2007 to 2020, on the main composite and hybrid materials on which it is investigated with the aim of developing medical applications, such as preoperative personalized bone implants. Attention is directed to the general qualities that these composite materials must have, from the physical-mechanical and clinical point of view, although occasionally other properties are also discussed. Most of the results that are presented have been obtained in experiments carried out with animal models, the main limitations that are faced when evaluating one or another type of implant material are also considered. The fundamental result of the present work is that it is not feasible to establish a predominance of some materials over others. Nevertheless; the synthesis of nano-hydroxyapatite, due to its similarity to natural bone apatite, should be present in any variant of composite material for bone implants.

Keywords: bone implant; osteogenesis; functional properties; bio-compatibility

1 Introduction

In the Rodas-Rivera article [1], it is mentioned that the pioneering research in reconstructive orthopedics dates to approximately 1911, when stainless steel with iron content was applied to immobilize bone fractures in the practice of traumatology. Such a procedure resulted in many drawbacks, from a clinical point of view, due to the deleterious effects of the high corrosion of the material. Subsequently, the vitallium alloy, which does not contain iron (around 1932), and titanium came into use around 1940. As a breaking point in the boom in metal-based orthopedic implant applications development, the works of Brånemark P-I., recognized as the father of contemporary dental implantology, are considered.

Perhaps the dental bone problem is the most documented in terms of bone repair. For the present review, the work of the authors Vallet-Regí and Arcos [2], who dedicated a chapter of their book to the methodological study of bone as a biological hybrid nanostructured material could be established as a starting point; they also study bio-mimetic materials for bone repair, classifying them into the class I and II hybrid materials. The objective of these authors revolved around the synthesis and description of the properties of organic and inorganic hybrid materials for dental bone applications.

Replacing a bone in an artificial way has become a viable solution to face or solve the difficulties that arise with xenograft, allograft, and autograft techniques, mainly related to the rejection of the implant due to the body's autoimmune reactions. Although autograft, for example, has important advantages due to the absence of an autoimmune reaction, the induction of osteogenesis brings with it serious limitations, such as those discussed in [3, 4]. Something widespread is to use the fibula to replace some other bone structure, but such practice can cause, for example, neurovascular injury, pain at the donor site, hematoma, an infection.

The main inorganic component in mammalian teeth and bone is hydroxyapatite, and on a nanometric scale, this material favors the adhesion of bone cells: osteoblasts, which are responsible for the synthesis of their matrix and are responsible for their growth and development. Carrying out an artificial bone replacement successfully depends, among other factors, on the characteristics of the prosthesis surface, since this is the initial interaction zone between the natural tissues of the living being and the constituent material of the implant. A process of integration between both "materials" is needed, first in that interface. For this reason, a contact surface is required that promotes the physiological activity of the osteoblasts.

The materials that have been studied and applied in bone implants are dissimilar. And apparently, collagen-hydroxyapatite compounds occupy a special place, whose fundamental advantage is the control of their biological and physicochemical properties [5].

The materials studied and tested to be used in bone implantology can be grouped into metallic and polymeric. However, it could be said that a clear dividing line is not established, because ceramic materials, glass, carbon fiber, and combinations of some of them, that is, composite materials in general, have also been studied with the same purpose. In this work, reference is made to metallic and nonmetallic materials. The use of one or the other has been subject to specific purposes. However, in general, the established requirements revolve around: biocompatibility, non-irritability of tissues, and non-toxicity; that are bio-inert and chemically stable [6]. Additionally, certain properties associated with the states of load, tension, and deformation fields are required; depending on the design and the functions to be performed by the implant, once placed. An attempt is made to guarantee such performance

with the help of these combinations between different types of materials. An additional combination of demands in bone restoration requires achieving resistance, hardness, and flexibility typical of composite biomaterials[1], capable of largely covering these demands, as presented in [6], where its authors state that this challenge is accompanied by strong biocompatibility, bioactivity and osteoconductivity.
Another important aspect in bone restoration is the vascularization of the artificial bone because this contributes to the acceleration of the adhesion of the implant to the muscular and bone tissues. Thus, regardless of the type of composite material used, different three-dimensional bioprinting methods layer by layer have come to light, to obtain a "tissue" as similar as possible to the complex microstructure of real bone tissue. An important review regarding the results in the above direction is reported in [7].
Advances in the application of artificially vascularized bone implants have been strongly linked to experimentation with animal models. And in this case, there are drawbacks because none of these models corresponds 100% to the human condition. Due to the lack of consensus regarding the use of test animals, it is also not possible to generalize the results obtained for similar problems, because they have been observed in models that differ significantly. An interesting debate about this questioning is presented by the authors Rücker, Kirch, Pullig, and Walles in [8].
The objective of this review is to pay attention to the different alloys and composite materials that have been developed to produce prostheses and bone implants, beyond the different sintering techniques applied to obtain the desired properties. The article is structured as follows: in the next section the materials and methods applied in the investigation are exposed. Then the metallic compounds and alloys that were constituted in proposals for the replacement of human bones, mainly in the maxillary region and the head, are summarized. In the third section, nonmetallic compounds are considered, mainly make of the combination of polymers and ceramics. The discussion, conclusions, and challenges derived from the analysis carried out are set out below. The proposed review gains importance under these clearly defined objectives: the required properties of the composites of a replacement bone tissue and the presentation of a range of materials developed from these requirements.
The next Figure 1 shows the graphical scheme that the review has followed.

[1]A biomaterial is defined as a material designed to interface with biological systems at in order to evaluate, support or replace any tissue, organ or function of the body (II International consensus conference on biomaterials, held in Chester, England, 1991)

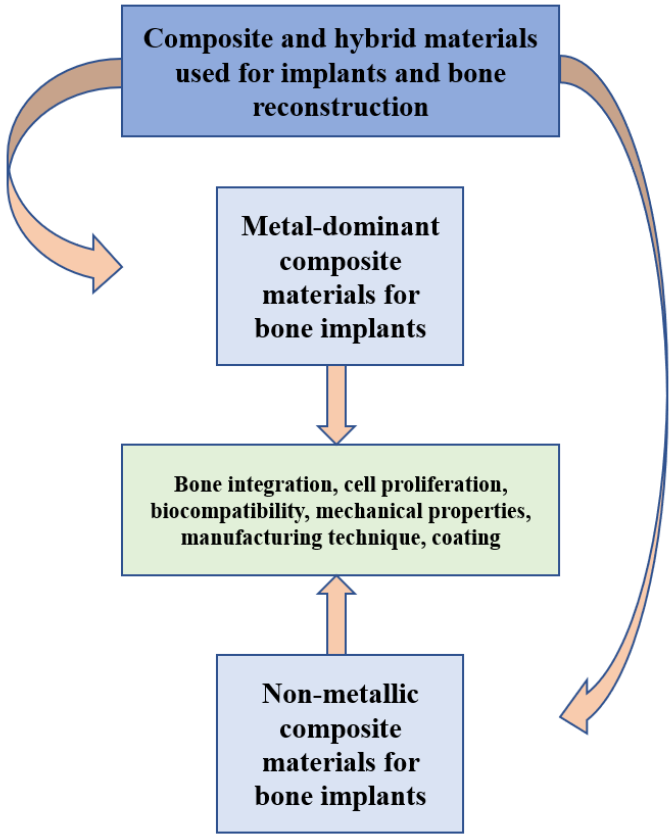

Figure 1: Graphic outline of the review.

