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REVIEW ARTICLES

How Does a Calcium Phosphate-Based Biomimetic Ceramic Function as a Direct Pulp-Capping Agent? A review

ABSTRACT

Alternative calcium phosphate-based (CaP) bioceramics are currently being developed for direct pulp capping (DPC). These substances have the potential to minimize the adverse effects of certain cements while promoting reparative and regenerative processes.

***Aim:** To compile available evidence of the biological processes triggered in the dentin-pulp complex when DPC is performed with CaP-based materials.*

***Methodology:** A literature search was conducted between 2014-2024 in 20 databases published using "pulp capping" and "calcium phosphates". Articles involving bioceramics combined with metals, non-metals (e.g., fluorides), or polymers were excluded.*

***Results:** Eighteen articles were selected. Information was classified into three categories: a)Pulp repair, b)ionic activity and their role in dentin growth regulation, and c)the environment. It was evidenced that CaP materials stimulate the proliferation and differentiation of pulp stem cells and fibroblasts into odontoblast-like cells, as demonstrated by the expression of ALP, OCN, DSPP, and DMP-1. These cells express nestin and promote the development of mineralized nodules, leading to the formation of a dentinal bridge. Essential ions, including calcium, phosphorus, hydroxyl, and magnesium, play key roles in regulating cell proliferation and differentiation processes. They maintain a pH of 7.0-8.2, leading to better integration with surrounding tissues, while also enhancing biomineralization and apatite formation.*

***Conclusion:** CaP-based materials have been shown to stimulate the proliferation and differentiation of pulp stem cells into odontoblast-like cells, which are primarily responsible for pulp repair and regeneration. These materials also stimulate the creation of a favorable environment by supplying essential ions to regulate pH, modulate protein expressions, and promote dentin mineralization.*

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Introduction

In contemporary dentistry, maintaining pulpal vitality in teeth has become a central therapeutic objective. The preferred treatments are indirect pulp capping (IPC) and direct pulp capping (DPC), both representing alternative techniques to root canal treatment for preserving pulp vitality when exposure occurs due to deep caries, mechanical instrumentation, or dental trauma (1) Indirect pulp capping involves the removal of most of the decayed dentin, followed by the subsequent placement of a bioceramic material to facilitate tooth restoration. In contrast, DPC involves placing a bioceramic material directly on the exposed pulp after caries removal to stimulate mineralization and tissue repair (2).

Bioceramics are inorganic, biocompatible, bioactive, conductive, non-corrosive, and chemically stable materials. They exert biological effects on cells and pulp tissue, supporting the control of inflammation, remineralization, and dentin repair. They also contribute to isolating the exposed tissue from the external environment. There are currently different bioceramic materials for direct pulp capping. These include calcium hydroxide-based formulations (CH)-which are increasingly falling out of use-; tri- and dicalcium silicate-based materials (MTA ProRoot*, MTA Angelus*, Biodentine*); and calcium phosphate-based materials (CaP) (3-6).

Although tri- and dicalcium silicate-based bioceramics (MTA or Biodentine) have shown improvements in their physical, chemical, and biological properties, their primary mechanism of action relies on dentin-bridge formation in proximity to the pulp. The formation of a hydroxyapatite-like layer along the bottom of the cavity and the maintenance of pulp vitality are achieved in more than 80% of the cases of DPC. However, these materials do not enable the replacement of the bulk of the tooth, the re-establishment of an ortho-dentin tubular microstructure, or the formation of an odontoblastic layer serving as a barrier. (7)

Calcium-phosphate-based (CaP) materials have been recently introduced for DPC. Their mechanism of action and effectiveness rely on facilitating pulp cell migration, inducing odontoblastic differentiation (8), and forming restorative dentin on the affected surface by releasing Ca^{+2} and OH^{-1} ions (4,8–12). The release of Ca^{+2} appears to play a critical role in the transduction and signaling of biological processes, as well as in the formation of mineralized matrices (1, 13-15). This explains why a new CaP QCP bioceramic derived from eggshell, has been developed (16). This novel QCP exists in different versions; version 5 consists of tricalcium phosphate (TCP), sintered hydroxyapatite (HAp), and amorphous HAp combined with other compounds or chemical elements such as carbonates, potassium, sodium, chlorine, and magnesium, without silicates or toxic anions or cations (3). Nevertheless, further studies are required to elucidate how this material interacts with the biological and cellular processes occurring within the dentin-pulp complex.

