Enamel remineralisation and efficacy of remineralising agents: A Review

Tanveer Abbas[1]*, Shahid Khan[2], Talib Hussain[2], Malik Arshman Khan[3]

[1]School of Health and Society University of Wollongong, Australia
[2]Women Medical and Dental College Abbottabad
[3]Abbottabad International Dental College Abbottabad, Pakistan.

Abstract

To review current information and technology for tooth remineralisation. Searches in the "Scopus" and "Web of Knowledge" databases, which date back to 1970s. English was the only language allowed. The study incorporated both original research and previously published reviews. Tooth remineralisation agents, products, and treatments have progressively increased in recent years due to the growing awareness of the significance of good dental health among patients and general community. Both in vitro and in vivo tooth remineralisation and demineralization research have been published regularly. Theobromine has been proposed as an effective remineralising agent and a viable alternative to fluorides in recent years. According to research, fluoride treatments can prevent dental enamel demineralization and remineralisation. An increasing number of products containing calcium salts or calcium-based compounds have been added to oral care products to boost the delivery and retentiveness of fluoride into teeth. Calcium salts or materials, which provide an additional source of calcium, may aid in accelerating enamel remineralisation or hinder demineralization processes. These effects are possible because calcium is a mineral. A new area of research inspired by bioactive materials for bone repair and regeneration, bioglass, in particular calcium silicates, shows promise for improving enamel health and is one type of bioglass that contains calcium silicate.

Keywords human tooth enamel tops, efficacy, remineralisation, bioglass, theobromine

1. Introduction

In terms of tensile strength, human tooth enamel tops all other tissues. The primary component of mature enamel is hydroxyapatite (HAP) in the form of crystallites, $Ca_{10}(PO_4)_6(OH)_2$. About 3% of the enamel is water, while the remaining 1% is organic matter, such as proteins and lipids (1). The crystallites are typically 50nm in width and 25 nm thick, and many microns long. A range of physical and chemical stressors are put on enamel, the outermost layer of the tooth. Acidic challenges from plaque and food, as well as high pressures (up to 700N), are all variables that contribute to tooth decay (2). HAP crystals, found at the outermost layer of tooth enamel, have a dynamic relationship with saliva and plaque fluid (3). The rate and amount of dissolution are influenced by the solution's calcium and phosphate ion content in addition to pH. The easiest way to describe the process is with the following equation. In a process known as demineralization, HAP can be dissolved at pH 5.5 (4). The demineralization of teeth is most frequently brought on by secreted acids.

When bacteria or acidic foods release acids during demineralization. Caries and erosion can occur as a result of tooth demineralization. Early identification and prevention of dental demineralization disorders, such as tooth remineralisation, have been advised as a clinical care strategy before resorting to restorative measures (5).

Saliva contains significant quantities of calcium and phosphate ions. An acid-blocking buffer is possible since it slows the dissolving process and mitigates the acid's effects. During high calcium/phosphate ion concentrations and high pH, the equilibrium can shift in favour of calcium phosphate re-precipitation and remineralisation of demineralized tooth tissues.

Studies on the remineralisation process of teeth have been conducted over many decades. Because of these investigations, techniques have been introduced to help either promote or prevent enamel demineralization, potentially improving oral health. The objective of this article is to provide a summary of the literature on enamel remineralisation methods and their mechanisms of action. Only original English-language research and reviews listed in the "Scopus" and "Web of Knowledge" databases were included in this study (6).

2. Efficacy of Theobromine

Theobromine is the main alkaloid that comes from the cacao plant. Its chemical name is 3,7-dimethylxanthine. Chocolate, tea, and other foods contain this water-soluble, crystalline, bitter powder. Chocolate, a food made from cacao beans, has been linked to an increased risk of dental caries (7). However, in recent years, there have been arguments made for the use of theobromine as an efficient remineralising agent and as a feasible alternative to fluorides (8). These reasons have been advanced in support of the use of theobromine. Calcium and phosphate are thought to create larger crystallites of the mineral hydroxyapatite in the presence of theobromine. These crystallites are thought to reinforce the enamel and prevent acid assault, which finally leads to cavitation. In addition, research indicates that cocoa bean husk is excellent at reducing mutant streptococci and has less toxicity than fluoride (9,10). Theobromine-containing toothpaste are commercially accessible and frequently used in the United States, although they are less popular internationally than other remineralising agents. Manufacturers' statements about the effectiveness of theobromine-containing dentifrices are based on scant research, and nothing is known about how theobromine compares to other conventional remineralisation agents. According to research by Parvathy et al., a substantial reduction in lesion depth was detected in all groups, with the highest reduction (increased remineralisation) reported for specimens treated in Group A with theobromine.

