Non-Fluoridated Remineralising Agents: A Review.

Abstract

Dental caries is a biofilm-mediated, sugar-driven, multifactorial disease characterized by a dynamic imbalance between demineralization and remineralization of the dental hard tissues. Although fluoride remains the cornerstone of modern caries prevention and remineralization, concerns regarding excessive fluoride exposure, fluorosis, limited effectiveness in pits and fissures, nutritional deficiencies and other practical limitations have stimulated the development of non-fluoridated remineralising agents. These agents act through various mechanisms, including the delivery of calcium and phosphate ions, enhancement of salivary remineralization, modification of the dental biofilm, biomimetic regeneration of enamel, and suppression of cariogenic microorganisms. Calcium phosphate-based systems such as amorphous calcium phosphate, casein phosphopeptide-amorphous calcium phosphate, functionalized tricalcium phosphate and bioactive glass have demonstrated considerable potential in promoting remineralization. Recent advances in nanotechnology, self-assembling peptides and enamel biomimetic systems have further expanded the possibilities for non-fluoride-based caries management. Biofilm modifiers, natural products and antimicrobial approaches also offer promising adjunctive strategies. This review discusses the rationale, classification, mechanisms of action and clinical applications of currently available and emerging non-fluoridated remineralising agents.

Keywords: Dental caries; remineralization; non-fluoridated agents; calcium phosphate; CPP-ACP; bioactive glass; biomimetic remineralization, newer remineralisation agents, recent advances in remineralisation, remineralisation cycle

Introduction

Dental caries is a biofilm-mediated, sugar-driven, multifactorial disease that results in the demineralization and eventual destruction of the hard tissues of teeth. It occurs due to acids

produced by microorganisms within the dental plaque biofilm following the metabolism of fermentable carbohydrates. Rather than being a continuously progressive process, dental caries is now understood as a dynamic pathological process involving repeated episodes of demineralization and remineralization.

The progression or reversal of a carious lesion depends upon the balance between pathological and protective factors. When pathological factors such as frequent sugar consumption, acidogenic and acid-tolerant microorganisms, reduced salivary flow and prolonged periods of low plaque pH predominate, there is a net loss of mineral and the lesion progresses. Conversely, when protective factors including saliva, calcium, phosphate and appropriate remineralising agents predominate, mineral deposition may occur, resulting in lesion arrest or reversal.

The concept of remineralization has therefore become central to modern minimally invasive dentistry. The management of early carious lesions has shifted from surgical restoration towards prevention, remineralization and biological repair. While fluoride has traditionally been considered the most important remineralising agent, increasing interest has focused on non-fluoridated alternatives capable of enhancing the natural repair potential of dental tissues.

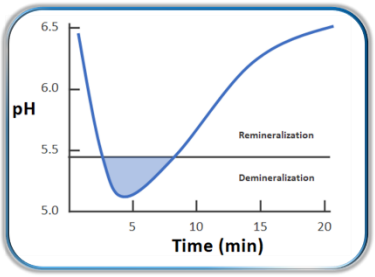
Role of Dental Plaque Biofilm in Caries Development

According to Newbrun, dental caries develops through the interaction of four major factors: the susceptible tooth surface, dental plaque biofilm, dietary carbohydrates and time.

The dental plaque biofilm plays an important role in the caries process because it provides an environment suitable for bacterial proliferation and growth. It also functions as an acid-base regulatory system at the tooth surface and serves as a reservoir for calcium and phosphate ions, facilitating mineral exchange between the tooth and saliva.

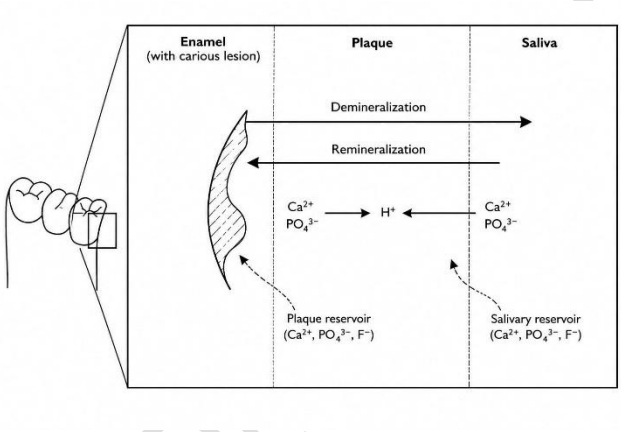
Following frequent consumption of fermentable carbohydrates, cariogenic microorganisms metabolize sugars and produce organic acids. These acids cause a reduction in plaque pH, resulting in undersaturation of the surrounding environment with respect to tooth mineral and initiating the process of demineralization.

