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A compendium on remineralizing agents in preventive dentistry

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Abstract
Dental caries is a complex, cyclical process involving repeated phases of demineralization and remineralization. Remineralization serves as the body's natural repair process, in which calcium and phosphate ions from oral fluid are redeposited into the hydroxyapatite (HAP) crystal structure of enamel. Minimal intervention is a key phrase in today's dental practice. Minimal Intervention Dentistry (MID) emphasizes preserving natural tooth structure through preventive care, early detection, and minimally invasive treatments. This approach focuses on managing dental caries at its earliest stages, aiming to reduce the need for extensive restorative procedures. The process of tooth remineralization has been extensively researched, leading to innovative technologies that promote enamel repair and prevent demineralization. Various remineralizing agents have been utilized to restore enamel and treat white spot lesions (WSLs). Fluoride has formed the mainstay of enamel remineralization for many decades. It is known to control caries predominantly through its topical effect inhibiting demineralization by forming fluorapatite on the enamel surface.

Recent research has moved towards biomimetic approaches. The term "Biomimetics" is derived from the Latin words "bios" which means life and "mimesis" which means to copy or mimic. Biomimetic remineralization has emerged as a transformative approach in dental research, aiming to restore the structural and functional integrity of demineralized enamel by emulating natural mineralization processes. This article reviews the progress in dental remineralization strategies and highlights the essential qualities of an effective remineralizing material.

Keywords: Remineralization, enamel, hydroxyapatite, white spot lesion, fluoride, biomimetics

Introduction

Dental caries is a multifactorial condition resulting from the demineralization of enamel due to acid production by cariogenic bacteria. [1] Demineralization of enamel is the process in which minerals, primarily hydroxyapatite is leached out of the enamel layer of teeth. White spot lesion is an early sign of enamel demineralization. [2] It represents the first stage of dental caries and their prevalence has been increasing in recent years. [3] White spot lesions appear as chalky or dull white areas on smooth tooth surfaces, especially where plaque accumulates. The chalky appearance of WSLs is caused by the difference between the refractive index (RI) of healthy and demineralized enamel. [4] This condition can be caused by fixed orthodontic treatments, inadequate oral hygiene, fluorosis, and genetic factors. [5] While traditional caries management has relied on restorative treatments, contemporary dentistry focuses on preventive and minimally invasive strategies, particularly through remineralization-based approaches.

Management of WSL Fluoride

Fluoride remains the most established and widely utilized agent for the remineralization of dental enamel. It plays a crucial role in preventing white spot lesions (WSL) through various applications, including fluoride mouthwashes, gels, toothpastes, varnishes etc. It helps prevent dental caries by modifying bacterial metabolism in dental plaque, inhibiting enzymatic processes, reducing acid production, and altering bacterial flora and metabolic activity. Additionally, fluoride minimizes demineralization and enhances the remineralization of early-stage carious lesions, particularly at low concentrations. [6]

Hanna Enerbäck *et al* through their experiments proved that to prevent demineralized lesions in the aesthetic zone, high-fluoride mouth rinse and high-fluoride toothpaste may be recommended. [7]

Bijle *et al* examined the effect of incorporating arginine in a 5% sodium fluoride (NaF) varnish on its remineralization potential and HGF-1 cytotoxicity. He concluded that incorporation of 2% Arg in NaF varnish enhanced the enamel remineralization potential of NaF varnish; while 8% Arg in NaF varnish was cytotoxic to HGF-1 cells. [8]

Cpp Acp

This approach involves the use of calcium phosphate particles dissolved in casein milk protein. It generates a supersaturated concentration of amorphous calcium phosphate around the tooth in the acidic environment of dental plaque. As a result, it is believed to enhance the remineralization process by facilitating the deposition of essential minerals back into the enamel. [9]

Rahmath Meeral proposed that casein phosphopeptide amorphous calcium phosphate-based fluoride products are effective preventive measures for young patients when compared with plain CPP ACP and other topical fluorides. [10]

Also, Shen P *et al* demonstrated varnish combining fluoride with casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) is more effective in enhancing white spot lesion (WSL) remineralization and fluoride uptake compared to a fluoride-only varnish. [11]

