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 – 2, Issue – 4, July – August - 2019, Page No. : 311 - 321

Enamel Remineralization : The Future of Dentistry

Dr. Payel Agarwala[1], Dr. Abhishek Das[2], Dr. Sudipta Kar,[3]Prof (Dr.) Goutam Kundu[4]

[1]PGT , [2]PGT, [3]Reader, [4]Professor & HOD, Department of Pedodontics & Preventive Dentistry, GNIDSR, Panihati, Sodpur

Corresponding Author: Dr. Sudipta Kar, Reader, Ph. D Scholar, Department of Pedodontics & Preventive Dentistry, GNIDSR, Panihati, Sodpur

Type of Publication: Original Research Paper

Conflicts of Interest: Nil

Abstract

The effective clinical measures to remineralize early enamel caries lesions are based on the principles of minimally invasive dentistry. Though the milestone of current noninvasive caries management principle is fluoride-mediated remineralization, a lot of new remineralization technique have been commercialized or are under research that claims to promote deeper remineralization of carious lesions, reduce the potential risks of fluorosis associated with high-fluoride containing products, and facilitate caries control over a period of time. This non-fluoride rematerializing system can be broadly divided into, biomimetic enamel regenerative technologies and the approaches enhance fluoride efficacy. In this paper we tried to discuss the rationale for non-fluoride enamel remineralization, its mechanism of action and challenges.

Keywords: Enamel caries, remineralization, fluorosis

Introduction

Dental caries pathophysiology is a dynamic process characterized by alternating periods of de-mineralization and remineralization. Lesion progression or its reversal depends on the equilibrium between the factors favoring the demineralizations (cariogenic bacteria, fermentable carbohydrates, salivary dysfunction) and the protective factors (antibacterial agents, sufficient saliva, remineralizing ions) that guide the lessons towards remineralization [Featherstone and Chaffee, 2018]. Remineralization occurs as a natural repair process where plaque/salivary calcium (Ca^{2+}) and phosphate ($PO_4^{3—}$) ions are deposited into crystal voids of the demineralized tooth structure, resulting in a net mineral gain. The presence of free fluoride (F–) ions in the oral environment can drive the incorporation of$Ca^{2+}$and $PO_4^{3—}$ ions into the crystal lattice, with the ensuing fluorapatite mineral significantly more resistant to a subsequent acid challenge [ten Cate, 1999] A better understanding of pathophysiology of caries development, its progress, and knowledge of physiochemical mechanisms behind the regenerative process has influenced the development of a number of innovative remineralization technologies besides the conventional fluoride mediated remineralization.

The rationale behind the utility of the non-fluoride remineralization systems

The process of physiological remineralization of the tooth and its supporting structures alone is not sufficient. The remineralization potential of saliva is documented [Stookey, 2008], to deliver $Ca^{2+}$and $PO_4^{3–}$ ions in a bioavailable form throughout our life for hard tissue

development and maintenance [Cochrane and Reynolds, 2012]. Saliva is supersaturated with phosphoprotein-stabilized Ca^{2+} and PO_4^{3-} ions, at physiological pH ensuring bioavailability of the ions for diffusion into the mineral deficient areas of lesions [Cochrane et al., 2010]. In some longitudinal studies based on the natural progress of white spot lesions (WSL) it has been found that though some WSL gets smaller, the majority of them are largely unaffected even after 2 years [Mattousch et al., 2007; van der Veenet al., 2007]. Lastly, the salivary remineralization is a very slow process [Dowd, 1999], with a tendency of gaining mineral only on the surface of the WSL due to the low ion concentration gradient from saliva into the lesion [Silverstone, 1972]. It is also seen that even Fluoride-mediated salivary remineralization is restricted only to the outer 30 μm of the tooth surface [Schmidlin et al., 2016]. This surfaceonly remineralization neither improves the aesthetics of the lesion nor the structural properties of the subsurface lesion [Cochrane et al., 2010]. The additional extrinsic sources of stabilized $Ca^{2+}$and PO_4^{3-} ions thus could augment the natural remineralization potential of saliva by increasing diffusion gradients for faster and deeper subsurface remineralization.