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2 Materials and methods

For the development of this work, the MEDLINE database was consulted (through the open access search engine PubMed, which also provides access to other journals that do not belong to this database), which allows consulting articles from the area biomedical. According to Wikipedia, "MEDLINE has about 4,800 journals published in the United States and in more than 70 countries" [9]. In addition, to know the main utilities of this database, examples of its use and, recommendations for it, could be consulted the article [10].
Information was also obtained with the help of the Library Genesis (LibGen) search engine, which allows access to free scientific content in PDF, DJVU, and other formats; from numerous academic publishers such as Cambridge UP, Springer, Oxford UP, Elsevier ScienceDirect, etc. [11] (Information on how to use this library can be found at [12]); and Google Scholar, which specializes in the search for scientific academic information in general [13].

The criteria for inclusion or exclusion of works in the searches carried out were based, first, on the year of publication of the articles. The interval between the years 2007 to April 2020 approximately was considered. Second, keywords related to the research field of interest were considered: fundamental materials used for the development of bone implants. Additionally, to a lesser extent, the intersection of this central issue with other edges of the problem, such as additive manufacturing and experimental models, was considered.

2.1 Applied methodology

The central criterion of article eligibility for the review has been the keywords considered for the work. The central keyword is bone implant. Then, the words osteogenesis, bio-compatibility, and functional properties, in that order, have been relevant. Thus, this criterion has been applied regardless of the database used as a search path; always respecting the established time interval.
In addition, some review articles have been included ([14], [15]) for their conclusions related to the central theme of this work. Others papers that address the study of other candidate materials to be applied in bone reconstruction processes and as sources for obtaining apatite ([16], [17], [18]); or where some difficulty or scientific challenge is reported regarding the development of bone implants ([19]).

3 Metal implants

The lack of biological compatibility has been the main challenge faced by metallic bone implants. However, this drawback has been largely overcome thanks to the development of bioactive materials and coatings obtained from them, which has allowed bone cells to find adherence to the metal and to reproduce. It could be stated that the trend, in terms of the application of pure metallic implants, is downward.
The main metals that have been studied and used in the development of prostheses and bone implants have been titanium, iron, aluminum, and their alloys. Several investigations have been focused on the behavior of the mechanical properties of these materials, in addition to the biocompatibility of the bone being replaced, depending on the functions within the human body. For example, in a 2007 communication by Hohenhoff G. and his colleagues [20], to achieve the appropriate elasticity of the implant, they propose to carry out a comparison between the elastic stiffness of the bone and the implant. A year later, results are reported that enhance the benefits of hydroxyapatite (HA) combined with titanium.
In [21], the use of titanium implants that were electropolished as scaffolds or substrates for nano-hydroxyapatite (nano-HA) is reported. Normal titanium

specimens and with the coating, were placed in the surgical sites of rabbit tibiae, leaving a space of $0.35\,mm$ on each side. The idea was to test the possibility of bone self-filling in the affected area, considering that it is not possible to achieve the optimal surgical adjustment during surgery. Then, with atomic force microscopy and after four weeks of healing, the similarity was verified in terms of bone formation, both for the electropolished implants and those coated with nano-HA. The results obtained did not allow to conclude that nano-HA chemistry and nano topography contributed to better bone formation in case of these healing models.

The results of López-Heredia et al. [22] are found in a similar line. These researchers, also in 2008, obtained macro-porous titanium implants with the help of rapid prototyping, controlling their shape and porosity. In short, two implants with pore diameters of $800\,\mu m$ and $1200\,\mu m$, respectively, were studied; in both cases with a porosity of around 60%, a compressive strength of $80\,MPa$ and a Young's modulus of $2.7\,GPa$; values all similar to those of cortical bone. By placing such implants bilaterally in the femoral epiphysis of 15 rabbits, after 3 to 8 weeks, the existence of abundant bone formation in the interior of these was verified. In the case of $Ti - 1200$, the bone increase was $23.9\% \pm 3.5\%$ and $10.3\% \pm 2.8\%$ on each side. While the amount of bone directly seated on the titanium was $35.8\% \pm 5.4\%$ and $30.5\% \pm 5.0\%$, respectively. This study suggested the candidacy of the rapid prototyping technique for successful application in orthopedics and maxillofacial. In addition, the need for considerations regarding animal bioethics and the interference that human beings have in it is present.

Subsequently, in 2015, three patients with different bone pathologies received implants printed in titanium, and the corresponding follow-up was carried out (see [23]). In that article, the entire workflow of the applied impression technique was described, which was electron beam melting (EBM), and it was concluded that the applied method is useful for obtaining personalized titanium prostheses and could improve the effectiveness of limb restoration surgery. According to the history of 3D printing, by 2012, the first mandibular prosthesis implant was achieved with this technology [13]. With the onset of the rise of 3D printing and rapid prototyping, possible adverse effects on human health also take on greater importance. Special attention was paid to the toxic effects of titanium dioxide (TiO_2) and nano-hydroxyapatite particles. In the review by the authors Wang J., Wang L. and Fan Y. [14], it is stated that the small portions produced by wear and tear could form complex particles protein and interact with blood components that, thanks to biological mechanisms, would cause fibrous capsule formation in local tissue. These particles could also reach the bloodstream and lodge in internal organs, affecting them. All this highlights the need to develop bio-mimetic materials with better biocompatibility properties.

A relevant study was carried out on the alpha-beta titanium alloy (Ti_6Al_7Nb) that contains 6% aluminum and 7% niobium [24]. Five types of scaffold-like structures, named A1, A2, A3, B, C, respectively, were developed using the additive manufacturing technique of selective laser fusion. The geometry and mechanical characteristics of the implants were designed based on data obtained from direct medical computed tomography scans. The results presented in the work show the correlation between the technological parameters applied for printing the structures and the functional characteristics obtained. The potential of additive manufacturing to achieve adequate levels of precision and complex geometry, with specific and desired mechanical properties, was confirmed. The best results were obtained for structure A3 (square-shaped), which showed the lowest deviation range and the lowest anisotropy in terms of mechanical properties.

In 2018, the article by Popov, Muller-Kamskii, Kovalevsky, Dzhenzhera, Strokin, Kolomiets, and Ramón [15] was published. These authors carried out a compilation and review of cases in which titanium implants were applied. In addition, they analyze the entire process, from performing the patient's tomography to implant placement. Continuing with a titanium alloy, specifically Ti_6Al_4V whose composition is completed with aluminum and vanadium, in [25], it is reported on a hydroxyapatite coating combined with 1% magnesium oxide (MgO) and 2% silver oxide (Ag_2O), with the aim of improving the biological and antibacterial properties of the implant, coated using the laser engineered net shaping technique (LENS) and plasma spray deposition. These types of coatings favor osteoconductivity; however, the metal-HA interface is affected by the difference between the respective coefficients of thermal expansion. It was also observed that the application of the LENS technique increases the adhesive bond strength in the contact zone by up to 52%, which in turn reduces the rapid cooling and balances the coefficient of thermal expansion between the plasma coating and the substratum. On the other hand, the MgO, Ag_2O compounds did not affect the adhesive bond, nor did they affect the proliferation of bone cells responsible for synthesizing the bone matrix. However, they did contribute positively to the long-term release of silver and to the prevention of non-aseptic loosening of the implants.

