International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Contemporary Advances in Non-Fluoridated Remineralizing Agents: A Literature Review

Dr. Manjari Pandian[1], Dr. Pradeep Daniel Gainneos[2], Dr. Devadhakshayani Venkatesan[3], Dr. Muthusri.B[4], Dr. Ekta Pendurkar[5]

[1,3,4,5]Post Graduate, Department of Pediatric and Preventive Dentistry, Vinayaka Mission's Sankarachariyar Dental College.
[2]Associate Professor, Department of Pediatric and Preventive Dentistry, Vinayaka Mission's Sankarachariyar Dental College.

Abstract

Background: Dental caries is a dynamic process involving cycles of demineralization and remineralization. With advances in dental science, the focus has shifted from restorative treatment to early diagnosis and minimally invasive management. Limitations of fluoride such as fluorosis risk and limited penetration into deeper lesions have increased interest in non-fluoride remineralizing agents that supply bioavailable calcium and phosphate and support natural enamel repair.

Aim: This review aims to explore the potential of non-fluoride remineralizing agents in the management of early dental caries, highlighting their mechanisms, types, and clinical relevance.

Materials and Methods: A comprehensive literature search was conducted using PubMed, Google Scholar, and Scopus. Studies evaluating calcium phosphate systems, bioactive glasses, natural agents, and peptides in enamel remineralization were included.

Results: Non-fluoride agents such as CPP-ACP, bioactive glass, nano-hydroxyapatite, and DCPD exhibit effective remineralization potential. Many mimic natural enamel processes and offer advantages over fluoride, including reduced toxicity and improved subsurface penetration.

Conclusion: Non-fluoride agents are promising alternatives to fluoride in early caries management, especially in fluoride-sensitive individuals. Further long-term clinical studies are required to establish standardized treatment protocols.

Clinical Significance: Non-fluoride remineralizing agents support minimally invasive caries management by enhancing natural enamel repair and reducing the need for restorative treatment. They are particularly beneficial for high-risk, fluoride-sensitive, and pediatric populations, offering safe and effective options for early caries reversal.

Keywords: Dental caries, Remineralization, Non-fluoride agents, CPP-ACP.

INTRODUCTION

Dental caries is now recognized as a dynamic process with alternating cycles of demineralization and remineralization, and it continues to be a significant global public health concern.(1) If untreated, demineralization starts at the atomic level on the crystal surface of enamel or dentin and continues until cavitation happens.(2) In contrast, remineralization is the natural healing process that replenishes lost

mineral content in demineralized enamel by redepositing calcium and phosphate ions into the hydroxyapatite lattice.(3) The availability of salivary calcium and phosphate is a major factor in fluoride's efficacy, despite the fact that it has long been considered the gold standard for encouraging remineralization. This limitation has prompted research into alternative non-fluoridated remineralizing technologies, in addition to worries about fluorosis and fluoride sensitivity.

In order to improve the natural remineralization process and provide non-invasive treatment of early, non-cavitated carious lesions, recent developments have concentrated on calcium phosphate-based systems and biomimetic techniques.(4) Instead of focusing on conventional surgical intervention, modern dentistry now prioritizes "prevention of extension." Using keywords associated with remineralization, demineralization, casein derivatives, and non-fluoridated remineralizing agents, a literature search was carried out in PubMed and Medline to investigate these new strategies.(5)

Methods

A literature review was conducted using PubMed, Scopus, and Google Scholar. Keywords included “non-fluoride remineralization,” “CPP-ACP,” “bioactive glass,” and “nano-hydroxyapatite.” In vitro, in vivo, and clinical studies focusing on primary and young permanent dentition were included. Exclusion criteria involved studies on fluoride-based systems alone or those not involving dental tissues.

Discussion

Pathophysiology of Demineralization and Remineralization

Demineralization begins when acids produced by plaque bacteria lower the pH below the critical threshold (pH 5.5), leading to enamel dissolution.(6) The natural healing process known as remineralization entails the redeposition of calcium and phosphate ions from saliva. However, early enamel lesions cannot be reversed by saliva alone; therapeutic agents are required. (7)

