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ORIGINAL ARTICLE

Ultrasonic measurement of dentin remineralization effects of dentifrices and silver diamine fluoride

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ABSTRACT

Objective: This study investigated the dentin remineralization effect of the application of a functionalized tri-calcium phosphate (fTCP) dentifrice and a silver diamine fluoride (SDF) solution.

Material and methods: The materials used were: a fluoride-containing dentifrice with fTCP (fTCP+), a fluoride-containing dentifrice without fTCP (fTCP−) and a 38% SDF solution. Following treatment, the dentin slabs were immersed in a 0.1-M lactic acid buffer solution and then placed in artificial saliva. This procedure was repeated three times daily for 28 days. The propagation time of longitudinal ultrasonic velocities (UV) and the Knoop hardness (KH) of the samples were measured. The samples were also observed using scanning electron microscopy.

Results: The SDF and fTCP+ groups showed higher UV than the fTCP − group regardless of the application method. The F-SDF group at 28 days showed significantly higher UV (4121 ± 102 m/s) than the F-fTCP + group (3731 ± 65 m/s) ($p < .05$). The F-SDF group at 28 days showed significantly higher KH (47.4 ± 2.2) than the F-fTCP+ group (43.3 ± 1.0) and the F-fTCP − group (42.9 ± 2.1) ($p < .05$). Closure of the dentinal tubules and crystal precipitation was detected on the surface of the fTCP+ group to a greater extent than the fTCP − group.

Conclusions: The fTCP-containing dentifrice and SDF solution effectively enhanced bovine dentin remineralization.

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Introduction

Human teeth are exposed to many physical, chemical and mechanical challenges during everyday life that cause varying levels of tooth decay. Root caries have increased in prevalence as people live longer and retain their natural teeth to old age [1]. Root caries formation is determined by the presence of a cariogenic biofilm and fermentable carbohydrates and is exacerbated by the complex dynamic of dentin tissue [2]. Apatite crystals in dentin have a higher carbonate content than enamel, and their demineralization process involves collagen breakdown, which makes their components more water soluble and susceptible to acidic dissolution than those in enamel [3]. Although root caries can be observed in young adults, exposure of the root surface due to periodontal disease leads to an increased prevalence of root caries in older adults [4]. Root surfaces are more susceptible to bacterial accumulation when cleaning is inadequate due to their roughness and retentive anatomy, leading an increased risk for the development and progression of root caries [5].

The management of root caries with evidence-based prevention guidelines has been proposed and includes the control of dietary carbohydrate intake, improved oral hygiene, antimicrobial agents, fluoride-containing dentifrice, casein phosphopeptide-stabilized amorphous calcium phosphate and bioactive glass application [6]. Fluoride use is considered the main effective non-invasive treatment to control root caries [7]. Tooth brushing with fluoridated dentifrice is a cost-effective tool because it combines the mechanical disruption of dental biofilm with fluoride delivery. The application of dentifrices containing higher concentrations of fluoride for controlling root caries has been compared with conventional fluoride dentifrices with conclusive evidence [8].

Dentifrices containing functionalized tricalcium phosphate (fTCP) provide and enhance bioavailable Ca and PO_4 ions to teeth. These ions act synergistically with fluoride, enhancing their effect [9]. fTCP is ball milled with sodium lauryl sulphate to produce particles reported to exhibit remineralizing effects in both *in vitro* and *in situ* studies. Furthermore, fTCP products provide more fluoride and ions to the tooth surface while preventing Ca from prematurely interacting with F ions to form CaF [10]. Teeth naturally absorb the components released from fTCP, preventing the initiation and further progression of demineralization and allowing remineralization. However, limited information is available regarding the effect of fTCP on dentin in root caries.

Silver diamine fluoride (SDF) is an alkaline topical fluoride solution containing two reasonably well-known ingredients: silver and fluoride ($Ag(NH_3)_2F$). SDF is effective not only for

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preventing and arresting dental caries but also for treating dentin hypersensitivity [11]. In contrast with silver nitrate ($AgNO_3$), which was often used to treat dentin hypersensitivity, SDF does not cause inflammation of pulp tissues [12]. Silver is a direct antimicrobial agent because it reacts with the thiol groups of amino acids and nucleic acids, disrupting the metabolic and reproductive pathways of the bacteria that cause cell death. Along with the emergence of SDF as a caries-arresting agent, there is growing interest in its use in the practicing community [13].

Ultrasonic measurement monitors the demineralization and remineralization process of bulk dentin. Increases and decreases in ultrasonic velocity (UV) are related to changes in the degree of mineralization. In the demineralization process, the acid reduces the stiffness of the dentin resulting in a reduction of the longitudinal wave velocity [14,15]. On the other hand, in the remineralization process, the increase in UV is directly proportional to the volume concentration of minerals. Thus, UV has been shown to be an index of both demineralization and remineralization of the tooth substrate. [16].