3. Efficacy of Fluoride as remineralising agent

Remineralisation substances are abundant, with fluoride being the most common and extensively utilised. The increased utilisation of fluoride-containing dentifrices can be credited with contributing to the declining prevalence of dental caries in a number of nations in today's world (11). The current hypotheses of mechanism show fluorides function mostly via topical processes by preventing demineralization and magnifying remineralisation via the formation of fluorapatite crystals in the presence of calcium and phosphate ions (12). Various amounts of fluoride-containing dentifrices have also been shown to have considerable remineralising effectiveness in preventing caries (13).

A lengthy history of research shows that fluoride is an excellent caries-prevention agent because it slows down enamel breakdown and speeds up enamel remineralisation. Brushing one's teeth consistently with toothpaste that contains fluoride can lessen the risk of developing cavities in one's teeth, which is a vital benefit for one's oral health (14). Early research into how fluoride might protect, and repair enamel showed that it could make enamel and dentine less acid-soluble (15). By reacting with HAP, fluoride can create fluorapatite (FA) and assist the transition of other calcium phosphate phases to fluorapatite. The solubility of HAP can be decreased by the formation of fluorapatite. The inorganic components of enamel are more reactive than HAP in its pure form because of non-stoichiometric effects and carbonate impurities. Therefore, it is not particularly difficult for FA or FHA to form on the enamel surface (16). Moreno et al. looked at how HAP dissolved in water at different levels of fluoride substitution. To get the best results, just half of the hydroxyl groups had to be replaced with fluoride, which resulted in the greatest lattice stability and minimum lattice-free energy. In these conditions, lattice ions have a lower inclination to dissolve and, on the other hand, a higher tendency to join the lattice. Ingram and Nash examined the Ca:P ratio alteration of three calcium-deficient HAP materials following incubation in 1, 2.5 or 5 ppm fluoride solutions.

An analysis of the holes in the crystal lattice caused by the acid attack showed that the developed FHA was the perfect place for calcium ions to move back into the holes in the crystal lattice. But the average fluoride concentrations in enamel are ineffective in protecting teeth against caries. The fluoride concentrations observed near the surface are normally about 2000 ppm in places where the water is not fluoridated, and they are typically around 3000 ppm in locations where the water is fluoridated. This means that between 6% and 8% of the OH^- in HAP is being replaced by F^-. Calculations demonstrate that concentrations of fluoride decline fast beyond the first 10-20 microns, and these values are much below those capable of reducing HAP's solubility (16). It was discovered in the 1980s that fluoride inhibits caries lesion formation through a topical action on demineralization and remineralisation processes at the tooth-oral fluid interface (17). Enamel demineralization can be prevented by low amounts of fluoride solution (18) and by increasing apatite precipitation (19). For example, fluoride concentrations up to 4 ppm accelerated the deposition of apatite minerals from mineralization solutions into surface softened enamel, after which the accelerating effect levelled off. This occurred because fluoride concentrations caused apatite to be deposited at a faster rate (20).

