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Wollastonite and tricalcium phosphate composites for bone regeneration

Compósitos de wollastonita e fosfato de tricálcio para a regeneração óssea

Compuestos de wollastonita y fosfato tricálcico para la regeneración ósea

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Abstract

In recent decades, researchers in bone tissue bioengineering have focused on developing and improving bioceramics efficient in presenting physical-chemical characteristics similar to bone tissue, aiming to mimic cellular events and mechanisms involved in osteogenesis. Among the materials used, wollastonite (W) has stood out in recent years, mainly due to its bioactivity. Besides, tricalcium phosphate (TCP) is also used primarily due to its osteoinductivity and osteoconductivity. Given their ionic compositions and the physical-chemical properties of W and TCP, scientists have associated these two materials during the synthesis of bioceramics that unite the characteristics of each material into a single biomaterial, called composite. This design enables a variety of association that allows improvements in the biological behavior of these materials. Therefore, W/TCP composites have shown excellent performance, *in vitro* and *in vivo*, as they start to exhibit fundamental properties for bone regeneration. These characteristics indicate the use of these new biomaterials in future clinical applications, especially in cases of extensive bone losses, which remain a significant challenge for scientists and biomedical professionals. Nevertheless, despite the advances achieved, many questions must be clarified, and essential to comprehend the mechanisms involved in osteogenesis after implantation. Thus, this study aimed to contextualize the use of W/TCP composites for bone regeneration, to support further studies necessary to identify the biological behavior of these bioceramics and ensure use in clinical practice.

Keywords: Biomaterials; Bone regeneration; Calcium phosphates; Calcium silicate.

Resumo

Nas últimas décadas, os pesquisadores da bioengenharia tecidual óssea têm se voltado para o desenvolvimento e aperfeiçoamento de biocerâmicas capazes de apresentar características físico-químicas semelhantes ao tecido ósseo, visando a mimetizar os eventos celulares e mecanismos envolvidos na osteogênese. Dentre os materiais utilizados, a wollastonita (W) tem se destacado nos últimos anos, principalmente em função da sua bioatividade; e o fosfato de tricálcio (TCP), em especial devido à sua osteoindutividade e osteocondutividade. Tendo em vista as suas composições iônicas e as propriedades físico-químicas da W e do TCP, os cientistas têm associado estes dois materiais durante a síntese de biocerâmicas que unem as características de cada material em um único biomaterial, denominado compósito. Esta concepção possibilita uma variedade de associação que viabiliza melhorias no comportamento biológico destes materiais. Consequentemente, os compósitos de W/TCP têm apresentado excelente desempenho, *in vitro* e *in vivo*, pois passam a exibir propriedades fundamentais para a regeneração óssea. Estas características indicam o uso destes novos biomateriais em aplicações clínicas futuras, em especial nos casos de perdas ósseas extensas, que permanecem sendo um grande desafio para os cientistas e profissionais da área biomédica. Contudo, apesar dos avanços alcançados, muitas questões precisam ser esclarecidas, determinantes para compreender os mecanismos envolvidos na osteogênese, após implantação. Diante do exposto, o presente trabalho tem por objetivo contextualizar a utilização dos compósitos de

W/TCP para a regeneração óssea, a fim de subsidiar novos estudos necessários para identificar o comportamento biológico destas biocerâmicas e assegurar a utilização na prática clínica.

Palavras-chave: Biomateriais; Regeneração óssea; Fosfato de cálcios; Silicato de cálcio.

Resumen

En las últimas décadas, los investigadores de la bioingeniería aplicadas al tejido óseo se han volcado en el desarrollo y perfeccionamiento de biocerámicas capaces de presentar características físico-químicas similares a las del tejido óseo, con el objetivo de imitar los eventos y mecanismos celulares implicados en la osteogénesis. Entre los materiales utilizados, han destacado en los últimos años la wollastonita (W), principalmente por su bioactividad; y en particular, el fosfato tricálcico (TCP) por su osteoinductividad y osteoconductividad. En vista de sus composiciones iónicas y de las propiedades físico-químicas del W y del TCP, los científicos han vinculado estos dos materiales durante la síntesis de biocerámicas que unen las características de cada material en un único biomaterial, llamado composite. Esta concepción permite una variedad de asociación que permite mejorar el comportamiento biológico de estos materiales. En consecuencia, los composites W/TCP han presentado un excelente rendimiento, *in vitro* e *in vivo*, pues estos empiezan a exhibir propiedades fundamentales para la regeneración ósea. Estas características indican el uso de estos nuevos biomateriales en futuras aplicaciones clínicas, especialmente en casos de pérdida ósea extensa, las cuales siguen siendo un gran reto para los científicos y profesionales biomédicos. Sin embargo, a pesar de los avances logrados, es necesario aclarar muchas cuestiones que son cruciales para comprender los mecanismos implicados en la osteogénesis posterior a la implementación. Conforme a lo expuesto, el presente trabajo tiene como objetivo contextualizar el uso de los compuestos de W/TCP para la regeneración ósea, con el fin de subsidiar nuevos estudios necesarios para identificar el comportamiento biológico de estos biocerámicos y asegurar su uso en la práctica clínica.

Palabras clave: Biomateriales; Regeneración ósea; Fosfatos de calcio; Silicato de calcio.

