Chapter 63

The effect of the incorporation of Mg in beta tricalcium phosphate: a brief review

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ABSTRACT
Beta tricalcium phosphate (β-TCP) is a well-known biomaterial in the area of bone substitutes, as it presents excellent biodegradability, as well as excellent biocompatible properties. Promoting greater stability and mechanical resistance to this phase, magnesium (Mg) appears as a promising candidate for doping β-TCP. Thus, this work aimed to review the effect of β-TCP doping with Mg. It has been found that small additions of Mg provide strong changes in β-TCP.

Keywords: Beta tricalcium phosphate (β-TCP), Doping, Magnesium (Mg).

1 INTRODUCTION

Biomaterials are implantable materials that perform their function in contact with living tissues, which emerge as solutions to problems related to the human body, promoting well-being and improving quality of life, contributing with their applications in the vast field of joint replacements and limbs, ocular implants, dental implants, artificial arteries and skin surgery (VALLET-REGÍ, 2010; DEVGAN and SIDHU, 2019). The use of materials to correct problems related to human health is not dated today, the advent of these records originates in antiquity. Where there are records of the use of linen and gold sutures in Ancient Egypt (2000 BC), as well as artificial teeth made from shells by the Maya (600 BC) (PIRES et al., 2015). Today, the medical implants and prostheses in use are designed to be ideal for usefulness and ease of use. This can be attributed to both; the advancement of engineering and technology, as well as progress in our understanding of interactions between biomaterials and living systems (BHORKAR and DHOBLE, 2021).

The current chemically produced materials intended for tissue engineering are non-degradable ceramics, bioinert metals, and synthetic polymers (YI et al., 2022; GAO et al., 2022). Among the different biomaterials, bioceramics is a large class of biomaterials used in clinical practice for the repair and reconstruction of diseased or damaged parts of the body in various forms, including solid parts, powders, granules, coatings on metallic joint prostheses, bone cement or porous scaffolds (PASCAUD et al., 2022). Calcium phosphates form a highly requested group when it comes to bioceramics, due to their excellent biocompatibility, osteoconductivity, and osteoinductivity (ZHAO et al., 2022).

After hydroxyapatite, tricalcium phosphate [Ca3(PO4)2, TCP] is the second most commonly used calcium phosphate compound for biomedical applications (PORSANI et al., 2020). Exhibiting three polymorphs: the low-temperature β-TCP and the high-temperature forms, α- and α′-TCP (CARRODEGUAS and AZA, 2011). Among these, the α′-TCP polymorph has no biological interest, due to the restricted stability field and spontaneous reconversion into α-TCP upon cooling. On the other hand, α-TCP can be retained at low temperatures as a metastable phase; however, it has limited biomedical applications due to its high resorption rate (0.0025g L-1 at 25°C) (FRASNELLI et al., 2019). β-TCP stands out among such polymorphs due to its biodegradation rate and absorption that is 10–20 times faster than HA, also demonstrating superior osteoconductivity when compared to HA (TAHERIMEHR et al., 2021).

However, the β to α phase transition affects the sintering behavior and final mechanical properties of the TCP components. Due to the increase in cell volume, the transition is associated with a volumetric expansion (~7%), which reduces shrinkage and prevents TCP from being more densified (FRASNELLI and SGLAVO, 2016). In addition to these physical issues, the β→α transition also generates an increase in solubility in a biological medium, leading to very rapid and uncontrolled resorption of the TCP bone substitute (SOMERS et al., 2021).

Therefore, as an alternative to postponing the β to α transition during heating, there is the possibility of introducing dopants into the β-TCP structure to increase its thermal stability, allowing a higher

temperature treatment (SOMERS et al., 2021). Magnesium (Mg) is known to be a doping element that plays an important role in bone metabolism by controlling the cellular activity of osteoblasts and osteoclasts (SINUSAITE et al., 2019). It is known that Mg-doped TCP exhibits more valuable results in terms of stabilization against other substitutional ions, such as K^+, Na^+ e Zn^{2+} (FRASNELLI e SGLAVO, 2016). Thus, this work aims to review the production of β-TCP doped with Mg, evaluating the effects of this modification.

2 MATERIAL AND METHODS

The methodology followed for the preparation of this literature review was a search in the ScienceDirect, Scopus, and Web of Science databases. Works were sought that discussed the doping of β-TCP using magnesium as a substituent metallic ion. Searching for research articles from 2016 to the present day was carried out.

BETA TRICALCIUM PHOSPHATE (β-TCP)

Calcium phosphates stand out as ceramic compounds with diverse applications in the biomedical area since they have not only a constitution similar to the mineral composition of bones and teeth, but also excellent bioactivity, absence of toxicity, biocompatibility, degradation rates variables, and osteoconductivity (GUASTALDI and APARECIDA, 2010). Among the multiple types of calcium phosphate (Table 1), both Hydroxyapatite and ($Ca_{10}(PO_4)_6(OH)_2$, HA) how much tricalcium phosphate ($Ca_3(PO_4)_2$, TCP) as the most commonly used materials in the bioceramic market (PORSANI et al., 2020; STEFANIC et al., 2013). Taking this into account, the succession of TCP in four crystalline forms is highlighted: A rhombohedral phase that is consolidated up to temperatures around 1125°C is called the beta phase (β-TCP), a monoclinic phase stabilized in the range of 1125 °C to 1430°C also called the alpha phase (α-TCP), and two other phases in which the first is identified as a high-temperature phase (exceeding 1430°C), super alpha (α'-TCP), and the other as a phase of notable pressures, γ phase (γ-TCP) (FRASNELLI and SGLAVO, 2016; DESCAMPS et al., 2008).

