American Journal of Engineering Research (AJER)
e-ISSN: 2320-0847 p-ISSN : 2320-0936
Volume-10, Issue-8, pp: 333-344
www.ajer.org
Research Paper Open Access

A brief review of beta tricalcium phosphate (β -TCP) doped with metal ions.

S. L. O. Costa[1], P. F. Silva[1], G. K. G. Carvalho[2], Y. B. A. Almeida[2], J. R. S. Farias[2], A. S. N. Braga [1,2]

[1] *Programa de Pós-Graduação em Engenharia de Materiais, Instituto Federal do Piauí, Teresina, PI, Brasil*
[2] *Universidade Federal do Piauí– -Av. Universitária, s/n, Teresina, PI, Brasil*
Corresponding Author: Slanna Larissa Olimpio Costa

ABSTRACT :*Beta tricalcium phosphate (β-TCP) has been increasingly highlighted in research due to its excellent properties such as: biocompatibility and bioactivity, on the other hand, the low flexural and tensile strength of ceramics and their biological behavior, makes there is a need to look for materials that satisfy these deficiencies. Metals and their alloys respond functionally in terms of replacing load-bearing structures in order to regenerate bone and biocompatibility. Thus, scientists have been looking for an alternative in doping in order to improve the performance of this promising bioceramic. Thus, the objective of this work was to carry out an exploratory research of articles published in the last six years, using the Science Direct, Web of Science and Scopus databases, on β-TCP doped with metals and alloys. A total of 62 articles on the subject were found, where the country that published the most was China, followed by India. Regarding dopants, magnesium was the most used. The results showed that researches have been growing over the last years and that the insertion of foreign ions in the β-TCP brings countless benefits for the origin of a promising biomaterial for biomedical applications.*

KEYWORDS: *Calcium phosphates, β-TCP, doped.*

Date of Submission: 14-08-2021 Date of acceptance: 29-08-2021

I. INTRODUCTION

Biomaterials can be defined by their function and interaction/replacement with the recipient tissue, thus, their mechanical, chemical and biological properties must be optimized [1] to achieve the best possible result for a given function and that is compatible with the environment biological [2]. It is known that calcium phosphate-based biomaterials have a high potential to restore and replace hard and damaged tissues such as bones. materials with enhanced physical and chemical, mechanical and biological properties [3].

Calcium phosphates have received a lot of attention with several applications, including: bone grafts [4], repair of bone defects from pathologies [5], dental implants [6] and bone regeneration [7], these applications are due the fact that these materials have excellent biocompatibility and similarities with the mineral phase of bones and teeth [8], therefore, they are widely used in surgeries such as orthopedic and dental implants [9].

Among calcium phosphates, β-TCP has excellent bioreabsorbability in the human biological environment that allows the progressive replacement of the host's natural tissue with the gradual degradation of the implanted material, making it ideal for biomedical applications [10], therefore, standing out more and more in research due to its excellent properties such as: biocompatibility, osteoconductivity, bioactivity, atoxicity and biodegradability [11], similarity with the apatite phase of natural hard tissues and especially its high rate of reabsorption in the body [12].

Despite the excellent properties that this bioceramic presents, there are some disadvantages such as: low mechanical strength due to its porous structure [13] and the presence of infections, a problem that is frequent in implants [14]. In order to solve this deficiency, studies prove that the addition of metallic ions improves mechanical properties [15], biological properties such as: osteogenesis [16] and osteoblast cell proliferation [17], in addition to structural changes in network parameters [18].

Based on this assumption, the objective of this work was to carry out an exploratory research of articles published in the last six years on β-TCP doped with metal ions, showing the effect of the dopant incorporated in the structure of this calcium phosphate, in order to present the consequences that doping induces in its biological, structural, chemical and mechanical functions.

II. MATERIALS AND METHODS

Data collection was carried out through an electronic search in the Science Direct, Web of Science and Scopus databases. The inclusion criteria defined were: articles published in the last six years about doped β-TCP, that is, those that have metal ion exchange, between the period from 2016 to 2021. The keywords were used as, in the search field, the combination of the following words: "beta tricalcium phosphate doped". The following were excluded from the research: review articles and book chapters.

For this review, the initial search resulted in a total of 62 (sixty-two) articles found in the search. Any other works that were not part of the research topic were excluded, such as: doping with another polymorph that was not β-TCP, for example α-TCP or the manufacture of composites. After reading the remaining papers, the papers that presented relevant potential for the study were selected, these were obtained in full and evaluated for doping, taking into account the number of articles over the years, the countries that published the most, as well. as the most used ions in substitutions with β-TCP.

III. TRICALCUM PHOSPHATES (TCP)

The tricalcium phosphate (Ca3(PO4)2, TCP) is a mineral of the calcium phosphates class that constitute an important class of materials [19], this material has four allotropic forms, where the transition temperatures and sequence of occurrence are: beta phase (β-TCP), alpha phase (α-TCP), super-alpha or alpha' phase (α'-TCP) and gamma phase (ϒ-TCP) [20]. The β-TCP phase is stable up to temperatures close to 1180°C which crystallizes in the rhombohedral system, the α-TCP phase is stable between 1180 to 1430°C and presents an orthorhombic crystalline system, whereas the α'-TCP phase crystallizes in the monoclinic system and at temperatures above 1430ºC and the Y phase is obtained at high pressures [21].

Among these phases, only two arouse interest for applications as biomaterials, they are the phases: α and β, the other phases are not used due to the difficulty of forming a single phase due to metastability [22]. The α-TCP phase has a high mechanical resistance in relation to the other phases, but it does not present a favorable performance in relation to in vivo implantation, as it has a high solubility rate in physiological environment, in addition to causing tensions due to density differences [23]. The β-TCP phase is the most suitable for ceramic implants, as it has favorable characteristics such as: chemical stability and greater bioactivity, as its structural arrangement allows a greater amount of Ca2+ and PO43- to be exchanged with the biological medium [24].

Tricalcium phosphates are used in bioactive mixtures that stimulate bone growth [25] because they have similarities with inorganic tissue components, do not present risks of disease infections, and also participate in the calcium/phosphorus balance [26], making them strong candidates to replace hydroxyapatite. In addition, they are easy to replace ions within their network structure, as well as an excellent ability to adapt their functional and biological properties, are recognized as osteocoducers, in addition to providing a resorbable temperature for the formation of new bone [27], therefore, there are countless investments by researchers for the development of a promising bioceramic [28].

IV. BETA TRICALCUM PHOSPHATE (B-TCP)

Beta tricalcium phosphate (β-TCP) has a chemical formulation: Ca3(PO4)2, crystallizes in the rhombohedral system, belongs to a space group R3c and is a unit cell with the following dimensions: a=b 1.04 nm and c=3.74 nm [29]. Its density theoretically ranges from 3.03 to 3.13 g/cm^3, but generally values are close to 3.07 g/cm^3 [24]. A unit cell contains 63 Ca atoms and 42 PO4 atoms [30], its structure is made up of two planar repeated domains, one with a Ca/P molar ratio of 60/42= 1.429 and the other with a Ca/P molar ratio of 66 /42= 1.571 [6]. Figure 1 represents the structure of β-TCP.