Efficiency and safety of fluoride products

The pivotal discovery of Fluoride as an anticarcinogenic agent is a benchmark in dentistry [ten Cate, 2015] and there is a noticeable decline in caries prevalence rates of developed countries from the latter half of the 20th century by itswidespread use [Fejerskov, 2004]. Multiple systematic reviews confirmes the role of fluoride products in preventing dental caries [Benson et al., 2013; Marinho et al., 2003, 2015, 2016; Shahid, 2017]. But the emerging epidemiological data are astonishing, with caries experience plateauing or even increasing in some population groups, even after the regular use of fluoride-containing dentifrices in these countries [Agustsdottir et al., 2010; AIHW, 2018; Dye et al., 2017]; This anguishing trend raises questions on whether the earlier reduction in caries prevalence rates will be continued into this century [Gimenez et al., 2016]. There are many factors that attributed to this reported pause in the decline of dental caries 1. Changing trends in the diet like processed and sugar-laden foods across the world limiting the repair potential of fluoride [Duggal et al., 2001]. While under normal physiological conditions, 2.salivary homeostatic mechanisms toremineralize early lesions are not adequate in highly cariogenic oral environments.3. High-risk groups (xerostomia patients, elderly individuals with risk of root caries) can also be benefited from boosters to improve the efficacy of fluoride as a remineralizing and preventive agent [Fontana, 2016]. So an obvious approach to improve the remineralizing potential of fluoride would be to just to increase the dose of fluoride to oral care products. It has been found that dentifrices with 5,000 ppm fluoride are better for remineralization of root caries lesions than 1,000–1,500 ppm fluoride-containing dentifrices [Wierichs and Meyer-Lueckel, 2015]. A dose-response relationship of decreasing caries incidence with increasing dentifrice fluoride concentration is seen [Walsh et al., 2010]. However, recently fluoride has been classified as a chemical neuro-toxicant could raise the question of safety regarding the use of high concentration fluoride products [Grand-jean and Landrigan, 2014]. Children today are exposed to fluoride from multiple sources,which potentially increases their risk of developing dental fluorosis [Zohoori and Maguire, 2018]. This “halo" effectof fluoride probably one of the cause for the increased prevalence of permanent tooth mottling in western countries [McGrady et al., 2012; Pendrys, 2000]. For this reason, The World Health Organization (WHO)

recommend the need to assess total fluoride exposure of the population of an area before introducing any additional fluoridation for caries prevention to prevent fluorosis.[Baez and Marthaler, 2014].Thesurface-only remineralization that occurs in the presence of high topical fluoride concentrations can also increase the incidence of occult caries ("fluoride syndrome") besides fluorosis in children and across all age groups [Ball, 1986]. Considering this narrow "dose gap" between the caries reduction benefit and fluoride side effects, the fluoride concentration in non-prescription toothpaste has been limited to within 1,000–1,500 ppm, while for children below 6 years this dose should be even lower and which is suboptimal for effective remineralization of early carious lesions. This the reason of the need for new-age remineralization technologies with an ability to complement fluoride, close the gap in its remineralizing efficacy, and effect a fuller consolidation of carious lesions [Lynch and Smith, 2012]. Effectiveness of non-fluorideremineralization systemwith lower fluoride concentrations can also potentially allow allaying the safety concerns related to consumer oral care products containing high fluoride concentrations.

Modern principles and outlooks towards Caries Management

Enamel caries is progressed as subsurface demineralization that if not reversed will result in mechanical failure and cavitation, that leads to a vicious restoration cycle. But a large proportion of our professional neglectbiological approach of caries management [Pitts, 2004], and continue with the restorative-only model that has often failed clinically and laid economic burdens on the patient. [Innes and Schwendicke, 2017; Pitts and Zero, 2016]. Theprincipal approach caries management of this era should be to "preserve the tooth structure and restore only when necessary" [Ismail et al., 2013]. And this can be possible by new remineralization systems which can regenerate lesion body structure (e.g., biomimetic peptide scaffolds) or can favour subsurface mineral gain by providing ions (e.g., calcium phosphate systems) and thus can significantly decrease the need for 'drill to fill' restorations and preserve tooth structure as much as possible.Remineralization should be recognized and utilized as far as possible for any tooth that has been subject to attack by caries because there is no real substitute for natural tooth structure.The conventional DMFT/dmft criteria of the WHO to detect and score the caries is also shifted towards the use of the International Caries Detection and Assessment System (ICDAS), where non-cavitated enamel lesions (ICDAS 1 and 2) are also included. Thus the proportion of patient diagnosed with dental caries has increased creating a significant opportunity for secondary prevention and non-operative care by using regenerative medicine-based dental products. So in this technically advanced era where the prime focus is on prevention and regeneration,dentistry also clearly needs minimally invasive remineralization measures, to improve patient experience and well-being and safety [Pitts and Wright, 2018].

