

EFFECTIVENESS OF FOUR HOME ORAL CARE PRODUCTS FOR PRIMARY ENAMEL RE-MINERALIZATION WITH EARLY CARIOUS LESION: AN IN-VITRO STUDY

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ABSTRACT

Introduction: Management of dental caries during early stages is considered a clinical problem in young children.

Objectives: The current in-vitro study assessed the influence of four home oral care products on re-mineralization of early caries lesions using enamel micro-hardness (EMH) test and morphological changes with scanning electron microscopy (SEM).

Material and methods: Sixty primary canine teeth were selected and randomly divided into 5 groups ($n = 12$ in each group). Samples were de-mineralized, and toothpaste slurries were prepared to treat de-mineralized enamel with a pH-cycling model. The groups were divided as follows: Group 1. Control (no intervention); Group 2. Fluoridated toothpaste; Group 3. Tooth mousse containing casein phosphopeptide-amorphous calcium phosphate (CPP-ACP); Group 4. Toothpaste containing bio-active glass and fluoride; Group 5. Tooth cream containing nano-hydroxyapatite, fluoride, and xylitol. EMH was evaluated in fifty specimens (each group, $n = 10$) at three times: before and after de-mineralization, and after 28 days of pH-cycling and treatment. Two samples from each group were observed with SEM. Data were analyzed with multiple-sample repeated measures ANOVA and Tukey's HSD post-hoc tests ($p < 0.05$).

Results: There was a significant difference in EMH between mean baseline values and de-mineralized enamel ($p < 0.001$). Re-mineralization significantly increased EMH in all treatment groups ($p < 0.001$). In group 5, the percent of EMH recovery was significantly greater than in other groups ($p < 0.001$). There were significant differences among the other three treatment groups (all $p < 0.001$). SEM images showed minerals deposited on the dissolved prismatic enamel in all groups.

Conclusions: The nano-hydroxyapatite-based tooth cream was the most effective home oral care product for re-mineralization of primary tooth enamel.

Key words: bio-active glass, casein phosphopeptide-amorphous calcium phosphate, dental caries, fluoride, nano-hydroxyapatite, primary enamel, re-mineralization.

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INTRODUCTION

Early caries lesions may be arrested, revert, or progress to cavitated lesions [1]. Using easy, conservative methods to re-mineralize these lesions in primary teeth is beneficial, and can be done individually with home oral care products [2, 3].

Fluoride is one of the best-known ions used to prevent dental caries. Topical fluoride is able to inhibit de-mineralization, promote re-mineralization, and reduce dental

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caries. To increase fluoride uptake in the enamel, calcium and phosphate ions are required, and the use of products containing these materials has been advocated [4]. Tooth Mousse® contains casein phosphopeptide (CPP), a milk protein able to bind calcium and phosphate, and thereby stabilize amorphous calcium and phosphate (ACP) to prevent ions' precipitation. CPP-ACP nano-complex is able to diffuse into sub-surface enamel, and this product can be used safely even in very young children [2, 5-7].

Bio-active glass materials are bio-compatible materials that can re-mineralize early caries lesions in low pH conditions by inducing fluorapatite formation due to the presence of calcium and phosphate in their glass structure [3]. BioMin F® toothpaste contains bio-active glass with 5% fluoro-calcium phosphosilicate. The low level of fluoride in its' composition makes this product safe to use in young children [8-11]. More recently, Remin Pro®, a water-based cream containing nano-hydroxyapatite (HAP) and fluoride with xylitol as a sweetener, was developed for home oral care. The nano-HAP fills superficial enamel lesions, fluoride enhances re-mineralization and prevents de-mineralization, and xylitol acts as an anti-caries agent [12-14].

