JOURNAL OF CLINICAL TRIALS AND EXPERIMENTAL INVESTIGATIONS

JCTEI

DOI: https://doi.org/10.5281/zenodo.7359788

REVIEW

Overview of current fluorine-free remineralization materials and methods as an alternative to topical fluoride: An up-to-date

Yelda Polat[1] **Sema Çelenk**[1]

1 Dicle University, Faculty of Dentistry, Department of Pediatric Dentistry, Diyarbakır, Turkey

Abstract

Dental caries is a common public health problem around the world, and it has been aimed to solve this health problem with many different materials and methods from the past to the present. With the demineralization process occurring in the tooth's hard tissues, mineral loss occurs and initial caries lesions and cavitations due to caries occur. On the other hand, the remineralization process can be defined as the removal of existing minerals and hard tissue loss with ions in saliva, newly developed or existing materials,s and methods. The success of fluoride in remineralization has been proven by many literature data and is accepted as the gold standard. Although the use of fluoride in preventive dentistry is the gold standard; Due to the possible side effects and the refusal of fluoride by parents and healthcare professionals, researchers have sought new remineralization materials and methods that can provide remineralization, increase the effectiveness of fluoride or be an alternative to fluoride, with the aim of reducing the fluoride concentrations used. In clinical applications, as an alternative to flora, mineral and ion technologies, sugar alcohols, plant-derived products, bioactive materials, nanotechnological products, calcium, and phosphate-derived other products contribute to the remineralization process and are among the current remineralization materials and methods. In this review, up-to-date information on fluorine-free remineralization materials, mechanisms of action, and clinical applications of new methods and technologies were examined in order to evaluate them in line with the results of scientific studies, and it was aimed to present the studies on this subject.

Keywords: Dental caries, fluorine-free materials, remineralization.

OPEN ACCESS

Correspondence:

Polat Y, Dicle University Faculty of Dentistry, Department of Pediatric Dentistry, Diyarbakır, Turkey

e-mail: yldplt@gmail.com

Specialty section:
This article was submitted to the Pediatric Dentistry section

Received: 20 October 2022
Revised: 30 October 2022
Accepted: 1 November 2022
Published: 26 November 2022

Introduction

Ion exchange between the hard tissues of the tooth and saliva causes demineralization and remineralization reactions, which result in caries when demineralization takes a dominant role (1). The causes of dental caries are numerous. The four fundamental elements must coexist, though. these include time, carbohydrates, microflora, and the host (dental hard tissues) (2). The demineralization process starts when the pH in the tooth's hard tissues drops below the threshold, generally accepted to be 5.5. By buffering the acids produced by the bacteria in the plaque with saliva, neutralization occurs, and the pH increase. Remineralization occurs when the pH of the plaque rises above 5.5, plaque and saliva become more saturated with minerals dissolved from the enamel than hydroxyapatite, and the precipitation process of the minerals starts. In the cavities created by demineralization, minerals accumulate during the remineralization process (3). Initial enamel lesions, or white spot lesions, are caused by the ongoing demineralization process in the tooth's hard tissues.

In order to stop the process of demineralization, aid in remineralization, and stop the onset of enamel lesions, the use of remineralization agents with various contents has grown over time in the context of preventive dentistry. Despite the fact that the gold standard for preventive dentistry is the use of fluoride-containing preparations, researchers have been looking for new remineralization materials and methods that could provide remineralization, boost the effectiveness of fluoride, or serve as an alternative to fluoride with evolving dental technologies in order to reduce the fluoride concentrations used. The purpose of this review is to provide an explanation of fluorine-free remineralization materials, methods, and technologies as well as to evaluate and summarize the clinical applications of new methods and technologies as well as their mechanisms of action. Table 1 displays the current materials and techniques for fluorine-free remineralization.

Mineral ion and technologies

Silver ion

In permanent dentition; Silver-containing compounds, which are used to prevent caries, as a cavity disinfectant, and to reduce hypersensitivity, started to be used in milk dentition in the 1840s to reduce the incidence of caries. Silver ion used in different compounds has been shown to reduce solubility in tooth structures and support remineralization in an acidic environment (4). Silver ion was used together with fluorine, but its use has become limited because it causes coloration. It has been reported that the use of a 38% solution of silver diamine fluoride once or twice a year prevents the formation of new caries by preventing demineralization, stops existing active caries lesions, reduces mineral loss, and has a bactericidal effect on cariogenic bacteria (5).

Iron ion

It has effects such as reducing enamel solubility at acidic pH and decreasing glycosyltransferase enzyme activity by showing bactericidal and bacteriostatic effects on Mutans Streptococci. Moreover, besides the positive properties of an iron ion such as preventing caries and reducing demineralization, undesirable properties such as the inability to provide remineralization, toxicity, and discoloration should be considered (6).

Sugar Alcohols

Xylitol

Xylitol, a natural 5-carbon sugar obtained from the extracts of beech trees, has a sweet taste comparable to sugar (7). The ability of xylitol to prevent caries is attributed to its inability to ferment by pathological bacteria and its antibacterial properties. Thanks to this feature, it prevents the binding of sucrose molecules, inhibits the metabolism of Mutans Streptococci, and as a result, demineralization is reduced. It is known that as a result of the use of products with xylitol, the flow of saliva increases, the buffering capacity of the saliva increases, and the pH value of the oral environment increases (8). Seppä, in his study, stated that a varnish containing 20% xylitol could be as effective in the remineralization of initial enamel lesions as fluoride varnishes. In addition, another feature of mutants streptococci acts to reduce vertical transmission from mother to child (9).

