Casein phosphopeptide-amorphous calcium phosphate nanocomplex (CPP-ACP) in dentistry: state of the art

Nanocomplejo de fosfopéptido de caseína-fosfato de calcio amorfo (CPP-ACP) en odontología: estado del arte

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ABSTRACT

Saliva and external agents containing different concentrations of sodium fluoride (NaF) promote the dental remineralization process. However, these resources may not be sufficient to counteract the multiple factors involved in the process of dental caries, especially in high-risk patients. There are alternatives that have been extensively researched, such as casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) which provides essential ions, like phosphate and calcium, acting as an adjuvant in the remineralization process. Manufacturers of CPP-ACP-based products also suggest that it can produce desensitizing effects. This nanocomplex has been used experimentally with some dental cements and adhesive protocols, but it is important to clarify the effects of this procedure, and the remineralizing/desensitizing advantages it offers. The objective of this topic review was to present the state of the art on the CPP-ACP nanocomplex. In terms of tooth decay prevention, this therapeutic option is not better than NaF. The nanocomplex provides a dental desensitizing action, but it is temporary and less effective than other alternatives like potassium nitrate or NaF. The experimental incorporation of CPP-ACP into dental cements should be controlled so as not to compromise the physico-chemical properties of the material. The use of dental products based on this nanocomplex as pre-treatment of the dental surface may decrease or increase the bonding strength of polymeric adhesive materials, but this effect is material dependent.

Keywords: casein phosphopeptide-amorphous calcium phosphate, dental demineralization, dental remineralization, tooth decay, dentin sensitivity

RESUMEN

La saliva y agentes externos que contienen diferentes concentraciones de fluoruro de sodio (NaF) favorecen el proceso de remineralización dental. No obstante, estos recursos podrían no ser suficientes para contrarrestar los múltiples factores involucrados en el proceso de caries dental, especialmente en pacientes con alto riesgo. Existen alternativas que han sido ampliamente investigadas, como el fosfopéptido de caseína-fosfato de calcio amorfo (CPP-ACP) que aporta iones esenciales como fosfato y calcio, actuando como coadyuvante en el proceso de remineralización. Los fabricantes de productos basados en CPP-ACP también sugieren que este es capaz de generar efectos desensibilizantes. Este nanocomplejo ha sido utilizado de forma experimental con algunos cementos dentales y en protocolos adhesivos, pero es importante esclarecer los efectos de dicha incorporación y las ventajas remineralizantes/desensibilizantes que ofrece esta alternativa. El objetivo del presente artículo de revisión de tema consistió en presentar el estado del arte sobre el nanocomplejo CPP-ACP. En términos de prevención de caries dental, esta opción terapéutica no es superior al NaF. El nanocomplejo ejerce acción desensibilizante dental, pero esta es transitoria e inferior a otras alternativas como nitrato de potasio o NaF. La incorporación experimental de CPP-ACP en cementos dentales debe ser controlada para no comprometer las propiedades fisicoquímicas del material. La utilización de productos dentales a base de este nanocomplejo como pretratamiento de la superficie dental puede disminuir o aumentar la resistencia de unión de materiales adhesivos poliméricos, pero este efecto es material-dependiente.

Palabras clave: nanocomplejo de fosfopéptido de caseína-fosfato de calcio amorfo, desmineralización dental, remineralización dental, caries dental, sensibilidad de la dentina
INTRODUCTION

Due to the dynamic conditions of the oral environment, both enamel and exposed dentin are subject to constant fluctuations in temperature, moisture, presence of biofilm and pH changes. The latter two are stimulated by the intake of carbohydrate-rich foods, which promotes the adhesion, proliferation and activity of various cariogenic bacteria which release acids that reduce hydroxyapatite into more soluble apatite. The cumulative effect of the aforementioned alterations and the influence of other factors such as time, reduction of the buffering capacity of saliva, and lack of oral hygiene favor the onset of incipient tooth decay lesions. However, the oral environment is dynamic and the re-incorporation of lost minerals occurs alternately to the dental demineralization processes with the help of saliva and its contribution of Ca\(^{2+}\) and PO\(_4\)\(^{3-}\) ions through a complex process called dental remineralization.