The primary aim of this review is to synthesize available data and construct a comprehensive map of the biological processes occurring in the dentin-pulp complex during direct pulp capping using calcium-phosphate (CaP)-based materials. This objective is addressed by analyzing research findings and information reported in the literature. Such an approach may contribute to the development of a theoretical model framework that enhances understanding of these biological processes and supports future research on the use of CaP-based materials in direct pulp capping procedures. Ultimately, this may help identify the most suitable types of CaP materials for direct dental pulp capping procedures.

Materials and methods

Literature search

A preliminary search was conducted for articles addressing direct pulp capping published in English and Spanish between 2014 and 2024. Due to the limited number of eligible studies, the search range was subsequently broadened to maximize the retrieval of relevant evidence and minimize selection bias.

The following databases were queried: PubMed, Embase, Cochrane Library, Web of Science, Wiley Online Library, Scopus, ScienceDirect, SciELO, LILACS, Google Scholar, ERIC, SpringerLink, Academia.edu, BASE, Dialnet, Science Research, Redalyc, RefSeek, Ciencias.Science, and WorldWideScience.

The search strategy included the following keywords: *"pulp capping"* and *"calcium phosphates"*. Articles were excluded if they mentioned different materials or bioceramics combined with metals, non-metals (e.g., fluorides), or polymers, as well as studies conducted on deciduous teeth or those using bioceramics in pulpotomy procedures.

Literature Selection

Two reviewers independently screened the working papers in three stages: title, abstract, and full-text assessment. Articles retrieved through snowball sampling were also considered, and duplicate texts or those not addressing the review question were excluded. Eligibility criteria were determined based on whether the studies addressed the research question.

Information Storage

All data were managed using Mendeley and organized in Excel spreadsheets, classified according to the database from which each article was retrieved.

Results

The search yielded a total of 18 articles, as detailed in Table 1. These comprised two systematic reviews, one in-vivo

Table 1
Flow diagram of the selected articles.