Xylitol

Xylitol is a non-fermentable sugar alcohol that exhibits sweetness comparable to that of sucrose and is widely employed as a sugar substitute. Beyond its role as a sweetener, xylitol has demonstrated significant benefits in

oral health, particularly in the prevention of dental caries. It is hypothesized that xylitol interferes with the synthesis of extracellular polysaccharides, which are essential for bacterial adherence to the enamel surface. Consequently, this inhibition may lead to a reduction in biofilm formation and acid production by cariogenic bacteria. The caries-preventive effects of xylitol are well established, and it has been incorporated into a variety of oral health products, including chewing gums, syrups, lozenges, sprays, mouthwashes, gels, toothpastes, and confectionery items. [12] Nayak *et al* have shown that 20% xylitol or 20% milled xylitol varnishes can be considered as an effective alternative to Fluoride for the remineralization of white spot lesions in primary and newly erupted teeth. [13] However Brown *et al*. concluded that xylitol conferred no additional clinically significant preventive effect against dental caries in adults with sufficient fluoride exposure. [14]

Silver Diamine Fluoride

Silver diamine fluoride (SDF) is a clear colorless solution containing both silver and fluoride ions. Silver ions interact with protein groups of sulfhydryl's and deoxyribonucleic acid, altering bonding and inhibiting hydrogen. It aids in the restoration of hydroxyapatite, which is persistently subjected to acid-induced demineralization. [15]

Faith Miaomiao Zheng *et al* showed that SDF is a caries-arresting fluoride agent with antibacterial and mineralising properties. It can inhibit biofilm formation, promote remineralisation, counteract demineralisation, prevent collagen degradation and occlude dentinal tubules. Hence SDF can be used to arrest caries in a simple, painless and non-invasive manner. [16]

Hydroxyapatite

Hydroxyapatite (HAP) is a bioactive and biocompatible material with a chemical composition closely resembling that of the apatite crystals found in human enamel. This makes make hydroxyapatite suitable for use in toothpastes aimed at remineralizing enamel. [17]

Elzbieta Paszynska *et al* through their experiments proved that hydroxyapatite is safe and efficient anticaries agent in oral care. [18]

Maurizio Bossù *et al* showed that the use of Biomimetic Hydroxyapatite toothpastes are valuable preventive measures against dental caries in primary dentition since it prevents the risk of fluorosis. [19]

Nanoparticles

In recent years, significant progress has been made in the use of nanotechnology for anti-caries dental materials, particularly nano-adhesives and nano-composite resins. Inorganic nanoparticles, due to their ability to disrupt bacterial metabolism and prevent biofilm formation, have become a focal point in dental applications. [20] Furthermore, fluoride-functionalized inorganic NPs have been investigated to enhance the efficacy of these materials. These modified nanoparticles not only contribute to the inhibition of demineralization but also facilitate remineralization by promoting apatite formation, thereby offering a promising strategy for enhancing the durability and resistance of enamel to caries progression. [21]

Nanoparticles of Amorphous Calcium Phosphate (NACP)

In an experiment by Fan M *et al* the NACP adhesive demonstrated strong bioactive properties by releasing calcium and phosphorus, neutralizing acids, reducing lactic acid production, and lowering bacterial counts. It showed the most effective enamel remineralization, with improved microhardness and notable mineral deposition. Hence, NACP adhesive exhibited good performance in remineralizing initial enamel lesion with cariogenic biofilm. [22]

Nano Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP)

Elgamily H *et al* through their experiments showed that toothpastes containing nCPP–nACP with probiotic strain proved a potential remineralizing property with a more promising antimicrobial efficiency. [9]

Nano hydroxyappetite

Nano-hydroxyapatite (N-HA) represents a critical source of mineral ions for enamel remineralization. Comprising crystals typically ranging from 50 to 1000 nm, N-HA closely mimics the composition and structure of biological apatite. [23] Its nanoscale dimensions confer a high surface area-to-volume ratio, significantly enhancing its binding capacity. This facilitates the effective delivery of calcium and phosphate ions to the enamel surface, contributing to the occlusion of micro-porosities in carious lesions. [24] Moreover, N-HA particles can infiltrate enamel micropores and function as nucleation sites, thereby promoting crystal growth and enhancing the structural integrity of the enamel. [24, 25]

In a comparative evaluation of efficacy of four remineralising agents namely CPP-ACP, Nano hydroxy appetite (N-HA), Sodium Fluoride (SF), ACP functionalized with fluoride (F-ACP) by Vitiello *et al*, it was found that in all groups tested, after seven days of application of remineralizing agents, complete remineralization was not obtained, but reorganization of the enamel structure from both quantitative and qualitative points of view CPP-ACP and N-HA gave better results compared to SF and F-ACP. [26]

Nano silver fluoride

Nano-silver fluoride (NSF) is a Silver nanoparticle product comprising chitosan and fluoride. Silver nanoparticle (AgNP) anticaries agents are not irritating and have an effective bactericidal effect against *S. mutans* dynamic biofilm. [27]

Rama Raji Sankaranarayanan compared the efficacy of re-mineralization of white spot lesions between two green synthesized nanoparticle varnishes namely nano silver fluoride and nano hydroxyapatite varnish. The remineralization efficacy of nano silver fluoride was found to be higher than that of nano-hydroxyapatite.

