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Preventive and remineralization agents in pediatric dentistry: review of the literature

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ABSTRACT

Tooth decay, which is most common in childhood, especially in the 2-5 age group, is a health problem that should be addressed as a priority. It has been reported that the application of remineralizing agents to early stage caries reduces early material loss and stops the progression of caries. In studies conducted from the past to the present, various caries preventive agents have been investigated and utilized within the scope of preventive dentistry for the early diagnosis of caries and prevention of carious lesions.

Keywords: Pediatric dentistry, primary teeth, remineralization agents

INTRODUCTION

The aim of modern and preventive dentistry is to protect oral and dental health and to take protective measures for this purpose. It includes; diet control, oral hygiene education, chemical and mechanical plaque removal, professional fluoride applications, fissure sealants and protective resin restorations. It has been reported that the application of remineralizing agents to caries at the initial stage reduces early material loss and stops the progression of caries especially decidious teeth.[1] From past to present, fluoride has been accepted as the gold standard in the treatment of enamel caries. In addition to fluoride, nanotechnological products for remineralization have also been the subject of research. For this purpose, agents such as nanohydroxyapatite (nHA), bioactive glass (calcium sodium phosphosilicate, NovaMin®), tricalcium phosphate (TCP) containing toothpastes and casein phosphopeptide amorphous calcium phosphate (CPP-ACP) have been developed. In addition, it has been reported in many studies in the literature that herbal-derived agents may also have remineralization effects. These agents have been reported as chitosan, licorice, galla chinensis, theobromine, propolis, grape seed extract, rosemary, and ginger.[2]

Many anti-caries agents have been researched and started to be used in order to prevent demineralization and ensure remineralization in pediatric dentistry. In this study, remineralization agents supported by remineralization studies especially in primary teeth are presented.

MINERAL AND ION TECHNOLOGIES

Fluoride Ion

Fluoride, recognized as the gold standard for preventing dental caries, continues to be widely accepted due to its antibacterial effects, inhibition of acid production by plaque bacteria, prevention of plaque formation, promotion of the formation of fluorohydroxyapatite from hydroxyapatite in tooth structure, and acceleration of calcium and phosphate deposition on tooth surfaces.[3-5] Systemic or topical application of fluoride has been reported to be more effective and safer in topical applications.[3,4]

Fluoride can be used alone as a caries preventive agent or in combination with other agents. In a study by Nalbantgil et al.[6], applying sodium fluoride (NaF)-containing fluoride varnish around orthodontic brackets, it was reported that fluoride varnish was more effective in remineralizing demineralized surfaces of teeth. Chu et al.[7] evaluated the effects of applying NaF and silver diamine fluoride (SDF) gels regularly to children aged 5-7 years with initial enamel caries for 12 months. The study reported that NaF and SDF gels prevented demineralization and promoted remineralization. In a study by Calvo et al.[8], it was reported that the application of 1.23% acidulated phosphate fluoride (APF) gel to demineralized tooth surfaces was an effective method for remineralization.

In addition to fluoride gels and varnishes, restorative materials containing fluoride have also been found to be highly effective in promoting remineralization. Alsaffar et al.[9] compared fissure sealants with and without fluoride in their studies and reported that fluoride-containing fissure sealants were more successful in preventing demineralization. In studies evaluating fluoride-releasing glass ionomers on demineralized lesions, Rodrigues et al.[10] reported that restorative materials with high fluoride release had higher remineralization efficacy.

When the results of studies in the literature are evaluated, it is widely accepted that fluoride and fluoride compounds are the most preferred materials in preventive dentistry applications due to their high remineralization efficacy, antibacterial properties, and easy accessibility. On the other hand, research on alternative remineralization agents continues due to the toxic effects of using fluoride at high concentrations in early childhood.[2]

Silver Ion

Silver ions, in the form of silver nitrate, have been employed in dentistry for desensitization of milk and permanent teeth, cavity disinfection, and caries prevention. It has been reported that silver ions facilitate the remineralization of demineralized tooth tissue even at low salivary pH values.[10-12] Studies have led to the development of silver diamine fluoride (SDF) due to the synergistic effect of silver with fluoride. SDF is used in different concentrations (10-12-30-38), with the 38% concentration being the most preferred in pediatric dentistry. SDF is utilized to prevent the formation and progression of caries, especially in young children with limited cooperation. Its main advantages include being non-invasive, cost-effective, easy and quick to apply, while disadvantages include causing black discoloration on the applied tooth surface and not being well-liked by pediatric patients.[13,14] Mei et al.[15] reported that a 38% SDF solution exhibited bactericidal effects on cariogenic bacteria, prevented demineralization, and reduced mineral loss from tooth surfaces.

