Dental Remineralization Therapies for Early Caries

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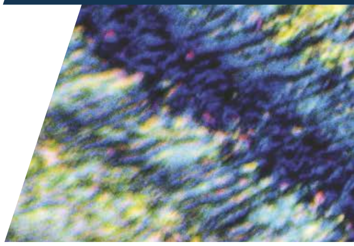
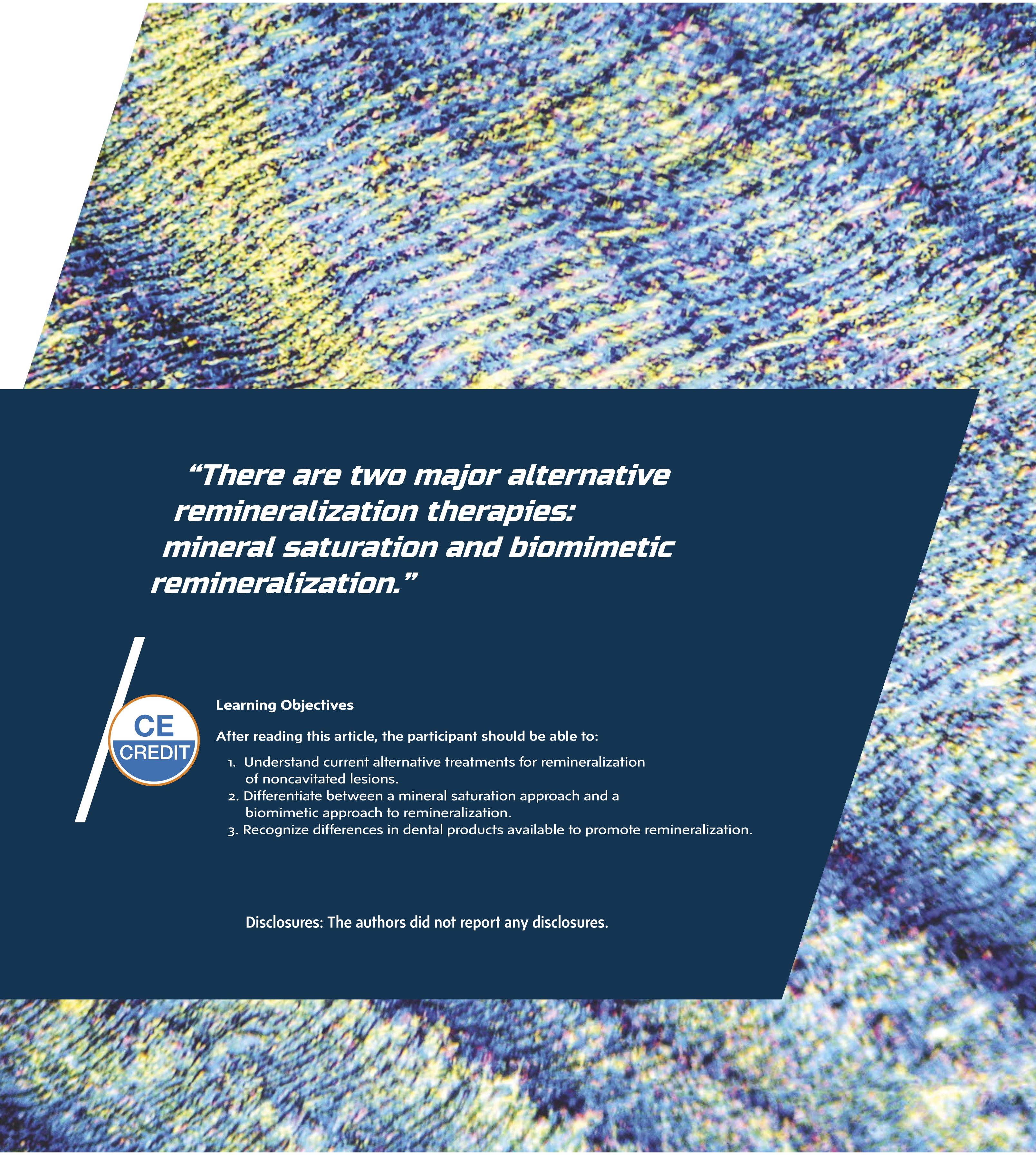
Abstract

