Review Article

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# Tooth Remineralization: Averting the Dental Decay

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## ABSTRACT

**Background**: Dental caries has been a major public health problem for many centuries as it is a highly prevalent multifactorial disease. Modern dentistry aims at non-invasive management of non-cavitated carious lesions via remineralization so as to prevent progression of the disease and to improve strength, aesthetics and function of teeth. Currently, various new technologies have been introduced for emphasis on enamel remineralization. Various remineralizing techniques and agents have been researched, and most of them gave significant positive results when used clinically. The purpose of this review article to put a light on various available remineralizing agents along with some recently introduced agents.

**Keywords:** Caries, CPP-ACP, Demineralization, Fluoride, Remineralization, Xylitol.

## INTRODUCTION

Worldwide, dental caries contributes 10 times more burden of oral disease than periodontal or any other common oral conditions.[1]Being a pandemic' disease dental caries has high prevalence worldwide and has a high percentage of nontreated carious cavities which causes discomfort, pain and functional limitations.[2] Caries is a cyclic event characterized by demineralization and remineralization and not a continuous and unidirectional demineralization of the mineral phase.[3] Domination of demineralization process leads to cavitation. It involves minerals loss at a depth below the enamel surface and mineral ions transportation from the advancing front toward the plaque and acid ions from the plaque to the advancing front.[4]

The availability of a variety of agents containing fluoride, bioavailable calcium and phosphate, and casein phosphopeptide amorphous calcium phosphate, self-assembling peptide remineralization of white spot lesions and carious lesions has been made possible. For ion deposition promotion into crystal voids in demineralized enamel and to produce net mineral gain, calcium and phosphate ions have been supplied from a source external to the tooth. The ongoing trend further bridges the traditional gap between prevention, non-invasive and surgical procedures.[5]

*Historical Aspect*

For dental caries treatment, minimally invasive approach incorporates the detection, diagnosis, interception and dental caries treatment on the microscopic level.[6]

It has been established in 1980s that fluoride can cause remineralization of demineralized enamel thereby controlling caries lesion.[7]**Fazzi et al (1997)** demonstrated the formation of fluorapatite crystals since the fluoride bound permanently to the enamel crystal.[8] Reduced acid solubility of fluorapatite because of lower carbonate content has been shown by **Duggal et al (2001)**.[9]Signs of toxicity has been shown by high fluoride content in systemic fluoride and dentifrices which led to development of

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nontoxic fluoride alternatives as effective remineralizing agents.[7]

Casein Phosphopeptides (CPPs) was first introduced by **Reynolds** in 1993 as an anti-cariogenic and anti calculus and in 1996 as amorphous calcium phosphate (ACP)-filled methacrylate composites.[10]Based on ACP technology, Enamelon toothpaste was developed by **Dr Tung** in 1999.[11] Mouth rinses and sugar-free chewing gums containing CPP–ACP were introduced in 2003, which remineralize the subsurface enamel lesions.[12]

Sodium calcium phosphosilicate (bioactive glass) was introduced as a remineralizing agent which provide calcium, sodium and phosphate ions and form hydroxyl carbonate apatite (HCA) which release ions for remineralization as it can attach to the tooth surface. Based on this formulation, "NovaMin" toothpaste was introduced by **Dr Len Litkowsky and Dr Gary Hack.**[13]Recently, biomimetic remineralization materials has been put forward by **Moradian**in 2001.[7]

*Demineralization &Remineralization*

**Silverstone (1977)** defined demineralization as the process of removing minerals, in the form of mineral ions from dental enamel. Formation of bacterial acids lowers the pH to the point where the hydroxyapatite mineral of enamel dissolves and thus minerals are lost which leads to cavitation in future.[14] The immediate fluid environment involved in demineralization of a toothisthe fluid phase of plaque i.e. 'plaque fluid' and not the saliva. Critical pH at which demineralization begins is an average of 5.5.[15]