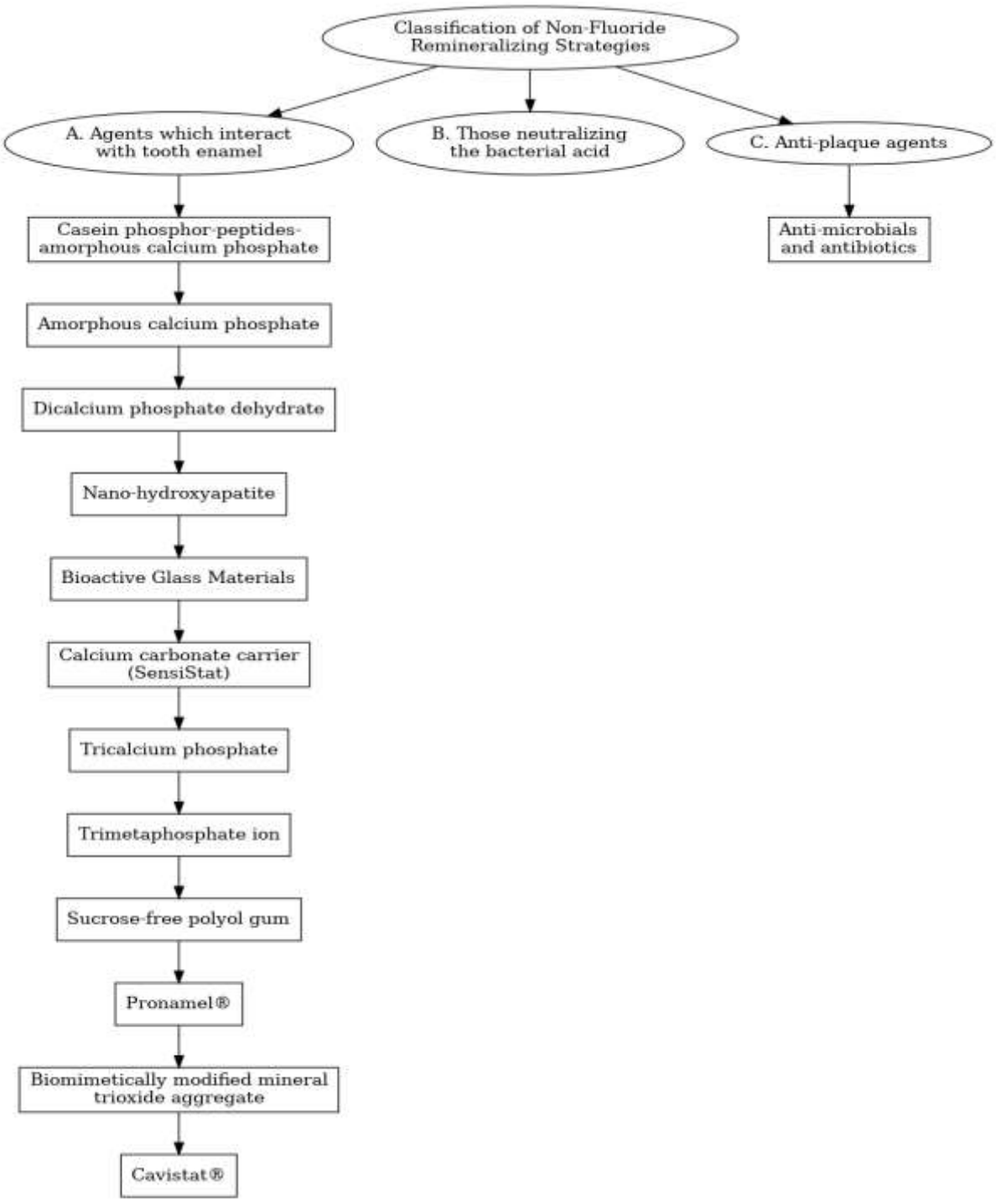
Table 1 : Reasons to Consider Non-Fluoride Remineralization Strategies(8,9)

Limited Effectiveness in Certain Areas
Risk of Fluorosis
Nutrition-Linked Toxicity
Not a Complete Solution
Legal and Public Pressure
Global Availability Issues
Safety of Long-Term Use

Table 2 : Ideal Characteristics of Remineralizing Agents(10)

Penetrate subsurface lesions
Deliver bioavailable calcium and phosphate
Avoid excessive calcification or calculus formation
Be biocompatible and stable in low pH
Function in xerostomic environments
Be non-toxic and enhance natural salivary action

Figure 1: CLASSIFICATION OF NON FLUORIDE REMINERALIZING STRATEGIES(11)



Casein Phosphopeptide–Amorphous Calcium Phosphate (CPP–ACP)