Oral care products containing fluoride have established efficacy in enamel remineralization. However, most of the available therapies have a limited impact, as their effect on reducing the prevalence of dental caries is reaching a plateau. New therapies have added potentially active ingredients, such as calcium phosphate, polyphosphates, arginine, xylitol, nanohydroxyapatite, and peptides, in their formulations to increase mineral saturation of the oral environment or to biomimetically remineralize the undermined lesions. Although remineralization techniques have advanced in recent years, most of them lack relevant evidence for assessing their true clinical potential. This article discusses the alternatives to fluoride currently available for remineralizing noncavitated enamel lesions. The adoption of these remineralization therapies can have a beneficial impact on contemporary dentistry, since they will translate conservative concepts into clinical practice and prevent the formation of dental cavities.

Key Words: remineralization, demineralization, fluoride, calcium, phosphate





> ***"There are two major alternative remineralization therapies: mineral saturation and biomimetic remineralization."***

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Learning Objectives

After reading this article, the participant should be able to:

1. Understand current alternative treatments for remineralization of noncavitated lesions.
2. Differentiate between a mineral saturation approach and a biomimetic approach to remineralization.
3. Recognize differences in dental products available to promote remineralization.

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Introduction

The management of early-stage dental caries **(Figs 1a & 1b)** has changed significantly based on the concepts of dental remineralization and minimally invasive dental therapies.[1] Dental remineralization is the process of bringing inorganic components from the surrounding environment into the previously demineralized dental structure.[2,3] The mechanisms behind this dynamic process foster the development of alternative treatments for mineralization-related diseases. It is inferred that the dental structure presents imperfect forms of hydroxyapatite (HA) that are directly related to the incorporation of different ions in the crystal lattice. This leads to the structuring of fragile HA crystals in calcium-deficient regions that are more susceptible to acid attack and solubility. Bacteria involved in caries disease can break down fermentable carbohydrates to produce organic acids with the ability to diffuse into the tooth through the water that permeates the crystals. Upon reaching a susceptible site on the crystal surface, the acids dissolve the calcium and phosphate ions between the crystals in the surrounding aqueous phase, leading to advancement of the caries lesion **(Figs 2-4)**.[3-5]

Among the therapies available, fluoride-based treatment presents an unequaled body of evidence that is generally considered to be the main reason for the lower occurrence of dental caries in most populations.[6] However, epidemiological research has shown a concerning trend related to a plateau in the decrease of caries, and, in some populations, caries incidence actually has increased even with the use of fluoridated products.[7-10] Several research studies on new remineralization therapies have been developed as a result. Most recent treatments have been designed to augment the efficacy of existing fluoride therapies rather than to replace them, but those that do not involve fluoride can become an alternative to this growing demand.[3] Some therapies have added potentially active ingredients in the for-

Figures 1a & 1b: Current remineralization therapies have opened the door to a nonsurgical, minimally invasive treatment approach, especially in cases such as (a) a noncavitated caries lesion on the facial surface of the mandibular molar and (b) a demineralized lesion on the facial surface of the maxillary incisor.

