

Non-fluoride systems for enamel remineralization: Types and mechanisms

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Abstract

Dental caries is a significant global public health issue, despite advancements in oral hygiene practices and the emergence of new protective substances. Although it is a progressive chronic condition, can be prevented and remineralized at an early stages without the formation of cavities. Minimally invasive dentistry emphasizes the importance of preventing strategies for remineralization of White spot lesions. New approaches are being developed to promote deeper lesion remineralization, minimize the risks associated with high fluoride levels, and ensure long-term carries control. Non-fluoride remineralization can be classified into two categories: those that enhance the efficacy of fluoride and biomimetic systems that imitate enamel regeneration. The aim of this brief paper is to review the some commonly used non-fluoride remineralization systems and mechanisms, challenges, and evidence underpinning some of the technological advances in enamel remineralization.

Keywords: Dental caries, remineralization, non-fluoride remineralization agents

1. Introduction

Dental caries is a prevalent health issue in most developed nations, affecting a significant number of children and adults (1).

Currently, dental caries is considered a preventable non-communicable disease (NCD) that impacts a significant portion of the population throughout their entire lives. Therefore, it exhibits various behavioral, socioeconomic, and lifestyle characteristics that are similar to other NCDs, such as obesity and diabetes. Consequently, it should be treated using an approach comparable to that used for the management of chronic diseases (2).

2. The caries balance

The pathophysiology of dental caries is not only gradual; demineralization and remineralization are dynamic processes. The progression or reversal of carious lesions hinges on the balance between demineralization-promoting pathological factors, such as cariogenic bacteria, fermentable carbohydrates, and salivary dysfunction, and protective factors, including antibacterials, adequate saliva, and remineralizing ions. This balance ultimately determines whether the process tips towards remineralization (Fig. 1) (3).

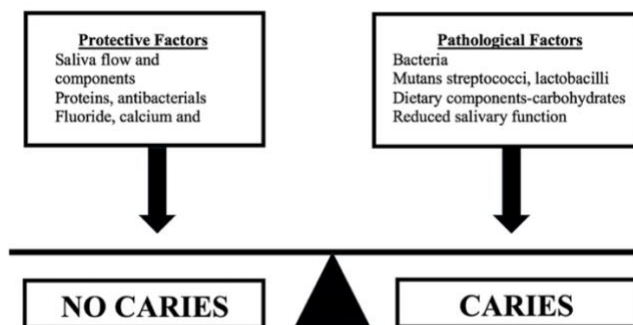


Figure 1. Schematic Diagram of the balance between protective and pathological factors in caries (4).

Remineralization is a natural repair process in which calcium (Ca^{2+}) and phosphate (PO_4^{3-}) ions from plaque or saliva are deposited to the demineralized tooth structure, leading to a net gain in minerals (5). Standard fluoride-based remineralization is the most well-supported method for managing tooth decay, and individuals and groups at high risk for cavities may benefit from using additional agents to enhance the benefits of fluoride (6, 7). The first International Conference on Novel Anticaries and Remineralizing Agents proposed that the primary objective of new remineralization therapies should be to "promote lifelong caries control by employing evidence-based, clinically

effective, multifactorial prevention methods for maintaining the equilibrium of the caries process" (8, 9). This paper examines the rationale behind the use of non-fluoride remineralization systems, along with the mechanisms, challenges, and evidence supporting various technological advancements in enamel remineralization therapies.

3. Natural remineralization alone is typically insufficient

The ability of saliva to promote the growth and maintenance of hard tissues throughout life by providing bioavailable calcium and phosphate ions is well-documented (10) and has developed over time (11). Saliva at its normal pH contains an excess amount of phosphoprotein-stabilized Ca^{2+} and PO_4^{3-} ions, which allows these ions to be readily available for diffusion into areas with low mineral content (12). Nevertheless, the studies that monitor the inherent development of white spot lesions (WSL) have discovered that while a few WSL diminish in size, the majority remain mostly unaltered even after a span of two years (13, 14). Furthermore, the net salivary remineralization process is characterized by a slow rate (15). Mineral gain typically occurs mainly on the surface of white spot lesions (WSL) because of the low concentration gradient of ions moving from saliva into the affected area (16). Salivary remineralization, which is accelerated by fluoride, is only effective on the outside 30 μm of the tooth (17). The process of remineralization that occurs only on the surface does not enhance the visual appearance or structural strength of the underlying lesion (12). By introducing external supplies of stable Ca^{2+} and PO_4^{3-} ions, the saliva's natural remineralization capacity can be enhanced. This is achieved by enhancing the diffusion gradients, resulting in faster and deeper subsurface remineralization (12).

4. Modern caries management

Enamel caries is a gradual loss of minerals beneath the surface of the tooth, which, if not addressed, can result in structural damage and the formation of cavities. This commonly leads to a cycle of repeated dental restorations. Despite long-standing recommendations for a biological approach to managing caries (18), many dentists continue to use a restoration-only approach, which has been shown to be poor in terms of both clinical outcomes and cost (19, 20). A worldwide agreement exists that the main strategy for managing modern tooth decay should be focused on "maintaining tooth structure and performing restorations only when absolutely necessary" (21). Innovative remineralization systems, such as biomimetic peptide scaffolds that regenerate the lesion body structure or calcium phosphate systems that

promote subsurface mineral gain, can greatly decrease the necessity for conventional dental restorations and aid in the preservation of tooth structure (9).

White spot lesions (WSLs), also known as Early Caries Lesions (ECLs), are the first indicators of enamel demineralization, and the use of remineralization therapy for their treatment is increasingly popular (22, 23, 24).

WSLs typically fall within the International Caries Detection and Assessment System (ICDAS) II 1-2 range (22- 24). Under normal physiological conditions, there is a balance between demineralization and remineralization at the enamel surface, which is influenced by fluctuations in pH levels (25). When this balance is disrupted, early caries can develop (26). It is important to note that orthodontic treatments involving fixed appliances can impede oral hygiene maintenance, resulting in plaque buildup and caries progression (27-29). This process directly leads to the formation of the WSLs. Additionally, WSLs are associated with the duration of bracket attachment, which raises concerns about orthodontic WSLs. These lesions are considered active until the brackets are removed (27, 30, 31). Caries management is undergoing a shift towards a minimally invasive approach, emphasizing the prevention, reduction, and reversal of caries in its early stages. (3, 22, 32). These initial lesions are considered treatable through interventions aimed at remineralization or arresting caries progression. If demineralization is not halted, the intact enamel surface will eventually break down, leading to the formation of cavities. (22, 33- 35).