Non-Fluoride Enamel Remineralizing Systems: Types and Mechanisms

The novel enamel remineralization systems have significantly developed in the past few years with many of them already in clinical use, while some are in different stages of development. The most important technologies are briefly summarized in Table below, categorized into (i) biomimetic regenerative systems and (ii) approaches that augment fluoride efficacy [NebuPhilip 2019]

Table 1: Non-fluoride enamel remineralizing technologies

Technology	Commercial product
Biomimetic systems	
1. Dentin phosphoprotein 8DSS peptides	Not available
2. P11-4 peptides	Curodont Repair/CurodontProtect
3. Leucine-rich amelogenin peptides	Not available
4. Poly(amidoamine) dendrimers	Not available
5. Electrically accelerated and enhanced remineralization	Not available
6 Nanohydroxyapatite	Apagard toothpaste/Desensin Oral rinse

Table 2: **Fluoride boosters**

1.	
Calcium-phosphate systems	
Stabilized calcium phosphates	
• –Casein phosphopeptide-amorphous calcium phosphate	Tooth Mousse/MI Paste crèmes Recaldent/Trident White sugar-free gum MI Paste One toothpaste
Crystalline calcium phosphates	
• –Functionalized β-tricalcium phosphate	
• –Calcium sodium phosphosilicate (NovoMin™ technology)	ClinPro toothpaste Oravive toothpaste
Unstabilized calcium phosphates	
• –Amorphous calcium phosphate (Enamelon™ technology)	Enamelon toothpaste
2.	
Polyphosphate systems	Oral-B Pro-Expert toothpaste
• –Sodium trimetaphosphate	
• –Calcium glycerophosphate	
• –Sodium hexametaphosphate	
3.Natural products	Not available
• –Galla chinensis	
• –Hesperidin	
• –Gum Arabic	

Biomimetic Remineralization

Fluoride-containing agents are effective in remineralizing enamel but do not have the potential to form organized apatite crystals [Ruan and Moradian-Oldak, 2015].Recently, there is a tendency to shift from reparative to regenerative biomineralization therapies, wherein diseased dental tissues are tried to replace with biologically similar tissues [Alkilzy et al., 2018b]. Enamel regeneration is challenging as because mature enamel is acellularin nature and does not resorb or remodel unlike bone or dentine [Moradi-an-Oldak, 2012]. Advancesin tissue engineering methods have yielded biomimetic methods that have demonstrated a strong potential for regenerating the hierarchical enamel microstructure.

Dentine Phosphoprotein-Derived 8DSS Peptides

Dentine phosphoprotein (DPP) is a non-collagenous extracellular matrix component in dentine which and play a critical role in tooth mineralization [Hsu et al., 2011]. Human DPP contains numerous repetitive aspartate-serine-serine (DSS) nucleotide sequences which promote hydroxyapatite (HA) formation. Studies show that DPP can generate HA crystals in calcium phosphate solutions [George et al., 1996; Prasad et al., 2010]. Several short functional peptides based on DPP have been designed as they give the number of advantages over full-length DPP such as higher purity and better conformational fit on enamel while avoiding allergies and immunogenicity [Hsu et al., 2011]. Among the DPP-derived peptides, the octuplet repeats of aspartate serine-serine (8DSS) are the most active in promoting biomineralization [Yarbrough et al., 2010].8DSS peptides have two mineral-binding surfaces and can strongly bind to free Ca^{2+} and PO_4^{3-} ions, and also to the HA surface [George et al., 1996; Yarbrough et al., 2010]. 8DSS peptides thus appear to have a dual mechanism, as they not only they limit the dissolution of Ca^{2+} and PO_4^{3-} ions from demineralized dentine, but also promote the capture of these ions to form new mineral deposits on demineralized enamel [Hsu et al., 2011; Yang et al., 2014]. The newly grown mineral had uniform deposition of small apatite crystals with significantly improved properties such as reduced surface roughness, and higher hardness and elastic modulus [Chung et al., 2012; Hsu et al., 2011]. A recent in vitro study gives evidence that the biomimetic 8DSS peptide, inhibits enamel demineralization on its own, and might significantly augment the ability of fluoride to do the same [Yang et al., 2016]. This synergistic action can be useful tolower fluoride concentration for caries prevention in children thus reducing risk of fluorosis. Till date, the proof of concept of 8DSS peptides has been shown only in vitro systems and is likely to present some challenges when used clinically. Whetherthese peptides can survive enzymatic action in the oral cavity or could lead to calculus formation as 8DSS binds with calcium strongly if not controlled is not established. However, if future clinical trials overcome the challenges, it holds great

potentials as a non-fluoride biomineralizing agent [Yang et al., 2014].

