LATEST EVOLUTIONS IN NON-FLUORIDATED REMINERALIZING TECHNOLOGIES- AN UPDATE

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ABSTRACT

Remineralization of caries lesions is naturally achieved by salivary ions, and it can be enhanced by external factors or elements such as fluoride. Numerous studies have demonstrated the remineralizing efficacy of fluoride therapies as well as the limitations with some groups of the population. Consequently, developing new remineralization therapies to close this gap in efficacy has been a priority for the last 2 decades. In this review, we summarize and briefly discuss some of the latest advances in remineralization therapies. As Modern dentistry aims to manage non-cavitated carious lesions non-invasively through remineralization in an attempt to prevent disease progression, and to improve form, function, strength and esthetics of teeth. More emphasis currently is being laid upon new technologies for enamel remineralization. Further studies are required on biomimetic molecules involved in calcium fluoride phosphate stabilization and nucleation that may provide further improvements in the development of novel remineralization treatments. The aim of this paper is to review the contemporary remineralizing systems available for remineralization therapy and their implementation into clinical practice.

INTRODUCTION

Dental caries remains the major public health problem in most countries. In the last decade, the focus in caries research has shifted to the development of methodologies for remineralization of carious lesions¹.

Remineralization is defined as the process whereby calcium and phosphate ions are supplied from a source external to the tooth to promote ion deposition into crystal voids in demineralized enamel to produce net mineral gain².

Demineralization begins at the atomic level on the crystal surface inside the enamel or dentin and can continue unless halted with the end point being cavitation.

“Extension for Prevention” has given way to the new paradigm of minimally invasive dentistry. The minimally invasive approach to treat dental caries incorporates the dental signs of detecting, diagnosing, intercepting and treating dental caries on the microscopic level². The principles of minimal intervention in the management of dental caries (adopted by the FDI General Assembly, 1st October, 2002, Vienna) are:

1. Modification of oral flora
2. Patient education
3. Remineralization of cavitated lesions of enamel and dentin
4. Minimal intervention of cavitated lesions
5. Repair of defective restorations³.

Recent investigations have primarily focused on various calcium phosphate based technologies which are designed to supplement and enhance fluoride’s ability to restore tooth mineral⁴.

Enamel & Dentin minerals

The mineral in dentine and enamel is not pure hydroxyapatite, but rather a mixture of compounds including a number of carbonated apatites, with greater diversity of composition in dentine than in enamel⁵. Fluorapatite is less acid soluble than hydroxyapatite, which in turn is less soluble than carbonated apatites. Because of this chemical inhomogeneity of enamel, the process of enamel remineralization is rather complex.

Nevertheless, calcium availability remains the singular limiting factor in enamel remineralization. One of the most important
properties of calcium phosphate/calcium fluoride materials is their solubility behavior, bearing in mind that the majority of calcium compounds are very insoluble.¹

**Remineralization of dentin**

The collagen fibrils in dentin serve as a scaffold for mineral crystallites that reinforce the matrix, supporting the surrounding enamel. From a biomechanical perspective, the mineralized dentin matrix preserves tooth function by helping to prevent propagation of cracks from the brittle enamel through the dentin-enamel junction into the dentin thus preventing fracturing of the enamel crown.⁶

When the carious lesion reaches the dentin matrix, it progresses much more rapidly as compared with the enamel thus creating different zones that reflect differences of mineral content, mechanical properties and optical appearance.⁵

Remineralization of carious dentin can occur either by a spontaneous incorporation of ions (calcium, phosphate and fluoride) from the oral fluid on to the remnant crystallites in the demineralized tissue or by treatments that incorporate the same ions from external sources.⁶

**Demineralisation and remineralisation**

Demineralization occurs by disassociation of lactic acid, produced by bacterial carbohydrate metabolism, with tooth mineral. The reaction leads to release of mineral ions into the solution:

\[ \text{Ca}_{10} \text{(PO}_4\text{)}_6 \text{(OH)}_2 + 14 \text{H}^+ \rightarrow 10 \text{Ca}^+ + 6 \text{H}_2\text{PO}_4^- + \text{H}_2\text{O} \]

The extent to which tooth mineral dissolves in a given solution is governed by the thermodynamic ion activity product (IAP):

\[ \text{IAP} = (\text{Ca}^{2+})^{10}(\text{PO}_4^{3-})^6(\text{OH}^-)^2 \]