SUGAR ALCOHOLS

Xylitol

Xylitol, a five-carbon sugar alcohol derived from cellulose, has been included in the composition of various products such as toothpaste, mouthwash, gum, medications, and gels. Xylitol cannot be fermented by cariogenic bacteria, reducing the adhesion of these bacteria to the tooth surface and lowering extracellular polysaccharide levels. Xylitol's antibacterial effect and its role in reducing *S. mutans* levels have been established. It has been reported that xylitol effectively buffers the decrease in plaque pH by increasing saliva flow rate. The increased levels of calcium and phosphate in stimulated saliva limit demineralization and enhance remineralization.[16] In an in vitro study, Siqueira et al.[17] found that a varnish containing xylitol had a significantly higher remineralization capacity compared to non-xylitol varnishes.[18]

Sorbitol

Sorbitol is referred to as a non-cariogenic sugar because it is fermented more slowly by cariogenic bacteria compared to sugars like glucose, sucrose, and fructose. Therefore, it causes less reduction in plaque pH. The caries-preventive effect of sorbitol has not been found to be as successful as xylitol when compared.[19]

Isomalt

Isomalt is commonly found in the content of sugar-free candies and gums. Like xylitol, it cannot be fermented by cariogenic bacteria, making it antimicrobial and non-cariogenic. It has the ability to bind calcium, thereby enhancing remineralization. Although isomalt's effect on caries is reported to be less successful than xylitol, it has been suggested that it may be more effective when used in combination with fluoride.[20,21]

PLANT-DERIVED AGENTS

Chitosan

Chitin is an amino polysaccharide found in the cell walls of insects, the shells of fungi, and the exoskeletons of crustaceans. Chitosan, obtained by the deacetylation of chitin, is biocompatible and has been used in medicine since the 1960s in wound dressings, surgical sutures, and bandages. It later found applications in wound treatment, cholesterol medications, and contact lenses. Chitosan is preferred in dentistry due to its antifungal and antibacterial effects. It has been reported to elevate plaque pH by buffering the effects of acids produced by cariogenic bacteria, thus supporting remineralization.[22] In a study by Hayashi et al.[23], individuals chewing gum containing chitosan reported a significant decrease in *S. mutans* counts in their saliva. In an in-vitro study examining the penetration of chitosan into enamel and its inhibition against demineralization, Arnaud et al.[24] reported that chitosan intervened in the demineralization process by inhibiting phosphorus release, resulting in higher microhardness values for teeth treated with chitosan.

Licorice Root

The medicinal use of *Glycyrrhiza glabra*, or licorice root, dates back to ancient times. It possesses anti-inflammatory, antiviral, antiallergic, and antioxidant effects. In dentistry, it is preferred in pediatric toothpaste formulations.[25,26] The presence of glycyrrhizic acid in licorice root has been found to inhibit the glucosyltransferase activity of *S. mutans*, preventing the synthesis of glucans in the biofilm. Due to this effect, it has been reported to have both caries-preventive and remineralization-promoting properties.[27,28]

Galla Chinensis

Galla chinensis (G. chinensis) is an extract derived from a traditional Chinese plant. Its use as a caries preventive agent is under investigation. Chu et al.[29] reported that this plant prevented demineralization and enhanced remineralization. In a study examining the mechanism of action of *G. Chinensis*, Zhang et al.[30] stated that it slowed down demineralization on the outermost layer of carious lesions, allowing ion penetration towards the lesion body.In in-vitro studies, Huang et al.[31] reported that using *G. chinensis* in combination with nanohydroxyapatite significantly increased the remineralization of initial enamel lesions. In comparative studies by Abdel-Azem et al.[32], it was reported that NaF and *G. chinensis* yielded similar results in terms of remineralization efficacy.