The effects of individual fluoride-containing agents on tooth remineralization have been reported, but few studies have compared them. The principal purpose of this study was to demonstrate the efficacy of dentifrices with different compositions and that of SDF in promoting dentin remineralization. This was determined using an ultrasonic measurement method.

Materials and methods

Fluoride-containing agents

The fluoride-containing agents employed in this study were a dentifrice containing sodium fluoride with fTCP (Clinpro 1450, fTCP+; 3 M Japan, Tokyo Japan), a dentifrice containing sodium fluoride (check-up standard, fTCP−; Lion Dental Products, Tokyo Japan), and a 38% SDF solution (Saforide, SDF; Toyo Seiyaku Kasei Co. Ltd., Osaka, Japan) (Table 1).

Initial preparation of root surface lesion

The procedure for artificially making a root surface lesion is shown in Figure 1. We cleaned and stored 70 freshly extracted bovine incisors without cracks or erosion in physiological saline for up to 2 weeks. Approximately two-thirds of the apical root structure of each tooth was removed using a diamond-impregnated disk in an IsoMet 1000 precision sectioning saw (Buehler, Lake Bluff, IL). The labial surfaces were wet ground with #240-grit silicon carbide (SiC) paper (Fuji Star type DDC; Sankyo-Rikagaku Co. Ltd., Saitama, Japan) to expose flat dentin surfaces. Then, the dentin blocks were carefully shaped into rectangles (4 × 4 × 1 mm) using a superfine diamond finishing bur (ISO #021; Shofu Inc., Kyoto, Japan). The specimen surfaces were successively ground on wet SiC paper to a grit size of #2000. The thickness and size of the specimens were measured using a CPM15-25DM dial

Table 1. Materials used in this study and their main ingredients.

Dentifrice and solution	Code	Active and inactive ingredient	Manufacture	Lot No.
Clinpro toothpaste 1450	fTCP+	1450 ppm sodium fluoride, fTCP, CPC, IPMP, dipotassium glycyrrhizinate sorbitol, concentrated glycerine, hydrated silica, tricalcium phosphate, carboxymethyl cellulose sodium, polyoxyethylene hydrogenated castor oil, sodium lauryl sulphate, titanium dioxide, sodium saccharin	3M Japan, Tokyo, Japan	2102BA
Check-up standard	fTCP−	1450 ppm sodium fluoride sorbitol, propylene glycol xylitol, sodium saccharin hydrated silica, sodium polyacrylate, sodium lauryl sulphate, xanthan gum, titanium dioxide, paraben	Lion Dental Products, Tokyo, Japan	180927A1
Saforide	SDF	38% silver diamine fluoride	Toyo Seiyaku Kasei, Osaka, Japan	808RA

CPC: cetylpyridinium chloride; fTCP: functionalized tri-calcium phosphate; IPMP: isopropyl methylphenol.

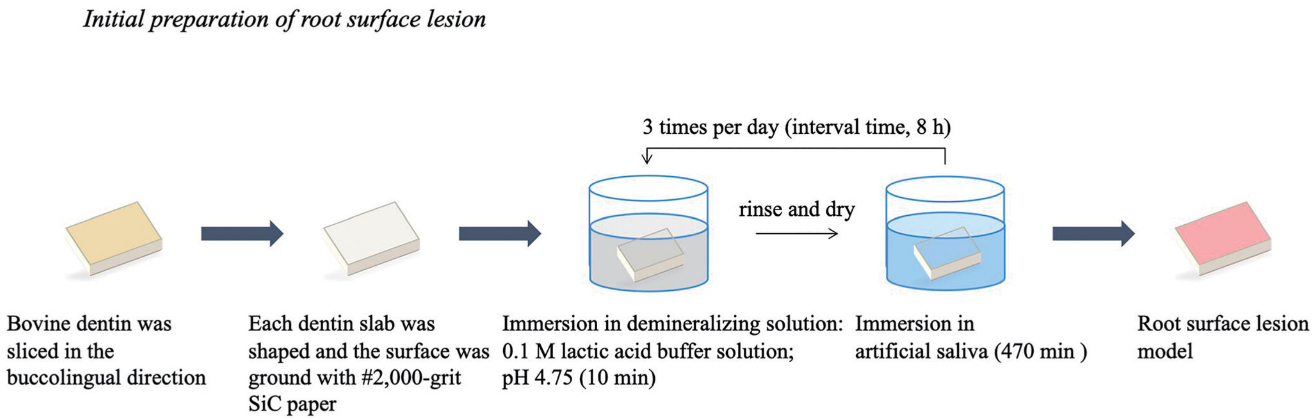

Figure 1. Production method for model root surface lesion.

gage micrometer (Mitutoyo Corp, Tokyo, Japan) and then covered with dental paraffin wax except the labial side of the dentin slab, which was used as the treatment surface.

