Topical Agents for Nonrestorative Management of Dental Erosion

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A nonrestorative approach to the management of dental erosion is the foremost option: controlling dental erosion. Nonrestorative approaches to dental erosion commonly include dietary analysis and counselling, oral health education and topical use of anti-erosive agents. Topical anti-erosive agents can be broadly categorised as fluorides, calcium phosphate-based agents, organic compounds and other anti-erosive agents. In the presence of saliva, fluorides promote the formation of fluorapatite on teeth through remineralisation.

Keywords: tooth erosion ; fluorides ; anti-erosive agents

1. Introduction

Dental erosion is the loss of minerals from the dental hard tissue caused by non-bacterial acids [1]. This chemical process often occurs with mechanical wear, such as abrasion and attrition, and is known as erosive tooth wear [1][2]. Erosive tooth wear damages the tooth structure, negatively affecting the aesthetics and the function of the natural dentition [1][2][3]. The loss of tooth structure with opening dentinal tubular often initiates dentine hypersensitivity, which can result in severe, persistent pain and discomfort [2][3]. With the increased consumption of acidic food and beverage, the prevalence of dental erosion has increased significantly over the past few decades [1][4][5]. The estimated global prevalence of dental erosion in primary dentition ranged from 30% to 50% and from 20% to 45% in permanent dentition [6]. Almost all middle-aged populations and more than half of children and adolescents are affected by dental erosion [7]. Therefore, dental erosion has a long-term impact on the oral and general health of the population [2][3].

Restorative treatment for dental erosion can be challenging, invasive and extensive [8][9]. Therefore, it is imperative to identify dental erosion at an early stage, and nonrestorative management aiming for preventive care should be provided [1][10]. Nonrestorative approaches to dental erosion commonly include dietary analysis and counselling, oral health education and topical use of anti-erosive agents [5][11][12]. Dietary analysis and counselling are important for preventing excessive consumption of acidic beverages and foodstuffs that potentially damage dentition [1][10]. Oral health education is essential to promoting the protective factors that effectively prevent dental erosion [10][13]. Among the various nonrestorative approaches, topical anti-erosive agents are commonly used to manage dental erosion [11][12].

2. Anti-Erosive Agents in the Literature

2.1. Fluoride Agents

Fluoride agents are the most common topical anti-erosive agents [5] and include sodium fluoride (NaF), amine fluoride (AmF), stannous fluoride (SnF_2), titanium tetrafluoride (TiF_4) and silver diamine fluoride (SDF). They are divided into two groups: conventional monovalent fluoride, such as NaF and AmF [5], and polyvalent fluoride with metal cations, such as TiF_4, SnF_2 and SDF [5][11][14]. Topical fluoride facilitates the formation of a protective layer on the tooth surface and enhances the acid resistance of dental hard tissue [14][15]. Some fluoride agents can modify salivary pellicle and enhance the acid resistance of salivary pellicle [16][17]. Fluoride can also inhibit the activation of matrix metalloproteinases (MMPs) in the dentine matrix [14][15].

2.1.1. Sodium Fluoride (NaF)

NaF is a conventional monovalent fluoride [5]. There are plenty of commercially available NaF products [18][19][20][21]. Over the counter, NaF toothpaste contains up to 1450 ppm fluoride [5][20]. NaF toothpaste with 5000 ppmF is also available as a prescription [5][22]. In addition, 5% NaF varnish containing 22,600 ppmF is a commonly used professional fluoride agent [5][20]. NaF application leads to a calcium fluoride-like layer (CaF_2) forming on the tooth surface [5][22]. This layer is a

protective barrier that blocks acid diffusion through the tooth's surface [23]. CaF acts as a reservoir of calcium and fluoride ions to enhance the remineralisation process of the hard tissue [5][22]. Sodium ions may interact with the salivary proteins in the acquired salivary pellicle [12][24]. It improves the re-adsorption of proteins on the eroded tooth surface and may enhance the erosive resistance of salivary pellicle [24]. Moreover, NaF is an MMP inhibitor that inhibits MMP activation [25] and maintains the demineralised organic matrix (DOM), which acts as a barrier to acid diffusion on the dentine surface [25] [26].

NaF reduced surface loss, mineral loss and microhardness change in enamel specimens after erosive challenges [20][27] [28]. However, some studies reported that the anti-erosive effects of NaF are limited [5][12][23][29][30].