The sub-surface lesion is reversible via a remineralization process. The increase in oral fluid calcium and phosphate drives the remineralization process.⁷

**The role of saliva**

The critical role played by salivary components in controlling the equilibrium between de- and remineralization is ably demonstrated when salivary output is compromised and patients suffer dramatic increases in risk for dental caries and/or dental erosion. Enhanced remineralization of white spot lesions by stimulated salivary flow (e.g. from chewing a sugar-free gum) illustrates dynamic protective effects of saliva.⁹

In the context of remineralization, an important component of saliva are its proteins, such as the glycoproteins which adsorb onto tooth structure to form the protective pellicle layer, and the phosphoproteins which regulate calcium saturation of the saliva.⁸ In other words, remineralization may be enhanced.

Saliva, enamel, bone, cementum, dentine and milk contain closely related phosphoproteins which bind and stabilize calcium and phosphate, orchestrating the behaviour of these ions in a pH dependant fashion.⁸

**Requirement of an Ideal Remineralisation**

1. Diffuses into the subsurface
2. Does not deliver an excess of calcium
3. Does not favor calculus formation
4. Works at an acidic pH
5. Works in xerostomic patients
6. For novel materials, shows a benefit over fluoride.⁶

**Indications**

1. To reduce caries in high-risk patients
2. Reduce dental erosion in patients with gastric reflux
3. To reduce decalcification in orthodontic patients
4. To repair enamel in cases involving white-spot lesions.⁶

**Mineral or ionic technologies: fluoride**

The first theories concerning the mechanism of action of fluoride were based exclusively on its pre-eruptive effect. Arnold, in 1957, was the first author to mention the post-eruptive effect of fluoride in the drinking water and the ability of topical fluoride to reduce the incidence of caries.⁸

The mechanism by which fluoride increases caries resistance may arise from both systemic and topical applications of fluoride and can be broadly grouped as follows: increased enamel resistance, increased rate of maturation, remineralization of incipient caries, interference with micro-organisms and improved tooth morphology.⁸

**Fluoride works primarily via topical mechanisms which include**

1. Inhibition of demineralization at the crystal surfaces inside the tooth
2. Enhancement of remineralization at the crystal surfaces (giving an acid resistant surface to the reformed crystals), and, at high concentrations
3. Inhibition of bacterial enzymes

Numerous laboratory studies for example lynch RJ, Navada R et al conducted a study on low levels of fluoride in plaque and saliva and their effects on the demineralisation and remineralisation of enamel conducted in 2004 and authors found that low levels of fluoride, typical of those found after many hours in resting plaque and saliva, and resulting from the regular use of fluoride dentifrices, can have a profound effect on enamel demineralization and remineralization.⁹

**Non Fluoride Remineralizing Agent**

**Casein phosphopeptides (CPPs)**

CPP–ACP is the acronym for a complex of casein phosphopeptides (CPPs) and amorphous calcium phosphate (ACP). Caseins are a heterogeneous family of proteins predominated by alpha 1 and 2 caseins.⁸

CPPS are phosphorylated casein-derived peptides produced by trypic digestion of casein. The CPP containing the amino acid cluster sequence -Ser(P)-Ser (P)-Ser (P)-Glu-Glu- has the ability to bind and stabilize calcium and phosphate in solution, as well as to bind dental plaque and tooth enamel. Through their multiple phosphoryl residues, the CPPs bind to form clusters of ACP in metastable solution, preventing their growth to the critical size required for nucleation and precipitation. The proposed mechanism of anticariogenicity for the CPP–ACP is that it localizes ACP in dental plaque, which buffers the free calcium and phosphate ion activities.⁹
**Effect of CPP–ACP on erosive lesions**

CPP–ACP paste may enhance the remineralization after an erosive challenge, and thus offers some protection for patients who are at risk for erosion. Adding CPP–ACP to soft drinks and sports drinks reduced their erosive potential on enamel when compared to those without it.

It can be incorporated into the pellicle in exchange for albumin, and thus inhibits the adherence of Streptococcus mutans and Streptococcus sobrinus, causing both neutralization and enhancement of remineralization.

The Recaldent technology was developed by Prof. Eric Reynolds of the University of Melbourne. CPP–ACP has been trademarked Recaldent and has been launched in sugarless chewing gum and confectionery. More recently, a sugar-free, water-based cream containing RECALDENT™ (CPP–ACP) (GC Tooth Mousse/Prospec MI Paste) has been made available to dental professionals.

