An Update On Tooth Remineralization

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Abstract: MID is of utmost importance in today’s dental practice as it focuses on least invasive treatment options possible in order to minimize the tissue loss and patient discomfort. So MID is the key principle in remineralization of early carious lesions non invasively by advocating a therapeutic or biological approach rather than traditional surgical approach for early surface lesions. The aim of this paper is to review contemporary and new remineralizing systems for remineralization therapy and their implementation into the clinical practice. Clinical relevance: Remineralization helps in management of hypocalcified areas, desensetization of exposed dentin by dental erosion and after debonding of brackets in lieu of completion of orthodontic treatment.

Keywords: casein derivatives, remineralizing agents, remineralization-demineralization.

Introduction

Dental caries is a multifactorial disease caused by the interaction of dietary sugars, dental biofilm and the host’s dental tissue within the oral environment. The process of caries formation is a cycle of remineralization and demineralization with various stages being either reversible or irreversible. A break in the equilibrium causes the tooth to remineralize or demineralize depending upon the concentration of the mineral saturation in the oral cavity. Oral bacteria excrete acid after consuming sugar, leading to demineralization. Upon this acid challenge, the hydroxyapatite crystals are dissolved from the subsurface.

In a neutral environment, the hydroxyapatite of the enamel is in equilibrium with saliva which is saturated with calcium and phosphate ions. At or below pH 5.5, H+ ions produced by the bacterial metabolites react preferentially with the phosphate group of the enamel crystals, converting PO4 2- ion to (HPO4) 2- ion which, once formed, can no more form the crystal lattice; at the same time H+ ions are buffered. This leads to enamel dissolution, termed as demineralization, which marks the beginning of early enamel caries.
Remineralization is the natural repair process for non-cavitated lesions. 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 gain.7 In other words, remineralization would be best defined as the redeposition of minerals lost by enamel, and this term has been used as a synonymous of enamel repair or rehardening.8

Mineral loss (demineralization) or gain (remineralization) by enamel is a dynamic physicochemical process occurring when oral bacteria form a biofilm on the enamel surface and this biofilm is exposed to fermentable dietary carbohydrates, sucrose being the most cariogenic of them.9

One of the key elements of a biological approach is the usage and application of a remineralizing agents to tooth surface. These agents are part of a new era of dentistry aimed at controlling the demineralization remineralization cycle, depending upon the microenvironment around the tooth.10 This article details the various agents that enhance and promote remineralization and their clinical implications.

**Indications of tooth remineralization**11

An adjunct preventive therapy to reduce caries in high-risk patients
To repair enamel in cases involving white-spot lesions
Reduce dental erosion in patients with gastric reflux or other disorders
To reduce decalcification in orthodontic patients
Before and after teeth whitening
Desensitize sensitive teeth.12

The requirements of an ideal remineralization material are as follows:11,13
- Should diffuse into the subsurface or deliver calcium and phosphate into the subsurface
- Should be able to work at an acidic pH
- Should work in xerostomic patients
- Should not deliver an excess of calcium
- Should not favor calculus formation
- Boosts the remineralizing properties of saliva

Any "remineralizing therapy" should follow two fundamental principles:8
1. Dental biofilm, the necessary factor responsible for caries lesions, should be controlled by toothbrushing.
2. Fluoride should be used either to arrest existing lesions or to reduce the progression of new ones.

**Fluoride**

It has been known since the 1980s that fluoride controls caries predominantly through its topical, not systemic, effect.1 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.

Four mechanisms are involved by which fluoride increases caries resistance viz; increased enamel resistance, increased rate of maturation, remineralization of incipient caries, interference with micro-organisms and improved tooth morphology.14

Enamel is dissolved by lowering of pH in dental plaque due to acid production every time sugar is ingested. However, if F- is present in the biofilm fluid, and the pH is not lower than the critical pH, hydroxyapatite (HA) is dissolved and at the same time fluorapatite is formed. This indirect effect of fluoride in reducing enamel demineralization when the pH drops is complemented by its natural effect on remineralization.15 This fluoride comes from topical...
sources such as drinking water, and fluoride products like toothpastes and varnishes. When the pH returns to pH 5.5 or above, saliva which is supersaturated with calcium and phosphate, forces mineral back into the tooth. Fluoride adsorsbs to the surface of the partially demineralized crystals and attracts calcium ions. Fluoride speeds up the growth of the new surface by bringing calcium and phosphate ions together which are preferably incorporated into the remineralized surface. This produces a surface which is now more acid resistant.16

Fluorides inhibit bacterial activity. In acid environment, fluoride combines with hydrogen to form HF which diffuses into the bacterial cell. Inside the cell HF breaks up and releases fluoride ions that interfere with the essential enzyme activity of the bacteria. Moreover, fluoride acts as reservoir after application of a fluoride treatment such as toothpaste, varnish or restorative material and is then released into the saliva over time.17,18

Fluoride can be used in combination with sodium, tin and titanium. The newly introduced titanium fluoride (TiF) exhibits enhanced uptake of calcium, and TiF pretreated enamel also shows loss of calcium during demineralization.19