If the pH is neutral & there are sufficient calcium& phosphate ions in environment demineralization can be reversed. The rate & amount of dissolution depends not only on pH, but also on concentration of calcium & phosphate ions in solution. Enamel and dentin undergo unlimited cycles of demineralization and remineralization during entire life. Either apatite dissolution can become neutral by buffering or calcium & phosphate ions in saliva inhibit dissolution through common ion effect which can rebuild partly dissolved apatite crystals & termed as remineralization.[16]

*Natural tooth Remineralization*

It is the process whereby partially demineralized enamel is repaired through the recrystallization of tooth enamel mineral salts **(Silverstone 1977).**[14]

Role of Saliva

Saliva can cause both remineralization and demineralization. Through saliva, remineralization occurs daily after an acidic challenge. As saliva is rich in calcium & phosphate ions, it allows demineralised tooth tissue to be remineralised. High calcium and phosphates concentrations in the saliva is maintained by various salivary proteins which may account for remineralisation and development of enamel.[17]

Requirements of a Remineralizing Agent[18]

- Calcium and phosphate delivery into the subsurface
- No delivery of excess of calcium
- No calculus formation
- Stop demineralization by working at acidic pH
- Should work in xerostomic patients as saliva alone cannot stop the carious process
- Enhance the remineralizing properties of saliva
- Show benefits over fluoride

Indications[19]

- Caries reduction in high-risk patients as an supplemental preventive therapy
- In patients with gastric reflux or other disorders to reduce dental erosion.
- For reduction of decalcification in orthodontic patients
- Enamel repair in white-spot lesions
- Fluorosis or sensitive teeth before and after teeth whitening

*Remineralizing Agents*

Fluoridated and Non Fluoridated[7]

*Fluoridated*

- ✓ Fluoride toothpaste
- ✓ TiF4
- ✓ CPP-ACFP

*Non Fluoridated*

- CPP-ACP
- Bioactive Glass

- Tricalcium Phosphate
- ACP Technology
- Self Assembling Peptide
- Dicalcium Phosphate Dihydrate
- Nanohydroxyapetite
- Sucrose free Polyol Gum
- Biomimetically modified MTA
- Anti plaque agents
- Electric field induced Remineralization
- Theobromine
- Arginine
- Oligopeptides
- Polydopamine
- PA

*Fluoride*[16]

Fluoride is effective in protecting enamel from caries by reducing enamel dissolution and enhancing enamel remineralisation processes.

Mechanism of Action

When enamel is exposed to ionic fluoride, it may be taken up with the formation of either fluorhydroxyapatite or calcium fluoride.

$Ca10(PO4)6(OH)2 + F– + H+ \rightarrow Ca10(PO4)6(OH)F + H2O$

The fluorhydroxyapatite formed will be situated in the outermost layers of enamel and form an integral part of the tissue that is only lost if the entire mineral is worn away or dissolved entirely.

Fluoride Toothpaste

Regular brushing of teeth with a fluoride containing toothpaste can reducedental caries incidence.Fluoride toothpastes contain 500–1500 ppm fluoride either in the sodium fluoride (NaF) form orin the complex monofluorophosphate form. The MFP molecule hydrolysis is caused by phosphatases when it meets the oral fluids and tissues and when it diffuses into plaque.Therefore, by using an adequately fluoridated toothpaste , this assists remineralization of any hard tooth tissues.[16]

CPP-ACFP

There is a synergism in remineralising potential when CPP-ACP is combined with fluoride. CPPs enhances efficacy of fluoride as a remineralizing agent by keeping fluoride ions in solution by forming fluoroapetite.[20]

Table 1: Mechanism of Action of Bioactive Glass.

