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REVIEW ARTICLE

Newer Nonfluoride Remineralizing Agents: An Insight

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ABSTRACT

Modern-day dentistry has shifted its focus from Black's "extension for prevention" to prevention of extension, however, the current ideology of dentistry stresses on management of noncavitated carious lesions noninvasively through remineralization in an attempt to prevent disease progression, and to improve strength, esthetics, and function of teeth. The oral cavity is an arena involving constant fight between remineralizing and demineralizing factors. This relationship determines the integrity and strength of the tooth structure. The lopsidedness leads to rapid demineralization and decomposition of the tooth structure. In recent past an irrefragable explosion of fervor in technologies for remineralization of enamel and dentin or desensitization of exposed dentin affected by dental erosion has taken place. Remineralization is an innate repair process of reinstating ions back in the hydroxyapatite's lattice structure. The fundamental aspect is the use of remineralizing agents to tooth structure to control the demineralization/remineralization activity. The present review draws attention to the current components available for remineralization therapy and its application in clinical practice.

Keywords: Demineralization, Fluoride, Hydroxyapatite, Remineralizing agents.

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INTRODUCTION

Dental caries is the most common totally preventable condition facing humanity. Its effect ranges from a minor inconvenience requiring caries removal and restoration to grueling pain and loss of masticatory function.[1] There exists an intricate coordination among bacteria, diet, and salivary components, which result in demineralization of the enamel. Bacterial action on dietary fermentable carbohydrates leads to the production of acids, which diffuses into the tooth and dissolves the carbonated hydroxyapatite mineral a process called demineralization.[2] Downturn in the pH of oral cavity results in demineralization and the oral environment becomes under saturated with mineral ions, relative to tooth's mineral content. If the demineralization prolongs, excessive loss of minerals, leads to loss of the enamel structure and eventually cavitation. In the event of pH rise, the reverse takes place, resulting in the deposition of mineral back to the tooth structure.[3] Thus, remineralization is the mechanism through which 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. The extensive studies on remineralization have led to the development of newer technologies that promote enamel remineralization and prevent enamel demineralization providing promising oral health assistance.[4] The essence of caries research and prevention lies in the opposition of the terms replacement or remineralization.

RATIONALE FOR SUBSTITUTION OF FLUORIDES

- Fluoride is highly effective on smooth-surface caries, but its effect is limited on pit and fissure caries.[5-8]
- A high-fluoride strategy cannot be followed to avoid the potential for adverse effects (e.g., fluorosis) due to overexposure to fluoride.[5,6]
- Toxicity of fluoride increases with inadequate nutrition.[5,7]
- Although fluoride has had a profound effect on the level of caries prevalence, it is far from a complete cure.[5,7]
- The antifluoride lobby which is mounting pressure poses certain legal limitations to the use of fluorides.[5,7,8]
- Certain countries do not have fluoridated products.[5,8]

IDEAL REQUISITES OF A REMINERALIZING AGENT

- Diffuses into the subsurface or delivers calcium and phosphate into the subsurface.[5,9]
- Does not deliver an excess of calcium.[5,9]
- Does not favor calculus formation.[5,6]
- Works at an acidic pH.[5,6]
- Works in xerostomic patients.[5,9]
- Boosts the remineralizing properties of saliva.[5,10]
- For novel materials shows a benefit over fluoride.[5,10]

CASEIN PHOSPHOR-PEPTIDES AMORPHOUS CALCIUM PHOSPHATE

Casein is a bovine milk phosphor-protein and a natural food constituent. It interacts with calcium and phosphate and is a natural food component. Professor Reynolds discovered it at the School of Dental Science, University of Melbourne, Australia.[11] Casein phosphor-peptides (CPP) is made up of cluster sequence Ser (P)-Ser (P)-Ser (P)-Glu-Glu from casein.[5,6,11] The CPP are produced from a tryptic digest of the milk protein casein, then aggregated with calcium phosphate, and purified by ultrafiltration. The material is pH responsive and with increasing pH the level of bound amorphous calcium phosphate (ACP) increases, stabilizing free calcium and phosphate so that spontaneous precipitation of calcium phosphate does not occur.

Mechanism of Action

The CPP have the potentiality to bind and stabilize calcium and phosphate in solution, as well as to bind to dental plaque and tooth enamel. Calcium phosphate is normally insoluble, i.e., forms a crystalline structure at neutral pH. However, the CPP keeps the calcium and phosphate in an amorphous, noncrystalline state that helps them enter the tooth enamel. The high concentration of calcium and phosphate ions in dental plaque has been extensively researched and proven to reduce the risk of enamel demineralization and promote remineralization of tooth enamel.[5,6,8,9,11] The CPP stabilize ACP, localize ACP in dental plaque, thereby maintaining a state of supersaturation with respect to tooth enamel, reducing demineralization and enhancing remineralization.[12] To conclude, there is comprehensive clinical as well as *in vitro* documentation proving the effects of CPP-ACP as a remineralizing agent.