Reasons to seek alternatives to fluoride:
1. Fluoride is highly effective on smooth-surface caries; its effect would seem to be more limited on pit and fissure caries.
2. A high-fluoride strategy cannot be followed to avoid the potential for adverse effects (e.g., fluorosis) due to overexposure to fluoride.
3. Although fluoride presents no problems when used properly, among certain parts of the world, there has been the suggestion that fluoride exposure should be limited.20

CPP-ACP (Recaldent)
In 1946, studies showed that that the anticariogenic properties of milk were due to casein, calcium and phosphate. Further investigation by the University of Melbourne in Australia showed that a particular part of the casein protein, casein phosphopeptides (CPP), was responsible for the tooth-protective activity. This technology was developed by Eric Reynolds.21 They showed that peptides containing the cluster sequence of amino acids -Ser(P)-Ser(P)-Ser(P)-Glu-Glu have a remarkable ability to stabilise calcium and phosphate and keep them in a soluble, amorphous state. In general, combining calcium and phosphate ions results in formation of insoluble calcium phosphate crystals. But in the presence of CPP, the calcium and phosphate remain in an ionic form that can diffuse into the tooth enamel and repair areas for remineralization.22

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 and b-caseins. CPPs are phosphorylated casein-derived peptides produced by tryptic digestion of casein.12

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, thereby helping to maintain a state of supersaturation with respect to tooth enamel depressing demineralization and enhancing remineralization.13 Adding CPP-ACP to soft drinks and sports drinks reduced their erosive potential on enamel when compared to those without.23,24 CPP
inhibits adherence of oral bacteria to saliva-coated hydroxyapatite beads (S-HA). 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.25
RECALDENT is an ingredient derived from casein, part of the protein found in cow's milk. 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.26
Recaldent is available in solutions, gums, lozenges and creams form. Chewing a sugarless gum containing RECALDENT™ (CPP-ACP), or applying GC Tooth Mousse27 immediately after brushing with a fluoride toothpaste, or even after administration of fluoride by a dental professional, enhances the remineralization activity of the fluoride.
It is pH responsive, i.e. with increasing pH, the level of bound ACP increases, stabilizing free calcium and phosphate and thus providing an anti-calculus action.21 The anti-caries action influences the properties and behavior of dental plaque through (1) binding with adhesion molecules on mutants Streptococci, impairing their incorporation into plaque, (2) elevating plaque calcium ion levels to inhibit plaque fermentation and (3) providing protein and phosphate buffering of plaque fluid pH to suppress overgrowth of aciduric species when fermentable carbohydrate is in excess.
Tooth crèmes using CPP-ACP (Recaldent technology) such as MIPaste and ToothMousse 27 recognize the importance of the neutral ion species, gaining access to the sub-surface lesion through a porous enamel surface. This is the reason why arrested white spot lesions should have a surface etching treatment before remineralization with Recaldent products, unlike fluoride treatments with conventional dentifrices (1000 ppm) that deposit surface mineral but do not eliminate a white-spot lesion. Thus, it is evident that other than for fluoride, the strongest level of clinical evidence for remineralization is for the CPP-based Recaldent technology, with both long-term large-scale clinical trials and randomized controlled clinical trials to support its efficacy.

Bioactive glass (calcium sodium phosphosilicate)
Bioactive glass (Bioglass) was invented by Dr. Larry Hench in 1960s.28 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. 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. 29 Novamin, a trade name for bioactive glass, is manufactured by Novamin Technologies Inc.(Alachua, FL, USA). It is technically described as an inorganic amorphous calcium sodium phosphosilicate (CSPS). The NovaMin Technology was developed by Dr. Len Litkowski and Dr. Gary Hack. Currently available products in the market are NovaMin: SootheRx, DenShield, NuCare-Root Conditioner with NovaMin, NuCare-Prophylaxis Paste with NovaMin, and Oravive.30,31
In the presence of water or saliva, NovaMin rapidly releases sodium ions. This increases the local pH and initiates the release of calcium and phosphate.
NovaMin particles act as reservoirs and continuously release calcium and phosphate ions into the local environment. This may continue over many days. Calcium-phosphate complexes crystallize into hydroxyapatite. Chemically and structurally, this apatite is nearly identical to bone and tooth mineral. NovaMin has been incorporated into toothpastes, gels and prophylactic pastes.

A novel delivery system for NovaMin is through an air polishing unit. This system provides the benefits of both tooth desensitization and smoothing of surface roughness, promoting a smoother, less plaque and stain retentive surface.

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. Also, women are at increased caries risk due to inadequate salivary calcium levels at different points in their lives, including ovulation, pregnancy and post-menopause, resulting in the same net effect as reduced saliva fluoride efficacy. 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.

