REVIEW ARTICLE

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Non Fluoridated Remineralizing Agents – A Review

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ABSTRACT:

Dental caries is the most prevalent disease affecting mankind. It affects the calcified tissue of the teeth, characterized by demineralization of the inorganic portion and destruction of the organic substance of the tooth. It is a reversible process until cavitation occurs and thus many remineralizing agents are available to halt and reverse the demineralization process before cavitation occurs. Fluoride is the most commonly used remineralizing agent. Although its efficiency is undoubtedly proven, it is still not ideal as its linked to fluorosis and limited efficiency in altered Ca and P levels. Thus in this review we aim to evaluate the literature on efficiency of Non Fluoridated remineralizing agents.

Keywords: Remineralizing agents, Non-Fluoridated, Agents.

INTRODUCTION

Dental caries is defined as a microbial disease of the calcified tissue of the teeth, characterized by demineralization of the inorganic portion and destruction of the organic substance of the tooth. Dental caries remains as one of the most widespread disease of mankind and is a single most common chronic childhood disease.[1]

The oral cavity is a battlefield of activities of demineralization and remineralization. Demineralization occurs from a complex chemistry between bacteria, diet and salivary components. A drop in the pH in the oral cavity results in demineralization and the oral environment becomes unsaturated with mineral ions relative to a tooth's mineral content. A goal of modern dentistry is to manage non-cavitated caries lesions non-invasively through remineralization in an attempt to prevent disease progression and improve aesthetics, strength, and function.[1]

Remineralization is defined as the process whereby calcium and phosphate ions are supplied from a source external to the tooth to promote ion deposition into crystal voids in demineralized enamel, to produce net mineral gain.

Ideal properties of remineralizing agents:[2]

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

Fluoride is a known agent since decades that helps in promoting remineralization. The efficacy of fluoride in preventing dental caries is beyond dispute. However, extensive use of fluoride mainly in the form of dentifrice has contributed to a rising incidence of dental fluorosis, particularly in preschool children, due to chronic ingestion of these products. Furthermore, the ability of fluoride to promote remineralization and inhibit caries formation in the oral environment is limited by the availability of calcium and phosphate in saliva, and ultimately in plaque fluid; thus in salivary dysfunction conditions, remineralization rate is not sufficient enough to prevent caries process

with consequent rampant caries. Fluorides are highly effective on smooth-surface caries than on pit and fissure caries; In certain parts of the world, it has been suggested that fluoride exposure should be limited.[3-4]

So there is a need for other remineralization agents alternative to fluorides. These agents are Non-fluoride topical remineralizing agents (NFTRA). They agents are commercially available in the form of toothpaste, chewing gum and varnishes. They have also been tested in other vehicles such as lozenges, mouth rinse and in foods and beverages.[5]

Some of the currently available NFTRAs are CPP-ACP, Sodium Calcium Phosphosilicate, Polyols, Nano-hydroxyapatite, Tricalcium phosphate, Dicalcium phosphate dihydrate and Theobromine.

REMINERALIZING AGENTS

Casein Phospho Peptide -Amorphous Calcium Phosphate (CPP-ACP):

There are three types of phosphopeptide based products: CPP, CPP-ACP, which contain 18% calcium ion and 30% phosphate ion in weight, and casein phosphopeptides with amorphous calcium fluoride phosphate (CPP-ACPF).CPP are peptides that are derived from the milk protein casein that are complexed with calcium and phosphate. CPP contain a cluster of phosphoseryl residues that stabilize nanoclusters of ACP in metastable solution. The CPP binds to spontaneously forming ACP nanoclusters and prevents their growth to the critical size required for nucleation and precipitation. [6]

The anti-caries action of CPP derivatives has a topical effect based on the following: modulation of bioavailable calcium phosphate levels because they maintain ionic phosphate and calcium super-saturation; buffer effects on plaque; increased remineralization and reduction of the hydroxyapatite solution; and difficulty for Streptococcus mutansand Streptococcus sobrinusto adhere and grow. CPP will bind to surfaces such as plaque, bacteria, soft tissue and dentin (owing to its sticky nature), providing a reservoir of bioavailable calcium and phosphate in the saliva and on the surface of the tooth. The ACP is released from the CPP complex during oral acidic challenges. Under these conditions, the CPP bound ACP would buffer plaque pH, and it would dissociate to calcium and phosphate ions. This would counteract a drop in pH thus preventing enamel demineralization. The increased calcium phosphate in the plaque buffers free calcium and phosphate ion activities and maintains a state of super-saturation of the ions in close approximation with the tooth.[6]

CPP-ACP is commercially available as MI paste and GC Tooth Mousse. MI paste is the first product for professional use that contains RECALDENT™ (CPP-ACP).

