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Review Article

Advances in Hard Tissue Remineralization

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Abstract

Introduction: More than 570 million children are affected with untreated caries lesions in deciduous teeth around the world. The prevalence of untreated dental caries was stable from 1990 to 2015 and then significantly increased in children between 1 - 4 years old, regarding such a pandemic of dental caries in various parts of the world. A better and advanced solution to the prevention of dental caries can help. One such method is "Remineralization of caries lesions," which is the salivary ions naturally attain and external factors or elements such as fluoride can further augment it. Nanotechnology has improved dental treatment and prevention measures. The use of nanoparticles for effective caries control is a new concept and because it not only remineralizes but can also act as an antibacterial and also load drugs for delivery. Adding active ingredients such as calcium, phosphate, stannous, xylitol, and arginine can augment the effect of fluorides on treatment. Despite such advancement in new remineralization strategies, further evidence is needed to evaluate their true clinical potential.

Aim of the Study: The aim of the review is to understand various new advances materials aids in remineralization process and prevent carious lesion.

Methodology: The review is a comprehensive research of PUBMED and CROSSREF from the year 1998 to 2019.

Conclusion: The mechanism of remineralization can be better understood by having a clear knowledge of the mode of implementation and mechanism of action of these newly evolve remineralizing agents. Thus, it is important for a clinician to be aware of all possible new techniques and also to understand the fact that it takes some significant time to establish a relationship with new technology like this.

Keywords: *Fluorides; Non-Fluoridated Remineralizing Agents; Nanoparticles for Remineralization*

Introduction

The hardest tissue in the human body is enamel owing to its higher mineral and inorganic contents. It is made up of 96% hydroxyapatite (HAP) formulated as $Ca_{10}(PO_4)_6(OH)_2$) by weight and has a crystalline structure. The enamel surface is constantly flushed with saliva and plaque fluid, and HAP crystals of enamel are in dynamic equilibrium with these aqueous phases. When pH is greater than 5.5, along with a high concentration of calcium and phosphate ions, the equilibrium can be shifted the other way; calcium phosphate can re-precipitate and remineralize the demineralized tooth structure. Enamel's resistance to erosion and further cavitation is significantly increased with levels of fluoride [1].

A century ago, a surgical approach for treating carious lesions was developed, including removal of significant unhealthy tissue and restore the prepared cavity from the appropriate restoration. This method of treatment was unavoidable due to the unavailability of any other alternatives. The current trend focuses on the early detection of caries and non-invasive methods of management of such lesions. Remineralization is the non-invasive mode of treatment for early carious lesions, which is a major development in the clinical management of caries. Remineralization of "white-spot" or early caries lesion confined to the enamel can be aided by a variety of agents containing fluoride, bioavailable calcium and phosphate, and casein phosphopeptide in-amorphous calcium phosphate, a self-assembling peptide [2].

Mechanism of demineralization/remineralization [3,4]

The bacterial carbohydrate metabolism forms lactic acid causing demineralization of tooth mineral, which leads to the release of mineral ions into the solution and is explained by the following reaction:

$$Ca_{10}(PO_4)_6(OH)_2 + 14H^+ \rightarrow 10Ca^+ + 6H_2PO_4 + H_2O$$

Thermodynamic ion activity product (IAP) decides the extent to which tooth mineral dissolves in a given solution is characterized by:

$$IAP = (Ca^{2+})_{10}(PO_4^{3})_6(OH)_2$$

The solution is in a state of equilibrium with the solid and is said to be saturated with respect to the solid when the ion activity product equals a constant called the solubility product constant of Ksp.

The only requirement for demineralization to occur is that the IAP in the demineralizing solution should be less than the Ksp.

$$(Ca^{2+})_{10}(PO_4^{3})_6(OH^-)_2 < Ksp \text{ (tooth mineral)}$$

Stages of demineralization/remineralization with fluoride

The process of demineralization of hydroxyapatite (HA) and remineralization with fluorapatite (FA) can be explained by the following stages:

- Stage 1: Intake of fermentable sucrose.
- Stage 2: Microorganisms of cariogenic plaque metabolize sucrose, emitting acid in the biofilm-tooth interface, and pH at interface falls below the critical pH of HA.
- Stage 3: The acidic ions are buffered by phosphate ions from oral fluid, resulting in undersaturation.
- Stage 4: The phosphate ions are released back to the oral fluid by the disintegration of HA till it supersaturates, causing demineralization.