OBJECTIVES

In light of the importance of using non-invasive methods to manage developing caries in young children, the aim of the present study was to compare home oral care products, e.g., fluoride toothpaste, CPP-ACP cream, toothpaste containing bio-active glass and fluoride, and a cream containing nano-HAP, fluoride, and xylitol, for their ability to re-mineralize artificial enamel caries lesions in primary teeth. Additionally, enamel surface micro-hardness after treatment with each product was evaluated, and surface changes with scanning electron microscopy (SEM) were observed. The hypothesis (H_0) was that there would be no significant difference between the re-mineralization effect of home oral care products on the enamel surface. The null hypothesis was contrasted with an alternative hypothesis (H_A) that a difference would exist.

MATERIAL AND METHODS

The current study was approved by the Ethics Review Committee of Shiraz University of Medical Sciences (approval No.: IR.SUMS.DENTAL.REC.1398.060). Sixty sound primary canine teeth were used: all teeth were extracted for orthodontic reasons from 6 to 8-year-old children, with their parents' permission in writing. Samples were disinfected for two weeks with 0.1% chloramine-T solution, and the crown was separated horizontally by 2 mm beneath the cemento-enamel junction. Intact enamel was diagnosed by stereo-microscopic examination, and the selected samples were mounted in acrylic resin. The buccal enamel surface was polished with 600-2,000 grit sandpaper with copious water cooling and then, aluminum oxide (0.5-3 μm) to create a flat surface [15]. The specimens were sonicated for 2 min with deionized water. Then, the samples were distributed randomly into 5 groups (n = 12 per group). Enamel surface micro-hardness (EMH) was measured in each tooth at the beginning of the study (baseline), after enamel de-mineralization, and at the end of 28 days of pH-cycling. Moreover, 12 teeth were randomly selected and observed with SEM. These samples did not undergo EMH testing. One operator (F.F.) performed all the procedures.

ENAMEL SURFACE MICRO-HARDNESS TEST

A paper sticker (2 × 2 mm window) was applied over the enamel, and the other parts of the teeth were covered with 2 layers of nail polish [16]. A Vickers' diamond indenter (MHV-1000Z, SCTMC, China) was used at a 50-g load for 15 seconds at five points, 100 μm apart to obtain Vickers' hardness number (VHN). Specimens with EMH between 214.61 and 302.65 VHN at baseline were included for the subsequent steps in this study. The specimens were then immersed individually in de-mineralization solution (pH = 4.4), and prepared according to JM ten Cate study [17].

SAMPLE PREPARATION

Each sample was immersed in 30 ml de-mineralization solution at 37°C. The solution contained: 2.2 mM $CaCl_2 \cdot 2H_2O$, 1.1 mM NaH_2PO_4, and 50 mM CH_3COOH (pH = 4.4). Final pH was monitored and adjusted with 1 M KOH. The solution were replaced with fresh solution after 48 hours. After 96 hours, each specimen was washed with de-ionized water for 20 seconds and air-dried, and a second EMH test was performed.

To model daily changes in the oral cavity, pH-cycling was applied. Daily cycle consisted of six 1-hour periods of immersion in de-mineralization solution and six 2-hour intervals in re-mineralizing solution. Samples were left in the re-mineralizing solution overnight. The cycle repeated every day for 28 days. Both solutions were replaced with fresh solutions after every daily cycle [18]. Artificial saliva solution composed of 2.200 g/l gastric mucin, 0.381 g/l sodium chloride (NaCl), 0.213 g/l calcium chloride ($CaCl_2 \cdot 2H_2O$), 0.738 g/l potassium hydrogen phosphate ($K_2HPO_4 \cdot 3H_2O$), and 1.114 g/l potassium chloride (KCl). The final pH was adjusted to 7.00 at 37°C with 85% lactic acid [19].

Two times a day, before the first and sixth re-mineralization phases on each day, the tooth surfaces were treated as explained below:

- Group 1. Control (no intervention): The teeth were immersed in the re-mineralizing solution, but did not receive re-mineralization treatment. The solution was replaced every other day for 4 weeks.