To make a root surface lesion artificially, all specimens were immersed in undersaturated 0.1 M lactic acid buffer solution (pH 4.75; 0.75 mM $CaCl_2 \bullet 2H_2O$ and 0.45 mM KH_2PO_4) for 10 min and then placed in artificial saliva (pH 7.0; 14.4 mM NaCl, 16.1 mM KCl, 0.3 mM $MgCl_2 \bullet 6H_2O$, 2.0 mM K_2HPO_4, 1.0 mM $CaCl_2 \bullet 2H_2O$, and 0.10 g/100 ml sodium carboxymethyl cellulose) at 37 °C. This procedure was repeated three times daily (interval time, 8 h) over 28 days.

Surface treatment conditions

The specimens with artificial root surface lesions were divided into seven treatment groups ($n = 10$) as follows (Figures 2 and 3):

1. Untreated group: specimens were immersed in 0.1 M lactic acid buffer solution for 10 min and then placed in artificial saliva. This procedure was repeated three times per day during the course of the experiment.
2. One-off brushing with dentifrice group (O-fTCP+ or O-fTCP−): on the first day of the experiment, dentifrice was applied once to the root surface lesion with a soft brush for 10 s [17] and then rinsed with tap water. These specimens underwent the same acidic challenge as the untreated group.
3. One-off application of SDF group (O-SDF): in accordance with the manufacturer's instructions, SDF was applied once to the root surface lesion with a microbrush (Shofu Inc., Kyoto, Japan), left for 3 min, and then rinsed with tap water on the first day of the experiment. These specimens underwent the same acidic challenge as the untreated group.
4. Frequent brushing with dentifrice group (F-fTCP+ or F-fTCP−): Dentifrice was applied to the root surface lesion with a soft brush for 10 s and then rinsed with tap water once daily. This procedure was repeated daily throughout the experimental period. These specimens underwent the same acidic challenge as the untreated group.
5. Frequent application of SDF group (F-SDF): SDF was applied to the root surface lesion with a microbrush, left for 3 min, and then rinsed with tap water. This procedure was performed once a week throughout the experimental period. These specimens underwent the same acidic challenge as the untreated group.

Brushing was performed using a micromotor handpiece (TorqTech CA-DC; J. Morita Manufacturing Corp, Kyoto, Japan) and a soft brush (Merssage soft brush, Shofu Inc.) at 1000 rpm and a constant pressure of 0.1 N monitored by a digital balance (AT200; Mettler-Toledo GmbH, Greifensee, Switzerland). All procedures were performed by one operator.

UV measurement

UV was measured using a system comprising a pulser-receiver (5900PR; Panametrics, Waltham, MA), a longitudinal wave transducer (V112; Panametrics), and an oscilloscope (Waverunner LT584; LeCroy, Chestnut Ridge, NY). Measurements were taken before starting the test and on