Sorbitol

Sorbitol is known as a sugar alcohol, which is widely used in many sugar-free products, including sweeteners, medicines, sugar-free gums, and lozenges (10). Although sorbitol can be fermented by S.Mutans; compared to dietary sugars such as sucrose, glucose, and fructose, the amount of acid produced is less, and for this reason, it is also called non-cariogenic sugar (11). The remineralizing effects of sorbitol and xylitol on initial enamel lesions are similar (10).

Table 1: Current fluorine-free remineralization materials and methods

Mineral ion and technologies	Sugar alcohol	Herbal products	Bioactive materials, nanotechnological products, and other biomimetics	Other products from calcium and phosphate	Other materials and methods
1. Silver ion 2. Iron ion 3. Fluoride	1. Xylitol 2. Sorbitol 3. Isomalt	1. Chitosan 2. Hesperidin 3. Grape seed extract 4. Galla chinensis 5. Theobromine 6. Propolis 7. Ginger 8. Rosemary 9. Licorice Root 10. Cacao	1. Bioactive glass 2. Tricalcium silicate 3. Nanohydroxyapatite 4. Amorphous calcium phosphate 5. Casein phosphopeptide – Amorphous calcium phosphate 6. Tricalcium phosphate 7. Self-assembling peptides 8. Amelogenin 9. Dentin phosphoprotein Derivative 8DSS Peptides 10. Dentin matrix Protein 1 11. Polyvinyl Phosphoric acid 12. Polyacrylic acid 13. L-glutamic acid 14. Agarose hydrogel agarose 15. Poly-amidoamine dendrimers	1. Dicalcium phosphate dihydrate 2. Calcium phosphoryl oligosaccharides 3. Calcium carbonate 4. Sodium trimetaphosphate 5. Calcium glycerophosphate 6. Calcium phosphate	1. Chlorhexidine 2. Triclosan 3. Arginine 4. Laser applications 5. Ozone Applications 6. Electrically accelerated and enhanced remineralization

Isomalt

Isomalt, also known as palatinite, is classified as a non-cariogenic sweetener used in chewing gums and candies. The calcium-binding property of isomalt; has allowed it to be evaluated as a product that can prevent caries and contribute to remineralization (12). Takatsuka et al. reported that isomalt contributes positively to the remineralization process and can show its main effect when used together with fluorine (13).

Herbal products

Chitosan

Chitosan, a biological polymer obtained by deacetylation of chitin, which is present in nature, is used in the prevention of dental caries due to its bactericidal and bacteriostatic effects (14). As a result of their in vitro study, Arnaud et al. reported that chitosan inhibits demineralization by preventing phosphorus release, shows a barrier effect against acid attack by advancing to the junction of enamel and dentin, and preventing demineralization (15). Chitosan is known to be effective in preventing demineralization of the hard tissues of the tooth, but there is limited information on its remineralization ability.

Hesperidin

Hesperidin is a bioflavonoid derived from citrus and its derivatives. It is also a substance that can prevent bone resorption with anti-inflammatory, anticarcinogenic, antioxidant, and hypoglycemic effects. Hesperidin prevents the stabilization of dentin collagen and demineralization as it acts as a mechanical barrier for the passage of ions in the stabilized tissue; It is thought that the stabilized collagen structure is involved in remineralization as a skeletal structure and positively affects this process. However, the data on the subject is quite limited (16).

Grape seed extract

This extract, which is formed by drying grape seeds and obtaining their extracts; it has anti-inflammatory, antioxidant, and antimicrobial effects and polyphenolic properties (17). Grape seed extract, which inhibits the glycosyltransferase enzyme of oral streptococci, prevents streptococci from clinging to the tooth surface, and prevents caries, has been proven to contribute positively to remineralization with mineral accumulation in different studies (18). It is estimated that the remineralization of the grape seed extract in the enamel increases the exogenous collagen cross-links and supports the formation of hydroxyapatites (19).

Galla chinensis

Galla Chinensis, an agent used to prevent caries in recent years, is known as a traditional herb in China and the extract obtained from this plant is used (20). In their study, Chu et al. examined the effect of the chemical content of the Galla Chinensis plant on the initial caries lesions and reported that Galla Chinensis can stabilize the enamel and increase remineralization (21). Galla Chinensis, which can show the remineralization process primarily in the subsurface layers, unlike fluoride ions, can be used in caries prevention and remineralization. However, more studies on its effectiveness are needed (22).

Theobromine

Theobromine, an alkaloid from the methylxanthine family with a crystalline structure, insoluble in water, is obtained from cocoa and is found in foods such as tea and chocolate. Theobromine increases the hardness of the enamel layer and creates a structure that is less permeable to caries (23). Amaechi et al. In their study concluded that theobromine was effective in increasing remineralization by providing the formation of apatites, and this effect was comparable to the remineralization induced by fluorine (24).

Propolis

Propolis is a resin-based compound obtained from plant extracts and used by honey bees (Apis Mellifera) to fill the gaps in their honeycombs; It is used in many areas such as creams, toothpastes, and cosmetic products. Its use as a food supplement continues to increase. The flavonoid group, which forms a large part of its resin, is the active component of propolis and is effective in the formation of antioxidant, anti-inflammatory, antibacterial, antifungal, and antiviral properties (25). It has also been proven in vitro and in vivo that propolis can inhibit the activity of the glycosyltransferase enzyme formed by S.Sobrinus and S.Mutans (26). However, it is known that the types of propolis used in studies investigating the effect of inhibiting demineralization are different from each other.