Table 1. Calcium Phosphates

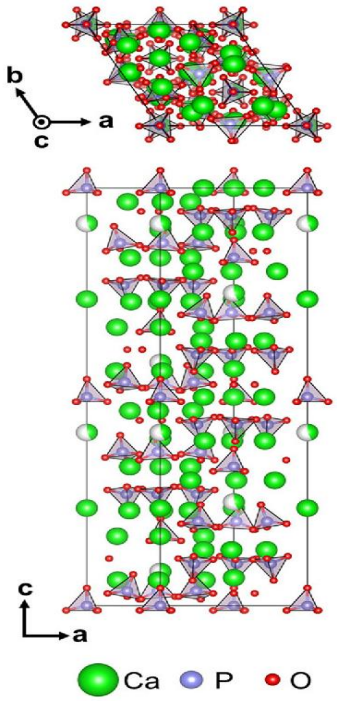
Calcium phosphate	Chemical formula	Ca/P ratio
Hidroxiapatita (HA)	$Ca_4O(PO_4)_2$	2,0
Fosfato de cálcio amorfo (ACP)	$Ca_{10}(PO_4)_6(OH)_2$	1,67
Fosfato tricálcico (α, α', β, γ) (TCP)	$Ca_3(PO_4)_2.nH_2O$	1,5
Fosfato tetracálcico (TeCP)	$Ca_3(PO_4)_2$	1,5
Mono-hidrogênio fosfato de cálcio di-hidratado (DCPD)	$Ca_8HPO_4.2H_2O$	1,0
Mono-hidrogênio fosfato de cálcio (DCP)	$CaHPO_4$	1,0
Pirofosfato de cálcio (CPP)	$Ca_2P_2O_7$	1,0
Priofosfato de cálcio di-hidratado (CPPD)	$Ca_2P_2O_7.2H_2O$	1,0
Fosfato heptacálcico (HCP)	$Ca_7(P_5O_{16})_2$	0,7
Di-hidrogênio fosfato tetracálcico (TDHP)	$Ca_4H_2P_6O_{20}$	0,67
Fosfato monocálcico mono-hidratado (MCPM)	$Ca(H_2PO_4)_2H_{20}$	0,5
Metafosfato de cálcio (α, β, γ) (CMP)	$Ca_3(PO_3)_2$	0,5
Fosfato Octacálcico (OCP)	$Ca_8H_2(PO_4)_2$	1,33

Source: GUASTALDI e APARECIDA, 2010.

However, the α and β phases are the only ones that have been gaining more and more visibility in the area of biomaterials, largely due to the difficulties of the others, given the high temperature and pressure conditions necessary to obtain them. That said, a general-purpose β-TCP ceramic was analyzed through biological tests and biomedical applications, and its superiority over other bioceramics was affirmed (DESCAMPS et al., 2008; VALENTIM et al., 2018). Therefore, not only because of its similarity with bone tissue and its ease of obtaining it but also because of its excellent properties regarding its biological capabilities, presenting both a good shelf life and a promising balance between absorption and degradation of the material (VALENTIM et al., 2018; SAITO et al., 2011; GOSH and SARKAR, 2016). Although, even with all this in vogue, it is worth mentioning that when compared to the α-phase, β-TCP presents inferiority with both its biocompatibility and its bio reabsorption (BOHNER, 2000). Even so, β-TCP has been gaining more and more prominence in the field of bone replacement and coating of bone prostheses, largely due to its "in vivo" reabsorption, which allows for progressive degradation, enabling replacement by new bone tissue. (YASHIMA et al., 2003)

Despite what was mentioned earlier, obtaining these phases does not have a fixed temperature for obtaining them, although it is stipulated at temperatures above 950°C that B-TCP is stable and that when it exceeds 1125°C, the transformation of phases from β to α this does not establish the conditions of synthesis and additives to which the material may have been submitted, which happens in complications to standardization of TCP acquisition temperatures (BOHNER, 2000; FARZADI et al., 2011). Since the influence of some impurities, such as Na, Si, Mg, and Sr, can significantly alter these temperatures. For example, concentrations around 8 mol% of Mg are capable of increasing the transformation temperature by almost 400°C, as magnesium acts as a β-phase stabilizer (SAITO et al., 2011; ENDERLE et al., 2005). However, in the case of a β-TCP solely composed of the chemical formula $Ca_3(PO_4)_2$ and molar ratio Ca/P = 1,5, It is of paramount importance to highlight the conclusion of its crystallization in the rhombohedral space group R3c, commonly described with a unit cell dimension of parameters: 10.435-10.438 Å for axis “a”, 37.39-37.43 Å for axis “ c”, α=90°, γ=120° (BOHNER et al., 2020; PORSANI et al., 2019). Figure 1 shows the crystalline structure of β-TCP.

Figure 1: Crystallographic structure of β-TCP



Source: Matsunaga et al. (2015)

As a result, many studies have been carried out around tricalcium phosphates, given their excellent properties. These studies address numerous aspects of it, from chemical formulation to transformations of crystalline phases. A large part of the research focuses on the bioactive qualities aiming at its performance in the biomedical area, however much has also been studied about its mechanical properties that present excellent attributes related to the hardening of the material. However, all of them have aspired to the same result, expanding, even more, the number of possible applications of the material (FERNANDEZ et al., 1999; LEMONS, 1996).