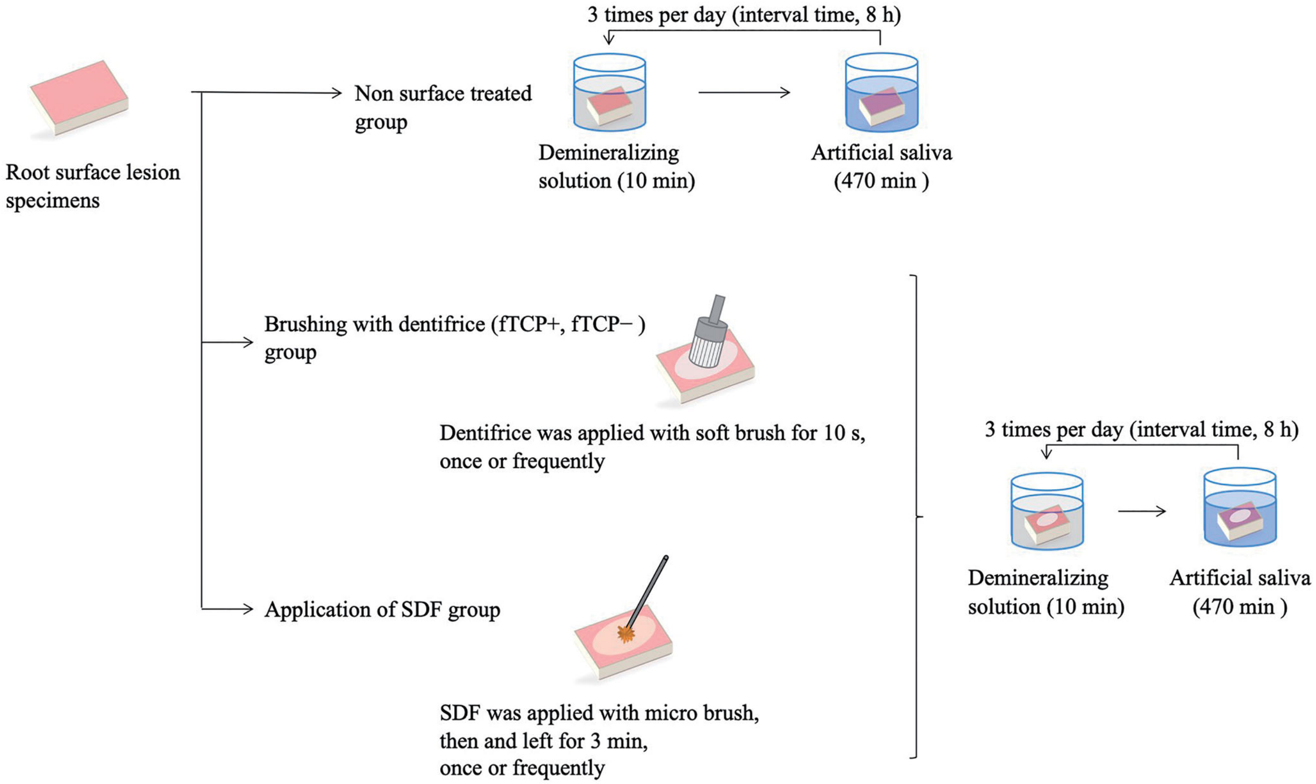

Figure 2. Steps of the experimental treatment of the specimens.