While brushing with fluoride-containing toothpaste, fluoride can be supplied to the tooth surface, saliva,

soft tissues, and any leftover plaque biofilm in the oral cavity. Fluoride may be applied to teeth using a CaF_2 like substance synthesised in a lab. This deposit has the potential to serve as a fluoride reservoir, which will enable it to defend the underlying mineral from any future acidic threats. When the pH is low, free fluoride can be liberated from the CaF_2 like deposit, inhibiting demineralization in the immediate microenvironment. Fluoride works as an inhibitor of acid-mediated demineralization and a promoter of remineralisation when the pH rises, so the presence of free fluoride serves to accelerate mineral production (21). The fluoride levels in saliva will be at their greatest during brushing, followed by a quick decline owing to oral clearance after brushing has been completed. But fluoride levels in saliva can be higher than normal for a long time, which could slow down the demineralisation process and speed up the process of remineralisation (22). Fluoride can be put into the biofilm and kept there, where bacteria or pieces of bacteria can hold it through calcium-fluoride bonds. Fluoride may be stored in these deposits because they can be involved in the remineralisation and demineralization processes just where they are required most, making them an essential source of fluoride for protecting teeth from caries (23). Fluoride concentrations in plaque have been shown to have an inverse correlation with the occurrence of dental caries in clinical investigations (24). Abrasion and erosion resistance and the development of erosion in the enamel can be improved by using high fluoride concentrations. The use of fluoride in high concentrations has been established in this context (25). Fluoride toothpaste and mouth rinses have been shown to prevent dental erosion compared to placebo (26). Toothpaste containing 1426ppm F as sodium fluoride or 1400ppm F as amine fluoride was found to preserve enamel from erosive acid challenges compared to placebo toothpaste. So, fluoride kinds of toothpaste have also been found to improve the remineralisation of citric acid softened enamel in vitro, in contrast with placebos. Only a few fluoride compounds and agents are readily available to the general public and healthcare professionals, including stannous fluoride, sodium monofluorophosphate, titanium tetrafluoride and ammonium fluoride. There is significant evidence that fluoride, in various applications and formulations, is effective in preventing dental caries (27).

4. Efficacy of Calcium

To maintain healthy teeth, calcium and phosphate must be present in sufficient amounts in saliva and plaque to influence the demineralisation and remineralisation processes. An increase in the calcium and phosphate content in saliva may protect against dental caries since it is inversely linked with caries occurrence (28). According to findings from epidemiological research, caries incidence appears to be inversely associated with the salivary calcium content (29). Solubility of enamel may have decreased due to an increase in calcium and phosphate concentration in saliva, which may explain this correlation. According to theoretical considerations, the combination of calcium and phosphate ions has a stronger impact on enamel saturation than the concentration of either ion alone (30). In vitro mechanistic investigations have confirmed this, demonstrating that calcium has a twenty-fold greater inhibitory effect on enamel disintegration than phosphate (31). At the same amount of super saturation, enamel remineralisation can be performed optimally with a calcium/phosphate ratio of 1.6 (32). Despite this, the Ca/P ratio in plaque fluid is approximately 0.3 (33). Calcium ion concentration has been suggested as the most important mineral element to promote enamel remineralisation and avoid demineralization (34). Many investigations, both in vitro and clinical, have looked into the possibility that calcium delivery through dental care products incorporating calcium salts would help enamel health. Calcium chloride mouth rinse, for example, has been proven to increase plaque calcium levels. As a result of this elevation in plaque calcium concentration, acid-softened enamel surfaces coated with a plaque in situ became less porous and harder (35). Enamel remineralisation is influenced by calcium levels, as shown in in vitro testing. Subsurface enamel lesions can be remineralised by increasing the calcium concentration in the remineralisation solution while maintaining the fluoride level (36). Other calcium-based remineralisation strategies have been identified. An in-situ investigation by Kitasako et al (37). for example, indicated that phosphoryl oligosaccharides of calcium (POs-Ca) could promote enamel remineralisation. Thirty-six patients wore implants with subsurface bovine enamel flaws inlay inlays. Chewing gum with POs-Ca had a higher mineral content recovery than placebo or control inserts, according to the research. Tricalcium phosphate-type materials can be used to remineralize acid-softened tooth enamel. -tricalcium (TCP) has been shown to release calcium ions and remineralise early enamel defects, for example, through an in vitro experiment.