B-TCP DOPED WITH Mg

Calcium phosphate-based biomaterials are gaining more and more prominence in changing their chemical formulation, since, even taking into account their excellent biocompatibility with the human bone mineral phase, composed of calcium phosphate, It is of great importance to mention that it is composed of several other components, such as Sodium (Na^+), magnesium (Mg^{2+}), carbonates (CO_3^{2-}) e several other ions found in smaller amounts (F^-, K^+) (GUASTALDI e APARECIDA, 2010; GROOT, 1993). Many microminerals or trace elements, present in human bone composition play extremely important roles in the growth, formation, and repair of bone tissue (FERREIRA et al., 2018). Thus, many calcium phosphates have been doped through ionic substitutions, with the aim of not only improving their already excellent bioactive properties but also their mechanical properties (GROOT, 1993; KIM et al., 2003). Since both synthetic HA and β-TCP are quite prone to the addition of some dopant element in their crystalline network (FERREIRA et al., 2018).

There are many beneficial components used in the doping process of biomaterials, however, when it comes to HA and β-TCP, the most commonly used to improve their physicochemical properties are Strontium (Sr), manganese (Mn) and Zinc (Zn) (SHEPHERD et al., 2012; ZOFKOVÁ et al., 2013). Which, the replacement of Ca2+ by Sr2+ in the HA and β-TCP structures is often found in bioceramics aimed at the treatment of osteoporosis, since the incorporation of strontium in them stimulates the formation of bone tissue, the replication of pre-osteoblasts, osteoid matrix synthesis, as well as, inhibits the differentiation and activity of osteoclasts, limiting bone resorption (CHEN et al., 2008). Concerning the integration of manganese into the system, it plays a very important role as a cofactor for several enzymes involved in the remodeling of the extracellular matrix, as well as demonstrating great relevance in the field of cell adhesion, since it plays a large role in the about the affinity of integrin bonds (MAYER et al., 1993). Moreover, in the case of zinc, it is extremely important to highlight its role in the process of bone metabolism, since it is integrally linked to the bone formation process, acting on the proliferation of osteoblasts and inhibition of osteoclasts (XUE et al., 2008). Other studies referring to Zn doping point out that it provides, to bioceramic materials, excellent anti-inflammatory properties (LANG et al., 2007).

However, magnesium has been increasingly highlighted as one of the main substitute ions for calcium in the crystalline tricalcium phosphate network, since it provides not only an increase in the mechanical strength of the material but also stability of the β-TCP phase (KAI et al., 2012). Since, in the process of synthesizing β-TCP in an aqueous medium, magnesium is normally incorporated into the structure, resulting in what is called β-TCMP (FONTES et al., 2007). The effects of modifying β-TCP with Mg are presented in the literature review below.

Bakheet et al. (2016) studied the electronic and optical properties of pure and Mg-doped β-TCP compounds. The results show the calculation of band gap values of 5.2eV and 3.4 eV for pure and Mg-doped β-TCP, respectively. The refractive index has values less than 1.0 at higher energy values for both materials. The real dielectric function reaches the stability stage at energies greater than 50 eV.

Park et al. (2016) evaluated disc surface characteristics of β-TCP substrates, which were not coated or reversed with HA and/or Mg, as a preliminary investigation of their potential to serve as bone graft materials, an additional beneficial effect of Coating of Mg with Ca was also found in this study. The results suggest that Ca and Mg ions have synergistic effects in controlling osteoblast function and may increase osteoblast adhesion, proliferation, and ALP activity.

Singh et al. (2016) verified the influence of cell culture media supplementation with a combination of Mg2+ and PO43− ions on the proliferation and differentiation of hMSCs in an amorphous β-TCMP phase. A low-temperature aqueous approach was used to synthesize high surface area nanocrystalline Mg2+-substituted β-tricalcium phosphate (β-TCMP) Scaffolds prepared with amorphous β-TCMP were able to support increased hMSC proliferation and differentiation compared to β -TCP commercially available. However, similar gene expression of mature osteoblast markers, OCN and COL-1, was observed

compared to biphasic β-TCMP. It was therefore concluded that the release of Ca2+ ions from β-TCMP scaffolds also plays a role in the regulation of osteogenic differentiation in these scaffolds.

Frasnelli and Sglavo (2016) evaluated the phase evolution of β-TCP bioceramics in the presence of Mg, and the β to α transformation in Mg-TCP systems was investigated in terms of dopants concentration and post-transformation cooling rate; the effect of suitable secondary heat treatment (annealing) to induce α to β reconversion was also analyzed. Mg-doped TCP powder was obtained by the solid-state reaction from powders of pure calcium carbonate, dibasic ammonium phosphate, and magnesium oxide. Magnesium was found to strongly increase the stability of the β polymorph by postponing the transformation temperature into the α phase. Therefore, during the sintering process of Mg-TCP powders, this allows for achieving greater densification. Torres et al. (2016) also clarified the kinetics of the α-TCP→ β-TCP phase transformation. Investigating the effects of cooling rate and extent of Mg doping on the thermal stability of α ↔ β-TCP were other intended targets. Mg-substituted β-Ca3(PO4)2 powders with different Mg contents (0-5 mol) were synthesized by an aqueous precipitation method. Concluding that the thermal stability of the β-TCP phase was significantly improved with increasing Mg doping extensions.

