ISSN No:-2456-2165

Enamel Remineralization: A Novel Approach to Treat Incipient Caries

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Abstract:- Remineralization is defined as the process whereby calcium and phosphate ions are supplied from a source external to tooth to promote ion deposition into crystal voids in demineralized enamel to produce net mineral gain. The remineralization produced by saliva is less and also a slow process, therefore remineralizing agents are required. Biomimetic approaches to stabilization of bio available calcium, phosphate, and fluorideions and the localization of these ions to non-cavitated caries lesions for controlled remineralization shows great promise for the non-invasive management of dental caries. The aim of this article is to give a brief update about remineralization agent aiming to "treat early caries lesion" non-invasively.

Keywords:- *Calcium-phosphate-based systems; Remineralization; fluoride; Non-invasive treatment.*

I. INTRODUCTION

Dental caries is an infectious microbiologic disease of the teeth that results in localized dissolution and destruction of the calcified tissues. An intricate coordination exists among bacteria, diet and salivary components. Bacterial action on dietary fermentable carbohydrates leads to the production of acids, which diffuses into the tooth and dissolve the carbonated hydroxyapatite mineral, a process called demineralization. Decrease 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.

Tooth remineralisation is a naturally occurring process in the oral cavity. It is defined as a process in which calcium and phosphate ions are sourced to promote ion deposition into crystal voids in demineralised enamel[1]. Remineralisation remains imperative towards the management of non-cavitated carious lesions and prevention of disease progression within the oral cavity. The process also has the ability to contribute towards restoring strength and function within tooth structure.

The process of caries formation is a cycle of remineralization and demineralization with various stages being either reversible or irreversible. White spot lesions (WSLs) are manifestations of the earliest stage of caries progression and are capable of being reversible[2].

II. MECHANISM OF NATURAL MINERALIZATION

Remineralization occurs on a daily basis due to the presence of saliva. Under normal physiological conditions (ie. pH 7), saliva is supersaturated with calcium and phosphate ions, required for effective remineralization and maintenance of the enamel surface integrity. Therefore, it can act as a natural buffer to neutralise acid and allow demineralised tooth tissues to be remineralised. If pH of the mouth becomes more acidic, the demineralisation process continues, which promotes the development of cavities. The critical pH of enamel is 5.5. At this pH, there is no mineral dissolution and no mineral precipitation. In the event of pH rise, the deposition of mineral is back to the tooth structure[3].The calcium and phosphate ions re-enter enamel when normal pH of saliva (ie. 6.8) is restored and thus remineralization occurs.

However, net salivary remineralization is a slow process due to the low ion concentration gradient from saliva into the lesion. Thus, the presence of additional extrinsic sources of stabilized Ca^{2+} and $PO4^{3-}$ ions could augment the natural remineralization potential of saliva by increasing diffusion gradients favouring faster and deeper subsurface remineralization.

III. REMINERALIZING AGENTS

A. Fluorides
B. Non-Fluoride remineralizing agents

a) Calcium-phosphate systems
   - Stabilized calcium phosphates
   - Crystalline calcium phosphates
   - Unstabilized calcium phosphates

b) Polyphosphate systems
   - Sodium trimetaphosphate
   - Calcium glycerophosphate
   - Sodium hexametaphosphate

c) Biomimetic agents and systems
- Dentin phosphoprotein 8DSS peptides
- P11-4 peptides
- Leucine-rich amelogenin peptides
- Poly(amido amine) dendrimers
- Electrically accelerated and enhanced remineralization
- Nanohydroxyapatite

d) Natural products
- Galla chinensis
- Hesperidin
- Gum Arabic

e) Ozone
f) Calcium Phosphate Ion Clusters (CPICs)
g) Lasers

IV. FLUORIDES

Fluoride is the most commonly used remineralizing agent. When the acid attacks the enamel surface, the pH begins to rise and fluoride present in the microenvironment causes enamel dissolution to stop. As the pH rises, new and larger fluoride crystals containing fluorapatite form, thereby, reducing the enamel demineralization and promoting remineralization. Fluoride varnish is one of the most commonly used products available commercially.Most fluoride varnishes contain 5% NaF (22,600 ppm fluoride),which allows the varnish to adhere to tooth surfaces in the presence of saliva. Fluoride varnish can be applied quickly and easily. It sets rapidly on tooth surfaces so that gagging andswallowing are minimized.[4]

Fig. 1: Fluoride Varnish

While under physiological conditions, fluoride mechanisms are often enough to remineralize early lesions, these are not adequate in highly cariogenic oral environments.[5] Evidently, there is a need for new-age remineralization technologies with an ability to close the gap in fluoride's remineralizing efficacy, and effect a fuller consolidation of carious lesions.