- Group 2. Fluoridated toothpaste: A single layer (0.25 g) of 1,450 ppm sodium fluoride toothpaste (Oral B, Iowa City, IA, USA) containing 0.6 ± 0.15 mg fluoride was applied over the enamel surface, and the teeth were stirred in 30 ml artificial saliva for 2 min at 100 rpm.
- Group 3. Tooth mousse: The enamel surface was treated with a layer of Recaldent™ (GC, Tokyo, Japan) for 2 min, and the re-mineralization assay was performed, as in the group 2. This cream contains 10% (wt/wt) CPP-ACP nano-complexes.
- Group 4. BioMin F®: A layer of BioMin F® toothpaste (BioMin Technologies Ltd., London, UK) containing calcium and fluoride (< 600 ppm) was applied on the de-mineralized surface for 2 min, as in the group 2.
- Group 5. Remin Pro®: The enamel was treated for 2 min as described above with a layer of Remin Pro cream (Remin Pro, VOCO GmbH, Cuxhaven, Germany) containing fluoride (1,450 ppm), nano-HAP, and xylitol.

The specimens were washed with de-ionized water for 20 sec after each pH-cycling treatment. During the study, the teeth were kept in a closed glass container.

The third EMH measurement was obtained in each tooth after 28 days. Percentage of EMH recovery in re-mineralized enamel was calculated as follows: %REMH = re-mineralized enamel micro-hardness – de-mineralized enamel micro-hardness × 100/sound tooth micro-hardness – de-mineralized enamel micro-hardness. The methods and materials used in the present study are shown in Figure 1 and Table 1.

SEM OBSERVATION

Two specimens of baseline, two de-mineralized enamel as well as two samples from the groups 2 to 5 were randomly selected for SEM evaluation. The specimens were polished with silicon-carbide grit paper under water cooling. Then, the teeth were dried, de-hydrated with alcohol, and coated with gold [20]. Surface micro-morphological changes were assessed by SEM (KYKY-EM3200, Shanghai, China) at 1,000 × magnification.

STATISTICAL ANALYSIS

IBM SPSS for Windows version 22.0 (Armonk, NY, IBM Corp.) was used for all statistical analyses. Shapiro-Wilk's test was applied to assess the normality of data distribution. Several sample repeated measures analysis of variance (RM-ANOVA) was used to assess interaction effects between the material and the three conditions. Mean micro-hardness and %REMH were compared between

TABLE 1. Materials used in the present study

Material	Chemical composition	Manufacturer
Fluoridate toothpaste	Sorbitol, aqua, hydrated silica, cocamidopropyl betaine, trisodium phosphate, aroma, cellulose gum, sodium phosphate, sodium fluoride, carbomer, sodium saccharine, 1,450 ppm fluoride	Oral B, Iowa, USA
CPP-ACP (tooth mousse, Recaldent)	Pure water, glycerol, CPP-ACP, D-sorbitol, CMC-Na, propylene glycol, silicone dioxide, titanium dioxide, xylitol, phosphoric acid, zinc oxide, sodium saccharin, ethyl p hydroxybenzoate, magnesium oxide, guar gum, propyl p-hydroxybenzoate, butyl p- hydroxybenzoate	GC, Tokyo, Japan
BioMin F (fluoride-containing bio-active glass toothpaste)	Glycerin, silica, PEG 400, fluoro-calcium phosphosilicate, sodium lauryl sulphate, titanium dioxide, aroma, carbomer, potassium acesulfame, fluoride content 530 ppm	BioMin Technologies Ltd., London, UK
Remin Pro	Nano-hydroxyapatite, xylitol, sodium fluoride (1,450 ppm fluoride)	VOCO GmbH, Cuxhaven, Germany

