ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)
IJDSIR : Dental Publication Service
Available Online at: www.ijdsir.com
Volume – 3, Issue – 3, May - 2020, Page No. : 459 - 465

Non-fluoride anticaries agents for caries management – An evidence-based review in current dental practice.

[1]Dhanya.K, Post graduate student, Department of Pedodontics and Preventive Dentistry, Faculty of Dental Sciences, M S Ramaiah University of Applied Sciences, Bangalore-54, Karnataka, India

[2]Prakash Chandra, Senior Professor, Department of Pedodontics and Preventive Dentistry, Faculty of Dental Sciences, M S Ramaiah University of Applied Sciences, Bangalore-54, Karnataka, India

[3]Latha Anandakrishna, Professor and HOD, Department of Pedodontics and Preventive Dentistry, Faculty of Dental Sciences, M S Ramaiah University of Applied Sciences, Bangalore-54, Karnataka, India

Corresponding author: Dhanya.K, Post graduate student, Department of Pedodontics and Preventive Dentistry, Faculty of Dental Sciences, M S Ramaiah University of Applied Sciences, Bangalore-54, Karnataka, India

Citation of this Article: Dhanya.K, Prakash Chandra, Latha Anandakrishna, "Non-fluoride anticaries agents for caries management –An evidence-based review in current dental practice.", IJDSIR- May - 2020, Vol. – 3, Issue -3, P. No. 459 – 465.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

Dental caries is a highly prevalent multifactorial disease and has been a major health problem for many centuries. The goal of modern dentistry is to manage non cavitated carious lesions non-invasively through remineralization to prevent disease progression and improve aesthetics, strength and function. Biomimetic approaches to stabilization of bioavailable calcium, phosphate, fluoride ions 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. This review gives a brief update about the current remineralization agents aiming to "treat early carious lesion" non- invasively.

Keywords: Remineralization, Anti Caries Agents, Non fluoride anti-caries agents.

Introduction

Demineralization and remineralization are common phenomenon which occurs inside our oral cavity. Remineralization is the body's natural repair mechanism for subsurface non-cavitated carious lesions. It is a process by which calcium and phosphate from saliva or other topical sources diffuses into the tooth and with the help of fluoride helps to rebuild on existing crystal remnants.[1] The rebuilt crystalline surface is composed of a veneer of well-formed mineral most likely similar to Fluor apatite which is much more resistant to acid attack compared to original structure.

Whether dental caries development is progressive, static or reversal is mainly dependent on a balance between demineralization and remineralization. Therefore, any factor which can push this balance toward the proceeding

of remineralization can be utilized as a weapon in the battle against dental caries.[2] This review gives a brief update about the current re-mineralizing agents aiming to treat early carious lesion non-invasively.

Classification of non-fluoride anticaries agents

Classification suggested for alternatives to fluoride is based on mode of action and according to the constituents. Mode of action is again classified into anti plaque agents, those neutralizing bacterial acid and agents which interacts with tooth enamel. The non-fluoride anti caries agents are classified based on constituents into phosphorus containing, calcium containing, metals, antimicrobials, antibiotics and miscellaneous agents.[3] Each of these anti-caries agents are discussed in detail below.

1) Anti plaque agents (Anti microbials and antibiotics)

a. Antimicrobial agents: Acid accumulation in dental plaque is the driving force for demineralization and caries development. Antimicrobial approaches, including the use of antimicrobial agents, represent a valuable measure for caries control.[4] Antimicrobial agents are generally delivered into the oral cavity by various delivery agents such as mouthwashes or toothpastes. It can also be applied in the form of gels, sprays chewing gums/lozenges or varnishes to slowly release the drug and achieve prolonged inhibitory effect.