Another result related to the Ti_6Al_4V alloy is reported in [26]. In this case, the authors of the article obtain porous scaffolds for maxillofacial application, applying selective laser melting (SLM). The printed prototypes were evaluated in terms of microstructure, specific mechanical properties and stress characteristics in the structure of meshes connected by rods, digitally performing layered cuts and by analysis with the Finite Element Method (FEM). The main results of this research refer that the SLM technique provides adequate printing quality and appropriate pore size, with good connectivity and less appearance of defects in the form of cracks. The mechanical response of the scaffolds was consistent with the properties of bone tissue: high strength and low Young's modulus. On the other hand, depending on the deformations caused by the different directions of the abutment and the size of the pores, it is possible to establish the disposition of the rod in the implant depending on the loads to which it will be subjected.

In [27], the application of the sol-gel[2] method to coat Ti_6Al_4V substrates with the nanostructured glass ceramic akermanite ($Ca_2MgSi_2O_7$) is reported. The presence of Mg is known to promote osteoblast proliferation and adhesion. It was evidenced that the akermanite phase can be synthesized at $900°C$ from a gel precursor by calcination. Through the methods of scanning, X-ray diffraction, and transmission electron microscopy, the structural morphology and phase composition of the coating were evaluated, confirming the presence of a homogeneous and flawless nanostructure. In vitro tests revealed a greater stimulation of cell propagation, when compared to uncoated samples. In other words, the synthesized coating of $Ca_2MgSi_2O_7$ is suitable for promoting cellular interaction with bone prostheses.

Continuing with the results of research related to the application of Ti_6Al_4V in implantology, reference is made to the work of Cheong and his team [28]. This time the objective was to evaluate how implant placement and the distribution of stress on it affect the bone growth pattern. It was also of interest to know how stress is altered in implants as a function of variations in the density of the tissue within the pores. By FEM analysis phenomenological modeling (remodeling), partial bone formation was predicted for laser sintered Ti_6Al_4V porous implants with two pore sizes: 700 and 1500 μm. The model was applied to an ovine condylar bone with defects, so the results of the FEM analysis could be compared with histological results in vivo. The main findings of this research were that bone remodeling reduces the Von Mises maximum effort by more than 20%, which protects the implant, in addition, the maximum effort of this does not reach the safe limits for fatigue of the alloy manufactured with additive technique. It is also important that the initial rehabilitation observes safe limits for the applied loads, while at the same time stimulating bone formation and preventing implant failure.

The same group of researchers, the authors of [28], continued their work with the Ti_6Al_4V alloy and the same pore sizes (700 and 1500 μm). In this case, the implants were electrochemically coated with three different ionic substitutions: hydroxyapatite (HA), silicon hydroxyapatite (SiHA), and strontium hydroxyapatite (SrHA); in addition, in vivo experimentation was performed on ovine femoral condylar defects (see [29]). The results showed that implants coated with HA and SrHA caused greater osseointegration, when compared with the

[2]Method of producing solid materials from small molecules. It consists of the conversion of monomers into a colloidal solution (sol) that acts as a precursor to an integrated network (or gel) of discrete particles or cross-linked polymers. It is used for the manufacture of metal oxides, especially silicon and titanium.

uncoated control models and models coated with HA and sprayed with plasma. On the other hand, no significant differences were observed in terms of pore size. Therefore, osseointegration of porous implants is more influenced by the presence of a bioactive coating and its rigidity than by the pore size.
Another titanium-based compound used as a coating for bone implants is titanium dioxide (TiO_2). In [30], it is reported on the effect of titanium dioxide nanotubes on the behavior of murine pre-osteoblastic cells MC3T3-E1 (well-established clonal osteogenic cell line, which provides an excellent model for the study of gene expression patterns in osteoblast differentiation). The fact that TiO_2-coated substrates provide the implant with a better ability to osseointegration and drug delivery opens great horizons for this type of coating. However, although the influence of the nanotube diameter on cell behavior has been well studied, the effects of the lateral space of the nanotubes remain unknown. This problem is studied by Necula M. G. and his team, for nanotubes of $78\,nm$ in diameter and lateral spaces of $18\,nm$ and $80\,nm$ (to form two variants). The researchers found that nanotube spacings have similar effects on cell proliferation in vitro, and compared to what occurs on a flat, titanium-only surface. Nevertheless, the structure with $80\,nm$ separation between nanotubes positively affects other aspects of cell dissemination, such as adhesion, morphology, organization of the cytoskeleton, focal adhesion patterns, and osteogenic differentiation. In other words, it would be worth including this new variable (space between TiO_2 nanotubes) in research related to the design and optimization of titanium-based implants.
Continuing the titanium coatings and their variations, perovskite, or calcium titanate ($CaTiO_3$) is an inorganic compound approached in terms of implantology by Chen and his team [31]. These researchers found that, after undergoing a hydro-thermal treatment at $175°C$ for 24 hours, the perovskite began to form surface crystals. And that to reduce the formation of these crystals and promote the formation of apatite, less time and the same temperature were required for the heat treatment. In this work, in vitro analyzes were performed with MC3T3-E1 cells and two types of coatings: micro-arc oxidation (MAO) and nano/micro hierarchical bioceramic coatings. The normalized alkaline phosphatase (ALP)[3] activities of MC3T3-E1 cells were $4.51\,\mu mol \pm 0.26\,\mu mol$ and $7.36\,\mu mol \pm 0.51\,\mu mol$, respectively, of p-NP protein/mg. That is, with the experimented coatings, a statistically significant ALP activity was observed for MC3T3-E1 cells; the hierarchical structure (nano+micro) proposed favors osteoblast proliferation and osteogenic differentiation, so such superficial treatments are invoked as promoters of osseointegration that every bone implant should guarantee.

[3]Enzymes that are present in almost all tissues of the body, being particularly high in bones, liver, placenta, intestines, and kidneys. Both its increase and decrease in plasma have clinical significance.

It is also important to consider the infectious conditions that can be caused by the implant. One of the most common failures of bone prostheses is caused by infection of biofilms, that is, immobile microbial communities that colonize and grow on the surfaces of medical implants, promoted by self-produced extracellular polymeric substances. Titanium has also played a role in research on this problem. Thus, in [19], Reigada, Pérez-Tanoira, Patel, etc., assess the potential application of anti-biofilm compounds that could be integrated into implants. The tests were carried out in vitro; but in scenarios very close to reality. The investigations were developed on a competition model, in which mammalian osteogenic sarcoma cells ($SaOS-2$), widely used to test new therapies against bone cancer, and Staphylococcus aureus coexist on a titanium surface. And it was also tested on preconditioned titanium with a high concentration of serum protein, the most abundant in blood serum, which prevents the transfer of fluid from the blood vessels to the tissues. The idea of these authors was to check whether the protective action previously observed when incubating titanium with $SaOS - 2$ cells improved in this way. This study revealed that a derivative of docosahexaenoic acid (DHA), which is an omega 3 fatty acid and one of whose functions is to provide the body with a reduced inflammatory response; specifically, DHA1, it would be potentially useful to coat biomaterials for internal applications of the human body, and to avoid the formation of biofilms.

One more metallic element, suggested for bone implants, is iron. In [32], the authors state that the combination of calcium silicate particles with iron would have good options for the development of biodegradable bone replacements. In this case, the calcium silicate behaves as an effective reinforcing phase to join iron or iron-based alloys, improving the performance in terms of degradation and biological quality. To reach such conclusions, these researchers obtained the composite through powder metallurgy processes; then they performed microstructure characterization, described the mechanical properties, observed apatite deposition, biodegradation behavior, and cell attachment and surface proliferation of these.