Fluoride-based approaches are widely regarded as the most effective method for preventing and treating white spot lesions (WSLs) (23, 36, 37). Fluoride reacts with saliva on the tooth enamel. It combines with phosphate and calcium ions to create larger crystals that contain more fluoride, which is known as fluorapatite. This process helps strengthen the enamel and promote remineralization (38). Nevertheless, existing fluoride treatments have been found to have restrictions, particularly when dental cavities have already appeared as white spots (27, 32, 39, 40).

Casein phosphopeptides (CPP) contain multiple phosphoryl sequences that can stabilize calcium phosphate in nanocomplexes, such as amorphous calcium phosphate (ACP). CPP binds to ACP in a metastable solution through its phosphoryl sequences, preventing the dissolution of calcium and phosphate ions. CPP-ACP also serves as a reservoir for bioavailable calcium and phosphate, thereby supporting the process of remineralization (38, 41). However, compared to fluoride, CPP-ACP does not achieve effective treatment results (42, 43, 44). The clinical advantages of tricalcium phosphate products over fluoride have not been demonstrated (27, 45, 46). The self-assembling peptide P11-4 (SAP P11-4) offers a novel approach for remineralization therapy of WSLs through biomimetic mineralization (27, 47- 49).

5. Non-fluoride enamel remineralizing technologies

In recent years, tremendous progress has been made in the development of new systems for enamel remineralization. Some of these systems are currently used in clinical settings, whereas others are still in the process of being developed. The most effective remineralizing technologies are detailed in Table 1 (9).

5.1 Biomimetic Remineralization

Fluoride-containing oral care solutions are effective in replenishing minerals in the enamel; however, they lack the ability to stimulate the formation of structured apatite crystals (50). Currently, there is a transition from reparative to regenerative biomineralization therapies, focusing on replacing damaged dental tissues with biologically similar materials (51). However, regenerating enamel presents a unique challenge because mature enamel is acellular and does not undergo resorption or remodeling like bone or dentin (52). Advancements in tissue engineering have led to biomimetic techniques that demonstrate significant promise for restoring the intricate microstructure of enamel (9).

5.1.1 Dentine Phosphoprotein-Derived 8DSS Peptides

Dentine phosphoprotein (DPP) is the predominant non-collagenous substance found in the extracellular matrix of dentine. It plays a vital role in tooth mineralization (53). Human DPP contains many repetitive aspartate-serine-serine (DSS) nucleotide sequences, which are thought to aid in hydroxyapatite (HA) formation. Research has demonstrated that DPP can induce the formation of HA crystals in calcium phosphate solutions. (54, 55). A number of concise functional peptides derived from DPP have been developed, providing benefits compared to the complete DPP protein, including increased purity, improved structural compatibility with enamel, and the prevention of allergies and immunogenicity often linked to animal proteins (53). Among the peptides derived from DPP, the octuplet repeats of aspartate-serine-serine (8DSS) are the most effective in enhancing biomineralization (56).

The 8DSS peptides possess two main surfaces that can bind minerals. They have a considerable affinity for both free Ca^{2+} and PO_4^{3-} ions, as well as the HA surface (54, 56). When applied to enamel, these peptides have the ability to inhibit the release of Ca^{2+} and PO_4^{3-} ions into the surrounding media, while facilitating their absorption from the solution. Therefore, it appears that 8DSS peptides facilitate mineral deposition using a two-fold method. Firstly, they restrict the release of Ca^{2+} and PO_4^{3-} ions from demineralized dentine; and secondly, they facilitate the binding of these ions to create fresh mineral deposits on demineralized enamel

(53, 57). The recently developed mineral demonstrates consistent accumulation of tiny apatite crystals, leading to notable enhancements in characteristics, such as decreased surface roughness, heightened hardness, and elevated elastic modulus (53, 58). A recent in vitro study has provided strong evidence that the biomimetic 8DSS peptide not only independently inhibits enamel demineralization but also significantly boosts the efficacy of fluoride in preventing demineralization (59). This mutually beneficial relationship has the potential to decrease the amount of fluoride needed to prevent tooth decay in children, therefore reducing their chances of developing dental fluorosis.

Currently, the effectiveness of 8DSS peptides has only been shown in laboratory settings and is expected to pose difficulties when used in clinical applications. It is unclear whether these peptides can resist enzymatic activity in the mouth, despite their short peptide structures, which should provide some resistance against hydrolytic enzymes. Another possible disadvantage is that, as a result of their high calcium-binding characteristics, 8DSS peptides may contribute to calculus formation if not adequately regulated. If future in vivo studies can confirm the clinical potential of 8DSS and address these challenges, it could become a highly promising non-fluoride biomineralizing agent (57).

Table 1. Non-fluoride enamel remineralizing Technologies [revised from (9)]

Biomimetic Remineralization	
1 -Dentine Phosphoprotein-Derived 8DSS Peptides	
2 -Self-Assembling P11-4 peptides	Curodont Repair/Curodont Protect
3 -Amelogenin	
4 -Poly(amido amine) dendrimers (PAMAM)	
5 -Electrically accelerated and enhanced remineralization	
6 -Nanohydroxyapatite	Apagard toothpaste/Desensin oral rinse
Fluoride boosters	
1 -Calcium-phosphate systems	
*Stabilized calcium phosphates	
-Casein phosphopeptide-amorphous calcium phosphate	GC Tooth Mousse/MI Paste Plus®Topical Tooth Cream Recaldent/Trident White sugar-free gum MI Paste® ONE Toothpaste(GC)
*Crystalline calcium phosphates	
- Functionalized β -tricalcium phosphate	3MTM ClinPro Toothpaste
- Calcium sodium phosphosilicate (NovoMin™ technology)	Oravive Toothpaste(GSK)
Calcium Carbonate (CaCO₃)	
Dicalcium phosphate dehydrate	R.O.C.S Baby
*Unstabilized calcium phosphates	
- Amorphous calcium phosphate (Enamelon™ technology)	Enamelon® Fluoride Toothpaste(Premier)
2 -Polyphosphate systems	
- Calcium glycerophosphate	Oral-B PRO EXPERT Toothpaste
- Sodium Trimetaphosphate (sTMP)	R.O.C.S Medical Minerals (Remineralizing gel)
- Sodium hexametaphosphate	
3 -Natural products	
-Galla chinensis	
-Hesperidin	
-Gum arabic	
-Theobromine	
-Grape Seed Extract	
-Chitosan	
4 -Xylitol	