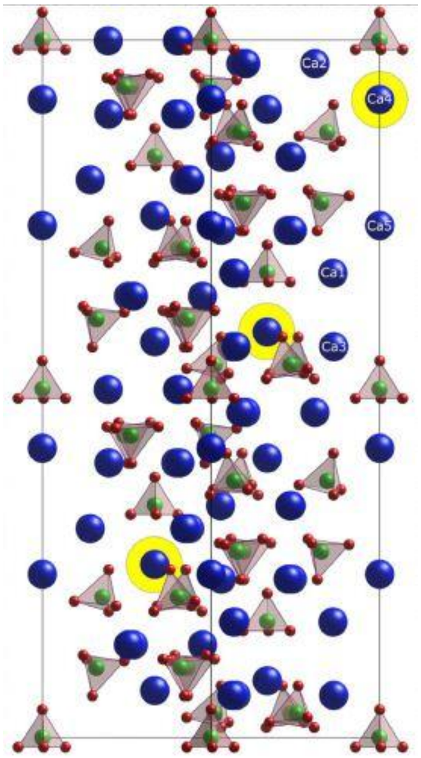

Figure 1- β-TCP structure
Source: [6]

The calcium ions in β-TCP occupy five different cationic sites, the Ca (1), Ca (2) and Ca (3) sites are in general positions with eight to nine coordinated oxygens, while Ca (4) and Ca (5) are in special positions, with an effective multiplicity of 1/3 of the other cation sites. Ca (5) exhibits approximately octahedral coordination, the Ca (4) site is only half occupied and exhibits a nine-coordination distortion, while the phosphor exhibits three different crystallographic positions with the multiplicity of P (1) equal to 1/ 3 of P (2), since it is in a special position [25]. Figure 2 shows the cationic sites in the β-TCP structure.

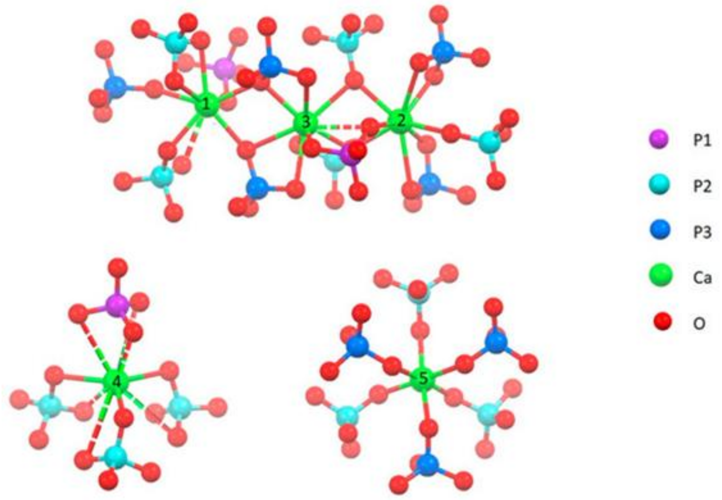

Figure 2- Representation of cationic sites in the β-TCP structure
Source:[25]

β-TCP can be synthesized by different chemical routes [10], including: wet precipitation, hydrothermal, solid state reaction, gel casting, chemical precipitation, calcination, selective laser sintering (SLS), micro-assisted combustion waves and sol-gel method [26, 31, 32-33]. Due to the diversity of methods for obtaining this phosphate and the mineral similarity to bones and teeth [27], they can be used in: restoration of maxillary defects, cranioplasty, spinal reconstruction, reconstructions in orthopedic surgery, treatment of cervical spondylosis, alveolar fillings after tooth extraction, in addition to administration routes for drug delivery [34-35].

Due to the wide range of syntheses and applications, the -TCP is considered one of the most important bioreabsorbable biomaterials, as it is naturally dissolved in the human body over time, has similarities in its composition with natural bone, in addition, it is found that there is a proliferation of regenerative cells, easily adhering to its surface [36]. Studies show that, while hydroxyapatite remains for a long time after the implantation period, beta tricalcium phosphate is replaced by new bone tissue more quickly, in relation to solubility, it is noteworthy that, the biodegradation of β-TCP (K β-TCP= 1.25 x10 -29) is much better than Hap (K Hap =2.35 x 10-59) [37-38].

It is a non-toxic, antigenic and non-cancer material and is used due to its osteoconductivity, ease of binding with the host tissue and fast bone repair [39-40]. Among the properties and advantages of this material, we can highlight, firstly, the possibility of cationic substitutions, secondly its bioactivity and osteoconductivity, and finally its biodegradation [41]. Among these, the one that has been explored is the modification of β-TCP with metal ions, as it is known that the structure of β-TCP allows to accommodate different ions with different charges, where the objective is to change the solubility and reabsorption, without modifying its biological properties, such as biocompatibility [42].

V. B-TCP DOPING

The properties of calcium phosphates can be modified by incorporation with foreign ions [43]. The rhombohedral structure of the β-TCP with space group R3c, it is undoubtedly less flexible than the HA structure, however it can host several ionic substitutions, especially the substitution of calcium ions with divalent cations [44]. The ease of ion replacement within the apatite and network structure of theβ-TCP has been examined extensively by researchers in their long efforts to develop materials that closely resemble natural hard tissues, assuming that the presence of dopants has a profound impact on phase assembly, structural and functional behavior [42].

Therefore, the academic community's interest in this topic is growing, where there has been an increase in the number of publications aimed at β -TCP doped with metal ions, over the last few years, as can be seen in Figure 3, which shows the increasing proportion of the number of articles published about β -TCP doped with metal ions. Where, in 2016, 14 (fourteen) articles were found, in 2017 the number decreased to 10 (ten) articles, in 2018 there was a drop in the number of publications totaling 09 (nine) works, in 2019 the number increased to 12 (twelve) articles and in 2020 the total of results pointed to 15 (fifteen) articles, until the present moment of the research, 02 (two) articles were found.

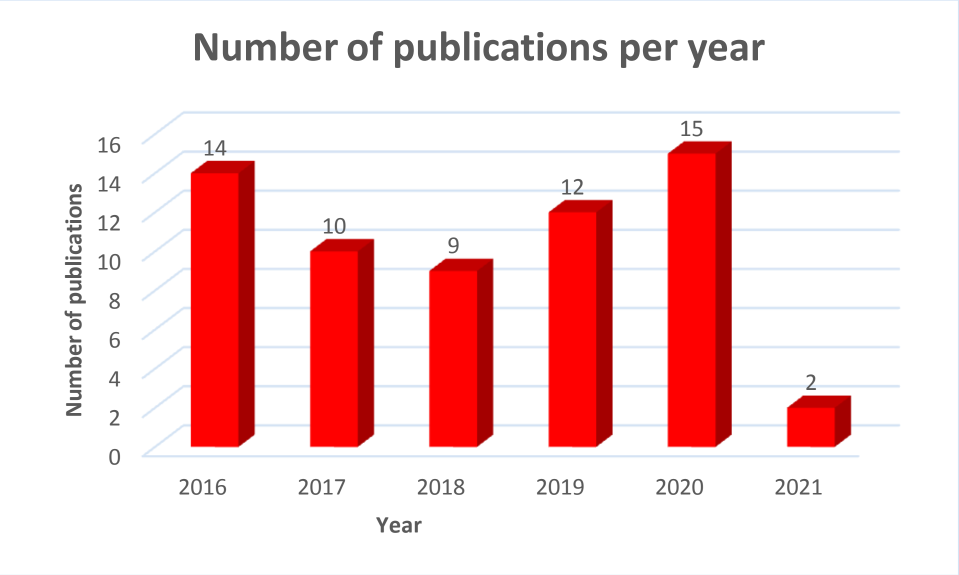

Figure 3: Number of publications per year

Publications on doped β-TCP have grown in recent years, and scientists have been striving to advance scientific research in the search for a solution that satisfies the deficiency of β-TCP in terms of mechanical and biological properties. Among the countries that published the most, China leads the surveys with 21% of publications, followed by India with 13%. Figure 4 shows the number of publications by country.

