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REVIEW ARTICLE **OPEN ACCESS**

Current Concepts in Remineralisation

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ABSTRACT
Modern dentistry aims to arrest the spread of caries progression and improve the aesthetics and functionality of teeth by offering minimally invasive management of early caries lesions with various remineralization agents. Fluoride is the best in these early caries treatments, but there are other novel breakthroughs that are either in the testing stage or have already reached the market. Numerous studies have shown both the limitations and the remineralizing effectiveness of fluoride therapy, which encouraged researchers to create additional remineralizing strategies. Even though a majority of novel remineralization strategies aimed to enhance the efficacy of fluoride by incorporating additional potentially useful chemicals in the formulation, some recent techniques have been launched with the goal of generating remineralizing scaffolds within the lesions. This review details the latest remineralizing approaches that promote remineralization and discusses their clinical implications.
Key words: *Fluorides, Calcium, Phosphate, Non-fluoridated agent, Casein derivatives, Xylitol*

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INTRODUCTION

The goal of contemporary dentistry is to prevent caries from developing in the first place and to treat early caries lesions with minimally invasive procedures using different remineralizing agents. Dental caries is a dynamic process consisting of alternating periods of remineralization and demineralization. According to Featherstone and Chaffee et al, the progression or the reversal of the lesion is based on the homeostasis between demineralization and remineralization favouring pathological and protective factors [1]. Remineralization is a natural repair mechanism in which oral cavity minerals are carried into tooth structures partly demineralized and thereby replacing minerals in enamel and dentin partially demineralized. There is fluoride mediated and non-fluoride-mediated therapies that promote the remineralization of teeth. Though fluoride-mediated therapies are the cornerstone, new strategies for remineralization developed that claim to promote deeper lesions remineralization.Remineralizing agents are part of minimal intervention dentistry, to control the cycle, depending on the microbial environment surrounding the tooth [2]. This review article details the current concepts in remineralizing agents and their clinical implications.

Ideal requirements [3]

1. Calcium and phosphate into the subsurface should be delivered.
2. Excess calcium shouldn't be delivered.
3. Calculus formation should not be promoted.
4. Should be active at acidic pH.
5. Should work in dry mouth cases.
6. Should improve the remineralization efficacy in saliva.
7. It is better than fluoride, for novel materials.

They are categorized into Fluoridated and Non-fluoridated remineralizing agents.[4]

FLUORIDE-MEDIATED REMINERALISING AGENTS

According to Walshi *et al*, in arresting caries lesions diverse fluoride therapies are found to be clinically effective [3]. Soi et al explained four mechanisms of fluoride action. Fluorapatite crystals are highly resistant to acid attack, so fluoride inhibits the demineralization of teeth. Second, calcium and phosphate are brought together by fluoride to become fluorapatite crystals which in turn enhance remineralization. Third, fluoride interferes with phosphoenol pyruvate (PEP) formation and inhibits the action of carious bacteria acid-producing [5].Flouride agents at high concentrations provide effective remineralization for non-cavitated lesions involving enamel in primary and permanent teeth. The recent development in fluoride therapy is the introduction of fluoride combinations with some metals to enhance remineralization. Combinations include silver diamine F (SDF) and stannous F (SnF2). For remineralizing caries lesions, SDF is highly effective in the crown and root surfaces [6]. Study by Fernandez et al. observed a superior effect of SnF2 formulations on enamel demineralization prevention in cariogenic biofilms existence [6].

The rationale for an alternative to fluoride

The presence of phosphate and calcium ions restricts fluoride's capacity to encourage remineralization. Moreover, Fluoride may be effective in treating smooth surface caries, but on pit and fissure caries its impact is minimal. Fluorosis caused by fluoride overexposure is another potential constraint. These limitations lead to non-fluoridated remineralization alternatives.

NON-FLUORIDATED REMINERALIZING AGENTS

Casein Phosphor-Peptides-Amorphous Calcium Phosphate (CPP-ACP):

Casein phosphopeptides are new in preventive dentistry. It has calcium and phosphate. Ca and phosphate are found to be stabilized by casein phosphor-peptides (CPP), which keeps them in a soluble form known as amorphous calcium phosphate (ACP).Calcium and phosphate present in saliva and oral biofilm influence demineralization–remineralization processes [7].