Stephan Curve



The relationship between carbohydrate intake and plaque pH is classically demonstrated by the Stephan curve. Following exposure to fermentable carbohydrates, plaque pH falls rapidly and may reach its minimum value within approximately five minutes. Subsequently, salivary buffering mechanisms gradually neutralize the acids, allowing plaque pH to return towards its resting level over approximately 30–60 minutes.When plaque pH falls below the critical level, mineral dissolution occurs. The traditionally accepted critical pH for enamel is approximately 5.5, although this value may vary according to the concentration of calcium and phosphate ions in the local environment.

Demineralization–Remineralization Cycle



The caries process may therefore be described as a continuous cycle consisting of the following stages:

1. Sugar exposure and acid production

   Frequent exposure to fermentable carbohydrates provides substrates for acidogenic microorganisms. These microorganisms metabolize sugars and produce organic acids, particularly lactic acid.
2. Fall in pH and demineralization

The acids diffuse into enamel and reduce the pH of the plaque fluid. When the surrounding environment becomes undersaturated with respect to tooth mineral, calcium and phosphate ions are lost from the enamel.

3. Dissolution of tooth mineral

   Hydroxyapatite crystals partially dissolve during prolonged acidic conditions. Initially, this results in a subsurface, non-cavitated lesion. At this stage, the process remains potentially reversible.

4. Recovery and remineralization

   Following the acidic challenge, saliva buffers the plaque acids and raises the pH. Calcium and phosphate ions from saliva and plaque fluid can then diffuse into the partially demineralized lesion and redeposit onto the remaining hydroxyapatite crystals.When remineralization exceeds demineralization, early carious lesions may be arrested or reversed.

Remineralization of Dental Hard Tissues

Remineralization is the natural repair process through which minerals lost during demineralization are redeposited within partially demineralized dental hard tissues. Calcium and phosphate ions diffuse into the porous enamel lesion and are deposited onto the remaining hydroxyapatite crystal lattice.

For effective remineralization, several conditions are necessary:

- Adequate availability of calcium and phosphate ions.
- Availability of these ions in the immediate environment of the demineralized tooth surface.
- Preservation of the partially dissolved hydroxyapatite crystal lattice, which acts as a framework for mineral deposition.
- Recovery of plaque pH towards neutrality following an acidic challenge.
- Adequate salivary flow and buffering capacity.

Natural remineralization, however, may not always be sufficient to completely reverse a lesion. Mineral deposition may occur predominantly in the superficial layer, potentially limiting penetration of minerals into the deeper subsurface lesion. Therefore, additional remineralising agents may be required to enhance the natural reparative capacity of saliva.

Rationale for the Development of Non-Fluoridated Remineralising Agents

- Limited availability and retention of fluoride in pits and fissures.
- Risk of fluorosis associated with excessive fluoride exposure during tooth development.
- Concerns regarding cumulative fluoride intake.
- Situations involving nutritional deficiencies and altered mineral availability.
- Restrictions or limitations on fluoride use in certain populations and regions.
- The need for additional calcium and phosphate delivery to promote deeper subsurface remineralization.
- The requirement for agents capable of modifying the biofilm and restoring the ecological balance of the oral environment.

Thus, non-fluoridated agents should not necessarily be considered replacements for fluoride. Many are more appropriately regarded as adjuncts that complement fluoride by improving the availability of calcium and phosphate or by acting through entirely different mechanisms.