Strontium (Sr), calcium (Ca), zinc (Zn), and magnesium (Mg) have also been incorporated into biomaterials to improve bone regeneration. In [16], the incorporation of Sr into the network based on dicalcium silicate (C_2S) is reported as a potential candidate for self-adjusting bioactive bone cement for orthopedics and stomatology. Through chemical coprecipitation, $Sr - C_2S$ powders were prepared in a molar ratio of $0.3\% - 6.8\%$, and the resulting cement showed good self-setting. It was also found that its apatite mineralization capacity is similar to that of bone cement based on C_2S. Such properties suggest that the $Sr - C_2S$ combination is self-stable for bone regeneration. Although it is recommended to develop additional research on its biological qualities.

Regarding Ca and Mg, the researchers Park, Hanawa, Chung, in [33], refer to the indistinct use of their ions, by means of a wet chemical treatment, to alter the micro-rough surface of an implant of titanium. The comparison of the results showed that the modification of the implant surface with Mg ions favors a better early osteogenic differentiation of mesenchymal stem cells, and the presence of these in an implant gives it better adhesion properties (especially plastic), and in vitro differentiation and proliferation. However, magnesium alloys corrode within the human body before, for example, a bone fracture heals. That is, corrosion occurs too fast. To try to avoid this inconvenience, in [34] the use of a biodegradable alloy of magnesium, aluminum, and zinc ($AZ91Mg$) is reported; whose surface is treated with the micro arc oxidation technique. This provides the formation of an intermediate layer on the alloy, which is then coated with a bioceramic nanocomposite based on bredigite (artificial zeolite), dioxide and fluorinated hydroxyapatite. This coating was carried out using the electrophoretic deposition technique, with which homogeneous coatings on metal of greater thickness are achieved. With this coating, the corrosion rate of $AZ91$ decreased from 0.57 ± 0.02 to $0.08 \pm 0.01\, mg/cm^2/h$, and at the same time there was a better bone regeneration that reached up to $56\% \pm 5\%$ (without the implant coating the regeneration was $27\% \pm 1\%$) and less inflammation of the surrounding tissue. Such results open new perspectives in relation to the application of Mg in implants and porous scaffolds based on this mineral. Regarding zinc (Zn), Yang H. and his team [35] fully evaluated binary combinations of this metal with magnesium (Mg), calcium (Ca), strontium (Sr), iron (Fe), copper (Cu), silver (Ag), manganese (Mn), and lithium (Li); as candidates for bone implants. These authors perform in vitro and in vivo experiments to study the mechanical properties, biodegradability, and biocompatibility of the respective alloys. It was found that the combinations of Zn with Li and Mg, in that order, exhibit the best role in terms of strengthening. And in general, adding amounts of Mg, Ca, Sr, and Li to Zn can lead to improvements in osseointegration, osteogenesis, and cytometability. It was also verified that for the alloy $Zn - 0.8Li - 0.4Mg$ the highest tensile strength is obtained ($646.69\, MPa \pm 12.79\, MPa$); while for $Zn - 0.8Li - 0.8Mn$ a higher elongation is obtained ($103.27\% \pm 20\%$). Thus, biodegradable, and biocompatible metals, based on Zn, with a resistance close to titanium in its pure state, are good orthopedic options in the case of loading applications. This study lays the foundations for future research regarding design strategies for bone implants based on Zn alloys.

Research has also been carried out on the use of steel as a material for implants. In [36], the authors address the problem of direct absorption of silicates by a hydroxyapatite - covered surface. A way to incorporate silicon into the coating is sought to improve the osseointegration of the implant. Thus, stainless steel discs, coated with HA and sprayed with plasma, were immersed in silica solution at different concentrations (between 0 and $42\, mM\, Si$), with neutral pH for 12 hours. The amount of silica absorbed by the surface was then measured once it was released from it. The changes of the surface characteristics were determined by atomic force microscopy (AFM) and by the measurement of the surface humidity. By applying staining, osteoblast cell adhesion was determined. The maximum absorption of Si by the HA-coated disk was observed for the concentration of $6\,mM$, and it was decreased with the increase of the Si concentration. Comparison of the highest and lowest Si adsorption values, performed by transmission electron microscopy (TEM), revealed an abundant presence of small amorphous nano-silica species. Such results, according to the researchers, suggest that amorphous nano-silica species, of adequate size, adhere to the surface of HA, modifying its properties, promoting in turn a greater cellular adhesion of the osteoblasts.

4 Nonmetallic implants

When the leading role of metals ceases to be fundamental, then polymers, ceramic materials, and others occupy that place. A kind of transition in the materials and techniques for obtaining bone prostheses is reflected in the article by Busuioc, Olaret, Stancu, Nicoara, and Jinga [17]. These researchers focus on the study of mineral scaffolds with controlled morphology and complex composition, and for this they use a polymeric template in the form of bands of non woven fibers obtained by electrospinning. The idea of the polymeric template is to guarantee a microstructure of adequate size, with an appropriate shape and arrangement of the pores, which will facilitate cell adhesion, proliferation, and differentiation. This process made it possible to obtain stable gelatinous structures in aqueous solutions, to which two types of mineral phases were added, namely, calcium phosphate deposited by chemical reaction and ultrasound irradiated barium titanate nanoparticles. This gave rise to hybrid compounds, which were then subjected to lyophilization and heat treatment to eliminate the scaffold template and consolidate the mineral phase as a possible material for the manufacture of implants with varied morphology. The richness of the results is enhanced by the fact that, by virtue of the heat treatment, the mineralogical composition changes from a mixture of brushite (hydrated calcium phosphate with additional hydroxyl anions) and hydroxyapatite to calcium pyrophosphate; while the microstructure mimics the fiber design for lower temperatures and is individualized as reinforced porous three-dimensional structures for higher temperatures.

In 2008, the work of Ziegler et al. [37] saw the light. These authors studied three types of porous carriers: hydroxyapatite biocrystal, alpha tricalcium phosphate (calcium phosphates have a chemical composition similar to the mineral phase of bone), and glassceramic. In this in vitro study, the implants were loaded with recombinant human bone protein (rh-BMP-2) and recombinant basic human fibroblast growth factor (rh-bFGF) in a determined concentration of phosphate buffered saline (PBS). In each case, the released growth factors were applied to $SaOS-2$ cells. The objective was to observe cell differentiation and proliferation after 3, 5, and 7 days of application of the load in each type of implant. The main finding of this experiment was related to the need to find a way to stabilize the proteins to achieve a prolonged osteoinductive and osteoproliferative potency of the growth factors, since time dependence was observed for the biological activity of the released growth factors of the synthetic implants studied, at least in the case of in vitro observations.

One more question of interest to researchers in the case of implants, is how osseointegration occurs in the natural bone-artificial bone phase. For example, in [38], the results of a study of computational simulation and medical imaging techniques are presented to estimate bone growth in cementless implants with rough coating. Lutz and Nackenhorst considered, bearing in mind that micro movements constitute a determining factor for osseointegration (their excess leads to the appearance of fibrous tissue), seven loads related to the usual movements of the implanted area. These researchers tested different combinations of parameters on the stiffness and thickness of the bone-prosthesis interface, making predictions regarding internal cell growth, thus opening the way for studies on the stability of a prosthesis.