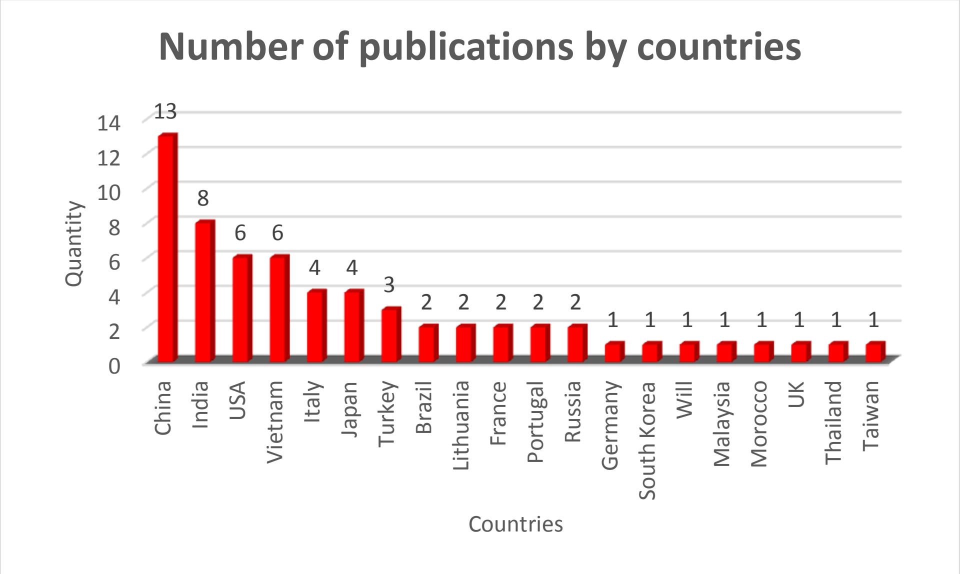

Figure 4: Number of publications by country

Ionic substitutions to improve the properties of β-TCP have led researchers to look for a chemical element that, implanted in living tissue, does not present any reaction to the host tissue, that is, biological rejections, inducing infections. Among the searches for the best doping element, the literature indicates that in the last six years magnesium (Mg^{2+}) has been widely used, followed by strontium and silver.

Mg^{2+} is one of the most important ions in hard tissues, as it is capable of controlling bone metabolism in vivo in its formation and resorption, in addition to easily replacing Ca^{2+} in the apatite network, considering its atomic radius (0.66Å) is much smaller than Ca (0.99Å) [46]. Regarding Sr^{2+}, in addition to participating in bone metabolism, it inhibits osteoclast activity, differentiation, proliferation and function, stimulating bone formation [47], it is used in the treatment of bone diseases such as: osteoporosis and helps post-menopausal women [48]. Ag+ ions, on the other hand, exhibit excellent antibacterial activity, which may be inhibited in bacteria such as Escherichia coli (E. coli) and Sthaphylococcus aureus (S.aureus), in addition to presenting a high thermal state and non-toxicity in human cells [49] .

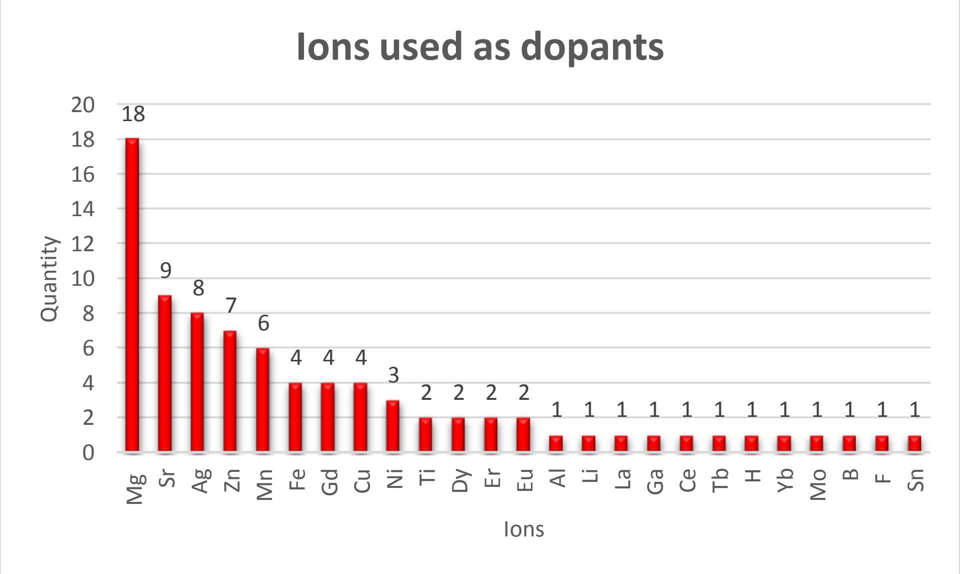

Figure 5: Ions used as dopants

Below are all the citations of the articles found in the Science Direct, Web of Science and Scopus databases, from the year 2016 to the present time of the research, highlighting the most used ions such as

Magnesium, Strontium and Silver, presenting the synthesis methods, the characteristics of the material after sintering (ionic substitutions), as well as the importance of the study for future research and its promising results for biomedical applications.

Singh et al. [50] combined silver (Ag) and chitosan doped beta tricalcium phosphate (β-TCP) powders deposited on titanium substrates, evaluating the structural changes due to Ag incorporation in β-TCP powders. The replacement of Ca^{2+} by Ag^{+} in the β-TCP structure led to significant contractions of the lattice parameters with the Ag^{+} ions preferentially occupying the Ca (4) sites of the β-TCP. Antibacterial tests revealed good Ag^{+} activity in combating microbial invasion with an efficiency that increased with increasing dopant concentration. The porosity of the coatings decreased almost linearly with the increase in doping levels, where the reduction in porosity increased the corrosion resistance of the coatings. Thus, the silver combination.

Frasnelli et al. [23] studied the effect of β-TCP doped with Mg^{2+} on the transition to the α-TCP phase, specifically with respect to the dopant concentration and post-transformation cooling rate and the effect of an adequate secondary heat treatment (annealing) to induce the reconversion from α to β phase is also analyzed. The results concluded that magnesium strongly increases the stability of the β polymorph, delaying the transformation temperature in one phase. Therefore, during the sintering process of Mg-TCP powders, this allows achieving greater densification. In the presence of magnesium, the transition from β to α phase is spontaneously reversible after cooling. This indicates that Mg^{2+} promotes the kinetics of reconversion from α phase to β phase in cooling or, at least, it proportionally decreases the kinetics of transition from phase β to phase α after heating, increasing the time needed to reach equilibrium. As for the possibility of reconverting the possible phase retained in the sintered TCP components by a secondary heat treatment (annealing), it has been shown that their surface area, much smaller compared to ground powders, makes the process more difficult and non-functional for TCP not doped. However, also in this case, magnesium promotes a kinetic and thermodynamic reconversion, from the α phase to the β phase, allowing the transition and decreasing the temperature of the initial process up to 680 °C. As for the possibility of reconverting the possible phase retained in the sintered TCP components by a secondary heat treatment (annealing), it has been shown that their surface area, much smaller compared to ground powders, makes the process more difficult and non-functional for TCP not doped. However, also in this case, magnesium promotes a kinetic and thermodynamic reconversion, from the α phase to the β phase, allowing the transition and decreasing the temperature of the initial process up to 680 °C. As for the possibility of reconverting the possible phase retained in the sintered TCP components by a secondary heat treatment (annealing), it has been shown that their surface area, much smaller compared to ground powders, makes the process more difficult and non-functional for TCP not doped. However, also in this case, magnesium promotes a kinetic and thermodynamic reconversion, from the α phase to the β phase, allowing the transition and decreasing the temperature of the initial process up to 680 °C.

