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Non-Fluoridated Remineralization Agents in Dentistry

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Abstract

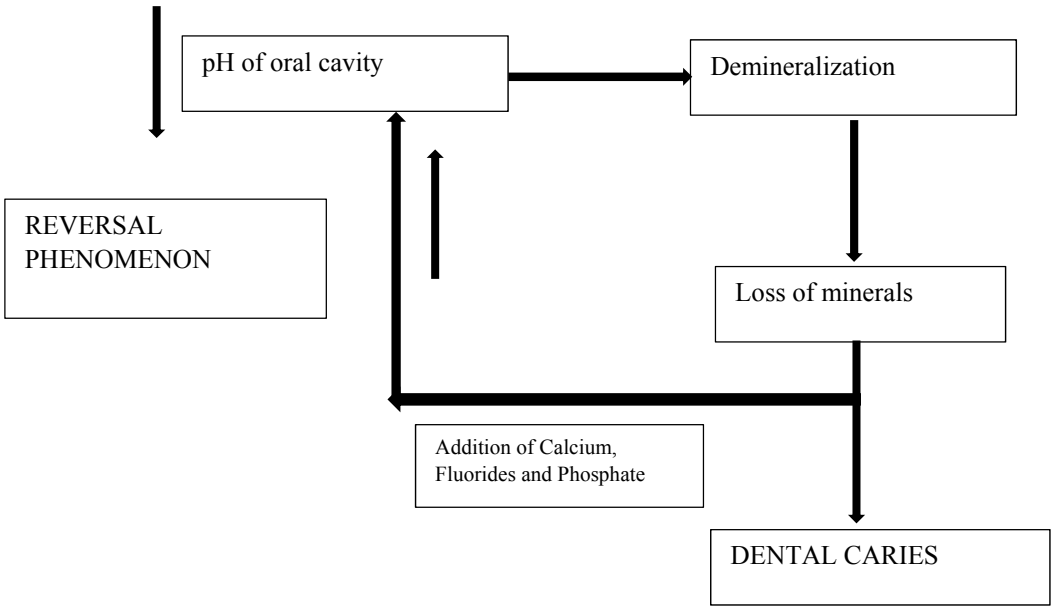
Managing non cavitated dental carious lesions non-invasively through remineralisation agents is a main goal and attempt to prevent further carious progression, and to improve and maintain the form and function of the teeth and oral cavity. The application of remineralisation agents to the non cavitated lesions has led to the development of novel technologies to arrest the further carious progression and prevent the decalcification process. This paper discusses the various non-fluoridated remineralisation agents available and their mode of action to preserve the functional integrity of the tooth structure.

Keywords: Remineralization- Demineralization, Non- Fluoridated agents, Casein derivatives

INTRODUCTION

Dental caries is an infectious microbiologic disease that results in destruction of calcified tissues. Caries is a dynamic process which occurs when demineralization exceeds remineralisation. But progression of dental caries is a slow process and during early stages non-invasive intervention can convert the lesion to inactive state from an active state. [1]

Early diagnosis of incipient carious lesions has led to a new transaction in preventive dentistry in the form of remineralisation. The ultimate treatment modality for caries management is use of remineralizing products. Presently fluoride, calcium phosphate-based systems, calcium sodium phosphosilicate etc that help in remineralization are available commercially. Recent investigations have primarily focused on various calcium phosphate based technologies which are designed to supplement and enhance fluoride's ability to restore tooth mineral.[2] This article discusses the different types of non-fluoride remineralizing agents and their mode of action and clinical applications.



Demineralization – Remineralization cycle

ALTERNATIVE TO FLUORIDES

- Fluoride and its derivatives are very effective on smooth-surface caries; but its effect would seem to be more limited on pit and fissure caries.
- A high-fluoride strategy cannot be followed to avoid the potential for adverse effects (e.g., fluorosis) due to overexposure to fluoride.