Currently, there are several adjuvant methods to speed up this process and prevent and control the progression of incipient carious lesions, also called white spot lesions (WSLs). Sodium fluoride (NaF) is the most commonly used agent and can be supplied systemically through fluoridated water or in common diet foods. It can also be applied topically through toothpastes, mouthwashes or gels and varnishes during dental consultation. The bioavailability of NaF in saliva causes its precipitation and stability on the dental structure, delaying the demineralization process and promoting the dental remineralization process. However, there have been discussions related to its use, due to the low solubility in the presence of Ca\(^{2+}\) and PO\(_4\)\(^{3-}\) ions in saturated solutions. In addition, the rapid deposition of NaF in the surface layer of the carious lesion limits a deep remineralization. The toxic effects of NaF at high concentrations have been controversial, due to the high risk posed by taking small doses from multiple sources. In fact, the cumulative effect of NaF during the early stages of life is sufficient to cause dental fluorosis.

Another preventive and therapeutic alternative tested in in vitro, in situ and in vivo studies and used in recent years is the casein phosphopeptide-amorphous calcium phosphate nanocomplex (CPP-
This nanocomplex is an agent that saturates saliva and biofilm, favoring the dental remineralization process by providing Ca$^{2+}$ and PO$_4^{3-}$ ions, which then become available, reducing the risk of hard dental tissues demineralization. Modifications to the original nanocomplex have recently been made, incorporating NaF concentrations to enhance its preventive effect. Several studies have compared the remineralizing action of the complex and NaF, traditionally used in the prevention and treatment of tooth decay lesions.\textsuperscript{13,14}

In addition, manufacturers of CPP-ACP-based products indicate that it produces a desensitizing effect. However, its clinical superiority over other strategies has not been proven, including potassium nitrate (KNO$_3$), fluorides, glutaraldehyde, hydroxyethyl methacrylate (HEMA), arginine-calcium carbonate complex, sodium calcium phosphosilicate (Bioglass 45S5), strontium acetate, oxalate, and laser.\textsuperscript{15} In turn, various concentrations of CPP-ACP have been incorporated experimentally into dental materials and used in adhesive laboratory procedures to promote additional benefits to the dental structure.\textsuperscript{16,17} That being said, it is important to know the remineralizing/desensitizing benefits of CPP-ACP compared to traditional strategies, as well as the products that incorporate this technology and their clinical effectiveness based on evidence. The goal of this topic review was to present the state of the art on the casein phosphopeptide-amorphous calcium phosphate nanocomplex.

**CASEIN PHOSPHOPEPTIDE-AMORPHOUS CALCIUM PHOSPHATE NANOCOMPLEX (CPP-ACP)**

CPP-ACP is a nanocomplex patented by Reynolds at the University of Melbourne, Australia.\textsuperscript{18} It is made up of the phosphopeptide casein protein (CPP), which is derived from milk and is structured by residues of phosphorylated serine and glutamic amino acid.\textsuperscript{19} In addition, it contains a precursor of dental hydroxyapatite: amorphous calcium phosphate (ACP), whose ions are phosphorylated by the serine residues in CPP.\textsuperscript{20} Several studies focus on its remineralizing and preventive tooth decay effect.\textsuperscript{12-14,16,19} In addition, it has been noted that it produces a desensitizing action,\textsuperscript{15} as well as additional bacteriostatic effects.\textsuperscript{20}