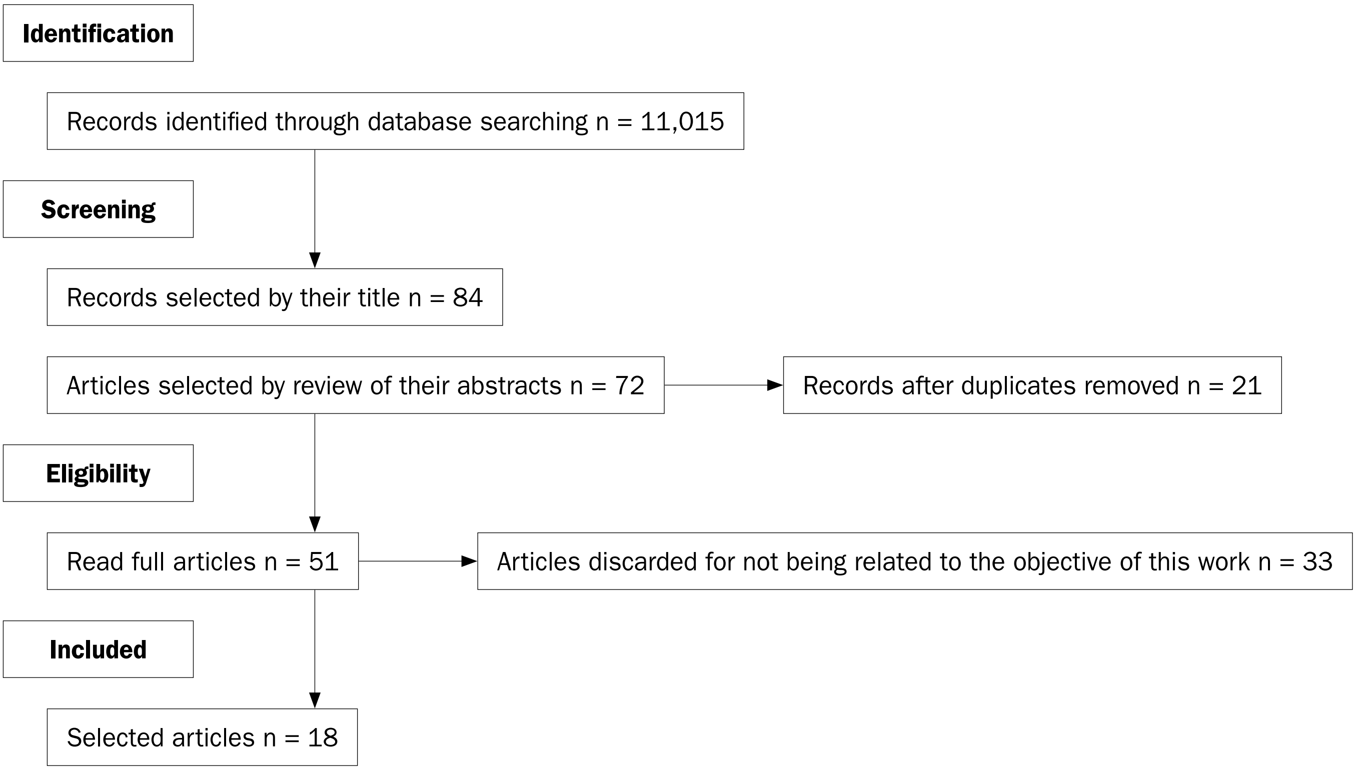

Table 2
Assessment of the reviewed articles

No	YEAR	AUTHOR	ARTICLE'S/SOURCE'S TITLE IN THIS JOB	USE IN THIS REVIEW
SYSTEMATIC REVIEW				
1	2021	Davaie S, Hooshmand T, Ansarifarda S	Different types of bioceramics as dental pulp capping materials: A systematic review (6)	Results
2	2021	C. CălinaM, Sajinb M, T Moldovanc, C.Comand, SI. Stratule, A.C.Didilescua	Immunohistochemical expression of non-collagenous extracellular matrix molecules involved in tertiary dentinogenesis following direct pulp capping: a systematic review (29)	Results
IN-VIVO STUDY				
3	2021	Guerrero-Gironés J, Alcaina-Lorente A, Ortiz-Ruiz C, et al	Biocompatibility of a ha/β-tcp/c scaffolds a pulp-capping agent for vital pulp treatment: An in vivo study in rat molars (22)	Results
IN-VITRO STUDY				
4	2021	Gu Y, Xie X, Zhuang R, Weir MD, Oates TW, Bai Y	A Biphasic Calcium Phosphate Cement Enhances Dentin Regeneration by Dental Pulp Stem Cells and Promotes Macrophages M2 Phenotype In Vitro (23)	Results
5	2020	Javid B, Panahandeh N, Torabzadeh H, Nazarian H, Parhizkar A, Asgary S	Bioactivity of endodontic biomaterials on dental pulp stem cells through dentin (10)	Results
6	2019	Koutroulis A, Kuehne S A, Cooper PR and Camilleri J	The role of calcium ion release on biocompatibility and antimicrobial properties of hydraulic cement (27)	Results
7	2019	Al-Saudi KW, Nabih SM, Farghaly AM, AboHager EA	Pulpal repair after direct pulp capping with new bioceramic materials: A comparative histological study (28)	Results
8	2019	Mahendran K, Ponnusamy C, Maloor SA	Histological evaluation of pulpal response to direct pulp capping using statins with α-tricalcium phosphate and mineral trioxide aggregate in human teeth (19)	Results
9	2018	Salah M, Kataia M M, Kataia E M, Alaa E, Din E, Essad M E	Evaluation of eggshell powder as an experimental direct pulp capping material (30)	Results
10	2015	Li S, Hu J, Zhang G, Qi W, Zhang P, Li P, Zeng Y, Zhao W, Tan Y	Extracellular Ca2+ Promotes Odontoblastic Differentiation of Dental Pulp Stem Cells via BMP2-Mediated Smad1/5/8 and Erk1/2 Pathways (24)	Results
11	2015	Gandolfi MG, Spagnuolo G, Siboni F, Procino A, Rivieccio V, Pelliccioni G A, C. Prat C, Rengo S	Calcium silicate/calcium phosphate biphasic cement for vital pulp therapy: chemical-physical properties and human pulp cells response (26)	Results
12	2014	González-Pita LC, Vargas-Sánchez PK , Delgado-Mejía E, Fittipaldi Bombonato –Prado K, Torres- Rodríguez C.	Response of undifferentiated pulp cells (OD-21) when using biomimetic ceramics for pulp coating (3)	Results
13	2014	Lee Ju- Lee JB, Park, SJ, Kim HH, Kwon, YS Lee, Kwang et al	Physical properties and biological/odontogenic effects of an experimentally developed fast-setting α-tricalcium phosphate-based pulp capping material (17)	Results
LITERATURE REVIEW				
14	2022	Siddiqui Z. Acevedo-Jake A M, Griffith A, Kadincesme N, Dabek K, Hindi D, Kim K K; Kobayashi Y, Shimizu E, Kumar V.	Cells and material-based strategies for regenerative endodontics (20)	Results
15	2021	Fiume E, Magnaterra G, Rahdar A, Verné E, and Baino F.	Hydroxyapatite for biomedical applications: A short overview. (18)	Results
16	2018	Shaofeng An	The emerging role of extracellular Ca2+ in osteo/odontogenic differentiation and the involvement of intracellular Ca 2+signaling: From osteoblastic cells to dental pulp cells and odontoblasts (25)	Results
17	2018	Chaughule, Ramesh S.	Physical Properties and Biocompatibility of Nanostructural Biomaterials Based on Active Calcium Silicate Systems and Hydroxyapatite. (21)	Results
18	2016	Karthikeson PS, Jayalakshmi S.	Pulp capping agents-A review (14)	Results