Ginger

Ginger (Zingiberaceae, Zingiber officinale Roscoe), stands out with its antimicrobial properties; It is one of the natural food sources used in various fields for centuries (27). Its effect on Mutans Streptococci, which is one of the important pathogens of caries formation, has been shown in different in vitro studies (28). While there are a limited number of studies investigating the effect of ginger on cariogenic microorganisms in the literature, there are not enough studies on its effect on remineralization.

Rosemary

Rosemary (Lamiaceae, Rosmarinus officinalis L.) has an important place in the plant kingdom with its antioxidant properties. It has antibacterial and antifungal properties due to its compounds with various polyphenolic properties, such as rosmarinic and carnosic acid (29).

Licorice Root

Licorice root has been used in medicine for many years due to its healing properties. The sweetener effect starts more slowly and lasts longer, unlike sugars. It prevents the formation of caries by increasing the stimulation of saliva due to its sweet taste (30). It has been reported that preventing the activation of the glycosyltransferase enzyme in mutants streptococci, prevents the formation of insoluble glucans necessary for the formation of biofilm (31).

Bioactive materials, nanotechnological products, and other biomimetics

Bioactive glass (NovaMin ®, calcium sodium phosphosilicate)

As a result of the contact of bioactive glass with saliva, bioactive glasses that provide the release of components such as phosphorus, calcium, and sodium by rapidly releasing the nanoparticles in their content and releasing ions have been put into use in dentistry, especially in recent years, gaining popularity due to being biocompatible materials (32). Novamin is a water-soluble bioactive glass containing calcium sodium phosphosilicate in its structure. As a result of the contact of bioactive glasses with saliva, phosphorus, calcium, and sodium ions begin to be released rapidly, and these ions directly from the beginning of remineralization with the formation of hydroxycarbonate apatite (33). In the field of dentistry; Bioactive glasses, which can be used in reducing dentin sensitivity, bone regeneration, vital treatments, and antibacterial treatments, have become more preferred due to their contribution to remineralization and their usage area has increased (34).

Tricalcium silicate

Tricalcium silicate is a bioactive material that can prevent demineralization and support remineralization due to its ability to form apatites in hard tissues. Tricalcium silicate has been the subject of many studies due to its ability to form apatite in the hard tissues of the tooth (34). Dong et al. In another study they carried out, stated that tricalcium silicate formed apatite formation by precipitating calcium and phosphate on the enamel surface and that it could be a material that can be used in the protection and remineralization of enamel. Again, the same study states that this material may be effective in reducing dentin sensitivity (35).

Nanohydroxyapatite

Normal enamel structure consists of 20-40 nm hydroxyapatite crystals and is called nanoparticles. The first materials produced artificially to strengthen the structure of enamel are in the form of microhydroxyapatite. However, nanohydroxyapatite has been developed in order to increase solubility and release more calcium and phosphate, as they are less soluble compared to other compounds containing calcium and phosphate (36). Recently, it has been stated that mouthwashes, toothpastes, and different agents combined with nanohydroxyapatite have the effect of remineralizing initial caries lesions. The contribution of nanohydroxyapatite to remineralization is provided by acting as calcium and phosphate storage (37).

Amorphous calcium phosphate (ACP)

Amorphous calcium phosphates remain in their original form in the oral environment at neutral or high pH. Calcium phosphates with amorphous structure form an initial solid phase precipitated from a highly saturated calcium phosphate solution. Since amorphous calcium phosphates have high bioactivity and cell adhesion, biocompatible and osteoconductive properties, they have found use in dental materials, especially in adhesive products, dental composites, and fissure sealants (38).

Casein phosphopeptide - Amorphous calcium phosphate (CPP-ACP)

Casein; It is a particulate protein with a width of 30-300 nm, which is found in the structure of foods such as milk, cheese, and yogurt, constituting 78% of the proteins contained in cow's milk (39). Milk and dairy products must be consumed in large quantities in order for their caries-preventing effects to emerge. For this reason, researchers have obtained casein phosphopeptide (CPP) as a result of the reaction of casein with the enzyme trypsin using the selective precipitation method (40). Caries prevention effects of CPP-ACP; By joining the structure of the dental plaque, it prevents demineralization by increasing the level of phosphate and calcium ions in the plaque significantly, CPP-ACP on the tooth surface binds the free phosphate and calcium in the dental plaque, preventing demineralization by oversaturating the tooth surface, and preventing demineralization by binding the bacteria in the dental plaque to the cell surfaces. colonization that may occur on the surface is prevented (41). In recent years, CCP-ACP; Due to its remineralizing feature, it is found in many products such as toothpaste, mouthwash, solution, and sugar-free gum. In a study in which mouthwashes containing CCP-ACP were evaluated in situ, it was stated that a high amount of remineralization could occur in initial enamel lesions (42). In a different study examining the effect of toothpaste containing casein phosphopeptide amorphous calcium phosphate on initial enamel lesions, it was reported that remineralization could be achieved by precipitation of calcium and phosphate on the tooth surface of the material (43).