AMORPHOUS CALCIUM PHOSPHATE

Amorphous calcium phosphate forms on the tooth enamel, within the dentinal tubules, and provides a calcium and phosphate reservoir. Research shows ACP on the enamel can prevent erosion by stimulating remineralization of tooth structure. Introducing calcium and phosphate back into the surface of the tooth with products containing ACP technology is an ideal strategy to reverse the demineralization process.

The ACP technology requires a two-phase delivery system to keep the calcium and phosphorous components from reacting with each other before use. Calcium sulfate and dipotassium phosphate are the sources of calcium and phosphorous salts. On mixing them, 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.[13] 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 EnamelCare toothpaste by Church and Dwight. Enamelon consists of unstabilized calcium and phosphate salts with sodium fluoride. The manufacturer claims that its liquid calcium (TM) formula delivers fluoride along with soluble calcium and phosphate, the building blocks of enamel.[9] It is also available as Discus Dental's Nite White Bleaching Gel and Premier Dental's Enamel Pro Polishing Paste. It is also present in the Aegis Pit and Fissure Sealant, produced by Bosworth.[14]

TRICALCIUM PHOSPHATE

Tricalcium phosphate (TCP) is a relatively newer material introduced as remineralizing agent. It is a combination produced by milling technique that fuses beta TCP and sodium lauryl sulfate or fumaric acid. When TCP comes into contact with the tooth surface and is moistened by saliva, the protective barrier breaks down making calcium, phosphate, and fluoride ions available to the tooth.[5,15] The milling process ensures that preceding utilization, the active calcium sites are shielded from premature interactions with fluoride, which could otherwise render both calcium and fluoride inactive. Tricalcium phosphate is believed to be means for enhancing the levels of calcium in plaque and saliva.[5,6] Functionalized TCP offers excellent advantage when delivered in a neutral pH environment contrary to acidic pH required by other calcium phosphate substances, which restrict the benefits to the tooth.[2,16] As functionalized TCP is less soluble relative to other forms of calcium phosphate,[17] when applied as a dentifrice in formulation with fluoride, this TCP ingredient can enhance mineralization and help build a high-quality, acid-resistant mineral without the need of high levels of calcium. It is believed that the organic coating impedes undesirable communication with fluoride that might dissolves away when particles come in contact with saliva.

Clinpro 5000 toothpaste is TCP, constituting calcium oxides, calcium phosphate, and free phosphates. It contains 5000 ppm of fluoride, which also aids in remineralization by attracting calcium and phosphate ions to the tooth's surface.[18] Tricalcium phosphate with 950 ppm fluoride treatment increases the hardness of the teeth *in vitro*[19] and also increases the surface microhardness of eroded enamel by chlorinated water *in vitro*.[15]

Researchers also advocate that TCP works best at neutral or slightly alkaline pH as a remineralizing agent.

XYLITOL

Xylitol is a widely accepted sugar substitute. It has been employed for many years as a nonacidogenic sweetener in numerous applications as it cannot be fermented by plaque bacteria. Chewing xylitol gum increases salivary flow rate and enhances the protective properties of saliva. This is due to higher concentration of bicarbonate and phosphate in the stimulated saliva. Xylitol acts by interfering with the metabolism of *Streptococcus mutans*. When *S. mutans* is transported into a cell, xylitol makes it to bind to proteins. This bond is unbreakable and the transport protein is unable to go out of the cell and bring more glucose into the cell. Because the bacteria are bound, they are unable to produce the sticky extracellular polysaccharides that bind bacteria together. As a result, there is less plaque buildup and the cariogenic bacteria cannot stick to the enamel.[20,21]

Xylitol has the ability to[20]:

- Reduce dental plaque formation
- Make plaque less adhesive
- Neutralize plaque acids by decreasing the production of lactic acid
- Reduce the levels of *S. mutans*
- Reduce cavities by up to 80%
- Demonstrate significant long-term reduction in caries (88–93%)
- Assist in the remineralization of tooth enamel
- Reduce gum tissue inflammation
- Help with dry mouth and bad breath.