Casein phosphopeptide–amorphous calcium phosphate (CPP-ACP) consists of nanocomplexes produced from bovine milk–derived casein phosphopeptides and amorphous calcium phosphate, providing a stable source of bioavailable calcium and phosphate. (12) The milk proteins that form the foundation of CPP are caseins, primarily alpha-1, alpha-2, and beta-caseins. (13)A particular amino acid sequence, Ser(P)-Ser(P)-Ser(P)-Glu-Glu, is present in these peptides, which are created by the enzymatic breakdown (trypsin digestion) of casein and have a strong affinity for calcium and phosphate ions. By binding these ions into

stable, crystallization-resistant clusters of ACP, CPP stops precipitation and permits bioavailability.(14, 46)

The anticariogenic action of CPP–ACP lies in its ability to maintain high concentrations of calcium and phosphate in dental plaque. This reduces demineralization and promotes enamel repair by buffering the oral environment and maintaining its supersaturation with these ions. Furthermore, CPPs can increase fluoride's efficacy in enamel remineralization by keeping fluoride ions in the plaque matrix.(15)

Effectiveness of CPP–ACP on Erosive Wear

CPP–ACP has shown promise in repairing enamel following acid exposure. When added to acidic beverages, it lessens their potential for erosion. Additionally, CPP can limit the colonization of cariogenic bacteria like Streptococcus mutans and Streptococcus sobrinus by interfering with bacterial adhesion to hydroxyapatite surfaces. This encourages the growth of less dangerous microbial species and aids in lowering the production of acid within dental plaque. Additionally, CPP strengthens the tooth's resistance to demineralization by integrating into the acquired pellicle.(16) Some researchers contend that there is still insufficient clinical evidence to support its long-term benefits in caries prevention, despite encouraging in vitro and in situ results. Commercially available as RecaldentTM, CPP–ACP is used in dental products (e.g., GC Tooth Mousse, MI Paste), lozenges, and sugar-free chewing gum.(17)

Table 3 : Review Of Literature

Author	Sample	Test material	**Studied properties**	Findings
Ozdas DO etal. (2015)(18) CPP-ACP as preventive therapy in children with cerebral palsy (Oral Health Prev Dent 2015)	15 children aged 3–8 years with severe cerebral palsy (CP)	Daily application of 10% CPP-ACP (GC Tooth Mousse) twice daily for 8 weeks	Plaque pH Saliva buffering capacity (weekly measurements)	Significant increase in salivary buffering capacity from 3rd week onward. • Plaque pH increased significantly from 4th week, indicating reduced acidogenicity. • Concluded CPP-ACP enhances salivary defense, reducing caries and erosion risk in CP children. • Suggested as safe, non-fluoride preventive therapy, especially beneficial where fluoride ingestion is risky.

Oliveira PRA et al. (2020)(19) (Effect of CPP-ACP on remineralization of artificial caries-like lesion: an in situ study)	10 adult volunteers (21–42 yrs); 160 enamel slabs from 80 extracted molars	• MI Paste (CPP-ACP) • MI Paste Plus (CPP-ACPF, 900 ppm F) • Fluoride dentifrice (Crest 1100 ppm NaF) • Control (fluoride-free dentifrice)	Surface and cross-sectional hardness; remineralization inhibition under cariogenic challenge	MP, MPP, and FD significantly reduced enamel demineralization compared to control. • Fluoride dentifrice (FD) showed the greatest preventive potential (20.27% ΔIHC). • CPP-ACP and CPP-ACPF were effective but not superior to fluoride alone. • All remineralizing agents inhibited lesion progression; control group failed to prevent demineralization.
Peres P (2021)(20) (Effectiveness of CPP-ACP and Fluoride Products in Tooth Remineralization) *In situ*	10 volunteers; 160 human enamel slabs with preformed lesions (two demineralization degrees)	MI Paste (CPP-ACP) • MI Paste Plus (CPP-ACPF, 900 ppm F) • Fluoride dentifrice (Crest 1100 ppm NaF) • Control (fluoride-free silica dentifrice)	Surface microhardness recovery (%SH) and remineralization potential	CPP-ACPF (MI Paste Plus) and Fluoride dentifrice showed the greatest enamel microhardness recovery. • Degree of initial demineralization influenced remineralization—more demineralized enamel responded better. • Both CPP-ACPF and fluoride enhanced remineralization significantly compared to control.
Sionov RV et al. (2021)(21) Tooth mousse containing CPP-ACP prevents biofilm formation of	In vitro; S. mutans biofilm model	GC Tooth Mousse (CPP-ACP) and GC Tooth Mousse	Planktonic growth, biofilm biomass (CV/MTT), CLSM/SEM analysis	Both CPP-ACP and CPP-ACPF inhibited biofilm formation by >90% at low concentrations (6–12 mg/mL) without killing

