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A review of the literature on non-fluoridated remineralizing agents for dental caries

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Abstract

Dental caries is a dynamic process affecting the hard structures of teeth resulting in continuous demineralization and remineralization and if untreated can resultin cavitation. The objective of contemporary clinical dentistry is to treat non-cavitated carious lesions by remineralizing them. Remineralization is a natural curing process that brings back the minerals to the hydroxyapatite (HAP) crystal lattice in ionic forms. To treat the initial non-cavitaed carious lesions, a number of newer remineralizing agents have been developed. In order to interact with the tooth, non-fluoridated remineralizing systems deliver phosphorous and calcium ions, alter the biofilm, and neutralize organic acids.

Keywords: Agents, dental caries, remineralizing

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1. Introduction

The hard tooth structures are affected by dental caries, a dynamic process [1]. The progression of an initial noncavitated lesion is determined by the dynamic balance between demineralization and remineralization. Modern dentistry now places more emphasis on preventing extension rather than Black's "extension for prevention" [2]. The traditional oral hygiene is frequently insufficient for controlling dental decay. In order to stop the progression of the disease, modern clinical practise emphasises the non-invasive treatment of non-cavitated lesions by means of remineralization [3]. Remineralizing agents are useful in the treatment of initial carious, early carious, and non-cavitated lesions. Remineralization is a natural healing process that brings back the minerals to the hydroxyapatite (HAP) crystal lattice in ionic forms. The re-deposition of phosphate and calcium mineral ions from saliva within the caries lesion takes place under physiological pH conditions that are close to neutral [1].

2. Concept of demineralisation-remineralisation

The ratio between remineralization and demineralization in the oral cavity, which occurs continuously, influence the strength and toughness of the tooth structure. Plaque and fermentable carbohydrates must remain on the tooth surface for the least amount of time in order for demineralization to occur. The period of time must be long enough for these carbohydrates to stay in the mouth and be broken down by oral microbes into acid. Following this exposure of the plaque to the carbohydrates, the pH rapidly decreases, which causes demineralization. This is primarily caused by the simultaneous loss of propionic acid from the plaque and the production of lactic acid. Plaque's acidic nature, though, only lasts for a short while before returning to normal after 30 to 60 minutes. Qaiser Remineralization starts when the pH rises and calcium and phosphate are present. Cavitations may result from continued demineralization. Minerals are simultaneously lost from the plaque and lost at the front of the lesion during the demineralization process [1].

3. Rationale for substitution of fluorides

It was well known in the 1980s that fluoride can prevent caries lesions from causing demineralized enamel to remineralize. Due to systemic fluorides' toxicity and the high fluoride content in toothpaste, nontoxic fluoride substitutes were later developed to serve as efficient remineralizing agents. Many diverse remineralizing techniques and agents have been studied, and many of them are currently being used in clinical settings with highly predictable positive outcomes [1].

• Fluoride has a limited impact on pit and fissure caries, but it is very effective against smooth-surface caries [2].

• Adopting a high-fluoride strategy will not prevent the possibility of negative effects (such as fluorosis) brought on by excessive fluoride exposure [2].
• Fluoride toxicity rises in the presence of malnutrition.

• Products in some nations are not fluoridated [2].

3. Ideal requisite of remineralization materials

It disseminate into the subsurface or distributes phosphate and calcium to the subsurface; prevents calculus formation; does not deliver too much calcium; operates at an acidic pH; is efficient in xerostomic patients; and enhances saliva's remineralizing capacities. The use of novel materials demonstrates an advantage over fluoride [1,2].

4. Classification of Remineralising agents

4.1. Fluorides-NaF, APF, Silver diamine fluorides,

4.2. Non fluoride remineralising agents

- ***A. Calcium phosphate compounds***- Casein Phosphopeptide- Amorphous Calcium Phos-phate (ACP), CPP-ACP, Sodium calciumphosphosilicate (bioactive glass), Tri-calcium Phosphate(TCP), beta TCP (β-TCP), Dicalcium Phosphate Dihydrate (DCPD),
- ***B. Nanomaterials***- Calcium fluoride nanoparticles, Nanohydroxy Apatite, ACP Nanoparticles, Polydopamine , Nanobioactive glass materials, PA
- ***C. Self Assembling Peptide***
- ***D. Natural remineralizing agents***- Xylitol, Grape seed extract, Yogurt Extract, cheese, Theobromine
- ***E. Others***-Lasers, Ozone

A. Calcium Phosphate Compounds

The main calcium form found in blood and milk from cows is calcium phosphate. The concentrations of phosphate and calcium in plaque and saliva, which are the main constituents of hydroxyapatite (HA) crystals, have a significant impact on the processes of tooth demineralization and remineralization [1].The first solid phase to emerge from a calcium phosphate solution that is highly supersaturated is amorphous calcium phosphate (ACP). ACP is easily converted into crystalline phases that are stable, such as apatitic or octacalcium phosphate products. It serves as a predecessor to bioapatite and a transitional phase during biomineralization [1].