To increase remineralization casein phosphopeptides maintain calcium and ionic phosphate supersaturation and modulate the calcium phosphate levels bioavailability.ACP controls CPP precipitation with calcium and phosphate ions. One molecule of CPP can hold 5 fluoride ions, 15 phosphate ions, and 25 calcium ions. Calcium phosphate causes the remineralization of subsurface enamel lesions [8].

Advantages:

1. It helps in localizing ACP in dental biofilm and also in buffering the freely available calcium and phosphate ions.
2. It improves fluoride ion's effectiveness as a remineralizing agent.
3. It prevents Streptococcus mutans and Streptococcus sobrinus binding and improves remineralization [9].

Disadvantages:

1. It is pH responsive

According to Bailey and Guclu et al, CPP-ACP products with better remineralizing and anticaries effects were observed compared to the fluoride-containing product [10, 11]. However, other studies conducted by Beerens et al. Brochner et al; Huang et al., contradict the results from the above studies [12-14]. Study by Shen et al. concluded that remineralization of enamel subsurface lesions enhanced by CPP-ACP compared to fluoride products alone [15].

i. CPP-ACPF

Casein Phosphopeptide–Amorphous Calcium Phosphate Fluoride. To promote remineralization properties fluoride is incorporated into the CCP-ACP formulation. However, studies conducted by Raphael and Singh et al observed that this modification was not effective as CPP-ACP alone [16, 17]. According to Llena et al. [18] CPP-ACPF has shown remineralization on smooth surface caries.

ii. β- Tricalcium Phosphate

TCP with fluoride combination was introduced to make acid-resistant minerals and provide greater enamel remineralization.It forms a protective barrier when used as toothpaste. Calcium, phosphate, and fluoride ions are released when TCP contacts saliva and the barrier breaks down [7]. β-TCP forms functionalized β-TCP (fβ-TCP) along with organic and or inorganic materials.

iii. Functionalized Tricalcium Phosphate (F-Tcp)

It is a hybrid comprised of beta-tricalcium phosphate (TCP) fused with sodium lauryl sulfate or fumaric acid. This combination results in "free" phosphate and "functionalized" calcium, to enhance Papas effectiveness. The purpose is to provide a targeted low-dose delivery system by creating a barrier that prevents fluoride-calcium premature interaction once applied to teeth [19].

When TCP contacts saliva and tooth, calcium, phosphate, and fluoride ions are released by breaking down the protective barrier. It was designed to promote fluoride activity in the tooth. Walsh et al study, comparing CPP-ACP and TCP in remineralizing early lesions found that CPP-ACP has a significant advantage over fTCP because they can deliver stabilized Ca2+ and PO4 3– ions over a longer time, whereas fTCP supplies few ions while brushing [20].

iv. Dicalcium Phosphate Dihydrate (DCPD)

DCPD is an apatite precursor. It turns into fluorapatite in combination with fluoride.Research data has shown that DCPD inclusion in a dentifrice increases free calcium ions levels, for up to 12 hours after brushing when compared to silica dentifrices [21].

v. Sodium Calciumphosphosilicate (Bioactive Glass)

Dr. Larry Hench in the 1960s invented bioactive glass [22]. Bioglass (BG) is composed of phosphate, calcium, sodium, and silicate. They deposit calcium phosphate when exposed to body fluids. It works as a biomimetic mineralizer and mimics mineralizing characteristics of the body and significantly impacts cell signaling benefiting the tissue structure and function [22]. Bioactive glass releases Na+, Ca2+, and PO4 3- ions when reacting with aqueous oral environment. These ions subsequently interact with saliva and result in a crystalline hydroxycarbonate apatite layer deposition, identical to tooth mineral.However, currently available studies are limited that support the remineralizing ability for clinical usage [23]. Hence more clinical trials are required to support its remineralizing capacity and clinical usage.

