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An Overview on Remineralizing Agents

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ABSTRACT *The outcome of dental caries is determined by the dynamic balance between pathological factors that lead to demineralization and protective factors that lead to remineralization. Pathological factors include acidogenic bacteria, inhibition of salivary function, and frequency of ingestion of fermentable carbohydrates. Protective factors include salivary flow, numerous salivary components, antibacterials, fluoride from extrinsic sources, and selected dietary components. While our knowledge of the dental caries process and its prevention has greatly advanced over the past fifty years, it is fair to state that the management of this disease at the level of the individual patient remains largely empirical. Minimal invasion dentistry is a key component in today's dental practice. Its first basic principle is remineralisation of early carious lesions, advocating a biological or therapeutic approach.This article details the various agents that enhances and promotes remineralisation.*

INTRODUCTION

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[1]. Remineralization takes places at a higher pH of 7.5 to 8.5 in the presence of calcium and phosphate in the water among the enamel or dentine crystals recrystalize on the surface of existing crystals remnants [2]. The calcium and phosphate come primarily from saliva and the mineral formed during remineralization is more resistant to acid than the original enamel or dentin mineral especially if fluoride is present to enhance remineralization and to be incorporated into the new crystals surfaces [2]. Ideally, remineralizing agents need to rapidly precipitate on partially demineralized tooth structure and transform into a more stable, less acid-soluble apatite than the hard tissue replaced. They would need to do this in the presence of saliva and before the next acid challenge comes in contact with the newly precipitated mineral. If the mineral phase that is formed is soluble in saliva or under acidic conditions, it will be rapidly lost. On the other hand, mineral that is taken up by the enamel may serve as a reservoir that could be released into fluid phase surrounding the enamel crystals during a caries attack and serve as a substrate for subsequent remineralization. If complete remineralization of subsurface lesions is the goal, then the agent must also be able to diffuse past the pellicle- covered enamel surface and into the subsurface lesion area. It has been found to be very difficult to diffuse calcium and phosphate ions into the deeper layers of carious enamel, and most remineralization is confined to the surface of a carious lesion [3]. Under conditions that favor remineralization, calcium will rapidly adsorb onto the surface layer and precipitate in the pores, thus blocking access to the deeper subsurface enamel lesion.

FLUORIDES

Arnold, in 1957, was the first to mention the post-eruptive effect of fluoride in the drinking water and the ability of topical fluoride to reduce the incidence of caries [5, 6]. Fluoride works primarily via topical mechanisms which include inhibition of demineralization at the crystal surfaces inside the tooth, enhancement of remineralization at the crystal surfaces and, at high concentrations, inhibition of bacterial enzymes. Low levels of fluoride in saliva and plaque help prevent and reverse caries by inhibiting demineralization and enhancing remineralization [7].. 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 microorganisms and improved tooth morphology [6]. When a carious lesion is already present, an acidic challenge is frequently occurring. Under this circumstance, when pH is below 5.5 – a critical pH for dental enamel, the remineralization can naturally take place since saliva is generally supersaturated with respect to dental enamel [8]. If fluoride is present in this acidic medium during dissolution of hydroxyapatite, the solution will be highly supersaturated with respect to hydroxyapatite and all potential mineral loss will actually be preserved in the partially demineralized dental crystals. In other words, traces of fluoride in the fluid phase can control mineral loss [8]. Thus, the frequent presence of fluoride in the oral environment during the acidic challenge is as relevant as it is its effect of incorporation. Hence the presence of fluoride at high concentrations is a key strategy for caries control or arresting carious lesions (Featherstone, 1999) [8].

CASEIN PHOSPHOPEPTIDE - AMORPHOUS CALCIUM PHOSPHATE (CPP-ACP, GC TOOTH MOUSSE)

The casein phosphopeptides (CPPs) are produced from the tryptic digest of casein, aggregated with calcium phosphate and purified through ultra filtration [6]. CPP–ACP is the acronym for a complex of casein phosphopeptides and amorphous calcium phosphate [9]. This Recaldent technology was developed by Eric Reynolds, Australia. 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 mul-

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tiple 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, thereby helping to maintain a state of supersaturation with respect to tooth enamel depressing demineralization and enhancing remineralization. The CPPs have been shown to keep fluoride ions in solution, thereby enhancing the efficacy of the fluoride as a remineralizing agent [9, 10, 11,12,13].It can be delivered via tooth mousse, chewing gum , mouth rinses, toothpastes and reduction of tooth sensitivity[12,14]. CPP–ACP can be used to remineralize early carious lesions [16]. It has the ability to counteract the action of acids in cases of erosion [17]. It has been proposed that CPP–ACP (Tooth-Mousse) has an edge over fluoride tooth paste when it comes to neutralizing acids in the oral cavity [18,19]. CPP–ACP alone or its combination with fluoride can be utilized as a prophylactic agent before the bonding of orthodontic brackets [20]. Recaldent influences the properties and behavior of dental plaque through binding to adhesion molecules on mutans streptococci and thus impairing their incorporation into dental plaque, elevating plaque calcium ion levels to inhibit plaque fermentation and providing protein and phosphate buffering of plaque fluid pH to suppress overgrowth of aciduric species under conditions where fermentable carbohydrate is in excess [2,21].