study, ten *in-vitro* studies, and five literature reviews (Table 2).

Calcium phosphates (CaP) are the main mineral component of teeth. Examples of CaP-based materials used for direct pulp capping (DPC) include hydroxyapatite (HA), Polyphasic calcium phosphates (Poly-CaP), and Tricalcium phosphate (TCP) (12, 14, 17, 18). Tricalcium phosphate (TCP) occurs in two primary forms: α-TCP and β-TCP. The α-form is more soluble and biodegradable, making it suitable for applications such as bone scaffolding and drug delivery. It is also a component of certain cements, where it forms carbonate apatite when mixed with calcium carbonate and monocalcium phosphate monohydrate. (19)

Pulp repair

The pulp–dentin complex has regenerative potential that induces the formation of tertiary dentin. The dentin matrix is not merely a scaffold for the development of mineralized tissue but also serves as a reservoir of growth factors. Dentinogenesis requires materials that stimulate the release of bioactive molecules to signal repair (20, 21).

In this process, stem cells and pulp fibroblasts proliferate and differentiate into odontoblast-like cells, as evidenced by the expression of specific markers, including ALP, OCN, DSPP, and DMP-1. These odontoblast-like cells produce tertiary dentin (17), express nestin, and promote the formation of mineralized nodules by the induction of ALP activity, which has been shown to be critical in the mineralization process (15, 22, 23).

Thus, CaP-based materials do not induce necrotic layer formation; instead, they promote dentin bridge formation, thereby creating a protective barrier that seals the pulp.

The dental pulp also has intrinsic defense mechanisms against external attacks. For instance, odontoblasts and pulp fibroblasts produce pattern recognition receptors (PRRs) capable of detecting bacteria through surface molecules. Activation of the nuclear factor kappa B (NF-KB) pathway subsequently induces the production of inflammatory cytokines and complement C5 pathway, which contributes to the regulation of inflammation (20). In addition, materials such as CaP release ions, which in turn create an environment conducive to this response (15).

Ions and their role in dentin growth regulation

Calcium has been demonstrated to play a pivotal role in various aspects of cellular function, including proliferation, differentiation, and mineralization. It has been observed to enhance the expression of bone morphogenic protein (BMP-2), which has been identified as a key driver of pulp stem cell differentiation. Furthermore, calcium has been shown to regulate the expression of Runx2, a protein that is involved in the formation of mineralization nodules. (6, 17, 22, 24, 25).

