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A compendium on remineralizing agents in dentistry

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Abstract
Dental caries is a multifactorial disease and has been a major public health problem worldwide.
It is an infectious microbiologic disease that causes destruction of calcified tissues of tooth. Nowadays, emphasis is being laid down on non-invasive management approach for non-cavitated lesions using remineralizing agents. The aim of this review is to update regarding the various remineralizing agents used in dentistry and their mode of action.

Keywords: Remineralizing agents, demineralization, remineralization

Introduction
Esthetic dentistry is a discipline within dentistry in which the primary focus is the alteration of functional and structural appearance of patient's oral structures, in conjunction with the treatment and prevention of oral disease. Dental caries is one of the main culprit to pleasing aesthetics. During the dental caries process, a cycle of demineralization and remineralization takes place with many stages either reversible or irreversible. White spot lesions are manifestations of the earliest stage of caries progression and can be reversed, but if the stage of demineralization persists, it ultimately leads to cavitation [1].
Modern day dentistry has shifted the focus from Black's extension for prevention to prevention of extension. Nowadays, non-invasive management of non-cavitated carious lesions through remineralization is being emphasized in order to prevent disease progression, and to improve aesthetics, strength and function of teeth.
Fluorides are agents well known to inhibit demineralization and promote remineralization. On application to the enamel surface, fluoride ions replace the hydroxide ions in the hydroxyapatite crystal structure of the teeth and forms fluorapatite[3]. The lower solubility of fluorapatite compared to that of hydroxyapatite results in higher acid resistance of the enamel when exposed to demineralization by bacterial acids. Fluoride also decreases the critical pH from about 5.5 to 4.5, thus decreasing the point at which demineralization occurs [5].

Rationale for alternative to fluoride
The ability of fluoride to promote remineralization is limited by the availability of phosphate and calcium ions. Hence, this can be the limiting factor [5]. Moreover, fluoride might be efficient on smooth surface caries but its effect is limited on pit and fissure caries. Overexposure of fluoride can also lead to fluorosis. These limitations have prompted researchers to search for non-fluoridated alternatives for remineralization.

Requirements of a remineralizing agent
- Should deliver calcium and phosphate into the sub- surface of tooth
- Should not promote formation of calculus [6]
- Should work efficiently at acidic pH so as to prevent demineralization during a carious attack
- Should be capable of enhancing the remineralizing properties of saliva.
- Should be able to work in patients with xerostomia since saliva cannot effectively stop the carious process
- The novel materials should be able to show some advantages over fluoride[7].

Indications of remineralizing agents

- An adjunct preventive therapy to decrease caries in high-risk patients.
- Reduce dental erosion in patients with gastric reflux or other disorders.
- To decrease decalcification in orthodontic patients.
- To repair enamel in cases involving white-spot lesions.
- Orthodontic decalcification or fluorosis or before and after teeth whitening and to desensitize sensitive teeth[8].

Remineralizing agents

Various remineralizing agents are available in the market. On the basis of composition, they can be classified as follows :-

(I) Non-fluoridated remineralizing agents

(a) CPP-ACP (Casein Phosphopeptides - Amorphous Calcium Phosphate)

CPPs are phosphorylated casein- derived peptides formed as a result of

Tryptic digestion of casein. The phosphoryl residues of CPP bind to ACP nanoclusters in metasolution, preventing their growth to the critical size which is essential for nucleation and precipitation.

CPP-ACP nanocomplexes decrease demineralization and promote remineralization by localizing ACP in dental plaque, which buffers free calcium and phosphate ion activities, hence aiding in maintaining a state of supersaturation in relation to tooth enamel [9-10]. CPP-ACP complexes are also able to diffuse into the body of the sub-surface enamel lesion because of their small size and ion neutrality. Moreover, the CPPs have been shown to keep fluoride ions in solution, hence increasing the effectiveness of fluoride as a remineralizing agent [11-12]. CPP-ACP has been trademarked as Recaldent, and is available in chewing gums, mouthrinse and confectionary. Moreover, a sugar-free, water-based cream containing RECALDENT ™ (CPP-ACP) is also available in market. (Prospec MI Paste/ GC Tooth Mousse) [13].