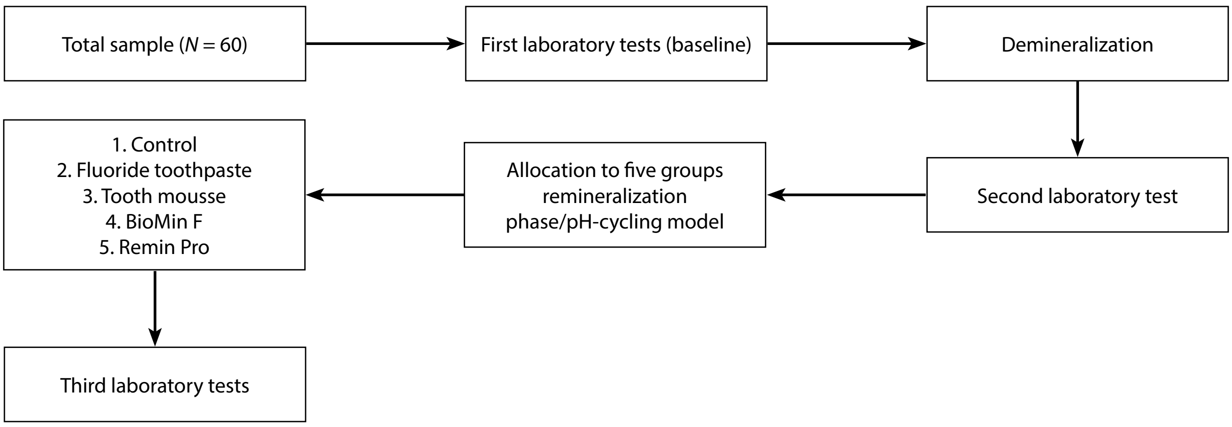

FIGURE1. Flowchart showing the methods used in this study

groups with one-way ANOVA and Tukey's HSD post-hoc tests. For each material, findings in each of the three conditions were compared with one-sample RM-ANOVA and Sidak's post-hoc tests ($p < 0.05$). Throughout all analyses, the significance level was set at $p < 0.05$.

RESULTS

In all the groups, EMH was measured and %REMH was calculated (Table 2). The mean EMH in selected teeth at baseline was 258.66 ± 43.99 VHN. After de-mineralization, EMH decreased significantly in each group (mean, 85.77 ± 39.00 VHN). There were no significant differences between groups at baseline ($p = 0.487$) or after de-mineralization ($p = 0.332$). A comparison of EMH values at all three times in groups 2, 3, and 4 revealed significant differences between the three values (all $p < 0.001$). Mean EMH was significantly reduced after de-mineralization compared with baseline in all groups (all $p < 0.001$). After re-mineralization, mean EMH increased significantly compared with de-mineralized enamels in all treatment groups (all $p < 0.001$). Although mean EMH was lower after re-mineralization compared with baseline measurements in groups 2, 3, and 4, no significant differences were seen between baseline EMH and micro-hardness measured after re-mineralization in group 5 ($p = 0.490$). One-way ANOVA test indicated significant differences in mean %REMH between groups ($p < 0.001$). Pair-wise comparisons showed that group 1 had the lowest mean %REMH (all $p < 0.001$). In group 5, %REMH was significantly higher compared to other groups (all $p < 0.001$). Mean %REMH in group 3 was significantly higher than in groups 2 and 1 (both $p < 0.001$), and mean %REMH in group 2 was higher compared with group 1 ($p = 0.039$).

SEM images showed that de-mineralization led to porosity and irregularities in the enamel surface, and the destruction of prism cores and peripheral enamel in some areas. Materials used in the four treatment groups were deposited in the spaces. Fluoridated toothpaste filled the enamel prism defects, although some unfilled spaces were observed. Tooth mousse containing CPP-ACP resulted in mineral deposition on the de-mineralized enamel, with some areas showing more homogenous crystals than in group 2. BioMin F® treatment filled the enamel porosity spaces and deposited mineral particles. Remin Pro® cream filled the irregularities; however, this product did not cover all de-mineralized surfaces (Figure 2).

DISCUSSION

The present study showed that different home oral care materials were effective to different degrees in increasing EMH in artificial early caries lesions in primary teeth.

In the present study, we used a method to produce early caries lesions based on a previous research [17]. In addition, a pH-cycling strategy is utilized to imitate daily pH changes in the oral cavity. Additionally, we used the micro-hardness test, which is a common method to assess the efficacy of re-mineralizing agents in de-mineralized enamel, and has been used in many studies [5, 10, 12, 16].