An important difference regarding the use of metals and nonmetallic materials for bone implants is the processing temperature of the material to obtain these and the possible modification of the properties of the compound as a result. Thus, in [39], Bernstein and his team studied a compound based on β tricalcium phosphate ($\beta - TCP$), which is a proven graft biomaterial, uniformly combined with polycaprolactone (PCL), which is an aliphatic polyester biodegradable with a low melting point of around $60°C$ and a glass transition temperature of around $-60°C$. By immersing this combination in simulated body fluid, at room temperature and at a pressure of $2.5\,GPa$ (high), known as cold sintering, the researchers observed the formation of a bone-like layer of apatite in vitro. Such observations assumed the viability of this compound to be used in implantology.

In [40], Fu, Yang, Tan, and Song carried out a study focused on one of the greatest limitations in terms of biodegradable implantology of bone tissue: the lack of bioactivity. These authors found, in in vitro experiments with the MC3T3-E1 cell culture, that for microcarriers based on the composition of polylactic co-glycolic acid (PLGA), which is a copolymer with proven qualities of biodegradability and biocompatibility, and hydroxyapatite (HA), when graphene oxide (GO) is incorporated, giving rise to the new biodegradable microcarrier GO-PLGA/HA, immobilization of bone morphogenic protein 2 (BMP-2) is achieved, which plays an important role in the development of bones and cartilage, induces osteogenesis and promotes bone regeneration. In summary, once the BMP-2 protein was immobilized, the GO-PLGA/HA microcarriers showed superlative bioactivities to support the adhesion, proliferation and osteogenic differentiation of MC3T3-E1 cells; growth factor consumption decreased, and a long-term osteoinductive effect was achieved. GO-PLGA/HA has good quality as a bone graft.

For their part, Sakamoto, Okamoto and Matsuda, in [41], report on the use in maxillofacial surgery, of screw and plate systems, made from non-sintered compounds of hydroxyapatite and poly (L-lactic acid) (PLLA). The designation of such compounds is u-HA/PLLA, which are osteoconductive and biodegradable. In the case of larger surgeries, due to their resistance to compression, tricalcium phosphate (β-TCP) implants are usually used; but it is necessary to guarantee the stabilization of the implant. In the present work, six cases of patients who underwent bone tumor resection were reported, and in them the u-HA/PLLA compound was applied as a stabilizer of the low porosity β-TCP block, mechanically placed strong.

Another contribution related to hydroxyapatite corresponds to Lytkina and her team [42]. These authors report the results of a study related to bone implants in laboratory animals, based on this compound modified with zinc ions. The composition of the hydroxyapatite phase was established by the X-ray diffraction method (XRD); while the methods of scanning electron microscopy (SEM), electron probe microanalysis (EPMA) and low-temperature nitrogen adsorption (BET) were applied to study the surface properties of the phase. It was observed that zinc is distributed uniformly on the surfaces of all samples in the crystalline phase $Ca_5(PO_4)_3(OH)$ of hydroxyapatite. On the other hand, for the concentration of zinc $Zn_{0.5}HA$, the additional phase $\beta - Ca_3(PO_4)_2$ or $\beta - TCP$ is formed, which acts significantly on surfaces reducing the average size and volume of pores (if compared with single phase products). From the biological point of view, the existence of antimicrobial activity was verified, an important aspect regarding the prevention of concomitant infections when used as components for bone implants.

An alternative form of hydro-thermal synthesis of hydroxyapatite from the eggshell is collected in the article by Noviyanti et al. ([43]), in which it was also observed how temperature affects the crystallinity, purity and morphology of the resulting product. All these properties were analyzed using the methods XRD, scanning electron microscopy energy dispersive spectroscopy (SEM-EDS), TEM, and Infrared Fourier Transform (FTIR). The synthesis was carried out at temperatures of $200°C$ (HA-200) and $230°C$ (HA-230), respectively, for two days, obtained for the main HA phase, purity of 96.5% for HA-200 and 99.5% for HA-230. Furthermore, the observed structure was hexagonal with an average particle size of $92.61\,nm$, suitable for implantology. In addition, the Ca/P ratio was lower (2.29) for HA-230, which gives it an ad-

vantage because for vertebrate animals, the highest percentage of phosphorus is concentrated in the skeleton, and the optimal Ca/P ratio is between $2:1$ and $1:1$.
As is known, seventy percent of bone is made up of hydroxyapatite (also called bone mineral). Therefore, it is fair to highlight the preclinical study carried out by Paré and his collaborators [18]. These authors set out to determine different strategies for bone regeneration and experimenting with rats implanted 3D printed discs made up of biphasic calcium phosphate (BCP) and carbonated hydroxyapatite (CHA) with a minimal tricyclic periodic structure in critical size defects, with or without adding total bone marrow. That is, the combination of synthetic calcium phosphate with active substances and cells is studied. However, this idea is limited from a clinical point of view, when using processed stem cells and synthetic active substances such as, for example, recombinant human bone morphogenetic protein 2, because the adaptation of the composition and architecture of CaP. Despite this, the researchers evaluated bone regeneration in the defect. The results were compared with a standard procedure based on BCP granules and total bone marrow. New bone formation was observed at 7 weeks, significantly greater in the CHA discs combined with bone marrow than that observed in the defect treated with the standard procedure. Results indicating that CHA-based implants with minimal tricyclic periodic structure are potentially better, but further clinical investigation is required.
Another compound studied for implantology is polylactic acid (PLA). In [44], Nasrin and his team address the problem of the use of laminated compounds of PLA and chitin (a substance made of nitrogenous carbohydrates, white and insoluble in water, which is the main material from which the outer coating is formed from the body of arthropods) obtained from the shell of the shrimp cephalothorax. The researchers made PLA-reinforced chitin films using concentrations between 1% and 20% of PLA. Films were obtained by solvent casting process. Then, another laminating process was carried out on the films by hot pressing at a temperature of $160°C$, to obtain the chitin-PLA compound (LCTP: chitin-PLA composites). In this resulting laminated compound, the effect of the variation of the chitin concentration was observed. Applying different techniques, the surface morphology, physical-mechanical and thermal properties were evaluated. Electron microscopy images showed a good distribution of chitin in the compound, thermogravimetric analysis (TGA: thermogravimetric analysis) allowed to verify that the complete degradation of chitin, the PLA film, the PLA film reinforced with 5% chitin (CTP2), and the LCTP compound, always at a temperature of $500°C$, were respectively 98%, 95%, 87% and 98%. For the LCTP, a tensile strength of $25.09\,MPa$ was obtained (higher than that obtained for the pure PLA film: $18.55\,MPa$, and for the CTP2 film: $8.83\,MPa$). For the LCTP compound, a lower water

absorption was observed (variation of 0.265% -1.061% after 30 min to 24 h of immersion) than that observed for PLA and CTP2. It was also found that the increase in the chitin concentration produced an increase in the mechanical properties of the LCTP compound, observing a strong phase interaction between the polymer and the chitin. Likewise, the antimicrobial and toxicity properties of the compound were evaluated. In summary, the laminated LCTP composite showed important qualities: higher tensile strength, high strength and low elongation, and higher E modulus. Its thermal stability is adequate, with lower water absorption capacity and antimicrobial activity than PLA and CTP2, which make it suitable for use as a bone implant.