Singh et al. (2016) studied the effects of the co-substitution of Mg2+ and Sr2+ in β-TCP on phase composition, physicochemical properties, proliferation, and mechanisms by which these scaffolds support osteogenic differentiation of hMSC. Doping was performed by hydrolysis of precipitated DCPD with Mg2+ and Sr2+. It was observed that even though β-TCP was the only crystalline phase detected using X-ray diffraction, the (Ca+Mg+Sr)/P ratio measured by ICP was much lower than 1.5, corresponding to β-TCP, for all conditions studied. They found that increased concentrations of Mg2+ and PO43 − were measured for samples prepared with increased concentrations of Mg2+. They further concluded that scaffolds prepared with 50% Mg β-TCP can support increased differentiation compared to commercially available β-TCP via the SMAD-dependent TGF-β and BMP signaling pathway. Substitutions of strontium and magnesium were also estimated by Kozelskaya et al. (2020) in the target composition sprayed with β-TCP on the physicochemical properties and deposition rate of the produced coatings. Tricalcium phosphate (TCP) (with theoretical molar ratio (Ca + M)/P = 1.5 where M represents Mg and/or Sr), i.e. β-TCP precursors containing Mg and/or Sr were synthesized using the adapted wet chemical precipitation method. It has been found that the presence of magnesium substitutions in the pulverized β-TCP target leads to slight reductions in the deposition rate. Theoretical calculations indicate that the decrease in unit cell volume due to magnesium replacements leads to a slight decrease in the rate of Mg-β-TCP coating deposition. The relationship between the unit cell volume of the sprayed powder and its deposition rate is revealed, with larger unit cell volumes generating higher spray rates.

Tripathi et al. (2018) focused on in vivo Mg-LC-β-TCP responses during long-term implantation with a focus on osteoblast- and osteoclast-like cell responses using an immunity staining method. Low crystallinity β-TCP granules incorporated with Mg were manufactured through a dissolution-precipitation process mediated by α-TCP solution immersed in an acidic solution containing Mg2+. Mg2+ incorporated

into β-TCP not only decreased the granule dissolution rate but also increased osteoblastic cell activity and suppressed osteoclast activity. With that, Mg-LC-β-TCP not only improved osteoconductivity but also has resilience through bone remodeling.

Gallo et al. (2019) evaluated the possible correlation between grain orientation and preferential dissolution in β-TCP and the influence of Mg doping on this correlation. Both undoped (neat) and Mg-doped β-TCP samples were processed. For non-doped samples, it was necessary to synthesize pure powder of CDHA (Calcium Deficient Hydroxyapatite) by precipitation in an aqueous medium. For Mg-doped samples, β-TCP powders were synthesized by the solid-state reaction from anhydrous dicalcium phosphate (CaHPO4, Calcium Phosphate GFS Chemicals, Art: 1548, purity ≥ 99.95%) and commercial hydroxyapatite powder (Ca5(PO4)3OH, Budenheim Tricalcium Phosphate, Art: C5381). Doping β-TCP with Mg ions decreased its solubility: both the acid attack and the cellular reabsorption process were delayed. They also concluded that the doping of β-TCP phases 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 since the initial dissolution was guided by grain orientation, where some grains were preferentially attacked, this occurred for the three compositions investigated (non-doped, low-Mg doped and high-Mg doped samples).

Guo et al. (2019) showed the effects of microwave irradiation on structure and morphology, β-TCP doped with Mg-5mol% (Mg5-TCP) was synthesized via chemical precipitation assisted by microwave irradiation under different times and temperatures in the microwave exposure. The best parameters were used to synthesize β-TCP substituted by different levels of Mg (0, 5, 10, and 14 mol%). It was verified that all samples did not show significant toxicity and Mg14-TCP had a better promotion in proliferation and differentiation. For Mg5-TCP and Mg10-TCP samples, due to the deposition of ions from the culture medium on ceramic discs, they did not show remarkable ease in comparison with pure β-TCP samples.

Cui et al. (2020) studied biphasic calcium phosphate (BCP) produced through chicken eggshells by hydrothermal reactions, investigating the synergistic effects of Mg substitution and particle size on the balance between the ion exchange reaction for β-TCP production and the dissolution-reprecipitation reaction for HA production. Their results indicated that β-TCP nanocrystals were formed through ion exchange reactions of Mg-calcite nanoparticles, while HA nanocrystals were produced mainly by dissolution-reprecipitation reactions mainly on eggshell surfaces in the hydrothermal system. The low Mg content (~ 2.0 mol.%) led to the formation of β-TCP through ion exchange reactions inhibiting the formation of HA crystals. Furthermore, BCP with different compositions (~28.6–77.8 wt% β-TCP) were produced using different eggshell particle sizes for hydrothermal.