**The remineralizing effect of CPP-ACP**

The remineralizing effect is caused by the stabilization of Ca$^{2+}$ and PO$_4^{3-}$ ions that are in solution, by binding the ACP to multiple amine residues of phosphorylated serine present in the CPP. Thus, it
enables the formation of nano-sized clusters, also called CPP-ACP nanoclusters, which increases the total surface area, as well as its interaction with the biofilm and dental structure. The clusters prevent nucleation and the spontaneous precipitation of Ca\(^{2+}\) ions, and behave like salivary proteins such as estaterin and other proline-rich proteins.\(^{21}\) The continued use of dental products containing CPP-ACP produces ion saturation in saliva and biofilm, making it available for subsequent precipitation in the form of ACP, favoring the dental remineralization process (Figure 1).\(^{22-24}\) Several laboratory studies have suggested that the remineralization process created by this nanocomplex decreases surface roughness and improves the micromorphological characteristics of the tooth enamel that has undergone post-treatment alterations like microabrasion, orthodontic stripping, bracket removal, or erosive processes.\(^{25-27}\)

Figure 1. Graphic representing the process of dental demineralization/remineralization. 1) Oral pH < 5.5 induces loss of hydroxyapatite (HA) minerals. 2) Saturation of the oral environment and biofilm with Ca\(^{2+}\) and PO\(_4^{3-}\) ions, promoting the dental remineralization process.

Source: By the authors

Other in vitro studies have shown that the remineralizing effect of products containing the CPP-ACP nanocomplex is similar to that produced by fluorides.\(^{28,29}\) However, this superiority has been questioned, as recently shown through the use of laser confocal microscopy to evaluate the remineralizing potential of a fluorinated varnish (protective fluor; Ivoclar Vivadent) (1,000 ppm), a CPP-ACP-based...
toothpaste (GC Tooth Mousse, Recaldent; GC Corp; Japan) and another toothpaste based on fTCP (functionalized Tri-Calcium Phosphate) (Clinpro Toothcreme, 3M). The results showed that the fluorinated varnish was more effective in decreasing the depth of incipient tooth decay lesions, followed by the CPP-ACP-based paste; however, the latter was better than the one containing fTCP.\(^30\) In 2015, Vyavhare et al compared the remineralizing effect of nano-hydroxyapatite (10%), NaF (1,000 ppm), CPP-ACP (10%) and deionized water (negative control) by means of Vickers microhardness and scanning electron microscopy (SEM), demonstrating that the use of nano-hydroxyapatite and NaF significantly increases microhardness and promotes the reduction of superficial defects and porosities of demineralized tooth enamel.\(^31\)

For these reasons, the remineralizing property of NaF has recently been integrated into dental products containing phosphopeptide to form a new complex called CPP-ACPF (casein phosphopeptide-amorphous calcium phosphate fluoride). It should be emphasized that there are no negative interactions between the two components; on the contrary, there is a synergistic effect that favors the contribution of essential chemical elements (PO\(_3\)^{-3}, Ca\(^{2+}\), NaF) to the dental structure, which is ideal to promote a comprehensive remineralization process.\(^32\) Evaluations made in human enamel by means of Vickers microhardness, SEM and laser fluorescence have shown that remineralizing CPP-ACP-based toothpastes that incorporate 0.2% NaF (e.g., MI Paste Plus™ / GC Tooth Mousse-Plus®) decrease the surface irregularities produced by demineralization and form more marked mineral deposits than those produced by pastes containing CPP-ACP only.\(^33,34\) However, the reinstatement of ions on the dental surface is observed only 7 days after starting treatment with Tooth Mousse-Plus®.\(^35\) Currently, there are several dental products that contain CPP-ACP, CPP-ACPF and ACP in different presentations, such as topical pastes, gels, varnishes, xylitol- or sorbitol-based chewing gums, and the like (Table 1).\(^36-38\)