2.1.2. Amine Fluoride Containing Agents (AmF)

Products containing AmF are available in different forms such as toothpaste, mouthrinse and solution [31][32][33][34][35]. In collaboration with the University of Zurich, a company (GABA, Schweiz, Colgate-Palmolive, Therwil, Switzerland) developed and patented AmF with NaF and $SnCl_2$ [12][36]. Using organic molecules as carriers, they demonstrated that AmF significantly reduced the solubility of the enamel and thereby increased the resistance of enamel against acid attack [12][36]. AmF provide CaF_2 precipitates as a protective layer on the tooth surface [12][37]. Moreover, AmF have a pronounced affinity regarding enamel by raising the quantity of fluoride in the saliva [37].

AmF combined with $SnCl_2$ or SnF_2 reduced human enamel or dentine loss after erosive challenges [12][38]. AmF alone decreased calcium ion release in human dentine specimens in acid challenges [39], but the protective effect was limited [34] [35][40].

2.1.3. Stannous Fluoride Containing Agents (SnF_2)

Anti-erosive products using SnF_2 or $SnCl_2$ with fluoride as active ingredients are available on the market [41][42][43]. The stannous ions worked synergistically with fluoride and enhanced the anti-erosive effects of fluoride [15][44][45]. Stannous ions in these products have a higher affinity for mineral contents than organic contents [15]. These stannous ions interact with hydroxyapatite and fluoride and form a layer of Sn_2OHPO_4, $Sn_3F_3PO_4$, Ca $(SnF_3)_2$ and CaF_2 on the tooth surface [36] [46][47][48][49]. This layer is more stable and acid-resistant than the layer formed after NaF application alone [15][36][46]. Moreover, stannous ions interact with salivary proteins in acquired salivary pellicle [16][24] and enhance the acid resistance of salivary pellicle [16][17]. Stannous ions can also inhibit the activation of MMPs in the dentine matrix and prevent the organic matrix of the demineralised dentine surface from degrading [50].

SnF_2 reduced surface loss, decreased calcium ions release and decreased the microhardness change in enamel specimens after erosive challenge [24][33][51][52]. Nevertheless, the protective layer of SnF_2 is not stable at neutral or alkaline conditions [15]. It should be noted that SnF_2/$SnCl_2$ may cause staining on the dental hard tissue with prolonged use [32].

2.1.4. Titanium Tetrafluoride (TiF_4)

No commercially available product of TiF_4 is currently available. TiF_4 reacts with the hydroxyapatite on the tooth surface and forms a glaze-like layer of titanium dioxide (TiO_2) and hydrated titanium phosphate ($TiPO_4$) [50][53][54]. The TiO_2 and $TiPO_4$ layer coats the tooth surface and acts as a protective layer against erosive challenges [53][54]. Furthermore, this layer promotes fluoride uptake to the tooth surface [50][53] and increases the CaF_2 deposits on the tooth surface [55]. The interaction of TiF_4 and fluorapatite was found in the subsurface area in the demineralised enamel [54][56]. This layer is more acid-resistant than the CaF_2 layer formed after NaF application [53].

TiF_4 reduced human dentine loss, decreased microhardness change in human enamel specimens and occluded human dentinal tubule in erosive attacks [50][57][58][59]. However, the extreme acidity of the TiF_4 solution may weaken its anti-erosive effect [60][61]. The interaction with saliva also reduces the protective effect of TiF_4, which is unavoidable in the oral cavity [54][62]. Another concern is that TiF_4 can cause reversible staining on the tooth surface [50][63][64].

2.1.5. Silver Diamine Fluoride (SDF)

SDF is an alkaline agent (pH ~10) [65]; 38% SDF is a solution that contains a high concentration of fluoride and silver ions [65][66]. Several SDF products are available on the market [66][67]. SDF application facilitates the deposition of silver compounds on the tooth surface and may act as a protective layer against dental erosion [16][67]. SDF reduces demineralisation and promotes remineralisation on the tooth surface by promoting the deposition of CaF_2 and the formation of fluorapatite crystals on the tooth surface [16][65][68]. SDF can also inhibit MMPs [69] and may decrease the erosive demineralisation of dentine [69].

SDF has been widely investigated in anti-caries activity but the evidence of SDF on managing dental erosion is insufficient [70]. SDF decreased bovine enamel and dentine loss after erosive challenges [16]. A main disadvantage of SDF is the permanent black staining on the tooth surface [66][69][70].