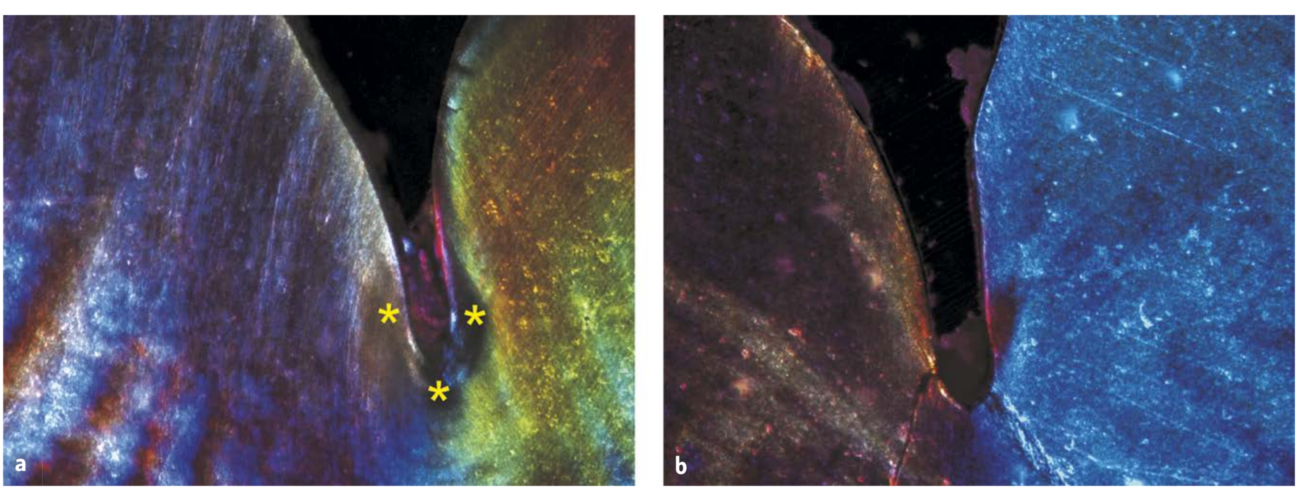

Figure 2: Photomicrographs of polarized light microscopy analysis (100×). (a) White spot lesion; yellow asterisks indicate the demineralized region. (b) Different view of the demineralized human molar.

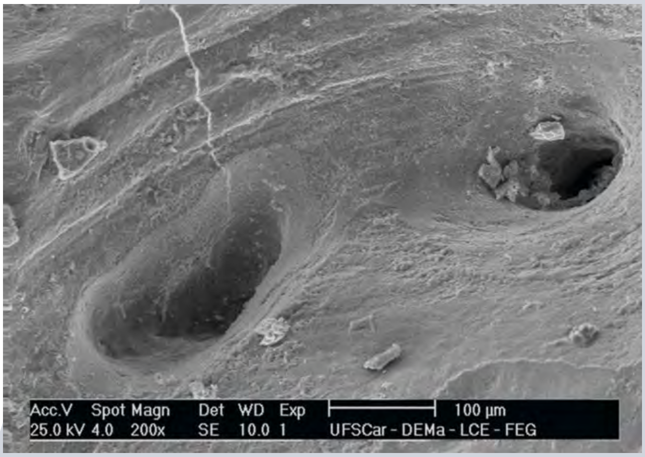

Figure 3: Demineralized lesion showing enlargement of demineralized dentinal tubules due to cariogenic bacteria. A small crack extending into the dentinal tubules is shown with scanning electron microscopy (SEM) at 200× magnification.

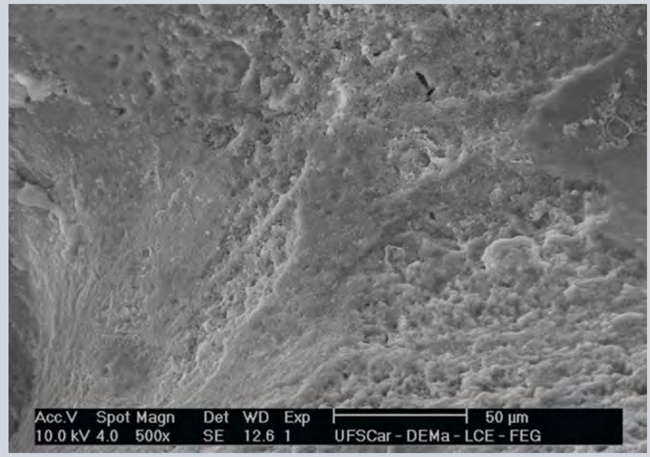

Figure 4: SEM at 500× magnification of the occlusal white spot lesion on the surface near the dental fissure. The noncavitated incipient enamel lesion was caused by biofilm buildup, in which bacteria break down dietary carbohydrates to form organic acids capable of demineralizing hydroxyapatite (pH < 5.5) to form the dental cavity.

mulations of their commercial products to increase mineral saturation, while others address the development of a mineral matrix within the demineralized lesions.[11]

Although remineralization techniques have advanced significantly in recent years, most of them lack relevant evidence for assessing their true clinical potential. This article reviews and summarizes the different alternatives that are currently available for remineralizing incipient noncavitated enamel lesions.