Tri-calcium phosphate (TCP) (Clinpro Tooth Crème) TCP is a bioactive formulation of tri-calcium phosphate and simple organic ingredients. TCP is a new hybrid material created with a milling technique that fuses beta tricalcium phosphate and sodium lauryl sulfate or fumaric acid. This results in a "functionalized" calcium and a "free" phosphate, so as to increase the efficacy of fluoride remineralization. When it is used in toothpaste formulations, a protective barrier is created around the calcium, allowing it to coexist with the fluoride ions. When TCP comes into contact with saliva, the protective barrier breaks down, making the calcium, phosphate and fluoride ions available to the teeth. The fluoride and calcium then react with weakened enamel to provide a seed for enhanced mineral growth relative to fluoride alone. Studies have shown that TCP provides superior remineralization when compared to a 5000 ppm fluoride and CPP-ACP.

ACP technology (enamelon, enamel care)
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 on to 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.

Sugar substitutes
Xylitol
It is a sugar alcohol that has been shown to have non-cariogenic as well as cariostatic effects. Its sources are fruits, berries, mushrooms, lettuce, hardwoods and corn on the cob. Xylitol results in:

- Reduction of dental plaque formation
- Neutralization of plaque acids by decreasing the production of lactic acid.
- Reduction of levels of S. mutans
- Reduction of cavities by up to 80%
- Remineralization of tooth enamel

Xylitol interferes with the metabolism of S. mutans. When S. mutans is transported into a cell, xylitol makes it to bind to proteins. Due to this bond, transport protein is unable to go out of the cell and bring more glucose into the cell, thereby, bacteria are unable to produce the sticky extracellular polysaccharides that bind bacteria together. This decreases caries incidence and promotes colonization of less virulent strains of bacteria that can ferment xylitol.

It has also been shown that a combination of fluoride and xylitol is more effective than fluoride alone. Best time to use xylitol is immediately after eating and clearing the mouth by swishing with water. Also it does not raise blood pressure or blood glucose levels as most sugar substitutes do. Studies have shown that the habitual chewing of xylitol gum by mothers can decrease the caries incidence in their children by preventing the transmission of S. mutans. Besides fluoride, calcium lactate also enhances remineralization when added to xylitol.

The recommended dose for maximum prevention of dental caries is minimum of 5-6 grams and three exposures per day (from chewing gum and/or candies). The A novel method of transporting calcium and phosphate in combination with xylitol has been developed using a NaF varnish. This varnish contains calcium and phosphate salts that have been nano-coated with xylitol. Xylitol coating produces a sustained release of the remineralizing ions. Saliva exposure dissolves the xylitol and frees the calcium and phosphate ions which further react with the fluoride in the varnish to form protective fluorapatite on the teeth.

Sorbitol is another sugar substitute that is used as an artificial sweetener. The abilities of xylitol and sorbitol to remineralize early enamel caries seem to be almost similar.

Isomalt is a noncariogenic sweetener that is widely used as a sugar substitute. Adding isomalt to a demineralizing solution has shown to significantly reduce tooth mineral loss.

**Grape seed extract**

When caries reach the dentin, the demineralized dentin matrix is further degraded, allowing bacteria to infiltrate the intertubular area. Thus, stability of dentin collagen is essential during the remineralization process, because it acts as a scaffold for mineral deposition. Polyphenols (plant-derived substances) have antioxidant and anti-inflammatory properties by interacting with microbial membrane proteins, enzymes and lipids. This changes the cell permeability and allows loss of proteins, ions and macromolecules. One such polyphenol is proanthocyanidin (PA), which accelerates the conversion of soluble collagen to insoluble collagen during development and increases collagen synthesis. Grape seed extract (GSE) has high PA content. PA-treated collagen matrices are non-toxic and inhibit the enzymatic activity of glucosyl transferase, F-ATPase and amylase.
Inhibition of glucosyl transferases by PA in turn inhibits caries.58,60,61 GSE can act as a potential adjunct or alternative to fluoride in the treatment of root caries during minimally invasive therapy.

**Calcium carbonate carrier – sensi stat**

The SensiStat Technology was developed by Dr. Israel Kleinberg of New York. The technology was first incorporated into Ortek's Proclude desensitizing prophy paste and later in Denclude.62 SensiStat technology is made of arginine bicarbonate, an amino acid complex, and calcium carbonate. Arginine complex is responsible for holding the calcium carbonate particles to the tooth surface and allows the calcium carbonate to slowly dissolve and release calcium which is then available to remineralize the tooth surface.63

**Ozone**

Ozone is a chemical compound consisting of three oxygen atoms (O3, triatomic oxygen). Ozone therapy is also proposed to stimulate remineralization of incipient caries following treatment for a period of about 6-8 weeks.64,65

**Conclusion**

Due to recent innovations and more inclination towards preventive care, the multifactorial disease process of demineralization and caries can be slowed down before more extensive treatment becomes necessary. Therefore the 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. Incidence of caries has shown to be reduced because of simple remineralization tools, techniques and products that have been found effective in reversing and controlling the caries process. With a clearer understanding of the implementation of these remineralizing agents, we can create a more favorable relationship in which remineralization can occur.11 Mostly published studies supporting these materials have been in vitro studies. The potential of remineralising agents is promising, but more studies are needed, including clinical trials supporting its efficacy in boosting remineralization.

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