Classification of Non-Fluoridated Remineralising Agents

Non-fluoridated remineralising agents can broadly be classified into the following groups:

1. Calcium and Phosphate-Based Systems	• Amorphous calcium phosphate (ACP) • Casein phosphopeptide–amorphous calcium phosphate (CPP-ACP) • Tricalcium phosphate (TCP) • Dicalcium phosphate systems • Bioactive glass • Calcium-based delivery systems • Calcium orthophosphate saccharose complex (Toothmin)
2. Nanotechnology-Based Systems	• Amorphous calcium phosphate nanoparticles • Bioactive glass nanoparticles • Calcium phosphate nanoparticles • Calcium fluoride nanoparticles • Nanohydroxyapatite
3. Biomimetic Remineralising Agents	• Self-assembling peptides • Polyacrylic acid-based systems • Oligopeptides • Amelogenin-based systems • Eggshell-derived calcium preparations • Keratin-based scaffolds • Dentin phosphoprotein-derived peptides
4. Non-Calcium-Based Systems and Biofilm Modifiers	• Arginine bicarbonate • Xylitol • Probiotics • Herbal preparations • Chemoprophylactic agents • Polydopamine • Theobromine • Galla Chinensis
5. Antimicrobial and Emerging Technologies	• Bacteriophage therapy • Replacement therapy • Photodynamic therapy • High-intensity focused ultrasound • Electric field-induced remineralization

Calcium and Phosphate-Based Remineralising Systems

1. Amorphous Calcium Phosphate

Amorphous calcium phosphate (ACP) is a highly soluble and reactive calcium phosphate compound capable of providing calcium and phosphate ions for remineralization. Its major advantage lies in its ability to maintain a reservoir of bioavailable mineral ions.ACP can release calcium and phosphate into the oral environment, promoting the formation and growth of hydroxyapatite crystals in demineralized enamel. However, one limitation of ACP is its relative instability and tendency to precipitate rapidly when calcium and phosphate ions are present together.In unstabilized ACP systems, calcium and phosphate may be delivered separately and subsequently mix in the oral environment. This interaction may result in rapid precipitation of amorphous calcium phosphate, potentially limiting the availability of ions for effective subsurface remineralization.

2. Casein Phosphopeptide-Amorphous Calcium Phosphate

Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) is one of the most extensively investigated non-fluoridated remineralising systems.Casein phosphopeptides derived from milk proteins stabilize amorphous calcium phosphate and maintain calcium and phosphate ions in a soluble and bioavailable form. This prevents their premature precipitation and allows them to remain available in saliva and plaque fluid.CPP-ACP has the potential to:

- Increase the concentration of bioavailable calcium and phosphate.
- Promote diffusion of minerals into subsurface enamel lesions.
- Enhance remineralization of early carious lesions.
- Support the natural remineralizing capacity of saliva.

An important advantage of CPP-ACP is its ability to produce a subsurface pattern of remineralization. It is available in several forms, including topical pastes, mousses, mouthrinses and chewing gums.Active white spot lesions may respond more favourably to CPP-ACP because of their porous structure and greater potential for mineral uptake. The agent is therefore of particular interest in the management of early enamel lesions and post-orthodontic white spot lesions.

3. Tricalcium Phosphate

Tricalcium phosphate (TCP) has been developed as a calcium and phosphate delivery system designed to improve mineral availability while maintaining compatibility with other

remineralising agents.Functionalized or modified TCP can be incorporated into single-phase aqueous or non-aqueous formulations. In such systems, a protective barrier may be created around the calcium-containing particles, preventing premature interaction with other ingredients.During use, contact with saliva disrupts this protective barrier and releases calcium and phosphate ions. The released ions can then participate in mineral deposition onto demineralized enamel.TCP has therefore been described as a potential mineral reservoir and seeding system that may enhance the availability of calcium and phosphate at the tooth surface.

4. Bioactive Glass

Bioactive glass, commonly described as calcium sodium phosphosilicate, is another important calcium phosphate-based remineralising material.When exposed to saliva or an aqueous environment, bioactive glass undergoes a series of ionic reactions. Sodium ions are released, producing an increase in local pH. This is followed by the release of calcium and phosphate ions.These ions can subsequently precipitate and form a calcium phosphate layer on the tooth surface, which may mature into an apatite-like mineral layer.