V. CALCIUM PHOSPHATE SYSTEMS

Presently, the remineralization in high caries risk patients is largely met by calcium phosphate systems.The presence of extrinsic sources of Ca^{2+} and PO_4^{3-} ions can increase diffusion gradients and augment the F^- ion-mediated remineralization. A number of unique calcium phosphate remineralization systems have been commercialized in recent years and categorized into 3 types:
- stabilized amorphous calcium phosphate systems
- crystalline calcium phosphate systems
- unstabilized amorphous calcium phosphate systems.

- **Casein Phosphopeptide-Amorphous Calcium Phosphate (CCP-ACP):** This remineralization system was developed based on the idea that the tryptic digestion of milk caseinate produced multiphosphorylated CPP, substantially increasing the milk protein's solubility and ability to stabilize Ca^{2+} and PO_4^{3-} ions.[5]

Fig. 2: Tooth Mousse Plus

CPP-ACP nanocomplexes buffer the free calcium and phosphate ion activity, thereby helping in sucrose maintaining the role of super saturation. The CPP stabilizes the calcium and phosphate in a metastable solution facilitating high concentration of the Ca^{2+} and PO_4^{3-} which diffuses in the enamel lesion when CPP-ACP comes in contact with the lesion.[6]Once present in the enamel subsurface lesion, the CPP-ACP would release the weakly bound calcium and phosphate ions, which would then deposit into crystal voids. The CPPs have a high binding affinity for apatite, hence, on entering the lesion, the CPPs would bind to the more thermodynamically favoured surface of an apatite crystal face. Hence, the CPPs, may have an important role in regulating anisotropic crystal growth and also inhibiting crystal demineralization.[7]

- **Functionalized β-Tricalcium Phosphate:** Crystalline β-tricalcium phosphate (β-TCP) was modified by coupling it with carboxylic acids and surfactants to yield functionalized β-tricalcium phosphate (fTCP) [Karlinsey et al. 2010]. The purpose of functionalizing β-TCP was to create barriers preventing premature fluoride-calcium interactions, thereby allowing it to act as a targeted low dose delivery system when applied to teeth via dentifrices or mouthwashes [Karlinsey and Pfarrer, 2012]. It was designed primarily to boost F– ion activity on the tooth surface, with remineralization driven mostly by salivary Ca2+ and PO43– ions.[5]
- **Unstabilized amorphous calcium phosphate:** It is a technology that applies calcium ions and phosphate ions separately so that amorphous calcium phosphate forms intra-orally.[8]

VI. POLYPHOSPHATES

Sodium trimetaphosphate (STMP)is a condensed inorganic phosphate.It is able to strongly bind to phosphate sites on enamel surface and remain adsorbed for a longer time compared to other phosphates. This leads to the formation of a protective layer on the enamel surface that limits acid diffusion of ions during a cariogenic challenge.[5]

VII. BIOMIMETIC AGENTS AND SYSTEMS

Oral care products containing fluoride are effective in remineralizing enamel but do not have the potential to promote formation of organized apatite crystals. Presently, there is an attempt to shift from reparative to regenerative biomineralization therapies, wherein diseased dental tissues are replaced with biologically similar tissues. Enamel regeneration is however particularly challenging as mature enamel is acellular and does not resorb or remodel itself unlike bone or dentin. Advances in tissue engineering methods have yielded biomimetic methods that have demonstrated a strong potential for regenerating the hierarchical enamel microstructure.[5]