For the ACP technique, a two-phase delivery strategy is necessary. The two salts now used as calcium and phosphorus sources are calcium sulphate and dipotassium phosphate. ACP, which has the potential to precipitate onto the tooth surface, is produced by the swift combination of the two salts. The ACP method was created by Dr. Ming S. Tung. In 1999, the Enamelon brand of toothpaste was the first to incorporate ACP [4].

ACP-filled Composites

Skrtic developed a restorative material that is biologically active and contains large quantities of phosphate and calcium ions to encourage the repair of tooth structure. ACP is filler that is encased in a polymer binder. It releases phosphate and calcium ions into saliva, which then deposit as an apatitic mineral into tooth structures, much like the HAP that naturally occurs in teeth and bone [1].

Dicalcium Phosphate Dihydrate (DCPD)

DCPD is a precursor to apatite and readily changes into fluorapatite in the presence of fluoride [1]. Dicalcium phosphate dehydrate (DCPD) rises the free calcium ions levels in plaque fluid in comparison to traditional silica dentifrices, and they remain elevated for up to twelve hours after brushing [2].

Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP)

In 1998, it was presented as a remineralizing agent. Casein, a milk phosphor-protein, is digested by trypsin to produce casein phosphopeptides (CPPs). Casein and calcium phosphate tryptic fragments build up and are subsequently purified using ultrafiltration. The small peptides that casein releases stabilise the calcium and phosphate ions. Casein phosphopeptide-stabilized amorphous calcium phosphate complexes (CPP-ACP) and casein phosphopeptide-stabilized amorphous calcium fluoride phosphate complexes (CPP-ACFP) are produced as a result [2,3]. It is commercially available as GC Tooth Mousse, Recaldent.

Tri-Calcium Phosphate [Clinpro Tooth Crème]/ β-TCP

The protective barrier breaks down when tricalcium phosphate, a more recent remineralizing agent, comes into contact with the tooth surface and is moistened by saliva. Additionally, it shares structural similarities with tooth enamel's hydroxyapatite. To avoid an early interaction between calcium and fluo-ride, the calcium environments of TCP are well protected. In laboratory and clinical tests, it was discovered that adding the functionalized TCP ingredient to NaF formulations resulted in mineral that was stronger and more acid-resistant than fluoride alone [4].

Studies have shown that compared to fluoride alone, the mixture of TCP and fluoride can boost enamel remineralization and construct more minerals that are resistant to acid. It forms a shield around the calcium, allowing it to coexist with the fluoride ions when it is incorporated into toothpaste formulations. When TCP comes into contact with saliva while brushing, the barrier breaks down and phosphate, calcium,and fluoride are released [1]. The structure of beta-TCP is comparable to that of apatite, and it retains special calcium environments that can interact with fluoride and enamel [3].

Functionalized TCP

Functionalized TCP, a low-dose calcium phosphate system, is present in a single-phase aqueous or non-aqueous topical fluoride formulation. It functions as a barrier when applied to the teeth, preventing early TCP-fluoride interface and allowing the targeted delivery of TCP [1].

Ion exchange resins

Researchers have given ion exchange resins (IER) a lot of credit for their versatility as drug delivery systems. Previous research has shown that IER are equally appropriate for drug delivery techniques such as controlled release, transdermal, nasal, topical, and taste masking. To encourage remineralization, ion exchange resin offers a controlled release system that delivers calcium, fluoride, phosphate, and zinc ions [2].

Trimetaphosphate ION

The formation of a barrier coating that can prevent or delay reactions of the crystal surface with its fluid environment and lessen demineralization during acid challenge is thought to be affected by the agent's adsorption to the enamel surface. The efficiency of TMP can be attributed to the fact that it either reduces calcium ion loss to solutions or promotes calcium ion diffusion into the enamel's interior [2].