5.1.2 Self-Assembling P11-4 Peptides

An optimal strategy for enamel regeneration would entail substituting the degraded enamel matrix with a biomimetic matrix that facilitates deep remineralization of enamel lesions (60). An encouraging advancement in this area is the discovery of a monomeric peptide, P11-4, which consists of 11 amino acids. This peptide is designed to self-assemble into hierarchical three-dimensional fibrillar scaffolds in response to local conditions, such as high ionic strength and acidic pH found within the lesion body (61). The P11-4 fibrillar matrix has a strong affinity for Ca^{2+} ions and serves as a nucleator for the formation of new hydroxyapatite (HA), leading to the remineralization of the lesion. (61, 62). In vitro investigations have demonstrated that the inclusion of P11-4 fibers in the lesion body expedites the production of hydroxyapatite (HA), resulting in the development of needle-shaped crystals oriented tangentially and an enhancement in the microhardness of the remineralized subsurface lesion (17, 63, 64).

P11-4 has shown encouraging outcomes as a biomimetic mineralization agent in both in vivo and clinical trials. Studies have demonstrated that it can effectively treat early occlusal and proximal lesions, which are more difficult to remineralize with fluoride compared to smooth surface lesions (60, 65-67). When applied to an initial carious lesion, the low-viscosity isotropic P11-4 rapidly penetrates the lesion body and, in the presence of cations and a pH below 7.4, transforms into an elastomeric nematic gel. This transformation leads to the assembly of a three-dimensional fiber matrix and subsequent biomineralization of the lesion (65). P11-4-treated carious lesions have shown significantly improved visual appearance and increased radiographic opacity, maintaining stability even 6-12 months post-treatment (66, 67). A recent randomized controlled trial (RCT) showed that the process of biomineralization, aided by P11-4 and combined with fluoride, is both safe and more effective than the current clinical gold standard of fluoride treatment alone (51).

The success of P11-4 is contingent upon the quality of an individual's saliva, namely its mineral content, pH, and flow rate. P11-4 relies on the natural remineralization process facilitated by saliva (67). This may diminish its effectiveness in patients suffering from xerostomia. Although P11-4 therapy represents notable progress in achieving directed enamel regeneration, it is necessary to conduct more extensive and controlled research over an extended period of time to validate and measure these findings. Additionally, these studies should aim to identify supplementary elements that can improve the healing processes.

5.1.3 Amelogenin

The enamel organic matrix, which contains a significant amount of amelogenin, plays a critical role in controlling the growth, form, and organization of hydroxyapatite (HA) crystals throughout the process of enamel mineralization. Nevertheless, fully developed enamel

does not include matrix proteins and is incapable of regenerating the mineral loss resulting from tooth caries or erosion (68). In recent times, a number of effective approaches have been suggested to recreate the intricate enamel microstructure utilizing synthetic systems based on amelogenin. Recombinant porcine amelogenin (rP172) has been discovered to stabilize clusters of calcium phosphate and stimulate the formation of enamel crystals structured in a hierarchical manner on acid-etched lesions. This process greatly improves the hardness and elastic modulus of enamel (69, 70). The biomimetic renewal of hydroxyapatite (HA) crystals resulted in the formation of a strong connection between the newly formed layer and natural enamel, guaranteeing the effectiveness and long-lasting nature of the restorations (9).

A cost-effective and safer substitute for full-length amelogenin is a leucine-rich amelogenin peptide (LRAP) consisting of only 56 amino acids. This peptide, which lacks phosphorylation, consists solely of the N- and C-terminal domains of the original amelogenin. These domains play crucial roles in guiding mineral development and binding (71). Laboratory experiments have demonstrated that the application of leucine-rich amelogenin peptide to enamel lesions decreases the depth of the lesions and stimulates the formation of enamel that closely resembles natural enamel. This is achieved by promoting the linear growth of fully developed enamel crystals along the c-axis (72-74). By adding mineralization inhibitors, such as inorganic pyrophosphate or matrix metalloproteinase, to synthetic amelogenin assemblies, it has been possible to effectively control the size, shape, and alignment of a new mineral layer that strongly adheres to the surface. This process also prevents unwanted protein blockage within the newly formed crystals (75, 76).

Nevertheless, one disadvantage of amelogenin-mediated enamel regeneration is the challenging extraction and storage of the protein, as well as the lengthy duration required for the formation of the restored enamel layer. Consequently, this approach may not be suitable for clinical applications. Moreover, although amelogenin has been demonstrated to stimulate the formation of apatite in laboratory settings, there is currently no conclusive proof that the same process occurs naturally within living organisms (68).

5.1.4 Poly (Amido Amine) Dendrimers (PAMAM)

Dendrimers are polymers with a highly branched structures, containing internal cavities, many reactive end groups, and a precisely determined size and shape (77). These dendrimers, which are inspired by amelogenin, are commonly referred to as "artificial proteins." They are capable of imitating the roles of organic matrices in controlling the process of dental enamel formation. Multiple laboratory experiments have demonstrated that amphiphilic, carboxyl-terminated, and phosphate-terminated PAMAM dendrimers exhibit a pronounced inclination to spontaneously form complex enamel crystal structures in a hierarchical manner (77-

81). The crystals produced by the PAMAM organic templates had the same structure, alignment, and mineral composition as the intact enamel. The hydroxyapatite nanorods closely mirror the original prisms (77).