Kotoka et al. [51] investigated the growth, characterization and electrochemical corrosion properties of silver-doped β-TCP deposited on biodegradable magnesium substrate using pulsed laser deposition (PLD). The results concluded that the addition of Ag improved the corrosion protection properties of the coating and the corrosion resistance increased with increasing dopant concentration. However, β-TCP doped with 10% by weight of Ag showed a lower corrosion resistance, possibly due to the galvanic coupling between the Mg substrate and the Ag nanoparticle. The coatings also provided lower corrosion resistance in physiological saline solution in comparison with Hanks' balanced salt solution.

Costa et al. [52] evaluated the impact of Mg-doped β-TCP granules (β-TCMP) on the healing of a critical-size defect in rat skulls, associated or not with resorbable barriers. According to the results presented, the association of GBR (guided bone regeneration) and β-TCP and β-TCMP granules 6 months after bone grafting significantly improved bone repair in the treatment of the defect in rat skulls compared to defects untreated or the use of the GBR technique alone, leading to a bone level approximately four to five times higher than in the blood clot group. The β-TCMP membrane group had 40.5% of the defect area filled with neoformed bone, even in the central part of the defect, instead of just at the edge, as seen in the other experimental groups.

Takeuchi et al. [53] synthesized β-TCP from starfish-derived calcium carbonates via the hydrothermal route. Initially Mg^{2+} was incorporated into the mineral's crystalline structure through irregularly shaped granules that were later converted into beta tricalcium phosphate containing magnesium by hydrothermal treatment of one day or more with an aqueous solution of $(NH_4)_2HPO_4$ at 200 °C. The study proved that the morphologies and crystalline phases of the granules after the hydrothermal treatment depended on the pHs and temperatures during the conversion due to the reaction rates of calcium phosphate formation from the solution and the calcite dissolution rate.

Park et al. [54] analyzed the use of magnesium and/or hydroxyapatite coatings on β-TCP substrates through sputtering in order to reduce the rapid degradation of β-TCP, seeking to make it more osteoconductive. The research used four groups in biocompatibility tests: pure β-TCP; coated with hydroxyapatite (HA-TCP); coated with magnesium (Mg-TCP) and multicoated with Mg and Ha (MgHA-TCP). The research results concluded that the 4 groups showed similar results in the bone regeneration process, concluding that the junction of Ca and Mg ions have a synergistic effect, which can increase the adhesion of osteoblastic cells, improving the osteoconductivity of these compounds, which the makes it a material of great potential for future applications in bone grafting and regeneration.

Singh et al. [55] synthesized scaffolds from biphasic mixtures of β-TCP doped with magnesium where the differentiation of human mesenchymal cells was analyzed compared to scaffolds of pure β-TCP, since there is the release of greater amounts of bioactive ions. The results proved that scaffolds prepared with doped β-TCP had improved proliferation and differentiation compared to pure β -TCP.

Singh et al. [56] studied the proliferation and differentiation of human mesenchymal stem cells from β-TCP scaffolds combined with Mg^{2+} or Mg^{2+} and Sr^{2+}. It was found that cells grown directly in structures prepared with only β-TCP replaced with Mg^{2+} were able to support statistically significantly increased alkaline phosphatase activity, osteopontin and osteoprotegerin expression compared to all compositions containing Mg^{2+} and Sr^{2+}, and β- TCP. Thus, it was concluded that the greatest differentiation observed was due to the release of bioactive ions instead of the surface microstructure,

Bakheet et al. [57] synthesized magnesium-doped β-TCP to replace calcium in the matrix of pure β-TCP to enhance electronic and optical properties that are not present in pure β-TCP. Refractive index, complex dielectric function, optical conductivity, optical reflectivity, extinction coefficient, absorption efficiency and electron energy loss were evaluated. It was concluded that such properties are significant to increase the quality of electronic and optical properties, being viable to synthesize improved β-TCP for dental and medical applications.

Gokcekaya et al. [58], evaluated the antibacterial and cytotoxic properties of silver (Ag) incorporated or coexisting in metallic form with different proportions applied to hydroxyapatite and beta tricalcium phosphate. The analysis of the results concluded that the antibacterial activity of β-TCP incorporated with Ag was superior to that of Hap coexisting with metallic Ag particles, the dissolution tests showed greater and more continuous release of Ag ions in β-TCP incorporated with Ag compared to Hap coexisting with metallic Ag particles, moreover, it was also proven that calcium phosphates incorporated with silver do not present cytotoxic activity. Thus, these results proved the effectiveness of β-TCP incorporated with Ag in the prevention of infections in long-term bioapplications.

Samanta et al. [59] analyzed and differentiated the properties and crystal structure of pure β-TCP and doped with magnesium and titanium in different proportions. The study concluded that there are no major differences in the structure and properties of β-TCP and its magnesium and titanium substitutes. The variation in the concentration of dopants did not alter any kind of significant change in grain size, porosity and crystal structure. The hemolysis study revealed that all compositions are highly hemocompatible, and although it is often claimed that such doping improves the performance of β-TCP, the present study did not reveal any marked improvement in the properties evaluated.

Tripathi et al. [60] evaluated the in vivo stability of magnesium-doped β-TCP granules synthesized in aqueous solution in order to use them as biomaterial in long-term adsorption (low dissolution rate) and bone formation in bone defects formed in the femur of rabbits. The study concluded that doping decreased the dissolution rate of the granules, as well as increased the activity of osteoblastic cells by suppressing the activity of osteoclasts, improving the osteoconductivity capacity through bone remodeling, as well as improving osteoconductivity and the ability to replace which are unique properties of β-TCP and essential for bone tissue regeneration.

Boanini et al. [61] used the combinatorial matrix-assisted laser technique to deposit thin gradient films with variable compositions of Sr-substituted hydroxyapatite (SrHA) and Zn-substituted tricalcium phosphate (ZnTCP) on titanium substrates as a tool to modulate the osteoblast / osteoclast response. The study concluded that the response of osteoblasts and osteoclasts co-cultured in the coatings is modulated by graded composition and varies with SrHA and ZnTCP content. In particular, the data indicate that the presence of SrHA inhibits osteoclast viability and differentiation, while ZnTCP has a beneficial action in the mineralization process, promoting osteoblast proliferation and osteocalcin production. In addition, intermediate compositions, containing SrHA and ZnTCP,

Wang et al. [62] synthesized β-TCP nanopowders co-doped with Sr^{2+} and Zn^{2+} ions varying the concentration of dopants from 0 to 4.8 mol%, where the crystal structure and the properties of beta tricalcium phosphate were analyzed after doping. The research result showed that the β-TCP phase was reached after heat treatment above 800 °C, the a-axis and c-axis lattice parameters gradually decreased with the increase of the Sr^{2+}/Zn^{2+} co-substitution level in the crystal lattice, in addition the study also confirmed that doping significantly improved the thermal stability of β-TCP. The material formed proved to be promising in bioapplications, however, such material did not present mineralization superior to pure β-TCP.

Zare et al. [63] investigated the effect of β -TCP doped with different concentrations of silver nanoparticles on gram-negative periodontal pathogens. The investigation results concluded that the addition of silver nanoparticles to β-TCP produced an antibacterial effect on the substance, reducing the growth rate of pathogens, which may reduce the risk of postoperative infection in alveolar bone defect repairs and bone grafts.