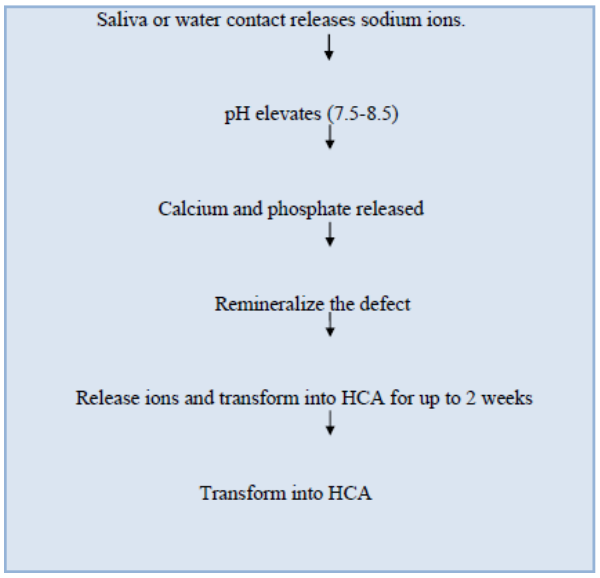
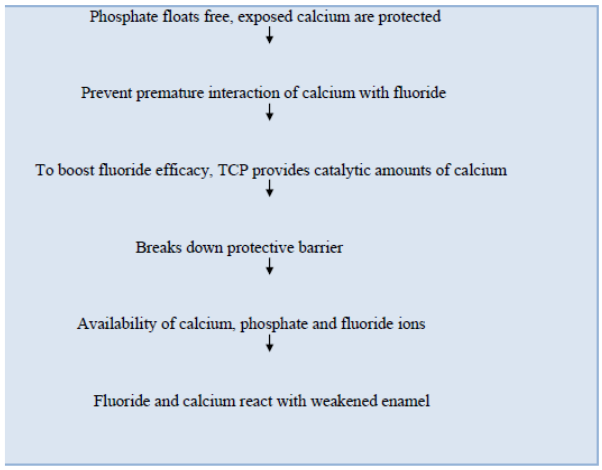



Table 2: Mechanism of Action of Tricalcium Phosphate.




**Jayarajan J et al (2011)** conducted an in vitro study and found that efficacy of CPP-ACFP containing paste (Tooth Mousse Plus) was more than CPP-ACP containing paste (Tooth Mousse) in remineralization of caries lesion.[21]

**Llena C et al (2015)** evaluated the effects of CPP-amorphous calcium phosphate (CCP- ACP) and CPP-amorphous calcium fluoride phosphate (CPP-ACFP) versus fluoride varnish on the remineralisation of enamel white spot lesions (WSLs) over a 12-week follow-up period in patients aged between 6 and 14 years and the DIAGNOdent values were significantly less in CPP-ACFP group at 4 weeks. Also, CPP-ACFP

show no significant effect in pit and fissure caries but have a specific smooth surface caries effect.[22]

Table 3: Mechanism of Action of ACP Technology.

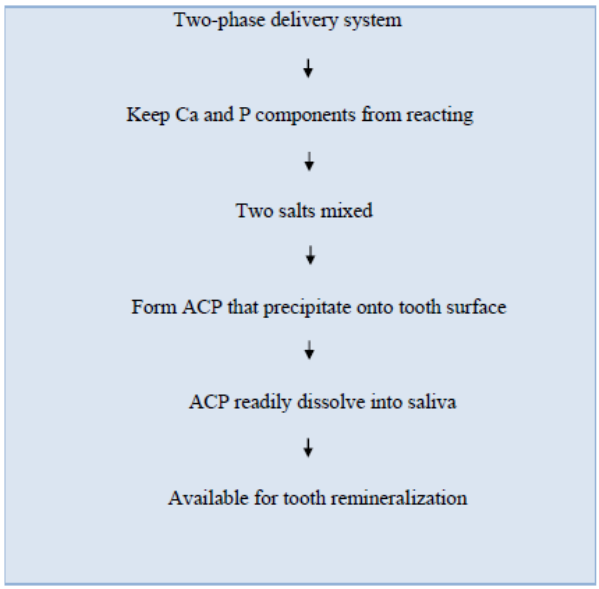
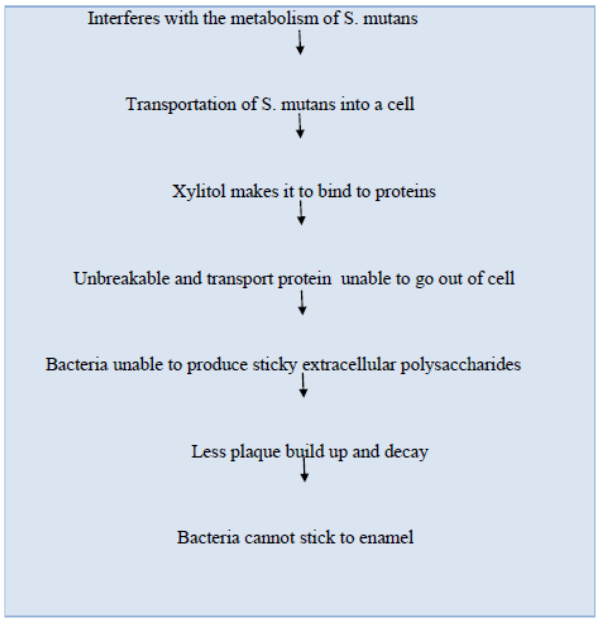