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Trademark (Manufacturer)</th>
<th>Commercial presentation</th>
</tr>
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<tbody>
<tr>
<td><strong>CPP-ACP</strong></td>
<td>MI Paste™ (GC) / Tooth Mousse™ (GC)</td>
<td>Topical paste</td>
</tr>
<tr>
<td></td>
<td>Trident Xtra Care® (Adams)</td>
<td>Chewing gum</td>
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<tr>
<td></td>
<td>Trident Total® (Adams)</td>
<td>Chewing gum</td>
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<tr>
<td></td>
<td>FUJI VII™ EP (GC)</td>
<td>Glass ionomer cement</td>
</tr>
<tr>
<td><strong>CPP-ACPF</strong></td>
<td>MI Paste plus™ (GC) / Tooth Mousse plus™ (GC)</td>
<td>Topical paste</td>
</tr>
<tr>
<td></td>
<td>MI Varnish™ (GC)</td>
<td>Varnish</td>
</tr>
<tr>
<td><strong>ACP</strong></td>
<td>NiteWhite™ (Phillips)</td>
<td>Clearing Gel</td>
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DayWhite™ (Phillips)  
Aegis® Ortho (Bosworth Co)  
Aegis® Pit and Fissure Sealant (Bosworth Co)  
Relief® ACP (Phillips)  
Enamelon® (Premier)  

Clearing Gel  
Dental adhesive  

Pit and fissure sealant  

Tooth desensitizing gel  
Toothpaste  

Dental desensitizing mechanism of CPP-ACP

Theoretically, the precipitated Ca$^{2+}$ and PO$_4^{3-}$ ions from the ACP are spread through the phosphorylated fibrils of the exposed intertubular dentin collagen, promoting the formation of apatite. However, it is mainly integrated into hypermineralized peritubular dentin, creating deposits at the intratubular level (Figure 2). This strategy seeks to partially block the external stimuli that influence the hydrodynamic behavior of dentin-pulpar fluid, a stimulation of nerve fibers present in deep dentin and consequently in the hypersensitivity of it. However, the blocking action at the dentinal level is partial, similar to that produced by other desensitizing strategies such as the arginine-calcium carbonate complex or strontium acetate.

Figure 2. Image representing the blocking of exposed dentinal tubules and mineral precipitation from CPP-ACP. T: exposed dentin tubule; PTD: peritubular dentin; ITD: intertubular dentin.
The stability of CPP-ACP mineral deposits formed at the level of exposed dentin could be affected by the action of brushing, acids from the diet, and phosphatases produced by oral bacteria, causing loss of phosphate groups in the phosphoserines of nanocomplex peptides.\textsuperscript{42,43} Therefore, multiple applications of topical dental products incorporating CPP-ACP are needed to promote the formation of significant precipitates of Ca\textsuperscript{2+} and PO\textsubscript{4}\textsuperscript{3–}.

**Bacteriostatic mechanism of the CPP-ACP nanocomplex**

The bacteriostatic mechanism is explained because the nanocomplex is able to bind to the biofilm matrix, saturating it with Ca\textsuperscript{2+} and PO\textsubscript{4}\textsuperscript{3–} ions from the ACP.\textsuperscript{44} It has been observed that pastes containing CPP-ACP and glass ionomer cement (GIC) with concentrations of this complex (from 3% to 10%) are able to increase local pH by promoting a neutralizing effect, masking the receptors of salivary molecules that allow bacterial adhesion. As a result, they slow down growth and decrease the number of colony-forming units of bacteria with high cariogenic potential, such as *Streptococcus mutans*.\textsuperscript{45-47} This positive effect was also observed in a short-term clinical study conducted in patients at high risk of tooth decay and chronic gingivitis, concluding that the use of a paste containing CPP-ACP reduced the count of bacteria from supragingival plaque and salivary samples in these patients, even one month after discontinuing its use.\textsuperscript{48}

**INDICATIONS AND EVIDENCE-BASED CLINICAL EFFECTIVENESS OF CPP-ACP**

**Dental Caries**

The first visible clinical sign of dental caries is the presence of white spot lesions (WSLs), compatible with demineralization.\textsuperscript{49} Several strategies, such as fluoride use, resin infiltration, and CPP-ACP have been used to achieve regression and improve the aesthetic appearance of these lesions.\textsuperscript{50}