At the beginning of tooth de-mineralization, mineral ions are dissolved and removed from HAP crystals, with the resulting appearance of spaces in the enamel. In the early stage, the crystals can re-grow from minerals in the saliva or re-mineralizing agents [1]. In the present study, the 1,450 ppm fluoridated toothpaste enhanced EMH in de-mineralized enamel, as found in previous studies [5, 6, 16]. Fluoridated products are known to be able to re-mineralize enamel by entering the micro-porosities and replacing OH^- ions with F^- ions. The fluoride ions attract calcium and phosphate ions, and lead to the formation of calcium fluoride (CaF_2) and fluorapatite [1]. This newly formed mineral is less soluble than the original HAP. Therefore, fluoride enhances enamel

TABLE 2. Mean ± SD enamel surface micro-hardness in the control and experimental groups (%REMH: percentage of micro-hardness recovery in re-mineralized enamel surfaces)

Group	Treatment stage			%REMH
	Baseline	De-mineralized enamel	Re-mineralized enamel	
1. Control	261.55 ± 38.48^{a,A}	82.75 ± 31.73^{b,A}	84.55 ± 19.04^{b}	0.91 ± 13.71^{A}
2. Fluoride toothpaste	264.86 ± 41.01^{a,A}	77.86 ± 28.00^{b,A}	161.51 ± 39.77^{c}	39.38 ± 7.30^{B}
3. Tooth mousse	239.63 ± 37.05^{a,A}	72.00 ± 39.46^{b,A}	165.56 ± 32.77^{c}	49.21 ± 7.68^{C}
4. BioMin F	266.65 ± 42.54^{a,A}	82.00 ± 47.01^{b,A}	189.94 ± 47.31^{c}	67.48 ± 9.29^{D}
5. Remin Pro	263.49 ± 54.59^{a,A}	101.22 ± 38.10^{b,A}	244.14 ± 56.17^{a}	86.91 ± 12.00^{E}

In each column, the mean micro-hardness values of materials were compared using one-way ANOVA and Tukey's HSD post-hoc tests; the means with different capital letters were significantly different (p < 0.05).
In each row, the mean micro-hardness values in treatment stages were compared using one-sample RM-ANOVA and Sidak's post-hoc tests; the means with different lowercase letters were significantly different (p < 0.05).
In the last column, mean values of %REMH were compared between materials using one-way ANOVA and Tukey's HSD post-hoc tests; the means with different capital letters were significantly different (p < 0.05).