Tricalcium phosphate

Tricalcium phosphate has two forms called alpha and beta. The beta form is less soluble than the alpha form, so the alpha form is preferred. Alpha tricalcium phosphate is known to support the remineralization of the hard tissues of the tooth by increasing the level of free calcium and phosphorus in the oral environment (44). Vogel et al., in their study, stated that chewing gum containing 2.5% alpha tricalcium phosphate may cause a small increase in calcium and phosphorus levels in saliva and plaque fluid (45). There are not enough studies on tricalcium phosphate in the literature. More detailed studies are needed for its use as a remineralizing agent.

Self-assembling peptides

It is thought that anionic peptides should be used in remineralization research due to the effects they have on the hard tissues of the tooth. This effect of anionic peptides is realized by decreasing mineral loss and increasing mineral amount. Unlike known remineralization agents, they form the skeletal structure that allows the precipitation of ions on the tooth surface, and the accumulation of minerals occurs with this skeletal structure (46). In the non-invasive treatment of early caries lesions, biomimetic remineralization with the combination of p11-4 self-assembled peptide and fluoride is quite safe, easy, and effective (47).

Amelogenin

Amelogenin has a critical role in the form, arrangement, and growth of hydroxyapatites during the mineralization of enamel. However, in mature enamel, matrix proteins are absent and mineral loss cannot be eliminated (48). It is estimated that the complex enamel microstructure can be increased by using synthetically obtained amelogenins (49). Amelogenin is difficult to obtain and store. The development of the enamel layer, which is tried to be formed with amelogenin, takes a long time. For this reason, it is not suitable for practical use in the clinic (48).

Dentin phosphoprotein derivative 8DSS peptides

Dentin Phosphoprotein Derived 8DSS Peptides (DPP) is the most abundant non-collagen extracellular matrix component in dentin and is also known to be involved in tooth mineralization (50). By preventing the dissolution of calcium and phosphate ions from demineralized dentin, 8DDS peptides promote mineral deposition on demineralized enamel and can also effectively bind to the hydroxyapatite layer on the enamel surface (51).

Dentin matrix protein –1 (DMP-1) derivative oligopeptides

Dentin Matrix Protein-1 (DMP-1) derivative oligopeptides are a type of non-collagenous protein that can stabilize phosphate and calcium minerals in the environment by forming the skeletal structure required for remineralization (52).

Polyvinyl phosphoric acid (PVPA)

Polyvinyl phosphoric acid (PVPA) provides biomimetic remineralization, reduces the functions of matrix metalloproteinases (MMP), binds Dentin Matrix Protein-1 (DMP-1) derivative oligopeptides with collagen, adds nano-sized particles in the Amorphous Calcium Phosphate structure to the newly formed collagen matrix and adds Dentin Matrix. It plays a role in the formation of skeletons in the protein structure (53).

Polyacrylic acid (PAA)

The skeletal structures of polyacrylic acid are used to stabilize the materials in the amorphous calcium phosphate structure by imitating the connection points of the calcium and phosphate structures of Dentin Matrix Protein-1 (DMP-1) (53).

L-glutamic acid

L-glutamic acid is used in the initial stage and progression of biomimetic remineralization of dentin and in the replacement of Dentin Matrix Protein-1 with regions containing excess glutamic acid (54).

Agarose hydrogel agarose

It has a polyanionic structure containing repeating monomers with a polysaccharide structure. Anionic groups form and enlarge the structures of hydroxyapatite crystals by binding to the positively charged ions in the collagen structure. In addition, it supports the transfer of calcium and phosphate ions to the dentin surface and the formation of hydroxyapatite crystals via directed ion diffusion (55).

Poly-amidoamine dendrimers (PAMAM)

Poly-amidoamine dendrimers are known as multi-branched polymers containing amelogenin, well-defined in size and shape, with cascading reactive ends and internal voids (56). Difficulties in obtaining, purifying, and storing amelogenin have generated synthetic PAMAM dendrimers. However, although it is thought that it can be used as similar to amelogenin in bioremineralization, in-vivo studies are limited to animal experiments only. However, PAMAM-mediated bioremineralization and amelogenin-induced bioremineralization are time-consuming processes, but it is estimated that lasers can be used to accelerate this process and regulate the growth of crystals (57).

Other products from calcium and phosphate

Dicalcium phosphate dihydrate

Dicalcium phosphate dihydrate (DCPD) is added to some toothpastes to increase the effect of fluoride on remineralization. It is known that with the release of calcium ions in the oral environment, calcium ions initiate the remineralization process in initial enamel lesions. For this reason, the addition of dicalcium phosphate dihydrate to toothpastes determines the amount of calcium and phosphate, and therefore it is stated that caries can be prevented and caries that may occur remain at the initial level and prevent their progression (58).

Calcium phosphoryl oligosaccharides

Calcium phosphoryl oligosaccharides (POs-Ca) in the biological and soluble form of calcium are formed as a result of the enzymatic hydrolysis of potato starch. The calcium in its structure is also biologically usable (59). However, it has been stated by many researchers that the materials used together with calcium phosphoryl oligosaccharides and fluorine contribute positively to remineralization by showing a synergistic effect when compared with those containing only calcium phosphoryl oligosaccharides (60).

Calcium carbonate (CaCO3)

Calcium carbonate is often found in toothpastes and is an alkaline chemical compound used as an abrasive (61). Although toothpastes containing calcium carbonate have an alkaline pH value, their solubility at neutral pH is quite low. In this way, the effect of calcium carbonate on the acidogenicity of dental plaque is also limited (62). Although the studies in the literature show that the addition of calcium carbonate to toothpastes gives positive results in terms of remineralization, it is known that more research is needed to compare it with newly emerging remineralization agents.