2.2. Calcium Phosphate-Based Agents

Calcium phosphate-based agents supply the necessary minerals that are lost due to the acid challenge of erosion [71]. Calcium phosphate-based agents include casein phosphopeptide amorphous calcium phosphate (CPP-ACP), calcium silicate sodium phosphate (CSSP), β-tricalcium phosphate (β-TCP), nano-hydroxyapatite (n-HAP), sodium trimetaphosphate/sodium hexametaphosphate (TMP/SHP), linear sodium polyphosphate (LPP), pyrophosphate and calcium lactate.

2.2.1. Casein Phosphopeptide Amorphous Calcium Phosphate (CPP-ACP)

CPP-ACP is used in oral health products such as varnish, cream, chewing gum and acidic drinks for the management of dental caries [11]. The addition of fluoride to CPP-ACP results in the formation of casein phosphopeptide amorphous calcium fluoride phosphate (CPP-ACFP). CPP-ACP comprises a high amount of calcium and phosphate ions [36][49]. These ions form a calcium hydrogen phosphate precipitation layer [49], which acts as a physical barrier between acids and tooth surfaces [72][73][74]. Notably, the precipitation layer showed non-homogeneous distribution and may be easily detached by acids [73][75]. Calcium and phosphate ions are maintained around the tooth surface even under acidic conditions and reduce demineralisation process [11][36][49]. It also promotes remineralisation by supplying the mineral ions on the eroded surface [11][36]. In addition, CPP-ACP can modify the acquired salivary pellicle by increasing the electron-dense layer of the pellicle [73][76].

In situ studies revealed that CPP-ACP reduced the surface loss, microhardness change and calcium ions release in human enamel specimens [73][77][78][79]. Similarly, in situ studies of CPP-ACFP reported that CPP-ACFP reduced bovine enamel loss [80] and decreased microhardness change in human enamel after erosive cycles [81]. The effectiveness of CPP-ACP depends on the concentration, the vehicles and time of application [73][74][75]. The optimal time of application of CPP-ACP is contradictory in the literature [73][82]. A previous study showed that CPP-ACP had a limited working time [73].

2.2.2. Calcium Silicate and Sodium Phosphate (CSSP)

CSSP has been used as an additive in oral hygiene products for many years [83]. CSSP provides calcium and phosphate ions and raises the concentration of the mineral ions surrounding the tooth surface to saturated levels [36][83]. Thus, it helps reduce the demineralisation on the tooth surface [32][36] and promotes the remineralisation process of erosive dental hard tissue [32][36][84]. The CSSP also forms a protective layer by depositing calcium silicate particles on the tooth surface [32][83].

No study has investigated the effect of CSSP alone. In situ studies of CSSP reported that CSSP reduced bovine enamel loss [83], decreased the human enamel hardness change [85] and decreased dentine permeability after erosive challenges when combined with fluoride [86]. However, the protective effect of CSSP has a relatively short effective time [32]. The protective layer is unstable and can be easily removed by a strong acid [84]. In addition, CSSP may induce demineralisation on the tooth surface by itself due to the high acidity of the agent [32].

2.2.3. β-Tricalcium Phosphate (β-TCP)

β-TCP is a bioactive agent mainly comprising calcium and phosphate [71]. β-TCP provides calcium and phosphate ions to the tooth surface [71]. The calcium and phosphate ions maintain saturation levels around the tooth surface and induce mineral deposition on the tooth surface [71][87]. Moreover, β-TCP provides nucleation of the remineralisation process [71][87]. This nucleation facilitates the remineralisation of the eroded surface [71].

No study has investigated the anti-erosive effect of β-TCP alone. Previous in situ studies of β-TCP revealed that β-TCP reduced calcium and phosphate ion release, surface loss and hardness change in human enamel specimens when used with fluoride [71][87][88][89].

2.2.4. Nano-Hydroxyapatite (n-HAP)

n-HAP or nano-sized zinc-carbonate-hydroxyapatite is a synthetic hydroxyapatite, of which its size is approximately 20–100 nm [90][91][92]. The common concentration of n-HAP ranges between 1 and 10% [90]. n-HAP chemically binds to the natural apatite on the tooth structure and forms a crystalised apatite layer [90][93]. In addition, n-HAP can release calcium ions to maintain the mineral ions at a high level around the tooth surface and oral environment, which decrease

demineralisation and increase remineralisation [90][94]. n-HAP can also be a template for crystal growth and remineralisation [93][95].