Theobromine

Theobromine, an alkaloid from the methylxanthine family, is found in high amounts in cocoa beans. While belonging to the same xanthine family as caffeine, their effects on teeth are different. It has been reported that caffeine increases the solubility of dental hard tissues, whereas theobromine reduces solubility. In an in-vitro study, Amaechi et al.[33] reported that theobromine increased the remineralization potential of teeth comparably to fluoride. Sulistianingsih et al.[34] reported that theobromine increased the microhardness of teeth with initial enamel caries and could be used for remineralization purposes.

Propolis

Propolis is a mixture containing resin produced by honey bees (*Apis mellifera*) from plant exudates to fill gaps in their hives. The active components of propolis, flavonoids, have antioxidant, antibacterial, antiviral, antifungal, and anti-inflammatory properties. It is effective against both Gram-positive and Gram-negative bacteria, particularly exhibiting strong efficacy against *Staphylococcus aureus* and *Salmonella*. The effectiveness of propolis in inhibiting the glucosyltransferase enzyme activity of *S. mutans* and *Streptococcus sobrinus*, both in vivo and in vitro, has been supported by studies. Additionally, propolis has been reported to have antibacterial activity against some anaerobic oral pathogens.[35-37] Zaleh et al.[38] reported that propolis significantly increased the microhardness of enamel lesions in initial enamel caries, and some studies on propolis's remineralization effect have yielded similar positive results.[39]

Grape Seed Extract (Polyphenols)

Polyphenols possess antioxidant, antitumoral, anti-inflammatory, and antibacterial effects. Proanthocyanidins, with high antioxidant capacity, are present in grape seed extract. One of the essential properties of proanthocyanidin is its ability to strengthen tissues containing collagen by increasing cross-linking of collagen. Some studies have reported that proanthocyanidin indirectly promotes hydroxyapatite growth by increasing exogenous collagen cross-links and inhibiting the glucosyltransferase enzymes of *S. mutans*, preventing caries.[40,41] In a study by Benjamin et al.[42], grape seed extract was reported to be significantly effective in remineralization. Mirkarimi et al.[43] noted in an in-vitro study on primary teeth that grape seed extract significantly increased the microhardness of teeth with initial enamel caries. A study by Nagi et al.[44] found grape seed extract to be effective in remineralization, consistent with the findings of other studies.

Rosemary

Rosemary (*Rosmarinus officinalis Lamiaceae*) is known for its antioxidant, anticarcinogenic, anti-inflammatory, antifungal, and antibacterial properties. The polyphenols it contains, such as carnosic acid and rosmarinic acid, provide these characteristics. It has been reported to have an inhibitory effect on Gram-positive bacteria such as *S. mutans*.[45,46] In a study by Al-Duboni et al.[47], the effectiveness of rosemary extract in the remineralization of initial enamel caries was examined. The results of fluorescence and microhardness evaluations indicated the effectiveness of rosemary in remineralization. Bilgin et al.[48], in their studies examining the remineralization capacities of various plant products, reported that a mixture of ginger-honey-rosemary increased the microhardness of initial enamel caries and was effective in remineralization. In an in-vitro study by Hossam[49], the remineralization capacity of fluoride, ginger, and rosemary was investigated, with rosemary being found to have remineralization capacity similar to fluoride.