- Stage 5: Disintegrated minerals are precipitated back onto the enamel surface by supersaturated oral fluids. It can be remineralized by getting deposited as a superficial layer of fluoride is applied in the topical form.

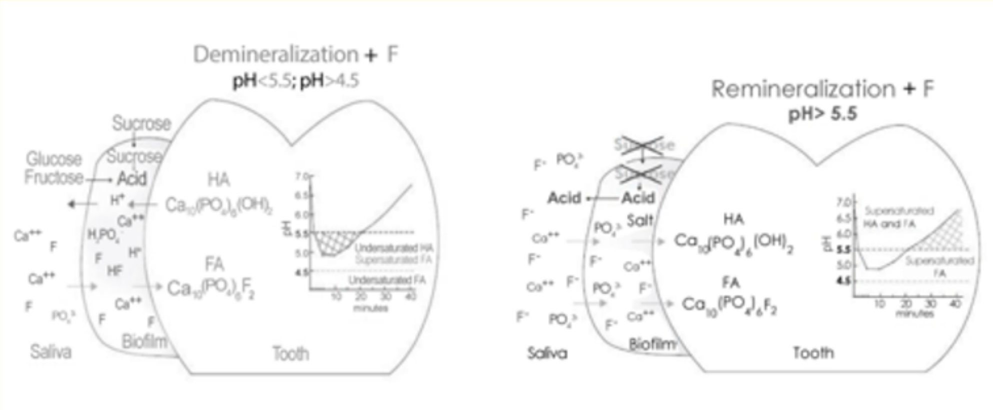

Figure 1: *Figure depicting various stages of demineralization and remineralization along with pH changes in the tooth surface [2,5].*

The remineralizing agents can be broadly classified as follows.

Fluoride remineralising agents

- Chitosan
- Casein phosphopeptide-amorphous calcium phosphate fluoride (CPP-ACPF).

Fluoride dentifrice: Many kinds of toothpaste adds fluoride as a remineralizing agent, which is mostly sodium fluoride (NaF), sodium monofluorophosphate (MFP), amine fluoride, and stannous fluoride. Calcium-containing abrasives in toothpaste have the potential to inactivate the fluoride, thereby affecting its availability [5].

If a satisfactory amount of detergent is not present, a similar reaction takes place between fluoride and silica to form fluorosilicates. Many factors affect the efficacy of fluoridated toothpaste, such as the quantity of toothpaste used, the concentration of fluoride, and personal differences, including the duration and frequency of brushing and rinsing behavior. Mouthwashes containing fluoride are indicated for school children over five years of age, people with high caries susceptibility, and individuals with dental appliances [3,4].

Non-fluoride remineralising technologies [5]

Technology		Commercial Product
Biomimetic Systems	Dentin phosphoprotein 8dss peptides	Not Available
	P11-4 peptides	Curodontrepair/curodontprotect
	Leucine-rich amelogenin peptides.	Not Available
	Poly (amido amine) dendrimers.	Apagard toothpaste/designs in oral rinse
	Electrically accelerated and enhanced remineralization	
	Nano hydroxyapatite	
Calcium Phosphate Systems	Stabilized calcium phosphates	Tooth mousse/mi
	Casein phosphopeptide amorphous calcium phosphate	Paste crèmes Recaldent/trident white sugar-free gum Mi paste one toothpaste
	Crystalline calcium phosphates Functionalised $^{\beta}$ tricalcium phosphate	Clinpro toothpaste
	Calcium sodium phosphosilicate (novomintm technology)	Oravive toothpaste
	Unstabilized calcium phosphates	
	Amorphous calcium phosphate (enamelontmtechnology)	
Polyphosphate Systems	Calcium glycerophosphate	
	Sodium trimetaphosphate	Oral-b pro expert toothpaste
	Sodium beta metaphosphate	

Table 1

Professionally applies fluorides

Topical fluoride solutions of fluoride-containing 8% stannous fluoride, 2% sodium fluoride, and 1.23% of acidulated phosphate fluoride solutions are used. Two-four quadrants can be treated at the same time.