Guo et al. [64] explored the influence of microwave irradiation time and temperature on the synthesis of Mg-doped β-TCP (Mg-β-TCP). The research concluded that the exposure of the doped product to microwaves can control the growth of the precursor crystal in the solution, obtaining smaller and more homogeneous particles. However, with increasing time and temperature, larger particles were formed and exposure to microwaves affected the structure defects. In addition, the study defined a temperature of 40 °C and a microwave irradiation time of 20 min for the synthesis of Mg-β-TCP, where magnesium doping did not show significant toxicity.

Boanini et al. [31] synthesized β-TCP doped with strontium and zinc ions in order to clarify the structural changes induced by ionic substitution. The research concluded that zinc can replace calcium in the β-TCP structure up to about 10% inducing a reduction in cellular parameters, while the substitution occurs up to 80% in the case of strontium causing a linear increase in the constants of network, and a slight modification resulted in a more symmetrical structure. Furthermore, the study also concluded that the Ca (5) octahedral site is the preferred site for the zinc ion while strontium adheres to the Ca (4) site. Thus, such results provide more details and information about the influence exerted by ionic substitution on the β-TCP structure,

Gallo et al. [65] analyzed the influence of magnesium doping on beta tricalcium phosphate and the effect of grain orientation on the phosphate resorption behavior, aiming to improve the efficiency of calcium phosphate bone substitutes by adjusting the resorption rate. Sintered samples of undoped and Mg-doped β-TCP (1 and 6 mol%) were immersed in acidic solution (pH 4.4) to mimic the environmental conditions found in active osteoclasts. The results concluded that any change in the β-TCP crystal parameters has a significant impact on its resorption process. Therefore, β-TCP phase doping by ions of biological interest, such as Mg, Sr, Cu or Fe should influence not only the cellular response, but also the mechanism and kinetics of reabsorption of the material itself.

Frasnelli et al. [66] synthesized pure and magnesium-doped β-TCP nanopowders consolidated by flash sintering, taking advantage of the improved thermal stability of β-TCP (due to Mg doping) and the high sinterability of the nanostructured starting material, using the precipitation method of aqueous solutions. It has been shown that the CDHA (calcium deficient hydroxyapatite) phase is very resistive, at least for an electric field below 2,000 V/cm, to ensure the critical condition necessary to trigger the thermal runaway mechanism; therefore, the flash event can only occur after the formation of β-TCP, where an empirical relationship that describes the inverse proportionality between the applied field and the beginning of the flash was found, pointing to the higher conductivity of the material doped with Mg.

Samanta et al. [67] evaluated the effect of dynamic loading on the bone regeneration performance of different porous β-TCP doped bioceramics. Three dopings were developed at the same rate of 5% with zinc, magnesium and titanium dopants and the synthesis of the pure β-TCP phase, where all samples were implanted in a femoral bone defect model (rabbit) to assess bone regeneration under load dynamics. The study concluded that the low frequency of axial vibration, combined with metal ion doping, had a prominent effect on new bone formation, where the Ti-β-TCP sample compared to the others showed the best performance. Overall, the doped samples showed significantly better bone regeneration under cyclic loading conditions than the pure β-TCP samples,

Massit et al. [68] investigated the preparation of calcium-deficient apatite (CDHA) obtained using the magnesium ion doping process. The result of the research concluded that the first product of the reaction was nanometric CDHA and magnesium-doped CDHA. Structural changes were observed during calcination, where 80% of the CDHA phase was converted to HA, and the rest to β-TCP denoting the formation of biphasic mixtures. Considering that the incorporation of Mg^{2+} in the CDHA structure causes the contraction of the crystal lattice, after calcination, the transformation of CDHA into pure β-TCP occurred at a temperature below 650 °C, inhibiting the formation of hydroxyapatite crystals.

Gokcekaya et al. [69] investigated the incorporation of silver into the crystal structure of β-TCP, seeking new pertinent information about the structural location of Ag atoms in β-TCP crystals. The research concluded that Ag atoms were located in Ca (4) places and vacancies, while incorporation in Ca (4) vacancies balanced the valence of the crystal structure, in which the divalent Ca atoms were exchanged with the monovalent Ag atoms. Thus, the study provides the first microscopic observation of atoms incorporated in the crystal structure of β-TCP, establishing the possibility of observation at an atomic scale of incorporation phenomena of various apatites.

Qin et al. [70] synthesized beta tricalcium phosphate coated with silver and graphene nanoparticles in order to improve compressive strength and lack of antibacterial properties. The results revealed that the introduction of 1% by weight of graphene to β-TCP can markedly increase the compressive strength of the material, where silver nanoparticles were successfully coated on the surface of β-TCP using dopamine as a binding and reducing agent. Furthermore, the material had excellent cell activity and can significantly promote cell proliferation due to the action of dopamine and the presence of hydroxyapatite in the sample. Therefore, the dysfunctional porous silver-doped β-TCP scaffold is a promising alternative for regenerative bone repair.

Chou, et al. [71] synthesized β-TCP doped with silver and zinc through the spray pyrolysis method, investigating the antibacterial activity of the formed samples. the results of the antibacterial tests showed that the activities of β-TCP specimens co-doped with Ag/Zn can reach the same level of activity as the sample doped with Ag. These observations correlate well, considering that the exothermic phenomenon contributes to the particle size of the Ag nanoparticles. In summary, with its great antibacterial performance and lower cost, βTCP co-doped with Ag/Zn can be considered a promising material in the areas of bone implants in the future.

Yuan et al. [72] synthesize silver-doped β-TCP, evaluating the changes in the introduction of silver into the crystal structure of calcium phosphate, taking advantage of the antimicrobial capacity of silver to manufacture biological products. The analyzes verified that the presence of silver does not alter the crystalline properties of β-TCP, the product formed constantly releases silver ions, which significantly inhibit the growth of Staphylococcus aureus and Escherichia coli bacteria, there was no cytotoxic activity or damage to renal function or hepatic in vivo, concluding that the product formed has the ability to repair bone defects while simultaneously acting as an anti-infective agent, demonstrating high potential for use as a long-term implant material.

Kozelskaya et al. [73] investigated the effect of strontium and magnesium substitutions on sputter composition of β-TCP on physicochemical properties and deposition rate in calcium phosphate coatings. It was concluded that the presence of strontium substitutions in the sprayed β-TCP target leads to a significant increase in the deposition rate of calcium phosphate coatings, while magnesium substitutions slightly reduce the deposition rate. This difference is due to the influence of magnesium and strontium substitutions in the crystal structure of the β-TCP powder. Theoretical calculations indicate that strontium substitutions lead to an increase in unit cell volume, which causes an increase in the deposition rates of Sr-β-TCP and Mg / Sr-β-TCP coatings,

Wang et al. [74] synthesized hydroxyapatite and β-TCP with the following strontium concentrations: 1, 5 and 15 mol % through chemical precipitation and high temperature calcination. The results showed that with the increase of Sr concentration, first there was a reduction of Hap, a phenomenon caused by the distortion of the Hap structure, however, when the Sr concentration reached 15% the percentage of Hap started to increase, the latter may be explained by the fact that the β-TCP phase transformation to a Ca-deficient apatite occurs. Therefore, the increase in lattice and volume parameters indicate that Sr was successfully incorporated into the crystal structure of β-TCP and Hap, being that the ionic radius of Sr2+ is greater than that of Ca2+.