1. Introduction

At present, there is a worldwide need to increase accessibility to treatments that use new health technologies, given the incidence of morbidities associated with globalization. In this scenario, researchers in tissue bioengineering and biomedical areas have been looking for alternatives for physical rehabilitation, improvement of life quality and self-esteem of individuals affected by trauma, resections, infections, neoplasms, congenital diseases, and other diseases that result in extensive tissue losses, conditions in which repair occurs due to fibrosis. These situations generally cause significant deformities and even entire member dysfunctions, which require multiple long-term reparative surgeries. Furthermore, they result in impairment of work functions and, in more severe cases, disability burdening the public health-care system.

Regarding bone tissue, during repair surgeries, autogenous graft use, considered the gold standard, is the ideal approach since it is biocompatible, osteoinductive, osteoconductive, and osteogenic. However, in cases of extensive bone loss, availability is limited, as its obtaining and supply are associated with morbidity of the donor site and infection risks. Therefore, the development of biomaterials to mimic the morphofunctional characteristics of bone tissue has become a pressing advance. Consequently, they can modulate the physiological events involved in the bone regeneration mechanism, reproducible on a large scale, and economically viable.

In this context, scientists in bone tissue bioengineering, an interdisciplinary and multiprofessional area in partnership with biomedical professionals, have focused on the production and improvement of biomaterials. They are interested in compounds with physical-chemical characteristics appropriate to bone tissue and three-dimensional structure (3D) with interconnected pores, essential for cellular events and mechanisms involved in angiogenesis and osteogenesis. These materials, unlike autogenous grafting, do not require any additional surgery in some applications, as they can be obtained synthetically from biodegradable and bioresorbable materials. Among the materials used as the substrate for the bone substitutes synthesis, wollastonite (W), a calcium silicate (SC) composed essentially of silicon (Si) and calcium ions (Ca^{2+}), has stood out in recent years for its bioactivity and ability to remain stable in humid media. Calcium phosphates (CaP), especially tricalcium phosphate (TCP), are other materials used in this context due to their osteoinductivity and osteoconductivity. They are essentially composed of phosphate ions (PO_4^{3-}) and Ca^{2+}, inorganic phase components of bone tissue. Nevertheless, it presents marked biodegradation, *in vitro* and *in vivo*, asynchronous to the bone regeneration mechanism.

Given these two bioceramics ionic compositions and the physical-chemical properties, the researchers have associated W with TCP for the synthesis of composites that unit the characteristics of each material into a single biomaterial. In addition to these advantages, this allows a range of mixtures and percentages of association that improve the biological behavior of biomaterials more than those presented when applied individually.

2. Methodology

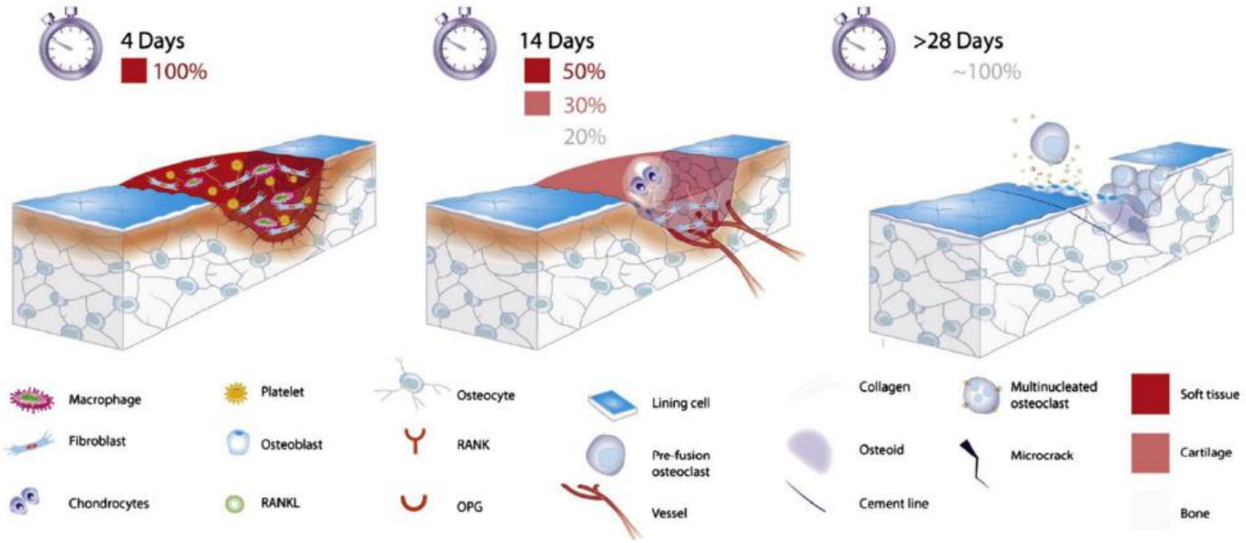
This study is a descriptive qualitative literature review that aims to show the state-of-the-art of composite ceramic biomaterials of wollastonite and tricalcium phosphate, which have gained prominence in the last decade, for bone regeneration. For this review preparation, the authors gave priority to articles published in the last ten years without disregarding the oldest publications, references in the area, and the topic addressed. For this purpose, the search was performed on the *Medical Literature Analysis and Retrievel System Online (PubMed/MEDLINE)*, *Virtual Health Library (VHL)*, *Scientific Electronic Library Online (SciELO)*, *Web of Science*, *Google Scholar*, and *Scopus* databases, using the following search terms: biomaterials, bone regeneration, calcium phosphates, calcium silicate, and wollastonite.