In relation to the latter strategy, Memarpour et al (2015) compared the effectiveness of a fluorinated varnish (22,600 ppm) (DuraShield; Sultan Healthcare, Hackensack, N.J., USA) against a paste containing CPP-ACP (GC Tooth mousse, Gc, Tokyo, Japan) for WSL regression in 140 children. Measurements of the lesion area and DEF index showed that the remineralizing product had a preventive effect similar to the fluorinated varnish. However, prolonged use of CPP-ACP decreased the presence of such non-cavitated lesions.\textsuperscript{51} Another clinical study conducted by Andersson showed that WSL regression can be achieved using the same product or toothpastes containing NaF. However, the visual
evaluations showed that patients who used CPP-ACP-based paste had better aesthetic results compared to NaF, possibly related to the presence of other minerals such as calcium from ACP incorporated into the dental structure.\textsuperscript{52}

The risk of developing WSLs is also high in patients with fixed orthodontic appliances, because the use of attachments like wires, elastics, bands, and brackets hinders correct oral hygiene, favoring biofilm retention.\textsuperscript{53,54} In 2011, Bröchner et al conducted a controlled clinical trial in 60 adolescents who had at least one WSL following removal of orthodontic appliances. The results from the light-induced quantitative fluorescence showed a significant size reduction of incipient cavity lesions after 4 weeks of using CPP-ACP-containing pastes, improving the clinical aspect of the lesions.\textsuperscript{55} A recently published systematic review included 12 controlled clinical studies that evaluated alternatives such as NaF (in carriers like toothpaste, varnish, and mouthwash) and toothpaste containing CPP-ACP. Overall, the latter proved to be significantly effective in preventing and regressing WSLs.\textsuperscript{56}

Another group of patients at high risk of incipient dental caries lesions are those who have degenerative salivary glands diseases, are undergoing cancer treatment such as chemotherapy or head and neck radiation therapy, or have physical or mental disabilities.\textsuperscript{57,58} In this context, an in situ study assessed the effectiveness of three remineralizing agents (CPP-ACP, CPP-ACPF and NaF at 0.05\%) in Sjogren’s syndrome patients. Several relevant aspects related to saliva were evaluated (flow rate, pH, buffering capacity and mineral concentrations), as well as the pH of biofilm. The study concluded that the use of CPP-ACP and CPP-ACPF caused a slight increase in saliva pH and a significant increase in bacterial plaque pH. In addition, the analysis by energy-dispersive spectroscopy and SEM performed on samples in situ showed that the use of these alternatives increased the concentrations of Ca\textsuperscript{2+} and PO\textsubscript{4}\textsuperscript{3–} in the dental surface, as well as the micromorphological defects of the enamel surface, which could be of clinical relevance to patients with this condition.\textsuperscript{59}

Patients with head and neck cancer undergoing radiation therapy are at high risk of dental caries, especially at the cervical, cuspид and incisal levels, characterized by rapid progression and high potential for destruction of dental tissues. Daily use of CPP-ACP and NaF applications in these patients tend to produce a greater preventive effect against post-radiation cavities.\textsuperscript{60} However, another study showed that there is no additional positive impact of this nanocomplex in terms of cavity prevention when associated with a 0.4\% tin fluoride-based gel in patients with nasopharyngeal carcinoma undergoing radiation therapy.\textsuperscript{61}
In relation to disabled patients, Özdas et al conducted a study in cerebral palsy children aged 3 to 8 years. First, pH measurements were performed on dental plaque and saliva buffer capacity. In addition, a CPP-ACP-based paste (GC Tooth mousse, GC, Tokyo, Japan) was applied, evaluating the abovementioned characteristics for a maximum period of 8 weeks. Decreased acidogenicity of bacterial plaque and increased buffering capacity of saliva was observed from the fourth week of treatment. However, there were no comparisons with other remineralizing agents, and clinical evidence for these specific cases is very limited as to draw conclusions.