**Amorphous calcium phosphate**

The ACP technology requires a two-phase delivery system to keep the calcium and phosphorous components from reacting with each other before use. The current sources of calcium and phosphorous are two salts, calcium sulfate and dipotassium phosphate.

When the two salts are mixed, they rapidly form ACP that can precipitate onto the tooth surface. This precipitated ACP can then readily dissolve into the saliva and can be available for tooth remineralization. It can be considered a useful adjuvant for the control of caries in orthodontic applications.

The ACP technology was developed by Dr. Ming S. Tung. In 1999, ACP was incorporated into toothpaste called Enamelon and later reintroduced in 2004 in Enamel Care toothpaste by Church and Dwight. It is also available as Discus Dental’s Nite White Bleaching Gel and Premier Dental’s Enamel Pro Polishing Paste. It is also used in the Aegis product line, such as Aegis Pit and Fissure Sealant, produced by Bosworth.

Experimental ACP composite has shown to efficiently establish mineral ion transfer throughout the body of the lesion and the mineral lost due to acid attack.

**Sodium calcium phosphosilicate (bioactive glass)**

Bioactive glass (Bioglass®) was invented by Dr. Larry Hench in 1960s. It acts as a biomimetic mineralizer matching the body’s own mineralizing traits while also affecting cell signals in a way that benefits the restoration of tissue structure and function.

Bioglass® in an aqueous environment immediately begins surface reaction in three phases, leaching and exchange of cations, network dissolution of SiO2 and precipitation of calcium and phosphate to form an apatite layer.

The net negative charge on the surface and loss of sodium causes localized breakdown of the silica network with the resultant formation of (silanol) Si (OH) groups, which then repolymerize into a silica-rich surface layer.

Within 3-6 h in vitro, the calcium phosphate layer will crystallize into the carbonated hydroxyapatite (CAP) layer, which is essentially the bonding layer.

Chemically and structurally, this apatite is nearly identical to bone and tooth mineral.

These Bioglass® surface reactions from implantation to formation of 100-150 mm².

**Novamin®,** a trade name for bioactive glass, is manufactured by Novamin Technologies Inc. (Alachua, FL, USA). It has been demonstrated that fine particulate bioactive glasses (<90 μm) incorporated into an aqueous dentifrice have the ability to clinically reduce the tooth hypersensitivity through the occlusion of dentinal tubules by the formation of the CAP layer. Allan I et al conducted a study in 2001 using bioactive glass compositions have demonstrated a significant anti-microbial effect toward caries pathogens (S. mutans, S. sanguis) upon exposure to bioactive glass powders as well as solutions and extracts. Caries can also result from inadequate saliva, without which fluoride is of limited value.

Thus, individuals who experience reduced calcium, phosphate and fluoride ions caused by hyposalivation can benefit from the use of bioactive glass. In addition, women are at increased caries risk.

Thus, the use of bioactive glass (Novamin Technology) in remineralization of enamel is quite promising, especially in patients with systemic problems, but further research needs to be undertaken to prove its efficacy. Thus, keeping the silica below 60 wt% and maintaining a high CaO/P2O5 ratio guarantees a highly reactive surface.

**Calcium Carbonate Carrier**

The SensiStat technology is made of arginine bicarbonate, an amino acid complex, and particles of calcium carbonate, a common abrasive in toothpaste.

The SensiStat Technology was developed by Dr. Israel Kleinberg of New York.

The technology was first incorporated into Ortek’s Proclude desensitizing prophyl paste and later in Denclude.

**Xylitol Carrier**

The use of chewing gum carrying xylitol increases salivary flow rate and enhances the protective properties of saliva. Moreover, the higher concentration of calcium, phosphate, and hydroxy ions in such saliva also enhances remineralization.

**Nano Hydroxyapatite**

Huang HB et al conducted A study in 2009 to determine the effect of nano-hydroxyapatite concentrations on initial enamel lesions under dynamic pH-cycling conditions. It was concluded that nano-hydroxyapatite had the potential to remineralize initial enamel lesions. A concentration of 10% nano-hydroxyapatite may be optimal for remineralization of early enamel caries.

**The Trimetaphosphate Ion**

The potential mode of action of trimetaphosphate ion (TMP) is likely to involve in adsorption of the agent to the enamel surface, causing a barrier coating that is effective in preventing or retarding reactions of the crystal surface with its fluid environment, and hence reducing demineralization during acid challenge.