Streptococcus mutans (BMC Oral Health 2021)		Plus (CPP-ACPF 0.2% F)		bacteria. Reduced S. mutans adhesion and EPS matrix. Effective anti-biofilm mechanism for orthodontic and pediatric use.
Prathima GS et al. (2021)(22) Effects of Xylitol and CPP-ACP Chewing Gum on Salivary Properties of Children with Molar Incisor Hypomineralization (MIH)	RCT; 32 MIH-affected children (8–10 yrs) divided into: Group I – CPP-ACP gum (Trident Recaldent) Group II – Xylitol gum (Spry)	CPP-ACP (Recaldent) chewing gum vs Xylitol gum	Salivary pH, flow rate, buffering capacity (measured at baseline, immediately, 15 & 30 min post-chewing)	Both groups showed significant increase in salivary pH, flow rate & buffering capacity immediately after chewing. • No significant intergroup difference, but CPP-ACP gum showed slightly higher buffering values. • Both gums recommended for MIH children to enhance salivary defense & prevent caries progression.
Alkarad L. et al. (2023)(23) Remineralization of teeth with casein phosphopeptide-amorphous calcium phosphate: analysis of salivary pH and salivary flow rate	Double-blind RCT; 50 Syrian children (aged 6–8 yrs), 25 received CPP-ACP (GC Tooth Mousse™), 25 placebo	GC Tooth Mousse (CPP-ACP) • Placebo mousse	Salivary pH and salivary flow rate measured at baseline (T0), immediately (T1), 30 min (T2), and 60 min (T3)	No significant difference between CPP-ACP and placebo in mean salivary pH or flow rate. • Both groups showed temporary rise in pH and flow immediately after application, followed by decline. • Concluded single short-term CPP-ACP application has minimal impact on salivary parameters. • Recommended longer-term studies for confirmation

Andrade M et al. (2024)(24) Effect of treatment with phosphate, casein phosphopeptide and fluoride on remineralization: in vitro study	In vitro; 60 bovine enamel blocks	① 1100 ppm F ② 1100 F + MI Paste Plus (CPP-ACPF) ③ 1100 F + Gel (4,500 ppm F + 5% TMP) ④ 1100 F + Gel (9,000 ppm F)	% Surface hardness recovery, ΔKHN, lesion depth, Ca and P content	1100F + TMP gel showed highest remineralization, 54% lower lesion depth than 1100 F. Increased Ca and P uptake in enamel. TMP + F outperformed CPP-ACPF. Suggests synergistic low-F + TMP protocol beneficial for early caries.

Amorphous Calcium Phosphate (ACP)

ACP-based technology involves using two separate compounds typically calcium sulfate and dipotassium phosphate that only react and form ACP upon mixing. When ACP is applied, it deposits on the surface of the enamel and gradually dissolves, releasing phosphate and calcium for remineralization.(25, 47)

By encouraging mineral recovery in demineralized areas, ACP has proven particularly helpful in orthodontic treatment. Experimental ACP-filled dental materials have been demonstrated to aid in the redistribution of minerals within early carious lesions. Dr. Ming S. Tung's technology has been used in professional-grade products like Nite White Gel and Enamel Pro Polishing Paste, as well as products like Enamelon® and Enamel Care toothpaste.(26, 48)

Bioactive Glass (Sodium Calcium Phosphosilicate)

Bioactive glass, when in contact with saliva, releases calcium, phosphate, and sodium ions. Hydroxycarbonate apatite (HCA), which resembles natural tooth mineral, is created by these ions. Up to two weeks after application, the freshly created HCA continues to provide remineralization while integrating into the enamel.(27)

One well-known example of bioactive glass technology is NovaMin®. It sticks to exposed dentin and creates a strong, acid-resistant mineralized layer. Long-term protection is aided by this continuous release of calcium ions. Products like SootheRxTM, DenShieldTM, and OraviveTM use NovaMin, which was created by Drs. Len Litkowski and Gary Hack (28).

Calcium Carbonate with Arginine (SensiStat Technology)

Dr. Israel Kleinberg invented SensiStat, a technology that combines calcium carbonate particles with an arginine bicarbonate complex. The amino acid arginine helps calcium carbonate bind to enamel and dentin surfaces. Once adhered, the calcium carbonate dissolves slowly, providing a controlled release of calcium ions that contribute to enamel repair. (29) Professional dental products like ProcludeTM and DencludeTM for managing sensitivity and promoting remineralization. (30) The amino acid arginine helps calcium carbonate attach to the surfaces of enamel and dentin. After adhesion, the calcium carbonate slowly dissolves, releasing calcium ions under controlled conditions that aid in enamel repair.(29)

Dr. Israel Kleinberg invented this technique, which is used in professional dental products like ProcludeTM and DencludeTM to control sensitivity and encourage remineralization.(30)

Xylitol as a Remineralizing Agent

Chewing gum that contains xylitol increases salivary flow, which raises the pH of plaque and improves saliva's ability to act as a buffer. This makes the environment unsuitable for demineralization. Elevated levels of calcium, phosphate, and bicarbonate—essential elements for enamel repair—are also present in the increased saliva.