Researchers have discovered that the milk protein derivative CPP-ACP acts as a potent anticariogenic agent (38). Ensuring that dental enamel remains saturated with ACP in plaque and on the surface of teeth reduces demineralization and encourages the regeneration of lost minerals. Effectiveness has been proven (26). hydroxyapatite nanoparticles are being studied to see if they might replace the mineral loss in tooth enamel caused by acid degradation (39). A toothpaste containing nano-HAP remineralised enamel subsurface lesions far more than an amine fluoride toothpaste control, for example, in an in vitro investigation. The repair was indistinguishable between groups that received nano-HAP toothpaste and those that received no treatment at all. In vitro studies have recently shown that nano-HAP may be effective at reversing the progression of early caries lesions, but only in the outer surface area of the lesions (40).

5. Efficacy of Fluoride and Calcium

Calcium and fluoride levels in plaque have been shown in several studies to be linearly related. Researchers believe plaque calcium concentration affects how long it can hold onto fluoride in the mouth. In reference (26) As, a result of this logic, efforts to boost the cariostatic efficiency of fluoride have centred on techniques of increasing calcium concentrations in the tooth biofilm. If you use a 150 mM calcium-lactate pre-rinse before a 228ppm fluoride rinse, for example, the fluoride levels in your saliva and plaque are higher an hour later than if you only use a sodium fluoride control mouth rinse. Calcium salts and calcium-containing compounds have been studied as a possible strategy to enhance the health benefits of fluoride toothpaste (41). As an example, calcium glycerophosphate (CaGP) added to a toothpaste containing calcium carbonate and silica has been documented (42). One hour before, during, or one hour after the sucrose challenge in an in vitro biofilm flow cell model established on bovine enamel, CaGP was pulsed. According to the findings of the study, pulsing before the sucrose challenge provided the highest protection from demineralization (43). CaGP-containing toothpastes have been shown to reduce caries in clinical trials, and the increase in calcium levels in plaque from CaGP has been related to this reduction in caries (44). A calcium carbonate/SMFP toothpaste with calcium glycerophosphate and micro-calcium carbonate has been described. According to studies, the toothpaste significantly increased calcium levels in plaque biofilms both in vitro and in vivo, as well as the remineralisation of demineralized enamel

(45). Fluoridated toothpaste containing silica and HAP has been proven to raise calcium levels on the tooth surface and in saliva 10 minutes after brushing (46). Citric acid treatments reduced enamel demineralization significantly in vitro trials with the same toothpaste compared to controls (47). TCP plus fluoride has been demonstrated in several research to improve enamel remineralisation and create more acid-resistant minerals than fluoride alone. This is a promising finding (48).

6. Efficacy of bioactive materials

Even though fluoride has been shown to reduce caries levels in the clinical setting, it appears to be insufficient in some patients, such as those with a high prevalence of caries or those frequently exposed to acidic foods or drinks. For example, bioactive materials may be a potential new lead in the search for innovative ways that might help remineralise the enamel or minimise demineralization (49). Materials that induce favourable responses from the body, such as attaching to bone tissue and creating calcium phosphate layers on a material's surface, are known as bioactive materials (BAM) (50). These materials, including bioactive glasses, glass-ceramics, and bio-materials, have been explored as artificial bone grafting materials (51). Bioactive materials have been studied for dental applications since the tooth is a kind of bone tissue (52). It's true that different bioactive technologies have been written about. They could be used to remineralise teeth because they boost calcium phosphate production.

7. Use of Bioglass for enamel remineralisation

While many studies on the possibilities of bone-substituting materials have been conducted since 1969, the discovery of bioglass and bioactive glass-ceramics has received much attention. Calcium, sodium, phosphate, and silicate are the main components of bioglass, which is a type of bioactive substance. When in contact with bodily fluids, they react by forming calcium phosphate on their surface. As with ordinary glass corrosion, the production of calcium phosphate on bioglass has been examined, and it is thought bioglass undergoes solution-mediated dissolution (53). The chemical composition and pH of the solution alter as dissolution products accumulate, resulting in surface locations and a pH favourable for calcium phosphate nucleation. Na^+ and H^+ ions in the bioglass particles interact in saliva, and the pH of the solution rises as a result of this exchange (54) Ca^{2+} and PO^{4-} are liberated