vi. TMP: Sodium Trimetaphosphate

STMP (Na3P3O9) can strongly bind to enamel surface phosphate sites for a longer time and is a condensed inorganic phosphate.A study by Danelon et al observed that TMP nanoparticles in a NaF-containing toothpaste increase its remineralization capacity [24]. In contrast, another study by Pancote et al noted that remineralizing ability of TMP is similar to standard F-concentration toothpaste when added to low-F-concentration toothpaste [25].

vii. 45S5 BG

Hench et al. originally developed 45S5 BG consisting of 45% SiO2, 24.5% Na2 O, 24.5% CaO, and 6% P2 O5 in weight. [26] It is biocompatible with remarkable controllable biodegradability osteoconductivity, and osteoinductivity. HCA layer is formed when it is exposed to an aqueous environment releasing sodium ions, which increase pH leading to the ion's precipitation.

NANOPARTICLES

Calcium Fluoride Nanoparticles

According to Xu HHK et al., nanoCaF2 addition increases cumulative fluoride release as the CaF2 nanoparticle has a 20-fold higher surface area compared with traditional glass ionomer cement.

Calcium Phosphate-based Nanomaterials

It has HAP, TCP, and ACP nanoparticles and releases calcium/phosphate ions, increasing HAP supersaturation in cavitated lesions.

Nano-Hydroxyapatite:

Nano-sized HAP (n-HAP) nanoparticles can bind to enamel surfaces and plaque and bacteria fragments [27]. Though the mechanism is not clear, it helps in remineralization through nanoparticle deposition in enamel or the formation of synthetic enamel on the tooth [27]. Some researchers hypothesize that nHA functions as a calcium phosphate reservoir, which would cause aggregated nanoparticles to fuse and create a closed layer, which would inhibit demineralization and cause remineralization [28].

A study by Juntavee et al [29] reported that nHA was better than fluoride in remineralizing cementum and enamel, and it was particularly successful in remineralizing around restoration margins whereas a study by Esteves-Oliveira et al [30] obtained contradicting results in which nHA could not significantly decrease demineralization. Even though the results from experiments of this agent are promising, the mechanical properties and stability are inferior, and limited clinical application because it takes longer duration for the mineral. Hence further evidence is warranted in this direction.

ACP Nanoparticles

They act as calcium and phosphate ion sources. Nanocomposites with nanoACP prevent demineralization at the restoration–enamel margins with less enamel loss [19].

Xylitol

Xylitol is a non-fermentable sugar alcohol having noncariogenic and cariostatic effects.When consuming xylitol as gum, it stimulates alkaline flow and mineral-rich saliva from the palate. A recent study by Cardoso et al showed its remineralizing potential when introduced to 20% varnishes [31].

Theobromine

Theobromine (3,7dimethylxanthine) is a white crystalline powder of the methylxanthine family. It is soluble in water, crystalline in structure, and found in chocolates and tea. Theobromine has anti-

glucosyltransferase properties and inhibits the activity of S mutans. It also generates hydroxyapatite crystallites of enlarged size in calcium and phosphate presence, which hardens enamel and makes it less susceptible to acid assault.In Amaechi et al. study, with theobromine and fluoride toothpaste higher mineral increase was observed [32]. Grace Syafira *et al.* after treatment with theobromine on the enamel surface have shown an increased enamel microhardness [33].

Self-Assembling Peptide

The self-assembling peptide has 11 amino acids, hence the name P11-4. In the presence of high ionic strength and acidic pH peptide self-assembles into hierarchical 3-dimensional fibrillar scaffolds [34]. Due to increased mineral gain and prevention of mineral loss, peptide therapy improves net mineral gain. A study by Kind et al. indicated that the self-assembling peptide P11-4 facilitates its remineralization by supporting the nucleation of de novo hydroxyapatite. As a biomimetic mineralizing agent P11-4 has demonstrated extraordinary results [35]. The efficacy of this agent to reverse initial carious lesions, which are resistant to fluoride remineralization, was noted by Alkilzy et al. and Brunton et al [36, 37]. P11-4 is a prominent therapy in guided enamel regeneration; however, a significant number of long-term trials are required to confirm these findings.