Calcium carbonate carrier (SensiStat)

At the State University of New York at Stony Brook's Oral Biology and Pathology department, Dr. Israel Kleinberg created SensiStat. In 2003, Ortek's Proclude desensitising prophy paste featured SensiStat for the first time in the marketplace. In 2004, Denclude, a professionally dispensed sensitivity paste for home use, was released. It is made up of a highly soluble arginine bicarbonate SensiStat component [2].

Cavistat

The ability of BasicMint, a sugarless mint with CaviStat® (an arginine bicarbonate calcium carbonate complex) to stop dental caries from developing in primary molars, was tested [2].

Remin Pro®

The cream Remin Pro® is water-based and contains calcium phosphate in the form of hydroxyapatite. Additionally, xylitol and fluoride have both been added to this product. The smallest irregularities caused by erosion and superficial enamel lesions are filled with hydroxyapatite [2].

B. Nanomaterials

Nanoparticle ion release profiles outperform microparticle ion release profiles. Because it is hard to use nanomaterials directly to remineralize teeth in the oral environment, they are frequently added to restorative materials as inorganic fillers, such as resin composites. This enables the release of phosphate, calcium, and fluoride ions, which help the hard tissues in the mouth to remineralize. [1].

Nano hydroxyapatite

One of the most bioactive and biocompatible materials is hydroxyapatite (HA). The morphology, crystal structure, and crystallinity of nanoparticles are comparable to those of the apatite crystal found in tooth enamel. Since the 1980s, nano-hydroxyapatite (nHA)-based toothpaste has been offered for sale in Japan; it received approval as an anti-caries agent in 1993. A sol-gel method has been used to create nano-hydroxy and fluorapatite in an ethanol base. Early enamel caries can best be remineralized with 10% nano-hydroxyapatite (n HA) [5].

Bioactive Glass /Sodium Calcium Phosphosilicate

Dr. Larry Hench invented bioglass in the 1960s. It has a biomimetic remineralization property that is equivalent to the body's mineralizing traits and controls cell signals simultaneously to help restore tissue structure and function. Calcium, sodium, phosphate, and silicate make up the "bioglass" (BG) class of bioactive materials. They react by beginning to deposit calcium phosphate on their surface when they come into contact with bodily fluids [3].

A breakthrough in remineralizing technology, bioactive glass materials have been introduced in numerous dental fields. Saliva contains ions of sodium, calcium, and phosphorous that can be used to remineralize the tooth surface when bioactive glass comes into contact with saliva. After the initial application, they continue to bind to the tooth's surface, release ions, and support remineralization [4].The brand name of a particulate bioactive glass is NovaMin. A bioactive glass called NovaMinTM contains SiO_2(45%), CaO(24.5%), Na_2O (24.5%), and P_2O_5 (6%). In addition to physically filling the open tubules, NovaMin particles would bind to the exposed dentin surface and create a protective HCA layer [1,3].

Calcium Fluoride Nanoparticles

Xu HHK et al. demonstrated that the addition of nano CaF2 enhances the cumulative fluoride release in comparison to the fluoride release in traditional glass ionomer cements [1] because the CaF2 nanoparticle (nano-CaF2) has a twenty-fold higher surface area than traditional glass ionomer cements.

Calcium Phosphate-based Nanomaterials

It contains nanoparticles of HAP, ACP and TCP in order to release phosphate/ calcium ions and raise the supersaturation of HAP in carious lesions [1].

Biomimetic Remineralization of the Dentin and Enamel

In relation to this theory, remineralization cannot occur in regions where seed crystallites are absent, particularly in completely demineralized dentin. ACP nanoprecursor particles that resemble liquid and are stabilised by proteins other than collagen that are analogous to noncollagenous proteins are used in biomimetic remineralization to backfill the demineralized dentin collagen [1].

Polydopamines

Dopamine spontaneously forms polydopamine, a form of oxidative polymerization that mimics DOPA and has a strong adhesive property to a multiplicity of substrates when wet. Remineralization was stimulated in demineralized dentin when the collagen fibres were coated with polydopamine, demonstrating that the binding of polydopamine to collagen fibre acts as a new nucleation site that will be advantageous for HA crystal growth [1].

PA

The molecular nucleus of PA, a bioflavonoid, is benzene-pyran-phenolic acid. Grape seed extract (GSE) contains PA, which when shared with a remineralizing solution at pH 7.4 can create visually insoluble HA complexes [1].