Self-Assembling P11-4 Peptides

An ideal enamel regenerative approach would involve substituting the degraded enamel matrix with a biomimetic matrix that favors in-depth remineralization of enamel lesions [Alkilzy et al., 2018a]. A monomeric peptide consisting of 11 amino acids called P11-4 is said to work on this principle. The P11-4 fibrillar matrix has a high affinity for Ca^{2+} ions and acts as a nucleator for de novo HA formation resulting in remineralization of the lesion body [Kind et al., 2017; Kirkham et al., 2007]. Analysis of in vitro data showed that the presence of P11-4 fibres in the lesion body resulted in faster HA formation, yielding tangentially arranged needle-shaped crystals, with increased microhardness of the remineralized subsurface lesion [Schmidlin et al., 2016; Sousa et al., 2017; Takahashi et al., 2016].P11-4 has shown promising results as a biomimetic mineralization agent in vivo and clinical trials. This reverse early occlusal and proximal are more resistant to fluoride remineralization than smooth surface lesions [Alkilzy et al., 2018a, 2015; Brunton et al., 2013; Schlee et al., 2014, 2018]. The low viscosity isotropic P11-4, when applied on the initial carious lesion rapidly, diffuses into the lesion body, where it transforms into an elastomeric nematic gel in the presence of cations and pH <7.4, leading to the 3-dimensional fibre matrix assembly and subsequent biomineralization of the lesion [Brunton et al., 2013]. 2018. A recent randomized controlled trial (RCT) demonstrated that biomineralization initiated by P11-4 in combination with fluoride is safe and more effective than the present clinical gold standard of fluoride treatment alone [Alkilzy et al., 2018b]. Butmore long-term controlled studies are needed to confirm and quantify these findings.

Amelogenin

The amelogenin-rich enamel organic matrix plays a crucial role in regulating the growth, shape, and arrangement of HA crystals during enamel mineralization. However, mature enamel lacks matrix proteins and cannot regenerate the mineral loss caused by dental caries [Ruan and Moradian-Oldak, 2015]. Currently, several strategies have been proposed to replicate the complex enamel microstructure using synthetic amelogenin-based systems. Recombinant porcine amelogenin (rP172) was found to stabilize calcium phosphate clusters and promote the growth of hierarchically arranged enamel crystals on acid-etched lesions, significantly improving its hardness and elastic modulus [Fan et al., 2009; Ruan et al., 2013, 2016]. A low-cost and safer alternative to the full-length amelogenin is a leucine-rich amelogenin peptide that is comprised of only 56 amino acids. The disadvantage of amelogenin-mediated enamel regeneration is a. the protein difficult to extract and store, b. the growth of the repaired enamel layer also takes an extended amount of time, making it potentially unsuitable for clinical use.

Poly (Amido Amine) Dendrimers

Poly (amidoamine) (PAMAM) dendrimers are highly branched polymers [Chen et al., 2013]. This amelogenin-inspired dendrimerscan mimic the functions of organic matrices in modulating the biomineralizationof tooth enamel so are referred to as ‘artificial proteins'. Many invitro studies have proved that amphiphilic, carboxyl-terminated, and phosphate-terminated PAMAM dendrimers exhibited a strong tendency to self-assemble into hierarchical enamel crystal structures [Chen et al., 2013, 2014, 2015; Wu et al., 2013; Yang et al., 2011]. However, so far limited to only animal experiments.Recently, it has been postulated that lasers could be used to speed up the biomineralization process [Sun et al., 2017].

Electrically Accelerated and Enhanced Remineralization

Electrically accelerated and enhanced remineralization (EAER) is a remineralization technology targeted at initial small enamel lesions with an objective of preserving all healthy tissue [Pitts and Wright, 2018. Unlike the biomimetic peptides, EAER does not "regenerate" lost enamel via matrix proteins or the organic capture of Ca^{2+} and PO_4^{3-}ions. An advantage that the EAER technology will have over syntheticsynthetic biomimetic peptides is that it proposes to utilize tools and chemicals commonly available in most dental practices. The early in vitro results using the EAER technologyare very promising, although a thorough evaluation of its remineralization potential will depend on results from in vivo studies, as well as studies independent of the technology developers.