Synthetic PAMAM dendrimers can potentially function as amelogenin analogs in biomineralization, effectively overcoming the difficulties associated with the extraction, purification, and preservation of natural proteins. Nevertheless, the practical use of these findings in medical settings is still distant, as the current research has only been conducted on animals and has not yet progressed to human trials. In addition, like amelogenin, the process of enamel remineralization mediated by PAMAM is time-consuming. This could limit its applicability in clinical settings unless its effectiveness can be improved. A recent suggestion proposes the use of lasers to expedite the biomineralization process and accurately regulate crystal formation in specific areas (82).

5.1.5 Electrically Accelerated and Enhanced Remineralization

Electrically accelerated and enhanced remineralization (EAER) is an innovative method designed to treat early and intermediate enamel lesions. Its objectives are to maintain healthy tissue, fully restore caries lesions, and enhance the mechanical qualities of treated enamel (83). This method employs iontophoresis to accelerate the movement of remineralizing ions into the innermost regions of subsurface caries lesions, establishing conditions that facilitate remineralization and enable the restored lesion to develop with ideal hardness and mineral density. EAER, in contrast to biomimetic peptides, does not restore missing enamel by means of matrix proteins or the organic sequestration of Ca^{2+} and PO_4^{3-} ions. Nevertheless, lesions treated with EAER resemble healthy enamel, as scanning electron microscopy does not reveal any obvious signs of broken rods or deteriorated prisms (83). A benefit of EAER over synthetic biomimetic peptides is its utilization of readily available tools and chemicals usually found in the majority of dental practices. The initial findings from in vitro testing of EAER show great promise. However, to fully evaluate its ability to promote remineralization, data from in vivo research and independent evaluations are necessary.

5.1.6 Nanohydroxyapatite (nHA)

Nanohydroxyapatite (nHA) is considered one of the most biocompatible and bioactive materials because its morphology, structure, and crystallinity closely resemble those of the apatite crystals found in enamel (84). These nanoparticles have a high affinity for enamel surfaces, as well as for bits of plaque and germs. The reduced particle size of nHA greatly enhances its surface area for adhesion and enables it to function as a filler, mending

minor cavities and indentations on the enamel surface (85). In vitro dynamic pH-cycling experiments have demonstrated that nHA has the potential to remineralize initial enamel lesions with effectiveness comparable to or even surpassing that of fluoride (86- 89). A further in vitro investigation revealed that the use of nHA gel has considerable promise in promoting the remineralization of enamel around repair margins (90).

The precise mechanism underlying the biomimetic function of nHA remains unclear. According to certain researchers, it is proposed that it facilitates remineralization by forming a fresh layer of artificial enamel surrounding the tooth or by introducing apatite nanoparticles into enamel imperfections (85, 91).

Others suggest that nHA functions as a calcium phosphate reservoir, maintaining supersaturation with respect to enamel minerals, thereby inhibiting demineralization and promoting remineralization (87).

Despite the availability of nHA products since the 1980s, there is still a lack of well-designed randomized controlled trials (RCTs) demonstrating their greater effectiveness than fluoride toothpastes. In addition, when conditions are neutral, nHA has a tendency to selectively promote the remineralization of the enamel caries lesion, but it does not fully achieve remineralization of the lesion (87). Further data is required for clinicians to endorse nHA products as a viable alternative to fluoride toothpaste or rinse.

Nanohydroxyapatite (n-HAp) is known for its high biocompatibility and bioactivity and has recently become widely accepted in the field of dentistry. Hydroxyapatite acts as a storage for calcium phosphate, which helps maintain the enamel minerals in a state of supersaturation. This reduces demineralization and improves remineralization (92).

NovaMin, a bioactive glass, serves as a biomimetic mineralizer that mimics the body's natural mineralizing processes while also influencing cell signals to support the restoration of tissue structure and function (93).

5.2 Fluoride Boosters

5.2.1 Calcium Phosphate Systems

5.2.1.1 Stabilized calcium phosphates

The future of non-fluoride remineralization lies in biomimetic-guided enamel regeneration; however, its widespread clinical implementation is yet a few years in the future. Currently, the focus on improving the ability of fluoride to promote remineralization in individuals at high risk for tooth decay is mostly achieved through the use of calcium phosphate systems. The effectiveness of topical fluoride treatment in promoting remineralization is typically hindered by the limited availability of Ca^{2+} and PO_4^{3-} ions, especially when saliva production is reduced (94, 95). Extrinsic sources of Ca^{2+} and PO_4^{3-} ions can enhance the diffusion gradients and amplify F-ion-mediated remineralization. In recent years, several

distinct systems for remineralizing calcium phosphate have been developed and marketed. Cochrane et al. (11) classified these systems into three types: (i) stabilized amorphous calcium phosphate systems, (ii) crystalline calcium phosphate systems, and (iii) unstabilized amorphous calcium phosphate systems (Table 1).

5.2.1.1.1 Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP)

CPP-ACP was developed based on the principle that tryptic digestion of milk caseinate produces multiphosphorylated casein phosphopeptides (CPP), significantly enhancing the milk protein's solubility and its ability to stabilize Ca^{2+} and PO_4^{3-} ions (96). CPP acts as a saliva biomimetic with a substantially greater calcium-stabilizing capacity than salivary proteins because of its higher phosphoserine residue content (10). CPP-amorphous calcium phosphate (ACP) nanocomplexes have excellent solubility in saliva, resulting in the formation of a diffusion gradient that facilitates their localization in supragingival plaque. During a cariogenic attack, the presence of low pH levels causes the release of Ca^{2+} and PO_4^{3-} ions. These ions prevent demineralization and encourage the remineralization of early stage lesions by causing the released ions forming solid deposits (97). Research has demonstrated that CPP-ACP creates a subsurface remineralization pattern that greatly enhances the appearance, durability, and ability to withstand acid of remineralized white spot lesions (WSL) (11, 98). CPP-ACP is the most thoroughly researched non-fluoride remineralizing agent, although the reported findings exhibit significant diversity. Multiple randomized controlled trials (RCTs) have shown that CPP-ACP products have markedly superior results in remineralizing teeth and preventing tooth decay compared to both placebo and fluoride-containing products (99-107). Nevertheless, several other randomized controlled trials (RCTs) have contradicted the aforementioned results by failing to observe any significant additional benefit for CPP-ACP (108-114).