3. Bone Tissue Bioengineering

Bone tissue is a type of conjunctive, specialized, composed mainly of type I collagen fibers, in its organic part, associated with inorganic hydroxyapatite (HA) crystals – $Ca_{10}(PO_4)_6(OH)_2$ formula (Kazek-Kęsik et al., 2014). Under physiological conditions, this tissue presents excellent reparative capacity consolidated by regeneration. During these events, angiogenesis and neovascularization are critical factors for the supply of nutrients and viability of complex cellular activities implicated in bone repairs, such as migration, fixation, proliferation, and differentiation (Fernandes-Yague et al., 2015; Kazek-Kęsik et al., 2014; Wang et al., 2013; Deng et al., 2017; Ke et al., 2017; Wang et al., 2017). These physiological mechanisms depend, among other factors, on the interaction between growth factors, osteoprogenitor cells, mesenchymal stem cells, and derived from the bone marrow. The latter is differentiated into an osteogenic cell and promotes protein synthesis fundamental to biomineralization (Nair et al., 2009; Fernandes-Yague et al., 2015) (Figure 1).

The repair mechanism of extensive bone lesions is not consolidated by regeneration due to the lack of a 3D framework that enables cellular and blood supply events (Deng et al., 2017; Wang et al., 2017; Li et al., 2018) and fibrosis formation occurs (Miguel et al., 2006; Miguel et al., 2013; Santos et al., 2019). In these situations, it is essential to restore bone tissue's structure and metabolic functions in the shortest possible time (Wang et al., 2017). As a result, in voluminous bone losses, the use of bone substitute grafts in the affected and destroyed areas is required (Kazek-Kęsik et al., 2014).

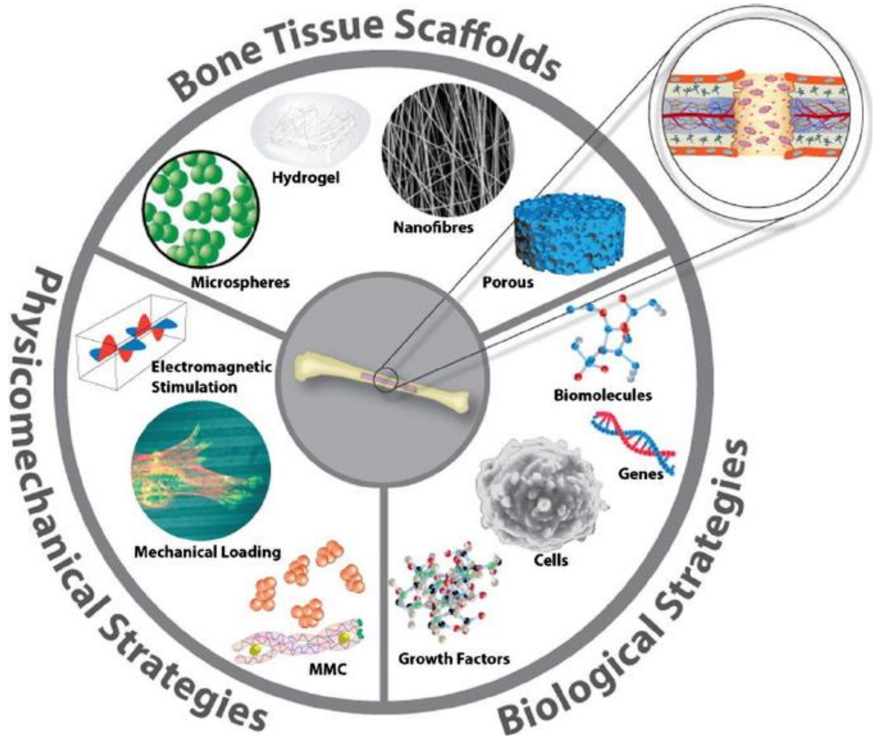
Figure 1. Different cell types and signaling molecules interaction during bone remodeling.



Chronology and dynamics of physiological events involved in bone regeneration mechanisms. Source: Fernandez-Yague *et al.* (2015).

In this context, it is indispensable to use bioactive, biodegradable, and bioresorbable biomaterials with geometry that favors cell adhesion, proliferation, and migration (Kao et al., 2014; Su et al., 2014; Fernandes-Yague et al., 2015) (Figure 2). These materials must also be reproducible on a large scale (Wang et al., 2013; Deng et al., 2017; Ke et al., 2017) to meet the clinical and socioeconomic demand to reach the less economically favored population.

Figure 2. Strategies for bone regeneration.