Additionally, calcium contributes to the maintenance of pyrophosphatase activity, thereby contributing to the preservation of mineralization and dentin bridge formation (26). Moreover, calcium reacts with carbon dioxide, inhibiting the respiration of anaerobic bacteria (25).

Phosphorus plays a crucial role in the odontogenic differentiation of human dental pulp stem cells (hDPSCs), promoting the expression of odontogenic markers such as RUNX2, OCN, DSPP, and DMP1, all of which are essential for dentin formation. Phosphorus is also a fundamental element in biomineralization, the process by which mineralized tissues, such as dentin, are formed. In this context, this element interacts with calcium to form hydroxyapatite, the main mineral component of dentin.

Hydroxyl ions derived from CaP are released in relatively smaller quantities. This reduced release limits their ability to induce necrotic layer formation and decreases their bactericidal capacity. Furthermore, it is anticipated that the lower release of hydroxyl ions does not provide the same protective barrier as observed in reactions with higher concentrations of these ions. (27).

Calcium and hydroxyl ions, components of the experimental material, stimulate alkaline phosphatase (ALP), while their pH enhances the expression of bone morphogenic protein-2 (BMP-2) (6,15). ALP is an enzyme produced during the early stages of odontoblast maturation (28). At the same time, it is a crucial marker for evaluating pulp coating materials, as it indicates the activity of odontoblast-like cells. Its expression may indicate the onset of cellular differentiation and, in turn, the start of tissue mineralization (10). In comparative studies, this experimental material (QCP5) showed ALP expression levels similar to those observed with MTA (3).

Furthermore, fibronectin also appears to be stimulated by hydroxyl and calcium ions. It acts as a reservoir of growth factors and signaling cues that promote odontoblast differentiation, adhesion, and proliferation (29).

Another cation presented in the experimental material, magnesium (Mg), is essential for enzymatic and cellular reactions, including the bone mineralization process. Several studies indicate that incorporating Mg into apatite crystals can improve odontoblast adhesion to apatite and, therefore, support bone formation (30).

Environment

The environment surrounding odontogenic mesenchymal stem cells (MSCs) is crucial in determining the outcome or prognosis of the pulp regeneration process. The natural pulp environment has been shown to regulate the homeostasis, proliferation, and differentiation of odontogenic MSCs.

Among the factors involved, pH plays a decisive role. An optimal pH range of 7.0 to 7.6 has been shown to favor cellular response (20), enhance odontoblastic cell activity, and increase ALP expression (10), thereby promoting calcification nodules (6, 10, 23) and apatite formation (28).

In one study, CaSi-αTCP silicate exhibited a high level of calcium ion release in its leachate, maintaining high pH levels (pH 8), in contrast to CaSi-DCDP, which showed a lower pH and reduced calcium ion release (26). Another study reported that αTCP maintained alkaline pH values consistently above 7.0 for 14 days without exceeding 8.2. This study also indicated that the alkaline environment created by the material is necessary for reparative dentin formation, as alkalinity appears to induce mild stimulation of cell differentiation (17).

Considering the experimental base material (QCP) in comparison with other similar materials, it can be expected that the pH generated when used as a pulp capping agent is less alkaline than that of calcium hydroxide (12-14), as it induces less inflammation, as demonstrated in in vitro studies (30,31).

Discussion

This review developed a map based on the available literature of the biological processes involved in calcium phosphate (CaP)-based direct pulp capping within the dentin-pulp complex. The information was classified into three main categories.

Calcium phosphate (CaP) is the common name for a family of minerals composed of calcium cations (Ca^{2+}) together with orthophosphate (PO_4^{3-}), metaphosphate (PO3–), or pyrophosphate (P2O74 –) anions, and, in some cases, hydrogen (H+) or hydroxide (OH–) ions (32).