In an *in vitro* study on the effect of a paste containing 10% CPP-ACP on enamel surface microhardness, it was shown that CPP-ACP can form subsurface mineral products through its interaction with hydrogen ions and subsequent diffusion into the enamel (115).

In *in vivo* studies evaluating the remineralization effect of CPP-ACP and fluoride mineral-containing agents on white/creamy and yellow/brown demarcated opacities on incisors in children, CPP-ACP appears to improve mineralization due to the stabilization of calcium and phosphate ions by casein phosphopeptide, a protein that carries these ions in the form of amorphous calcium phosphate (116, 117).

Gokkaya et al. investigated the *in vitro* effect of CPP-ACP and fluoride-containing varnish on preventing enamel erosion and found that CPP-ACP-containing agents had a statistically significant effect in preventing dental erosion (118).

Published literature and systematic reviews present contradictory findings, with certain evaluations indicating that CPP-ACP shown substantial remineralizing and caries preventative effects (119-121), while others conclude that despite studies reporting that long-term remineralizing or white spot lesions should be combined with fluoride to maximize remineralization efficacy, the evidence is limited (6, 122-125).

The inconsistent findings from CPP-ACP remineralization research can be partially ascribed to a restricted comprehension of CPP-ACP technology. Several randomized controlled trials (RCTs) that concluded that CPP-ACP did not provide better remineralization than fluoride failed to consider the distinct remineralization patterns induced by CPP-ACP and fluoride. CPP-ACP promotes the process of restoring minerals in the subsurface of enamel lesions, whereas fluoride mainly contributes to the restoration of minerals on the surface of the enamel (126). Completely remineralized white spot lesions (WSLs) not only have enhanced appearance and durability, but they are also more resilient to future acid attacks (9).

In highly cariogenic environments, such as those with xerostomia or more than six sugar exposures per day, the ability of CPP-ACP to deliver high concentrations of stabilized Ca^{2+} and PO_4^{3-} ions can be especially advantageous. This is because fluoride and salivary homeostatic mechanisms alone are insufficient to repair developing lesions in these conditions (127).

The presence of studies with insufficient statistical power and potential conflicts of interest among rival product makers can lead to inconsistent findings in systematic reviews. Additional independent, extended longitudinal trials that specifically target high-risk population groups are necessary to ascertain whether CPP-ACP therapy can produce better remineralization of early lesions in comparison to fluoride-based products (127). Additional research may help determine be used to evaluate WSL-affected teeth and the effectiveness of mineralizing agents (116).

5.2.1.2 Crystalline calcium phosphates

5.2.1.2.1 Functionalized β -Tricalcium Phosphate

Functionalized tricalcium phosphate (fTCP) is created by milling tricalcium phosphate with sodium lauryl sulfate. This process stabilizes the solution and maintains high concentrations of calcium, phosphate, and fluoride in white spot lesions (128). Including the functionalized TCP ingredient in NaF formulations has been shown to produce stronger, more acid-resistant minerals compared to fluoride alone in both laboratory and clinical evaluations (129). A novel 5,000 ppm fluoride dentifrice, Clinpro® 5000, was recently introduced by 3M ESPE. This 1.1% NaF silica-containing paste incorporates an innovative functionalized tricalcium phosphate (fTCP) ingredient, which has been shown to enhance remineralization performance compared to fluoride-only systems in developmental formulations (130).

The modification of crystalline β -tricalcium phosphate (β -TCP) involves combining it with carboxylic acids and surfactants, resulting in functionalized β -TCP (fTCP) (131). The objective of functionalizing β -TCP was to establish barriers that would prohibit early fluoride-calcium interactions. This would enable it to serve as a precise and controlled delivery mechanism for low doses when administered to teeth using dentifrices or mouthwashes (132). The primary purpose of its design is to enhance the activity of F^- ions on the surface of the tooth, while remineralization is mainly driven by the presence of Ca^{2+} and PO_4^{3-} ions in saliva (9).

Despite being commercially available, there is a lack of comprehensive evidence on the effectiveness of this substance in remineralization. Existing studies are restricted to laboratory experiments that do not fully capture the intricate biological processes of lesion remineralization. Based only on the underlying mechanisms, it appears that CPP-ACP will possess a notable edge over fTCP in the remineralization of initial lesions. Although the pH-responsive CPP-ACP nanocomplexes are capable of delivering stable Ca^{2+} and PO_4^{3-} ions for a long duration, fTCP seems to provide just a limited quantity of unbound ions during the brief brushing phase before being expelled from the mouth (133). It would be premature to make a clinical recommendation on the use of fTCP products without evidence from well-designed randomized controlled trials (RCTs).

In an in vitro study comparing CPP-ACPF, CPP-ACP, and TCP with various nanotechnological systems in artificial caries lesions formed on enamel surfaces, TCP showed the lowest values in terms of remineralization efficiency compared to the others (134).

5.2.1.2.2. Calcium Sodium Phosphosilicate (NovoMin™ technology)

Calcium sodium phosphosilicate is a type of bioactive glass material that was originally created to serve as a biocompatible substance for the purpose of bone regeneration. Within the watery environment of the mouth, it releases sodium (Na^+), calcium (Ca^{2+}), and phosphate (PO_4^{3-}) ions. These ions then combine with saliva to form a layer of crystalline hydroxycarbonate apatite. This layer is identical in structure and chemical composition to the minerals found in the teeth (135). Initially used in a toothpaste to treat sensitive dentin, calcium sodium phosphosilicate has also been proposed as a possible agent for remineralizing tooth enamel (136). Nevertheless, the evidence from laboratory research conducted in controlled environments and within the body is lacking in strength and is also inconsistent (137, 138). Furthermore, there is a lack of clinical data obtained from randomized controlled trials (RCTs) to substantiate its effectiveness in promoting remineralization.

5.2.1.2.3 Calcium Carbonate ($CaCO_3$)

Calcium carbonate ($CaCO_3$) is an alkaline buffering agent utilized in toothpaste as an abrasive (139). Toothpaste containing calcium carbonate ($CaCO_3$) has a basic pH, but its solubility at neutral pH is quite minimal. This limits the effect of $CaCO_3$ on the acidogenicity of dental plaque (140).