Sodium Calcium Phosphosilicate:

Bioactive glass is made of synthetic mineral containing sodium, calcium, phosphorous and silica (sodium calcium phospho silicate) which are all elements naturally found in the body. NovaMin is a bioactive glass in the class of highly biocompatible materials that were originally developed as bone-regenerative.[7] These materials are reactive when exposed to body fluids and deposit hydroxycarbonate apatite (HCA), a mineral that is chemically similar to natural tooth mineral. [8]

When these particles comes in contact with saliva or water, they release sodium, calcium and phosphorous ions into the saliva which are available for remineralization of the tooth surface. These particles also attach to the tooth surface and continue to release ions and re-mineralize the tooth surface after the initial application. These particles have been shown, in in-vitro studies, to release ions and transform into HCA for up to two weeks. Ultimately these particles will completely transformed into HCA which is the mineral our teeth and bones are made of and results in 80 % tubular occludance and desensitization.[8]

Polyols:

Xylitol, sorbitol, saccharin and aspartame have all been used as sugar substitutes for the

purpose of reducing dental caries in a wide variety of products including sweets, candies, chewing gum, oral hygiene products and pharmaceutical products.[9]

Xylitol is one of the non-sugar sweeteners permitted for use in foods. White spot lesions were observed to remineralize during clinical studies of xylitol. Xylitol is regarded as the best of all nutritive sugar substitutes with respect to caries prevention. Levine et.al, in a briefing paper on xylitol, described xylitol as exhibiting both passive and active anti-caries properties.[10]

Remineralization is due the increased flow of saliva, rich in calcium and phosphate. Anti-caries action of xylitol is likely to be due to its effect on plaque and plaque organisms. But the biggest disadvantage of polyols is their liability to cause osmotic diarrhoea if eaten in large amounts. [11]

Nano Hydroxyapatite:

Hydroxyapatite (HA) is one of the most biocompatible and bioactive materials and is widely used to coat artificial joints and tooth roots. Nano-sized particles are similar to the apatite crystal of tooth enamel in morphology, crystal structure and crystallinity. Recent studies have reported that addition of Nano-hydroxyapatite to toothpastes and mouthwashes potentially remineralize the artificial carious lesions.[12]

Tri Calcium Phosphate:

Tri Calcium Phosphate (TCP) or functionalized Tri Calcium Phosphate (f-TCP), is a unique technology involving mechano-chemical ball milling of tri-calcium phosphate with simple organic ingredients that results in a functionalized or bioactive tri-calcium phosphate. Tri calcium phosphate was selected over other calcium phosphate systems because it appears as a transitional phase in hydroxyapatite conversion; is biocompatible and bioactive in the oral cavity; and contains sites within its structure that can be activated with simple organic molecules. TCP is available as alpha tri calcium phosphate and functionalized beta tri calcium phosphate. Beta TCP is less soluble than alpha TCP, and thus in an unmodified form is less likely to provide bio-available calcium. It is used in products such Cerasorb®, Bio-Resorb® and Biovision®.[13]

Unlike other calcium-based additives, only low levels of functionalized TCP are needed to produce strong, acid-resistant mineral nucleation without negatively affecting fluoride's proven benefits. Additionally, tri-calcium phosphate can be custom-tailored for a variety of oral care products.[36] TCP can be combined with a ceramic such as titanium dioxide, or other metal oxides, to limit the interaction between calcium and phosphate, and make the material more stable in solution or suspension.[13]

The major advantage of this calcium phosphate system is that it is stable in aqueous environment and does not affect the fluoride activity when added in the dentifrices. It has been suggested that fluoride combination with f-TCP provides greater remineralization, fluoride uptake and also decreases the dose of fluoride required to achieve the same degree of remineralization.[14]

Dicalcium Phosphate Dihydrate (DCPD):

Dicalcium phosphate dihydrate (DCPD/CaHPO4.2H2O) is an acidic calcium phosphate phase which can form from tooth mineral. The reaction of DCPD with fluoride to form fluorapatite (FAP) occurs very rapidly under appropriate conditions and this can be a mechanism for the incorporation of permanently bound fluoride.[15]Under acidic conditions, the presence of calcium fluoride facilitates the conversion of DCPD to FAP which has better crystallinity. [16]

Theobromine:

Theobromine (3,7dimethy-lxanthine), a white crystalline powder, is an alkaloid readily available in cocoa and chocolate. Its levels are higher in dark chocolates than in milk chocolates. Higher-quality chocolate tends to contain more Theobromine than lower-quality

chocolate. The mean Theobromine content of cocoa beans is appropriately 20.3 mg/g.[17]