It has been well established that calcium phosphates (CaPs) are characterized by different Ca/P molar ratios, ranging from 0.5 for brushite to 1.67 for hydroxyapatite and even up to 2.0 for tetracalcium phosphate. The Ca/P molar ratio drives the biological performance of the specific CaP being used. For instance, CaP ceramics with a Ca/P molar ratio of 1.59 (HAp: 53%, α-TCP: 21%, β-TCP: 26%) have been reported to significantly enhance cell proliferation and the expression of extracellular matrix genes. Thus, the chemistry of CaP is of utmost importance and should be carefully considered, given that different CaP phases are defined by diverse Ca/P molar ratios, which in turn result in varying calcium (Ca^{2+}) to phosphate (PO_4^{3-}) ion release ratios, which directly influence their in vitro performance.

Furthermore, the calcium-to-phosphorus (Ca-P) ion release ratio in the surrounding environment determines whether the used CaP will exhibit osteoinductive or osteoconductive properties (33), as well as its mineralization potential. When this ratio approaches 1.67, the compound is more stable in the body and less soluble (18). The working experimental material is expected to maintain such stability as it contains non-stoichiometric hydroxyapatites (Has) that prevent deviations from the ideal Ca/P value (31).

Conversely, very low Ca/P ratios, such as that of MCPM, entail a narrow pH stability range (0-2.0), accompanied by high solubility (ca. 17 g/L at 25°C), making it unsuitable for biological purposes. As the ratio increases to 1.0, as in brushite, the equilibrium pH ranges from 2.0 to 6.0, and its solubility decreases dramatically to 0.088 g/L at 25°C.

Biodegradation of implanted CaPs may occur through mechanical degradation in biological fluids, physicochemical processes, or biological cell activity. These mechanisms can alter chemical composition, as in the case of TCP (ratio = 1,5), which exhibits incongruent dissolution. This means that the concentration of Ca and orthophosphates does not accurately reflect the composition of solid TCP, leading to the redeposition of a limited amount of calcium-deficient apatite with a ratio of 1.5. It is important to note that TCP cannot be formed by simply mixing calcium and phosphate solutions at a 1.5 ratio; instead, it requires heating calcium-deficient apatite at high temperatures to produce beta TCP, or above 1200°C for alpha TCP.

In summary, the CaP ratio rules the acid-base behavior, solubility, stability, surface area-to-volume ratio, degradation pathways, and its kinetics (34).

On the other hand, osteoinduction is defined as the ability to induce progenitor cells, such as dental pulp stem cells (DPSCs) and regenerative modified dental pulp stem cells (MDPSCs), to differentiate into odontoblast-like cells, which are responsible for dentin formation (35). A related concept is osteoconduction, which refers to the ability of the material to act as a scaffold or template that guides the formation of new bone along its surface. In this process, the surface adsorbs circulating proteins from the biological environment, on which bone cells attach, migrate, proliferate, and differentiate, ultimately leading to matrix production (36).

Both osteoconduction and osteoinduction rely on several factors, including the surface characteristics of CaPs, such as roughness, topography, crystallinity, solubility, composition, and porosity. Some studies have suggested that calcium phosphates are osteoinductive even in the absence of supplements due to their surface chemistry, zeta potential, and isoelectric point. Together with pH, these variables influence protein adsorption, osteoblastic differentiation, and osteointegration. Each CaP phase, such as hydroxyapatite (HA), tricalcium phosphate (TCP), and biphasic calcium phosphate (β-TCP), offers distinct bioactive properties (37).

Although many studies have focused on the osteoconductivity or osteoinductivity of Ca-P bioceramics, the relationship between these two properties remains poorly understood. β-tricalcium phosphate (β-TCP) is one of the most widely used and potent synthetic bone graft substitutes. It is not only osteoconductive, but also osteoinductive. These properties, combined with its cell-mediated resorption, enable complete regeneration of bone defects. However, its clinical outcomes are sometimes considered "unpredictable," likely due to a poor understanding of β-TCP physicochemical properties. In this sense, the β-TCP crystallographic structure has not been fully elucidated. Recent evidence suggests that sintered β-TCP may be coated with a Ca-rich alkaline phase, and a hydrothermal treatment may enhance its apatite-forming ability and osteoinductivity. Moreover, β-TCP grain size and porosity can be significantly modified by trace amounts of β-calcium pyrophosphate or hydroxyapatite impurities (38).