Ginger

Ginger (*Zingiber officinale* Roscoe, *Zingiberacae*) is a plant that has been used since ancient times worldwide. It is known for its anti-inflammatory, antibacterial, and non-toxic properties and has been approved for safety by the US Food and Drug Administration (FDA). It finds applications in various medical fields, including gastrointestinal diseases, cardiovascular diseases, joint diseases, cancer, and symptomatic relief (sore throat, nausea) in some viral diseases. Gingerol, found in ginger, imparts antibacterial properties by causing the dissolution of bacterial cell membranes. Polyphenols in ginger, such as beta-carotene, ascorbic acid, flavonoids, and flavonols, provide antioxidant properties. Especially flavonoids and their derivatives, being lipophilic, disrupt bacterial cell membranes, exhibiting antibacterial effects. Inhibition efficacy against both Gram-positive and Gram-negative bacteria has been observed. Ginger has also been reported to inhibit the growth of respiratory pathogens such as Haemophilus influenza, *Staphylococcus aureus, Streptococcus pyogenes*, and *Streptococcus pneumoniae.*[50-52] Ginger has demonstrated inhibitory effects on oral flora, including *S. mutans, Porphyromonas gingivalis, Prevotella intermedia*, and *Porphyromonas endodontalis.*[50,53] In an in-vitro study conducted by Hassan et al.[54], the remineralization capacities of ginger, rosemary, and fluoride varnishes were examined, and all three materials were reported to be usable for remineralization, with the ginger group showing the highest remineralization efficacy. In another in-vitro study by Hossam[49], the remineralization activities of ginger, rosemary, and fluoride varnishes were investigated for initial enamel caries, and the ginger group exhibited the highest remineralization efficacy.

BIOACTIVE MATERIALS AND NANOTECHNOLOGICAL PRODUCTS

Bioactive Glass (Calcium Sodium Phosphosilicate, NovaMin®)

Bioactive glasses were first used in medical applications for bone regeneration in the 1960s. In dentistry, they are employed for vital pulp treatments, remineralization, and other purposes. Bioactive glasses consist of amorphous silicate compounds and are biocompatible. They can form a chemical bond with vital tissues. In the oral environment, they release calcium, sodium, and phosphate, reacting with oral fluids to create hydroxycarbonate apatite (HCA) and promoting remineralization. NovaMin® is a well-known brand associated with bioactive glass. Combining NovaMin® with fluoride in toothpaste has been found to prevent demineralization and enhance remineralization.[55,56] Bioactive glasses alter the plaqe pH by releasing ions at high concentrations, exhibiting antibacterial effects through this mechanism.[57] In an in-vitro study by Prabhakar and Arali[58], the remineralization efficacy of sodium fluoride and bioactive glass on initial enamel caries was compared, and it was suggested that bioactive glasses could be an alternative to fluoride-containing products.

Nanohydroxyapatite

Hydroxyapatite is a compound with the molecular formula $Ca_{10}(PO_4)_6(OH)_2$ and a calcium-phosphorus ratio of 1/67. Various forms of calcium phosphate exist in nature, with hydroxyapatite being the most stable and least soluble among them. The similarity of synthetic hydroxyapatite crystals to the hydroxyapatite structure in hard tissues such as bones and teeth has led to its widespread use in medical fields. These materials are bioactive and have proven successful in bone regeneration. Synthetic hydroxyapatites fall within the class of biocompatible materials due to their close resemblance to hydroxyapatite structures in dental tissues.[59,60]

The synthesis of nanohydroxyapatites (nHA) can be achieved through various methods. As the method changes, the sizes of the synthesized nHA crystals also vary. nHA, with a Ca/P ratio of 1/67 using the sol-gel technique, is produced to be closest to the natural enamel structure and is most suitable for dental use. It has found applications in dental surgery, implantology, addressing dentin sensitivity, and remineralization. The morphological similarities of these nano-particles to dental hydroxyapatite contribute to their effectiveness in remineralization. An increase in the percentage and amount of nHA in the material used for remineralization enhances the precipitation of Ca_2+ ve PO_4^{3-} ions, leading to increased remineralization effectiveness.[61,62]

The exact working mechanism of nHA-containing products in remineralization is not fully determined. Some researchers report that remineralization occurs due to nHA deposition in the porous structures of the enamel[63,64], while others suggest that nHA acts as a depot, releasing calcium ions into the environment when needed.[65,66] In an in-vitro study conducted by Tschoppe et al.[67], toothpaste containing nHA showed higher remineralization compared to amine fluoride-containing toothpaste, as indicated by micro-radiography values. Swarup and Rao[68] compared the remineralization efficacy of 2% NaF with nHA agents in their in-vitro studies, reporting more significant mineral increase and formation of a surface morphology close to biological enamel in the nHA group.