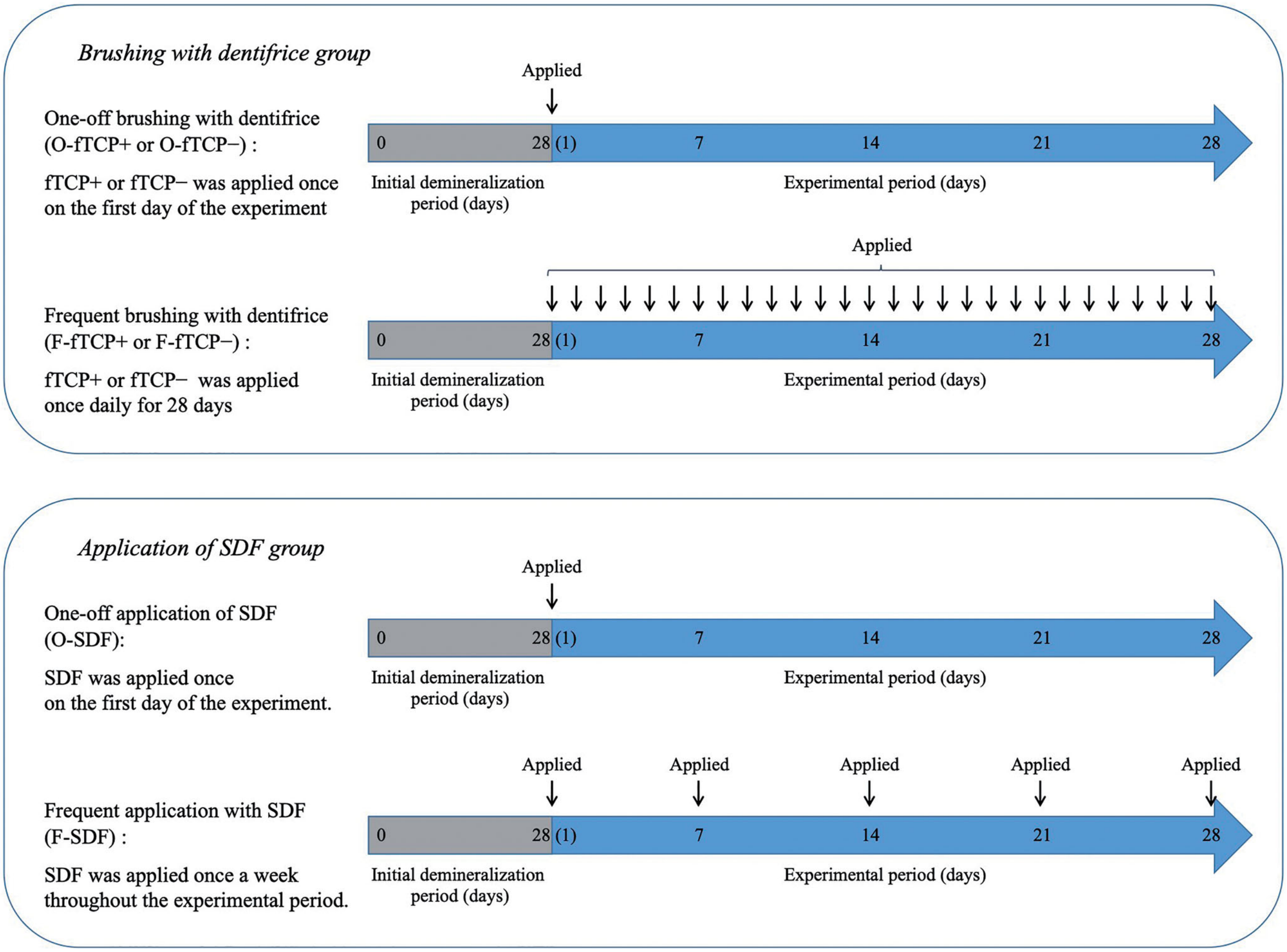

Figure 3. Outline of sample treatment period.

days 1, 7, 14, 21, and 28. The equipment was initially calibrated using a standard procedure with 304 stainless steel calibration blocks (2211 M; Panametrics) [18]. The transducer was oriented perpendicular to the contact surface of each sample to obtain an echo signal. The ultrasonic waves propagated from the transducer to the tooth were transmitted through the tooth and detected by the transmitter on the opposite side. All measurements were performed at 23 ± 1° C under a relative humidity of 50 ± 5%.

Microhardness test

After the ultrasonic measurement had been performed for the frequently treated groups, the Knoop hardness (KH) of the surface of each sample was determined. The indenter was kept on the surface for 30 s with a 0.25-N load using a microhardness tester (DMH-2; Matsuzawa, Tokyo, Japan). Three measurements were performed per sample, and the mean surface hardness value was used as the KH number of the sample.

Statistical analysis

The UV and KH data were analyzed by two-way factorial analysis of variance, with the measurement period and treatment as factors. Post hoc pairwise tests among groups were performed using Tukey's honestly significant difference test. The level of significance was set at a *p*-value of .05. Calculations were performed using Sigma Plot 11.2 statistical software (SPSS Inc., Chicago, IL).

Scanning electron microscopy (SEM)

Ultrastructural observation of the specimens' surface was conducted using field emission SEM (ERA 8800FE; Elionix Ltd., Tokyo, Japan). The specimens were dehydrated in ascending concentrations of *tert*-butanol (50% for 20 min, 75% for 20 min, 95% for 20 min and 100% for 2 h) and then freeze dried for 30 min. The surfaces were coated with a thin film of gold in a vacuum evaporator (Quick Coater Type SC-701; Sanyu Denshi Inc., Tokyo, Japan) and then observed at an accelerating voltage of 10 kV.

Results

The average UVs of the dentin in each group are shown in Tables 2 and 3. The differences in storage periods were greater than expected by chance after allowing for the effects of storage conditions, so multiple comparisons were performed on the data. The average UVs of all groups in the

Table 2. Influence of one-off application of fTCP+, fTCP− and SDF on ultrasonic velocity of bovine dentin.

	Initial demineralization period (day)		Experiment period (day)			
	0	28 (1)	7	14	21	28
Non-surface treated	3938 (124)aA	3000 (61)bA	2871 (66)cA	2742 (49)dA	2708 (49)dA	2684 (49)dA
O-fTCP+	3952 (53)aA	3002 (129)bA	3349 (120)cB	3312 (137)cB	3265 (118)cB	3219 (118)cB
O-fTCP−	3816 (170)aA	2989 (59)bA	3160 (70)cC	3137 (55)cC	3109 (47)cC	3054 (69)bcC
O-SDF	3828 (167)aA	3034 (110)bA	3816 (44)aD	3719 (73)acD	3678 (61)cD	3593 (60)cD

Unit: m/s, $n = 10$, values in parenthesis indicate standard deviations. Within groups, means with the same lowercase letter, are not significantly different. Between groups at the same periods, means with the same uppercase letter, are not significantly different ($p > 0.05$).

Table 3. Influence of frequent application of fTCP+, fTCP− and SDF on ultrasonic velocity of bovine dentin.

	Initial demineralization period (day)		Experiment period (day)			
	0	28 (1)	7	14	21	28
Non-surface treated	3938 (124)aA	3000 (61)bA	2871 (66)cA	2742 (49)dA	2708 (49)dA	2684 (49)dA
F-fTCP+	3958 (161)aA	3037 (137)bA	3416 (60)cB	3631 (71)dB	3704 (66)dB	3731 (65)dB
F-fTCP−	3815 (150)aA	3034 (91)bA	3209 (49)cC	3370 (91)dC	3410 (84)dC	3437 (94)dC
F-SDF	3898 (71)aA	3038 (58)bA	3881 (111)aD	4080 (116)cD	4100 (108)cD	4121 (102)cD

Unit: m/s, $n = 10$, values in parenthesis indicate standard deviations. Within groups, means with the same lowercase letter, are not significantly different. Between groups at the same periods, means with the same uppercase letter, are not significantly different ($p > 0.05$).