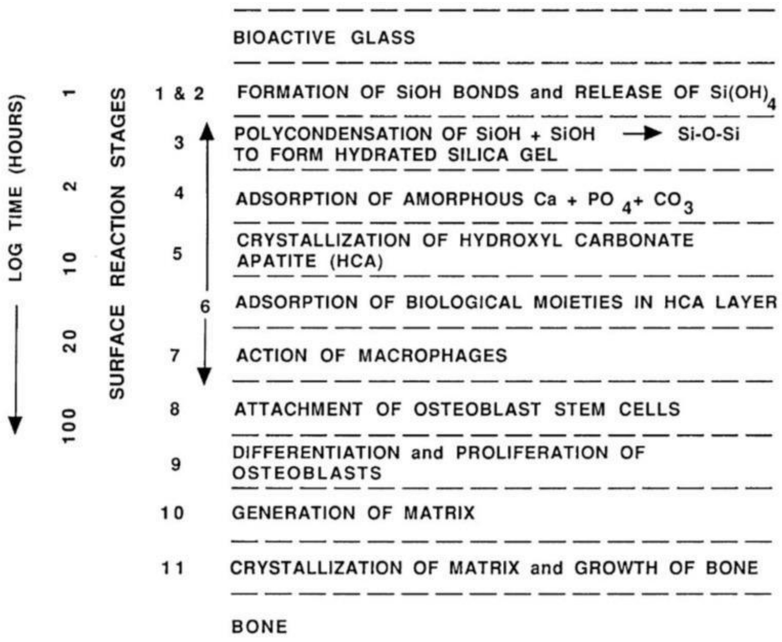
Different methods, biomaterials, and therapeutic resources used for bone tissue regeneration. Source: *Graphical abstract* prepared by Fernandes-Yague *et al.* (2015).

4. Wollastonite and Tricalcium Phosphate Composites

During the new biomaterials synthesis, CS and CaP have been choice materials (Nair et al., 2009; Sole; Grima, 2018) given this combination has shown promising results as bone substitutes used individually (Lin et al., 2009; Wang et al., 2012; Santos et al., 2020).

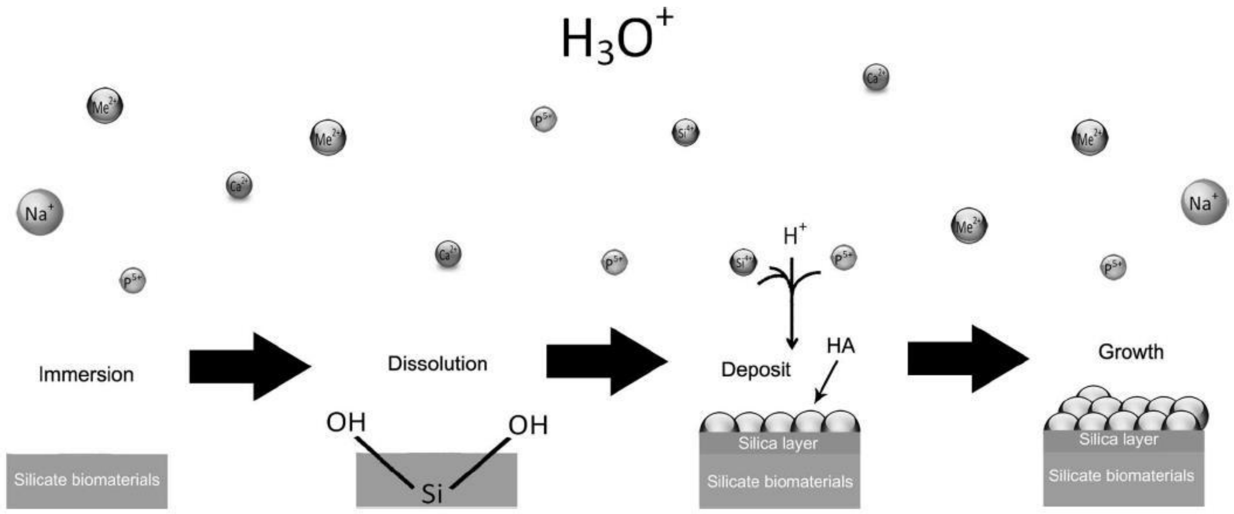
During the mechanism of apatite formation on the CS surface, Ca^{2+} ions initially detach from the material surface, provoke supersaturation in the fluids where they are immersed, and give rise to the silanol groups (Si-OH) formation on the material surface, which becomes conducive to apatite nucleation and crystallization (Ni; Chang, 2009; Gandolfi et al., 2011; Wang et al., 2012; Mohammadi et al., 2014; Fernandes, 2015; Dziadek et al., 2017) (Figures 3 and 4). The presence of the Si-OH groups stimulates the adhesion and growth of osteogenic strain cells (Gandolfi et al., 2010; Wang et al., 2012; Dziadek et al., 2017). Therefore, as soon as the apatite nuclei are formed, they grow spontaneously, integrating the ions of Ca^{2+} and PO_4^{3-} of the surrounding fluid (Ni; Chang, 2009).

Figure 3. Mechanism of apatite formation on the CS surface.



The sequence of events and surface reactions occur at the interface of the SC-based bioglass and the body fluid. Source: Hench (1991), Cao & Hench (1996), Hench *et al.* (2010), Dorozhkin (2013), Fernandes (2015).

Figure 4. Apatite formation in the CS biomaterial.

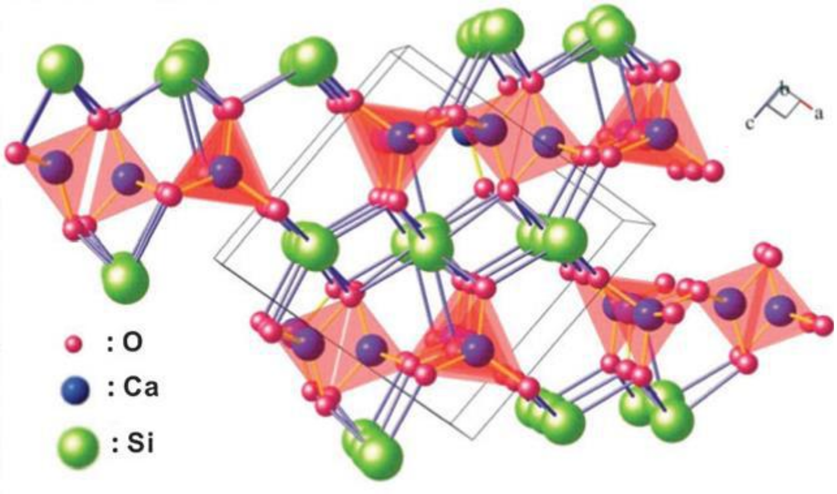


Once apatite nuclei form on the biomaterial's surface, they grow spontaneously, absorbing CaP ions. Source: Mohammadi *et al*. (2014).