Saikiran et al. (2020) analyzed the phase composition, crystallite, and thermal stability of the synthesized nanopowders, in addition to studying the effect of F co-substitution on the thermal stability of Zn /Mg substituted hydroxyapatite, produced with calcium hydroxide (Ca(OH)2) and diammonium hydrogen phosphate (DAP, (NH4)2HPO4) as precursors for calcium and phosphorus, respectively, for the

microwave synthesis of nanocrystalline substituted hydroxyapatite powders. The presence of characteristic peaks of β-TCP, in the annealed samples of 5MgHA and 5Mg50FHA, at 31.05° and 34.35° indicate thermal dissolution in the annealing at 900°C. The volumetric fraction of β-TCP, observed in the annealed samples, decreased from 34.98% to 19.35%, with the addition of fluorine in the 5MgHA sample. It can be concluded that fluorine co-doping increases the thermal stability of Zn/Mg substituted hydroxyapatites. Annealing the 5 MgHA sample resulted in an increase in crystallite size from 14.19 nm to 29.22 nm. Likewise, in the case of the 5Mg50FHA sample, the crystallite size increased from 16.02 nm in the synthesized sample (5Mg50FHA) to 40.65 nm in the annealed sample (5Mg50FHA-900).

Deyneko et al. (2020) revealed the relationship between the crystalline structure and the luminescence properties of Ca8MEu(PO4)7 (M = Mg, Zn, Cd, Ca) in β-TCP-type compounds. Produced in the air by the solid-state method from stoichiometric mixtures of CaCO 3 (99.99%), CaHPO4·2H2O (99.99%), CdO (99.99%), and Eu2O3 (99.99%) revealed the influence of M 2+ cations on photoluminescence excitation and emission spectra. The excitation spectra of Ca 8 M Eu(PO 4)7 phosphors showed the strongest absorption at 395 nm, which matched well with the commercially available n-UV emitting GaN-based LED chip. The emission spectra of Ca8MEu(PO4) 7 (M = Mg, Zn, Cd, Ca) indicated an intense red emission due to the 5D0 → 7F2 transition of Eu 3+.

Massit et al. (2020) clarified the effect of Mg doping on the TCP structure. Magnesium-substituted calcium-deficient apatite (Mg-CDHA) with an Mg/(Ca+Mg) ratio equal to 0.05 was synthesized by the precipitation method. It was observed that the incorporation of Mg2+ in the structure of CDHA promoted contraction in the network and after calcination, the transformation of CDHA into pure β-TCP occurred at a temperature below 650ºC by inhibiting the formation of HA crystals.

Somers et al. (2021) further studied the effect of Mg and Sr doping on thermal stability and conventional and microwave sintering of β-TCP. Three doping rates were used for each dopant individually (2.25, 4.50, and 9.00 mol%) and two co-doped compositions (2.00 mol% and 4.00 mol% of Mg2+ and Sr2+ simultaneously) were used. tested. It was observed that the replacement of Ca2+ by Mg2+ leads to a decrease in the unit cell parameters of the β-TCP structure and, therefore, to a shift of the diffraction peaks to higher 2θ values. The lattice contraction caused by Mg2+ substitution increases the stability of the β phase and postpones the β→α transition. Furthermore, the greater the amount of doping, the more pronounced this effect. It was also confirmed that magnesium has a stronger effect than strontium on β-phase stabilization for the same amount of doping. While for the two co-dopings, the effect is similar to that of Mg doping with an overall decrease of the unit cell parameters and a shift to higher values of 2θ for the diffraction peaks compared to the non-doped TCP.

Massit et al. (2021) obtained β-TCP and Mg-βTCP through the precipitation method and evaluated the influence of Mg substitution on the network parameters of the β-TCP unit cell. The analyzed doping rate was 0.05, 0.10, and 0.15. It was concluded that the size of the Mg-CDA crystallite decreased with

increasing Mg2+ content. It was observed that both cell parameters and cell volume increase unusually with Mg content.

Kon et al. (2021) tested two types of calcium phosphate biomorphic bone scaffolds (GreenBone™): One made of ion-doped hydroxyapatite/β-tricalcium phosphate (GB-1) and another made of undoped hydroxyapatite only (GB-2) and evaluated the regenerative capacity of the scaffold. It was demonstrated that, when implanted into a critical cortical defect in sheep, both GB-1 and GB-2 scaffolds were able to promote effective vascularization, osteogenesis, and osseointegration involving the entire scaffold volume, thus leading to scaffold regeneration. In the case of GB-1, the osteogenesis process was completed after just 3 months, obtaining a complete replacement of the scaffold by new mature bone, a critical aspect to recovering adequate biomechanical functionality. The presence of Mg2+ ions in the GB-1 scaffold could mimic the conditions found during natural osteogenesis and contribute to promoting complete regeneration of the segmental bone defect.

Jamarillo et al. (2021) evaluated scaffolds with Schwarz D geometry obtained by 3D printing using a biodegradable and bioactive paste, consisting of 65.5% calcium phosphate and without magnesium. 28.5% glass borate (BGBS), 3% attapulgite, and 2% water by weight. Calcium phosphate is associated with β-tricalcium phosphate (β-TCP). The scaffolds with calcium and magnesium phosphates (β-TCP/Mg) showed better degradability and bioactivity than scaffolds without Mg. Both scaffolds showed porosity and pore interconnectivity. Mesenchymal stem cells showed good adhesion and cell proliferation in contact with the scaffolds. Mg-doped scaffolds were better promoters of cell proliferation, in addition to not having a cytotoxic effect.