**Dental sensitivity**

There are several dental desensitizing strategies such as NaF, KNO₃ and strontium used in a traditional way. Recently, the arginine/calcium carbonate complex, bio-active glasses (Bioglass 45s5) and CPP-ACP are being used. In relation to the latter, several clinical studies in the literature have made comparisons with conventional methods. As an example, Mahesuti determined the efficacy of MI Paste™ (GC America, GC, USA) and a KNO₃-based gel (UltraEZ, Ultradent Products, Inc) in decreasing dentin hypersensitivity levels. The results showed that both dental products are effective but patients treated with KNO₃ experienced decreased pain within two days of treatment start, while the group treated with CPP-ACP showed improvements only after 7 days. This difference in terms of effectiveness was also shown by Madhavan et al, who compared the effect of a paste containing CPP-ACP against NaF and propolis after 1, 7, 15, 28, 60 and 90 days, concluding that although all agents reduce the levels of dentin pain, patients treated with CPP-ACP-based paste took more days to experience a significant effect.

It is important to note that the aforementioned cases are characterized by the presence of permeable dentin exposed to the oral environment, which enables the diffusion of KNO₃ up to the nerve endings of deep dentin, or the partial block of dentinal tubules by deposits of Ca²⁺ and PO₄³⁻. However, patients subjected to dental whitening with hydrogen peroxide or carbamide-based materials generally experience transient pain during or after treatment, especially when high concentrations of whitening agents or light sources are used. In these cases, dentin exposure to the oral environment is not necessarily present; therefore, pain has a different etiology and the synergistic effect of desensitizing therapies is required to improve the conditions during esthetic treatment.
Under conditions of transient post-whitening pain, CPP-ACP-based paste has a desensitizing effect similar to 5% KNO₃ and 0.7% sodium monofluorophosphate after 1 and 7 days as shown in a randomized controlled clinical study. Maghaireh also compared the desensitizing potential of this paste against a 2% NaF gel in patients subjected to tooth whitening with 35% hydrogen peroxide after 1, 3, 7 and 14 days. The study showed that the concentration incorporated in the paste reduces the levels of post-treatment dental pain, but did not present additional therapeutic effects compared to the other strategies. However, this desensitizing action in transient post-whitening pain is not observed in patients using xylitol-based chewing gums containing CPP-ACP (in a lower concentration, 0.6%), compared with conventional chewing gums.

Currently, there are whitening materials such as DayWhite™ and Nitewhite™ that include ACP in their chemical composition. When comparing the desensitizing effectiveness of the latter against other materials with 15% carbamide peroxide incorporating KNO₃, there were no differences in pain levels between the two treatments. In general, results from clinical studies suggest that CPP-ACP-based dental products (especially toothpastes at concentrations of 10%) have a desensitizing effect; however, it does not appear to be higher than other strategies, like KNO₃ or NaF.

CPP-ACP AND DENTAL MATERIALS

Interaction between the CPP-ACP nanocomplex and dental whitening materials

In addition to the sensitivity experienced during and after dental whitening, another controversial topic regarding dental whitening materials is their possible interaction with other agents or compounds present in the dental structure, different from pigments. In this specific case, some in vitro studies suggest that the action of CPP-ACP-based dental products does not interfere with the oxide-reduction reactions (like redox) generated between the whitening agent and the structure of chromophores responsible for dental pigmentations; in consequence, it does not affect the aesthetic result of treatment. Another therapeutic alternative to in-office dental whitening is the application of gases with hyperoxidizing potential such as ozone (O₃), which represents an allotropic form of oxygen (O₂). However, by means of the spectrophotometric values of Delta L* (lightness difference), Delta A* (red-green difference) and Delta E (total color difference), it has been confirmed that the
concomitant use of a CPP-ACP-based paste during dental whitening does not affect the oxidizing potential of O₃.⁷⁴