Mechanism of action: Continuous wetting of enamel is prevented by Fluoride Gels that cling to teeth [5].

Fluoride varnish: Topical fluoride have the disadvantage that it rapidly loses in the form of soluble fluoride from teeth. Fluoride varnish in the form of a waterproof sealant was introduced to overcome this drawback. This procedure not only improves the reaction time between fluoride and enamel but also provides a long-term effect. Commercially available sodium fluoride-based varnishes are Duraphat and polyurethane-based varnish Fluorprotector [5].

Fluoride releasing restorative materials [5,6]

One of the conventional restorative materials used for the long term is glass ionomer cement which releases fluoride and gets incorporated into enamel HA crystals, cavity walls and bacteria, inhibiting acid production-furthermore the ability of these materials for fluoride recharge aids in long term effects of inhibition of caries [5,6].

A recent material which is known to be a hybrid of glass ionomer cement and composite resin known as Compomers, released fluoride in low quantity and consists of silicate glass particles, sodium fluoride and polyacid-modified monomer without any water. When compared to glass and hybrid ionomers, compomers release a smaller amount of fluoride [5,6].

A similar material that exhibits properties of both composite and glass ionomer cement is Giomers, which consists of pre-reacted glass ionomer particles and resin. They release fluorides in greater quantities than compomer or composites and exhibit good esthetic properties [5,6].

Pit-and-fissure sealants release free fluorides from strontium-fluoride aluminosilicate glass, which is present in it as a filler that undergoes hydrolysis in the presence of water [5,6].

Chitosan

Chitosan inhibits the growth of mutans streptococci because of the positively charged chitosan binding to negatively charged *S. mutans* cell surfaces. This results in a substantial reduction in the development of the dental plaque biofilm [7].

Chitosan-amelogenin (CS-AMEL) hydrogel is known to induce biomimetic remineralization on either on etched enamel or on artificial enamel lesions *in-vitro*. As a result of this, Enamel-like crystals formed, and the depth of the lesion decreased. Due to adhesion provided by the amino groups of chitosan through electrostatic interactions, remineralization did not stop even when the pH plunged below 6.5 [8].

CPP-ACPF

To increase its remineralization efficacy, fluoride has been added to the CCP-ACP formulation. CPP-ACPF are known to have a specific remineralizing effect on smooth surface caries lesions; however, the same is not seen with pit and fissure lesions. According to a study, CPP-ACPF was more effective than NaF control in remineralizing incipient caries lesions. CPP-ACP (Recaldent) CPP-ACP is a stabilized system of calcium and phosphate that has been extensively researched for the past two decades. When applied, the sticky CPP part of the CPP-ACP complex attaches quickly to the enamel, biofilm, and soft tissues, distributing the calcium and phosphate ions exactly where it is required. The free calcium and phosphate ions transfer to the enamel rods from the CCP, and reform the apatite crystals [9].

Xylitol sugar-free chewing gums

In randomized clinical trials, chewing gums with xylitol have proven to lessen caries incidence when compared with no chewing gum [10].

Mechanism of action: Chewing this sugar-free gum stimulates saliva, which promotes anti-cariogenic activity. With the addition of salivary biomimetic such as CPP-ACP, the anti-cariogenic efficacy of sugar-free gum has been increased. By providing bioavailable calcium and phosphate ions to the tooth structure, saliva's buffering and remineralization capacity is significantly increased [11].

Calcium carbonate carrier (Sensistat)

Dr Israel first developed SensiStat which was commercially available in 2003 as desensitizing prophylactic paste and as sensitivity paste for home use. A professionally dispensed sensitivity paste (Denclude) was launched in 2004 for home use. It is composed of highly soluble arginine bicarbonate and is surrounded by particles of the poorly soluble calcium carbonate.

Mechanism of action: The composition forms an adhesive paste-like plug that not only blocks the open tubules but also sticks to the dentinal tubule walls. Sensi Stat is alkaline in nature, so it reacts with the calcium and phosphate ions of the dentinal fluid to make the plug chemically adjoining with the dentinal walls making it more secure [5].