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from the particle structure due to this ion exchange, and a silica-rich layer forms on the bioglass surface as a result of silanol (Si-OH) synthesis. This silica-rich layer allows the precipitation of calcium phosphate onto the bioglass surface through increased calcium and phosphate concentration and pH value in the solution. Dentinal tubule occlusion by bioglass has been demonstrated (55). It has been demonstrated in both in vitro and in vivo investigations that bioglass particles may be deposited on dentinal surfaces and then occlude dentinal tubules by causing a carbonated HAP-like substance to develop (56). In terms of dental enamel de- and re-mineralization applications, there have been few documented investigations. In vitro, Burwell looked into the possibility that bioglass may aid in the restoration of enamel white-spot lesions (57). Results demonstrated that after 10 days, the bioglass and 5000ppm F combination generated much better remineralisation than the 5000ppm F alone treatment. However, SEM methods still clearly noted the loss of prismatic enamel structure with demineralization. In vitro research found no significant protection from the surface softening effects of orange juice challenges when compared to a control group that received no treatment at all. Bioglass-containing toothpaste was shown to have no significant remineralisation of orange juice degraded surfaces compared to the control group (58).

8. Calcium silicate glass

As indicated in the study, wollastonite (-CaSiO$_3$), pseudo-wollastonite (-CaSiO$_3$), Ca$_2$SiO$_4$ and Ca$_3$SiO$_5$ have been shown to stimulate the fast synthesis of HAP in simulated body fluid (SBF) and chemically integrate into the structure of real bone tissue following implantation, as indicated in the study.

It has been determined how HAP forms on a calcium silicate surface. Surface layers of calcium silicate are formed after immersion in simulated body fluid (SBF), where calcium ions interact with H+ to generate the silanol groups (Si–OH) in the surface layer. For example, this leads to a rise in the concentration of the acidic group Si–O–, which finally forms a negatively charged surface. Because of this, calcium ions in SBF solution are drawn to the interface of calcium silicate and the solution. Because of this, HAP is precipitated on the calcium silicate surface due to the high concentration of Ca^{2+} ions at the interface, together with PO$_4^{3-}$ ions from SBF. Root canal filling products based on calcium silicate have been employed. Calcium silicate-based restorative materials like mineral trioxide aggregate (MTA) have been reported.

MTA includes dicalcium and tricalcium sulphate silicates and bismuth oxide, with traces of calcium sulphate. 138-140 Root canal filling materials that have been demonstrated to cause HAP development in SBF include Ca$_3$SiO$_5$/CaCl$_2$ and CaCl$_2$/SiO$_2$. Studies have revealed that calcium silicates may be used to reduce the sensitivity of dentine. Cement made of calcium silicate was proven in vitro by Gandolfi et al (59).

Studies have revealed that calcium silicates may be used to reduce the sensitivity of dentine. It has been shown that calcium silicate cements may significantly lower the permeability of dentine specimens in vitro, and the effectiveness persists for one week in artificial saliva following application. Dentine tubules can be occluded by Ca$_3$SiO$_5$, the major component of calcium silicate cement. In vitro studies have demonstrated a direct correlation between Ca$_3$SiO$_5$ deposition on the dentine surface and Ca$_3$SiO$_5$ penetration into the dentine tubules. After one week of incubation in artificial saliva, HAP was produced on the dentine by the deposited Ca$_3$SiO$_5$ particles. This dense surface layer was around three microns thick. Calcium silicate materials have also been examined for remineralising tooth enamel. As shown by their results, on acid-etched enamel surfaces with an initial thickness of 250–350 nm, Dong et al. showed that a Ca$_3$SiO$_5$ treatment could efficiently promote fresh HAP development after 1 day of incubation in SOF. After 7 days of SOF incubation, the layer thickness grew to 1.7-1.9 microns. Also, human saliva was treated with Ca$_3$SiO$_5$ to see if it would cause HAP production. In a pH-cycling in vitro model, Wang et al. (60) studied the impact of Ca$_3$SiO$_5$ on decreasing enamel demineralization. It was shown that a Ca$_3$SiO$_5$ treatment had the same effect on decreasing enamel demineralization as 1000 ppm fluoride. Enamel demineralization was significantly reduced by using Ca$_3$SiO$_5$ in conjunction with 1000 ppm fluoride, as opposed to the other treatments.