Current Alternative Remineralization Therapies

There are two major alternative remineralization therapies: mineral saturation and biomimetic remineralization **(Table 1)**.

Mineral Saturation

Mineral saturation therapies are designed to directly increase the mineral concentration in the environment around the demineralized tissue (saliva or biofilm). It is relevant to clarify the advantages and limitations of fluoride as a remineralizing agent as it is still considered the standard therapy versus other remineralization systems.[12] Although fluoride is recognized as the main active ingredient for the remineralization and arrest of caries progression,[1,13] the reversal of demineralized lesions by these therapies is effective mainly on the lesion surface, with a reasonable chance of developing lamination if applied in high concentrations.[14] Lamination is characterized by the remineralization process of the porous surface layer, in which enamel pore clogging hinders the penetration of mineral ions into the lesion body, preventing the complete remineralization of the underlying tissue.[15] Most new therapies try to overcome these limitations by adding other potentially active ingredients to the formulation, such as calcium, phosphate, arginine, and xylitol.

Casein phosphopeptide-amorphous calcium phosphate: Casein phosphopeptides (CPP) are composed of milk-derived phosphoproteins that act similarly to the proteins responsible for tooth biomineralization[16] and are capable of stabilizing calcium and phosphate ions in an amorphous calcium phosphate solution (ACP) to create complexes of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP).[1,17] When CPP-ACP comes in contact with dental structures, these nanocomplexes can bind onto tooth surfaces, soft tissue, and dental plaque to provide a reservoir of bioavailable calcium and phosphate ions. These will be released gradually as pH falls to create a state of supersaturation in the oral environment by boosting the dental remineralization process.[2,18] There is evidence supporting that CPP has an antibacterial and buffering effect on dental plaque and also on the proliferation and adherence of Streptococcus mutans and Streptococcus sobrinus.[19] Although many studies have shown significantly better antibacterial and remineralization results compared to placebo or to fluoride-containing products,[20,21] others contradict these results, showing no superior effect of CPP-ACP[22,23] compared to fluoride therapies.[1,6,24]

Functionalized β-tricalcium phosphate: Modifications were made to crystalline β-tricalcium phosphate (β-TCP) by coupling it with carboxylic acids and surfactants to produce a functionalized β-tricalcium phosphate.[25] This functionalization process was performed to create a barrier capable of preventing early fluoride and calcium interactions and to enable a targeted low-dose delivery system to the teeth.[26] The purpose of β-TCP was to increase the activity of fluoride ions in remineralization, carried out mainly by the bioavailability of Ca^{2+} and PO_4^{3-} ions on the lesion surface.[11] Although this technology is already commercially available, data on its remineralizing ability are

Table 1. Alternative Remineralization Therapies

Therapies	Commercial Product
Mineral Saturation	
stabilized calcium phosphate • casein phosphopeptide-amorphous calcium phosphate (CPP-ACP)	• MI Paste tooth crèmes (GC America; Alsip, IL) • Trident White sugar-free gum (Cadbury Adams USA; Parsippany, NJ)
crystalline calcium phosphates • functionalized β-tricalcium phosphate (fTCP) • calcium sodium phosphosilicate (CSPS)	• Clinpro tooth crèmes (3M ESPE; St. Paul, MN) • BioMin C toothpaste (BioMin Technologies; Stoke-on-Trent, UK)
unstabilized calcium phosphate • amorphous calcium phosphate (ACP)	• Enamelon toothpaste (Premier Dental Products; Plymouth Meeting, PA)
polyphosphate systems (STMP) • sodium trimetaphosphate • calcium glycerophosphate • sodium hexametaphosphate	• Oral-B Pro-Expert toothpaste (Procter & Gamble; Weybridge, Surrey, UK)
arginine	• Rapid Relief Sensitive toothpaste (Toms of Maine; Kennebunk, ME)
xylitol	• Trident sugar-free gum (Cadbury Adams USA)
Biomimetic Remineralization	
nanohydroxyapatite • nHAP	• Apagard toothpaste (Sangi; Tokyo, Japan)
self-assembling peptide • P11-4	• Curodont Repair/Curodont Protect toothpastes (Credentis AG; Windisch, Switzerland)

scarce and limited to laboratory studies and a few clinical trials that are not representative of the complex reality underlying dental remineralization.