Cements based on CS, for example, were used in dentistry, initially, as protective agents of the dental pulp and root canal sealants, both in the lateral perforations and at the apex of the roots (Gandolfi et al., 2009; Gandolfi et al., 2010; Osorio et al., 2012). However, they have disadvantages, for example: prolonged hardening time and complex handling when applied as root canal shutter (Gandolfi et al., 2009; Gandolfi et al., 2010). These limitations have aroused interest in developing composites capable of mimicking the bone tissue structure (Wang et al., 2013). Therefore, adding extra chemical compounds to SC-based cement produces small changes in the hardening and expansion time of these materials so that they can be added to their composition to improve biological properties (Gandolfi et al., 2009). In this context, among the SC, W has gained notoriety in recent years due to its stabilization in humid media and bioactivity, which makes it suitable for use in regenerative bone techniques (Gandolfi et al., 2009; Lin et al., 2009; Gandolfi et al., 2010; Srinath et al., 2019).

Wollastonite is a mineral of natural or synthetic origin, acicular, non-metallic, belonging to the class of calcium metasilicates ($CaSiO_3$) (Factori, 2009; Ge et al., 2019). Naturally, it occurs from metamorphic and magmatic mechanisms involving intrusive carbonate and magmatic rocks, resulting from the variation of heat and pressure of limestone and silica. It is usually found in white coloration but can be gray, brown, or red, depending on the number of impurities present in its chemical structure – bonds with other minerals (Factori, 2009). In nature, it has a theoretical composition of 48% calcium oxide (CaO) and 52% silicon dioxide (SiO_2), sometimes associated with other minerals such as aluminum (Al), iron (Fe), magnesium (Mg), titanium (Ti), manganese (Mn), and potassium (K). Compared to these minerals, W is the only natural with the ability to organize in acicular and needle shape (Factori, 2009; Zhao et al., 2013; Anjaneyulu & Sasikumar, 2014; Santos et al, 2016; Srinath et al., 2020). The synthetic W, pyroxene type (simple chain structure), which consists of three tetrahedrons, has higher chemical purity and a more crystalline structure than the natural compound, the central aspect that differs between the two origins (Factori, 2009; Anjaneyulu; Sasikumar, 2014). When obtained synthetically, it presents stable physical-chemical characteristics, which allows it to produce the three types present in nature. The triclinic form is the most common and predominant; on the other hand, monoclinic parawollastonite (β-$CaSiO_3$) forms obtained at low temperatures and triclinic pseudowollastonite (p-W), obtained at high temperatures (above 1200°C), are rarely found (De Aza et al., 2000; Yan et al., 2006; Factori, 2009; Anjaneyulu; Sasikumar, 2014). Although p-W is stable polymorphic silica at temperatures above 1030ºC, it has a crystalline structure capable of directly connecting with bone tissue (Carrodeguas et al., 2008; De Aza; Guitian; De Aza, 1994).

Figure 5. Wollastonite molecular structure illustration.



Oxygen (O), Ca, and Si ions organization in the W crystalline structure.
Source: Adapted from Zhao *et al*. (2013).

For biomedical purposes, W has been synthesized, processed, and used in different geometric presentation formats and shapes, such as metal alloy coatings, microspheres, granules, or sintered or non-sintered porous 3D *scaffolds* (Sola; Grima, 2018; Yu et al., 2018; Ge et al., 2019; Srinath et al., 2019; Kamboj et al., 2020; Santos; Meireles; Miguel, 2020; Santos et al., 2021; Monção et al., 2022). This is related to the fact that when compared to the other bone replacement materials used clinically, such as CaP, W has higher bioactivity due to the release effect of Ca^{2+} and silicate (SiO_3^{2-}), substantial during the osteogenesis mechanism (Ni; Chang, 2009; Hesaraki et al., 2009; Yu et al., 2018; Ge et al.., 2019). However, it is noteworthy that different ionic concentrations of Si, in addition to Ca^{2+} and SiO_3^{2-}, may be responsible for the disparity in the cellular proliferation of biomaterials (Fei et al., 2012; Srinath et al., 2020). Si promotes neovascularization, through direct or indirect induction, of the release of angiogenic factors by fibroblasts, which activate their receptors in endothelial cells and initiate the cascade of chemical reactions involved in the angiogenesis mechanism (Deng et al., 2017; Nair et al., 2009; Li et al., 2018). Therefore, although Si, documented, promotes cell adhesion, proliferation, and differentiation, the relationship between this ion concentration and the cellular response is not yet fully clarified (De Aza et al., 2013). Moreover, very high Si concentrations seem to cause cell death (Messenguer-Olmo et al., 2012; Lin et al., 2015).