Biomimetically modified mineral trioxide aggregate

Due to scarcity of apatite seed crystallites along the lesion surface for heterogeneous crystal growth are less in number in dentin compared to enamel, it is more difficult to remineralize dentin than enamel. The remineralizing potential of biomimetically mineral trioxide aggregate (MTA) in phosphate-containing simulated body fluid (SBF) is by incorporating sodium tripolyphosphate and polyacrylic acid as biomimetic analogs of matrix proteins. This aids in remineralizing artificial caries like dentin which was evaluated, and it revealed that biomimetic analogs in modified MTA provide a potential delivery system for remineralization of dentin at the end of 6 weeks; thus, this opens a major scope of applications of MTA in dentistry [12].

Nanomaterials

Silver nanoparticle (NAg)

Silver ion exhibits a broad spectrum of antibacterial properties, deactivates enzymes and inhibit DNA replication in bacteria and many other microbes. At the nanoscale, the silver ion as Nag, increases surface area ratio by producing silver particles smaller and improved antibacterial effects. Although its antibacterial property is enhanced, the effect of NAg on bonding strength is still debated. Some authors report that the antibacterial effect of NAg increased in a dose-dependent manner from 0.05% to 0.1%, with no effect on bonding strength or color [13].

Nano-zinc (NZn) and Nano-zincoxide (NZnO)

NZn can dissolve and release nano zinc particles which brings antibacterial activity at a wide antimicrobial spectrum. NZn can diminish the expression of MMPs which are known to degrade resin and dentin matrix thus or longing the lifespan of adhesives. NZnO when compared to micron Zno has greater surface potential energy and can release additional zinc ions to kill bacteria. The addition of Zn^{2+} to total-etch adhesive can impede MMPs activity, safeguard mineral crystal formation at the eosin-tooth interface, lessen the disintegration of dentin collagen bundle, upgrading the nano-mechanical properties [14].

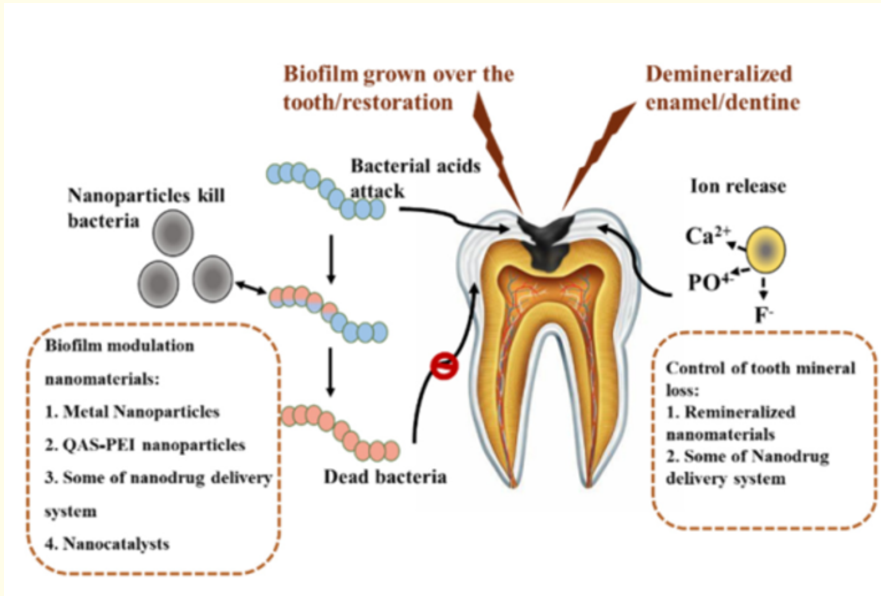

Figure 2: *Figure showing effects of nanoparticles on remineralization process of tooth [15].*

Other metal nanoparticles

TiO_2 nanoparticles ($NTiO_2$) when combined into glass-ionomer cement in the concentration of 3% and 5% (w/w), it was shown to have antibacterial activity against *Streptococcus mutans* in direct contact test. $NTiO_2$-containing dental adhesives in concentration (80% v/v) also had potent antibacterial efficacy against *Streptococcus mutans* biofilms as well as good biocompatibility. MgO nanoparticles (NMgO) modified glass-ionomer cement have also demonstrated effective antibacterial and antibiofilm activity against two cariogenic microorganisms (*Streptococcus mutans* and *Streptococcus sobrinus*) [16,17].

