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REMINERALIZING AGENTS IN PEDIATRIC DENTISTRY: A REVIEW OF LITERATURE

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ABSTRACT

There is a dynamic balance between demineralization and remineralization in the oral cavity that determines the occurrence of dental caries. If the demineralization phase continues for a long period of time, there is mineral loss beneath a relatively intact enamel surface leading to the initial carious lesions known as "white spot lesions" Remineralization of such early carious lesions may be possible with a variety of remineralizing agents, fluoride being the cornerstone in caries prevention. The goal is to manage non cavitated lesions non invasively through remineralization in an attempt to prevent disease progression and improve aesthetics, strength, and function. Hence, the purpose of this review is to have an in-depth knowledge of the various remineralizing agents aiming to treat early carious lesions.

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INTRODUCTION

There is a dynamic balance between demineralization and remineralization in the oral cavity that determines the occurrence of dental caries.[1]If the demineralization phase continues for a long period of time, there is mineral loss beneath a relatively intact enamel surface leading to the initial carious lesions known as "white spot lesions" Remineralization is the process where demineralized enamel is repaired through the recrystallization of tooth enamel mineral salts (Silverstone 1977).[2] Early carious lesions (white spot lesions) can be remineralizedwith a variety of remineralizing agents available nowadays, fluoride being the cornerstone in caries prevention. Remineralizing agents are the agents that helps in remineralization of the early carious lesion by replenishing lost minerals like calcium, phosphate ions into the tooth structure. Hence,

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The goal is to manage non cavitated lesions non-invasively through remineralization in an attempt to prevent disease progression and improve aesthetics, strength, and function.

Ideal properties of remineralizing agents[3]:

- Should deliver calcium and phosphate into the sub-surface
- Should not deliver any excess amount of calcium
- Should interfere with formation of calculus
- Should work at an acidic pH so as to stop demineralization during acid attack
- Should be able to work in xerostomic patients
- Should be able to boost the remineralizing properties of saliva.

Indications

- An adjunct preventive therapy to reduce caries in high-risk patients
- Reduce dental erosion in patients with gastric reflux or other disorders

- To reduce 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.[4]

Various remineralizing agents available nowadays are:

1. Fluoridated agents
2. Non fluoridated agents.

- Casein phospho-peptide-amorphous calcium phosphate (CPP-ACP)
- Amorphous calcium phosphate (ACP)
- Tri-calcium phosphate (TCP)
- Nano-hydroxyapatite (nHA)
- Bioactive glass materials

3. Natural agents

- Xylitol
- Cheese
- Theobromine
- Grape seed extract (GSE)

4. Newer agents

- Ozone
- Self-assembling peptides
- Remineralization using iontophoresis
- Remineralization using lasers.

Fluoride: Fluoride is a known agent since decades that helps in promoting remineralization. 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 micro-organisms and improved tooth morphology.[5] Fluoride might be highly effective on smooth surface caries but its effect is limited on pit and fissure caries. Overexposure of fluoride can also cause fluorosis. All these limitations have prompted researchers to look for non-fluoridated alternatives for remineralization.[3]

Casein phosphopeptide- amorphous calcium phosphate (CPP-ACP): Casein is the major protein group found in milk. This protein nanotechnology was developed by Eric Reynolds and co-workers. The casein phosphopeptides (CPPs) are produced from the tryptic digest of casein, aggregated with calcium phosphate and purified through ultrafiltration.[6]

Mechanism of action: Casein phosphopeptide forms nanoclusters with amorphous calcium phosphate thus providing a pool of calcium and phosphate which can maintain the super saturation of saliva. Since CPP–ACP can stabilize calcium and phosphate in the solution, it can also help in the buffering of plaque pH and so calcium and phosphate level in plaque is increased. Therefore calcium and phosphate concentration within the subsurface lesions is kept high which results in remineralization. It is available as tooth crèmes, toothpastes chewing gums and as varnish along with fluoride.