Nanohydroxyapatite

Nanohydroxyapatite a synthetic product which in structure, crystallinity and in morphology is very similar to appetite crystals of enamel[Hanning and Hanning, 2010]. They are considered one of the most biocompatible and bioactive materials which not only binds with enamel surface but also with fragments of bacteria and plaque. Due to their nanosize, they act as a filler to repair small holes and depression on the enamel surface [Pepla et al., 2014]. In vitro dynamic pH-cycling experiments have nHA had the potential to remineralize initial enamel lesions with comparable or even superior efficacy to thatof fluoride as seen in vitro dynamic pH- cycling experiments [Huang et al., 2009, 2011; Najibfard et al.,2011; Tschoppe et al., 2011]. The mechanism of nHA biomimetic function isnot clearly known. Some proposed that it promotesremineralizationby creating a new layerof synthetic enamel around the tooth or correct the enamel defects by depositingapatite nanoparticles [Li et al., 2008;Pepla et al., 2014]. However, some others have suggested that it acts as acalcium phosphate reservoir[Huang et al., 2011]. Till date, there are no well-designed RCTs that are evidential to prove its superiority over fluoride dentifrices although they have been available since the1980s.

Fluoride Boosters

Calcium Phosphate Systems

Future of non-fluoride remineralization could well be the biomimetic guided enamel regeneration. Though clinical use of them is still a few yearsaway. Presently, in caries prone individual the remineralizing efficacy of fluoride is largely met by calcium phosphate systems.But on topical application Ca^{2+} and PO_4^{3-} ions arenot bioavailable sufficiently for remineralization and is exacerbated under a condition like hyposalivation. [Reynolds et al., 2008; Vogel et al., 2008].Extrinsic supply of Ca^{2+} and PO_4^{3-} ions can is needed to increase diffusion gradients and potentiate the F– ion-mediatedremineralization. Cochrane et al. [2010] categorizedthe commercially available calcium phosphate remineralizationsystem into 3 types: (i) stabilized amorphous calciumphosphate systems; (ii) crystalline calcium phosphate systems; and (iii) unstabilized amorphous calcium phosphatesystems (Table 1).

Casein Phosphopeptide-Amorphous Calcium Phosphate.

It has been postulated that tryptic digestion of milk caseinateproduced multiphosphorylated casein phosphopeptides (CPP), eventually increases the milk protein's solubility and stabilize Ca^{2+} and PO_4^{3-} ions [Reynolds,1987]. CPP is a saliva biomimetic and can stabilize the calcium more than salivary proteins because of its phosphoseryl residues.[Cochrane and Reynolds, 2012]. CPP-amorphouscalcium phosphate (ACP) complex are easily soluble in saliva and create adiffusion gradient that helps them to localize in supragingival plaque.In Low

pH conditions, the release of Ca^{2+} and PO_4^{3-} ions facilitates that eventually inhibitdemineralization and potentiate the remineralization of the incipientlesion by precipitation of the released ions [Reynolds,2009]. CPP-ACP is probably the most researcher non-fluorideremineralizing agent. In many RCTs it has been seen remineralizing and anticariesefficacy of CPP-ACP products are better in comparison to a placebo ora fluoride-containing product [Bailey et al., 2009; Gucluet al., 2016; Heravi et al., 2018; Juarez-Lopez et al., 2014;Krithikadatta et al., 2013; Llena et al., 2015; Morgan et al.,2008; Rao et al., 2009; Robertson et al., 2011]. Some RCTs have though provided the opposite result. This may be due to poor understanding of the different remineralization pattern of fluoride and CCP-ACP complex. Fluoride produces only surface- only remineralization whereas CPP-ACP promotes subsurface remineralization, [Shen et al., 2011]. AsCPP-ACP providehigh concentrations of stabilized Ca^{2+} and PO_4^{3-} and could be beneficial in the high cariogenic environment (e.g., xerostomia, > 6 sugar exposures/day). But more longitudinal studies on the more high-risk group is needed for the comparative study of benefit by these two products [Gonzalez-Cabezas and Fernandez,2018].

Functionalized β-Tricalcium Phosphate.