CASEIN PHOSPHOPEPTIDE- AMORPHOUS CALCIUM FLUORIDE PHOSPHATE (CPP-ACFP, GC TOOTH MOUSSE PLUS)

A dentifrice containing CPP-ACP with fluoride provides remineralization which is superior to both CPP-ACP alone and to conventional and high fluoride dentifrices this synergy between CPP-ACP and fluoride had been identified in studies which showed that MI Paste (without fluoride) remineralized initial enamel lesions better when applied as a topical coating after the use of a fluoride dentifrices[2, 22]. In the absence of such "environmental" fluoride, the predominant mineral that will be formed in enamel subsurface lesions during remineralization with CPP-ACP will be hydroxyapatite. It is now known that CPP can stabilize high concentrations of calcium, phosphate and fluoride ions at all pH values from 4.5 up to 7.0, and is able to remineralize enamel subsurface lesions observed at all ph values in this range, with a maximal effect at pH 5.5[2]. In fact, at pH values below 5.5, CPP-ACFP produces greater remineralization than CPP-ACP, and the major product formed when remineralization is undertaken with CPP-ACFP is fluorapatite, which is highly resistant to acid dissolution. The remineralized mineral was more resistant to subsequent acid challenge [2, 23].

AMORPHOUS CALCIUM PHOSPHATE (ACP, ENAMELON)

ACP was firstly described by Aaron S. Posner in the mid 1960s [24]. It was obtained as an amorphous precipitate by accident when mixing high concentrations (30 mM) of calcium chloride and sodium acid phosphate (20 mM) in buffer [25]. It is also used as filler in ionomer cements to fill carious lesions or as a colloidal suspension in toothpastes, chewing gums or mouthwashes to promote demineralization of carious lesions and/or to prevent tooth demineralization [26]. The ACP technology was developed by Dr. Ming S. Tung [9]. 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 [9, 27]. 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 [9, 28]. An inherent technical issue with Enamelon™ is that calcium and phosphate are not stabilized, allowing the two ions to combine into insoluble precipitates before they come into contact with saliva or enamel.

BIOACTIVE GLASS (NOVAMIN)

Bioactive glass was invented by Dr. Larry Hench in1960s[6]. NovaMin is a bioactive glass-ceramic material , wherein the active ingredient is a calcium sodium phosphosilicate that reacts when exposed to aqueous media and provides calcium and phosphate ions that form a hydroxy-carbonate apatite (HCA) with time [29]. Novamin adheres to exposed dentin surface and forms a mineralized layer that is mechanically strong and resistant to acid. There is continuous release of calcium over time, which maintains the protective effects on dentin [30].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 [6]. 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 [9,31].

TRI-CALCIUM PHOSPHATE (CLINPRO)

Tricalcium phosphate has the chemical formula $Ca_3 (PO4)_2$, and exists in two forms, alpha and beta. 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) [32,33]. 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 [7]. A major problem with use of TCP is the formation of calciumphosphate complexes, or if fluorides are present, formation of calcium fluoride occurs which inhibit remineralization by lowering the levels of bioavaliable calcium and fluoride [7]. For this reason, TCP levels would have to be kept very low, in the order of less than 1%. To overcome such problems, TCP can be combined with a ceramic such as titanium dioxide, or other metal oxides [2]. It has been suggested that the organic coating prevents undesirable interactions with fluoride, but may dissolves away when particles contact saliva[7,34]. Products available with TCP include a 5000 ppm sodium fluoride dentifrice and a 5% sodium fluoride varnish.Studies have concluded that TCP provided superior surface and sub-surface remineralization compared with a 5000 ppm fluoride and CPP-ACP[6,35].

HYDROXYAPATITE (REMINPRO)

Nano-hydroxyapatite (n-HAp) is considered one of the most biocompatible and bioactive materials.Their size, morphology , chemical composition and crystallinity are

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comparable to that of dentin and are said to remineralised enamel[36].Concentration of 10% nanohydroxyapatite is optimal for remineralisation of early enamel caries[37].Hydroxyapatite crystals can effectively penetrate the dentinal tubules and obturate them and can cause closure of tubular opening of the dentin with plugs within ten minutes as well as regeneration of a surface mineral layer[36,37].Reminpro (Voco,Germany) is a water based cream which contains calcium phosphate in the hydroxyapatite form[16].In addition fluoride and xylitol also have been added to this product[38].Fluoride gets converted to flourapatite when 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[40].It has been recommended for the management of dentinal hypersensitivity to prevent enamel demineralization and to promote remineralization of enamel subsurface lesions[39]. It provides extra protection for teeth, thus helps neutralize acids from acid-forming bacteria in plaque [40].

ANTICAY TECHNOLOGY (CALCIUM SUCROSE PHOSPHATE-CALCIUM ORTHOPHOSPHATE COMPLEX;TOOTHMIN, ENAFIX)

Anticay, a calcium sucrose phosphate-calcium orthophosphate complex, supplies both calcium and phosphate in a soluble form [41]. It is a fine, white, nonhygroscopic powder with a neutral blend taste .It contains approximately 11.5% calcium on a dry weight basis [41]. This complex helps reduce the acid solubility of enamel [41]. Anticay may function in three ways,it may slow down the acid solubility of enamel and increase the rate of remineralization by a common ion effect,it may inhibit the formation of plaque and its adherence to an enamel surface and it may inhibit the acid producing process in plaque [41]. Anticay may also buffer the cariogenic acids[42,43]Anticay is soluble in water at all pH values[41]. This anticay technology has been incorporated into toothpastes like Toothmin (Abbott health care) and Enafix (group pharmaceuticals ltd, India).

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 [9]. 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 [6]. 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 [9].

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