Ceramic has also been investigated for application purposes in implantology. A promising result for tissue engineering and orthopedics is reported in [45]. Banerjee, Bandyopadhyay, and Bose synthesized a new biphasic calcium phosphate ceramic to improve its bio-degradation properties, based on tricalcium phosphate (TCP) and calcium pyrophosphate (CP). The results of the study showed superiority of the TCP/CP combination when compared with the TCP and CP variants separately, in terms of resistance; it also showed a controlled resistance degradation in stimulated body fluid, from $62.2\,MPa \pm 2.1\,MPa$ to $40.5\,MPa \pm 1.0\,MPa$ in a period of 28 days. Likewise, the in vitro interaction study with human fetal osteoblasts showed the cytometability and good absorption capacity of the drug alendronate by the compound, which is used for the treatment and prevention of osteoporosis.

Carbon fibers and the semicrystalline thermoplastic technical polymer, known as polyetheretherketone (PEEK), are also added to ceramics as a material for implants. Petersen, in [46], using a rat tibia model, compares a bisphenol-epoxy composite rod (bisphenol A is used mainly in the manufacture of polycarbonate plastics and epoxy resins; the latter are a class of reactive polymers and prepolymers, containing epoxide groups[4]), reinforced with carbon fiber, with a diameter of $1.5\,mm$; with a screw of similar dimensions made of Ti_6Al_4V, for holding bone implants. The main findings of this research were that carbon fiber in the polymeric matrix composite acts as an electrically conductive microcircuit. Reliability is demonstrated experimentally in terms of stimulation of tissue growth through the elimination of excess electrons produced under respiratory stress. In addition, the conductivity of carbon fiber has potential biocompatible properties to remove excess harmful electrons through electrochemical gradients towards areas of negative charge and lower concentrations. This fiber can osseointegrate with living bone.

Regarding PEEK, in [47], Liu and his team report on the addition of inorganic nanohydroxyapatite (nHA) and multiwalled carbon nanotubes (MWCNT). They used fusion and injection molding processes to obtain the hybrid PEEK

[4]An epoxide, in Organic Chemistry, is a cyclic ether made up of an oxygen atom attached to two carbon atoms, which in turn are linked to each other by a single covalent bond.

composites reinforced with nHA and MWCNT. Seeking the viability of using such compounds in applications for load-bearing implants it is that the other two materials are added to PEEK, as this gives the biocomposite greater biocompatibility, and increases the tensile strength of the modulus of elasticity. In this research, properties such as wettability, structural behavior, and osteoblastic cell adhesion were studied. And, the behavior of cell proliferation and differentiation of these compounds, as well as their mineralization. For both cases of fillers, by means of X-ray diffraction and SEM observation, the incorporation in the polymeric matrix of the hybrids was verified. Specifically, the hybrid showed tensile properties superior to those of human cortical bone. In addition, the PEEK/(15% nHA)-(1.88% MWNT) variant, is hydrophilic and favors the adhesion, proliferation, and differentiation of osteoblasts on its surface, therefore, it is the one with the greatest potential for application in orthopedic loadbearing implants.

It is also known that the mechanical properties of hydroxyapatite are not the best. In [48], Lawton and his team report on the use of MWCNT which, thanks to their high tensile strength and degree of rigidity, can be used as HA reinforcement. In addition to studying the properties of diametral tensile strength and compressive strength of this compound, the biocompatibility of these was also estimated. The study was carried out for two types of compounds, namely, HA was precipitated (by the wet precipitation method) in the presence of MWCNT nanotubes in its original form (p), and for functionalized nanotubes (f); that is, improved in terms of their solubility property (in their original form they are not soluble) in aqueous solutions and other organic solvents. For both variants, polyvinyl alcohol (PVA) or hexadecyl trimethylammonium bromide (HTAB) was used as a surfactant. This research showed that both MWCNTs and surfactants play an important role in the growth and nucleation of HA. Likewise, the compounds based on f-MWCNT presented better dispersion and interaction with HA particles in relation to the compounds based on p-MWCNT. The mechanical resistance of both variants was better in relation to the pure HA compounds. Additionally in both cases, biocompatibility was confirmed.

The cellular proliferation of a porous implant is closely linked to its mass transport capacity. A study of this property was developed by Li, Chen and Fan [49], since the useful life of an implant depends directly on its ability to exchange nutrients and waste, something essential for cell proliferation and differentiation. In this work, the mass transport properties for porous implants with different unit cells are predicted numerically, with the help of Computational Fluid Dynamics (CFD), keeping the porosity constant. From the selection of three typical types of unit cells: diamond (DO), rhombic dodecahedron (RD), and octet truss (OT). Unit cells were quantitatively designed, shape parameters were measured and calculated, and porous scaffolds were created with the same contour size for each type, respectively. The study concluded that, for porous implants, regardless of the placement environment, porosity, and scaffold size, unit cell differentiation could cause dissimilarity in mass transport properties. The DO type cell shows greater tortuosity, more appropriate area, and a smoother shear stress distribution than the other two cells, which would provide a better environment for implant fixation and tissue regeneration. On the other hand, RD and OT type cells showed better mass transport properties due to a higher maximum speed than for DO. Such results are of great value for unit cell selection and optimization of biological performance for 3D printed bone implants.

The topic related to the application of 3D printing and additive manufacturing techniques also occupies a prominent place when working with nonmetallic compounds. In [50], the possibility and capacity of applying extrusion printing as a way of controlling the spatial distribution of HA nanoparticles on 3D composite scaffolds is shown. The authors of this work combine the advantages of degradable synthetic polymers (for example, PPF: polypropylene fumarate), and HA nanoparticles, which are osteoconductive and provide compressive strength. They printed 3D scaffolds made up of well-defined layers with interconnected pores, characteristics much needed in a bone implant. With the help of a thermogravimetric analysis, the amount of HA per layer was monitored. The aggregation tendency of the HA particles within the polypropylene fumarate were also evaluated with the aid of computed tomography.

Additive impression has shown its advantages in the manufacture of synthetic bone models and in terms of adapting the implants to the characteristics of each transplanted individual. However, the impression resolution is one of the limitations of this technique, from the point of view of Materials Mechanics, at the level of trabecular complexity. Thus, in [51], Wu, Spanou, Diéz-Escudero, and Persson investigated the possibilities of using fused deposition modeling (FDM), seeking a better imitation of real bone, both from the point of view of its mechanical properties, as from the aspect of biodegradability. The filament tested by these researchers is a degradable polymeric compound of poly (lactic acid) (PLA) and hydroxyapatite, evaluating three ratios of PLA/HA, namely 5%, 10% and 15% by weight of HA. With these formulations, they printed scale models of human trabecular bone and morphometric and mechanical properties were evaluated in them, applying compression tests, screw extraction, and computed tomography. The results obtained were promising, applying a scale factor of $2 - 4$ regarding the replication of the trabecular structure of FDM and PLA. When the PLA is incorporated, the morphological quality of the impression is reduced; but potentially the mechanical properties are improved. The enlarged models showed slightly improved strength when compared to other commonly used polymer foam synthetic bone models.

An important summary on additive manufacturing (AM: additive manufacturing) of bioceramics can be found in [52]. In this review work, the authors explore some novel bioceramics AM techniques used in bone restoration. As a main result, it is highlighted that, despite the great advances achieved, these techniques are still in an initial stage, since they will have to face challenges related to vascularization, the integration of 3D printing technologies, improvement of mechanical properties of bioceramics, to achieve total biocompatibility, absolute understanding of the bonding mechanism between bone mineral and collagen, among others.