Amorphous calcium phosphate (ACP): The ACP technology was developed by Dr. Ming S. Tung In 1999. ACP was incorporated into toothpaste called Enamelon and later reintroduced in 2004 as Enamel Care toothpaste.[7]

Mechanism of Action: 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. The conversion of ACP to apatite at physiological pH occurs initially as 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. The surface actions of ACP would, paradoxically, reduce surface porosity and it can fill in surface defects in tooth enamel and cause cosmetic improvements in dimpled, abraded or etched tooth enamel. For these reasons, ACP has been included in prophylaxis pastes and in bleaching gels.

ACP technology: 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.[8] Single phase ACP systems are formulated without water, to keep the ACP from reacting to form apatite.

Tricalcium phosphate (TCP): Tricalcium phosphate is a bioactive formulation of tri-calcium phosphate and simple organic ingredients. It has the chemical formula $Ca_3(PO_4)_2$ Preparation of TCP. Particles of TCP or TCP alloys are coated with sodium lauryl sulphate (SLS) or other surfactants, or with carboxylic acids (such as fumaric acid), polymers and copolymers, by pulverizing the TCP or TCP alloy together with the coating material a planetary ball mill for several days. It has been suggested that the organic coating prevents undesirable interactions with fluoride, but may dissolves away when particles contact saliva.

It 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). 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. The average size of the TCP particles can then be adjusted by milling them. Typically, particles range from 0.01 to 5 microns in size. Beta TCP is less soluble than alpha TCP, and thus in an unmodified form is less likely to provide bioavailable calcium.

Nano hydroxyapatite: Hydroxyapatite (HA) is one of the most biocompatible and bioactive materials.[9] Nano-sized particles are similar to the apatite crystal of tooth enamel in morphology, crystal structure and crystallinity. Toothpaste based on nano-hydroxyapatite (nHA) has been commercially available in Japan since the 1980s, and was approved as an anti caries agent in 1993. Nano-hydroxy and fluorapatite have been synthesized using a sol-gel technique in an ethanol base. 10% nano-hydroxyapatite (n HA) is optimal for remineralization of early enamel caries.

Bioactive glass: A bioactive material is defined as a material that stimulates a beneficial response from the body, particularly bonding to host bone tissue and to the formation of a calcium phosphate layer on a material surface. Bioactive glass (Bioglass) was invented by Dr. Larry Hench in 1960s. It acts as a biomimetic mineralizer matching the body's own

mineralizing traits while also affecting cell signals in a way that benefits the restoration of tissue structure and function. Bioglass in an aqueous environment 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.

Xylitol: Xylitol is a non-cariogenic five-carbon sugar alcohol that occurs naturally in plants and is used as a substitute for sugar. The dental significance of xylitol was discovered in Finland in the early 1970s. Xylitol is believed to be a "tooth-friendly", non-fermentable sugar alcohol. The main properties of this sweetener is that it is not fermented to acids, less formation of plaque and reduced number of Mutans streptococci in saliva. The perception of sweetness obtained from consuming xylitol initiates the body to secrete saliva that acts as a buffer system against the acidic environment created by the microorganisms in the dental plaque. Increase in salivary pH can raise the falling pH to its neutral pH within few minutes of xylitol consumption. This indicates that xylitol can induce remineralization of deeper layers of demineralized enamel by facilitating Ca_2^+ movement and accessibility.

Cheese: There has been keen interest of researchers in cheese as a potential Remineralizing agent. Several experimental results have reiterated the efficacy of cheese as a remineralizing agent. Cheese is a powerful sialogogue. It elevates levels of calcium, and/or possibly phosphorus, in dental plaque which might inhibit demineralization through a common-ion effect, or might enhance remineralization during the periods of high pH.