(b) Amorphous Calcium Phosphate (ACP) Technology

The ACP technology comprises of a two-phase delivery system in order to prevent the calcium and phosphorous constituents from interacting with each other before its use. In this, calcium sulfate and dipotassium phosphate are the salts which act as sources of calcium and phosphorous. When these two salts are mixed, they yield ACP which can precipitate on to the tooth surface. This precipitated ACP can then dissolve into the saliva and contribute to remineralization [14].

The ACP technology was introduced by Dr. Ming S. Tung [15]. In the year 1999, ACP was introduced into toothpaste called Enamelon. However, one issue with Enamelon™ is that calcium and phosphate are not stabilized, hence the two ions combine into insoluble precipitates even before they are into contact with enamel or saliva. This is unlike Recaldent™, in which the casein phosphoproteins aids in stabilizing calcium and phosphate [16].

(c) Bioactive Glass or Bioglass (Sodium calcium phosphosilicate)

Bioglass acts as a biomimetic mineralizer because it simulates the body's natural mineralizing traits. It also affects cell signals so that restoration of structure and function of tissue may occur [17].

Bioactive glass releases sodium, calcium and phosphorous ions as soon as it comes in contact with saliva. These released ions directly forms hydroxycarbonate apatite(HCA). They also bind to the suface of tooth and continue to release ions and aid in remineralization after the initial application. It has been observed that these particles release ions and convert into HCA for upto 2 weeks. These particles will ultimately transform completely into HCA [18]. In a study, it was observed that composites with incorporated bioglass enhanced remineralization of the surrounding dental tissues [19].

The bioactive glass is traded as Novamin, which was formulated by Dr. Len Litkowski and Dr. Gary Hack[7].

(d) Tri-Calcium Phosphate

Tri-calcium phosphate is developed by a milling procedure which results in fusion of beta tricalcium phosphate (TCP) and sodium lauryl sulfate or fumaric acid.

TCP comprise of calcium environments that are available for reaction with fluoride and tooth enamel. It also possesses structural resemblance with the hydroxyapatite of tooth enamel. The calcium environments of TCP are well protected in order to prevent premature interaction between calcium and fluoride. When it comes in contact with saliva, the calcium, phosphate and fluoride ions of TCP become available to the enamel and promote remineralization of the enamel[20].

(e) Dicalcium Phosphate Dihydrate (DCPD)

Dicalcium Phosphate Dihydrate is a precursor for apatite, which in the presence of fluoride readily converts into fluorapatite. It has been observed that inclusion of Dicalcium Phosphate Dihydrate in dentrifices increase the levels of free calcium ions in plaque fluid, and these remain elevated for upto 12 hours after brushing, in comparison to conventional silica dentrifices [7].

(f) Nanohydroxy Apatite

Nano-hydroxyapatite (n-HAP) is one of the most biocompatible and bioactive materials, and has gained immense popularity in dentistry in recent years. There is similarity between Nano- HAP (n-HAP) and the apatite crystal of tooth enamel in terms of morphology and crystal structure. Hence, it can be substituted for the natural mineral constituent of enamel for repair biomimetically [1].

During the nano-HA remineralization, the acicular crystals of nano-HA get sedimented onto the tooth enamel and directly fill up defects and micropores on demineralized surfaces. As a result there is decrease in defects and cavities of the enamel surface and the increase in hardness of the enamel surface.

Amin M *et al* [21] conducted a study and concluded that commercially available Nano-HAP pastes are effective in decreasing the dentinal hypersensitivity if used for 6 months as a desensitizing agent.

(g) Self Assembling Peptide

Peptide treatment for early caries lesion is the area of current research. Peptide treatment has shown to increase net mineral gain by the combined effect of increased mineral gain and inhibition of mineral loss of tooth.

The beta-sheet-forming peptides, P114 that self assemble themselves to form three-dimensional scaffolds under defined environmental conditions have been shown to nucleate hydroxyl apatite de novo and to have potential applications in mineralized tissue regeneration, mimicking the action of enamel proteins during tooth development. The anionic groups of the P114 side chains attracts calcium ion a, thereby inducing the precipitation of HAP in situ [22]. The use of a bimimetic peptide such as P114 also has the additional benefit

of effecting 'natural' repair by regenerating the mineral itself.

(h) Electric Field-Induced Remineralization

This technique was introduced by Wu in order to remineralize completely demineralized dentinal collagen matrix and also to decrease the time taken in mineralization. This was achieved through this technique in the absence of both calcium phosphates and their analogues with the help of electrophoresis [23].