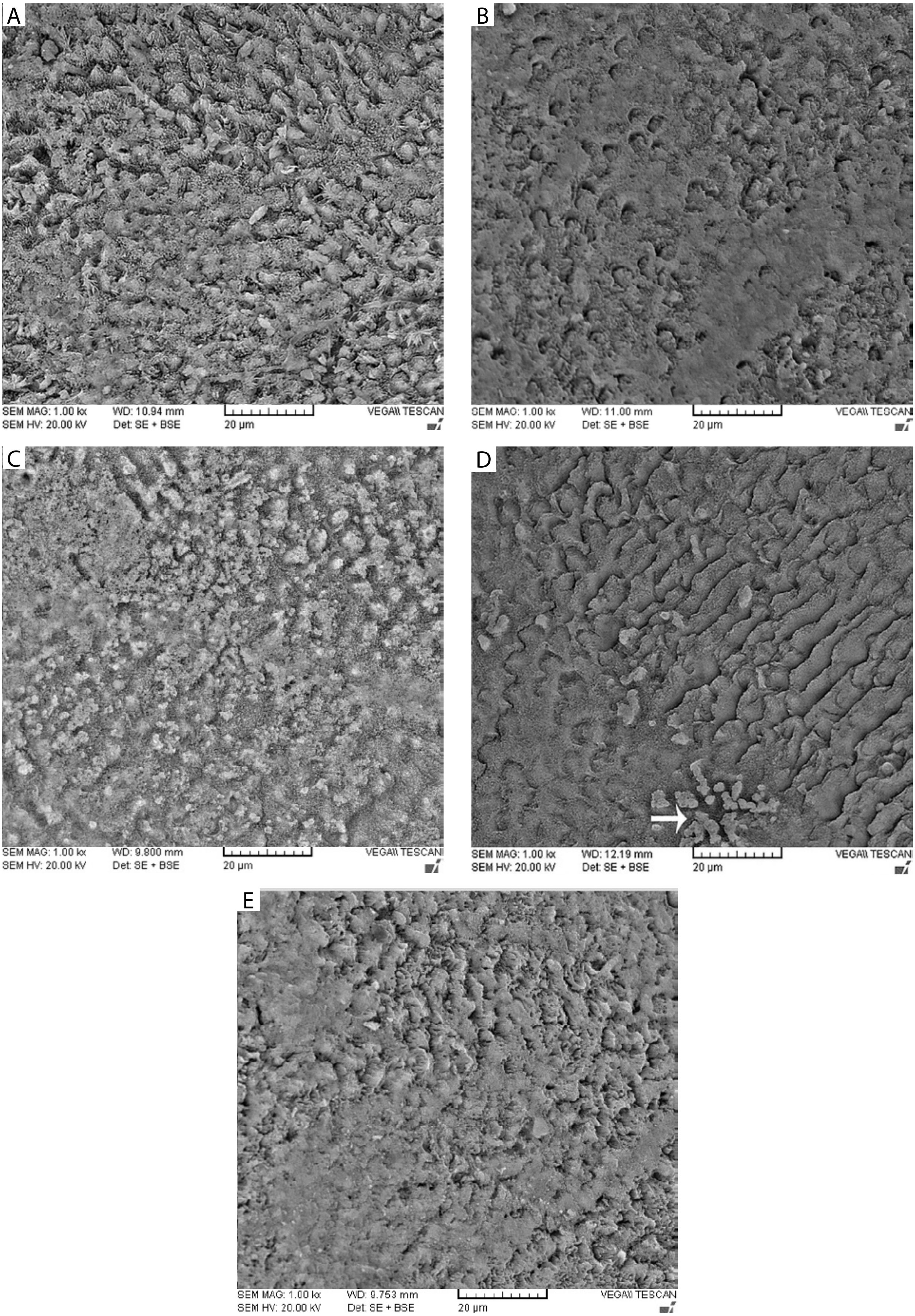

FIGURE 2. Scanning electron microscopy images of de-mineralized enamel (**A**), after application of fluoridated toothpaste (**B**), CPP-ACP (**C**), BioMin® F toothpaste with mineral deposition (arrow) (**D**), and Remin Pro® cream (× 1,000) (**E**)

re-mineralization and helps to counteract de-mineralization. However, consuming large doses of fluoride raises concerns due to the increased risk of fluorosis in children. The American Academy of Pediatric Dentistry (AAPD) recommends that children under the age of six use no more than a pea-sized or smear of fluoride toothpaste, together with parental supervision and rinsing after brushing, to minimize or completely eliminate the danger of fluorosis [21]. However, in order to form fluorapatite, calcium and phosphate need more than fluoride ions [4].

Casein phosphopeptide-ACP was developed to increase enamel re-mineralization by calcium and phosphate. The formation of new crystals is followed by an increase in EMH [2]. In the present study, there was a significant difference in %REMH between the fluoridated toothpaste and the CPP-ACP groups, in accordance with previous studies [5, 6, 15, 16]. This finding may be related to an increase in Ca/P ratio after the use of CPP-ACP on de-mineralized enamel, compared with a lower ratio with fluoride toothpaste [15]. However, various studies reported that the re-mineralization efficacy of fluoride toothpaste was greater than that of a CPP-ACP-containing product [7, 22].