SensiStat, created by Dr. Israel Kleinberg from the Department of Oral Biology and Pathology at New York Stony Brook State University, was introduced in 2003. It consists of arginine bicarbonate, which dissolves easily, and low-soluble $CaCO_3$ particles. When applied, it forms a paste-like scab in the tiny channels of dentin, effectively eliminating dental sensitivity. Additionally, it can be used to treat early surface demineralization and prevent the progression of severe caries that would require restoration (141).

A study by Cury et al., comparing toothpaste with CPP-ACP and $CaCO_3$, demonstrated that both types of toothpaste had remineralization effects; however, the toothpaste containing CPP-ACP showed significantly greater remineralizing efficacy (140).

It has been reported that toothpaste containing arginine, $CaCO_3$, and so NaF provides remineralization on the tooth surface and protects against acid attacks (142). Additionally, arginine and $CaCO_3$ have been included in dentifrice formulations to offer similar benefits as nano-hydroxyapatite (nanoHAp), specifically to enhance mineral deposition on exposed surfaces, which helps in the occlusion of dentinal tubules (143). Although studies have shown that the addition of calcium carbonate to toothpaste results in positive outcomes for remineralization, further research is needed to compare it with newly developed remineralization agents.

5.2.1.2.4 Dicalcium phosphate dehydrate

Dicalcium phosphate dihydrate (DCPD) serves as a precursor to apatite and readily converts to fluorapatite in the presence of fluoride ions (144). Research has demonstrated that incorporating DCPD into toothpaste enhances the concentration of free calcium ions in the plaque fluid, with elevated levels persisting for up to 12 hours after brushing, compared to traditional silica-based toothpastes (145). It is well-established that the release of calcium ions in the oral environment triggers the remineralization process in early enamel lesions. Consequently, the incorporation of dicalcium phosphate dihydrate into toothpastes influences the availability of calcium and phosphate ions. This addition helps prevent the development of caries and can halt the progression of existing carious lesions, keeping them at an early stage (146).

In an in vitro and in vivo thesis study evaluating enamel remineralization with R.O.C.S. Baby toothpaste containing DCPD and 10% xylitol, toothpaste containing theobromine, and toothpaste containing NaF, no statistically significant difference was found in lesion

depth reduction and enamel surface remineralization compared to the negative control group (147).

5.2.1.3. Unstabilized calcium phosphates

5.2.1.3.1 Amorphous Calcium Phosphate (Enamelon™ technology)

The ACP, an unstable calcium phosphate system, has been used in a fluoride toothpaste with two chambers. This toothpaste is specifically intended to release Ca^{2+} and PO_4^{3-} ions separately into the oral cavity (148). While brushing, the ions present in the mouth combine and form ACP or amorphous calcium fluoride phosphate, which precipitates instantly. Both ACP and amorphous calcium fluoride phosphate are inherently unstable and undergo rapid transformation into the more stable forms of hydroxyapatite (HA) or fluorhydroxyapatite. Prior to this phase shift, the Ca^{2+} and PO_4^{3-} ions are temporarily accessible for subsurface lesion remineralization (11).

The efficacy of ACP technology is supported by a solitary randomized controlled trial (RCT) conducted on patients with radiation. The trial revealed that ACP technology outperformed conventional fluoride toothpaste in reducing the occurrence of root caries. However, no significant disparities were observed in the control of coronal caries (149). An important issue associated with the use of an unstabilized calcium phosphate system is its ability to encourage the formation of dental calculus. In addition, Amorphous Calcium Phosphate (ACP) quickly captures and isolates loose fluoride ions in the mouth, hence decreasing their accessibility for the process of repairing tooth enamel. Due to the scarcity of data and the existence of superior alternatives, oral solutions utilizing ACP remineralization technology have restricted therapeutic usefulness (9).

In an in vitro study comparing CaGP and xylitol-containing gel, 1100 ppm NaF and 10% CPP-ACP toothpaste, 0.45% SnF_2 -1150 ppm F toothpaste (Enamelon), 1450 ppm NaF toothpaste, and deionized water, it was found that Enamelon showed a similar percentage of Surface Microhardness Recovery (SMHR) as the other toothpastes and significantly increased remineralization compared to the deionized water group (150).

5.2.2 Polyphosphate systems

5.2.2.1 Calcium Glycerophosphate (CaGP)

Calcium glycerophosphate (CaGP), an organic phosphate salt, has a significant impact on enamel health. It reduces plaque volume by increasing calcium and phosphate levels within the plaque, effectively preventing decay. Both in vitro and in situ studies have demonstrated that toothpastes containing low levels of fluoride and calcium glycerophosphate (CaGP) have superior caries-preventive effects compared to standard fluoride toothpastes. CaGP-containing products enhance the resistance of hydroxyapatite, providing protective benefits. When used alongside fluoride, these products

are believed to synergistically enhance the effectiveness of caries prevention. The remineralization potential of various CaGP-containing products is currently being utilized. Recognized as a safe food ingredient by the FDA, calcium glycerophosphate-fortified foods are considered a promising alternative or complement to fluoride in dental care (151, 152).

Sivet et al. conducted an in vitro study comparing surface microhardness results on human tooth enamel using different remineralization agents including CaGP, fluoride, and CPP-ACP. The study suggested that CaGP could serve as an alternative to fluoride (150).

CaGP, which effectively increases mineral levels, is used for the prevention and remineralization of caries-free lesions. Its mechanism is based on the release of calcium and phosphate ions, which is why it is considered for treating demineralized or hypomineralized lesions (153). According to a study conducted on children with Molar Incisor Hypomineralization (MIH), CaGP use for three months was observed to reduce hypomineralization in affected enamel (98). Utilizing CaGP-containing gel led to a statistically significant rise in enamel mineral density in permanent incisors afflicted by MIH, namely in areas with white/cream and yellow/brown distinct opacities (154).

In an in vitro study using natural carious dentin samples, calcium glycerophosphate was compared with other remineralization agents using various methods. It was observed to increase surface hardness in natural carious teeth compared to the negative control group (155).