Table 4. Influence of frequent application of fTCP+, fTCP− and SDF on Knoop hardness number of bovine dentin.

	Initial demineralization period (day)		Experiment period (day)			
	0	28 (1)	7	14	21	28
Non-surface treated	55.3 (2.1)aA	29.5 (1.9)bA	28.9 (2.3)bcA	27.1 (1.8)bcA	26.6 (1.5)cA	26.6 (1.5)cA
F-fTCP+	54.3 (2.3)aA	29.5 (2.5)bA	35.6 (2.5)cB	41.8 (2.4)dB	42.3 (2.2)dB	43.3 (1.0)dB
F-fTCP−	55.4 (2.0)aA	30.7 (2.3)bA	36.1 (0.7)cB	38.2 (2.2)cC	40.7 (1.6)dB	42.9 (2.1)dB
F-SDF	54.9 (2.8)aA	31.0 (3.3)bA	46.4 (1.2)cC	47.3 (2.8)cD	47.4 (3.9)cC	47.4 (2.2)cC

$n = 10$, values in parenthesis indicate standard deviations. Within groups, means with the same lowercase letter, are not significantly different. Between groups at the same periods, means with the same uppercase letter, are not significantly different ($p > .05$).

initial demineralization period decreased from 3952 to 2989 m/s. The UV of the untreated group gradually decreased from 2871 to 2684 m/s during the experimental period. However, the UVs of the O-fTCP+, O-fTCP− and O-SDF groups increased after day 7 and then gradually decreased. Significantly higher velocities were recorded for the O-SDF group on each measurement day. Increased sonic velocities were observed during the experimental period for the F-fTCP+, F-fTCP− and F-SDF groups. The F-SDF group exhibited significantly higher values, followed by the F-fTCP+ and F-fTCP− groups during the experimental period.

The average KH numbers of the dentin samples are presented in Table 4. The KH number of all groups decreased from 55.4 to 29.5 during the initial demineralization period. Although the KH numbers of the untreated group gradually decreased throughout the experiment, those of the F-fTCP+, F-fTCP− and F-SDF groups significantly increased from days 14, 21 and 7, respectively. The F-SDF group recorded significantly higher KH numbers on each measurement day compared with the F-fTCP+ and F-fTCP− groups.

Representative SEM images of samples are shown in Figure 4. SEM images of the dentin surfaces revealed morphological differences among the treatment groups. The dentin surface was covered with a smear layer and dentinal tubules were not observed before the initial demineralization period. Morphological changes on the dentin surfaces were noticeably observed in the frequent application groups compared with the one-off application groups at the end of the 28-day experimental period. The dentinal tubules were totally occluded, and some precipitations were observed in the F-SDF group. Closure of the dentinal tubules and crystal precipitation were detected on the surface of the fTCP+ group to a greater extent than the fTCP− group.

Discussion

It has been suggested that the anti-caries effect of fluoride use on root surface caries is related to the intrinsic mineral and organic constituents of the root surface. Fluoride suppresses mineral loss during the acid dissolution process and enhances remineralization in a physicochemical manner similar to that occurring in enamel. Fluoride availability in saliva and plaque fluid, even at low levels, is important to maintain the surface integrity of teeth and avoid subsurface caries formation [19].

A review paper reported a dose–response related to the fluoride concentration in topical fluorides and that dentifrices containing high fluoride concentrations provided a superior anti-caries effect compared with dentifrices with lower fluoride concentrations [20]. The amount of fluoride in dentifrice is restricted to <1500 ppm in Japan, which is less than optimal in negatively influencing bacterial growth and metabolism to a significant degree [21]. A higher fluoride concentration may be more effective on root surfaces than conventional fluoride concentrations in dentifrices due to the intrinsic differences in the mineral and organic components comprising enamel and dentin and in their susceptibility to acid dissolution [22]. Given the fluoride concentration limitation in Japan, other methods to prevent root caries with fluoride concentrations <1500 ppm or other approaches