Sodium trimetaphosphate (STMP)

It has been stated by many studies and researchers that the ability to prevent demineralization increases with the addition of sodium trimetaphosphate to toothpastes. Danelon et al. In their study, in which they examined the remineralization capacity of materials with sodium trimetaphosphate added and low in fluoride content on initial enamel lesions, they stated that the addition of sodium trimetaphosphate brought the remineralization effect of preparations with low fluoride content to the same level as materials containing high amounts of fluoride (63).

Calcium glycerophosphate (CaGP)

It has been reported that materials containing calcium glycerophosphate (CaGP) increase the structural resistance of hydroxyapatites and thus show a protective effect (64). In another study by Sezer et al., the effectiveness of a remineralization agent containing calcium glycerophosphate and xylitol applied to incisors with molar hypomineralization was investigated, and it was reported that this material provided remineralization in incisors with molar-incisor hypomineralization during a 3-month follow-up period (65).

Calcium phosphate

Calcium phosphate particles in materials used to provide remineralization of dentin are promising products to provide biomimetic remineralization of dentin, as they constitute the basic inorganic building blocks of the existing dentin structure (66). In another study, it was determined that nano calcium phosphate particles can increase the surface area for the arrangement of organic matrix on demineralized dentin (67).

Other materials and methods that contribute to the remineralization process

Chlorhexidine

Chlorhexidine, which is widely used in dentistry due to its broad spectrum and other antibacterial properties, also contributes positively to the remineralization process. In their study, Kim et al. examined the remineralization in dentin using different chlorhexidine concentrations on demineralized dentin blocks and found that 0.2% and 2% chlorhexidine application could positively affect remineralization in dentin (68). It can be said that the inhibition mechanism of chlorhexidine on matrix metalloproteinase is promising in dentin remineralization. Various chlorhexidine concentrations have been applied in studies on the bonding capacity of resin and dentin, and it has been reported that an inhibition effect on matrix metalloproteinase (MMP) is observed at all these concentrations (69).

Triclosan

Triclosan has a broad antimicrobial spectrum as well as antifungal properties. However, its activity depends on formulation and concentration. Triclosan can also inhibit gram-positive and gram-negative bacteria and many more viruses and fungi. Triclosan is known to have broad-spectrum activity even at low concentrations (70). Considering the results of the in situ studies conducted by Silva et al., they reported that triclosan would contribute positively to remineralization (71).

Arginine

Arginine is a semi-essential amino acid found in proteins or peptides that make up saliva in humans. Ammonia production neutralizes the acidic environment created by increasing pH and sugar metabolism and provides a more alkaline environment that reduces cariogenicity (72).

Laser applications

Laser applications are used in many fields of dentistry, including many medical fields. The laser beam causes melting and recrystallization in the enamel prisms, causing structural changes in the enamel layer and forming larger hydroxyapatite crystals in the superficial regions of the enamel layer, thus making the enamel layer less permeable to acid penetration (73). Although there have been many studies evaluating the contribution of lasers to remineralization only, or the use of lasers with other remineralization materials, the results are inconsistent, and more clinical studies are needed to explain the effectiveness of lasers on remineralization.

Ozone Applications

Ozone is a gaseous agent consisting of three oxygen atoms and it has been reported that with its strong oxidation feature, it forms the protein layer that protects the existing lesion and facilitates mineral deposition by making the dentinal tubules open in the basic environment provided by the destruction of all microorganisms and their products. The resulting hypermineralized tissue has a more resistant structure against acid attacks that will occur later. A large number of studies have been conducted in the field of dentistry investigating ozone's antimicrobial properties and its ability to prevent caries. In most of the clinical research studies, they stated that the effect of ozone on caries is a promising alternative to known methods (74).

Electrically accelerated and enhanced remineralization (EAER)

Electrically accelerated and enhanced remineralization (EAER) technology is known as a recently developed remineralization technology that aims to treat existing healthy tissue in order to protect the existing healthy tissue, restore the lost tissue in the carious lesion, and improve the structural properties of the enamel layer. This new generation technology, which uses iontophoresis to accelerate the flow of ions, contributes positively to remineralization. In vitro studies on EAER technology are very promising, but should be supported by in-vivo studies to evaluate the capacity and results of remineralization (75,76).

Conclusions

Although it is tried to create an alternative to fluorine-induced remineralization with remineralization materials and methods that are currently in use or are still under development, the success of fluorine in remineralization treatments has been proven by many studies, gives successful clinical results and still continues to be the "gold standard". Among all these remineralization materials and methods, the most suitable, economical, and practical ones should be offered and applied to the patients.

Conflict of interest:

The authors report no conflict of interest.

Funding source:

No funding was required.

Ethical approval:

No need for reviews.