The results of the present study showed that BioMin F® toothpaste increased EMH in de-mineralized enamel. This may be related to the composition of BioMin F®, which contains fluoro-calcium phosphosilicate. After the paste is applied, the bio-active glass is slowly dissolved by saliva and subsequently, calcium and phosphate ions are released. The fluoride in the paste allows calcium and phosphate to penetrate into the sub-surface of lesions and re-mineralize enamel [11]. During this controlled ion release, OH^- ions are exchanged for fluoride ions (< 600 ppm), and fluorapatite begins to form [3, 8, 9]. The fluoride content in toothpaste leads to the formation of CaF_2 mainly, resulting in reduced apatite formation. Some studies on the re-mineralization potential of BioMin® F in de-mineralized enamel found the efficacy of this product to be greater than fluoride toothpastes [10, 11]. Shihabi *et al.* [23] showed that fluoride toothpaste and a bio-active glass-containing toothpaste increased enamel re-mineralization in primary teeth to an equal extent.

In the present study, Remin Pro® cream increased %REMH significantly more than the other three treatments. Although the fluoride and bio-active glass toothpastes compared in the present study contained fluoride in their composition, the nano-HAP component in addition to fluoride in Remin Pro® cream may have led to an increased re-mineralization. In addition, the higher fluoride content of Remin Pro® (< 1,450 ppm) compared with BioMin F® may contributed to the superiority of Remin Pro®. The larger %REMH after treatment with Remin Pro® compared with CPP-ACP may be related to the presence of nano-HAP in the material. Nano-HAP particles are similar in content to the tooth structure, and their small size facilitates the release of calcium and phosphate ions, which can then bind to the de-mineralized enamel. After the nano-particles adhere to the surface, they form micro-clusters that cover the de-mineralized surface [24, 25]. Through two methods, HAP-containing toothpaste enhances the re-mineralization of caries lesions [26, 27]. First, HAP particles can dissolve in bacterial bio-films and increase bio-availability of calcium and phosphate ions in the immediate environment of the tooth surface. Second, HAP particles are capable of being directly deposited in the micro-porosities of de-mineralized tissue, where they enhance crystal formation and deposition by persistently drawing calcium and phosphate ions from the surrounding re-mineralization solution [28-30]. The second mechanism could be employed in the current study. Consistent with our results, earlier studies found that toothpastes containing nano-HAP were more effective in re-mineralizing early caries lesions than fluoride-containing or CPP-ACP-containing toothpastes [24, 25, 31]. A clinical study recommended using MI Paste Plus® and Remin Pro® cream as an alternative to fluoride for the treatment of early caries lesions in permanent teeth [12]. In another study, Remin Pro® increased the micro-hardness of de-mineralized enamel more than a 2% sodium fluoride gel, or a cream containing CPP-ACP and fluoride [13]. The differences in the results between studies may be due to differences in the duration and methods of re-mineralization as well as the method of measuring EMH [24, 25, 31].

In the present study, SEM was used to examine enamel surface alterations after treatment with the re-mineralizing agents. As also reported in previous studies, de-mineralization resulted in enamel prism destruction [5, 16]. All treatments led to some degree of particle diffusion to the de-mineralized enamel, suggesting a formation of an apatite layer on the de-mineralized surface [5, 11, 16].

One of the limitations of the present study was the use of laboratory conditions to simulate clinical conditions. To overcome this limitation, we selected teeth, in which mean EMH at baseline and after de-mineralization was within the range of values reported earlier [16]. To date, few studies have compared the efficacy of these re-mineralizing agents in de-mineralized enamel of primary teeth [23, 31], so comparisons with other studies were likewise limited. Also, the inclusion of a non-homogeneous set of oral care products appears to be a limitation of the study, as we sought to compare the most important dental care products for children, regardless of their compositions. Additional in-vitro and in-vivo studies are needed to obtain further information on the effects of the different products compared in the current research.

CONCLUSIONS

The non-invasive materials enhanced the recovery of enamel surface micro-hardness (determined as %REMH) in re-mineralized teeth. The recovery of %REMH was significantly greater in the Remin Pro group cream containing nano-HAP, fluoride, and xylitol compared with the groups treated with other products. The present findings support using this material in clinical setting to manage early childhood caries in young children.

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CONFLICT OF INTERESTS

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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