5.2.2.2. Sodium Trimetaphosphate

An effective method for decreasing the likelihood of fluorosis while still preserving the ability of regular toothpastes to prevent tooth decay is to substitute some of the fluorides with polyphosphate salts such as sodium trimetaphosphate (STMP), calcium glycerophosphate, or hexametaphosphate (156, 157, 158). Out of all the polyphosphates, STMP has been shown to be the most effective in preventing tooth decay. It not only stops the loss of minerals from the teeth but also helps in the process of rebuilding them (159, 160).

Sodium trimetaphosphate ($\text{Na}_3\text{P}_3\text{O}_9$) is a type of inorganic phosphate that has a high affinity for phosphate sites on the enamel surface. It has a longer adsorption time compared to other phosphates (161). This process forms a defensive coating on the outer layer of the tooth, which restricts the spread of acid when exposed to substances that cause tooth decay (161). Multiple laboratory and field experiments have verified that STMP can reduce the loss of minerals, even when fluoride concentrations are low (160, 162, 163, 164). The STMP adsorption does not impede the diffusion of Ca^{2+} and F^- ions into the enamel, despite the presence of the protective barrier. Studies conducted on in situ models have demonstrated that adding STMP to a low-fluoride product produces remineralization effects comparable to those of a fluoride formulation with a concentration of 1,100 parts per million (ppm) (165, 166). Furthermore,

the inclusion of STMP in traditional fluoride dentifrices and varnishes greatly improves their capacity to restore artificial caries lesions (167, 168).

Prior clinical trials examining the caries preventative benefits of STMP yielded inconsistent findings (169, 170). Nevertheless, a recent 18-month randomized controlled trial (RCT) conducted under double-blind conditions showed that a low-fluoride dentifrice with a concentration of 500 parts per million (ppm), supplemented with sodium trimetaphosphate (STMP), was considerably more successful than a dentifrice with a fluoride concentration of 1,100 ppm in reducing the occurrence of tooth decay in children (171). Additional clinical trials are required to ascertain whether STMP has the potential to impact the reversal of non-cavitated lesions.

5.2.2.3 Sodium hexametaphosphate

Sodium hexametaphosphate ($\text{Na}_6\text{P}_6\text{O}_{18}$) (SHMP) is a cyclic inorganic phosphate compound with the ability to adsorb to enamel and the tendency to form complexes with cations (172). It consists of 10-12 repeating pyrophosphate subunits, which results in superior coverage and adhesion to the tooth surface compared to pyrophosphate. SHMP effectively prevents tooth staining and eliminates any remaining stains by effectively absorbing dental minerals and removing pellicle proteins, which are proteins that carry stains (173). It also has anti-inflammatory properties that can relieve gingivitis and is beneficial for the treatment of dental hypersensitivity (174).

Sodium hexametaphosphate has exhibited the stain removal and prophylactic activities in toothpastes, mouth rinses, and chewing gums (175).

SHMP also possesses qualities that prevent stain and caries formation. Anionic SHMP can be adsorbed into the cationic regions of the enamel surfaces. It creates a defensive coating on the surface of the mine to guard against erosive and acidic elements. Furthermore, SHMP possesses three phosphate groups that serve as sites for ion retention, including Ca^{+2} and CaF^+ ions (176). During the remineralization phase, the process of mineralization repairs the degraded surface, allowing pigments dissolved in saliva to penetrate the newly produced mineral phase. This leads to the formation of the unaesthetic "brown spot" of hardened initial enamel caries. Although SHMP has limited characteristics, its utilization in conjunction with other remineralizing agents effectively prevents degradation and surface discoloration (177).

5.2.3 Natural Products

5.2.3.1 *Galla chinensis*

A fascinating inclusion in the category of remineralizing agents is the utilization of plant-derived natural products. These substances have demonstrated the

capability to effectively alter the balance between the demineralization and remineralization processes in tooth decay. One of the most promising options is *Galla chinensis*, which is a leaf gall created by parasitic aphids. Studies have shown that *Galla chinensis* is helpful in preventing the loss of minerals from teeth, promoting the restoration of minerals, and improving the effectiveness of fluoride (178, 179). While the exact mechanisms are not well comprehended, it is theorized that polyphenols in *G. chinensis* engage with and stabilize the remaining organic matrix, obstructing the paths for ion diffusion and decelerating the process of demineralization (180, 181). The process of remineralization by *G. chinensis* is thought to be facilitated by several polyphenolic chemicals that function as transporters of Ca^{2+} ions into the damaged area (182). Additional natural substances, such as hesperidin, a flavonoid found in citrus fruits, and gum arabic, a substance derived from the Acacia tree, have been discovered to inhibit the process of acid-induced demineralization and promote the process of remineralization, even without the presence of fluoride (183, 184).

5.2.3.2 Hesperidin

Hesperidin is a bioflavonoid that is obtained from citrus fruits and their by-products. It possesses several advantageous characteristics, including anti-inflammatory, anticancer, antioxidant, and hypoglycemic benefits. Hesperidin has the ability to hinder the breakdown of bones and stable the collagen in dentin, which helps prevent the loss of minerals by functioning as a physical barrier that limits the movement of ions in stabilized tissue. The stable collagen structure is thought to enhance remineralization by serving as a structural framework, therefore exerting a favorable influence on the remineralization process. Nevertheless, there is limited research on this subject (183).

5.2.3.3 Gum Arabic

Gum arabic is a resinous substance obtained from the stems and branches of *Acacia senegal* and other similar African *Acacia* species. The substance mostly comprises polysaccharides with large molecular weights and has significant amounts of calcium, magnesium, and potassium salts. These salts, when subjected to hydrolysis, produce arabinose, galactose, rhamnose, and glucuronic acid (184).

Onishi et al. found in their in vitro study that the remineralization rate of molars exposed to gum arabic was similar to that of molars exposed to NaF, and the rates of both were significantly higher than that of molars exposed to the negative control group. Gum arabic increased the remineralization of enamel caries lesions, suggesting an inhibitory effect on dental caries (184).

5.2.3.4 Theobromine

Theobromine, a natural alkaloid derived from *Theobroma cacao*, differs from caffeine by a single methyl group. Recent efforts have explored its use as a remineralizing agent and potential fluoride alternative. Theobromine, which promotes the formation of larger hydroxyapatite crystallites in a calcium and phosphate-rich environment, strengthens enamel and enhances its resistance to acid attacks (185).