Crystalline β-tricalcium phosphate (β-TCP) was coupled with carboxylic acids and surfactants to produce functionalized β-tricalciumphosphate [Karlinseyet al., 2010]. This functionalizing of β-TCP was done to create barriers that prevent premature fluoride-calcium interaction so that it can act as a targeted low dose delivery system when used in dentifrices or mouthwashes [Karlinsey and Pfarrer, 2012]. It mainly boosts up the F^- ion activity on the tooth surface, but remineralization done mostly by salivary $Ca^{2+}$and PO_4^{3-} ions.

Calcium Sodium Phosphosilicate.

Calcium sodium phosphosilicate is a bioactive glass material. It was developed as a biocompatible bone regenerative agent. Later it has been seen to release Na+, $Ca^{2+,}$ and PO_4^{3-} ions, in the oral environment. This ions interact with saliva and deposit a crystalline hydroxycarbonate apatite layer that is very much similar to tooth mineral [Burwell et al., 2009]. Calcium sodium phosphosilicatewas initially used for the treatment of dentine hypersensitivity but in some studies, it has been suggested that it could be useful for enamel remineralization too [Wefel, 2009].

Amorphous Calcium Phosphate

ACP is an unstabilizedcalcium phosphate system. When intentionally incorporatedinto a dual-chamber fluoride toothpaste it separately delivers Ca^{2+} and PO_4^{3-} ions into the mouth [Tung and Eichmiller, 2004]. On brushing, there is an intraoral mixing of Ca^{2+} and PO_4^{3-} ions which precipitate ACPor amorphous calcium fluoride phosphate. ACP and amorphous calcium rapidly transform into more stable HA or fluorhydroxyapatite. Before theirthisphase transformation, the Ca^{2+} and PO_4^{3-} ions transiently bioavailable for subsurface lesion remineralization [Cochrane et al., 2010].

Polyphosphates

Sodium Trimetaphosphate.the potential risk of fluorosis can be reduced by replacing fluoridewith polyphosphate salts like sodium trimetaphosphate(STMP), calcium glycerophosphate, or hexametaphosphate without affecting the anticaries activity [da Camara et al., 2016; Takeshita et al., 2016; Zaze et al., 2014. STMP is the most effective anticaries agent with an ability to inhibit demineralization and enhance remineralization [Freire et al., 2016; Takeshita et al., 2011].

STMP (Na3P3O9) is an inorganic phosphate which strongly binds to phosphate end on enamelsurface and

remain adsorbed for a longer time compared to other phosphates [McGaughey and Stowell, 1977]. This forms a protective layer on the enamel surface that limits diffusion of carious ions during a cariogenic attack [McGaughey and Stowell, 1977]. In situ examination have shown that supplementation of a low-fluoride dentifrices with STMP produced same remineralization effects to a formulation containing 1,100-ppm fluoride [Danelon et al., 2013; Takeshita et al., 2016], while conventional fluoride dentifrices and varnishes significantly increases their remineralization of artificial caries lesions when STPM is added with them [Danelon et al., 2015; Manarelli et al., 2015]. Additional clinical studies are needed to ascertain the influence of STMP on the reversal of non-cavitated lesions.

Natural Products

Plant-derived natural products that have demonstrated the capability o to beneficially shift the de-/remineralization caries equilibrium.GallaChinensis, a leaf gall produced by parasitic aphids, is most promising among them [Cheng et al., 2008, 2010]. Hesperidin, a citrus flavonoid, and gum arabic, an Acacia exudate, are other natural products that have been found to suppress acid-dependent demineralization and augment remineralizationeven under fluoride-free conditions [Islam et al., 2012; Onishi et al., 2008].

Conclusions

The preventive and minimally invasive dentistry era has begun and demands the need for developing newer techniques to remineralize enamel caries lesions. While fluoride-mediatednatural repair of early lesions is depended on so many factors like diet oral hygiene saliva quality and patient compliance. On contract to that Non-fluoride remineralization, systems are less depended on these factors. They also improve the structure, aesthetics, and acid resistance of the remineralizedlesion. Furthermore, these strategies can prevent a non-cavitated lesion from being subjected to a “death spiral of restorations” due to secondary caries [Qvist, 2008]. They are aimed to reduce fluorosis but enhance their efficacy in very low potential doses. Thus a biomimeticstrategy for enamel regeneration is the future where organized enamel apatite crystals which attach with tooth surface are grown to replace demineralized tissue. Guided enamel regeneration and some of the biomimetic technologies discussed here are steppingus closer to the reality of growing artificial enamel.

Disclosure Statement

The authors have no conflicts of interest.

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