Bioactive Glass

Dr. Larry Hench's invention of bioactive glasses (Bioglass) in the late 1960s revolutionized regenerative medicine by enhancing the body's natural ability to generate new bone. This breakthrough introduced a completely new approach to biomaterials. In dentistry, bioactive glass supplies essential elements like calcium and phosphate to the oral environment, aiding in tooth remineralization. [28, 29]

Omran T, Mostafa M, Abd El-Raouf E found that the mineral content of the demineralized enamel significantly

increases using Biomin (bioactive glass) containing toothpastes twice daily for two weeks. The use of bioactive glass toothpastes as a remineralizing agents are promising in repairing early carious lesions. [30]

Also, in a comparative evaluation of the remineralizing potential of 2 types of bioactive glass with casein-phosphopeptide stabilized-amorphous calcium phosphate (CPP-ACP) by Salah *et al* the application of Biomin F paste (bioactive glass) over a 4-week period, both in-office and at home, resulted in the improvement of white spot lesions (WSLs). Compared to Novamin (bioactive glass) and CPP-ACP, Biomin F also showed a significantly greater reduction in fluorescence intensity, indicating enhanced potential for lesion remineralization. [31]

Probiotics

Over the last ten years, multiple biotic approaches have been proposed for caries prevention, with prebiotics, probiotics, and synbiotics emerging as the key categories.

Mohammed Nadeem Bijle showed that the synbiotic fluoride therapy enhanced enamel remineralization with no biocompatibility concerns. [32]

Increased ammonia production neutralizes bacterial acids linked to caries, preventing enamel mineral loss. The prebiotic L-arginine (at 1 %/2 % by wt.) in a 5 % NaF varnish enhanced the enamel fluoride uptake and remineralization potential of the conventional 5 % NaF varnish. [33]

Recently, a randomized comparative trial was done by Murugesan *et al* to assess the effectiveness of probiotic and fluoride toothpaste on enamel mineralization and Streptococcus mutans levels in cleft lip and/or palate patients undergoing fixed orthodontic appliance therapy. It showed that Streptococcus mutans levels in the probiotic-containing toothpaste were lesser when compared to the fluoridated toothpaste group. [34]

El Moshy *et al* explored the use of agarose hydrogel combined with enamel matrix derivative (EMD), with or without nano-hydroxyapatite (n-HA), for repairing demineralized human enamel. The results showed that the n-HA-EMD-agarose hydrogel improves enamel surface hardness and boosts mineral deposition, highlighting its potential as an effective biomimetic treatment for enamel remineralization. [35]

Self Assembling Peptides

P11-4, a self-assembling peptide with the sequence CH_3CO-Gln-Gln-Arg-Phe-Gln-Trp-Gln-Phe-Gln-Gln-$GlnNH_2$,

represents a significant advancement in biomimetic regenerative dentistry. Commercially formulated as Curodont Repair (Credentis AG, Switzerland), it is specifically engineered for the non-invasive treatment of incipient carious lesions on smooth enamel surfaces. Upon topical application, P11-4 undergoes self-assembly under physiological conditions to form a three-dimensional nano fibrous scaffold within the subsurface lesion. This scaffold mimics the natural extracellular matrix and provides a conducive environment for nucleation and oriented growth of hydroxyapatite crystals**,** thereby facilitating de novo enamel regeneration and structural remineralization of early carious lesions.

Shanbhag *et al* showed that P11-4 promoted the regeneration of incipient caries-like lesions. However, there is added benefit when this peptide is used in combination with a fluoridated calcium-phosphate-based agent. [36]

Atteya *et al*. assessed the effects of self-assembling peptide (P11-4), nanosilver fluoride (NSF), and sodium fluoride (NaF) on the remineralization of white spot lesions in permanent teeth. Results showed that P11-4 and NSF varnish reduced ICDAS scores, caries activity, and DIAGNOdent readings. However, the reduction in ICDAS scores was not significantly different from that observed with NaF. [37]

Resin Infiltration

Resin infiltration is a minimally invasive technique in which microporous enamel areas of non-cavitated initial carious lesions are filled with low-viscosity, light-cured resins (infiltrants), thereby inhibiting further progression of caries. [38] In addition to its preventive role, resin infiltration has demonstrated efficacy in esthetically masking white spot lesions. [39] This masking effect is attributed to the refractive index of the infiltrant (1.52), which closely approximates that of enamel/apatite (1.62), in contrast to the lower refractive indices of water (1.33) and air (1.00). As a result, light scattering is significantly reduced with increasing infiltration, leading to improved visual integration of the lesion with surrounding enamel. [40]

Bourouni *et al* by their analysis showed that resin infiltration has a significantly higher masking effect than natural remineralization or regular application of fluoride varnishes. This makes it a suitable option for esthetically concealing enamel white spot lesions and mild to moderate fluorosis. [41]

Herbal Remineralising Agents

Plant-derived alkaloids and phytochemicals are gaining recognition in dentistry for their dual role in combating harmful oral bacteria and promoting enamel remineralization. These natural compounds help restore mineral content in teeth while preventing further demineralization.