C. Self-Assembling Peptide

Recent advances in research have exposed the consequence of peptide therapy, which revealed a combined effect of boosted mineral gain and slowed mineral loss from the tooth [1]. Anionic P114 is a self-assembling peptide that was produced intelligently. Self-assembling peptides create well-defined hierarchical 3-dimensional fibrillar scaffolds in response to specific environmental triggers, resulting in a new class of well-defined biopolymers with a wide range of potential uses. By replenishing the mineral itself, a bimimetic peptide like P114 has the added benefit of facilitating "natural" repair [4]. Initial surface lesions on the occlusal and proximal surfaces may reverse as a result of P11-4. Even six to twelve months after treatment, the radiopacity and aesthetics of P11–4 treated carious lesions remained stable [6].

Vickers microhardness and scanning electron microscope-energy dispersive X-ray (SEM-EDX) analysis were used by Nanwal et al. to compare the effects of remineralizing agents (nano-hydroxyapatite [n-HAP], NovaMin, calcium sucrose phosphate [CaSP], and Pro-Argin) on the surface characteristics of slenderized enamel. The stripped enamel surface was significantly remineralized by each remineralizing agent. When compared to other test agents, CaSP showed promising results by efficiently and considerably remineralizing the enamel lesions [7].

D. Natural remineralising agents

Xylitol

A nonfermentable sugar alcohol that is friendly to teeth, xylitol has been shown to have both cariostatic and noncariogenic effects. It has anticariogenic effects by deactivating S. mutans and preventing plaque from generating acids and polysaccharides. When taken as mints or gum, it will promote a greater flow of mineral- and alkaline-rich saliva from small salivary glands in the palate. Salivary flow improves the body's ability to buffer acids, and its high mineral content provides the minerals required for the body to remineralize the worn-down enamel [1].

Grape seed extract

Grapeseed extract contains a type of polyphenol called proanthocyanidin (PA). Polyphenols are compounds derived from plants that have antioxidant and anti-inflammatory properties. Proanthocyanidin speed up the alteration of soluble collagen into insoluble collagen [4].

Yogurt Extract

Milk proteins stop enamel demineralization by sticking to the enamel surface. In addition, milk enzymes aid in limiting the growth of cariogenic bacteria.Yogurt's acidic pH causes calcium ions to release, helping to remineralize enamel [4].

Cheese

Researchers have a keen interest in cheese as a possible remineralizing agent. The efficacy of cheese as a remineralizing agent has been confirmed by numerous experimental findings. Cheese is an effective communicator. Increased calcium and/or phosphorus levels in dental plaque may prevent demineralization through a common-ion effect or may promote remineralization during high pH periods [5].

Theobromine

Theobromine contains two different types of compounds that have cariostatic properties: one is antibacterial and the other is antiglucosyltransferase [8]. Theobromine displays crystalline growth in the enamel, making it less vulnerable to acid attack [6]. It is found in cocoa (240 mg / cup) and chocolate (1.89%).

E. Other remineralisng agents

Lasers in remineralization

Light amplification by stimulated emission of radiation is referred to as LASER. In 1972, a ruby laser was first used to propose the use of lasers in the dental caries prevention. The use of lasers to remineralize the tooth structure has been suggested as an addition to traditional fluoride therapy. According to Hossain et al., CO2 laser irradiation in combination with 2% NaF was more effective than CO2 laser irradiation alone at preventing dental caries [5].

Ozone

It is a chemical substance that has strong oxidising properties. In order to kill the bacterial cell membrane, ozone attacks the thiol groups of cysteine amino acids.By turning acidogenic and aciduric microorganisms into normal commensals, ozone can promote remineralization. The remineralizing solution HealOzone (KaVo GmbH, Germany), which contains xylitol, calcium, fluoride, zinc and phosphate, is currently accepted for the treatment of caries. It can be applied as 2100 ppm of ozone with a 5% concentration for 40 seconds at a flow rate of 615 cc/min [3].

5. Challenges for future

In contrast to dormant lesions, active white spot lesions are more likely to undergo remineralization. This is because their surface is more porous, which makes it easier for ions to penetrate it. To guarantee efficacy, these novel remineralizing agents still require direct clinical validation. Problems with ingredient compatibility are a common aspect of formulation difficulties. The formulation of these products, which deliver a new agent (in this case, calcium ions) and fluoride concurrently from single-phase products, may present difficulties [4, 9].

6. Conclusion

In contemporary dentistry, non-cavitated caries lesions are managed non-invasively through remineralization to halt disease progression and improve appearance, strength, and function. The nonfluoride remineralization techniques will help a lot of people. We'd be able to restore the health of oral tissues with the help of the more recent nontoxic alternative remineralization strategies.

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