The major actions of bioactive glass include:

- Release of calcium and phosphate ions.
- Increase in local pH.
- Promotion of mineral deposition.
- Formation of an apatite-like protective layer.
- Occlusion of exposed dentinal tubules.

Because of these properties, bioactive glass has applications not only in remineralization but also in the management of dentinal hypersensitivity.

5. Calcium Orthophosphate Saccharose Complex (Toothmin)

Toothmin is a calcium orthophosphate saccharose complex developed as a biomimetic agent for the remineralization of enamel. It acts by supplying bioavailable calcium and phosphate ions, while the saccharose component assists their delivery and deposition on areas of mineral loss. This process promotes mineral recovery and may aid in the repair of early carious lesions. In vitro investigations have reported improved mineral deposition and favourable changes in enamel surface characteristics following its use. As it functions through a

calcium–phosphate-based mechanism without relying on fluoride, Toothmin is considered a potential option for managing early enamel demineralization.

Nanotechnology-Based Remineralising Agents

Nanotechnology has introduced new possibilities in remineralization because nanoparticles possess a high surface area and improved interaction with dental hard tissues.

1. Nanohydroxyapatite

Nanohydroxyapatite has attracted considerable attention because of its structural and morphological similarity to the mineral component of enamel.The nanoparticles can act as a source of calcium and phosphate and may integrate with partially demineralized enamel. Their small particle size and large surface area may improve interaction with enamel defects and promote mineral deposition.Nanohydroxyapatite is therefore considered a biomimetic material capable of supporting the repair of early enamel lesions.

2. Amorphous Calcium Phosphate Nanoparticles

ACP nanoparticles provide a large surface area for the release of calcium and phosphate ions. Their nanoscale dimensions may improve diffusion and interaction with demineralized enamel.

3. Bioactive Glass Nanoparticles

Bioactive glass nanoparticles provide similar ionic benefits to conventional bioactive glass but offer increased surface reactivity. Their high surface area may facilitate more rapid ion release and mineral deposition.

4. Calcium Phosphate-Based Nanoparticles

These nanoparticles act primarily as reservoirs of calcium and phosphate ions. They have potential applications in toothpastes, restorative materials and preventive formulations.

5. Calcium Fluoride Nanoparticles

Calcium fluoride nanoparticles have a high surface area and may serve as reservoirs capable of releasing fluoride under appropriate conditions. Their incorporation into restorative materials has been explored to enhance long-term mineral availability.

Biomimetic remineralisation systems

1. Self-Assembling Peptide P11-4

Self-assembling peptide P11-4 represents an important advancement in biomimetic remineralization.Under appropriate environmental conditions, these peptides undergo self-assembly and form a three-dimensional scaffold within an early carious lesion. This scaffold acts as a framework that may facilitate nucleation and growth of hydroxyapatite crystals.The ability to provide a matrix within the lesion makes self-assembling peptides particularly interesting because natural remineralization is dependent on the presence of a suitable crystal framework.

2. Amelogenin-Based Systems

Amelogenin is an important protein involved in natural enamel formation. Recombinant amelogenin and related biomimetic systems have been investigated for their ability to stabilize calcium phosphate clusters and promote organized crystal growth.Such systems aim to recreate the hierarchical arrangement of enamel crystals. Experimental studies have suggested that amelogenin-based approaches may promote mineral deposition and improve the mechanical properties and hardness of acid-demineralized enamel.This approach represents an important step towards true biological regeneration rather than simple mineral replacement.

3. Dentin Phosphoprotein-Derived Peptides

Dentin phosphoproteins and their derived peptides have been investigated for their ability to regulate calcium phosphate mineralization.These peptides may help stabilize mineral phases and reduce the dissolution of calcium phosphate from demineralized dentin. Their ability to influence mineral nucleation and crystal growth makes them potential candidates for biomimetic dentin remineralization.

4. Other Biomimetic Systems

Several other experimental materials have been investigated for their potential remineralising properties, including:

- Polyacrylic acid-based systems
- Oligopeptides
- Chicken eggshell-derived calcium solutions
- Keratin-based scaffolds

These materials attempt to provide either mineral ions, a scaffold for crystal growth or a favourable environment for mineral nucleation.