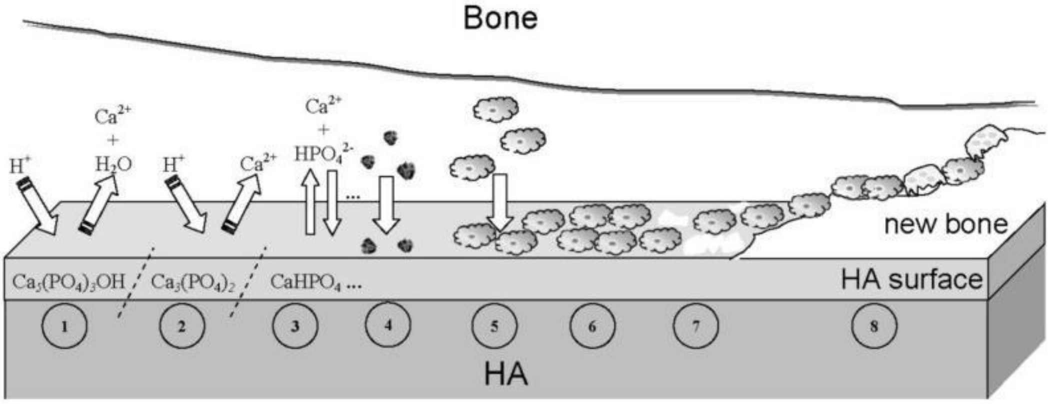
At the moment it is used to make bioactive glasses (bioglasses), W enables the obtaining of biocompatible, biodegradable, osteoconductive materials with notorious bioactivity (Encinas-Romero et al., 2013; Saadaldin; Dixon, Rizkalla, 2014). In body fluids, both W and p-W form an apatite layer through ion exchange between the fluid's hydronium ion (H_3O^+) with Ca^{2+} ions from p-W. As a result, an amorphous Si hydrogel layer is formed, and the pH increases from 9.0 to 10.5 at the interface between W and body fluid (Encinas-Romero et al., 2013). Thus, the medium alkalinization and the formation of the Si hydrogel layer show the superior bioactivity of W to other biomaterials (De Aza et al., 1994; Al-Noaman et al., 2013; Motisuke et al., 2014; Srinath et al., 2019).

The time of W binding to bone tissue occurs faster due to its greater superficial reactivity, a property attributed to the surface characteristics of the biomaterial that affect the proteins' adsorption, the degree of contact of physiological fluids on the biomaterial, and, in turn, on cell bonding, spreading, proliferation and differentiation. Thus, the superficial material morphology is a factor that directly determines the interaction between tissue and biomaterial since it participates in the modulation of cellular activity surrounding the implant surface (Morejón Alonso, 2011; Santos et al., 2021).

The presence of Si in the W composition carries important biological aspects in bone regeneration (Srinath et al., 2019). However, this ion, found in the soil, is present in human and animal tissues and is more abundantly distributed in connective tissues, bones, tendons, muscles, hair, feathers, and skin (Lin et al., 2015). Si constitutes specific glycosaminoglycans and polyuronides, where it is firmly attached to the polysaccharide matrix. In the human body, Si concentrations range from 0.6 ppm in serum to 41 ppm in muscle, and 57 ppm in lung tissue. In other animal species, such as rats and monkeys, Si concentrations are similar to those of humans, at about 25 ppm in the femur and <1 ppm in serum (Lin et al., 2015). Studies have suggested that Si additions in ceramic composites influence cell metabolism, promote gene expression related to bone activity, and stimulate the cell proliferation of osteoblasts (Motisuke et al., 2014; De Aza et al., 2007; Carrodeguas; De Aza, 2011). Although the exact mechanisms related to the Si action in bone tissue are not yet fully elucidated, it is proposed that there is both a structural and metabolic role (Meseguer-Olmo et al., 2012). Nevertheless, the W use in the synthesis of the composite has been widely proposed to improve the osteogenic potential and osteointegration, which can be modulated as the quantities and proportions of the materials that make up the composites are adjusted (Encinas-Romero et al., 2013; Goswanni et al., 2013; Santos et al., 2021).

In addition to CS, bioceramics based on CaP have been extensively used as substrate for synthesizing and processing different biomaterials for bone regeneration (Nair et al., 2009; Schickle et al., 2011; Meseguer-Olmo et al., 2012). This is mainly due to its biocompatibility, similarity with the inorganic chemical composition of the bone matrix, osteoconductivity, which allows the adhesion, differentiation, and proliferation of osteoprogenitor cells, and the absence of immune-mediated rejection (Nair et al., 2009; Hesaraki et al., 2009; Schickle et al., 2011; Wang et al., 2012) (Figure 6).

Figure 6. Cellular and molecular phenomena occurred on the CaP surface during apatite formation.