**The CPP-ACP nanocomplex and the mechanical properties of water-based dental cements**

The remineralizing properties of glass ionomer cements (GICs) on demineralized dental regions have been widely reported in the literature.⁷⁵,⁷⁶ However, in comparing the remineralization patterns of both options, it has been found that GICs act only on the surface of cavity lesions, while CPP-ACP-based pastes remineralize their entire body.¹⁶ Therefore, an *in vitro* study added various concentrations of CPP-ACP into a GIC, specifying that such incorporation must be controlled because concentrations higher than 8% extend the setting time, a factor that can affect the clinical use of this material.⁷⁷ However, another *in vitro* study showed that the addition of just 1.56% (in weight) of CPP-ACP into a GIC increased the material’s tensile and compression strength.⁷⁸ Under experimental conditions, this remineralizing nanocomplex has also been incorporated into temporary eugenol zinc oxide-based cements (Freegenol™ and Temp-Bond® NE) at various concentrations. Similarly, it has been shown that there is a directly proportional relationship between the added percentage and the negative effect on some of its physical and chemical properties, such as solubility and tensile/compression strength.⁷⁹

**The CPP-ACP nanocomplex and adhesion to the dental structure**

The CPP-ACP nanocomplex has been used in several experimental *in vitro* protocols as dental surface treatment prior to the application of polymer adhesive materials.¹⁶,¹⁷ Clinically, this seeks to seal dentin tubules, reduce post-operative sensitivity and promote the remineralization of previously demineralized dentin or enamel, through the addition of ions promoted by ACP. However, mineral deposits on the dental surface could lead to negative effects on the adhesive interface, as shown by Adebayo et al (2010), who observed microscopic defects in the adhesive interface formed by a one-step self-etching adhesive used on dentin previously treated with a CPP-ACP-based paste. On the contrary, these micromorphological alterations were not observed when a two-step self-etching adhesive was used.¹⁷

It is important to note that there is a direct relationship between the characteristics of the adhesive interface and bonding strength (BS) values of these materials on dental hard tissues. Several studies have shown that prior application of pastes including the remineralizing nanocomplex does not affect
the BS of conventional or two-step self-etching adhesive systems on healthy dentin affected by cavities or healthy enamel. However, when one-step self-etching adhesive systems are applied to enamel previously treated with CPP-ACP, the BS values of these simplified polymeric materials are significantly reduced. This fact can be explained because the mineral deposits of the ACP on the enamel structure cannot be easily modified by the acidic functional monomers contained in one-step adhesive systems and consequently hinder the interaction with and binding to this structure. However, a different situation occurs with conventional adhesive systems because the prior use of phosphoric acid promotes the formation of considerable micromorphological alterations for mineral deposits and the retention of polymeric material, without decreasing bonding strength values.

In general, in vitro evidence shows that the effects of incorporating CPP-ACP into adhesive systems are material-dependent, with a higher tendency to favoring conventional systems and impairing the behavior of one-step adhesive systems due to the reaction of the functional monomer phosphoric radical with the cations released by the agglomerates. A similar mechanical impact has been observed when comparing conventional resinous and self-etching cements, but the available evidence on the influence of adding them into these polymeric materials is still very limited.

CONCLUSIONS

- The use of dental products incorporating CPP-ACP has a preventive potential for dental caries, but this potential is not higher than sodium fluoride. However, there is a greater tendency to regression of enamel white spot lesions when using products containing CPP-ACP or CPP-ACPF.

- The dental desensitizing effect promoted by CPP-ACP or CPP-ACPF-based products is transient and less effective than other strategies.

- The experimental incorporation of CPP-ACP into dental cements should be controlled so as not to affect the physical-chemical properties of the material.

- The CPP-ACP pre-treatment impact on the bonding strength of adhesive systems to enamel and dentin is material-dependent.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest, nor commercial relations that could trigger commitments or responsibilities in the development of this review.
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