Contributions

Research concept and design: **YP, SÇ**
Data analysis and interpretation: **YP, SÇ**
Collection and/or assembly of data: **YP, SÇ**
Writing the article: **YP, SÇ**
Critical revision of the article: **YP, SÇ**
Final approval of the article: **YP, SÇ**

References

1. Yon MJY, Gao SS, Chen KJ, Duangthip D, Lo ECM, Chu CH. Medical Model in Caries Management. Dent J (Basel). 2019;7(2):37.
2. Reich E, Lussi A, Newbrun E. Caries-risk assessment. Int Dent J. 1999;49(1):15-26.
3. Hemagaran G, Neelakantan P. Remineralization of the tooth structure – the future of dentistry. IJPRIF. 2014;6(2):487-93.
4. Peng JJY, Botelho MG, Matinlinna JP. Silver compounds used in dentistry for caries management: A review. J Dent. 2012;40(7):531-41.
5. Rosenblatt A, Stamfort TCM, Niederman R. Silver diamine Fluoride (SDF) may be better than fluoride varnish and no treatment in arresting and preventing cavitated carious lesions. J Dent. 2009;88(8):116-25.
6. Alves KMRP, Franco KS, Sassaki KT, Buzalaf MAR, Delbem ACB. Effect of iron on enamel demineralization and remineralization in vitro. Arch Oral Biol. 2011;56(11):1192-8.
7. Horst JA, Tanzer JM, Milgrom PM. Fluorides and Other Preventive Strategies for Tooth Decay. Dent Clin North Am. 2018;62(2):207-34.
8. Makinen KK, Saag M, Isotupa KP, Olak J, Nõmmela R, Söderling E, et al. Similarity of the effects of erythritol and xylitol on some risk factors of dental caries. Caries Res. 2005;39(3):207–15.
9. Seppä L. Fluoride varnishes in caries prevention. Med Princ Pract. 2004;13(6):307-11.
10. Makinen KK. Sugar alcohols, caries incidence and remineralization of caries lesions:a literature review. Int J Dent. 2010;2010:981072.
11. Hayes ML, Roberts KR. The breakdown of glucose, xylitol and other sugar alcohols by human dental plaque bacteria. Arch Oral Biol. 1978;23(6):445–51.
12. Featherstone JD, Rodgers BE, Smith MW. Physicochemical requirements for rapid remineralization of early carious lesions. Caries Res. 1981;15(3):221-35.
13. Takatsuka T, Exterkate RA, ten Cate JM. Effects of Isomalt on enamel de- and remineralization, a combined in vitro pH-cycling model and in situ study. Clin Oral Investig. 2008;12(2):173-7.
14. Shıbasaki K, Sano H, Matsukubo T, Takaesu Y. Effects of low molecular chitosan on pH changes in human dental plaque. Bull Tokyo Dent Coll. 1994;35(1):33–9.
15. Arnaud TM, de Barros Neto B, Diniz FB.Chitosan effect on dental enamel de-remineralization: an in vitro evaluation. J Dent. 2010;38(11):848-52.
16. Islam SM, Hiraishi N, Nassar M, Sono R, Otsuki M, Takatsura T, et al. In vitro effect of hesperidin on root dentin collagen and de/re-mineralization. Dent Mater J. 2012;31(3):362-67.
17. Perumalla AVS, Hettiarachchy NS. Green tea and grape seed extracts - Potential applications in food safety and quality. Food Res Int. 2011;44(4):827-39.
18. Benjamin S, Sharma R, Thomas SS, Nainan MT. Grape seed extract as a potential remineralizing agent: a comparative in vitro study. J Contemp Dent Pract. 2012;13(4):425-30.
19. Nagi S, Hassan S, Abd El-Alim S, Elmissiry M. Remineralization potential of grape seed extract hydrogels on bleached enamel compared to fluoride gel: An in vitro study. J Clin Exp Dent. 2019;11(5):e401-e407.
20. Cheng L, Ten Cate JM. Effect of Galla chinensis on the in vitro remineralization of advanced enamel lesions. Int J Oral Sci. 2010;2:15-20
21. Chu JP, Li JY, Hao YQ, Zhou XD. Effect of compounds of Galla Chinensis on remineralization of initial enamel carious lesions in vitro. J Dent. 2007;35(5):383-7.
22. Xie Q, Li JY, Zuo YL, Zhou XD. The effect of Galla chinensis on the growth of cariogenic bacteria in vitro. Hua Xi Kou Qiang Yi Xue Za Zhi. 2005;23(1):82-4.
23. George D, Bhat SS, Antony B. Comparative evaluation of the antimicrobial efficacy of aloe vera tooth gel and two popular commercial toothpastes: an in vitro study. Gen Dent. 2009;57(3):238-41.
24. Amaechi BT, Porteous N, Ramalingam K, Mensinkai PK, Ccahuana Vasquez RA, Sadeghpour A, et al. Remineralization of artificial enamel lesions by theobromine. Caries Res. 2013;47(5):399-405
25. Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). Food Chem Toxicol. 1998;36(4):347-63.
26. Duailibe SA de C, Gonçalves AG, Ahid FJM. Effect of a propolis extract on Streptococcus mutans counts in vivo. J Appl Oral Sci. 2007;15(5):420-3.
27. Park M, Bae J, Lee DS. Antibacterial activity of [10]-gingerol and [12]-gingerol isolated from ginger rhizome against periodontal bacteria. Phytother Res. 2008;22(11):1446-9.
28. Trindade Grégio AM, Miyamoto Fortes ES, Ribeiro Rosa EA, Baggio Simeoni R, Takaki Rosa R. Antimicrobial Activity from Zingiber Officinalle on Oral Cavity Pathogens. Estudos de Biologica. 2006;28(62):61-6.
29. Moreno S, Scheyer T, Romano CS, Vojnov AA. Antioxidant and antimicrobial activities of rosemary extracts linked to their polyphenol composition. Free Radic Res. 2006;40(2):223-31.