Amelogenin

Amelogenin plays a significant role in overviewing the regulation of HA crystals in mineralization. Mature enamel doesn't have matrix proteins and hence cannot regenerate. Various therapies have been introduced with synthetic amelogenin-based systems to replicate the enamel. It was discovered that the porcine recombinant amelogenin (rP172) stabilized calcium phosphate.[38] In vitro study by Bagher et al and Mukherjee et al demonstrated that leucine-rich amelogenin peptide-treated enamel lesions decreased the depth of the lesion and enabled enamel biomimetic regeneration [39, 40].The difficulty in extracting and storing the protein makes it potentially inappropriate for clinical usage, which is a concern associated with amelogenin-mediated enamel regeneration. Furthermore, to date, there is no evidence of biomineralization in vivo.

*Electrically Accelerated And Enhanced Remineralization (EAER***)**

It uses iontophoresis to promote remineralizing ions flow into the caries lesion's deepest site and produces a favorable environment for remineralization, which gives optimal hardness and mineral density for the repaired lesion. In contrast to biomimetic peptides, EAER does not "regenerate" lost enamel through matrix proteins or the Ca2+ and PO43- ions uptake [41]. The in vitro results are very challenging, however in vivo studies are needed for clinical use.

Polyamide

Poly(amidoamine) (PAMAM) dendrimersare similar to amelogenins and are also known as artificial proteins. These amelogenin-inspired dendrimers control the synthesis of HAP crystals. Chen et al evaluated PAMAM dendrimer effect modified with the carboxylic acid groups (COOH) on HAP crystallization on the etched enamel surface, concluding its ability to act as an organic template on the demineralized enamel surface and inducing the formation of HAP crystals [42].However, they are not in clinical usage as limited clinical evidence is available so far.

Arginine Bicarbonate

An amino acid with particles of calcium carbonate has the ability to adhere to the mineral surface. The release of calcium from calcium carbonate helps in remineralization whereas carbonate may cause a slight side in pH.In research by Cheng et al., arginine dramatically boosted fluoride uptake when combined with fluoride compared to fluoride alone [43].

Polydopamines

Polydopamine has a strong adhesive property to substrates under wet conditions and is created by the oxidative polymerization of dopamine in aqueous solutions. It has been discovered that collagen fiber binding polydopamine acts as a nucleation site for HA crystal development [44].

Biomimetically Modified Mineral Trioxide Aggregate

Incorporating polyacrylic acid and sodium tripolyphosphate as biomimetic analogs in phosphate-containing stimulated bodily fluid increases the remineralization efficiency of mineral trioxide aggregate (MTA). The biomimetic analog in MTA by releasing biomimetic material from set MTA enhances dentin's remineralization.

Proanthocyanidin

PA is a naturally occurring plant substance. It upregulates collagen cross-links and inhibits acid production by *S. mutans*.It is in grape seed extract (GSE), and when combined with pH 7.4 remineralizing solution, it can create visibly insoluble HAP complexes. Cheng et al. noted when treated with proanthocyanidins-rich GSE an increase in the microhardness of demineralized dentine [44]. PA when combined with CPP amorphous calcium fluoride phosphate (CPP-ACFP) on remineralization of artificial root caries, a synergistic effect was noted in Epasinghe et al [45].

CONCLUSION

Preventive and minimally invasive dentistry demands newer approaches to remineralize early caries lesions. The rationale of the current remineralizing agents is to advocate a therapeutic approach instead of the conventional technique in order to remineralize early carious lesions. With the appropriate remineralizing strategy, a non-cavitated lesion is prevented from progressing into a cavitated lesion which would require restoration to make the tooth functional. The future of remineralization technology would aim at the development of a biomimetic strategy for hard tissue regeneration. Although various remineralization techniques have made substantial strides in recent years, the evidence for the majority of them is not enough to determine their inbuilt clinical potential. Dentists can deliver modern, high-quality dental treatment using the least invasive techniques if they comprehensively understand the current remineralizing agents and technologies.

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