He et al [75] synthesized β-TCP containing phosphate glasses doped with Ga and Sr through the extrusion and microperforation method. The scaffolds (TCP/PGs) containing Gallium showed cell proliferation and inhibited osteogenic differentiation in vitro, as well as osteoclastic activities. Samples containing Sr and Ga achieved better results regarding cell proliferation, and in vitro tests were also performed. In vivo tests, results containing Ga inhibited bone resorption, whereas samples implanted in rabbit defects containing Ga and Sr did not suppress bone resorption but neither did they promote bone regeneration.

From the review, it is clear that β-TCP is a biocompatible and readily available synthetic material and that, together with the alternative of doping with foreign ions, it has been introduced in the market with the purpose of repairing bone defects in clinical fields such as: orthopedics, dentistry, neurosurgery, maxillofacial and spinal, therefore it is increasingly necessary to know the behavior of these osteoconductive materials. It is noteworthy that since the 70s, when the first histological observations showing this bioreabsorption capacity were reported, studies on this bioceramic have only increased, and new observations and reliable methods for the production of β-TCP have been proposed in recent years.

VI. CONCLUSION

Through the present study, it was found that biomaterials have stood out for presenting several applications in the biomedical area, such as: reconstructive surgery, development of bone graft substitutes, bone regeneration, tissue engineering and others. It was noticed that the sintering of β-TCP with doping ions improves the antibacterial characteristics, in addition, it presents good corrosion resistance and excellent bioactive characteristics, absence of significant cytotoxic effect as well as an increase in compressive strength. According to the databases used, from 2016 to the present moment, 62 articles were published, over the six years it was found that, in general, there was an increase in the number of works, demonstrating an interest on the part of the scientific community in researching doped β-TCP, China was the country that published the most works, followed by India. In relation to the doping ion, magnesium was the most explored in the last six years. Therefore, the study of β-TCP proved to be extremely important, as it is a promising study for the improvement of regenerative techniques in tissue engineering, contributing to people's quality of life.

REFERENCES

[1]. Hudecki A, Kiryczyński G, Łos M J. Chapter 7 - Biomaterials, Definition, Overview, 2019.

[2]. Özkale B, Sakar M S, Mooneya D J. Active biomaterials for mechanobiology. Biomaterials .2021.

[3]. Roohani-esfahani, S. I.; No, Y. J.; Lu, Z.; Ng, P. Y.; Chen, Y.; Shi, J.; Pavlos, N. J.; Zreiqat, H. A bioceramic with enhanced osteogenic properties to regulate the function of osteoblastic and osteocalastic cells for bone tissue regeneration. Biomedical Materials (Bristol), 2016.

[4]. Wang M, Ge X, Cui Z, Wu S, Zhu S, Liang Y, Li Z, Lu W W. Influences of strontium on the phase composition and lattice structure of biphasic calcium phosphate. Ceramics International, 2021.

[5]. He F, Lu T, Feng S, Wang Y, Huang C, Zhang Y, Deng X, Ye J. Alliance of gallium and strontium potently mediates the osteoclastic and osteogenic activities of β-tricalcium phosphate bioceramic scaffolds. Chemical Engineering Journal, 2021.

[6]. Bohner M, Santoni B L G, Dobelin N. β-Tricalcium Phosphate for Bone Substitution: Synthesis and Properties. Acta Biomaterialia, 2020.

[7]. Ruiz-Aguilar C., Olivares-Pinto U, Drew R.A.L, Aguilar-Reyes E.A, Alfonso I. Porogen Effect on Structural and Physical Properties of β-TCP Scaffolds for Bone Tissue Regeneration. IRBM. 2020.

[8]. Legeros RZ. Propriedades dos biomateriais osteocondutores: fosfatos de cálcio. Clinical Orthopaedics and Related Research., 2002.

[9]. Takya, C. M.; Granjeiro, J. M.; Maia, M. D. C. Avaliação da compatibilidade biológica de biomateriais – ensaio in vivo. Biomateriais em Odontologia, 2011.

[10]. Ghosh R, Sarkar R. Synthesis and characterization of sintered beta-tricalcium phosphate: comparative study on the effect of preparation route. Materials Science and Engineering C 67, 2016.

[11]. Dorozhkin S. V. "Calcium orthophosphate-based biocomposites and hybrid biomaterials" Journal of Materials Science, 2009.

[12]. Shim, K. S; Kim, H. J; Kim, S. E; Park, K. Simple surface biofunctionalization of biphasic calcium phosphates for improving osteogenic activity and bone tissue regeneration. Journal of Industrial and Engineering Chemistry, vol.68, p.220-228, 2018.

[13]. Dorozhkin, S. Bioceramics of calcium orthophosphates. Biomaterials, v. 31, p. 1465–85, 2010.

[14]. Chen, J.; Peng, Y.; Zheng, Z.; Sun, P.; Wang, X. Silver-releasing and antibacterial activities of polyphenol-based polyurethanes. Journal of Applied Polymer Science, v. 132, p. n/a-n/a, 2015.

[15]. Motameni, A.; Dalgic, A. D.; Alshemary, A. Z.; Keskin, D.; Evis, Z. Structural and Biological Analysis of Mesoporous Lanthanum Doped βTCP For Potential Use as Bone Graft Material. Materials Today Communications, 23, 101151, 2020.

[16]. Jian He, Yu Zhang, Xiaoyi Liu, liJun Peng, Huiling Li, Chengdong Xiong, Lifang Zhang. Load-bearing PTMC-beta tri-calcium phosphate and dexamethasone biphasic composite microsphere scaffolds for bone tissue engineering. Materials Letters 260, p. 126939, 2020.

[17]. Wu Tingting, Shi Haishan, Liang Yongyi, Lu Teliang, Lin Zefeng, Ye Jiandong. Improving osteogenesis of calcium phosphate bone cement by incorporating with manganese doped β-tricalcium phosphate. Materials Science & Engineering C (2019).

[18]. Santos V, I, Merlini C, Aragones Á, Cesca K, Fredel M C. In vitro evaluation of bilayer membranes of PLGA/hydroxyapatite/β-tricalcium phosphate forguided bone regeneration, Materials Science & Engineering C (2020).

[19]. Sinusaite, L.; Popov, A.; Antuzevics, A.; Mazeika, K.; Baltrunas, D.; Yang, J. C.; Horng, J. L.; Shi, S.; Sekino, T.; Ishikawa, K.; Kareiva. A.; Zarkov, A. Fe and Zn co-substituted beta-tricalcium phosphate (β-TCP): Synthesis, structural, magnetic, mechanical and biological properties. Materials Science & Engineering C, 112, 110918, 2020.

[20]. Eslaminejad, M. B.; Bordbar, S.; Nazarian, H. Odontogenic differentiation of dental pulp-derived stem cells on tricalcium phosphate scaffolds. Journal of Dental Sciences, 8 (3), p. 306–313, 2013.

[21]. Xie L., Yu H., Deng Y., Yang W., Liao L., Long Q. Preparation, characterization and in vitro dissolution behavior of porous biphasic α/β-tricalcium phosphate bioceramics. Materials Science and Engineering: C. 59, 1007-1015. 2016.

[22]. Elliott, J. C. Structure and chemistry of apatite and other calcium orthophosphates. Elsevier, Amsterdan, p. 111, 1994.

[23]. Frasnelli M., Sglavo V. M. Effect of Mg2+ doping on beta–alpha phase transition in tricalcium phosphate (TCP) bioceramics. Acta Biomaterialia. 33, p. 283-289, 2016.