9. Conclusions

With the growing awareness of the importance of good dental health, the number of teeth remineralisation agents, products, and treatments have steadily increased in recent years. Both in vitro and in vivo tooth remineralisation and demineralization research have been published regularly. Dental enamel demineralization and remineralisation can be prevented with typically successful fluoride treatments. Efforts to increase fluoride's efficacy have been attempted by incorporating calcium salts or calcium-containing components into dental care products that may boost the delivery and retention of

fluoride into the oral cavity. As an extra source of calcium, calcium salts or materials may help the teeth and gums remineralise or slow down the demineralisation process. Bioglass, particularly calcium silicate type materials, shows potential for enamel health benefits and is an emerging study topic inspired by the notion of bioactive materials for bone repair and regeneration.

References

1. Mann A, Dickinson M. Nanomechanics, chemistry and structure at the enamel surface. Monographs in oral science. 2006 Jan 1;19:105.

2. Jones FH. Teeth and bones: applications of surface science to dental materials and related biomaterials. Surface science reports. 2001 May 1;42(3-5):75-205.

3. Sollböhmer O, May KP, Anders M. Force microscopical investigation of human teeth in liquids. Thin Solid Films. 1995 Aug 15;264(2):176-83.

4. LeGeros RZ. 6. Calcium Phosphates in Enamel, Dentin and Bone. InCalcium phosphates in oral biology and medicine 1991 (Vol. 15, pp. 108-129). Karger Publishers.

5. Markowitz K. Tooth sensitivity: Mechanisms and management. Compendium (Newtown, Pa.). 1993 Aug 1;14(8):1032-4.

6. Dorozhkin SV. Surface reactions of apatite dissolution. Journal of colloid and interface science. 1997 Jul 15;191(2):489-97.

7. Li X, Wang J, Joiner A, Chang J. The remineralisation of enamel: a review of the literature. Journal of dentistry. 2014 Jun 1;42:S12-20.

8. LeGeros RZ. 6. Calcium Phosphates in Enamel, Dentin and Bone. InCalcium phosphates in oral biology and medicine 1991 (Vol. 15, pp. 108-129). Karger Publishers.

9. Irawan MIP, Noerdinand A Eriwati YK: The effect of time in the exposure of theobromine gel to enamel and surface hardness after demineralization with 1% citric acid. J Phys Conf Ser. 2017, 884:

10. Arman S: A neural analysis of theobromine vs. fluoride on the enamel surface of human teeth. Diss Abstr, 2007:150.

11. Arthilakshmi, Sharmin DD: Comparative evaluation on antimicrobial activity of theobromine and two commercial kids fluoride toothpaste—an in vitro study. Int J Dent Oral Health. 2016, 2:52-56.

12. Nakamoto T, Falster AU, Simmons WB: Theobromine: a safe and effective alternative for fluoride in dentifrices. J Caffeine Res. 2016, 6:

13. Aoun A, Darwiche F, Al Hayek S, Doumit J: The fluoride debate: the pros and cons of fluoridation. Prev Nutr Food Sci. 2018, 23:171-180. 10.3746/pnf.2018.23.3.171

14. Ullah R, Zafar MS: Oral and dental delivery of fluoride: a review. Fluoride. 2015, 48:195-204.

15. Arnold WH, Dorow A, Langenhorst S, Gintner Z, Bánóczy J, Gaengler P: Effect of fluoride toothpastes on enamel demineralization. BMC Oral Health. 2006, 6:8. 10.1186/1472-6831-6-8

16. Stamm JW. Multi-function toothpastes for better oral health: a behavioural perspective. International Dental Journal. 2007 Oct;57(S5):351-63.

17. Sthephen KW. Fluoride toothpastes, rinses, and tablets. Advances in Dental Research. 1994 Jul;8(2):185-9.

18. Shannon IL, Trodahl JN. Effect of waterborne fluoride on fluoride concentration and solubility of dental enamel. Australian Dental Journal. 1977 Dec;22(6):428-31.

19. Moreno EC, Kresak M, Zahradnik RT. Fluoridated hydroxyapatite solubility and caries formation. Nature. 1974 Jan;247(5435):64-5.