CALCIUM SODIUM PHOSPHOSILICATE (BIOACTIVE GLASS)

Dr Larry Hench discovered Bioactive glass (Bioglass®) in 1960s. It functions as a biomimetic agent resembling the body's innate mineralizing traits and affecting cell signals in a way that benefits the restoration of tissue structure and function.[20,22] In an aqueous environment Bioglass® immediately begins surface reaction in three phases, leaching and exchange of cations, network dissolution of SiO_2, and precipitation of calcium and phosphate to form an apatite layer. Morphologically and synthetically, this apatite resembles bone and tooth mineral. The surface reactions from implantation to formation of 100 to 150 µm CAP layer occur in 12 to 24 hours.[20,23,24]

NovaMin® is a trade name for bioactive glass, manufactured by Novamin Technologies Inc. (Alachua, FL, USA). It was developed by Dr Len Litkowski and (isppd) 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.[6,25,26] NovaMin contains calcium sodium phosphosilicate, which comprises 45% SiO_2, 24.5% Na_2O, 24.5% CaO, and 6% P_2O_5 that result in the formation of new hydroxyl carbonate apatite crystals. Researchers have demonstrated a significant antimicrobial effect toward caries pathogens (*S. mutans, S. sanguis*) upon exposure to bioactive glass powders as well as solutions and extracts.[27] Individuals struggling with reduced calcium, phosphate, and fluoride ions caused by hyposalivation can aid from the use of bioactive glass. Thus, the use of bioactive glass in remineralization of enamel is quite promising, especially in patients with systemic problems, however, future research needs to be ventured to authenticate its potency.

ION EXCHANGE RESINS

Ion exchange resins (IER) have been appreciably acknowledged by researchers due to their all-around properties as drug delivery vehicles. Studies in the past have revealed that IER are equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical, and taste masking.[28] Ion exchange resin provides a controlled release system, which supplies calcium, fluoride, phosphate, and zinc ions, to promote remineralization. Torrado et al[29] evaluated a dentifrice containing mixture of ion-exchange resins and concluded that inclusion of calcium phosphate ion-exchange resins helps promote remineralization.

In resin infiltration technique, low viscosity resin of type tri-ethylene glycol dimethacrylate with a sufficiently high (> 200 cm/second) penetration coefficient is applied on the white spot lesion after acid etching with 15% hydrochloric acid gel for 2 minutes, which halts the progression of lesion.

GRAPE SEED EXTRACT

Root caries notably prevails among the elder individuals due to gingival recession and the exposure of susceptible root surface.[20,30] An important approach regarding preventive therapies for root caries is to promote remineralization of demineralized dentin.[20,31-34] Polyphenols are plant-derived substances having antioxidant and anti-inflammatory properties.[35-37] They interact with microbial

membrane proteins, enzymes, and lipids, thereby altering cell permeability and permitting the loss of proteins, ions, and macromolecules. Proanthocyanidin (PA) is one such polyphenol which is a bioflavanoid-containing benzene-pyran-phenolic acid molecular nucleus.[37] Proanthocyanidin expedites the conversion of soluble collagen to insoluble collagen during development and increases collagen synthesis.[34] Grape seed extract (GSE) is rich in PA content. In addition, PA-treated collagen matrices are nontoxic and inhibit the enzymatic activity of glucosyl transferase, F-ATPase, and amylase. Glucosyl transferases produced by *S. mutans* polymerize the glucosyl moiety from sucrose and starch carbohydrates into glucans. Thus, inhibition of glucosyl transferases by PA in turn inhibits caries.[20,36,38,39] Grape seed extract can act as a promising and potent supplement or substitute to fluoride in minimally invasive management of root caries.

TRIMETAPHOSPHATE ION

The possible mechanism of action of trimetaphosphate (TMP) ion is believed to influence in adsorption of the agent to the enamel surface, creating a barrier coating i.e., competent in inhibiting or retarding reactions of the crystal surface with its fluid environment, thereby reducing demineralization during acid challenge.[6] The efficacy of TMP can be associated to the fact that TMP benefits the diffusion of calcium ions to the inner of enamel or reduced their loss to the solutions.[40] Also, biomimetic remineralization using sodium-TMP is an encouraging method to remineralize artificial carious lesions, particularly in areas devoid of seed crystallites.[41] Gu accentuated the role of sodium 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.[42]

DICALCIUM PHOSPHATE DIHYDRATE

Incorporation of dicalcium phosphate dehydrate (DCPD) in a dentifrice upsurges the levels of free calcium ions in plaque fluid, and they remain elevated for up to 12 hours after brushing, in comparison to conventional silica dentifrices.[10] Calcium from DCPD is integrated into enamel and has been detected in plaque 18 hours posttreatment after brushing with a DCPD dentrifice which fosters improved remineralization of teeth in combination with fluoride.[43] The interaction of DCPD and fluoride forming fluorapatite may provide a potentially encouraging remedy for remineralization of caries lesions *in vivo*.[44]