Table 4: Mechanism of Action of Xylitol.




TiF4 Technology

Titanium ion readily hydrolyze $H_2O$ to expel proton (H+) and render the solution of low pH value. Titanium ion imparts oxygen a strong tendency to form titanium phosphate complex. The bond thus formed is not easily substituted even at low pH (pH 1) by protons (H+), which renders the altered tooth surface demineralization resistant.[23]

*Nonfluoride Remineralization*

Dental caries management must be a preventive approach rather than just curative. Caries is used for both the carious process which occurs in the biofilm and dental caries (and cavities), which occurs in the tooth.[24]

According to mode of action[24]

- Agents interacting with enamel of the tooth
- Those causing neutralization of the bacterial acid
- Anti-plaque agents

Agents interacting with enamel of the tooth

Casein-Phosphor-Peptide-Amorphous-Calcium-Phosphate (CPP-ACP)[24,25,26]

In 1998, CPP-ACP (Tooth Mousse, GC India) was introduced by Prof. Reynolds as a remineralizing agent at the school of Dental Sciences at the University of Melboune in Australia. It has anti-cariogenic activity which reduce enamel demineralisation and promote remineralisation. Casein, a bovine milk phosphor protein is a natural food component interact with calcium and phosphate. CPP which aggregated with calcium phosphate, have been produced from a tryptic digest of the milk protein casein. CPP contain the cluster sequence of -Ser (P)-Ser (P)-Ser (P)-Glu-Glu from casein.Through these sequences, CPP prevents calcium and phosphate ions dissolution by binding to ACP in metastable solution. By forming metastable solutions, CPP stabilize calcium and phosphate ions under alkaline and neutral and conditions which are supersaturated with respect to the calcium phosphate phases.

Mechanism of Action

- CPP bind to dental plaque, tooth enamel, stabilize and bind calcium and phosphate in solution
- Normally, calcium phosphate is insoluble,but CPP keeps calcium and phosphate in amorphous state in which calcium and phosphate ions enter the tooth enamel
- High calcium and phosphate ions concentrations in dental plaque reduce enamel demineralization risk, thereby promoting tooth enamel remineralization

- CPP stabilize and localize ACP in dental plaque which maintain a state of supersaturation with respect to tooth enamel, which reduces demineralization and enhances remineralization
- CPPs enhances fluoride efficacy as a remineralizing agent by keeping fluoride ions in solution
- Therefore, the supersaturated levels of ionic calcium and phosphate at tooth surface increase the efficacy of remineralisation

**Oshiro et al (2007)** demonstrated the effect of CPP-ACP paste on tooth mineralization using field emission scanning electron microscopy and it was observed that CPP-ACP paste effectively prevents enamel and dentin demineralization more effectively than the placebo paste (CPP-ACP free).[27]

Bioactive Glass[24,28]

Bioactive materials promote the enamel remineralization or reduce the demineralization process. It 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 materials induce calcium phosphate formation, and have potential applications in tooth remineralisation. Hench & Anderson bioactive glass in 1969. Bioactive glass formulation contains 45 wt% $SiO_2$ 4.5 wt% $Na_2O$ and CaO and 6 wt% $P_2O_5$.The mechanism of action has been described in (Table I).