b. Topical antibiotics: Topical antibiotics not absorbed from the GI tract can be used in mouth rises and gels for plaque control & for gingivitis. Eg: Vancomycin, Bacitracin, Kanamycin, Niddamycin, Polymyxin-B are used commonly. They have the disadvantage that these can induce bacterial resistance problems, hence the use of these antibiotics has been reduced.[5]

c. Chlorhexidine: Chlorhexidine is a bis-biguanide. It consists of two 4 chloro-phenyl rings and two bis-biguanide groups symmetrically connected to a hexamethylene chain. This provides the molecule with both hydrophilic and hydrophobic properties. Chlorhexidine is effective against gram positive, gram negative organisms, yeast, fungi and viruses. Chlorhexidine has shown to inhibit bacterial growth and bio film formation. Chlorhexidine exhibits anti plaque and anti-bacterial properties.[6] A major part of the effectiveness of chlorhexidine is due to its substantivity. It is commonly used in dentistry as chlorhexidine mouth rinse and varnish.

d. Metals: A whole range of metals has been investigated in many different types of clinical trials as anti caries agents. They have many disadvantages to be used like organo-leptic properties when used in oral care products as simple salts (eg. Aluminum, Molybdenum, Barium and Copper) Because of potential toxicity there is a restriction in the concentration at which they can be safely used.[7]

i) Silver: In dentistry, silver compounds have been used as early as the 1840s, when silver nitrate was used for reducing the incidence of caries in the primary dentition. Later it was used as a caries preventing agent for permanent molars, a cavity sterilising agent and as a dentine desensitiser.[8] In the 1960s, silver was advocated to combine with fluoride as an anti caries agent presumably for a combined beneficial effect.

ii) Silver nitrate : The use of AgNO3 was reported in the 1840s'. It was the first silver compound used for arresting caries. Silver nitrate can penetrate both sound and carious dentine, vital and non- vital dentin, and have a mild, self-limiting, localized effect on the pulp.[8]

iii) Silver diammine fluoride (SDF): Silver diammine fluoride can be used as an anti caries agent mainly due to its ability to reduce the solubility of tooth tissue against chemical acid challenge, and to facilitate enamel remineralization. It has also been shown to inhibit bacterial growth by utilizing bacterial and biofilm models. The exact role and mechanism of action of silver

compounds is still unclear. In vitro studies revealed that the possible mode of action may be linked with its interaction with tooth tissue, as well as its antibacterial ability on cariogenic bacteria.[8] For clinical use of SDF, the manufacture recommends the patient to rinse the mouth with water or saline after topical application of SDF to remove the excess agent. Rubber dam or Vaseline is recommended to avoid accidental contact of gingival and mucous tissue and deep cavities. SDF solution should be diluted to decrease the chance of pulpal irritation.[7]

e. Sugar substitutes: Dietary sugars such as sucrose, glucose and lactose can be fermented by MS such as S. mutans and S. sobrinus to produce lactic acid which is involved in the etiology of dental caries. Sugar substitutes exhibit potential anti-caries effect in several aspects including: Inhibition of insoluble glucan synthesis from sucrose; Decrease in mutans streptococcus numbers in whole saliva and plaque; Increase in the buffering capacity and pH of dental plaque; and Interference with enamel demineralization and an increase in enamel remineralization.[9]

i) Xylitol : Xylitol is a naturally occurring sweetener found in the fibers of many fruits and vegetables, including various berries, corn, husks, oats, and mushrooms. It is one of the most extensively studied sugar substitutes. It prevents streptococcus mutans from binding to sucrose molecule. Which results in increased concentration of amino acids and ammonia thus neutralizing plaque acids with increasing salivary flow.[9] The salivary proteins have a stabilizing effect which enhances remineralization.