20. Ingram GS, Nash PF. A mechanism for the anticaries action of fluoride. Caries research. 1980;14(5):298-303.

21. Buzalaf MA, Pessan JP, Honório HM, Ten Cate JM. Mechanisms of action of fluoride for caries control. Fluoride and the oral environment. 2011;22:97-114.

22. Malinowski M, Duggal MS, Strafford SM, Toumba KJ. The effect on dental enamel of varying concentrations of fluoridated milk with a cariogenic challenge in situ. Journal of dentistry. 2012 Nov 1;40(11):929-33.

23. Varughese K, Moreno EC. Crystal growth of calcium apatites in dilute solutions containing fluoride. Calcified Tissue International. 1981 Dec;33(1):431-9.

24. Feagin FF. Effective fluoride concentrations to promote apatite mineralization at the enamel surface. Ala J Med Sci. 1973;10:107-14.

25. Cate JM. Current concepts on the theories of the mechanism of action of fluoride. Acta Odontologica Scandinavica. 1999 Jan 1;57(6):325-9.

26. Zero DT, Fu J, Espeland MA, Featherstone JD. Comparison of fluoride concentrations in unstimulated whole saliva following the use of a fluoride dentifrice

and a fluoride rinse. Journal of Dental Research. 1988 Oct;67(10):1257-62.

27. Wiegand A, Attin T. Influence of fluoride on the prevention of erosive lesions-a review. Oral Health and Preventive Dentistry. 2003 Sep 1;1(4):245-54.

28. Fowler C, Willson R, Rees GD. In vitro microhardness studies on a new anti-erosion desensitizing toothpaste. The Journal of Clinical Dentistry. 2006 Jan 1;17(4):100-5.

29. Pessan JP, Toumba KJ, Buzalaf MA. Topical use of fluorides for caries control. Fluoride and the Oral Environment. 2011;22:115-32.

30. MASAMURA K, INABA R, IWATA H. Salivary calcium and total protein in relation to dental caries. Nippon Eiseigaku Zasshi (Japanese Journal of Hygiene). 1995 Oct 15;50(4):886-92.

31. Sewón L, Mäkelä M. A study of the possible correlation of high salivary calcium levels with periodontal and dental conditions in young adults. Archives of Oral Biology. 1990 Jan 1;35:S211-2.

32. Delbem AC, Pessan JP. Alternatives to enhance the anticaries effects of fluoride. InPediatric Restorative Dentistry 2019 (pp. 75-92). Springer, Cham.

33. Tanaka M, Kadoma Y. Comparative reduction of enamel demineralization by calcium and phosphate in vitro. Caries Research. 2000;34(3):241-5.

34. Exterkate RA, Damen JJ, Ten Cate JM. A single-section model for enamel de-and remineralisation studies. 1. The effects of different Ca/P ratios in remineralisation solutions. Journal of dental research. 1993 Dec;72(12):1599-603.

35. Margolis HC. An assessment of recent advances in the study of the chemistry and biochemistry of dental plaque fluid. Journal of Dental Research. 1990 Jun;69(6):1337-42.

36. Ten Cate JM. In situ models, physico-chemical aspects. Advances in dental research. 1994 Jul;8(2):125-33.

37. 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 remineralisation and crystallization of enamel subsurface lesions in situ. Journal of dentistry. 2011 Nov 1;39(11):771-9.

38. Karlinsey RL, Mackey AC, Walker ER, Frederick KE. Preparation, characterization and in vitro efficacy of an acid-modified β-TCP material for dental hard-tissue remineralisation. Acta Biomaterialia. 2010 Mar 1;6(3):969-78.

39. Reynolds EC, Cain CJ, Webber EL, Black CL, Riley PF, Johnson IH, Perich J. Anticariogenicity of calcium phosphate complexes of tryptic casein phosphopeptides in the rat. Journal of dental research. 1995 Jun;74(6):1272-9.

40. Li L, Pan H, Tao J, Xu X, Mao C, Gu X, Tang R. Repair of enamel by using hydroxyapatite nanoparticles as the building blocks. Journal of Materials Chemistry. 2008;18(34):4079-84.