Anti-caries mechanism of mental nanoparticles

"Contact inhibited mechanism": In a process known as the micro-dynamic effect, the metal nanoparticles comprising of positively charged metal ions attach to the negatively charged cell membranes on microorganism. Metal ions then infiltrate the cell membrane into the microbial body and react with the thiol group (-SH) present on the microbial protein; this impedes the synthesis of protein and nucleic acid. Electron transport system, material transfer system, and respiratory system of microorganisms are destroyed metal ions, resulting in microbial death. The metal ions (such as Ag^+) continuously contact other bacteria once and replicate the same mechanism, thus maintaining a lasting antibacterial effect. The bactericidal and inhibitory activities of metal ions are diminished in the following order: $Ag^+ > Hg^{2+} > Cu^{2+} > Cd^{2+} > Cr^{3+} > Ni^{2+} > Pb^{2+} > Co^{3+} > Zn^{2+} > Fe^{3+}$ [15].

"Reactive oxygen species (ROS) mechanism": The trace metal elements play a catalytic role which are dispersed on the surface and are the active centres that can absorb energy in the environment, activating the oxygen on the material surface and generating hydroxyl radicals and reactive oxygen atoms. This mechanism will destroy the cell proliferation ability to reduce or even eradicate bacteria due to the strong redox effect.[18]

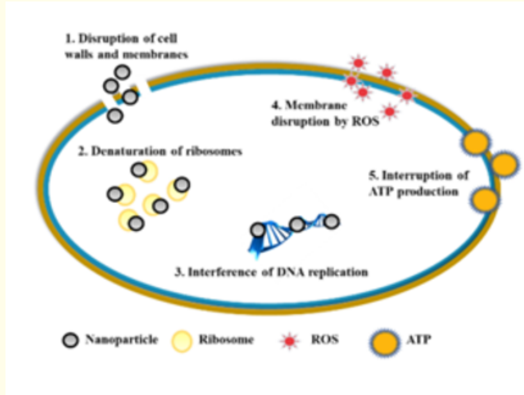

Figure 3: *Figure showing anti-caries mechanism of nanoparticles [15].*

Nanosized amorphous calcium phosphate particle (NACP)

NACP discharges greater levels of Ca^{2+} and PO_4^{3-} when compared with amorphous calcium phosphate. NACP discharges more ions at acidic pH, this leads to acid invasion neutralization. This mechanism, increasing the pH value from 4 to 6.5 does avoid dental caries and assists in remineralization [19].

Bioactive glass nanoparticle (NBG)

In the presence of saliva or water, bioactive glass releases Ca^{2+} and PO_4^{3-} to form a mineralized layer porous in nature and similar to hydroxyapatite. Due to its smaller grain size, the surface are is increased and so are the surface free energy and the binding energy. This results in improved physical and chemical properties of NBG. The research showed that NBG helps antibacterial ions (such as Ag^+) release to achieve the antibacterial effect by maintaining a high alkaline pH and interfering with the degradation of collagenase [20].

Electrically accelerated and enhanced remineralization (EAER)

This is a recent advancement of remineralization that depends on iontophoresis technology that is to speed up the flow of remineralizing ions into the innermost part of the subsurface caries lesion, creating an environment that encourages remineralization of the lesion, which later on matures. The repaired lesion exhibits ideal hardness and mineral density. The EAER differs from biomimetic peptides as it does not "regenerate" lost enamel via matrix proteins or the organic capture of calcium and phosphate ions, but the enamel treated with EAER has a very similar appearance to healthy enamel, with no evidence of broken enamel rods or degraded prisms seen under scanning electron microscopic examination [21].

Conclusion

Modern dentistry deals with the management of non-cavitated carious lesions with a mineralization process rather than the old conventional surgical process. The significance of oral health among dental patients and consumers leads to a higher demand in the number of tooth remineralization agents, products, and procedures in the modern era. More research is undergoing in efforts to increase the efficacy of fluoride, addition of calcium salts or calcium-containing materials to oral care products, which increases the delivery and retention of fluoride into the oral cavity. It is, therefore, necessary for a clinician to be aware of the different modes of actions of remineralizing and when and how to use them.

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