2. Anticaries agents neutralizing bacterial acid

a) Calcium carbonate carriers**:** Calcium carbonate as an abrasive was first added widely to toothpaste formulations during 1850's. The elevation in the concentration of calcium ion and in pH results in an increase in the degree of saliva saturation value with respect to hydroxyapatite, favouring apetitic mineral deposition in the lesions. This is the basis for calcium carbonate caries-preventive effect. Octa calcium carbonate containing toothpastes possesses good retention properties on oral proteinaceous surfaces, such as mucous membrane, tongue and pellicle.[10,11] Potential benefit of calcium carbonate particles retained in plaque is their ability to act as a calcium reservoir, releasing calcium as they dissolve during acid challenges and thus increasing calcium levels in plaque[2].

3. Agents which interact with tooth enamel

a. Casein derivatives: Casein is a phosphoprotein in bovine milk. It accounts for 80 percent of its total protein, primarily as calcium phosphate stabilized micellular complexes. It was first discovered by Prof. Reynolds at the School of Dental Science at the University of Melbourne in Australia. They are used alone as CPP (Casein Phosphor Peptide), CPP-ACP (Casein Phospho Peptides with Amorphous Calcium Phosphate), CPP-ACPF (Casein Phosphor Peptide with Amorphous Calcium Fluoride Phosphate). Technical name is casein phospho-peptides-amorphous calcium phosphate (CPP-ACP).[12]

i. Casein Phospho Peptides (CPP): Originated from alpha and beta casein containing specific sequence acid motif. Consists of 3 serine po4 and followed by 2 glutamic acid residues cluster sequence. At neutral pH these acid motifs are highly charged have ability to bind to minerals Ca, Zn, Mn, Se, Fe, Seryl group which are the main site for calcium. It modulates bio- availability of calcium phosphate levels by maintaining ionic phosphate and calcium super saturation to increase remineralization. [12,13]

ii. Amorphous Calcium Phosphate (ACP): Control the precipitation of CPP with calcium and phosphate ions. It has the advantage of availability of calcium, phosphate, and fluoride in one product. Each molecule of CPP can

bind up to 25 calcium ions, 15 phosphate ions, and 5 fluoride ions. Under alkaline conditions the calcium phosphate is present as an alkaline amorphous phase complexed by the CPP referred to as Casein Phospho peptide- Amorphous Calcium Phosphate (CPP-ACP).[12, 14]

iii. CPP-ACP technology: CPP-ACP binds readily to the surface of the tooth as well as to the bacteria in the plaque surrounding the tooth and deposits a high concentration of ACP near the tooth surface. It diffuses into dental plaque displaying a buffering capacity counteracting pH drop caused by acidogenic bacteria. A high concentration of Ca and P in the dental plaque makes it acid resistant remineralized enamel and reduce the risk of enamel demineralization. CPP keeps calcium and phosphate in an amorphous non crystalline state which can easily enter enamel. Increase in the concentration of ions in the lesion results in the formation of HA or fluorapatite via crystal growth. Direct binding of CPP to plaque bacterial surface results in reduction of ca and Pi diffusion into the plaque.[12,13,14]

b. Tri-meta-phosphate ion (TMP): The potential mode of action of TMP is not fully understood but is likely to involve adsorption of the agent to the enamel surface, thereby slowing the exchange of ions with the oral environment, and hence reducing demineralization during acid challenge. The effect of TMP has been found to be additive to fluoride[4].

c. Dicalcium phosphate dehydrate: CaHPo4.2H2O chemically called as Calcium Hydrogen Phosphate Dihydrate. Obtained from brushite crystalized from aqueous solutions at PH< 6.5. DCPD (brushite) and (OCP) octa calcium phosphate are the precursors in the formation of apatite. DCPD is added to tooth paste both for caries protection coupled with F containing compounds such as NaF/Na_2PO_3. Inclusion of 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[3]. DCPD increases the level of free calcium in the plaque fluid remain elevated to 12 hrs. DCPD is unique for its F stability. It improves the effects of fluoride in the mouth. It is more effective in preventing plaque pH drop compared to silica coupled fluoride. toothpastes**.**

d. Nano hydroxyapatite: Hydroxyapatite in nano particle crystallite form. Thermodynamically stable form of calcium phosphate nano particles in the 20 nm size ($1/850^{th}$ the width of a human hair) mimic the building blocks of natural enamel. The first toothpaste containing synthetic HAP as biomimetic as an alternative to remineralization was introduced in Europe in 2006. Hydroxyapatite crystals can effectively penetrate the dentin tubules and obturate them and can cause closure of the tubular openings of the dentin with plugs within 10 minutes as well as a regeneration of a surface mineral layer. Effective as an enamel repair material and anti caries agent with pH <7. [3,15]