In one study, the osteoconductivity of HA, BCP, and β-TCP was studied based on the osteoblastic differentiation *in vitro* and *in situ*, as well as calvarial defect repair *in vivo*. Osteoinductivity was assessed using pluripotent mesenchymal stem cells (MSCs) *in vitro* and heterotopic ossification in muscles in vivo. Results showed that the cell viability, alkaline phosphatase activity, and the expression of osteogenesis-related genes -including osteocalcin (OCN), bone sialoprotein (BSP), alpha-1 type I collagen (Col1a1), and runt-related transcription factor 2 (Runx2)- ranked as BCP > β-TCP > HA. Conversely, alkaline phosphatase activity and expression of osteogenic differentiation MSCs genes, each ranked as β-TCP > BCP > HA. On the other hand, when tested *in vivo*, calvarial defect implantation of Ca-P bioceramics ranked as BCP > β-TCP ≥ HA, whereas intramuscular implantation ranked as β-TCP ≥ BCP > HA. Further investigation revealed that the Ca/P ratio of the surrounding environment influences both osteoconductivity and osteoinductivity of Ca-P bioceramics. Thus, controlling the appropriate calcium-to-phosphorus release ratio is a critical factor in determining the osteoinductivity potential of Ca-P bioceramics in bone tissue engineering. (39)

The remineralization process begins with nucleation. Nucleation is the transient formation of clusters (Posner Clusters) (40,41), which, once sufficiently large, overcome the thermodynamic barrier and become viable, thereby serving as growth sites for crystal formation.
In turn, the transformation from a liquid aqueous phase to a solid insoluble phase can follow different and complex pathways. Two main processes are generally distinguished, depending on the presence or absence of a pre-existing solid surface, i.e., homogeneous and heterogeneous nucleation. In homogeneous nucleation, the new solid phase forms in the absence of any pre-existing solid surface (e.g., solid bone). Both types of nucleation require solution supersaturation. Additionally, the degree of supersaturation determines the topography, crystal size, and shape of the resulting solid phase. Supersaturation is thus the primary driving force for nucleation. In the case of protein-mineral composites, these principles apply mainly to the mineral component, as proteins are inherently difficult to crystallize.
Heterogeneous nucleation follows a different mechanism that requires the presence of a solid surface. When this surface meets certain conditions, strong

epitaxial growth may occur. If this surface does not permit epitaxy, the newly formed solid may still deposit, but the binding is weak. It is important to note that this description depicts only initial and final states, but the underlying chemical process can be considerably more complex. This phenomenon has been described by Ostwald's rule of stages, also known as the Ostwald-Lussac rule, which states that systems frequently undergo phase or chemical transformations, beginning with the least stable and often the most soluble phase, before transitioning through a series of intermediate steps that culminate in the most thermodynamically stable phase.

In the case of CaP, this sequence begins with the formation of MCPM. Then it proceeds through successive CaP phases, such as brushite, ultimately forming apatite -in the absence of fluoride ions. In intercellular fluids, the mechanism is clearly heterogeneous due to the presence of numerous particles acting as foreign nucleating agents. This pathway is considerably easier than homogeneous nucleation.

It is feasible to obtain non-stoichiometric apatite from brushite aqueous solutions at alkaline pH. However, the amount of calcium-deficient apatite formed will be limited, as indicated by the low Ca/P molar ratio (0.5), which suggests that calcium is the limiting reactant. When additional calcium or alkaline cations are present, the mass of apatite increases. (42)

During the dissolution process, CaPs release calcium (Ca^{2+}) and phosphate (PO_4^{3-}) ions through solution-protein and cell-mediated mechanisms, resulting in the ionic transfer of calcium and inorganic phosphate from the solid to the liquid phase (43). This release modulates extracellular concentrations of Ca^{2+} and PO_4^{3-}. These ions are sensed by cells through a Ras/Ref/ERK-dependent pathway or an adenosine-governed mechanism exerting control over cellular functions (33). Calcium ions provide powerful extracellular signals for odontoblast differentiation (44), while PO_4^{3-} favors enhanced RANKL-RANK binding, leading to heightened nuclear factor kappa B (NF-κB) signaling. This cascade promotes robust dentin differentiation and further supports dentin modeling. (33)

CaPs appear to influence angiogenesis -a crucial process for the efficient transport of various nutrients, chemokines, inflammatory cells and cytokines- and stimulate the differentiation of vascular mesenchymal stem cells and vascular lining resident stem cells (VW-MSCs) and odontoblast like cell differentiation (33, 43) Functioning capillary network of proangiogenic factors delivery such as vascular endothelial growth factor (VEGF) (35), basic fibroblast growth factor (bFGF) and Platelet-derived growth factor (PDGF). Actually, CaP doping with elements such as Strontium, Copper, Cobalt, Iron, Magnesium, and Gold could allow greater control of the repair and regeneration mechanisms of dentin (33, 43, 45).