- **Dentin Phosphoprotein-Derived 8DSS Peptides**: Dentin phosphoprotein (DPP) is the most abundant non-collagenous extracellular matrix component in dentin and is known to play a critical role in tooth mineralization. Human DPP contains numerous repetitive aspartate-serine-serine (DSS) nucleotide sequences that are believed to promote hydroxyapatite (HA) formation, with studies showing that DPP can generate HA crystals in calcium phosphate solutions [George et al., 1996; Prasad et al., 2010].
- **Self-Assembling P11-4 Peptides**: This peptide self-assembles into hierarchical 3-dimensional fibrillar scaffolds in response to local conditions such as high ionic strength and acidic pH found in the lesion body. The P11-4 fibrillar matrix has a high affinity for Ca^{2+} ions and acts as a nucleator for de novo HA formation resulting in remineralization of the lesion body.[5]
- **Amelogenin:**The amelogenin-rich enamel organic matrix plays a critical role in regulating the growth, shape, and arrangement of HA crystals during enamel mineralization. Several promising strategies have been proposed to replicate the complex enamel microstructure using synthetic amelogenin-based systems.
- Disadvantages are that the protein is difficult to extract and store as well as the growth of the repaired enamel layer also takes an extended amount of time, making it potentially unsuitable for clinical use.[5]
- **Poly (Amido Amine) Dendrimers:**Poly (amido amine) (PAMAM) dendrimers are highly branched polymers. These amelogenin-inspired dendrimers are referred to as “artificial proteins” as they can imitate the functions of organic matrices in modulating the biomineralization of tooth enamel. Several in vitro studies have demonstrated that amphiphilic, carboxyl-terminated, and phosphate terminated PAMAM dendrimers exhibited a strong tendency to self-assemble into hierarchical enamel crystal structures [Chen et al., 2013, 2014, 2015; Wu et al., 2013; Yang et al., 2011]. The new crystals created by the PAMAM organic templates had the same structure, orientation, and mineral phase of the intact enamel, with the HA nanorods closely paralleling the original prisms [Chen et al., 2013].
- **Electrically Accelerated and Enhanced Remineralization (EAER):** EAER is a recently developed remineralization technology targeted at initial and moderate enamel lesions with the treatment objectives of preserving all healthy tissue, restoring the full depth of the caries lesion, and improving mechanical properties of the treated enamel. [5]
- **Nanohydroxyapatite:** Synthetic nanohydroxyapatite is considered one of the most biocompatible and bioactive materials having similar morphology, structure, and crystallinity to the apatite crystal within enamel. The nano-sized particles can strongly bind to enamel surfaces and with fragments of plaque and bacteria. The small size of the particles that compose nanohydroxyapatite considerably increase its surface area for binding as well as allowing it to act as a filler to repair small holes and depressions on the enamel surface.[5]

VIII. NATURAL PRODUCTS

A. Galla Chinensis:

It is a leaf gall produced by parasitic aphids; it is hypothesized that polyphenols present in Galla chinensis interact with and stabilize the organic matrix remnants, thereby blocking the ion diffusion pathways, and slowing demineralization [Huang et al., 2017; Zhang et al., 2015].

Fig. 3: Galla chinensis

B. Hesperidin:

A citrus flavonoid, and gum arabic, an Acacia exudate, are other natural products that have been found to suppress acid dependent demineralization and boost remineralization even under fluoride-free conditions.[5]

C. Ozone:

Ozone is the layer of earth's stratosphere protecting us from the harmful radiations. It is an effective oxidizing agent that operates by attacking thiol groups of cysteine amino acid and decimates the cellular membrane of carious bacteria. Ozone is capable of altering acidogenic and aciduric microorganisms to normal commensals permitting remineralisation to occur.[3]