Non-Calcium-Based Remineralising Systems

- Arginine Bicarbonate

Arginine is an amino acid that can influence the ecology and pH of the oral biofilm.Caries-free individuals have been reported to demonstrate a more favourable arginine metabolism within the oral environment. Arginine can be metabolized by certain oral microorganisms, producing alkaline products that increase plaque pH.Arginine bicarbonate-containing products therefore aim to:

- Increase alkali production.
- Raise plaque pH.
- Counteract acidogenic conditions.
- Encourage a shift from a cariogenic to a less cariogenic oral environment.

Certain formulations combine highly soluble arginine bicarbonate with calcium carbonate particles, which can provide an additional mineral source.

- Xylitol

Xylitol is a non-fermentable sugar alcohol that cannot be readily metabolized by many cariogenic bacteria to produce acid.Its potential benefits include:

- Reduction in acid production.
- Reduction in cariogenic bacterial activity.
- Stimulation of salivary flow when consumed as chewing gum.
- Promotion of a less cariogenic oral environment.

- Probiotics

Probiotics have been investigated as biological modifiers of the oral microbiome.The concept involves promoting beneficial microorganisms capable of competing with cariogenic species

and reducing the dominance of acidogenic bacteria. Probiotics may therefore contribute to ecological biofilm modification rather than directly delivering minerals.

- Herbal and Natural Products

Natural products have gained increasing attention because of their potential antibacterial, antioxidant and remineralising properties.Investigated products include:

- Sumac-derived preparations.
- Gum Arabic derived from Acacia species.
- Grape seed extract.
- Ginger extract.
- Green tea extract.
- Yogurt-derived products.

These agents may act by inhibiting cariogenic microorganisms, reducing acid production, modifying the biofilm or contributing minerals and other biologically active compounds.Their clinical effectiveness, however, may vary according to formulation, concentration and method of delivery

- Theobromine

Theobromine is a naturally occurring methylxanthine, mainly obtained from cocoa. It has been investigated as a promising non-fluoride remineralising agent due to its ability to stimulate the development of larger, more stable and highly crystalline hydroxyapatite crystals. This enhancement in crystal structure can increase enamel hardness and improve its resistance to acid attack. Experimental studies have shown that theobromine may decrease enamel demineralization and facilitate remineralization, with certain studies reporting effects comparable to fluoride-based formulations. Its relatively low toxicity and potential for long-term application further support its role as an adjunct in preventive dentistry.

- Polydopamine

Polydopamine is an emerging biomimetic material inspired by the adhesive proteins of mussels.It has been investigated as a potential surface-modifying and mineralization-promoting material. Its ability to adhere to dental surfaces and interact with mineral ions may make it useful as a platform for future biomimetic remineralization systems.

- Galla Chinensis

Galla Chinensis is a traditional natural product derived from Chinese galls and contains substantial amounts of tannins and other polyphenolic constituents. In addition to its antimicrobial activity, it has shown potential for enhancing enamel remineralization and preventing caries. The tannins present in Galla Chinensis can bind with calcium ions and form calcium–tannin complexes over the enamel surface, creating a protective layer that may facilitate subsequent mineral deposition. Experimental evidence indicates that it can limit enamel demineralization, promote remineralization and suppress cariogenic microorganisms. Therefore, its combined remineralising and antimicrobial actions make Galla Chinensis a promising natural adjunct in caries prevention and early lesion management.

Antimicrobial Approaches to Caries Management

An alternative approach to remineralization is to reduce or eliminate the pathological microbial challenge.

- Bacteriophage Therapy

Bacteriophage therapy involves the use of viruses that specifically infect bacteria. In dental caries, bacteriophages may potentially be used to selectively target cariogenic microorganisms without extensively disturbing the beneficial oral microbiome.

- Replacement Therapy

Replacement therapy aims to replace highly cariogenic microorganisms with less pathogenic or non-pathogenic bacterial strains.The objective is to create a stable oral microbiological environment that is less capable of producing acids and initiating demineralization.