One in situ study reported that n-HAP decreased the human enamel hardness change after erosive challenge [90]. However, it was also reported that n-HAP had limited preventive effects on dental erosion [90].

2.2.5. Sodium Trimetaphosphate/Sodium Hexametaphosphate (TMP/SHP)

TMP and SHP are inorganic polyphosphate compounds [29][96]. TMP is usually used as an additive in fluoride varnish, toothpaste and mouthrinse, whereas SHP is mainly added to fluoride toothpaste [14][29][49]. TMP can provide an acid-resistant layer by adsorbing onto the hydroxyapatite structure of the tooth surface and the collagen of the dentine surface [29][97][98][99]. The phosphate structures in the protective layer can incorporate the CaF_2 layer due to fluoride application [98]. SHP has a similar action to TMP on the tooth surface [14]. Additionally, SHP may infiltrate into the demineralised organic contents at the dentine surface and facilitates the formation of a scaffold for remineralisation [14]. SHP also enhances the level of acid-resistant salivary proteins in the acquired salivary pellicle [49][97].

No study has investigated the anti-erosion effect of TMP or SHP alone. In situ studies demonstrated that TMP or SHP reduced surface loss and decreased surface microhardness change in bovine enamel when combined with fluoride [100][101]. A low concentration of TMP/SHP worked synergistically with fluoride [99], while a high concentration of TMP/SHP may reduce the anti-erosive effect of fluoride [100].

2.2.6. Linear Sodium Polyphosphate (LPP)

LPP is a long-chain polyphosphate agent commonly used as the additive of non-alcoholic drinks [102][103]. LPP has phosphate groups that can bind with positively charged particles on the tooth structure [102][103] and forms an acid-resistant layer [103][104]. The LPP also works synergistically with fluoride and stannous ions in controlling dental erosion [102][103].

LPP decreased bovine enamel loss in in situ erosive challenges when combined with fluoride [104]. Likewise, in vitro studies demonstrated that LPP decreased surface loss and hydroxyapatite dissolution in bovine enamel and dentine when combined with $SnCl_2$ and fluoride [102][103]. LPP is more effective on enamel than on dentine because dentine has fewer binding sites for LPP [102]. However, some studies showed that LPP might compete with the anti-erosive protein in the salivary pellicle [104] or fluoride [105] for the binding site on the tooth surface and decrease their protective effect against dental erosion [104][105].

2.2.7. Pyrophosphate

Pyrophosphate or phytate is an organic polyphosphate, which is mainly found in cereals and seeds [106]. It is a cyclic structure with six phosphate groups without direct phosphate–phosphate bonds [105][106]. The pyrophosphate rapidly adsorbs and multi-point binds with hydroxyapatite of the tooth surface [105]. Moreover, it inhibits the diffusion of the ions between acids and the tooth surface [105][106]. Thus, pyrophosphate reduces erosive demineralisation [105][106].

One in situ study reported that pyrophosphate completely inhibited the remineralisation property of fluoride [105]. It may also compete with other mineral ions and inhibit them from binding to the tooth surface [105].

2.2.8. Calcium Lactate

Calcium lactate or calcium effervescent tablets have been used to prevent the softening of dental hard tissue caused by erosive drinks [28][48]. Calcium lactate mouthrinses or solutions provide extra calcium ions in the saliva [28][48] and reduce the demineralisation of the tooth during acid attacks [48]. Moreover, calcium ions may react with the fluoride in the oral cavity and increase CaF deposition on the tooth surface [28][107]. The CaF acts as a fluoride and calcium ion reservoir and promotes remineralisation [93][95].

An in vitro study reported that calcium lactate with fluoride decreased bovine enamel loss after erosive challenges [107]. However, an in situ study reported that a calcium lactate-containing solution could not prevent enamel erosion [48].

2.3. Organic Compounds

Anti-erosive organic compounds include polymer agents, such as polymethylvinylether-maleic anhydride (PVM/MA), carbopol and propylene glycol alginate (PGA), and these agents are derived from animals or plants' carbohydrates; lipids; or proteins, such as arginine, aspartame, sugarcane cystatin (CaneCPI-5), casein, chitosan, palm oil, epigallocatechin gallate (EGCG), Euclea natalensis plants and proanthocyanidin.