TMP as a templating analog of dentin matrix phosphoproteins for inducing intrafibrillar remineralization of apatite.
nanocrystals within the collagen matrix of incompletely resin infiltrated dentin.  

**Alpha & Beta Tricalcium Phosphate**

It is used in products such as Cerasorb, Bio-Resorb, and Biovision.

Tricalcium phosphate (TCP) has also been considered as one possible means for enhancing the levels of calcium in plaque and saliva.

Alpha TCP is formed when human enamel is heated to high temperatures. It is a relatively insoluble material in aqueous environments (2mg/100 mL in water). Crystalline beta TCP can be formed by combining calcium carbonate and calcium hydrogen phosphate, and heating the mixture to over 1000 degrees Celsius for 1 day, to give a flaky, stiff powder.

The average size of the TCP particles can then be adjusted by milling them range from 0.01 to 5 microns in size. Beta TCP is less soluble than alpha TCP, and thus in an unmodified form is less likely to provide bio-available calcium.

**Dicalcium Phosphate Dehydrate**

Inclusion of dicalcium phosphate dehydrate (DCPD) in a dentifrice increases the levels of free calcium ions in plaque fluid, and these remain elevated for up to 12 hours after brushing, when compared to conventional silica dentifrices.

Calcium from DCPD was incorporated into enamel and detected in plaque 18 hours post-treatment after brushing with a DCPD dentifrice which fastered improved remineralization of teeth in combination with fluoride.

The reaction of DCPD and fluoride forming fluorapatite may provide a potentially promising treatment for remineralization of caries lesions in vivo.

**Grape Seed Extract**

Root caries is especially prevalent among the elderly population due to gingival recession and the exposure of susceptible root surface. Dentin mineral is dissolved by acid produced from the oral bacterial biofilm and the demineralized dentin matrix is further degraded, allowing bacteria to infiltrate the intertubular area.

The preservation and stability of dentin collagen may be essential during the remineralization process, because it acts as a scaffold for mineral deposition.

It has also been suggested that the presence of an organic matrix may reduce the progression of erosion in dentin. One of the important strategies regarding preventive therapies for root caries is to promote remineralization of demineralised dentin. Polyphenols are plant-derived substances that have antioxidant and anti-inflammatory properties. They interact with microbial membrane proteins, enzymes and lipids, thereby altering cell permeability and permitting the loss of proteins, ions and macromolecules. One such polyphenol is proanthocyanidin (PA), which is a bioflavonoid-containing benzene-pyran-phenolic acid molecular nucleus.

The PA accelerates the conversion of soluble collagen to insoluble collagen during development and increases collagen synthesis. Grape seed extract (GSE) has a high PA content. PA-treated collagen matrices are non-toxic and inhibit the enzymatic activity of glucosyl transferase.

This constitutes the sucrose-dependent pathway for S. mutans to establish on the tooth surface and is of central importance in plaque formation and development of caries.

The adherent glucan also contributes to the formation of dental plaque, in which accumulation of acids leads to localized decalcification of the enamel surface by facilitating bacterial adherence to the tooth surfaces, interbacterial adhesion and accumulation of biofilms.

**Challenges of Implementing New Remineralization Technology**

Therapeutic benefits of calcium phosphates or other calcium salts is via increased levels of calcium in dental plaque or increased levels of bioavailable fluoride. However, few studies have confirmed that the calcium-based agent actually reached the target tissue and resulted in anti-caries benefits. Formulation challenges typically involve ingredient compatibility issues.

Products are designed to deliver a new agent (i.e., calcium ions) and fluoride simultaneously from single-phase products and may present formulation challenges such as long-term fluoride compatibility.

Pre-clinical models may not necessarily be predictive of clinical performance for these non-fluoride agents and that new agents still require direct clinical validation to ensure efficacy.

**CONCLUSION**

In the last few decades, advances in technologies, changes in lifestyle, modifications in the diet, and longer life expectancy are some of the many factors which have affected the health and esthetics of tooth enamel and dentin. With a clearer understanding of the implementation of these remineralizing agents and new technologies accessible to dentists, we can create a more favorable relationship in which remineralization occurs more often than demineralization. A goal of modern dentistry is the non-invasive management of non-cavitated caries lesions involving remineralization systems to repair the enamel with fluorapatite or fluorhydroxyapatite. With a clearer understanding of the implementation of these remineralizing agents, we can create a more favorable relationship in which remineralization can occur. It is important for dental professionals to be aware that it takes significant time to establish the bonafides of a new technology.

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