(II) Herbal remineralizingagents

(a) Xylitol

Xylitol is a non-fermentable sugar alcohol, produced from xylan-rich hardwood such as birch and beech wood. It causes inactivation of *S. mutans* and inhibition of plaque's ability to produce acids and polysaccharides, hence exerting anti-cariogenic effects. It also stimulates increased salivary flow when consumed as chewing gums resulting in increased buffering capacity against acids and high mineral content provides the minerals to remineralize the tooth[24]. Xylitol is not fermented by cariogenic bacteria and, thus, does not lower the pH of plaque hence preventing enamel demineralization and proliferation of bacteria.

Miake *et al* [25] did a study to determine the remineralization effects of xylitol on enamel. They concluded that 20% xylitol induced remineralization at deeper depths of around 50 to 60µm by increasing calcium ion accessibility and movement.

(b) Grape Seed Extract

Grapeseed extract contains proanthocyanidin (PA) which is a type of polyphenol. Polyphenols are plant-derived substances that have anti-inflammatory and antioxidant properties.

Proanthocyanidin acts *via* accelerating the conversion of soluble to insoluble collagen. Collagen matrices which are subjected to proanthocyanidin are biocompatible and inhibit the activity of enzymes like amylase, glucosyl transferase and F-ATPase. PA inhibits glucosyl- transferases which are produced by Streptococcus mutans, thereby resulting in caries inhibition.

A study conducted by Zhao *et al* [26] demonstrated that 1, 2 and 3mg/mL grape seed extract inhibited progression of artificial enamel caries lesion. Epasinghe *et al*. conducted an *in vitro study* and concluded that proanthocyanidin when combined with CPP-ACFP (CPP amorphous calcium fluoride phosphate) shows synergistic effect on remineralization of artificial root caries [27].

(c) Yogurt Extract

Milk proteins inhibit demineralization of enamel by getting adsorbed on the enamel surface. Milk enzymes also plays a role in decreasing the growth of cariogenic bacteria. At acidic pH, calcium ions are released from yogurt and thus helps in remineralization of enamel [28].

A study by Varghese *et al* [29] proved that yogurt extract was effective in inhibiting enamel demineralization of enamel. Another study [30] showed that yogurt extract enhances the saliva secretion which may contribute to its remineralizing properties.

(d) Psidium Cattleianum Leaf Extract

Psidium cattleianum is also known as strawberry guava. The main active agents present in P.cattleianum are flavonoids. These flavanoids, (predominantly kaempferol, quercetin and cyanidin), and tannin (ellagic acid) possess antibacterial activity. These leaf extracts do not contain detectable quantities of calcium, phosphate or fluoride.

P. cattleianum leaf extract acts by inhibiting the protein expression related to general metabolism, especially the carbohydrate metabolism of S. mutans biofilms. As a result, the membrane-associated proteins like glycosyltransferases also get inhibited. Brighenti *et al* [31]. conducted a study and concluded that Psidium cattleianum aids in enamel remineralization in situ.

Crivelaro de Menezes TE *et al* [32] observed that Psidium cattleianum aqueous extracts enhances enamel remineralization through increase in microhardness.

(e) Hesperidine

Hesperidine is a flavanoneglucoside and was first isolated by Lebreton from the white inner citrus peels. It acts by interacting with collagen matrix and induces remineralization. This results in stability of collagen matrix and promotes remineralization as collagen matrix acts like a scaffold for deposition of minerals [33].

Challenges in the implementation of remineralizing agents

Active white spot lesions are more likely to undergo remineralization as compared to inactive lesion [34]. This is because they have surface which is more porous and therefore allows better penetration of ions. Possible approaches which are suggested includes: Acid etching [35], Microabrasion [36], Bleaching/ Deproteination [37-38] or their combination.

Another problem is that the clinical performance of these non-fluoridated remineralizing agents might not necessarily get predicted by the pre-clinical models and therefore these new remineralizing agents still require direct clinical validation to ensure efficacy [39].

Conclusion

Remineralizing agents are part of a new era of dentistry aimed at controlling the demineralization/ remineralization cycle, depending upon the microenvironment around the tooth. The rationale of these agents is the remineralization of early carious and non-carious white lesions, advocating a biological or therapeutic approach rather than the traditional surgical approach. With a clearer understanding of these remineralizing agents and new technologies accessible to dentists, we can provide quality dental care using minimally invasive methods.

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