- Photodynamic Therapy

Photodynamic therapy combines a photosensitizing agent with light of an appropriate wavelength to generate reactive oxygen species capable of destroying microorganisms.It may be useful as an adjunctive approach for reducing cariogenic microbial load.

- High-Intensity Focused Ultrasound

High-intensity focused ultrasound is an emerging technology that may influence tissue and microbial environments through localized energy delivery. Its possible role in caries prevention and remineralization remains an area of ongoing research.

- Electric Field-Induced Remineralization

Electric field-induced remineralization is an experimental approach designed to enhance the movement and deposition of mineral ions within demineralized dental tissues.By influencing ion transport, electric fields may potentially improve mineral penetration into subsurface lesions. However, this technology requires further investigation before widespread clinical application.

Other Adjunctive and Emerging Approaches

Ozone

Ozone has been investigated primarily for its antimicrobial effects. By reducing the microbial challenge and modifying the caries-associated biofilm, it may create conditions more favourable for natural remineralization.

Resin Infiltration

Resin infiltration is not a remineralization method but represents a minimally invasive technique for managing non-cavitated enamel lesions. Low-viscosity resin penetrates the porous lesion and may inhibit further diffusion of acids and dissolved minerals.

Ion Exchange Systems

Ion exchange systems are being explored as mechanisms for controlled delivery of calcium, phosphate and other ions to the tooth surface.

Laser-Based Approaches

Various laser systems have been investigated for their ability to modify enamel structure and increase resistance to acid dissolution. Laser therapy may also be used in combination with topical remineralising agents.

Clinical Relevance in Pediatric Dentistry

Non-fluoridated remineralising agents have particular relevance in pediatric dentistry, as children frequently develop early enamel lesions, white spot lesions and caries associated with high sugar exposure. They may be useful for the management of non-cavitated enamel lesions, prevention of early childhood caries, treatment of post-orthodontic white spot lesions, management of children at high caries risk, situations requiring additional calcium and phosphate supplementation, patients in whom fluoride exposure requires careful monitoring, and management of enamel defects and early demineralization. However, the selection of a

remineralising agent should be individualized based on the child's caries risk, salivary status, dietary habits, lesion activity and ability to comply with preventive measures.

Future Perspectives

The future of non-fluoridated remineralization is likely to focus on biomimetic and targeted approaches rather than simple surface mineral deposition.Important future directions include:

- Development of nanoparticles with controlled ion release.
- Biomimetic scaffolds capable of promoting organized enamel regeneration.
- Self-assembling peptides for subsurface lesion repair.
- Combination therapies involving calcium, phosphate and biofilm modifiers.
- Personalized remineralization strategies based on individual caries risk and oral microbiome.
- Selective antimicrobial approaches that preserve beneficial microorganisms.
- Smart materials capable of releasing ions in response to acidic conditions.

The ideal future remineralising system may combine mineral delivery, biofilm modification and biomimetic tissue regeneration within a single formulation.

Conclusion

Dental caries is a dynamic disease characterized by repeated cycles of demineralization and remineralization. The modern management of early carious lesions therefore emphasizes biological repair and preservation of tooth structure rather than surgical intervention.Non-fluoridated remineralising agents provide several promising approaches to enhance the natural repair capacity of dental hard tissues. Calcium and phosphate-based systems such as ACP, CPP-ACP, TCP and bioactive glass primarily improve mineral availability, whereas nanomaterials increase surface reactivity and facilitate biomimetic mineral replacement. Self-assembling peptides, amelogenin-derived systems and other biomimetic materials represent a more advanced approach aimed at reproducing the natural mechanisms of enamel and dentin mineralization.Biofilm modifiers such as arginine, xylitol, probiotics and natural products address another essential component of caries management by reducing the pathological challenge and promoting a healthier oral ecosystem. Emerging antimicrobial technologies and physical methods may further expand future options for non-fluoride caries management.

Although fluoride remains an important component of preventive dentistry, non-fluoridated remineralising agents have significant potential as adjuncts and, in selected situations,

alternatives. The future of caries management lies in combining effective mineral delivery with biofilm control and biomimetic regeneration to achieve true preservation and repair of dental hard tissues.

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