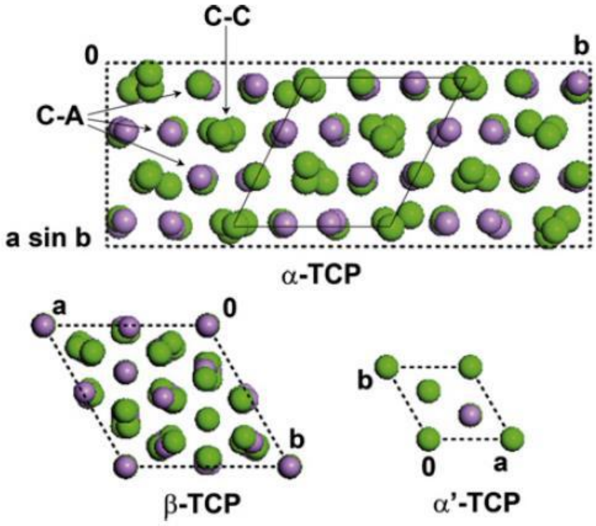


Events involved in the apatite formation on the CaP surface: (1) Solubilization of the CaP surface after implantation; (2) Continued solubilization of the CaP surface; (3) Balance between physiological solutions and the modified CaP surface; (4) Proteins and/or other organic compounds adsorption; (5) Cellular adhesion; (6) Cell proliferation; (7) Onset of bone neoformation; and (8) Neoformed bone. Source: Bertazzo *et al.* (2010) and Dorozhkin (2013).

The TCP ($Ca_3(PO_4)_2$) has been widely used as a bone substitute due mainly to its chemical similarity with biological apatite and being osteoinductor (Ni; Chang, 2009; Lin et al., 2009; Fei et al., 2012; Osorio et al., 2012; Meseguer-Olmo et al., 2012; Wang et al., 2012; Liu et al., 2013; Saadaldin et l., 2014; Deng et al., 2017). This bioceramic occurs in pathological conditions, such as dental, salivary, and urinary calculus, and carious lesions and calcifications in soft tissues (Siqueira & Zanotto, 2011). However, it can be prepared by precipitation or solid-state reaction methods from Ca and P precursors processed in different presentation forms, such as blocks or granules sintered at high temperatures (Hesaraki et al., 2009). Among the TCP synthesis pathways, the most used are: wet and solid-state reactions (Morejón Alonso, 2011). In the latter, the material is heated at a temperature above 1000ºC, increasing average particle size and allowing impurities to be removed during synthesis. This bioceramic is chemically stable and can allow ionic substitutions without promoting significant changes in its spatial arrangement in the *β*-TCP allotropic form (Guastaldi; Aparecida, 2010; Cho; Chung & Rhee, 2011; Gomes et al., 2012).

There are three TCP polymorphs: low temperature, *β*-TCP, and the two high-temperature forms, *α* and *α′*-TCP. The latter has aroused little practical interest, as it only exists at temperatures above ≅1465±5°C and reverts to *α*-TCP by cooling below the transition temperature. However, *β*-TCP is stable at room temperature, and reconstructively transforms to ≅1115±10°C in *α*-TCP form, which can be retained during cooling to room temperature (Carrodeguas & De Aza, 2011; Meseguer-Olmo et al., 2012; Carrodeguas et al., 2008; Ahn et al., 2015). The appearance of the *γ*-TCP phase is possible only under high-pressure conditions (Guastaldi; Aparecida, 2010; Gomes et al., 2012; Pires; Bierhalz & Moraes, 2015). The *α* and *β* phases are chemically identical; however, in the biological environment, they behave differently. The *β* phase is more used in single-phase or biphasic compounds because it has a higher solubility index than the *α* phase and higher specific surface energy (Carrodeguas & De Aza, 2011) (Figure 7). It was evidenced that the α-TCP phase presents higher cytotoxicity than the *β*-TCP phase because *α*-TCP is more soluble and hydrolyses more rapidly in a Ca deficient HA than the other CaP. Cytotoxicity is associated with the hydrolysis of this material that would release phosphoric acid into the culture medium, causing acidification, which promotes cell death (Domingues, 2013).

Figure 7. Schematic representation of *α*-TCP, *β*-TCP, and *α′*-TCP unit cells.



Ca (green), P (magenta) ions organization. C-C, cation-cation column; C-A, cation-anion column. Source: Carrodeguas; De Aza (2011).

In addition to temperature, the TCP biological behavior, especially biodegradation, is conditioned to other factors such as pH, ionic concentration of the medium, physical-chemical composition, and crystallinity. Therefore, other techniques have been used to obtain TCP, such as centrifugation, autoclave, dry, and calcination (Tanaka et al., 2008). In general, the dissolution of a CaP is related to the Ca/P molar ratio (Morejón Alonso, 2011). The higher is Ca molar concentration, the less soluble the CaP will be. The pH is also a factor to be considered in the degradation of *in vivo* ceramics. As the pH decreases, the more soluble CaP becomes due to the ionic exchange with the physiological environment (Guastaldi & Aparecida, 2010). The biodegradability of these bioceramics can be explained by the material's physical-chemical properties, such as the solubility degree of the material at different pH values, and biological factors, such as phagocytosis. The solubilization of CaP crystals promotes ionic exchange with the interstitial medium, which stimulates cell migration, protein adsorption, and deposition of CaP and P in the HA form (Carrodeguas & De Aza, 2011; Domingues, 2013).

The TCP polymorphic structure has gained prominence due to its bioactivity, osteoconduction, and, especially, solubility and high biodegradation and bioabsorption rates, *in vitro* and *in vivo* (Siqueira et al., 2019; Schickle et al., 2011). These characteristics favor bone growth and replacement within TCP-based materials. However, the reabsorption rate of this bioceramic is so high that the material is reabsorbed even before the consolidation of the bone regeneration mechanism, although it still promotes tissue integration by HA precipitation, followed by bone growth in the neoformed crystal (Hesaraki et al., 2009). Moreover, TCP has low mechanical resistance, so it must somehow be improved before *in vivo* implantation (Lin et al., 2009; Hesaraki et al., 2009; Deng et al., 2017). Consequently, this bioceramic has been little used in clinical applications individually (Lin; Chang; Shen, 2009; Fei et al., 2012; Schickle et al., 2011; Deng et al., 2017). Therefore, it is essential to search for bone substitutes that provide support for osteoprogenitor cells to deposit osteoid matrix to be mineralized and that exhibit a biodegradation rate compatible and proportional to the speed of the bone neoformation mechanism (Nair et al., 2009; Wang et al., 2012; Schickle et al., 2011; Deng et al., 2017; Ke et al., 2017).