5 Discussion

Composites applied in personalized bone implantology must have the properties of a biomaterial, that is, they must interact with biological systems. Among them, the bioactive compounds are more weighted, due to their ability to combine with living bone tissue. The three main properties considered in the present work are: osteogenesis, biocompatibility and functionality. Table 1, Table 2, and Table 3 show, respectively, summaries on the behavior of the inclusion of the aforementioned properties within the research objectives in the consulted bibliography, differentiating in each case whether the studied or applied material presents a predominance of metallic or nonmetallic elements (implant type). The experimental model used, the main findings of each investigation, and the scope or impact of the journal where the result has been published are also considered. In this sense, within the tables, reference is made to the quartile ($Q_i, i = 1, ..., 4$) where the publication is contained according to the SCImago Journal & Country Rank (SJR), which is a website that includes journals and scientific indicators, which are used to evaluate and analyze scientific publications, based on the information contained in the Scopus database (Elsevier).

Table 1: Summary on osteogenesis.

Implant type	**Condition/Model**	**Main findings**	**Reference**	**Journal Impact Index**
Electro polished titanium.	Rabbit	The findings do not support that nano-HA chemistry and nanotopography enhance bone formation when placed in a gap-healing model.	[21]	Q2-Q1
Alpha-beta titanium alloy coated with nanostructured glass ceramic.	In vitro	Evaluation of the structural morphology and phase composition of the coating.	[27]	Q3
Porous alpha-beta titanium alloy.	Bovine	The fatigue performance of the implant is determined by the level of bone growth.	[28]	Q2

Continued on next page

Table 1 – continued from previous page

Implant type	**Condition/Model**	**Main findings**	**Reference**	**Journal Impact Index**
Titanium coated with hydroxyapatite, and hydroxyapatite combined with silicon and stroncio.	In vivo.	For porous implants, osseointegration is driven less by the pore size than by the presence of a bioactive coating and the overall rigidity of the implant.	[29]	Q1
Substrates coated with titanium dioxide nanotubes.	In vitro.	An assessment was obtained on the effects of titanium nanotube spacing on osteoblast cell function.	[30]	Impact Factor: 3.623 (2020), 5-Year Impact Factor: 3.920 (2020) Covered in PubMed
Metallic (unspecified) with nano/micro hierarchical bioceramic coatings.	Not detailed.	The hydro-thermal treatment applied, for a shorter time, led to the formation of apatite and caused a decrease in the formation of calcium titanate crystals, which provokes superficial damage.	[31]	Impact Factor: 3.623 (2020), 5-Year Impact Factor: 3.920 (2020) Covered in PubMed
Iron matrix, with bioceramic calcium silicate as reinforcement phase.	In vitro.	The addition of calcium silicate to iron appears to be an effective approach to develop biodegradable bone implants with acceptable biomedical performance.	[32]	Q1
Titanium.	Not detailed.	Alteration of the surface chemistry of microstructured titanium implants by wet chemical treatment with magnesium ions has a greater effect in promoting early osteogenic differentiation of mesenchymal stem cells than calcium ions.	[33]	Q1
Magnesium, aluminum, and zinc alloys, coated with a bioceramic nanocomposite based on dioxide, bredigite, and fluorinated hydroxyapatite.	In vivo.	Better bone regeneration was observed with a lower degree of inflammatory response in the tissue surrounding the coated implant, when compared with the uncoated ones. The coating strategy can be used on biodegradable magnesium bone implants, which require a reduced corrosion rate and improved osseointegration.	[34]	Impact Factor: 3.623 (2020), 5-Year Impact Factor: 3.920 (2020) Covered in PubMed
Stainless steel.	In vitro.	Amorphous silica nanoparticles are easily adsorbed by the hydroxyapatite surface, changing their characteristics and improving the cell adhesion of the osteoblasts.	[36]	Q1
Porous carriers of hydroxyapatite, alpha tricalcium phosphate, and a neutralized glass ceramic	In vitro.	The biological activity of the growth factors released from the surface of synthetic implants is time dependent.	[37]	Q1-Q2
Uncemented implant with rough coating.	Simulation	Stability of the osseointegration at the bone implant interface.	[38]	Q3
Dense nanocomposites based on bio-active synthetic bone.	In vitro.	Immersion of the composites in simulated body fluid resulted in the deposition of a bone-like layer of apatite, suggesting the ability of these materials to bind to native bone tissue after implantation.	[39]	Q1
GO-PLGA/HA biodegradable microcarriers.	In vitro.	Graphene oxide infusion could effectively improve the surface properties of microcarriers and the adhesion, proliferation, and differentiation of osteogenesis of MC3T3-E1 cells.	[40]	Q1

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Table 1 – continued from previous page				
Implant type	**Condition/Model**	**Main findings**	**Reference**	**Journal Impact Index**
Calcium phosphate.	Rat	The proven architectures are potentially advantageous in bone repair; but the procedure requires additional clinical investigations.	[18]	Q1-Q2

In the investigations summarized in Table 1, osteogenesis has been evaluated in relation to factors such as growth, regeneration, and repair of bone tissue, as well as osteogenic differentiation, and adhesion of osteoblasts.

Table 2: Summary on bio-compatibility.

Implant type	**Condition/Model**	**Main findings**	**Reference**	**Journal Impact Index**
Porous titanium.	Rabbit.	Possibility of manufacturing macro-porous titanium implants with controlled shape and porosity, using rapid prototyping, candidate technique for orthopedic and maxillofacial applications.	[22]	Q2-Q1
Titanium printed implants.	In vivo.	Possibility of improving the effectiveness of limb rescue surgeries.	[23]	Q2
Iron matrix, with bioceramic calcium silicate as reinforcement phase.	In vitro.	The addition of calcium silicate to iron appears to be an effective approach to develop biodegradable bone implants with acceptable biomedical performance.	[32]	Q1
Magnesium, aluminum and zinc alloy, coated with a bio-ceramic nanocomposite based on dioxide, bredigite and fluorinated hydroxyapatite.	In vivo.	Better bone regeneration was observed in the tissue surrounding the coated implant, when compared with the uncoated ones.	[34]	Impact Factor: 3.623 (2020), 5-Year Impact Factor: 3.920 (2020) Covered in PubMed.
Zinc binary alloys.	In vitro.	The results have significant implications for understanding the degradation behavior and biological responses of the alloys studied in bone environments.	[35]	Q1
Uncemented implant with rough coating.	Simulation.	The clinical success of the implant were evaluated.	[38]	Q3
Prototype based on hydroxyapatite modified with zinc ions.	Laboratory animals (not detailed)	Modified zinc hydroxyapatite ions have antimicrobial activity and can reduce or prevent the development of concomitant infections when used as components in bone implants.	[42]	Q1
Calcium Phosphate Ceramic.	In vitro.	The developed biphasic ceramic, with controlled drug release, appears feasible for orthopedic and tissue engineering applications.	[45]	Q1
Carbon fiber.	Rat.	Carbon fiber reinforcement in a polymeric matrix composite demonstrates experimental reliability in stimulating tissue growth by removing excess electrons produced under certain circumstances.	[46]	Q2-Q3
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				Table 2 – continued from previous page
Implant type	**Condition/Model**	**Main findings**	**Reference**	**Journal Impact Index**
Hybrid composites based on PEEK.	Not detailed.	The PEEK/(15% nHA) - (1.88% MWNT) hybrid has the potential to be used as an orthopedic implant.	[47]	Q1
Hydroxyapatite reinforced with carbon nanotubes.	Not detailed.	More biocompatible composites were obtained than composites of hydroxyapatite.	[48]	Q1

Bio-compatibility has been valued in terms of the improvement of implant effectiveness, biomedical performance, biological response, and clinical success. And also evaluating regeneration and bone growth. All this by virtue of the summary of the main findings in Table 2.