According to research by Miake et al., xylitol promotes deeper calcium ion penetration into demineralized enamel, which aids in subsurface lesion regeneration.(31)

Nano-Hydroxyapatite

Nano-hydroxyapatite closely mimics the mineral component of natural enamel. Under dynamic conditions such as pH cycling, it has been shown to be effective in remineralizing early carious lesions. Studies suggest that a 10% concentration of nano-hydroxyapatite may provide optimal remineralization, restoring both mineral content and surface hardness.(32)

Trimetaphosphate Ion (TMP)

TMP may work by adhering to enamel surfaces, forming a protective coating that impedes demineralization during acidic challenges. It acts as a barrier that reduces the interaction between enamel and acids in the oral environment.(33)

Furthermore, sodium TMP has shown potential to act like natural phosphoproteins in dentin, aiding in the intrafibrillar deposition of apatite crystals inside demineralized collagen matrices, enhancing dentin remineralization.(34)

Alpha-Tricalcium Phosphate (α-TCP)

α-TCP has been included in dental materials like Cerasorb®, Bio-Resorb®, and Biovision® for its remineralizing capacity. Chewing gums with α-TCP have demonstrated the ability to increase free calcium levels in saliva and plaque, enhancing remineralization of enamel and neutralizing acidic challenges.(35)

Dicalcium Phosphate Dihydrate (DCPD)

DCPD-based dentifrices increase free calcium levels in dental plaque for up to 12 hours post-brushing. These calcium ions are gradually incorporated into enamel, promoting remineralization. When combined with fluoride, DCPD can facilitate the formation of fluorapatite, which is more acid-resistant than hydroxyapatite. Evidence shows that calcium from DCPD remains detectable in plaque even 18 hours after brushing, indicating prolonged activity. (36)

Additional Non-Fluoride Remineralizing and Anti-Caries Agents

Pronamel

Despite the name suggesting enamel-related benefits, Pronamel™ (manufactured by GlaxoSmithKline, UK) is not categorized as a true remineralizing agent. It lacks calcium-based compounds commonly found in remineralization formulations. However, clinical evaluations have demonstrated its protective effects against enamel erosion caused by dietary acids and acidic beverages such as fruit juices. Studies show that

after acid exposure followed by treatment with Pronamel, the basic prismatic and interprismatic structure of enamel remains intact, indicating some preservation of enamel integrity without direct remineralization.(37,49)

Biomimetically Enhanced Mineral Trioxide Aggregate (MTA)

Recent research has explored the remineralizing potential of modified Mineral Trioxide Aggregate (MTA) when used in a phosphate-rich environment. By incorporating biomimetic components such as polyacrylic acid and sodium tripolyphosphate, the modified MTA mimics natural matrix proteins involved in dentin mineralization. These biomimetic substances released from the set MTA can stimulate the repair of caries-affected dentin. Additionally, the presence of polyphosphate may serve as an alternative phosphate source when natural supply is insufficient. This advancement not only broadens the clinical utility of MTA in restorative dentistry but also aligns with the concept of biomimetic remineralization strategies.(38)

Sucrose-Free Polyol Chewing Gums

Evidence from multiple studies and meta-analyses strongly supports the caries-preventive benefits of chewing gums sweetened with polyols (e.g., xylitol, sorbitol) compared to non-chewing controls. These gums not only stimulate salivary flow—which improves pH buffering and promotes remineralization—but also limit the growth of acid-producing bacteria. Over time, this leads to a measurable reduction in the incidence of dental caries.(39)

Xylitol

A broad spectrum of xylitol-containing products—including lozenges, syrups, toothpastes, and candies—have shown effectiveness in reversing early carious lesions. Xylitol helps reduce mutans streptococci levels and enhances salivary function, which plays a critical role in enamel recovery. Other agents such as triclosan, iodine solutions, and various chlorhexidine-based formulations (including varnishes, gels, and rinses) have demonstrated antibacterial activity against cariogenic bacteria. These products, alongside sialogogues (saliva-stimulating agents), contribute significantly to caries prevention and may aid in halting or even reversing the progression of early lesions.(40)