REVIEW OF LITERATURE

Author	Year	Type of study	Material used	Duration of the study	Results
JS Wefel et.al[18]	1987	In-vitro	Di Calcium Phosphate Di-hydrate	1 Day	Di Calcium Phosphate Di-hydrate treatment appears to remineralize artificial caries-like lesions effectively
Vogel GL et.al[19]	1998	In-vivo	Alpha-Tricalcium-Phosphate	1 Day	The deposition of a mineral reservoir in plaque and saliva by the experimental gum may help resist future cariogenic challenges
T Ooshima et.al[20]	2000	In-vitro	Cocoa bean husk extract	-	Significant reduction in adherence of S Mutants to hydroxyapatite crystal
Sullivan RJ et.al[21]	2001	In-vivo	Di Calcium Phosphate Di-hydrate	6 Days	The Di Calcium Phosphate Di-hydrate dentifrice was significantly superior than the silica dentifrice in preventing caries, which indicates that Di Calcium Phosphate Dihydrate alone exhibits anti-caries efficacy
Matsumoto M et.al[22]	2004	In-vitro In-vivo	Cocoa bean husk extract	-	Significant reduction in caries incidence was observed when the extract was introduced through drinking water with minimum effective concentration being 1mg/ml of water
Burt BA[23]	2006	Review	Sorbitol and Xylitol chewing Gum	-	The regular use of xylitol sweetened gum is a way to prevent caries, and it

					can be promoted as a public health preventive measure.
Y. Shibata et.al[24]	2008	In-vitro	β-Tricalcium Phosphate, Hydroxyapatite	10 Days	The mineral density of carious dentin exposed to β-Tricalcium phosphate increased more than that with hydroxyapatite.
Machiulskiene V et.al[25]	2009	In-vivo	Sorbitol/Carbamide Gum; Sorbitol Gum; Xylitol Gum; Control Gum; No Gum	3 Years	Caries preventive effect of chewing sugar-free gum is related to the chewing process itself rather than being an effect of gum sweeteners or additives, such as polyols and carbamide
RuchiVashisht et.al[26]	2010	Ex- Vivo	CCP-ACP	14 Days	CPP-ACP showed significant remineralization in artificial enamel lesions
Peter Tschoppe et.al[27]	2010	In-vitro	Nano-hydroxyapatite, Amine Fluoride	5 Weeks	Toothpaste containing Nano-hydroxyapatite revealed higher remineralizing effects compared to amine fluoride tooth pastes
Gianmaria F. Ferrazzano et.al[28]	2011	In-vivo	CPP-ACP	1 Month	CPP-ACP are able to promote remineralization of early enamel lesions
Goplpayegani et.al[29]	2012	In-vitro	Bioactive Glass, Fluoridated dentifrice	5 Days	Bioactive Glass have a greater effect on remineralization of carious lesions when compared to Fluoride containing dentifrice
J ShanthiSwaroop et.al[30]	2012	In-vitro	Nano-hydroxyapatite	1 Day	Use of biomimetic Nano-hydroxyapatite as remineralizing agent holds promise as a new synthetic enamel biocompatible

					material to repair early carious lesion
ArunBalakrishnan et.al[31]	2013	In-vitro	CPP-ACP, f-TCP, Calcium Sodium Phosphosilicate	30 Days	CPP-ACP showed better remineralizing potential than the other 2 agents
PadminiSomasundaram et.al[32]	2013	In-vitro	CPP-ACP, Fluoridated Dentifrice	14 Days	Enamel surface treated with CPP-ACP paste exhibited least lesion depth followed by Fluoridated Dentifrice
ShafieAhamed et.al[33]	2014	In-vitro	Bioactive Glass, Fluoridated Dentifrice, CPP-ACP, CPP-ACPF	10 Days	Bioactive Glass has shown better remineralizing agent
Adit Bharat Mehta et.al[34]	2014	In-vitro	Bioactive Glass, CPP-ACP	10 Days	Application of Bioactive Glass, more effectively remineralized the carious lesion when compared with CPP-ACP
Duygu et.al[35]	2014	In- Situ	Xylitol, Sorbitol, Xylitol- Sorbitol	21 Days	The use of sugar-free chewing gum had no effect on the Ca/P ratio of demineralized enamel surfaces. The hardening of the demineralized enamel surfaces may vary according to the type of chewing gum.
Su- Yeon Jo et.al[36]	2014	In-vitro	f-TCP CPP-ACP 1,000-ppm fluoride	2 Weeks	f-TCP and CPP-ACP containing toothpastes seemed to be more effective in reducing white spot lesions than 1,000 ppm fluoride containing toothpastes
SaranyaMony et.al[37]	2015	In-vitro	Bioactive Glass, Fluoridated Dentifrice	15-30 Days	Bioactive Glass was found to be effective in improving the Ca/PO_4 ratio and hardness in a

					demineralized enamel than Fluoridated dentifrice
Tetsuo Nakamoto et.al[38]	2016	Invitro	Theobromine	-	Theobromine is a better alternative than fluoride. Theobromine can be used as an ingredient of dentifrices and even if swallowed accidentally, there are no adverse effects.

CONCLUSION

Non fluoridated remineralizing agents alone when used also has clinical efficacy but usage of these agents along with fluoridated agents have superior efficacy. So these agents are to be used only as adjuncts to fluoridated agents so that clinical efficacy is superior and efficient.

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How to cite this article: Srilatha KT, Nikitha BS, Sukumaran A, Bhargavi M, George R. Non Fluoridated Remineralizing Agents – A Review. Arch of Dent and Med Res 2016;2(3):58-66.