Srikanth et al. demonstrated that cocoa bean shell extract is effective in reducing the number of mutans streptococci and plaque accumulation in children (186).

Another study showed that theobromine facilitates remineralization by promoting apatite formation comparable to fluoride levels (187).

Kargül et al. (188), Irawan et al. (189), Suryana et al. (190) reported that theobromine increases enamel surface hardness values.

Durhan et al. conducted a clinical study to investigate the impact of fluoride toothpaste and theobromine-containing toothpaste on salivary pH, buffering capacity, and *Streptococcus mutans* levels in children with early childhood caries. Both toothpastes showed statistically significant enamel remineralization. Theobromine was particularly noted for its additional benefits in raising salivary pH and decreasing *S. mutans* levels. Consequently, toothpastes containing theobromine are suggested as effective agents for remineralizing white spot lesions and preventing early enamel lesions (191).

ARJ da Silva and colleagues concluded in their meta-analysis and review on the effects of theobromine on white spot lesions that the use of theobromine increases the microhardness of dental enamel subjected to demineralization, effectively promoting remineralization of this tissue comparable to the success achieved with fluoride use (192).

5.2.3.5 Grape Seed Extract

Grape seed extract contains proanthocyanidins, which are antioxidants that interact with microbial cell membrane proteins and lipids, leading to cell membrane lysis and consequently arresting root caries. It inhibits the glucosyltransferase enzyme produced by *S. mutans*, thereby preventing dental caries. Grape seed extract is a powerful alternative to fluoride for preventing root caries in elderly patients (193).

Fluoride-based solutions may not be as well accepted by the general public as natural remineralizing agents are. Prior to their utilization in clinical trials, it will be imperative to conduct chemical characterization and standardization of these natural compounds.

5.2.3.6 Chitosan

Chitin is a widely available amino polysaccharide found in nature, and its most suitable medical derivative, chitosan, is notable for its non-toxicity, biological compatibility, and chemical structure (194). Chitosan is

utilized in dentistry due to its antifungal and antibacterial properties (195, 196, 197).

Research indicates that chitosan is effective in protecting against dental caries and plaque formation. Its mucoadhesive properties make chitosan a promising candidate for oral drug delivery systems (198). Structurally, chitosan is a pure polymer that extends the adhesion time of oral gels and prolongs drug release. Its antifungal activity inhibits the adhesion of *Candida albicans* to human buccal cells. Studies have shown that buccal tablets made of chitosan microspheres containing chlorhexidine diacetate can extend drug release in the buccal cavity, thereby enhancing the antimicrobial activity of chlorhexidine (199).

Additionally, research has found that higher concentrations of chitosan lead to increased penetration into the enamel, with the extent of penetration being influenced by the enamel-dentin interface (200).

5.2.4 Xylitol

Xylitol is considered non-fermentable sugar alcohol. Its main properties include not being fermented into acids, forming less plaque, and reducing the number of *Mutans streptococci* in saliva (201, 202). Xylitol inhibits the activity of glucosyltransferase, which prevents the bacteria *S. mutans* from using glucose and sticking to the surface of the tooth, therefore reducing the formation of cavities (203).

Some researchers have suggested that xylitol may play a role in enamel demineralization and remineralization processes by acting as a Ca^{2+} carrier necessary for remineralization (204).

When consumed as mints or gum, xylitol stimulates an increased flow of alkaline and mineral-rich saliva from the small salivary glands in the palate. This increased salivary flow enhances the buffering capacity against acids and provides the minerals needed to remineralize the damaged areas of the enamel (205). (204).

The limited anticariogenic activity of xylitol may be related to its passive substitution of fermentable carbohydrates, which results in a decrease in acid generating potential, an increase in salivary flow, and suppression of cariogenic *Streptococcus mutans* (206). However, recent studies aimed at establishing xylitol as an effective caries suppressant have produced unfavorable results (203).

In vitro studies have demonstrated that, compared to glucose, sucrose, and fructose, the fermentation of xylitol is significantly reduced, and xylitol did not lower the pH below the critical value of 5.5 (207, 208). However, some studies comparing xylitol mouth rinse with fluoride rinse observed no change in acidogenic potential (209). Lee et al. reported in their study that xylitol consumption did not provide any additional benefit over fluoride treatment (210).

In their study, Cocco et al. reported a significant reduction in incipient dental caries and caries progression in the group chewing xylitol gum for one year compared to the group chewing gum sweetened with isomalt, sorbitol, mannitol, and maltitol (211).

In one of the two in vitro studies, xylitol's remineralization capability was supported when used in combination with fluoride (212), whereas the other study did not support this finding (213). The evidence regarding xylitol's promotion of remineralization remains inconclusive (203).

6. Conclusions

The current focus on preventive and minimally invasive dentistry highlights the need for the development of novel techniques to promote the remineralization of enamel caries lesions. The spontaneous repair of early lesions can be facilitated by fluoride, but the effectiveness of this process relies on factors such as the quality of saliva and the patient's adherence to dental hygiene and dietary recommendations. Remineralization systems that do not contain fluoride are not strongly influenced by these parameters and can greatly improve the structure, appearance, and ability to resist the acid of the remineralized lesion. Moreover, employing efficient procedures for remineralization without the use of fluoride can help prevent non-cavitated lesions from progressing into a cycle of repeated restorations due to secondary caries at the interface between the enamel and the restoration (214).

Currently, the majority of non-fluoride remineralizing systems available for purchase focus on improving the effectiveness of fluoride and reducing its potential dangers. Alternatively, a biomimetic approach to enamel regeneration could be a potential future direction. This involves replacing demineralized tissue with ordered enamel apatite crystals that are firmly bonded to the tooth surface. The objective of remineralization treatment techniques is to achieve guided enamel regeneration. Biomimetic technologies addressed in this context contribute to the advancement of artificial enamel development, bringing us closer to this ultimate aim.

Although non-fluoride enamel remineralizing methods show potential, clinical evidence supporting their effectiveness is generally lacking, unclear, or restricted to a small number of preclinical investigations. High-quality randomized controlled trials (RCTs) are necessary to ascertain whether these novel remineralizing methods provide any supplementary advantages compared to conventional fluoride remineralization. These investigations are particularly necessary for products that are already available in the market.

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