IDEAL REQUIREMENTS OF REMNIERALIZING AGENTS [2]

- Diffuses into the subsurface or delivers calcium and phosphate into the subsurface
- Does not deliver an excess of calcium
- Does not favour calculus formation
- Works at an acidic pH
- Works in xerostomia patients
- Boosts the remineralizing properties of saliva
- For novel materials, shows a benefit over fluoride

MEASURES TO PREVENT DEMINERALIZATION

1. **Newer Chemoprophylactic agents**
   Traditionally products like chlorhexidine, triclosan etc, were used but due to their drawback being short retention time in oral cavity, these materials failed. Recently, a mineral binding micellar drug delivery system was developed, which not only binds fast within tooth surface, but also releases encapsulated drug over a longer period of time.[3]This was accomplished by covalently conjugating the tooth binding moieties to the ends of pluronic copolymer using chick chemistry.[4] Recent advances in novel active plant extracts includes water soluble component of Labiatae family; berry juice of Vaccinium plant,an essential oil composition from Coleus forskohlii ; they all showed significant inhibitory action against Streptococcus mutans. [5-7]
2. **Anti microbial peptides (AMP's)**
   Recently AMP's have gained attention due to their robust killing activity against a wide spectrum of bacteria's, including drug resistant strains. These peptides are amphiphatic mixture of alpha helical & beta sheet & has overall cationic charge. They bind to LPS (negatively charged) of microbial membrane, and then they penetrate inside the cell & kill by intracellular mechanisms. Reynolds et al, recently found AMP's can be derived from milk protein casein.[8]
3. **Probiotics**
   They are live micro-organisms which when administered in adequate amount, confer a health benefit on the host (WHO). It acts by either disrupting plaque biofilm or production of antimicrobial compounds that inhibit oral bacteria. Long term consumption of milk containing L.rhamuosus GG strain reduces initial caries. Ingestion of L. reuteri ATCC 55739, Bifidobacterium DN-173 010 reduces S.mutans in saliva. Mollstam et al , discovered new strains of Lactobacillus , including L.reuteri CF2-7F (ATCC PTA-4965) ,MF2-3(ATCC PTA-4964), FJ-Prodentis (ATCC PTA-5289) & FJ3 (ATCC PTA-5290), that have good antimicrobial action on S.mutans.[9]
4. **Replacement therapy**
   The so-called replacement therapy is a measure that has emerged with advances in gene engineering & DNA recombinant technology, which has shown to reduce pathogen in oral flora. Mutated strains of S.mutans lack ability to metabolize carbohydrates into acids. Non-acid producing S.mutans strain BCS3-L1 is developed which is active against other S.mutans strain to replace naturally occurring cariogenic strains in oral cavity. This strain is less cariogenic & more stable and is currently awaiting evaluation for its efficacy in humans. In another study, the ability of S.mutans to produce extracellular glucans is blocked in a mutation by deleting the GTF-C gene.[10]
5. **Bacteriophage therapy**
   Bacteriophage are viruses that attack bacteria. Its characteristics include target specificity, patients allergic to antibiotics , cost effectiveness & no side effects. Delise & Rotkowski have described bacteriophage lytic for S.mutans. Recently lytic phage is also discovered for S.salivarius. Hence, the isolation and identification of lytic bacteriophage to oral pathogens is considered to be an approach towards phage therapy of dental caries. [11]
6. **Photodynamic therapy (PDT)**
   They have promising results for inactivation of microorganisms related to caries. It is a treatment which utilizes light for activation of photosensitizing agent in presence of oxygen which results in reactive radical's formation inducing cell death. PDT has antimicrobial properties in a process called ―photodynamic inactivation or photodynamic antimicrobial therapy‖. For PDT against S.mutans; erythrosine is appropriate photo sensitizer because it acts against these Gram positive bacteria; also has hydrophilic tendency& even at low concentrations may have photodynamic effects. Considering erythrosine; there should be light source with wavelength close to 530 nm; which may be achieved with low cost LED's.[12]
7. **Sugar substitute**
   They are alternative sweeteners which may be artificial or natural. Recently natural sweeteners have gained prime attention; which includes Stevia. Stevia is an accepted sugar substitute of family Astereciae that contains Rebaudioside A & Stevioside which possess natural sweetening & pharmaceutical properties. Its focusing characteristics includes 0 carb, 0 glycemic index, 0 calories, 100 % natural, 300 times sweeter than sucrose & its nontoxicity. It is anticariogenic and antiperiodontophatic. It is active against S.mutans, S.sorbinus, L.acidophilus, and C.albicans. It has anti plaque effect by reducing biofilm formation & is also healing agent at periodontium level. It has numerous systemic effects too. Still implications of using Stevia in pediatric population is awaited.[3]