They produce bioactive calcium and phosphate which penetrates more into porosities beneath the demineralized region as potential remineralizing substances. Nano HA has the potential to precipitate on the lesion surface because of its strong bioactivity coupled with physical and chemical with natural enamel. A concentration of 10% nano-hydroxyapatite is optimal for remineralization of early enamel caries. Hydroxyapatite has been used in toothpastes (as fillers), Pit-and-fissure sealants, GIC and Composites. NHA containing dentifrices can be recommended in children and those who are concerned with dental fluorosis. It is strongly recommended in to xerostomic patients with diminished amount of saliva. It can occlude the dentinal tubules so can be used in the treatment of dentin hypersensitivity.[15]

e. Bioactive glass materials

NovaMin is one of the bioactive glass ceramic material that provide calcium and phosphate upon reaction which are all elements naturally found in the body. Novel features include its ability to act as a biomimetic mineralizer, matching the body's own mineralizing traits. It can bind to existing bone and act as scaffolds for new bone growth. They can affect cell signals benefiting restoration of tissue function and structure. NovaMin has been incorporated into several products, including dentifrices and gels. It is a breakthrough in remineralization. Bio-glass in an aqueous environment immediately begins surface reaction in 3 phases: a) Leaching and exchange of cations, b) Network dissolution c) Precipitation of calcium and phosphate to form apatite layer.[16]

NovaMin reacts with saliva allowing sodium ions to exchange with hydrogen ions, raising ph. Net negative charge on surface & loss of sodium-localized breakdown of silica network-formation of sialanol groups. Sialanol groups precipitates into silica rich surface layer(3-6hrs). The Ca $(PO)_4$ layer crystallizes into the carbonated HA layer (bonding layer). The bioactive glass surface reactions from implantation to formation of 100-150 µm CAP layer takes 12-24hrs).[3,16]

f. Tri calcium phosphate: TCP is a new hybrid material created with a milling technique that fuses beta tricalcium phosphate (ß-TCP) and Sodium lauryl sulfate or fumaric acid resulting in a "functionalized" calcium and a "free" phosphate, designed to increase the efficacy of fluoride remineralization[1]

Tricalcium phosphate has the chemical formula $Ca_3(PO4)_2$, and exists in two forms, alpha and beta. TCP is like apatite structure and possesses unique calcium environments capable of reacting with fluoride and enamel. While the phosphate floats free, these exposed calcium environments are protected, preventing the calcium from prematurely interacting with fluoride. TCP provides catalytic amounts of calcium to boost fluoride efficacy and may be well designed to coexist with fluoride in a mouth rinse or dentifrice because it will not react before reaching the tooth surface.

One of the drawbacks of TCP is the formation of calcium-phosphate complexes or if fluorides are present, formation of calcium fluoride, which would inhibit remineralization by lowering the levels of bioavailable calcium and fluoride. For this reason TCP levels have to be kept very low in order of less than 1%. Studies have concluded that TCP provided superior surface and sub-surface remineralization compared with a 5000 ppm fluoride and CPP-ACP.[18] Products available with TCP include a 5000 ppm sodium fluoride dentifrice (Clinpro™ 5000 1.1% Sodium Fluoride Anti-Cavity Toothpaste) and a 5% sodium fluoride varnish (Vanish™ 5% Sodium Fluoride White Varnish with TCP).

g. Sucrose free polyol gums

Polyol gums offer a valuable adjunct in caries prevention and remineralization. The first chewing gum developed with the aim of reducing caries & oral health was released in Finland in 1975. Chewing gums provides oral clearance and saliva stimulation, plaque pH neutralization and remineralization.[19] Chewing gums particularly sugar-free gums, offer a valuable adjunct to caries prevention and remineralization program.

