International Journal of Applied Dental Sciences 2020; 6(3): 177-182

ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2020; 6(3): 177-182

www.oraljournal.com
Received: 15-06-2020
Accepted: 18-07-2020

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Novel Approaches in hard tissue remineralization: An Overview

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Abstract
Preservation of tooth structure by prevention of mineral loss occurring on its surface remains the primary goal of modern dentistry. This can be achieved by strengthening the natural repair mechanism of remineralisation. The remineralization process is a natural repair mechanism to restore the minerals again, in ionic forms, to the hydroxyapatite (HAP) crystal lattice. In this process, calcium and phosphate mineral ions are redeposited within the tooth surface from plaque and saliva. Thereby making the appetite crystals more resistant to acid dissolution. Thus, the emphasis currently is being laid upon new technologies for enamel remineralization.
The aim of this paper is to review the contemporary remineralizing systems along with the newly introduced agents available for remineralization therapy.

Keywords: Demineralization, Remineralization, Silver diamine fluoride, ACP-CPP, Tricalcium phosphate

1. Introduction
Despite its dreadful nature and multi factorial etiology, dental caries is a preventable disease if preventive intervention is applied at an early stage. Thus, prevention of caries initiation and halting the progression of early lesions are the desirable modes of caries management. The process of caries formation is a cycle of remineralization and demineralization, when the demineralization process predominates, it leads to cavitation.
This calls for shifting a focus the development of methodologies for the detection of the early stages of caries lesions. Remineralization aids in filling of voids by depositing ions facilitating the natural repair process thereby reversing the demineralised state of enamel. Remineralizing agents have been introduced to serve the same purpose. Fluorides were the pioneers in remineralization technology but over the years variety of novel agents have proven to be effective in hard tissue reminerlization. This article provides an overview of the various remineralizingagents and their roles in the remineralization of tooth tissue.

2. Fluorides
Fluoride is the first remineralizing agent which has proven to be effective in prevention g dental caries. It makes enamel resistant to caries by both systemic use and topical applications
Firstly, it reduces enamel demineralisation and enhances remineralisation of incipient lesions by the rise in ph brought upon by fluoride present in the microenvironment. Fluoride inhibits dissolution of enamel due to acid attack and results in the formation of new and larger fluoride crystals containing fluorhydroxyapatite. [1, 2, 3, 4]
Secondly, fluoride hastens the formation of fluorapetite crystals by utilising calcium and phosphate ions which were made available by its retention on the dental hard tissue. Third, it interferes with the production of phosphoenol pyruvate (PEP), thus inhibiting the activity of acid producing carious bacteria. [5]
Fluoride modifies the morphology of pits and fissures by making them shallow by enhancing post eruptive maturation so that substrate and bacterial retention does not takes place in them, thereby rendering them less vulnerable to acid attack. [6] The various types of topical fluorides used in dentistry are: Sodium fluoride (NaF), sodium mono-fluorophosphate, stannous fluorides and acidulated phosphate fluoride (APF). All these fluorides are inorganic in nature

and are available in the form of solutions, varnishes, foam, gels, dentifrices etc. [7, 8]

2.1 Fluoride-containing Dentifrices

Fluoride dentifrices are considered as most effective agents for preventing enamel demineralization. Incorporation of fluorides in dentifrices has led to 40-60% reduction of dental caries, when compared to those achieved with non-fluoride ones. [9, 10, 11, 12, 13, 14]

Dentifrices exert their preventive effect by means of their components. The chemical characteristics and interactions of different components determine their action in caries prevention.

The concentration of these substances vary in different formulations and depends upon the objectives intended. Abrasives constitutes 25 to 60% of a toothpaste. [15,16]

Abrasives are insoluble particles that allow the mechanical removal of bacterial plaque; some examples are: dicalcium phosphate (CaHPO4), calcium pyrophosphate (Ca2P4O7), aluminium hydroxide (Al(OH)3), calcium carbonate (CaCO3), silicas, zeolites, and hydroxyapatite (Ca (PO) OH).[17]

Dentifrices contain the therapeutic or active agents in various chemical forms mainly as sodium fluoride, sodium monofluorophosphate, amine fluoride or combinations of these. Sodium fluoride is a highly ionizable compound and provides free fluoride. However, Sodium monofluorophosphate requires prior enzymatic action for the release of fluoride. [18, 19]

In MFP, fluoride is covalently bonded to the phosphate, phosphatases-enzymes, present in plaque and saliva act on the MFP molecule causing its hydrolysis, thus releasing active fluoride.