Rugg- Gunn et al (1975) demonstrated that eating cheese after a sugar- containing snack raised the pH of plaque back to a safe level.[10]

Theobromine: Theobromine (3,7dimethylxanthine) is a white crystalline powder of methylxanthine family. It differs from caffeine by only one methyl group (1,3,7 dimethlyxanthine). It is believed theobromine, in the presence of calcium and phosphate, forms hydroxyapatite crystallites of an increased size that strengthen the enamel, making it less susceptible to acid attack, which eventually leads to cavitation. Falster et al. 1993 conducted a study and it was shown that pure cocoa powder prevents dental caries. An increase in the percentage of cocoa extract in the diet caused a proportionate reduction in dental caries. It was suggested that cocoa extract has an anticaries potential. The cariostatic property of theobromine accounts for the presence of two types of substances: one which exhibits antiglucosyltransferase and the other anti-bacterial activity.

Grape seed extract: Grape seed extract is a rich source of proanthocyanidins which strengthen collagen-based tissues by increasing collagen cross-links. Grape seed extract decreases the degradation rate of the dentin matrix after bacterial collagenase treatment, indicating an inverse relationship between concentration of GSE and collagen solubilization by enhancing remineralization.[1]

Ozone: The word ozone was first introduced by Schonbein in 1840. Ozone (O3) is a powerful oxidizing agent which neutralizes acids, affects the cell structures and metabolism of microorganisms. Ozone has immediate direct effect on carious lesion by eliminating the acid producing bacteria and by delaying indirect effect by promoting the remineralization of the lesions. Al-Duboni in 2013 conducted a study to evaluate the efficiency of ozone alone and with a remineralizing solution and concluded that Ozone treatment either alone or combined with a remineralizing solution is effective for remineralization of initial fissure caries lesions.[11]

Self-assembling peptides: Amino acids are the building blocks of peptides which further forms protiens.[12] The location of amino acid side chains which have a terminal –COOH or –NH2, can be designed in a way so as to control the interaction between adjacent peptides.[13] The interaction of these amino acids can be modified in a way such that they are capable of organizing themselves into various architectures. (Acar a) This is known as self assembly of molecules.[14]

The remineralization occurs through incorporation of calcium and phosphate ions from saliva after the peptide forms a new enamel matrix.[15]A white spot lesion of the enamel contains porosities. Monomeric peptide P11-4, on application penetrates these porosities owing to its low viscosity. Under the influence of the conditions present in a carious environment, the peptide undergoes self assembly to form a viscous fibrous scaffold. The anionic groups of peptide P11-4 present in the scaffold, attract calcium ions and are capable of precipitation of hydroxyapatite crystals de novo. The nucleator attracts ions from tissue fluids and organizes them into a crystalline structure.[16]

Remineralization using iontophoresis: Iontophoresis is the process of depositing ionic drugs into tooth surfaces with low voltage electric current. The term iontophoresis is simply defined as ion transfer (ionto = ion; phoresis = transfer). This method can able to achieve deeper penetration of drug ions in to the desired target area than obtained with only topical application. Due to an application of current iontophoresis technique, remineralization takes place at a faster rate in the incipient lesion as the main mechanism of action of fluoride is by the formation of calcium fluoride (CaF2) layer on the tooth surface which acts as a fluoride reservoir.[17,18]

Lasers in remineralization: LASER stands for Light amplification by stimulated emission of radiation. The use of lasers in caries prevention was first suggested in 1972 using a ruby laser. It has been proposed that the lasers can be used as an adjunct to conventional fluoride therapy in remineralizing the tooth structure. Hossain et al. reported that the combination of CO_2 Laser with 2% NaF was more potent in preventing dental caries than CO_2 laser irradiation alone.

CONCLUSION

Recently the focus has been shifted in the development of methodologies for the use of non-invasive treatment for early carious lesions. One such non-invasive treatment of early carious lesions is remineralization.

Understanding the remineralization process allows dentist to treat the lesion before cavitation. Remineralization of whitespot lesions may be possible with a variety of currently available agents containing fluoride, bioavailable calcium and phosphate, and casein phosphopeptide in-amorphous calcium phosphate, self-assembling peptide etc. 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**.**

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