Studies have demonstrated the caries preventing qualities of frequent use of chewing gums sweetened with dietary sugar alcohols-xylitol and sorbitol. Potential negative effects of chewing gum including its potential to be a choking hazard in young children, be subject to littering, exert a laxative effect and to contribute to temporo-mandibular dysfunction (TMD). Therefore, it should be reminded not to give gum to children younger than school age and to dispose of chewed gum responsibly.[19]

h. Polymers: Polymers have been used to restore decayed teeth since the late 1940's. New strategies have emerged recently, both for preventive treatments and to remineralize decalcified dental structures affected by caries.

i) Caries Infiltration with Low-Viscosity Polymers.

Monomers modified to enable impregnation of white spot lesions with photo cross linkable materials of low viscosity. These infiltrates occlude the lesion porosity and blocks further diffusion pathways for cariogenic acids. Polymer resins are much more resistant to acid degradation than enamel apatite. Further cavitation is prevented after infiltration and photo polymerization. [20]

ii) Polymers for Assisted Remineralization of Carious Dentin.

Guided tissue mineralization represents a novel strategy in collagen bio-mineralization. This strategy utilizes nanotechnology and biomimetic principles to achieve intrafibrillar and extra-fibrillar remineralization of a collagen matrix in the absence of apatite seed crystallites. Calcium and phosphate ions are sequestered by biomimetic analogues of non-collagenous proteins.[20]

iii) Polymer Induced Liquid Precursor (PILP) System.

A recent polymer-assisted bio mineralization method. PILP process is based on the action of minute amounts of acidic polypeptides which are added to a remineralization solution. The anionic polymer functions being sequestering calcium ions, which then builds up a charge to sequester phosphate or carbonate, thus inducing liquid-liquid phase separation in the crystallizing medium and hence facilitating formation of mineral inside collagen fibrils. Several anionic polymers could sequester calcium and phosphate ions and form amorphous precursors that could infiltrate the intrafibrillar spaces in demineralized collagen. These includes poly-L aspartic acid (PASP), poly-L-glutamic acid (PGLU), poly vinyl phosphonic acid (PVPA) and polyacrylic acid (PAA).[20]

i. Self-assembling peptide: Peptide treatment for early caries lesion is the area of current research. Anionic P114 is a safe rationally designed self-assembling peptide. Curodont™ Repair is a novel treatment, developed by Credentis, for the early treatment of tooth decay and other dental lesions (prior to cavitation). The treatment is based on a novel technology called Curolox™. Curodont™ Repair is a liquid that contains a peptide called P 11-4.

When applied to the tooth the peptide diffuses into the subsurface micro-pores and forms a 3D scaffold made up of small fibres. At certain peptide concentrations P 11-4 switches from a low viscosity isotropic liquid to an elastomeric gel (pH 7.4). The anions of the P114 side chains would attract ca++ ions inducing mineral deposition in situ. The scaffold mimics proteins found in teeth development and supports hydroxyapatite (a calcium phosphate ceramic which makes up to 50% of bones) crystallisation around it to regenerate tooth enamel, over a period of three months. The use of biomimetic peptide such as P114 has the advantage of effecting natural repair by regenerating the mineral itself.

Before application, the tooth is prepared and cleaned which involves polishing (with normal prophy paste), wiping with diluted NaOCl (placed on a cotton swab), etching (20 seconds; 35% phosphoric acid) and rinsing with water and drying. This preparation takes about 3-5 minutes depending on experience. Curodont™ Repair is generally applied once but can be applied again after a couple of months, if needed, for better cosmetic result. Treatment may lead to the reversal or arrest of the decay, if caught in the early stages[21].