The fluoride released is absorbed to the mineral surface, as a CaF2 or a CaF2-like deposit, in free or bound form. [20]

The efficacy of conventional toothpastes containing 1,000 ppm fluoride have been documented in many studies, but evidence suggests that tooth- paste containing 5,000 ppm fluoride can further reduce demineralization and enhance remineralization. [21]

5,000 ppm fluoride dentifrice has a fluidic or gel-like formulation and it has been reported to provide faster dispersion in saliva and higher fluoride uptake into enamel, thus it is recommended for high caries risk patients, including those with orthodontic brackets, prostheses and restorations, those with xerostomia, or those genetically susceptible to tooth decay.[22]

However, the use of toothpastes with high fluoride content has always raised concerns when used in children. This has been associated with an increased susceptibility to develop dental fluorosis in children, [23, 24] especially in a children aged below 6 yrs. [25, 26]

Fluoride in toothpastes contributes with approximately 57 to 81.5% of the total intake of fluoride in children aged between 12 months and 6 years. [27, 28]

3. Dicalcium Phosphate Dihydrate (DCPD)

Dicalcium phosphate dihydrate (DCPD/CaHPO4.2H2O) is an acidic calcium phosphate phase that readily turns into fluorapatite in the presence of fluoride. [29]

Under acidic conditions, the presence of calcium fluoride facilitates the conversion of DCPD to FAP which has better crystallinity. 1DCPD is added to toothpaste both for caries protection and as a gentle polishing agent. Researches have shown that inclusion of DCPD in a dentifrice increases the levels of free calcium ions in the plaque fluid, and these remain elevated for up to 12 hours after brushing, when compared to conventional silica dentifrices. [30, 31]

Also, there is enhanced calcium incorporation into Enamel from DCPD, also increased levels are detected in plaque up to 18 h. [32]

The use of remineralizing artificial saliva incorporated with DCPD is a promising approach for patients suffering from xerostomia for managing both dental caries and hyposalivation. [33, 34]

Also the dissolution rates for DCPD, OCP and HAP crystals are invariably found to decrease even in undersaturation conditions. [35]

4. CPP- ACP-

Milk products have been proved to exert a protective effect against the development of dental caries due to their anticariogenic properties.The anticariogenic properties of milk are due to the presence of casein, calcium, and phosphate, which are responsible for resistance to acid dissolution. Caseins belong to a heterogeneous family of proteins while casein phosphopeptides (CPPs) are phosphorylated casein-derived peptides produced by tryptic digestion of casein.

The CPP component, which contains 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.[36]

CPP can also bind to dental plaque and tooth enamel. The calcium phosphate in these complexes is biologically available for remineralisation of subsurface lesions in tooth enamel. The multiphosphoseryl sequences in CPP have ability to stabilize calcium phosphate in nanocomplexes in solutions like amorphous calcium phosphate (ACP). Through these sequences, CPP binds to ACP in metastable solution preventing the dissolution of calcium and phosphate ions. ACP is the initial solid phase that precipitates from a highly supersaturated calcium phosphate solution and can convert readily to stable crystalline phases such as octacalcium phosphate or apatitic products. It plays as a precursor to bioapatite and as a transient phase in biomineralization.

During the conversion of ACP to apatite there is dissolution of ACP, then reprecipitation of a transient OCP solid phase through nucleation growth, and, finally, hydrolysis of the transient OCP phase into the thermodynamically more stable apatite by a topotactic reaction.

This process occurs at a physiological pH. The ACP-CPP also acts as reservoir of bio-available calcium and phosphate and maintains the solution supersaturated, thus facilitating remineralization. [37] Thus, CPP-ACP complex is known to inhibit demineralization and enhance remineralization or possibly both.