Additionally, CaPs increase pH and enhance BMP-2 expression at both the mRNA and protein levels, as well as BMP-2 promoter activity. BMP-2 is a crucial regulator of odontogenic differentiation and has been shown to stimulate odontoblast differentiation, as well as the formation of mineralized nodules and dentin, both *in vitro* and *in vivo* (46)

Depending on the environment induced within the dental pulp, calcium phosphate (CaP) materials can stimulate the differentiation of dental pulp stem cells (DPSCs) into specific neuronal cells in the nervous system. Exposure to CaP materials has been shown to induce DPSCs to differentiate into neuron-like cells that not only exhibit neuronal characteristics but also express neural markers and display functional neuronal properties (47). This process can be influenced by calcium and neurotrophic growth factors, such as nerve growth factors (NGF), which play a key role in the development, maintenance, and repair of the nervous system.

Dentin mineralization is a complex process involving the interplay of collagen, calcium phosphate, and various non-collagenous proteins, each contributing distinct roles to the formation of hard tissue. Among the roles these three proteins play in dentin mineralization, the following can be listed: 1) dentin matrix protein (DMP1) may act as both a signaling molecule and nucleator; 2) dentin phosphoprotein (DPP) is crucial for calcium phosphate nucleation; and 3) dentin sialoprotein (DSP) may contribute to the mechanical properties of the dentin-enamel junction.

DMP-1, a tooth-specific phosphoprotein, was first identified in the mineralized dentin matrix. Its fundamental role in hydroxyapatite nucleation within the collagen matrix of bone and dentin during mineralization is attributable to its acidic nature and its ability to bind calcium ions. The presence of DMP-1 and dentin sialophosphoprotein (DSPP) throughout development suggests that these proteins are necessary for maintaining dentin matrix.

In contrast, osteocalcin (OCN) is involved in the inhibition of mineralization. OCN has been shown to bind calcium ions through its γ-carboxyglutamic (GLA) residues, thereby preventing phosphate binding to hydroxyapatite crystals and hindering crystal growth. (16)

González et al. demonstrated that the ALP activity of the experimental material (QCP5) was comparable to that of the control group and MTA. This suggests that the pH generated by the material remained within the necessary range for mineralization, preventing inhibition of ALP expression by excessively alkaline pH conditions (1,3).

Despite broad evidence of the benefits of extracellular calcium for cell differentiation and remineralization, Li et al. conducted a study on third molars showing that cells exposed to calcium exhibited enhanced odontoblast differentiation. However, these cells reported reduced ALP expression on control days 14 and 21, while still demonstrating higher mineralized matrix deposition (24). This phenomenon may be explained by the fact that calcium stimulates ALP activity— a marker of odontoblast-like cell differentiation and function—during the initial days. After this proliferative phase, ALP activity decreases, and the formation of the mineralized matrix appears to proceed independently of this protein. Hence, it is believed that ALP is required to trigger mineralization, but not indispensable for subsequent calcification processes. Nevertheless, its specific role remains unclear (25)

This literature review compiled the available data to address the objective of this study. The various ions and material components cited are expected to act either independently within a single composition or in symbiotic combination.

Conclusion

Calcium phosphates promote the proliferation and differentiation of pulp stem cells into odontoblast-like cells, which are primarily responsible for pulp repair and regeneration. The ions released into the medium—such as calcium, magnesium, phosphate, and hydroxyl—have been shown to contribute to pH regulation, the expression of proteins including ALP, OCN, DMP-1, DSPP, COL1A1, and MEPE, as well as mineralization, and the formation of hydroxyapatite and dentin.

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