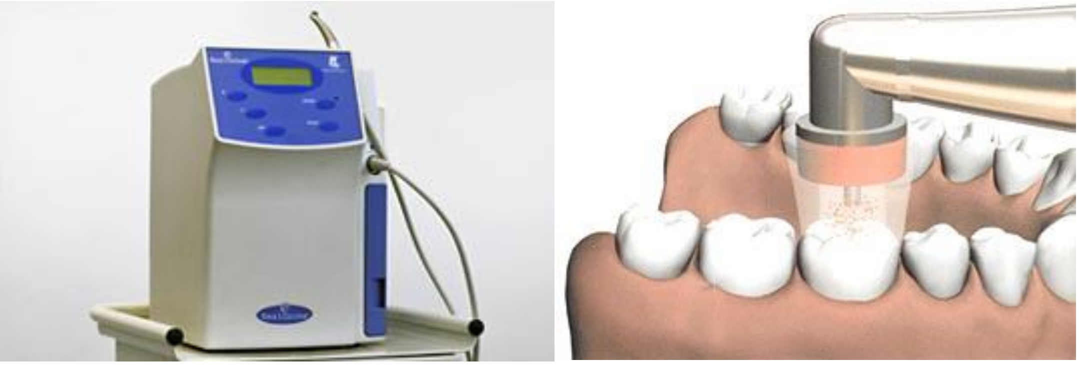

Fig. 4: Healozone

Currently, HealOzone (Ka Vo GmbH, Germany) remineralizing solution, comprising xylitol, fluoride, calcium, phosphate and zinc, is recognised for treatment for caries. It can be used as 2100 ppm of ozone 5% at a flow rate of 615cc/minute for 40seconds. The mechanism of HealOzone action is related to ozone's potent antimicrobial properties and its ability to oxidize proteins associated with caries.[3]

D. Calcium Phosphate Ion Clusters (Cpics):

Although a range of materials, such as composite resins, ceramics, and amalgam, have been developed for the restoration of tooth enamel, they have failed to achieve permanent repair because of the imperfect combination between these foreign materials and the native enamel. However, the HAP layer newly regrown by epitaxial remineralization can be integrated into native enamel such that the repair would be permanent, and this process may be developed as an effective cure for enamel erosion in clinical practice.

The key to ideal enamel repair is the precise duplication of its hierarchical and complicated structure. Calciumphosphate ion clusters (CPIC), can grow a thin layer of protective shield on teeth. The transparent, crystal-like mineral has a structure resembling fish scales and a high mechanical strength which is almost similar to the enamel of a human tooth. This rationally designed material (composed of CPICs) can be used to produce a precursor layer to induce the epitaxial crystal growth of enamel apatite, which mimics the biomineralization crystalline-amorphous frontier of hard tissue development in nature.[9] After repair, the damaged enamel can be recovered completely because its hierarchical structure and mechanical properties are identical to those of natural enamel. The suggested phase transformation–based epitaxial growth follows a promising strategy for enamel regeneration.[9]

E. Lasers:

Lasers appear to be beneficial in preventing caries of sound enamel surfaces. By changing surface structures and their physical properties, including melting and re-crystallization of the enamel's hydroxyapatite crystals, the acid resistance can be improved and the enamel's demineralization can be significantly inhibited. The organic matrix of enamel is influenced by laser treatment, and the acid solubility of enamel is reduced, with a decrease in carbon in the enamel.[10]

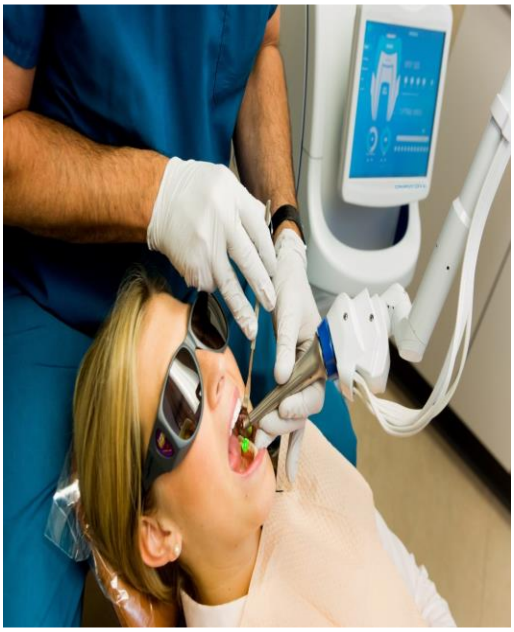

Fig. Laser application

Several types of lasers, such as erbium-doped yttrium aluminium garnet (Er:YAG), neodymium-doped yttrium aluminium garnet (Nd:YAG), and carbon dioxide (CO_2), have been used for caries inhibition.

IX. CONCLUSION

Goal of modern dentistry is recently focusing on non-invasive management of non-cavitated lesions involving remineralization systems to repair the enamel and improve aesthetics, strength and function. In individuals at risk of disease, procedures should be instituted to prevent the onset of disease, and in those in whom disease is already evident, the lesions should be treated non-invasively by remineralization with bioavailable calcium, phosphate, and fluoride ions to restore the strength and aesthetic appearance of the lesion and to increase resistance to future acid challenge. Further studies may provide further improvements in the development of novel remineralization treatments. With a clearer understanding of the implementation of these remineralizing agents, a more favourable relationship can be established to attempt remineralization.

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