Bioactive glass containing calcium sodium phosphosilicate: Calcium sodium phosphosilicate (CSPS) is a bioactive glass that releases Na^+, Ca^{2+}, and PO_4^{3-} ions when it comes in contact with the aqueous oral environment. These ions have the ability to interact with saliva, and, as a result, deposit a layer of crystalline apatite that is structurally and chemically very similar to dental apatite.[27] Some studies have demonstrated properties related to dental remineralization and anti-cariogenic/anti-plaque characteristics of these bioactive glasses.[28,29] A fluoride-containing bioactive glass (BioMin, BioMin Technologies) was also developed with fluoride, strontium, potassium, and zinc ions embedded within the glass itself. Zinc ions play a bactericidal role, while potassium contains neural-desensitizing properties and strontium/fluoride can assist the caries remineralization process. This configuration allows the release of Sr^{2+}, Ca^{2+}, PO_4^{3-}, and F^- ions directly into the initial lesions of dental caries to recover the demineralized tissue.[30,31]

Amorphous calcium phosphate: A nonstabilized calcium phosphate system is available in fluoridated toothpastes and has the advantage of providing Ca^{2+} and PO_4^{3-} ions to the patient's oral cavity during dental hygiene.[32] The toothbrushing process allows the Ca^{2+} and PO_4^{3-} ions to be mixed with saliva on the dental surface, producing immediate precipitation of ACP or amorphous calcium fluoride phosphate (ACFP). Due to the instability of ACP and ACFP, these compounds are rapidly transformed into HA or fluorapatite, which are more thermodynamically stable and insoluble crystalline phases of apatite.[11] However, before they precipitate, the Ca^{2+} and PO_4^{3-} ions remain temporarily bioavailable in the oral environment to promote remineralization of the subsurface lesions.[2] Studies have shown a superior effect of ACP compared to conventional fluoridated dentifrices; however, others have found an inferior or no additional effect.[21-23] Additionally, there is some concern that ACP may facilitate the deposition of dental calculus on the teeth surface due to the rapid transformation into the crystalline phase in the oral environment.[2,11,33]

Sodium trimetaphosphate: To reduce the risk of patients developing fluorosis, some of the fluoride ions present in conventional dentifrices were replaced by sodium trimetaphosphate (STMP), calcium glycerophosphate, or sodium hexametaphosphate.[34] STMP is a cyclic polyphosphate salt capable of strongly binding to the phosphate sites present on the enamel surface; consequently, the effects of its adhesion are not easily disassembled and can remain longer compared to other phosphates.[35] In addition to the property of adsorption on tooth structure, STMP also forms a protective layer against the diffusion of acid in a cariogenic event.[35] Therefore, it is considered effective against caries disease and capable not only of inhibiting demineralization, but also of boosting remineralization.[36] The ability to minimize mineral loss has been demonstrated in several studies showing the effectiveness of the protective layer against acid diffusion, but not against the diffusion of Ca^{2+} and F^- ions in enamel remineralization.[37,38] However, there is no consensus among those studies regarding the effectiveness of STMP in the remineralization of enamel structure.[39]

Arginine: Several studies have demonstrated the effectiveness of the amino acid arginine in affecting the pH and ecology of oral biofilms.[3] This promising effect on the pH of the dental biofilm could aid in mechanical plaque control and balance between the biofilm and the host homeostasis.[40] Accordingly, the amino acid was incorporated into toothpaste (1.5% arginine) with insoluble calcium and sodium monofluorophosphate (1450 ppm fluoride) to recover early caries lesions and to prevent the onset of erosive lesions if used at least twice daily for routine oral hygiene.[41] When applied intraorally, the amino acids are deaminated by the enzymatic system arginine deaminase present in saliva, which releases ammonia, a highly alkaline compound responsible for increasing the pH within the oral environment. This process provides optimal conditions for remineralization with the sodium monofluorophosphate-releasing fluoride ions and the calcium carbonate calcium ions.[42] A systematic review concluded that the arginine + F + Ca formulation possibly provides a higher antimicrobial effect.[43] Contrary to the above study, however, another systematic review showed that there is insufficient evidence to support the superior antimicrobial efficacy of arginine-containing toothpastes due to the high risk of commercial bias in these studies.[44] Therefore, more high-quality, long-term studies with less bias should be performed.