Qi et al (2022) prepared several scaffolds of β-TCP with gyroid structures doped with different amounts (0% by weight, 1% by weight, 3% by weight, and 5% by weight) of magnesium oxide (MgO) using the digital light processing (DLP). Their results show that Mg doping prevented the transformation of β-TCP into α-TCP during the sintering process since network contraction due to the incorporation of Mg 2+ in the β-TCP structure increases the stability of the β phase -TCP and helps to increase the transformation temperature of the β → α phase, so the α-TCP content is decreased in Mg-doped TCP scaffolds. It was also observed that Mg doping promoted a decrease in grain size during the sintering process, as well as significantly improving the mechanical strength and even decreasing the degradation rate of the β-TCP scaffolds. In vitro studies confirmed that compared to pure TCP, Mg-TCP had better osteogenic, angiogenic, and immunomodulatory effects, and 3Mg-TCP has optimal properties.

Through this review, the strong impact of the incorporation of magnesium (Mg) on the structure of β-TCP was verified, even in small quantifications, causing significant changes in its properties.

3 CONCLUSION

Beta tricalcium phosphate (β-TCP) is a calcium phosphate with unique properties that strongly direct it toward biological applications. Mg appears to be an excellent candidate for cationic substitutions in β-TCP, providing improvement in intrinsic properties of β-TCP such as osteoconductivity. Low levels of doping are enough to cause changes in the structural, optical, or electronic properties of β-TCP.

REFERENCES

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 B-tricalcium phosphate compound.** Jurnal Teknologi (Sciences & Engineering) 78:3 (2016) 167–172

BHORKAR, I; DHOBLE, A. S. **Advances in the synthesis and application of self-assembling biomaterials.** Progress in Biophysics and Molecular Biology, Volume 167, December 2021, Pages 46-62

BOHNER M; SANTONI, B. L. G; DOBELIN, N. **β-tricalcium phosphate for bone substitution: Synthesis and properties.** Acta Biomaterialia, Volume 113, 2020, Pages 23-41

BOHNER, M. **Calcium Orthophosphates in Medicine: from Ceramics to Calcium Phosphate Cements.** Injury, 31, 37-47, 2000.

CARRODEGUAS, R. G; AZA, S**. α-Tricalcium phosphate: Synthesis, properties and biomedical applications.** Acta Biomaterialia, 7, 10, 3536-3546, 2011

CHEN, Y.W.et al. **In vitro study on the influence of strontium-doped calcium polyphosphate on the angiogenesis-related behaviors of HUVECs.** J mater Sci Mater Med, v.19, n.7, p.2655-62, 2008.

CUI, W; SONG, Q; SU, H; YANG, Z; YANG, R; LI, N; ZHANG, X. **Synergistic effects of Mg-substitution and particle size of chicken eggshells on hydrothermal synthesis of biphasic calcium phosphate nanocrystals.** Journal of Materials Science & Technology 36 (2020) 27–36

DESCAMPS, M., et al. **Manufacture of macroporous β-tricalcium phosphate bioceramics.** Journal of the European Ceramic Society. 28: 149-157, 2008.

DEVGAN, S; SIDHU, S. S. **Evolution of surface modification trends in bone related biomaterials: A review.** Materials Chemistry and Physics, Volume 233, 15 May 2019, Pages 68-78

DEYNEKO, D. V; MOROZOV, V. A; ZHUKOVSKAYA, E. S; NIKIFOROV, I. V; SPASSKY, D. A; BELIK, A. A; LAZORYAK, B.I. **The influence of second coordination-sphere interactions on the luminescent properties of b-Ca3(PO4)2-related compounds.** Journal of Alloys and Compounds 815 (2020) 152352

ENDERLE, R., GOTZ-NEUNHOEFFER, F; GOBBELS, M; MULLER, F. A; GREIL, P. **Influence of magnesium doping on the phase transformation temperature of β-TCP ceramics examined by Rietveld refinement.** Biomaterials. 26, 3379-3384, 2005.

FARZADI, A., SOLATI-HASHJIN, M; BAKHSHI, F; AMINIAN, A. **Synthesis and characterization of hydroxyapatite/β-tricalcium phosphate nanocomposites using microwave irradiation.** Ceramics International, Volume 37, Issue 1, January 2011, Pages 65-71

FERNANDEZ, E.; GIL, F. G.; GINEBRA, M. P.; DRIESSENS, F. C. M.; PLANELL, J. A; BETS, S. M. **Calcium phosphate bone cements for clinical applications.** Journal of Materials Science: Materials in Medicine, v. 10, p. 169 - 176, 1999.

FERREIRA, M. M; BRITO, A. F; BRAZETE, D; PEREIRA, I. C; CARRILHO, E; ABRANTES, A. M; PIRES, A. S; AGUIAR, M. J; CARVALHO, L; BOTELHO, M. F; FERREIRA, J. M. F.**Doping β-TCP as a Strategy for Enhancing the Regenerative Potential of Composite β-TCP—Alkali-Free Bioactive Glass Bone Grafts. Experimental Study in Rats.** Materials (Basel). 2019 Jan; 12(1): 4.

FONTES, S, S; GOMES JUNIOR, G. G; SADER, M. S; OGASAWARA, T. **Análise temodinâmica e aplicada ao beta fosfato tricálcico dopado com magnésio.** 51º Congreeso Brasileiro de Cerâmica, 3 a 6 de junho de 2007. Salvador- BA.