Grape Seed Extract

Grape seed extract (GSE), contains high levels of proanthocyanidins (PA). It has been reported that PA strengthens collagen-based tissues by increasing collagen cross-links and accelerating the conversion of soluble collagen to insoluble collagen. [42]

Deepak Sharma *et al* compared the efficacy of grape seed extract and Sodium Fluoride on surface and subsurface enamel lesions. Grape seed extract exhibited comparable remineralizing efficacy to sodium fluoride on both surface and subsurface enamel lesions. These findings suggested that grape seed extract could be a viable natural alternative to fluoride for the prevention and treatment of dental caries. [43]

Propolis

Propolis, miswak, and chitosan are natural substances recognized for their beneficial effects on oral health, particularly in combating dental caries through antimicrobial properties and promoting enamel remineralization.

Miswak extract is rich in calcium, while its fluoride content is low. Propolis has different amounts of calcium and

phosphorus according to its phytogeographic origin. While chitosan nanoparticles, due to their nontoxicity and biodegradability, are used as drug delivery vehicles through encapsulating nanoparticles of biologically active drugs.

Mariem O Wassel and Dalia Sherief compared the remineralizing potential of Propolis, miswak, and chitosan based dental varnishes either without or with 5% NaF to 5% NaF varnish in primary teeth enamel samples with artificial enamel lesions. Chitosan-nanoparticles and miswak containing varnishes were most effective in remineralizing enamel lesions probably due to the release of F^{-}, Ca^{++}, PO_4^{---} ions compared to NaF varnish that released F^{-} only. [44]

Hesperidin

Hesperidin is a naturally occurring flavonoid glycoside found primarily in citrus fruits. It was first isolated in 1828 by French chemist Lebreton. It has shown promise in promoting dentin remineralization by interacting with collagen proteins. This interaction helps stabilize the collagen matrix, which is crucial for preventing the loss of calcium and phosphate ions and facilitating their redeposition in tooth tissues. [45]

Hiraishi *et al* examined the effect of Hesperidin on preservation of collagen matrix of tooth. Hesperidin preserved collagen and inhibited demineralization, and enhanced remineralization even under the fluoride-free condition. [46]

Ozone Therapy

Ozone therapy in dentistry offers multiple benefits in managing dental caries. Its oxidative proteolytic action breaks down the organic components of demineralized enamel, enhancing the penetration of remineralizing agents like fluoride or nano-hydroxyapatite. Additionally, ozone disrupts cariogenic bacteria within dental biofilms, altering the microbial environment and making it challenging for harmful bacteria to recolonize, thereby favoring the growth of normal commensal organisms. Pyruvic acid, produced by cariogenic bacteria, contributes to lowering the pH, promoting demineralization. Ozone oxidizes pyruvic acid into acetate and carbon dioxide, with acetate having a higher pKa, thus enhancing pH buffering in dental plaque and promoting remineralization. [47]

S. R. Samuel investigated the effect of ozonated water in remineralizing artificially created initial enamel caries and proved that ozonated water can be considered an effective agent in reversing the initial enamel caries alongside with nano-hydroxyapatite compared to nano-hydroxyapatite alone and saliva. [48]

Conclusion

In recent years, restorative dentistry has increasingly shifted toward conservative and preventive approaches, with remineralization emerging as a preferred strategy for managing early carious lesions and regenerating lost tooth structure. By focusing on the identification, preservation, and non-restorative treatment of incipient caries, this approach not only conserves healthy tooth tissue but also reduces clinical burden, treatment costs, and patient discomfort. Alongside these clinical advantages, scientific advancements have propelled the development of novel remineralizing agents that go beyond surface-level repair. While conventional materials like fluoride, CPP–ACP, and bioactive glass continue to show clinical success, current research is increasingly focused on biomimetic technologies that replicate natural mineralization within demineralized collagen matrices. Despite promising results, further investigations are needed to address challenges related to subsurface lesion penetration, material stability, and long-term clinical performance. Future research should aim to develop multifunctional remineralizing agents that integrate regenerative, antimicrobial, and protective capabilities—paving the way for minimally invasive, biologically driven dental care.

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