[24]. Frasnelli M., Sglavo V. M. Effect of Mg2+ doping on beta–alpha phase transition in tricalcium phosphate (TCP) bioceramics. Acta Biomaterialia. 33, p. 283-289, 2016.

[25]. Porsani, N. K.; Santos, M. K.; Rocha, A. M.; Trombini, V.; Ana, P. A.; Tercini, M. B.; Setz, L. F. G. Beta-phosphate tricalcium colloidal processing. Ceramics International 46 (3), 2648-2653, 2019.

[26]. Guastaldi A C, Aparecida A H. fosfatos de cálcio de interesse biológico: importância como biomateriais, propriedades e métodos de obtenção de recobrimentos. Quimica Nova, Vol. 33, No. 6, p. 1352-1358, 2010.

[27]. Park, Y.M.; Ryu, S.Y.; Stevens, R.; Park, H.C. Preparation of whisker shaped hydroxyapatite / β-tricalcium phosphate composite. Materials Chemistry and Physics, 2007.

[28]. Tanaka, T., Komaki, H., Chazono, M., Kitasato, S., Kakuta, A., Akiyama, S., Marumo, K., 2017. Basic research and clinical application of beta-tricalcium phosphate (beta- TCP). Morphologie 101, 164–172. 2017.

[29]. Dorozhkin SV. Calcium orthophosphate deposits: Preparation, properties and biomedical applications. Materials Science and Engineering C: Materials for Biological Applications. 2015.

[30]. Hu C, Xue Z, Wang X, Xu D. Molecular dynamics exploration of the amorphous surface structures and properties of the biomimetic β-tricalcium phosphate. Applied Surface Science 484, p. 72–82. 2019.

[31]. Boanini, E.; Gazzano, M.; Nervi, C.; Chierotti, M. R.; Rubini, K.; Gobetto, R.; Bigi, A. Strontium and Zinc Substitution in β-Tricalcium Phosphate: An X-ray Diffraction, Solid State NMR and ATR-FTIR Study. Journal of Functional Biomaterials, vol.10, n°20, 2019.

[32]. Lin Y, Cai S, Jiang S, Xie D, Ling R, Sun J, Wei J, Xu K S, G. Enhanced corrosion resistance and bonding strength of Mg substituted β-tricalcium phosphate/Mg (OH)2 composite coating on magnesium alloys via one-step hydrothermal method. 2019.

[33]. Zhang L, Zhang C, Zhang R, Jiang D, Zhu Q, Wang S. Extraction and characterization of HA/b-TCP biphasic calcium phosphate from marine fish. Materials Letters 236, p. 680–682. 2019.

[34]. N G Janssen, R. Schreurs, AP de Ruiter, H. -C. Sylvester-Jensen, G. Blindheim, G.J. Meijer, R. Koole, H. Vindenes: Microstructured beta-tricalcium phosphate for alveolar cleft repair: a two-centre study. International Journal of Oral and Maxillofacial Surgery. 48: 708–711. 2019.

[35]. Abdelrahman I. Rezk, Tae In Hwang, Ju Yeon Kim, Ji Yeon Lee. Functional composite nanofibers loaded with b-TCP and SIM as a control drug delivery system. Materials Letters 240, p.25–29.2019.

[36]. Ates, T.; Dorozhkin, S. V.; Kaygili, O.; Kom, M.; Ercan, I.; Bulut, N.; Firdolas, F.; Keser, S.; Gursoy, N. C.; Ozercan, I. H.; Eroksuz, Y.; İnce, T. The effects of Mn and/or Ni dopants on the in vitro/in vivo performance, structural and magnetic properties of β-tricalcium phosphate bioceramics. Ceramics International, 45, 22752-22758, 2019.