CPP–ACP is a two-phase system which when mixed together reacts to form the ACP material that precipitates onto the tooth structure and elevates calcium levels in the plaque fluid. GC Tooth Mousse PlusTM and MI Paste PlusTM are formulations of CPP–ACP with incorporated fluoride to a level of 900 ppm, where the fluorides give additive effects in reducing caries experience.

It is available as toothpastes, chewing gum, lozenges, and mouth rinses. Reynolds et al. have reported that the addition of 2% CPP– ACP to the 450 ppm fluoride mouth rinse significantly increases the incorporation of fluoride into plaque. Oliveira et al. also have demonstrated a greater protective effect against demineralization on smoother surfaces if CPP–ACP was combined with fluoride than without fluoride. [38]

4.1 Fluoride incorporated ACP-

Fluoride ion incorporated into the ACP phase was stabilized by the CPP to produce a novel ACFP, this (CPP-ACFP) complex contains nanocomplexes of milk protein [39, 40] which was observed to be responsible for anti-cariogenic effect. It was reported that addition of fluoride to CPP-ACP could give a synergistic effect on enamel remineralization of early carious lesions.When CPP-ACFP is applied to the oral environment, the sticky CPP part of the CPP-ACFP complex binds readily to the enamel, biofilm, and the soft tissues, delivering the calcium phosphate ions, thereby maintaining a supersaturated state of essential minerals. Fluoride ions help in remineralisation by forming fluorapatite in the presence of calcium and phosphate ions over the enamel surface. [41]

5. Bioactive Glass

Bioglass (BG) is a class of bioactive material which is composed of calcium, sodium, phosphate, and silicate. They are reactive when exposed to body fluids and deposit calcium phosphate on the surface of the particles. [42] Bioactive glass materials have been introduced in many fields of dentistry and are considered as a break through in remineralizing technology.

In vitro and in vivo studies have shown that BG particles can be deposited onto dentine surfaces and subsequently occlude the dentinal tubules by inducing the formation of carbonated HAP-like materials. [43]

5.1 Novamin

Novamin, is derived from bioactive glass particulates of highly biocompatible materials. It comprises SiO_2 (45%), Na_2O (24.5%), CaO (24.5%) and P_2O_5 (6%).Though, it was originally developed as bone regenerative material, it was later recognised as a potent remineralizing agent.

Novamin releases calcium and phosphate ions intraorally to help the self-repair process of enamel. A silica-rich surface layer forms through polycondensation of hydrated silica groups, on which precipitation of ions happens which crystallizes over time to form a hydroxyl-carbonate apatite. Although it is used extensively as a desensitizing agent reports also claim that the chemical reactions that promote apatite formation may enhance the remineralization. [44]

On contact with the aqueous media, it releases silica, calcium, phosphorous, and sodium ions which initiates the remineralisation of hard tooth structure and occludes dentinal tubules.

The particle reaction continues and deposition of calcium and phosphate complex takes place which crystallizes to calcium hydroxyl apatite, also known as Hydroxycarbonate apatite. [45]

In the aqueous environment of the tooth, sodium ions from the Novamin particles rapidly exchange with hydrogen cations (in the form of H_3O^+) to release calcium and phosphate (PO_4^{3-}) ions. There will be a localized transient increase in pH during the initial exposure of the material due to the release of sodium. This increase in pH helps to precipitate the extra calcium and phosphate ions provided by the Novamin particles to form a precipitated calcium phosphate layer. As these reactions continue, this layer crystallizes into hydroxycarbonate apatite (HCA) which is chemically and structurally equivalent to naturally occurring biological apatite. [46, 47]

6. Xylitol

Xylitol is a non-fermentable sugar alcohol, which reduces plaque formation thereby reducing number of Mutans streptococci in saliva. [48, 49]

It is regarded as the best of all nutritive sugar substitutes with respect to caries prevention. The basic property of this sweetener is that it is not fermented to acids, which proves advantageous in exerting non-cariogenic as well as cariostatic effects. It exerts the anticariogenic effects by the inactivation of S. mutans and inhibition of plaque's ability to produce acids and polysaccharides. When consumed as mints or gum, it will stimulate an increased flow of alkaline and mineral-rich saliva from small salivary glands in the palate. Increased salivary flow results in increased buffering capacity against acids and high mineral content will provide the minerals to remineralize the damaged areas of enamel. [50]