Novamin was developed by Dr. Len and Dr. Hack which is manufactured by Novamin technology and is a trade name for bioactive glass. Intraoral release of phosphate and calcium ions help in the enamel's self-repair process. On bioactive glass powders exposure as well as solutions and extracts, it demonstrated a significant anti-microbial effect toward caries pathogens (S. mutans, S. sanguis).

**Vashisht et al (2010)** examined the remineralization effect of topical NovaMin and sodium fluoride gel on caries-like lesions in permanent teeth. NovaMin dentifrice show greater remineralization effect on carious-like lesions in permanent teeth when compared with dentifrice containing 0.5% fluoride ion (equal to 5,000 ppm fluoride).[29]

**TahaAA et al (2017)** extensively studied the Bioglass45S5 regarding the remineralization of white spot lesions. They compared the remineralization potential of bioactive glasses, topical fluoride and CPP-ACP treatment and concluded that enamel remineralization is more effectively and earlier enhanced by bioactive glasses.[30]

Tricalcium Phosphate[24,31]

A new hybrid material created with milling technique fuses beta TCP and sodium lauryl sulfate or fumaric acid which results in a "functionalized" calcium and a "free" phosphate to enhance the fluoride remineralization efficacy. The mechanism of action has been described in (Table II).

TCP enhances the levels of calcium in plaque and saliva.TCP Product : 5% sodium fluoride varnish and 5000 ppm sodium fluoride dentifrice. Clinpro 5000 toothpaste is TCP, consistsof calcium oxides, calcium phosphate and free phosphates. It has high fluporide concentration (5000 ppm) of fluoride that helps in remineralization. Clinpro 5000 is not suitable for overnight use and is applied as toothpaste.

**Rirattanapong et al (2011)** stated that teeth hardness increases in vitro when treatment with Tricalcium phosphate with 950 ppm fluoride paste was done and also increases the surface microhardness of eroded enamel by chlorinated water in vitro.[32]

**Rao R et al (2017)** evaluated the remineralization potential of fluoride using Duraphat fluoride varnish, ReminPro paste, ClinPro Tooth Creme and control group (no surface treatment). ClinPro tooth Creme showed the best remineralization potential followed by Duraphat and ReminPro.[33]

ACP Technology[24,31]

ACP was incorporated into toothpaste known as Enamelon in 1999 and later reintroduced by Church and Dwight in Enamel Care toothpaste in 2004.Calcium sulphate and dipotassium phosphate are the sources of calcium and phosphorous. Mechanism of action has been shown in (Table III).

Because of their high solubility under oral conditions and ability to form apatite, ACP

compounds are prime candidates for remineralization therapy. With Enamelon™ calcium and phosphate are unstable which allow the two ions to combine into insoluble precipitates before they come into contact with enamel or saliva.

Dicalciumphospahte dihydrate[7,24]

It is the mineral brushite which at pH <6.5 can be easily crystallized from aqueous solutions. It act as a caries protection and gentle polishing agent when added to toothpaste. Effects calcium and phosphate which were added to remineralise the demineralised dentin apart from available saliva substitutes were investigated and it was found that OCP are capable of dentin remineralization as modified saliva natura solutions are slightly supersaturated with respect to DCPD.

For dental caries and hyposalivation management, the use of artificial saliva (i.e., modified saliva natura) is a promising approach. When compared with conventional silica dentifrices, DCPD addition in dentifrice increases the free calcium ions levels in plaque fluid, which remain elevated for upto 12 hr after brushing. With DCPD, there is increased calcium incorporation into enamel and increased levels in plaque upto 18 hours.