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, 39, 13, 3883-3892, 2019

FRASNELLI, M; SGLAVO, V. M**. Effect of Mg^{2+} doping on beta–alpha phase transition in tricalcium phosphate (TCP) bioceramics.** Acta Biomaterialia, Volume 33, 15 March 2016, Pages 283-289

GALLO, M; SANTONI, B. L. G; DOUILLARD, T; ZHANG, F; GREMILLARD, L; DOLDER, S; HOFSTETTER, W; MEILLE, S; BOHNER, M; CHEVALIER, J; TADIER, S. **Effect of grain orientation and magnesium doping on b-tricalcium phosphate resorption behavior.** Acta Biomaterialia 89 (2019) 391–402

GAO, J; FENG, L; CHEN, B; FU, B; ZHU, M. **The role of rare earth elements in bone tissue engineering scaffolds - A review.** Composites Part B: Engineering, Volume 235, 15 April 2022, 109758

GHOSH, R; SARKAR, R. **Synthesis and characterization of sintered beta-tricalcium phosphate: A comparative study on the effect of preparation route**. Materials Science and Engineering: C, Volume 67,2016,Pages 345-352

GROOT, K. **Clinical applications of calcium phosphate biomaterials: a review.** Ceramics International, v. 19, p. 363-366, 1993.

GUASTALDI, A. C; APARECIDA, A. H. **Fosfatos de cálcio de interesse biológico: Importância como Biomateriais, propriedades e métodos de obtenção de recobrimentos.** Quím. Nova. 2010; v.33, pp. 1352-1358

GUO, X; LONG, Y; LI, W; DAI, H. **Osteogenic effects of magnesium substitution in nano-structured b-tricalcium phosphate produced by microwave synthesis.** J Mater Sci (2019) 54:11197–11212

JACK E. LEMONS. **Ceramics: past, present, and future.** Bone Vol. 19, no.l Suppl. July, 121S128S,1996.

JAMARILLO, N; MORENO, A; SANCHEZ, R; OSPINA, V; PELAEZ-VARGAS, A; GARCIA, C; PAUCAR, C. **Influence of composition of β-tcp and borate bioglass scaffolds on cell proliferation of adipose tissue-derived mesenchymal stem cells: osteogenic differentiation.** MRS Advances, 6, 434-443, 2021.

KAI, K.C.; CUNHA, T.F.; HIGA, O.Z.; MARCHI, J. **Avaliação da citotoxicidade de cerâmicas de fosfato tricálcico dopadas com magnésio e zinco.** Congresso Latino Americano de Órgãos Artificiais e Biomateriais, 22-25de Agosto, 2012. Natal -RN

KIM, S. R.; LEE, J. H.; KIM, Y. T.; RIU, D. H.; JUNG, S. J.; LEE, Y. J.; CHUNG, S. C.; KIM, Y. H**. Synthesis of Si, Mg substituted hydroxyapatite and their sintering behaviors**, Biomaterials, v. 24, p. 1389-1398, 2003.

KON, E; SALAMANNA, F; FILARDO, G; MATTEO, B. D. SHABSHIN, N; SHANI, J; FINI, M; PERDISA, F; PARRILLI, A; SPRIO, S; RUFFINI, A; MARCACI, M; TAMPIERI, A. **Bone Regeneration in Load-Bearing Segmental Defects, Guided by Biomorphic, Hierarchically Structured Apatitic Scaffold.** Front. Bioeng. Biotechnol, 27 September 2021

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 β-tricalcium phosphate: Analysis of the physicochemical properties and deposition rate of coatings.** Applied Surface Science 509 (2020) 144763

LANG, C; MURGIA, C; LEONG, M; TAN, LW, PEROZZI, G; KNIGHT, D; RUFFIN, R; ZALEWSKI, P. **Anti-inflammatory effects of zinc and alterations in zinc transporter mRNA in mouse models of allergic inflammation.** Am J Physiol Lung Cell Mol Physiol. 2007, Feb; 292(2):L577-84.

MASSIT, A; YACOUBI, A. E; KHOLTEI, A; IDRISSI, B. C. E. **XRD and FTIR Analysis of Magnesium Substituted Tricalcium Calcium Phosphate Using a Wet Precipitation Method.** Biointerface research in applied chemistry, Volume 11, Issue 1, 2021, 8034 – 8042

MASSIT, A; YACOUBI, A. E; REZZOUK, A; IDRISSI, B. C. E. **Thermal Behavior of Mg-Doped Calcium-Deficient Apatite and Stabilization of β Tricalcium Phosphate.** Biointerface research in applied chemistry Volume 10, Issue 6, 2020, 6837 – 6845

MATSUNAGA, M; KUBOTA, T; TOYOURA, K; NAKAMURA, A. **First-principles calculations of divalent substitution of Ca (2+) in tricalcium phosphates.** Acta biomaterialia, 23, 329-337, 2015.

MAYER, I; DIAB, H; REINEN, D; ALBRECHT, C. **Manganese in apatites, chemical, ligand-field and electron paramagnetic resonance spectroscopy studies.** Journal of Materials Science, 28, 2428-2432 (1993).