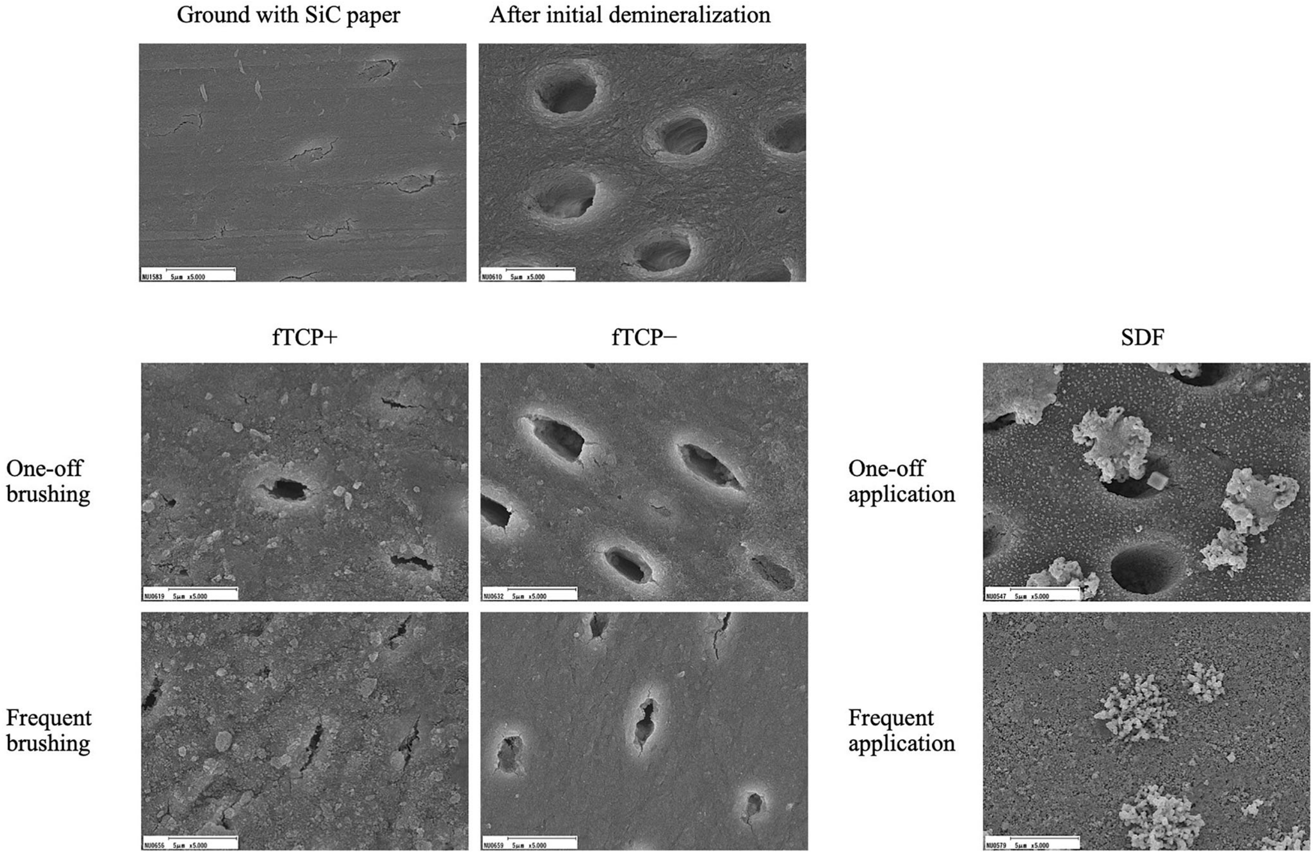

Figure 4. Representative SEM images of the dentin surface of each group (5000× magnification). The initial treatment removed the smear layer on the specimen surface, and dentinal tubule openings were observed. Morphological changes on the dentin surfaces were noticeably observed after the 28-day experimental period in the frequent application groups compared with the one-off application groups. The dentinal tubules were totally occluded, and some precipitates were observed in the frequently treated SDF group.

utilizing solutions, varnishes or coatings should be considered in clinical situations.

Ultrasonic measurement is a non-invasive technique, and so it is possible to follow the process of demineralization or remineralization of the tooth structure using it. In addition, this method may be superior for grasping the changes in a single specimen over time. On the other hand, it is difficult to measure the remineralization depth. Transverse microradiography (TMR) is often used to quantify demineralization or remineralization phenomena that occur in tooth structure. A linear relationship has been reported between the square root of the KH number of the demineralized dentin and the mineral density measured by TMR [23]. Therefore, we determined mineral density using ultrasonic equipment and measurements of microhardness in this study. Furthermore, we observed morphological changes on the dentin surface using SEM to support our findings.