Sucrose free polyol gum[31,34,35]

Xylitol is a non- cariogenic five -carbon sugar alcohol that is found naturally in plants and is used as a substitute for sugar. It is believed to be a "tooth-friendly". Mechanism of action is described in (Table IV) Xylitol can cause:

- Reduce formation of dental plaque
- Reduce plaque adhesiveness
- Neutralization of plaque acids by decreased production of lactic acid
- Reduction in the S. mutans levels
- Upto 80% reduction in cavities
- Long-term caries reduction (88-93%)
- Tooth enamel remineralization
- Reduction in gum tissue inflammation
- Reduction in dry mouth and bad breath

Xylitol coating inhibits early reaction and results in sustained remineralizing ions release. It act as a carrier for calcium required for remineralization. When exposed to saliva, xylitol dissolves. As a result, phosphate and calcium ions gets free which form protective fluorapatite on the teeth when react with the fluoride in the varnish. For the maximum dental caries prevention of 7-20 g/day. Xylitol can be best used soon after eating and clearing the mouth by swishing with water.

Advantage

Do not raise blood pressure or blood glucose levels. Thus, when used with fluoride or even alone, it act as an effective remineralizing agent.

**Auerkari EI et al (2010)** conducted a study to found the effects of xylitol exposure on the remineralization as reflected instructure, hardness and composition of demineralized enamel. Non significant difference was seen in the mean hardness of the groups treated with 20 or 50% xylitol. However, significantly higher mean enamel hardness after immersion was seen in the xylitol-containing remineralization solution when compared with the demineralized samples ($p<0.05$).[36]

Biomimetically Modified MTA[7,24]

For remineralization of dentin, biomimetic analogs in modified MTA provides a potential delivery system. It widens MTA applications in dentistry as it release biomimetic analogs from set MTA. When availability is compromised, polyphosphate in the MTA serve as a supplementary phosphate source.

Those neutralising bacterial acids

In this, agents containing calcium can be used. For eg, Calcium lactate, Calcium phytate and calcium glycerophosphate. They increase plaque calcium and phosphate levels. Toothpastes containing ammoniated toothpaste, chlorophyll and anti-enzyme pastes can be used.[24]

Antiplaque Agents

Anti-microbial and antibiotics

For plaque reduction and their ability to reduce mutans streptococci, Mouthrinse have been evaluated including sodium dodecyl sulphate, chlorhexidine, triclosan, sanquinarin cetylpyridinium chloride, essential oils, and various metal ions.[19]

- Self-assembling Peptide

Recent developments had shown the role of treatment with peptide where it proved a combined effect of inhibition of mineral loss from the tooth and increased mineral gain. The β-sheet-forming peptides, P114, self-assembles to form three-dimensional scaffolds under defined environmental conditions to nucleate HAP. Side chain of anionic groups of P114 attract Ca+ + ions, thereby inducing the precipitation of HAP in situ.[37]

Electric Field-induced Remineralization

This technique was introduced by Wu for remineralization of completely demineralized dentin collagen matrix and to reduce the mineralization time which can be achieved in the absence of both calcium phosphates and their analogs with electrophoresis.[38]

Theobromine

Member of the xanthine family which is seen in cocoa (240 mg/cup) and chocolate (1.89%) and enhance crystalline growth of the enamel. Amaechi et al evaluated the remineralisation potential of sodium fluoride dentifrice and theobromine and a significantly higher amount of mineralization was seen with theobromine and fluoride toothpaste relative to artificial saliva. Grace Syafira et al. have shown an increased enamel microhardness after treatment with theobromine on the enamel surface. Meanwhile, Nasution AI noticed the increase in enamel surface hardness by the application of fluoride is higher than the theobromine.[7]

## CONCLUSION

Modern dentistry goal is the management of non-cavitated carious lesions by a non-invasive method via remineralization to prevent disease progression and improve strength, aesthetics and function. With a clear understanding of application of these remineralizing agents, a more favorable relationship can be created in which remineralization can occur.

## CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

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