Immunizations

Recent work has focused on using S.mutans antigens for initiating an antibody reaction & finally elimination of S.mutans colonization in the body. This is mediated by secretory IgA antibodies. The antigen I/II specific sIgA is able to inhibit S.mutans from its adherence to hydroxyapatite & its subsequent colonization on tooth surface (Hajishengallis).[13] Methods like vaccine focused on glucosyltransferase enzymes & glucans binding protein of bacteria has been tested; which shows an exaggerated immune response, inhibiting aggregation of S.mutans in animal models to some degree.[14]

NON-FLUORIDE REMINERALIZING AGENTS

1. **Complex of casein phosphopeptides–amorphous calcium phosphate (CPP-ACP):**

   CPP–ACP is the acronym for a complex of casein phosphopeptides (CPPs) and amorphous calcium phosphate (ACP). Caseins are a heterogeneous family of proteins predominated by alpha 1 and 2 and β-caseins. CPPs are phosphorylated casein-derived peptides produced by tryptic digestion of casein. CPP-ACP has shown to reduce demineralization and enhanceremineralization of the enamel subsurface carious lesions.[15]

   CPP also is believed to have an antibacterial and buffering effect on plaque and interfere in the growth and adherence of Streptococcus mutans and Streptococcus sorbinus.[16] The Recaldent technology was developed by Prof. Eric Reynolds of the University of Melbourne. CPP– ACP has been trademarked Recaldent and has been launched in sugarless chewing gum and confectionery. More recently, a sugar-free, water-based cream containing RECALDENT™ (CPP–ACP) (GC Tooth Mousse/Prospec MI Paste) has been made available to dental professionals.[17]

2. **Amorphous calcium phosphate**

   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.[18] The ACP technology was developed by Dr. Ming S. Tung. 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.[19]

3. **Sodium calciumphosphosilicate (bioactive glass)**

   When bioactive glass comes in contact with saliva, it rapidly releases sodium, calcium, and phosphorous ions into the saliva that are available for remineralization of the tooth surface. The ions released form hydroxycarbonate apatite (HCA) directly. They also attach to the tooth surface and continue to release ions and remineralize the tooth surface after the initial application. These particles have been shown to release ions and transform into HCA for up to 2 weeks. Ultimately, these particles will completely transform into HCA.[20] 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. 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. [21]

4. **Calcium carbonate carrier – SensiStat**

   The SensiStat technology is made of arginine, bicarbonate, an amino acid complex, and particles of calcium carbonate, a common abrasive in toothpaste. The arginine complex is responsible for adhering the calcium carbonate particles to the dentin or enamel surface and allows the calcium carbonate to slowly dissolve and release calcium that is then available to remineralize the tooth surface. The SensiStat Technology was developed by Dr. Israel Kleinberg of New York. The technology was first incorporated into Ortek's Proclude desensitizing prophy paste and later in Denclude. [22]

5. **Nano-hydroxyapatite**

   Nano-hydroxyapatite had the potential to remineralize initial enamel lesions. A concentration of 10% nano-hydroxyapatite may be optimal fo remineralization of early enamel caries.[23]

6. **The trimetaphosphate ion**

   The potential mode of action of trimetaphosphate ion (TMP) is likely to involve in adsorption of the agent to the enamel surface, causing a barrier coating that is effective in preventing or retarding reactions of the crystal surface with its fluid environment, and hence reducing demineralization during acid challenge. Gu highlighted the role of sodium TMP as a templating analog of dentin matrix phosphoproteins for inducing intrafibrillar remineralization of apatite nanocrystals within the collagen matrix of incompletely resin infiltrated dentin.[24]

7. **Alpha-tricalcium phosphate**

   It is used in products such as Cerasorb, Bio-Resorb, and Biovision. Tricalcium phosphate (TCP) has also been considered as one possible means for enhancing the levels of calcium in plaque and saliva. Some small effects on free calcium and phosphate levels in plaque fluid and in saliva have been found when an experimental gum with 2.5% alpha-TCP by weight was chewed, when compared to a control gum without added TCP. [25]

8. **Dicalcium phosphate dehydrate**

   Inclusion of dicalcium phosphate dehydrate (DCPD) in a dentifrice increases the levels of free calcium ions in

plaque fluid, and these remain elevated for up to 12 hours after brushing, when compared to conventional silica dentifrices.[26] Calcium from DCPD was incorporated into enamel and detected in plaque 18 hours post-treatment after brushing with a DCPD dentrifice which fosters improved remineralization of teeth in combination with fluoride.

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. 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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