PARK, KD; JUNG, YS; LEE, KK; PARK, HJ. **Behavior of Osteoblast-Like Cells on a b-Tricalcium Phosphate Synthetic Scaffold Coated With Calcium Phosphate and Magnesium.** The Journal of Craniofacial Surgery, Volume 27, Number 4, June 2016

PASCAUD, K; MERCE, M; ROUCHER, A; DESTRIBATS, M; BACKOV, R; SCHMITT, V; SESCOUSSE, R; BROUILLET, F; SARDA, S; RÉ, M. I. **Pickering emulsion as template for porous bioceramics in the perspective of bone regeneration.** Colloids and Surfaces A: Physicochemical and Engineering Aspects, Available online 10 March 2022, 128748

PIRES, A. L. R; BIERHALZ, A, C, K; MORAES, A. M. **Biomateriais: Tipos, Aplicações e Mercado.** Quím. Nova 38 (7), Ago 2015

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

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, 2020, Issue 3, v.46, pp. 2648-2653

QI, D; SU, J; LI, S; ZHU, H; CHENG, L; HUA, S; YUAN, X; JIANG, J; SHU, Z; SHI, Y; XIAO, J. **3D printed magnesium-doped β-TCP gyroid scaffold with osteogenesis, angiogenesis, immunomodulation properties and bone regeneration capability *in vivo.*** Biomaterials Advances, Available online 17 March 2022, 212759

SAIKIRAN, A; VIVEKANAND, M; PRAHALAD, M; YUVAN, S; RAMESHBABU, N**. Microwave synthesis of Zn/Mg substituted and Zn/Mg-F co-substituted nanocrystalline hydroxyapatite.** Materials Today: Proceedings 27 (2020) 2355–2359

SAITO, L; CARDOSO, H. A. I; MOTISUKE, M; ZAVAGLIA, C. A. C. **Estudo das propriedades mecânicas e morfológicas de beta – fosfato tricalcico sinterizado com a adição de diferentes concentrações de NaF.** 55º Congresso Brasileiro de Cerâmica, 29 de maio a 01 de junho de 2011, Porto de Galinhas, PE, Brasil

SHEPHERD, J. H; SHEPERD, D. V; BEST, S. M. **Substituted hydroxyapatites for bone repair.** J Mater Sci Mater Med. 2012 Oct; 23(10):2335-47.

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 67 (2016) 636–645

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 64 (2016) 219–228

SINUSAITE, L; RENNER, A. M; SCHUTZ, M. B; ANTUZEVICS, A; ROGULIS, U; GRIGORAVICIUTE-PURONIENE, I; MATHUR, S; ZARKOV, A. **Effect of Mn doping on the low-temperature synthesis of tricalcium phosphate (TCP) polymorphs.** Journal of the European Ceramic Society, Volume 39, Issue 10, August 2019, Pages 3257-3263

SOMERS, N; JEAN, F; LASGORCEIX, M; CURTO, H; URRUTH, G; THUAULT, A; PETIT, F; LERICHE, A. **Influence of dopants on thermal stability and densification of β-tricalcium phosphate powders.** Open Ceramics, Volume 7, September 2021, 100168

STEFANIC, M; KRNEL, K; KOSMAC, T. **Novelmethod for the synthesis of a â-tricalcium phosphate coating on a zirconia implant.** Journal of the European Ceramic Society, 33 (15-16), 3455–3465, 2013

TAHERIMEHR, M; BAGHERI, R; TAHERIMEHR, M. **In-vitro evaluation of thermoplastic starch/ beta tricalcium phosphate nano-biocomposite in bone tissue engineering.** Ceramics International, Available online 17 February 2021

TORRES, P. M. C; ABRANTES, J. C. C; KAUSHAL, A; PINA, S; DOBELIN, N; BOHNER, M; FERREIRA, J. M. F. **Influence of Mg-doping, calcium pyrophosphate impurities and cooling rate on the allotropic ↔-tricalcium phosphate phase transformations.** Journal of the European Ceramic Society 36 (2016) 817–827

TRIPATHI, G; SUGIURA, Y; TSURU, K; ISHIKAWA, K. **In vivo stability evaluation of Mg substituted low crystallinity ß-tricalcium phosphate granules fabricated through dissolution–precipitation reaction for bone regeneration.** Biomed. Mater. 13 (2018) 065002

VALENTIM, R. M. B; ANDRADE, S. M. C; DOS SANTOS, M. E. M; SANTOS, A. C; PEREIRA, V. S; DOS SANTOS, I. P; DIAS, C. G. B. T; DOS REIS, M. A. L. **Composite based on biphasic calcium phosphate (HA/β-TCP) and Nanocellulose from the açaí tegument.** Materials **2018**, 11(11), 2213.

VALLET-REGÍ, M. **Evolution of bioceramics within the field of biomaterials.** Comptes Rendus Chimie, Volume 13, Issues 1–2, January–February 2010, Pages 174-185

XUE, W. ET AL. **Synthesis and characterization of tricalcium phosphate with Zn and Mg based dopants.** J. Mater. Sci: Mater. Med., v. 19, p. 2669-2677, 2008.

YASHIMA, M., et al. **Crystal structure analysis of β-tricalcium phosphate $Ca_3(PO_4)_2$ by neutron powder diffraction.** Journal of Solid State Chemistry. 175:272-277, 2003.

YI, J; LIU, Q; ZHANG, Q; CHEW, T. G; OUYANG, H. **Modular protein engineering-based biomaterials for skeletal tissue engineering.** Biomaterials, Volume 282, March 2022, 121414

ZHAO, C; LIU, W; ZHU, M; WU, C; ZHU, Y. **Bioceramic-based scaffolds with antibacterial function for bone tissue engineering: A review.** Bioactive Materials, Available online 23 February 2022

ZOFLOVÀ, I.; NEMCIKOVA, P; MATUCHA, P. **Trace elements and bone health.** Clin Chem Lab Med. 2013 Aug;51(8):1555-61.