CaviStat Technology

CaviStat® is a proprietary combination of arginine bicarbonate and calcium carbonate, developed as a component in sugar-free mint products. Clinical trials have shown that mints containing this formulation can significantly reduce both the development and progression of carious lesions, particularly in children's primary and first permanent molars. The mechanism involves neutralizing plaque acids and supplying calcium ions to support enamel stability. This approach offers a cost-effective and easy-to-use method for caries control, particularly in populations with high caries risk.(41)

B. Agents That Neutralize Bacterial Acids

One of the key approaches to preventing demineralization of tooth structure involves neutralizing the acids produced by cariogenic bacteria. Compounds like calcium carbonate act by buffering the plaque environment, thereby stabilizing the pH and protecting enamel. Similarly, sodium bicarbonate helps create an alkaline setting in the oral cavity, which counters the acid attack and supports remineralization.(42)

Additionally, calcium-based compounds such as calcium lactate, calcium glycerophosphate, and calcium phytate are used to elevate calcium and phosphate concentrations in plaque, making minerals more available for enamel repair. Certain toothpaste formulations that include , or anti-enzyme components have also been explored for their ability to resist acid-mediated enamel loss and contribute to oral health maintenance.(43)

C. Antiplaque and Antimicrobial Agents

Use of Antimicrobials and Antibiotics

Controlling dental plaque formation is essential for caries prevention. Various antimicrobial and antibiotic agents have been employed to reduce plaque accumulation and suppress mutans streptococci, the primary bacteria involved in caries development. Ingredients in commonly tested mouthrinses include chlorhexidine, triclosan, essential oils, cetylpyridinium chloride, sanguinarine, sodium dodecyl sulfate, and metal ions such as tin, zinc, and copper.

However, the potential toxicity of some metals (like aluminum, molybdenum, barium, and copper) limits their safe concentrations in oral care products. Among the various antiplaque agents, chlorhexidine and triclosan have shown the most promising evidence for reducing dental caries.(44)

Despite its effectiveness, chlorhexidine has limitations. When used as a mouthrinse, it reduces certain surface-level bacteria but does not penetrate deeply enough into the biofilm to eliminate all harmful microorganisms. This highlights the need for improved antibacterial agents and more effective delivery systems.

On the other hand, xylitol, when consumed via chewing gums or lozenges, has been clinically validated to reduce levels of cariogenic bacteria and consequently lower caries incidence. Nonetheless, innovations in controlled-release technologies that can deliver optimal therapeutic doses—especially those tailored for children—could represent a major advancement in caries prevention. Combining these technologies with fluoride could significantly improve oral health outcomes by minimizing bacterial acid attacks and promoting remineralization.(50)

Challenges in Implementing New Remineralization Technologies

Although calcium phosphates and other calcium-based salts aim to enhance remineralization by increasing calcium levels in dental plaque or improving fluoride bioavailability, limited evidence confirms that these agents actually reach the target tissues and produce consistent anti-caries effects. Product formulation also presents significant challenges, particularly regarding ingredient compatibility. Many formulations attempt to deliver calcium ions and fluoride together in a single-phase system, but maintaining long-term stability—especially fluoride compatibility—can be difficult. Additionally, pre-clinical models often fail to accurately predict clinical outcomes for non-fluoride agents, highlighting the need for robust, well-designed clinical trials to validate their true effectiveness(45)

Conclusion

Non-fluoride remineralizing agents offer diverse mechanisms to combat enamel demineralization and promote remineralization. From protein-based systems like CPP–ACP to inorganic compounds like bioactive glass, nano-hydroxyapatite, and calcium phosphates, these agents present promising alternatives or adjuncts to fluoride. While many show potential in vitro and in situ, continued clinical research is necessary to validate their long-term efficacy and guide their optimal use in daily dental practice.

Reference:

1. Featherstone JD. Dental Caries: A dynamic disease process. Aust Dent J 2008;53:286-91.
2. K. Chokshi, A. Chokshi, S.S. Sebastian, A. Zaheer, S. Mohan, R.S. Dhanya. (2016). Newer Nonfluoride Remineralizing Agents: An Insight. International Journal of Oral Care Research. 4(4):291-296.
3. Cochrane NJ, Cai F, Huq NL, Burrow MF, Reynolds EC. New approach to enhance remineralization of tooth enamel. J Dent Res 2010;89:1187-97.
4. Fejerskov O. Changing paradigms in concepts on dental caries: Consequences for oral health care. Caries Res 2004;38:182-91.
5. S. Qaiser, D. Devadiga, M.N. Hegde. (2020). Remineralising Agents: An Updated Review. Research Journal of Pharmaceutical, Biological and Chemical Sciences.11(1):181-188
6. Featherstone JDB. Dental Caries: A dynamic disease process. Australian Dental Journal, 2008; 53: 286 – 91.
7. M.K. Arifa, R. Ephraim, T. Rajamani. (2019). Recent Advances in Dental Hard Tissue Remineralization: A Review of Literature. International Journal of Clinical Pediatric Dentistry. 12(2):139–144.
8. Goswami M, Saha S, Chaitra TR. Latest developments in non-fluoridated remineralizing technologies. J Indian Soc Pedod Prev Dent 2012;30:2-6.
9. Brown WE. Physicochemical mechanisms in dental caries. J Dent Res 1974;53:204-16.
10. Walsh LJ. Contemporary technologies for remineralization therapies: A review. Int Dent SA 2009;11:6-16.
11. Kalra DD, Kalra RD, Kini PV, Prabhu CA. Nonfluoride remineralization: An evidence-based review of contemporary technologies. Journal of Dental and Allied Sciences, 2014; 3(1): 24 - 33.
12. Reynolds EC. Casein phosphopeptide-amorphous calcium phosphate and the remineralization of enamel. US Dentistry, 2006: 51- 4.
13. Rose RK. Effects of an anticariogenic casein phosphopeptide on Ca diffusion in streptococcal model dental plaques. Arch Oral Biol 2000;45:569-75.
14. Reynolds EC. Casein phosphopeptide-amorphous calcium phosphate: The scientific evidence. Advances in Dental Research, 2009; 21: 25 - 9.
15. Reynolds EC. Remineralization of enamel subsurface lesions by casein phosphopeptide-stabilized calcium phosphate solutions. J Dent Res 1997;76:1587-95.
16. Schupbach P, Neeser JR, Golliard M, Rouvet M, Guggenheim B. incorporation of caseinoglycomacropeptide and caseinophosphopeptide into the salivary pellicle inhibits adherence of mutans streptococci. J Dent Res 1996;75:1779-88.
17. Llena C, Fomer L, Baca P. Anticariogenicity of casein phosphopeptides-amorphous calcium phosphate: A review of the literature. J Contemp Dent Pract 2009;10:1-9.
18. Özdas DÖ, Tuna EB, Yilmaz EY, Avtepe Z. Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) May Be an Alternative Preventive Therapy in Children with Cerebral Palsy. Oral Health & Preventive Dentistry [Internet]. 2015 [cited 2024 May 7];13(5):441-8
19. Oliveira PRA de, Barboza CM, Barreto LS da C, Tostes MA. Effect of CPP-ACP on remineralization of artificial caries-like lesion: an in situ study. Brazilian Oral Research [Internet]. 2020 Jun 24,34:e061.
20. Peres P, Schubach L. Mônica Almeida Tostes. Effectiveness of CPP-ACP and fluoride products in tooth remineralization. 2021 Aug 15;20(4):635-42.