Xylitol: Xylitol is a nonfermentable sugar commonly used as a sugar substitute, especially in chewing gums and other types of candies, due to its antimicrobial and potentially anticarious effects.[45] It acts as a carrier or reservoir of calcium phosphate and directly interferes with the formation and adhesion of bacterial plaque to the dental surface.[46] This sugar substitute can neutralize the pH of plaque and reduce lactic acid production. In addition, Streptococcus mutans levels are decreased due to the inhibition of bacterial metabolism, and, consequently, the dental remineralization process is stimulated.[47] Fluoride concentrations may provide some additional benefits to xylitol, since this nonfermentable sugar retains remineralization when no more fluoride is available.[48] Other compounds, such as calcium lactate, may also increase the remineralization process if added to xylitol.[49] Sorbitol and isomalt also are artificial sweeteners and have noncariogenic properties similar to xylitol.[49] However, data on the efficacy of xylitol in the remineralization of dental caries are still scarce.

Biomimetic Remineralization

Biomimetic remineralization therapies are designed to replace undermined tissues by biologically forming a mineralized structure similar to the tooth. In an attempt to restore the enamel microstructure and to repair dentition, these therapies regenerate the apatite crystals as this regeneration actually occurs in the oral environment.

Nanohydroxyapatite: Synthetic nanohydroxyapatite (nHA) has properties similar to those of dental apatite not only in morphology, structure, and crystallinity, but also in biocompatibility and bioactivity.[50] The nHA particles diffuse into the enamel subsurface, providing Ca^{2+} and PO_4^{3-} ions to remineralize areas in

KEY POINTS

- **Minimally invasive dentistry has improved the effectiveness of dental remineralization therapies.**
- **New therapies are being designed to improve fluoride effectiveness by adding potentially active ingredients such as calcium, phosphate, arginine, xylitol, and self-assembling peptides.**
- **Mineral saturation therapies increase the mineral availability in the oral cavity (saliva, biofilm, and tooth) to remineralize the affected tissues.**
- **Biomimetic remineralization therapies have shown potential to repair early carious lesions.**

which minerals have been lost due to acid erosion. Thus, it acts as a filler to repair small defects and depressions on the enamel surface.[51] In a clinical study, an nHA toothpaste (Apadent Total Care) showed encouraging results regarding enamel remineralization rate, acid resistance dynamics, and tooth sensitivity in patients.[52] Furthermore, nHA under neutral conditions acts primarily on the superficial remineralization of enamel caries lesions, but the complete remineralization process of the lesion body has not yet been observed.[53]

Self-assembling peptides: The self-assembling peptide P11-4 is commercially available as Curodont Repair. Dental prophylaxis should be performed to remove biofilms and mineral deposits that may block or hinder the monomers' diffusion in the lesion body. In addition, etching the lesion surface is recommended to open the enamel pores and facilitate the diffusion of the monomers into the dental subsurface.[41] Because this therapy can take several weeks to achieve complete remineralization of the caries lesion, it should be used concomitantly with other fluoride-containing treatments (dentifrices, varnishes, gels, and foams).[54,55] When diffused into the lesion body, P11-4 mimics enamel matrix proteins to form a 3D matrix on the subsurface of the initial caries lesion. The 3D matrix has a high affinity for Ca^{2+} ions and will function as a nucleator for HA formation.[54] It undergoes hierarchical self-assembly in which "tapes" and "ribbons" are formed within seconds, and for the next 24 hours, fibrils and fibers are present in the dental structure. Laboratory studies found that P11-4 was able to spread into the caries lesion body and to induce remineralization by nucleation of de novo HA.[56] In addition, a clinical study showed promising results regarding this therapy's safety for human use, and, when applied in combination with fluoride varnish (22,600 ppm fluoride), this peptide showed a superior effect to fluoride varnish alone in the remineralization of early caries lesions.[57]

"...epidemiological research has shown a concerning trend related to a plateau in the decrease of caries incidence and, in some populations, caries actually has increased even with the use of fluoridated products."