[37]. Kannan S., A. Lemos, JHG Rocha, JMF Ferreira, Caracterização e me-desempenho mecânico do β-Ca 3 (PO 4) 2 estabilizado com Mg preparado a partir de Mg-sub-apatite deficiente em Ca stituted, Journal of the American Ceramic Society. 89, p. 2757–2761. 2006.
[38]. Bose S., S Tarafder, SS Banerjee, NM Davies, A. Bandyopadhyay, Understandingresposta in vivo e variação de propriedade mecânica em β- dopado com MgO, SrO e SiO_2TCP, Bone 48, 1282–1290, (2011).
[39]. Cacciotti I., A. Bianco, High thermally stable Mg-substituted tricalcium phosphate via precipitation, Ceramics International. 37, p. 127–137. 2011.
[40]. Dorozhkin S.V., Calcium Orthophosphate-Based Bioceramics and Biocomposites, Wiley-VCH, Weinheim, Germany, p.416. 2016.
[41]. Kumta, P.N.; Sfeir, C.; Lee, D.; Olton, D.; Choi, D. Nanostructured calcium phosphates for biomedical applications: novel synthesis and characterization. Acta Biomaterialia, p. 65-83, 2005.
[42]. Basu S & Basu B. Doped biphasic calcium phosphate: synthesis and structure. Journal of asian ceramic societies., Vol. 7, p. 265. 2019.
[43]. Boanini, E.; Gazzano, M; Bigi, A. Ionic substituutions in cálcio phosphates synthesized at low temperature. Acta Biomaterialia. 6, 1882–1894. 2010.
[44]. Zhang, M, Wu, C, Li, H ,Yuen, J , Chang, J ,Xiao, Y. Preparation, characterization and in vitro angiogenic capacity of cobalt substituted β-tricalcium phosphate ceramics. Journal of Materials Chemistry. 22, p. 21686–21694, 2012.
[45]. Zhang, M, Wu, C, Li, H ,Yuen, J , Chang, J ,Xiao, Y. Preparation, characterization and in vitro angiogenic capacity of cobalt substituted β-tricalcium phosphate ceramics. Journal of Materials Chemistry. 22, p. 21686–21694, 2012.
[46]. Frasnelli M, Sglavo V. M. Effect of Mg2+ doping on beta–alpha phase transition in tricalcium phosphate (TCP) bioceramics. Acta Biomaterialia. 33, p. 283-289. 2016.
[47]. Kazemi, M; Dehghan M. M, Azami, M. Biological evaluation of porous nanocomposite scaffolds based on strontium substituted β-TCP and bioactive glass: An in vitro and in vivo study. Materials Science and Engineering C, vol.105, 2019.
[48]. Herrero, S; Pico, Y. Treatments for women with postmenopausal osteoporosis, which is new? How can we manage long-term treatment? European Journal of Pharmacology. vol.779, p.8-21, 2016.
[49]. Yuan, J.; Wang, B.; Han, C.; Huang, X.; Xiao, H.; Lu, X.; Lu, J.; Zhang, D.; Xue, F.; Xie, Y. Nanosized-Ag-doped porous β-tricalcium phosphate for biological applications. Materials Science & Engineering C, 114, 111037, 2020.
[50]. Singh, R. K.; Awasthi, S.; Dhayalan, A.; Ferreira, J. M. F.; Kannan, S. Deposition, structure, physical and invitro characteristics of Ag-doped β-Ca3(PO4)2/chitosan hybrid composite coatings on Titanium metal. Materials Science and Engineering C, 62, 692-701, 2016.
[51]. Kotoka, R.; Yamoah, N. K.; Mensah-Darkwa, K.; Moses, T.; Kumar, D. Electrochemical corrosion behavior of silver doped tricalcium phosphate coatings on magnesium for biomedical application. Surface & Coatings Technology, 292, 99-109, 2016.
[52]. Costa, N. M. F.; Yassuda, D. H.; Sader, M. S.; Fernandes, G. V. O.; Soares, G. D. A.; Granjeiro, J. M. Osteogenic effect of tricalcium phosphate substituted by magnesium associated with Genderm® membrane in rat calvarial defect model. Materials Science and Engineering C, 61, 63-71, 2016.
[53]. Takeuchi, A.; Tsuge, T.; Kikuchi, M. Preparation of porous β-tricalcium phosphate using starfish-derived calcium carbonate as a precursor. Ceramics International, vol.42, p.15376-15382, 2016.
[54]. Park, K. D.; Jung, Y. S.; Lee, K. K.; Park, H. J. Behavior of Osteoblast-Like Cells on a b-Tricalcium Phosphate Synthetic Scaffold Coated With Calcium Phosphate and Magnesium. The Journal of Craniofacial Surgery, vol.27, n.4, p.898-903, 2016.
[55]. Singh, S. S.; Roy, A.; Lee, B.; Banerjee I.; Kumta, P. N. Synthesis, characterization, and in-vitro cytocompatibility of amorphous β-tri-calcium magnesium phosphate ceramics. Materials Science and Engineering C, vol.67, p.636-645, 2016.
[56]. Singh, S. S.; Roy, A.; Lee, B.; Kumta, P. N. Study of hMSC proliferation and differentiation on Mg and Mg–Sr containing biphasic β-tricalcium phosphate and amorphous calcium phosphate ceramics. Materials Science and Engineering C, vol.64, p.219-228. 2016.
[57]. Bakheet, A. M. A.; Saeed, M. A.; Sahnoun, R.; Isa, A. R. M.; Mohammed, L.; Mahmood, T. Density functional theory study of the electronic and optical properties of pure and magnesium doped β-tricalcium phosphate compound. Jurnal Teknologi, vol.78, n°3, p.167-172, 2016.
[58]. Gokcekaya, O.; Ueda, K.; Ogasawara, K.; Kanetaka, H.; Narushima, T. In vitro evaluation of Ag-containing calcium phosphates: Effectiveness of Ag-incorporated β-tricalcium phosphate. Materials Science and Engineering C, vol.75, p.926-933. 2017.
[59]. Samanta, S. K.; Chanda, A.; Study on the Structure and Properties of Crystalline Pure and Doped β-Tri Calcium Phosphate Ceramics. Materials Today: Proceedings 5 p. 2330–2338, 2018.
[60]. Tripathi, G.; Sugiura, Y.; Tsuru, K.; Ishikawa, K. In vivo stability evaluation of Mg substituted low crystallinity ßtricalcium phosphate granules fabricated through dissolution– precipitation reaction for bone regeneration. Biomedical Materials, vol.13, n065002, 2018.
[61]. Boanini, E.; Torricelli, P.; Sima, F.; Axente, E.; Fini, M.; Mihailescu.; I. N.; Bigi, A. Gradient coatings of strontium hydroxyapatite/zinc β-tricalcium phosphate as a tool to modulate osteoblast/osteoclast response. Journal of Inorganic Biochemistry, vol.183, p.1-8, 2018.
[62]. Wang, J.; Qian, J.; Xu, W.; Wang, Y.; Hou, G.; Sun, T.; Luo, L. Effects of Sr2+/Zn2+ co-substitution on crystal structure and properties of nano-β-tricalcium phosphate. Ceramics International, vol.44, pág 6096–6103, 2018.
[63]. Zare, M.; Haghgoo, R.; Taleghani, F.; Niakan, M. Antibacterial activity of β -Tricalcium phosphate containing nanosilver particles on periodontal Gram-negative pathogen. Journal of Stomatology, Oral and Maxillofacial Surgery, vol.120, n°6, p.545-548, 2018.
[64]. Guo, X.; Long, Y.; Li, W.; Dai, H. Osteogenic effects of magnesium substitution in nanostructured b-tricalcium phosphate produced by microwave synthesis. Journal of Materials Science, vol.54, n°16, p.11197–11212, 2019.
[65]. Gallo, M; Santoni, B L G; Douillard, T; Zhang, F; Gremillard, L; Dolder, S; Solène T, Hofstetter, W; Meille, S; Bohner, M; Chevalier, J. Effect of grain orientation and magnesium doping on β-tricalcium phosphate resorption behavior. Acta Biomaterialia. v. 89, p. 391-402, 2019.
[66]. Frasnelli, M.; Pedranz, A.; Biesuz, M.; Dirè, S.; Sglavo, V.M. Flash sintering of Mg-doped tricalcium phosphate (TCP) nanopowders. Journal of The European Ceramic Society, [S.L.], v. 39, n. 13, p. 3883-3892, 2019.
[67]. Samanta, S K; Devi, K. B; Das, P; Mukherjee, P; Chanda, A; Roy, M; Nandi, S K. Metallic ion doped tri-calcium phosphate ceramics: effect of dynamic loading on in vivo bone regeneration. Journal of The Mechanical Behavior of Biomedical Materials, [S.L.], v. 96, p. 227-235, 2019.
[68]. Massit, A.; Yacoubi, A. E.; Rezzouk, A.; Idriss, B. C. E. Thermal Behavior of Mg-Doped Calcium-Deficient Apatite and Stabilization of β Tricalcium Phosphate. Biointerface Research in Applied Chemistry, vol.10, n°6, p.6837-6845, 2020.
[69]. Gokcekaya, O.; Ueda, K.; Narushima, T.; Nakano, T. Using HAADF-STEM for atomic-scale evaluation of incorporation of antibacterial Ag atoms in a β-tricalcium phosphate structure. Nanoscale, vol.12, p.16596–16604, 2020.

[70]. Qin, L.; Yi, J.; Xuefei, L.; Li, L.; Kenan, X.; Lu, X. The preparation of a difunctional porous β-tricalcium phosphate scaffold with excellent compressive strength and antibacterial properties. RSC Advances, vol.10, p.28397–28407, 2020.

[71]. Chou, Y. J.; Ningsih, H. S.; Shih, S. J. Preparation, characterization and investigation of antibacterial silver-zinc co-doped β-tricalcium phosphate by spray pyrolysis. Ceramics International, 46, 16708-16715, 2020.

[72]. Yuan, J.; Wang, B.; Han, C.; Huang, X.; Xiao, H.; Lu, X.; Lu, J.; Zhang, D.; Xue, F.; Xie, Y. Nanosized-Ag-doped porous β-tricalcium phosphate for biological applications. Materials Science & Engineering C, 114, 111037, 2020.

[73]. Kozelskaya, A.I.; Kulkova, S. E.; Fedotkin, A. Y.; Bolbasov, E. N.; Zhukov, Y. M.; Stipniece, L.; Bakulin, A. V.; Useinov, A. S.; Shesterikov, E. V.; Locs, J.; Tverdokhlebov, S. I. Radio frequency magnetron sputtering of Sr- and Mg-substituted βtricalcium phosphate: Analysis of the physicochemical properties and deposition rate of coatings. Applied Surface Science, 509, 144763, 2020.

[74]. Wang, M; Ge, X; Cui, Z; Wu, S; Zhu, S; Liang, Y; Li, Z; Lu, W. Influences of strontium on the phase composition and lattice structure of biphasic calcium phosphate. Ceramics International. 2021

[75]. He F, Lu T, Feng S, Wang Y, Huang C, Zhang Y, Deng X, Ye J. Alliance of gallium and strontium potently mediates the osteoclastic and osteogenic activities of β-tricalcium phosphate bioceramic scaffolds. Chemical Engineering Journal, vol.412, p. 128709, 2021.