21. Sionoy RV, Tsavdaridou D. Agawi M, Zaks B, Steinberg D, Shalish M. Tooth mousse containing casein phosphopeptide-amorphous calcium phosphate prevents biofilm formation of Streptococcus mutans. BMC Oral Health. 2021 Mar 19;21(1).
22. Prathima GS, Narmatha M, Selvabalaji A, et al. Effects of Xylitol and CPP-ACP Chewing Gum on Salivary Properties of Children with Molar Incisor Hypomineralization, Int J Clin Pediatr Dent 2021;14(3):412-415.
23. Alkarad L. Alkhouli, M. Dashash, M. Remineralization of teeth with casein phosphopeptide-amorphous calcium phosphate: analysis of salivary pH and the rate of salivary flow. BDJ Open [Internet]. 2023 Apr 11 [cited 2023 Jun 22]:9(1)
24. Andrade M, Castro M, Carlos A, Leal G, CANNON ML, DANELON M. Effect of treatment with phosphate, casein phosphopeptide and fluoride on the remineralization; in vitro study. Brazilian Oral Research. 2024 Jan 1,38
25. Tung MS, Eichmiller FC. Dental Applications of Amorphous Calcium Phosphates. J Clin Dent 2003;10:1
26. Sullivan RJ, Charig A, Haskins JP, Zhang YP, Miller SM, Strannick M, et al. In vivo detection of calcium from dicalcium phosphate dihydrate dentrifrice in demineralized human enamel and plaque. Adv Dent Res 1997;11:380-7.
27. Du M, Tai BJ, Jiang H, Zhong J, Greenspan D, Clark A. Efficacy of dentifrice containing bioactive glass (NovaMin) on dentine hypersensitivity. J Dent Res 2004;83:13-5.
28. Tai BJ, Bian Z, Jiang H. Anti-gingivitis effect of a dentifrice containing bioactive glass (NovaMin) particulate. J Clin Periodontol 2006;33:86-91.
29. Nizel AE, Harris RS. The Effects of Phosphates on Experimental Dental Caries: A Literature Review. J Dent Res 1964;43:1123-35
30. McClure MJ. Further studies on the cariostatic effect of organic and inorganic phosphates. J Dent Res 1963;42:693-9.
31. Miake Y, Saeki Y, Takahashi M, Yanagisawa T. Remineralization effects of xylitol on demineralised enamel. J Electron Microsc
32. Huang SB, Gao SS, Yu HY. Effect of nano-hydroxyapatite concentration on remineralization of initial enamel lesion in vitro. Biomed Mater 2009;4:55-9.
33. Gonzalez M. Effect of Trimetaphosphate Ions on the process of Mineralization. J Dent Res 1971;50:1055-60.
34. Gu LS, Kim J, Kim YK, Liu Y, Dickens SH, Pashley DH, et al. A chemical phosphorylation-inspired design for Type I collagen biomimetic remineralization. Dent Mater 2010;26:1077-89.
35. Vogel GL, Zhang Z, Carey CM, Chow LC, Proskin HM. Composition of plaque and saliva following a sucrose challenge and use of an alpha-tricalcium-phosphate-containing chewing gum. J Dent Res 1998;77:518-24.
36. Walsh LJ. Contemporary technologies for remineralization therapies: A review. Int Dent SA 2009;11:6-16.
37. Pradeep K, Kumar PR. Remineralizing agents in the non-invasive treatment of early carious lesions. Int J Dent Case Rep 2011;1:73-84.
38. SkrticD,AntonucciJM,EanesED,BrunworthRT.Silica-andzirconia- hybridized amorphous calcium phosphate: Effect on transformation to hydroxyapatite. J Biomed Mater Res 2002;59:597-604.

39. RethmanMP,Beltrán-AguilarED,BillingsRJ,BurneRA,ClarkM,Donly KJ, *et al*. Non-fluoride caries preventive agents. Full report of a systematic review and evidence-based recommendations. ADA Center for Evidence Based Dentistry; 2011.
40. Uppala S.A review of the literature on non-fluoridated remineralizing agents for dental caries. International Journal of Chemical and Biochemical Sciences. 23(3) (2023): 196-200.
41. Acevedo AM, Montero M, Sanchez FR. Clinical evaluation of the ability of CaviStat® in a mint confection to inhibit the development of dental caries in children. J Clin Dent 2008;19:1-8.
42. Yamamotoa O, Ohiraa T, Alvareza K, Fukudab M. Antibacterial characteristics of CaCO3-MgO composites. Mater Sci Eng 2010;B173:208-12.
43. Chhabra KG, Shetty PJ, Prasad KVV, Mendon CS, Kalyanpur R. The beyond measures: Non flouride preventive measures for dental caries. J Int Oral Health 2011;3:1-8.
44. Featherstone JD. Delivery challenges for fluoride, chlorhexidine and xylitol. BMC Oral Health 2006;6 Suppl 1:S8.
45. Wefel JS, Harless JD. The use of saturated DCPD in remineralization of artificial caries lesions in vitro. J Dent Res 1987;66:1640-3
46. Ranjitkar S, Rodriguez JM, Kaidonis JA, Richards LC, Townsend GC, Bartlett DW. The effect of caseinphosphopeptide- amorphous calcium phosphate on erosive enamel and dentin wear by toothbrush abrasion. J Dent 2009;37:250-4.
47. Pfarrer AM, Faller RV. Fluoridating Efficiency and the Integrity of Product Delivery Systems. Cincinnati, OH, USA: Procter & Gamble Co. Available from: http://www.dentalcare.com/media/en-US/journals/.../ iadr98pp_1694.pdf. [Last accessed on 2012 Jul 25].
48. Eversole SL, Faller RV, Bitten ER, Featherstone JB. Conventional and 'Remineralizing' Toothpastes Compared in Two pH Cycling Models. USA, San Francisco, CA: Procter & Gamble Co.
49. Poggio C, Lombardini M, Colombo M, Bianchi S. Impact of two toothpastes on repairing enamel erosion produced by a soft drink: An AFM *in vitro* study. J Dent 2010;38:868-74.
50. Singh M, Kaur M. Fluoride alternatives: A review of the present status. J Contemporary Dent Sci 1:54-61