Summary

The development of intelligent restorative materials has been a tremendous step forward for dentistry; however, the authors believe that the hesitance of some clinicians to adopt new materials and techniques may account for their slow acceptance by the market. If the strategies of developing new materials and early diagnosis of noncavitated caries lesions were coupled, patients' recovery would be quicker and safer. Most remineralization strategies do not yet have relevant evidence for assessing their true clinical potential, but the choice of treatment should consider the effectiveness, affordability, acceptability, and easy delivery for the patient. Of the current proposed alternatives, biomimetic strategies for enamel regeneration have shown promising results and likely will be the future of remineralizing treatment due to the formation of enamel crystal apatite to replace the demineralized tissue. The adoption of these remineralization therapies can have a beneficial impact on contemporary dentistry, since they will translate conservative concepts into clinical practice and prevent the formation of dental cavities. Therefore, the challenge for the next decade will be to emphatically promote a change in the habits of the population and/or to continue to develop new products/technologies that can counteract the demineralization process and bring dentistry to a more conservative level.

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JCD Self-Instruction

Basic Science | (CE) Exercise No. jCD40 | AGD Subject Code: 010

CE CREDIT

3 Hours Credit

This Continuing Education (CE) self-instruction examination is based on the article *Dental Remineralization Therapies for Early Caries* by Shelyn Akari Yamakami, DDS, MSc; Regina Guenka Palma-Dibb, DDS, MSc, PhD; and Hiroe Ohyama, DDS, DMD, MMSc, PhD. This article appears on pages 96-104.
The exam is free of charge and available to AACD members only. AACD members must log onto www.aacd.com/jcdce to take the exam. Note that only Questions 1 through 5 appear in the printed and digital versions of the *jCD*; they are for readers' information only. This exercise was developed by members of the AACD's Written Examination Committee and *jCD*'s Contributing Editors.

1. What are the two major alternative approaches for remineralization?

a. Mineral saturation without biomimetic remineralization.
b. Biomimetic saturation and mineral remineralization.
c. Biomimetic demineralization and mineral saturation.
d. Mineral saturation and biomimetic remineralization.

2. What is the main function of casein phosphopeptides?

a. Providing for the destabilization of calcium and phosphate ions promoting lamination.
b. Binding to tooth surfaces, soft tissue, and dental plaque.
c. In large quantities, reducing the bioavailability of calcium and phosphate ions.
d. Offering a microbial boosting effect on dental plaque.

3. Functional ß-tricalcium phosphate does which of the following?

a. Creates a barrier capable of promoting early fluoride and calcium interaction.
b. Enables calcium and fluoride to act as a targeted low-dose delivery system.
c. Decreases the activity of fluoride ions during remineralization.
d. Utilizes carboxylic acids to inhibit the bioavailability of phosphate ions.

4. In a mineral saturation approach, which of the following is recognized as the main active ingredient?

a. fluoride
b. calcium
c. phosphates
d. xylitol

5. Amorphous calcium phosphate

a. is a stabilized product available in fluoridated toothpaste.
b. has the ability to provide calcium and phosphate ions during dental hygiene.
c. remains stable, providing calcium and phosphate ions for extended periods of time.
d. has shown no clinical evidence of remineralization of surface lesions.

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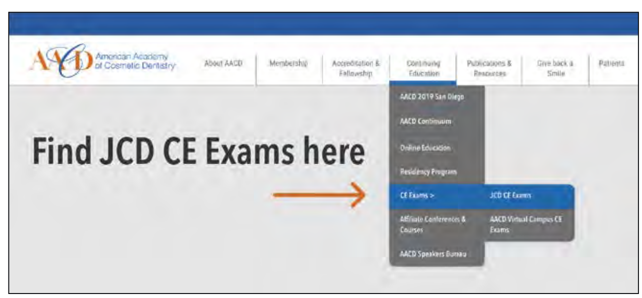

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