Conclusion

The goal of modern dentistry is the non-invasive management of non cavitated caries lesion involving

remineralization systems to repair the enamel. With the clear understanding of these remineralizing agents we will be able to create a more favourable relationship in which remineralization can occur**.** It is important for dental professional to be aware that it takes significant time to establish the benefits of a new technology.

References

1. Featherstone JD, Doméjean S. The role of remineralizing and anticaries agents in caries management. Advances in dental research. 2012 Sep;24(2):28-31.
2. Ten Cate JM. Novel anticaries and remineralizing agents: prospects for the future. Journal of Dental Research. 2012 Sep;91(9):813-5.
3. Kalra DD, Kalra RD, Kini PV, Allama Prabhu CR. Nonfluoride remineralization: An evidence-based review of contemporary technologies. J Dent Allied Sci 2014; 3:24-33
4. Chen F, Wang D. Novel technologies for the prevention and treatment of dental caries: a patent survey. Expert Opin Ther Pat. 2010 May; 20(5): 681–694
5. Agarwal R, Singh C, Yeluri R, Chaudhry K. Prevention of Dental Caries-Measures beyond Fluoride. Oral Hyg Health 2014; 2: 122.
6. J Autio-Gold. The Role of Chlorhexidine in Caries Prevention. Operative Dentistry, 2008, 33-6, 710-716
7. KG Chhabra, Preetha J Shetty, Prasad K V V et.al. The beyond measures: Non fluoride preventive measures for dental caries. JIOH 2011; 3(2):1-8
8. J.J.-Y. Peng, M.G. Botelho, J.P. Matinlinna. Silver compounds used in dentistry for caries management: A review journal of dentistry 2014;531-54.
9. Pramod Yadav, Bakshish Kaur, Ruchi Srivastava et al. Sugar substitutes and health: IOSR Journal of Dental and Medical Sciences2014;13(8):68-75
10. R J M Lynch Bebington, J M ten Cate. The anti-caries efficacy of calcium carbonate-based fluoride toothpastes: International Dental Journal (2005) 55, 175–178.
11. Goswami M, Saha S, Chaitra TR. Latest developments in non-fluoridated remineralizing technologies: journal of Indian society of pedodontics and preventive dentistry 2012:1(30):1-6
12. Reynolds EC. Casein phosphopeptide-amorphous calcium phosphate: the scientific evidence. Adv. Dent. Res. 2009; 21(1):25–9.
13. Gupta R, Prakash V. CPP-ACP complex as a new adjunctive agent for remineralisation: a review. Oral Health Prev Dent. 2011; 9(2):151–65.
14. Tooth mousse launched. British Dental Journal. 2004 Oct 23; 197(8):509–509.
15. Kantharia N, Naik S, Apte S, Kheur M, Kheur S, Kale B. Nano hydroxyapatite and its contemporary applications. JDRSD 2014; 1:15-9
16. Amit kumar, Swati Singh, Gautam Thumar, Aditya Mengji. Bioactive Glass Nanoparticles (NovaMin®) for Applications in Dentistry. Journal of Dental and Medical Sciences 2015; 14:30-35.
17. AlAmoudi SA, Pani SC, AlOmari M. The effect of the addition of tricalcium phosphate to 5% sodium fluoride varnishes on the microhardness of enamel of primary teeth. International journal of dentistry. 2013.
18. Michael WJ Dodds Journal of the Irish Dental Association 2012; 58 (5): 253-261
19. Thais Thomé, Maria C.G. Erhardt, Ariene A. Leme et.al. Emerging polymers in dentistry. Advanced Polymers in Medicine Springer International Publishing Switzerland 2015;265-295.
20. Curodont™ Repair and Curodont Protect™ for the treatment and prevention of tooth decay. Horizon Scanning Centre 201