In this scenario, researchers have sought to improve the physical-chemical properties of CS-based biomaterials, especially W, concerning their relatively slow hardening time, and to reduce hardening time and expand their clinical use, new CS biomaterials can be designed by adding different raw materials, to obtain the composites (Gandolfi et al., 2009).

De Aza *et al.* (1997) developed a bioactive ceramic, formed by p-W and α-TCP, called *Bioeutectic*®. This composite is synthesized by a slow solidification, at a eutectic temperature of 1500°C, for four hours. When this system is around 1205°C, there is a transition from a crystalline to an amorphous phase. At the end of this process, a binary compound with 60% p-W and 40% of α-TCP is obtained. By raising the W to higher temperatures, p-W becomes a bioglass and fuses to the α-TCP. The material obtained presents a dense structure and is organized in almost spherical colonies, with a 20±5 μm average size and 10-0.9 μm a diameter (De Aza et al., 2007). The osteoconductive potential and bioactivity of *Bioeutectic*® have been tested in several experimental models. *In vitro* experiments were carried out with osteoblasts culture in simulated body fluid and parotid gland saliva. These studies evaluated the physical-chemical properties and the osteoconductive potential of this composite. In the *in vivo* tests, *Bioeutectic*® was implanted in adult rabbit tibia and rat femur. Both models demonstrated a rapid dissolution of α-TCP in pseudoapatites and protein-mediated osteoblast adhesion (De Aza et al., 2007; Guastaldi& Aparecida, 2010). The main TCPs disadvantage is its mechanical resistance, equal to or less than the spongy bone part, and rapid biodegradability. Despite this, p-W functioned as a mechanical reinforcement for α-TCP and provided bioactivity to the compound, with the Si, Ca, and P release to the physiological environment (De Aza et al., 2007; Guastaldi & Aparecida, 2010; Morejón Alonso, 2011).

Studies have shown that the W presence in the composite improves the TCP mechanical properties, such as compressive stress resistance, and allows the consolidation of bone neoformation more rapidly inside W/TCP composites (Nair et al., 2009; Hesaraki & Safari; Shokrgozar, 2009; Sole; Grima, 2018; Siqueira et al., 2019). Despite this, the compressive strength of these composites decreases with the increase of the W content (Lin et al., 2013). Thus, it is emphasized that avoiding excessive loads on these biomaterials is necessary during the early stages of bone repair (Nair et al., 2009).

One of the main changes resulting from apatite substitution by SiO_3^{2-}, in composites based on TCP and W, is related to the biomaterials surface electrical load that becomes more negative than stoichiometric HA. This may be responsible for the increase in osteoclast activity (Nair et al., 2009), cells responsible for biodegradation and bioabsorption of the bone matrix. These materials can also facilitate the native cells' migration and proliferation to the implantation site and undergo biodegradation at a speed almost proportional to the mechanism of bone neoformation (Nair et al., 2009; Dziadek et al., 2017). However, it is not yet clear whether pure W, or composites, could regulate the gene expression and proteins related to osteogenesis and promote cell differentiation (Fei et al., 2012). Despite this, it has been documented that composite biomaterials containing Si induce greater osteopontin expression and release, alkaline phosphatase, type I collagen, and osteocalcin (Nair et al., 2009; Fei et al., 2012; Meseguer-Olmo et al., 2012; Wang et al., 2012). Thus, the physical-chemical characteristics of these biomaterials, such as porosity, Si content, and the ability to attract osteoclasts by osteopontin secretion, similar to osteoinductive proteins; in combination, they can improve biodegradation and bioresorption mechanism (Nair et al., 2009), and, consequently, bone regeneration. Lately, Monção *et al.* (2022) evaluated W/TCP composites by Raman spectroscopy and observed band formation with vibrational aspects similar to biological apatite, associated with the collagenic material deposition. These authors also showed that apatite deposited around biomaterials presented crystallineness similar to that observed in the bone tissue of the control group.

Given the abovementioned, it is evident that new studies need to be conducted to elucidate the uncertain points that still exist about the ideal Si content and the best association percentage between W and TCP.

5 Conclusion

The association of W with TCP has resulted in obtaining composites with excellent performance, *in vitro*, and *in vivo*, since these two ceramics have intrinsic properties fundamental to the mechanism of bone neoformation. Therefore, it is evident that these composites present physical-chemical characteristics that indicate the use of these new biomaterials in future clinical applications, especially in cases of extensive bone losses, a condition increasingly present in today's society worldwide.

Furthermore, despite advances observed in different studies, some questions need to be elucidated, citing the ideal profile of the Si release, the influence of this ion on the biodegradation profile of composites, and cell behavior during osteogenesis. Consequently, further studies are needed to determine the biological behavior of W/TCP composites with different percentages of association and different formats and shapes of presentation after *in vivo* implantation and to ensure use in clinical practice.

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