30. Akan H, Balos M. GAP Bölgesinden toplanan meyan kökü (Glycrrhiza glabra L.) taksonunun ihracat durumu, etnobotanik özellikleri ve tıbbi önemi. Fırat Üniv Fen ve Mühendislik Bilimleri Derg. 2008;20(2):233-41.
31. Sela MN, Steinberg D, Segal R. Inhibition of the activity of glucosyltransferase from Streptococcus mutans by glycyrrhizin. Oral Microbiol Immunol. 1987;2(3):125-8.
32. Haghgoo R, Ahmadvand M, Moshaverinia S. Remineralizing effect of topical NovaMin and nano-hydroxyapatite on caries-like lesions in primary teeth. J Contemp Dent Pract. 2016;17(8):645-9.
33. Ergin E, Eden E. Mine lezyonlarının farklı ajanlarla remineralizasyonu. Turkiye Klinikleri J Pediatr Dent-Special Topics. 2015;1(3):57- 64.
34. Ceyhan T, Günay V, Capoğlu A, Sayrak H, Karaca C. Production and characterization of a glass-ceramic biomaterial and in vitro and in vivo evaluation of its biological effects. Acta Orthop Traumatol Turc. 2007;41(4):307-13.
35. Dong Z, Chang J, Deng Y, Joiner A. Tricalcium silicate induced mineralization for occlusion of dentinal tubules. Aust Dent J. 2011;56(2):175-80.
36. Huang SB, Gao SS, Yu HY. Effect of nano-hydroxyapatite concentration on remineralization of initial enamel lesion in vitro. Biomed Mater. 2009;4(3):034104.
37. Yamagishi K, Onuma K, Suzuki T, Okada F, Tagami J, Otsuki M, et al. Materials chemistry: a synthetic enamel for rapid tooth repair. Nature. 2005;433(7028):819.
38. Zhao J, Liu Y, Sun WB, Zhang H. Amorphous calcium phosphate and its application in dentistry. Chem Cent J. 2011;5:40.
39. de Pinto Sinfiteli P, Coutinho TCL, de Oliveira PRA, Vasques WF, Azevedo LM, Pereira AMB, et al. Effect of fluoride dentifrice and casein phosphopeptide-amorphous calcium phosphate cream with and without fluoride in preventing enamel demineralization in a pH cyclic study. J Appl Oral Sci. 2017;25(6):604- 11.
40. Çetin B, Avşar A, Ulusoy AT. Kazein içerikli besinler ve dental ürünler. Atatürk Üniv Diş Hek Fak Derg. 2011;2011(4):24-31.
41. Sudjalim TR, Woods MG, Manton DJ. Prevention of white spot lesions in orthodontic practice: a contemporary review. Aust Dent J. 2006;51(4):284-9.
42. Reynolds EC, Cai F, Shen P, Walker GD. Retention in plaque and remineralization of enamel lesions by various forms of calcium in a mouthrinse or sugar-free chewing gum. J Dent Res. 2003;82(3):206-11.
43. Rahiotis C, Vougiouklakis G. Effect of a CPP-ACP agent on the demineralization and remineralization of dentine in vitro. J Dent. 2007;35(8):695-8.
44. Cochrane NJ, Saranathan S, Cai F, Cross KJ, Reynolds EJ. Enamel subsurface remineralization with casein phosphopeptides stabilized solution of calcium, phosphate and fluorid. Caries Res. 2008;42(2):88-97
45. Vogel GL, Zhang Z, Carey CM, Ly A, Chow LC, Proskin HM. Composition of plaque and saliva following a sucrose challenge and use of an alpha tricalcium-phosphate-containing chewing gum. J Dent Res. 1998;77(3):518-24.
46. Brunton PA, Davies RPW, Burke JL, Smith A, Aggeli A, Brookes SJ, et al. Treatment of early caries lesions using biomimetic self-assembling peptides - a clinical safety trial. Br Dent J. 2013;215(4):E6.
47. Alkilzy M, Santamaria RM, Schmoeckel J, Splieth CH. Treatment of carious lesions using self-assembling peptides. Adv Dent Res. 2018;29(1):42-7.
48. Ruan Q, Moradian-Oldak J. Amelogenin and enamel biomimetics. J Mater Chem B. 2015;3(16):3112-29.
49. Fan Y, Sun Z, Moradian-Oldak J. Controlled remineralization of enamel in the presence of amelogenin and fluoride. Biomaterials. 2009;30(4):478-83.
50. Yarbrough DK, Hagerman E, Eckert R, He J, Choi H, Cao N, et al. Specific binding and mineralization of calcified surfaces by small peptides. Calcif Tissue Int. 2010;86(1):58-66.
51. Hsu CC, Chung HY, Yang J-M, Shi W, Wu B. Influence of 8DSS Peptide on Nano-mechanical Behavior of Human Enamel. J Dent Res. 2011;90(1):88-92.
52. Nijhuis AW, Nejadnik MR, Nudelman F, Walboomers XF, Riet J, Habibovic P, et al. Enzymatic pH control for biomimetic deposition of calcium phosphate coatings, Acta Biomater. 2014;10(2):931-9.
53. Gu LS, Kim YK, Liu Y, Takahashi K, Arun S, Wimmer CE, et al. Immobilization of a phosphonated analog of matrix phosphoproteins within cross-linked collagen as a templating mechanism for biomimetic mineralization. Acta Biomater. 2011;7(1):268-77.
54. Cao CY, Mei ML, Li QL, Lo EC, Chu CH. Methods for biomimetic remineralization of human dentine: a systematic review. Int J Mol Sci. 2015;16(3):4615-27.
55. Ning TY, Xu XH, Zhu LF, Zhu XP, Chu CH, Liu LK, et al. Biomimetic mineralization of dentin induced by agarose gel loaded with calcium phosphate, J Biomed Mater Res B Appl Biomater. 2012;100(1):138-44.
56. Chen J, Cao X, Guo R, Shen M, Peng C, Xiao T, et al. A highly effective polymerase chain reaction enhancer based on dendrimer-entrapped gold nanoparticles. Analyst. 2012;137(1):223-8.
57. Sun M, Wu N, Chen H. Laser-assisted Rapid Mineralization of Human Tooth Enamel. Sci Rep. 2017;7(1):9611.
58. Sullivan RJ, Charig A, Blake-Haskins J, Zhang YP, Miller SM, Strannick M, et al. In vivo detection of calcium from dicalcium phosphate dihydrate dentifrices in demineralized human enamel and plaque. Adv Dent Res. 1997;11(4):380-7.
59. Zhang YP, Din CS, Miller S, Nathoo SA, Gaffar A. Intraoral remineralization of enamel with a MFP/DCPD and MFP/ silica dentifrice using surface microhardness. J Clin Dent 1995;6(2):148-53.
60. Kitasako Y, Tanaka M, Sadr A, Hamba H, Ikeda M, Tagami J. Effects of a chewing gum containing phosphoryl oligosaccharides of calcium (POs-Ca) and fluoride on remineralization and crystallization of enamel subsurface lesions in situ. J Dent 2011;39(11):771-9.
61. To-o K, Kamasaka H, Nishimura T, Kuriki T, Saeki S,Nakabou Y. Absorbability of calcium from calcium-bound phosphoryl oligosaccharides in comparison with that from various calcium compounds in the rat ligated jejunum loop. Biosci Biotechnol Biochem. 2003;67(8):1713-8.
62. Cury JA, Simões GS, Del Bel Cury AA, Gonçalves NC, Tabchoury CPM. Effect of a calcium carbonate-based dentifrice on in situ enamel remineralization. Caries Res. 2005;39(3):255-7.
63. Danelon M, Takeshita EM, Sassaki KT, Delbem AC. In situ evaluation of a low fluoride concentration gel with sodium trimetaphosphate in enamel remineralization. Am J Dent. 2013;26:15-20.
64. Grenby TH. Trials of 3 organic phosphorus containing compounds as protective agents against dental caries in rats. J Dent Res. 1973;52(3):454-61
65. Sezer B, Tuğcu N, Durmus B, Bekiroglu N, Kargula B. Efficacy of mineral containing gel for remineralization in MIH-affected incisors: a 3-months clinical study. 64th ORCA Congress. Caries Res. 2017;51:362.
66. Perkin KK, Turner JL, Wooley KL, Mann S. Fabrication of hybrid nanocapsules by calcium phosphate mineralization of