Tricalcium Phosphate

Tricalcium phosphate (TCP) interacts with oral fluids, releasing ions due to its calcium and phosphate content. The ions released by TCP raise the pH of the environment and actively participate in the remineralization mechanism.[69] Various forms of TCP, including beta and functional TCP forms, have been combined with fluoride and incorporated into toothpaste formulations (e.g., 3M ESPE, Clinpro™ Tooth Crème). The combination of TCP with fluoride is reported to have a synergistic effect on remineralization.[70] Studies by Thimmaiah et al.[71] indicated that the combined form of TCP with fluoride increased the Ca/P mass percentage after demineralization. Hamba et al.[72] compared the remineralization efficacy of fluoride and non-fluoride TCP, reporting higher remineralization in the fluoride TCP group, suggesting independent mechanisms for fluoride and TCP in remineralization.

Casein Phosphopeptide Amorphous Calcium Phosphate (CPP-ACP)

Milk and dairy products have anticariogenic properties, but consuming large amounts is necessary for them to exhibit this effect naturally. Research has focused on isolating protective factors from milk to incorporate them into oral care products. Casein phosphopeptide (CPP), obtained through selective precipitation, is a phosphoprotein with a serine-serine-glutamate-glutamate amino acid sequence. This structure allows CPP to stabilize calcium and phosphate ions at high concentrations independently of pH (both acidic and basic pH). CPP-ACP-containing agents have been found to act as reservoirs for calcium and phosphate, promoting hydroxyapatite formation and remineralization even in conditions with decreased pH.[73,74]

Recaldent™ technology, marketed as MI Paste® in the United States and Japan and Tooth Mousse™ in Europe and Australia, contains 10% CPP-ACP.[75] In an in-vitro study by Iijima et al.[76], CPP-ACP-containing sugar-free gum showed superior remineralization compared to an equivalent gum without CPP-ACP. Morgan et al.[77] found that sugar-free gum containing CPP-ACP significantly slowed demineralization and increased remineralization compared to the control group.

Casein Phosphopeptide Amorphous Calcium Fluoride Phosphate (CPP-ACFP)

When combined with fluoride, CPP-ACFP exhibits a synergistic effect in both preventing cavity formation and promoting remineralization. CPP facilitates the prevention of decay and remineralization by depositing its calcium and phosphate ions on the tooth surface in the presence of demineralization. Fluoride, on the other hand, acts by forming fluoroapatite with fluoride ions in the teeth and dental plaque, contributing to decay prevention and remineralization. The significant advantage of CPP-ACFP is the presence of calcium, phosphate, and fluoride together in its composition.[78] In a study by Thimmaiah et al.[71], remineralization efficacy was compared for fluoride, TCP, nHA, and CPP-ACFP, with the best EDX values observed in TCP and CPP-ACFP agents. Yazıcıoğlu et al.[79] reported that applying CPP-ACFP for 4 minutes daily over 4 weeks significantly remineralized initial caries lesions. Imani et al.[80] stated that both CPP-ACP and CPP-ACFP could reduce caries prevalence and enhance remineralization during and after orthodontic treatment. Jayarajan et al.[81] compared the remineralization efficacy of artificial saliva, CPP-ACP, and CPP-ACFP in in-vitro studies, reporting significant remineralization in all three groups, with the highest values in the CPP-ACFP group.

Self-assembling Peptides

Self-assembling peptides can form a scaffold structure that allows ion accumulation on hard tissues, facilitating mineral accumulation and exhibiting a remineralization effect.[82] Kind et al.[83] demonstrated in their studies that the application of self-assembling peptide (P11-4) could support enamel mineralization, facilitating sub-surface remineralization of enamel lesions. Takahashi et al.[84] reported the effectiveness of self-assembling peptides in remineralization in their studies.

CONCLUSION

Today, many agents are used for remineralization purposes. Among these agents, fluoride is still considered the gold standard. Although claims that high-dose fluoride use in children may cause cognitive problems are not confirmed in the literature, they are met with concern by parents. For this reason, other remineralization agents are the subject of research as alternatives to flora.

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Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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