Ozone

Ozone is the layer of earth's stratosphere protecting us from the harmful radiation causing skin cancers. It is an effective oxidizing agent that operates by attacking thiol groups of cysteine amino acid and decimates the cellular membrane of carious bacteria.[45] Ozone is capable of altering acidogenic and aciduric microorganisms to normal commensals permitting remineralization to occur. Currently, HealOzone (KaVo GmbH, Germany) remineralizing solution, comprising xylitol, fluoride, calcium, phosphate, and zinc, is recognized for the treatment of caries. It can be used as 2100 ppm of ozone ± 5% at a flow rate of 615 cc/minute for 40 seconds. It has been proposed that tooth remineralization might be promoted with the assistance of salivary minerals and usable fluorides or remineralizing chemicals, bringing about a tooth surface i.e., more resistant to future acid attacks. The mechanism of Heal Ozone's action is related to ozone's potent antimicrobial properties and its ability to oxidize proteins associated with caries.

CALCIUM CARBONATE CARRIER (SensiStat)

Dr Israel Kleinberg developed SensiStat at the Department of Oral Biology and Pathology at State University of New York at Stony Brook. SensiStat was first introduced commercially in 2003 in Ortek's Proclude desensitizing prophy paste, and later in Denclude, a professionally dispensed sensitivity paste for home use launched in 2004. It consists of highly soluble arginine bicarbonate component of SensiStat, or is surrounded by particles of the poorly soluble calcium carbonate component, and because of the adhesive properties of the composition forms a paste-like plug that not only fills the open tubules but also adheres to the dentinal tubule walls. Due to its alkalinity, the SensiStat also reacts with the calcium and phosphate ions of the dentinal fluid to make the plug chemically contiguous with the dentinal walls and, therefore, more secure. It is approved by US FDA (number K002989).[5] SensiStat can be used to treat early surface demineralizations, and halt development to frank caries that requires restoration.

BIOMIMETICALLY MODIFIED MINERAL TRIOXIDE AGGREGATE

It is more difficult to remineralize dentin than enamel due to the paucity of apatite seed crystallites along the lesion surface for heterogeneous crystal growth. The remineralization potential of mineral trioxide aggregate (MTA) in phosphate-containing simulated body fluid (SBF) by incorporating polyacrylic acid and sodium tripolyphosphate as biomimetic analogs of matrix proteins for remineralizing artificial caries-like dentin was evaluated and it revealed at the end of 6 weeks that biomimetic analogs in modified MTA provides a potential delivery system for remineralization of dentin, thus widening the scope and applications MTA in dentistry. Inculcation of

polyphosphate in the MTA may serve as an accessory source of phosphate in critical times.[46]

CAVISTAT

A sugarless mint known as BasicMint containing CaviStat® (an arginine bicarbonate calcium carbonate complex) was evaluated for its capability of preventing the development of dental caries in the primary molars and first permanent molars of 10-year-old children and showed caries reduction drastically by 50%.[47] CaviStat is now used as an additive in toothpastes and mints as it is a simple and economical means for reducing substantially one of the most prevalent diseases in these children.

Remin Pro®

Remin Pro® is a water-based cream containing calcium, phosphate in the hydroxyapatite form. In addition, fluoride and xylitol have also been included in this product. Hydroxyapatite fills the superficial enamel lesions and the tiniest irregularities that arise from erosion.[48] Fluoride gets converted to fluorapatite when it comes in contact with saliva; thus, strengthens the tooth and renders it more resistant to acid attacks. Xylitol reduces the harmful effects of bacteria and their metabolic product lactic acid. Usage of Remin Pro® after bleaching showed a considerable increase in microhardness, which was comparable with GC tooth mousse.[49,50] It is credited to the presence of 1450 ppm fluoride, which is 61% higher than GC tooth mousse.

CONCLUSION

Due to changes in dietary habits and lifestyle, there is an increasing incidence of dental caries. The dynamic balance between demineralization and remineralization determines the progression of initial noncavitated lesion. Evidence suggests that initial noncavitated lesions can be remineralized using appropriate technologies, both fluoride, and nonfluoride based. The nonfluoride remineralization strategies will be of benefit to many. With the newer nontoxic alternative remineralization strategies, we would be able to reestablish the health of oral tissues without being under the risk of adverse effects of fluoride and provide direct preventive strategies to the high caries risk individuals.

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