Our findings showed that the fTCP+ groups exhibited significantly higher sonic velocities compared with the fTCP − groups during the experimental period. Higher sonic velocities indicate the incorporation of minerals into the dentin, showing that remineralization of the samples has occurred [16]. The remineralization process occurs when minerals lost during erosion are replaced during subsequent exposure to saliva containing Ca and PO_4 ions. SEM images of the samples in the fTCP+ groups showed a homogenous layer on the dentin surface that occluded the dentinal tubules. The fluoride concentration of fTCP+ is the same as fTCP−, but fTCP+ contains fTCP as an active ingredient and sodium fluoride, which exhibit remineralizing effects both *in vitro* and *in situ* [9]. We observed the positive effects of remineralization to a greater extent in the fTCP+ groups compared with the fTCP− groups (one-off and frequent application). When toothpaste comes into contact with saliva during brushing, the biofilm barrier is destroyed and Ca, PO_4, and F become available to the tooth. Teeth naturally absorb these components, preventing the initiation and further progression of demineralization and allowing remineralization [24]. A rapid exchange of sodium ions (Na^+) with hydrogen cations (H^+ or H_3O^+) from the solution occurs in aqueous environments. The migration of Ca^{2+} and $PO_4{}^{-3}$ groups to the fTCP particles forms a CaO–P_2O_5-rich film on the particle surface that crystallizes into hydroxycarbonate apatite [25]. Deposits on the dentin surface were observed under SEM in the F-fTCP+ group. It can be inferred that the observed deposit on the dentin surface may play a role in increasing UV. It has been proposed that the chemical reactions that promote apatite formation are useful to enhance remineralization and prevent demineralization of root caries [26].

A drastic increase in UV and KH number after the 28-day test period were observed in the F-SDF group. SEM observation revealed precipitated materials on the dentin surface and complete occlusion of dentinal tubules. Different SDF concentrations have been applied in clinical trials, with 38%

SDF being the most effective. A 38% SDF solution (44 800 ppm F) was significantly more effective in arresting dental caries than a 12% SDF solution or no application in primary dentition [27]. SDF has shown impressive efficacy in arresting and preventing caries, often without the need for excavation of infected dentin. SDF can remineralize carious dentin and increase resistance to acid lysis and enzymatic digestion due to the flattened layer of the silver protein complex [28]. The treated lesions showed increased mineral density and hardness and decreased lesion depth. SDF also suppressed the degradation of the dentin organic matrix, which mainly consists of type I collagen [29]. When SDF is applied to teeth, it penetrates 50–200 µm into dentin and accumulates 2–3 times more fluoride below the surface of the tooth than remineralization with other fluoride solutions [30].

Our findings indicated that frequent SDF application was substantially more effective for dentin remineralization compared with a one-off application. It is suitable when fewer applications are required to reduce the treatment cost, and the treatment effect is unimpaired. Application only to the lesion appears as effective as applying it directly to other teeth and surfaces to prevent dental caries. While a single application appears to be insufficient for a lasting effect, annual reapplications have significant success, and semiannual applications have a greater effect [31]. SDF treatments are easy to administer, inexpensive, safe and less frequent than other preventive treatments. Therefore, the use of SDF for the prevention and arrest of caries may be an alternative to more complex treatments in the elderly population because of its low cost and simple application. However, the main side effect is that lesions arrested by SDF exhibit dark staining, which may significantly deter its use. The silver ions in SDF turn to metallic silver in the presence of light, resulting in a dark discolouration that can spread deep into the tooth [32]. The effect of potassium iodide (KI) application to SDF-treated surfaces on the dark lesions has been examined, but the study concluded that KI could help but did not dramatically improve the dark colours [33]. Therefore, this drawback of SDF application is still a problem, and care should be taken when using SDF in aesthetic areas in adult patients.

The use of dentifrices containing fTCP and of SDF solution promoted dentin remineralization under our experimental conditions. Frequent use of fluorinated dentifrice significantly increased UV and KH compared with no dentifrice treatment. Sodium fluoride dentifrices containing fTCP are much more capable of promoting remineralization than dentifrices without fTCP. SDF application resulted in the highest UV and KH. This was supported by our SEM observations that revealed the closure of dentinal tubules and deposits on the dentin surface. For people with a low risk of caries, daily use of dentifrice containing fTCP as a preventive treatment might be more cost-effective. SDF application is indicated for patients with extremely high caries risk, those who cannot tolerate conventional dental treatment, patients who are medically compromised, and those in health disparity populations with little access to care. The amount of fluoride in dentifrice is restricted to <1500 ppm in Japan, and we thus used dentifrices containing 1450 ppm fluoride in this study. Therefore, to verify the effectiveness of fluoride-containing dentifrices with fTCP, it is necessary to confirm the remineralization effects of dentifrices containing a high concentration of biologically available fluoride. Further, the ultrasonic method in this study monitored changes in the bulk dentin specimens. Thus, it is difficult to measure the depth of the remineralization and demineralization zone directly. Therefore, further research is needed to investigate the effect of SDF or dentifrices with fTCP at different depths from the dentin surface.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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