shell cross-linked polymer micelles and nanocages. Nano Lett. 2005;5(7):1457-61.

67. Shibata Y, Yamamoto H, Miyazaki T. Colloidal beta-tricalcium phosphate prepared by discharge in a modified body fluid facilitates synthesis of collagen composites. J Dent Res. 2005;84(9):827-31.
68. Kim D-S, Kim J, Choi K-K, Kim S-Y. The influence of chlorhexidine on the remineralization of demineralized dentine. J Dent. 2011;39(12):855-62.
69. De Munck J, Van den Steen PE, Mine A, Van Landuyt KL, Poitevin A, Opdenakker G, et al. Inhibition of enzymatic degradation of adhesive-dentin interfaces. J Dent Res. 2009;88(12):1101-6.
70. Schweizer HP. Triclosan: a widely used biocide and its link to antibiotics. FEMS Microbiol Lett. 2001;202(1):1-7
71. Silva MFDA, Giniger MS, Zhang YP, Devizio W. The effect of a triclosan/copolymer/fluoride liquid dentifrice on interproximal enamel remineralization and fluoride uptake. J Am Dent Assoc. 2004;135(7):1023-9.
72. Ástvaldsdóttir Á, Naimi-Akbar A, Davidson T, Brolund A, Lintamo L, Attergren Granath A, et al. Arginine and Caries Prevention: A Systematic Review. Caries Res. 2016;50(4):383-93.
73. Poosti M, Ahrari F, Moosavi H, Najjaran H. The effect of fractional CO2 laser irradiation on remineralization of enamel white spot lesions. Lasers Med Sci. 2014;29(4):1349-55.
74. Tandan M, Gupta S, Tandan P. Ozone in Conservative Dentistry & Endodontics: A Review. Int J Clin Prev Dent. 2012;8(1):29-35.
75. Pitts NB, Wright JP. Reminova and EAER: Keeping Enamel Whole through Caries Remineralization. Adv Dent Res. 2018;29(1):48-54.
76. Akleyin E, Polat Y, Yavuz Y. Three-Year Dentition Follow-up of a Paediatric Case with Malignant Infantile Osteopetrosis: A Review of the Literature. J Clin Tri Exp Invest. 2022;1(2):41-8.