2.3.1. Polymethylvinylether-Maleic Anhydride (PVM/MA)

PVM/MA is a film-forming polymer, which is commonly used as an additive in beverages [108]. It is added to oral health products to control dental erosion [108]. PVM/MA binds to the mineral ions in the enamel and forms a protective layer [108][109]. It also binds to mineral ions and type I collagen in the dentine [110]. However, the protective layer formed by PVM/MA could easily be removed by acids because of the weak bond of PVM/MA with the tooth [108]. PVM/MA also helps with fluoride retention on the tooth surface and sustains fluoride release for a longer period [109][110][111].

An in situ study reported that PVM/MA enhanced surface hardness on bovine enamel after erosion compared with the control group [111]. Previous in vitro studies showed that PVM/MA positively interacted with fluoride and reduced surface loss in human and bovine dentine specimens [108][110][111].

2.3.2. Carbopol

Carbopol is a high molecular weight polymer with a negatively charged centre, which allows it to chelate with calcium ions [40][112]. Carbopol strongly binds with calcium ions [17][40] and forms a protective layer that covers the tooth surface [40][112]. Some studies have demonstrated that carbopol enhanced fluoride adsorption and promoted fluoride retention in the oral cavity [40][112].

Studies reported that carbopol with fluoride reduced enamel loss, increased enamel hardness and decreased the hydroxyapatite dissolution in erosive challenges [40][112]. However, the acidity (pH = 2.7–3.3) of carbopol may intensify the dissolution of dental hard tissue [40]. Carbopol also competes with salivary proteins for the binding sites on the tooth surface and may interfere with the anti-erosive potential of the acquired salivary pellicle [17].

2.3.3. Propylene Glycol Alginate (PGA)

PGA is a natural polymer derived from brown seaweeds that is commonly used in the food and biomedical industry, such as emulsifiers, stabilisers and thickening agents [108][113]. It has low toxicity, low cost, and high viscosity and biocompatibility [108][113]. The carboxylic groups of the PGA can bind to the calcium ions on the tooth surface and provides a protective layer [108][113]. The anti-erosive effect of the PGA is affected by the hydrogen ion level in acidic solutions because the hydrogen ions bind with the carboxylic groups of PGA and change the number of available carboxylic groups in PGA that can bind to calcium ions on the tooth surface [113]. PGA also competes with salivary proteins in salivary pellicle for binding sites on the tooth surface [113]. PGA with fluoride reduced bovine enamel and dentine loss after erosive challenge [108][113]. Notably, PGA alone cannot protect the tooth surface from erosion [108][113].

2.3.4. Arginine

Arginine is a positively charged amino acid that has a strong affinity to the dentine surface [56][114]. It improves the attachment of calcium to the tooth surface and promotes calcium carbonate precipitation [49][115][116]. This precipitation layer enhances the resistance of dental hard tissue to acids [115][116]. The precipitation layer helps to occlude dentinal tubules and alleviates dentine hypersensitivity [114][115].

The combined application of arginine with fluoride or calcium carbonate showed a positive result in controlling erosion [114][116][117]. The previous in situ studies demonstrated that arginine with fluoride decreased dentine permeability to acids by occluding human dentinal tubule [114][118]. In vitro studies reported that arginine reduced the hardness change and surface loss on bovine enamel [56][116].

2.3.5. Aspartame

Aspartame is a synthetic dipeptide and an artificial non-saccharide sweetener [119]. It is widely used as a sugar substitute in food and drink products [119]. Aspartame can be degraded to phenylalanine, aspartic acid and methanol [119]. Phenylalanine contains carboxylic and amino groups that can capture hydrogen ions in the erosive acids and can reduce the acidity of the acids [119]. Hence, it can reduce the demineralisation of the enamel surface [119][120].

A previous study showed that the anti-erosive effect of aspartame is limited [120]. All in situ and in vitro studies that investigated the anti-erosive property of aspartame revealed aspartame had no significant protective effect on the bovine enamel compared to no treatment [119][120].

2.3.6. Sugarcane Cystatin (CaneCPI-5)

CaneCPI-5 is a novel synthesised sugarcane cystatin [121]. It strongly binds to hydroxyapatite of the enamel surface and forms a protective layer [121][122]. The CaneCPI-5 can also improve the protective effect of the salivary pellicle by

increasing the number of acid-resistant proteins such as cystatin B [121][123][124]. In addition, CaneCPI-5 inhibits MMPs and reduces the severity of dentine erosion [122][123].

One in situ study revealed that CaneCPI-5 reduced bovine enamel loss in erosive challenge [121]. In vitro studies reported that CaneCPI-5 reduced surface loss in bovine enamel and dentine and hardness change in bovine dentine [122][123].

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