41. Joiner A, Schäfer F, Hornby K, Long M, Evans M, Beasley T, Abraham P. Enhanced enamel benefits from a novel fluoride toothpaste. International Dental Journal. 2009 Aug;59(S4):244-53.

42. Duke SA, Ress DA, Forward GC. Increased plaque calcium and toothpaste containing calcium glycerophosphate and sodium monoflu-orophosphate. Caries Res. 1979;13:57-9.

43. Sidi AD, Wilson RF. Fluoride, calcium and inorganic phosphorus concentrations in approximal plaque collected from young adults 1 and 24 h after toothbrushing with fluoride toothpastes. Caries research. 1991;25(5):330-4.

44. Lynch RJ, Ten Cate JM. Effect of calcium glycerophosphate on demineralization in an in vitro biofilm model. Caries research. 2006;40(2):142-7.

45. Hornby K, Evans M, Long M, Joiner A, Laucello M, Salvaderi A. Enamel benefits of a new hydroxyapatite containing fluoride toothpaste. International dental journal. 2009 Dec;59(6S1):325-31.

46. Karlinsey RL, Mackey AC, Walker ER, Frederick KE. Surfactant-modified β-TCP: structure, properties, and in vitro remineralisation of subsurface enamel lesions. Journal of Materials Science: Materials in Medicine. 2010 Jul;21(7):2009-20.

47. Featherstone JD. Remineralisation, the natural caries repair process—the need for new approaches. Advances in dental research. 2009 Aug;21(1):4-7.

48. Zhao W, Chang J, Zhai W. Self-setting properties and in vitro bioactivity of Ca3SiO5/CaSO4· 1/2H2o composite cement. Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials. 2008 May;85(2):336-44.

49. Mitchell JC, Musanje L, Ferracane JL. Biomimetic dentin desensitizer based on nano-structured bioactive glass. Dental Materials. 2011 Apr 1;27(4):386-93.

50. Sanders DM, Hench LL. Mechanisms of glass corrosion. Journal of the American Ceramic Society. 1973 Jul;56(7):373-7.

51. Earl JS, Leary RK, Muller KH, Langford RM, Greenspan DC. Physical and chemical characterization of dentin surface following treatment with NovaMin

technology. The Journal of clinical dentistry. 2011 Jan 1;22(3):62-7.

52. Burwell AK, Litkowski LJ, Greenspan DC. Calcium sodium phosphosilicate (NovaMin®): remineralisation potential. Advances in Dental Research. 2009 Aug;21(1):35-9.

53. Wang X, Megert B, Hellwig E, Neuhaus KW, Lussi A. Preventing erosion with novel agents. Journal of dentistry. 2011 Feb 1;39(2):163-70.

54. Liu X, Ding C. Morphology of apatite formed on surface of wollastonite coating soaked in simulate body fluid. Materials Letters. 2002 Dec 1;57(3):652-5.

55. Liu X, Ding C, Chu PK. Mechanism of apatite formation on wollastonite coatings in simulated body fluids. Biomaterials. 2004 May 1;25(10):1755-61.

56. Tran XV, Gorin C, Willig C, Baroukh B, Pellat B, Decup F, Opsahl Vital S, Chaussain C, Boukpessi T. Effect of a calcium-silicate-based restorative cement on pulp repair. Journal of dental research. 2012 Dec;91(12):1166-71.

57. Wang X, Sun H, Chang J. Characterization of Ca3SiO5/CaCl2 composite cement for dental application. Dental Materials. 2008 Jan 1;24(1):74-82.

58. Gandolfi MG, Iacono F, Pirani C, Prati C. The use of calcium-silicate cements to reduce dentine permeability. Archives of oral biology. 2012 Aug 1;57(8):1054-61.

59. Dong Z, Chang J, Deng Y, Joiner A. In vitro remineralisation of acid-etched human enamel with Ca3SiO5. Applied surface science. 2010 Feb 1;256(8):2388-91.

60. Wang Y, Li X, Chang J, Wu C, Deng Y. Effect of tricalcium silicate (Ca3SiO5) bioactive material on reducing enamel demineralization: An in vitro pH-cycling study. Journal of dentistry. 2012 Dec 1;40(12):1119-26.

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