Table 3: Summary on functional properties.

Implant type	**Condition/Model**	**Main findings**	**Reference**	**Journal Impact Index**
Hydroxyapatite combined with titanium.	Not detailed.	The appropriate elasticity for the implant is achieved.	[20]	Q1
Alpha-beta titanium alloy containing 6% aluminum and 7% niobium.	In vitro.	Confirmation of the potential of additive manufacturing to achieve adequate levels of precision and complex geometries, with specific and desired mechanical properties.	[24]	Impact Factor: 3.623 (2020). 5-Year Impact Factor: 3.920 (2020) Covered in PubMed
Titanium coated with hydroxyapatite.	Not specified.	Tightly bonded interfaces with no gaps. Increased adhesive bond strength.	[25]	Q1
Alpha-beta titanium alloy whose composition is completed with aluminum and vanadium.	Printed samples.	Based on different deformation behaviors, appropriate pore size and position, structures can be selected for future implant designs based on loading conditions.	[26]	Q2
Porous alpha-beta titanium alloy.	Bovine.	Caution is necessary in the use of widely porous implants in loading situations. Certain regions may be at risk for fatigue failure.	[28]	Q2
Iron matrix, with bioceramic calcium silicate as reinforcement phase.	In vitro.	The addition of calcium silicate to iron appears to be an effective approach to develop biodegradable bone implants with acceptable biomedical performance.	[32]	Q1
Zinc binary alloys.	In vitro.	The results have significant implications for understanding the degradation behavior and biological responses of the alloys studied in bone environments.	[35]	Q1
Dense nanocomposites based on bioactive synthetic bone.	In vitro.	The ability of these materials to bind to native bone tissue.	[39]	Q1
				Continued on next page

Table 3 – continued from previous page				
Implant type	**Condition/Model**	**Main findings**	**Reference**	**Journal Impact Index**
β-Tricalcium Phosphate.	Observation of evolution in six cases of bone tumor.	u-HA/PLLA plates and screws can be used to stabilize hard-type β-TCP blocks in the reconstruction of bone tumor resection.	[41]	Q1
Reinforced PLA films.	Not detailed.	The resulting laminated composite material showed combined advantages of its components: higher tensile strength, elongation break, and E-modulus. It also showed adequate thermal stability, as well as lower water absorption capacity. All of this makes it suitable for its use as a bone implant.	[44]	Q1
Calcium Phosphate Ceramic.	In vitro.	The developed biphasic ceramic, with controlled drug release, appears feasible for orthopedic and tissue engineering applications.	[45]	Q1
Hybrid composites based on PEEK.	Not detailed.	The PEEK/(15% nHA) - (1.88% MWNT) hybrid has the potential to be used as an orthopedic implant.	[47]	Q1
Hydroxyapatite reinforced with carbon nanotubes.	Not detailed.	More biocompatible composites were obtained than composites of hydroxyapatite.	[48]	Q1
Porous implants (material not specified)	Numerical study.	Porous structures with a symmetric unit cells in the midline may have superior mass transport properties than diagonally symmetric structures. The importance of the difference in the morphology of the pores and the type of symmetry was demonstrated.	[49]	Q2
Propylene fumarate scaffolds with hydroxyapatite gradients.	Does not apply.	Information is provided on the fabrication and characterization of composite scaffolds that contain particle gradients and have good applicability for future tissue engineering efforts.	[50]	Q2-Q3
PLA/HA composite structures.	Does not apply.	Reproduction of trabecular morphology using 3D printed PLA/HA compounds could be a promising strategy for synthetic bone models, if high print resolution can be guaranteed.	[51]	Q1-Q2

In terms of mechanical or other qualities of an implant, Table 3 shows that the investigations have been oriented towards the achievement of a desired mechanical response to the adhesive bond strength, loading conditions, risk for fatigue failure, mass transport properties, as well as to the biomedical performance in general.

An analysis of the previous tables proves that, in quantitative terms, the research efforts in which the problems related to osteogenesis, biocompatibility, and mechanical and other qualities of the implant, are similar (15, 11 and 16 articles, respectively). The manufacturing technique also occupies a place within the challenges analyzed. Zafar and his team in [52], carried out a revision work aimed at an exploration of applications of additive manufacturing based on bioceramics, in bone tissue engineering.

For the time interval reflected in this work, of all the articles reviewed, dedicated to the observation of the favorable and/or unfavorable effects of different types of biomaterials used in implantology (both for the development of implants, and for the development of coatings of these), in approximately 53.3%

of them, are reported results whose fundamental basis are metallic materials and alloys. While in 46.7% approximately the investigations are centered on polymeric, ceramic, and carbon composite materials. Percentages that show that research on materials for bone regeneration applications reaches similar levels for both metallic and nonmetallic elements.
It is also appreciable, due to the publication dates of the reviewed works, that in the last five years the research has focused mainly on polymeric and ceramic composites. And the rise of the latter is also justified by the own development of the composite materials in general, and the technologies to obtain them.

6 Conclusions

The problems related to osseointegration, cell proliferation, biocompatibility, that is, limitations from the biological point of view, seem to be the main obstacle in the race to obtain the ideal material for human bone implants. The competencies of an implant, from the physical-mechanical point of view, seem to take a back seat, since the volume of research devoted to these benefits is less. Perhaps the latter is a less complex objective compared to the challenges imposed by the human body as a machinery of the highest level of perfection-imperfection that it is in biological terms. However, from the point of view of the resistance of one or another type of material, rigidity should also be considered as an important factor when setting goals regarding the quality of life (after trauma) that one wishes to achieve and the possible secondary effects that this would cause to the patient.
Understanding as a composite materials are those that are used for the development of bone prostheses and implants, and what results from, for example, an autograft with some type of artificial coating. It is therefore not possible to clearly establish a predominance of some materials over others, or a prevailing material or compound for this class of applications. Although it seems that the synthesis of nanohydroxyapatite, due to its familiar proximity to natural bone apatite, should be present in any variant of composite material for bone implants. All above faces one more adverse factor, decisive in this race, namely, the limited possibilities regarding the use of living human models in experimentation. Problem of high bioethical complexity in the first place.
A fundamental factor that comes to light in this review is that there is no absolute best material or bio-scaffold, but there may be the most suitable biomaterial with respect to a precise and identified clinical application and not with respect to its properties.
Or perhaps the response to the question regarding the predominant or optimal material or compound for implants and bone regeneration, is not unique? The most innovative in this field of study is personalized implantology, adjusted to the characteristics of each patient. Considering the wide range of variables of

all kinds of nature, which must be observed for this customization (a set that could be assumed to be infinite), it would be worth thinking about an artificial intelligence system whose input covers the mechanical, physical, chemical, and biological properties, that the implant would have to satisfy (for example, what bone is to be restored or repaired, what are its functions, what is the person's health status, what is their genetic history, etc.). And that its output will be a valuable aid for making decisions regarding the material or compound to use in each particular case.

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