Some researchers indicated that xylitol might be involved in the enamel demineralization and remineralizing process by acting as a ca^{2+} carrier required for remineralization. [51]

However, researchers differ in their view about the added effectiveness of xylitol, when combined with fluoride. Milburn et al. have shown that fluoride varnish, containing xylitol-coated calcium and phosphate, had the greatest initial fluoride release in the first four hours, exceeding 10 times than that of other varnishes such as Enamel Pro, Duraphat, or Vanish. However, Brown et al. could not find any added clinically relevant preventive effect of xylitol on caries in adults with adequate fluoride exposure. [52]

7. Functionalized Tricalcium Phosphate (fTCP) -

TCP is originally produced by milling TCP with sodium lauryl sulfate. The combination of TCP with fluoride can provide greater enamel remineralisation and build more acid-resistant mineral relative to fluoride alone. [53]

fTCP stabilizes fluoride in solution and maintains high concentration of calcium, phosphate and fluoride in white spot lesions.When it is used in toothpaste formulations, a protective barrier is created around the calcium, allowing it to coexist with the fluoride ions. During toothbrushing, TCP comes into contact with saliva, causing the barrier to dissolve and releasing calcium, phosphate, and fluoride. It provides a barrier that prevents premature TCP–fluoride interactions and also facilitates a targeted delivery of TCP when applied to the teeth. fTCP is commercially available as a novel 1.1% NaF silica containing paste Clinpro-R, which is a novel 5,000 ppm fluoride dentifrice, also contains containing an innovative functionalized tricalcium phosphate (fTCP) ingredient .On evaluating development formulations, this paste has been shown to boost remineralization performance relative to fluoride-only systems. [54, 55]

8. Silver diamine fluoride (SDF)

Silver di amine fluoride is a newer remineralizing agent that has gained popularity in recent years owing to its excellent remineralizing properties. Silver diamine is a silver halide metal complex which contains ammonia and silver fluoride; the ammonia ions combine with silver ions to produce a complex ion called the diamine-silver ion. This complex is more stable than silver fluoride alone and stabilises high concentrations of silver and fluoride in solution. Due to its higher stability, it can be kept in constant concentration for a period of time. [56, 57, 58]

SDF has the highest fluoride concentration (44,800 ppm fluoride ion) among all available topical fluoride preparations, which contributes to its ability to remineralise tooth surface.

Upon application of SDF to a demineralized or infected surface, a silver-protein conjugate layer forms, increasing resistance to acid dissolution and enzymatic digestion. SDF reacts with hydroxyapatite and generate calcium fluoride, which is a reservoir of fluoride, and facilitate further remineralization. [59, 60, 61, 62]

In a study, the surface of arrested caries in exfoliated teeth with SDF treatment showed a high remineralized zone.[63]Similarly, an ex vivo study reported that mineral density and microhardness of the surface layer of the arrested caries after SDF applications was comparable with the unaffected sound dentin. [64]

Moreover, this microhardness was attained at a greater depth of approx.150micrometers compared with the control lesions treated with deionised water, the levels of calcium and phosphorus increased from the surface to a depth of 300micrometers.[65]

Studies using scanning electron microscopy observed dense precipitates covering tooth surfaces after application of SDF. [66]

SDF application decreased the lesion depth of a demineralised tooth surface by promoting absorption of calcium. Other studies discovered calcium fluoride and silver phosphate when enamel powder or dentine powder were mixed with SDF. Elemental analysis revealed that the weight percentages of calcium and phosphorus in demineralised dentine treated with SDF were significantly higher than those of calcium and phosphorus in demineralised dentine without SDF treatment. [67] Moreover, demineralised dentine treated with SDF had less mineral loss than did demineralised dentine with no SDF treatment.

9. Conclusion

Preventive and minimal intervention dentistry needs to be emphasized in order to achieve non-invasive management of initial caries lesions. Currently introduced remineralizing systems have proven to be effective and promising. Though, There is a need to generate substantial clinical evidence through randomized clinical trials to support their efficacy. The present review is an attempt to document the actions and benefits of remineralizing systems and highlight their importance in hard tissue remineralisation.

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