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INFLUENCE OF SELF-ASSEMBLY PEPTIDES USAGE IN COMBINATION WITH FLUORIDES AND CALCIUM PHOSPHATE COMPOUNDS UPON REMINERALIZATION FOR INCIPIENT CARIOUS LESIONS

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CPP-ACPF, Fluoride, pH-cycling, Remineralization, Self-assembly Peptides, Surface Microhardness.

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ABSTRACT

Introduction: The natural healing process for non-cavitated lesions is remineralization (Remineralization is considered the main natural process for non-cavitated lesions healing). Fluoride is the main constituent of numerous remineralizing agents and casein phosphopeptides amorphous calcium phosphate fluoride (CPP-ACPF) have already proved their remineralizing potential. Regenerative biomimetic approaches in remineralization have been introduced in the market based on the use of self-assembly peptides (SAP) and already showed an effective remineralizing effect. **Aim *:*** To clarify the effect of combining fluoride or CPP-ACPF with SAP compared to the remineralizing potential of SAP on its own. **Materials and Methods*:*** Artificial enamel lesions were created on the buccal surfaces of 60 samples. Samples were randomly distributed into two equal groups (30 ones /each). Group (B0): received no biomimetic material, group (B1): biomimetic material was applied. Each group was further subdivided randomly into 3 subgroups of 10 specimens each according to the remineralizing material used; either (R0) artificial saliva, (R1) fluoride, or (R2) CPP-ACPF. Specimens of enamel were put through a pH-cycling model for 8 days. A Vickers microhardness tester was used in assessing surface hardness (SMH) before demineralization of the specimens as a baseline, after demineralization, after remineralization, and after pH cycling. The resulting values were analyzed using ANOVA. **Results*:*** The percentages of microhardness change were compared after remineralization and pH-cycling, in which, we found that regardless of remineralizing agents; group B1 showed a statistically significantly higher value than group B0. Regardless of biomimetic material, group R2 showed a statistically significantly highest mean percentage change. And when combined, group B1R2 had the statistically significant highest value of all groups. **Conclusion*:*** SAP showed superior remineralization potential in comparison to fluoride and CPP-ACPF-based remineralizing agents. SAP showed a synergistic effect when combined with both fluoride and CPP-ACPF. However. Its synergistic effect was superior with CPP-ACPF-based varnish.

INTRODUCTION

Caries is a worldwide spreading disease. It is a reversible dynamic process[(1)]. Controlling the existing environmental conditions and application of remineralizing agents can lead to the arrest of caries progression and healing of the lesion. Understanding the carious process leads to the innovation of non-invasive treatment modalities. The natural healing process for non-cavitated lesions is remineralization. It uses fluoride to aid calcium and phosphate ions in rebuilding a new surface on the subsurface remnants of crystals [(2,3)].

Fluoride is the main constituent of several remineralizing agents; since it is considered a fundamental component of the remineralization process. However, its remineralizing potential depends on the existence of calcium and phosphate ions in the buccal cavity. Furthermore, it is claimed that it only leads to surface remineralization leaving a subsurface demineralized area [2,4].

These shortcomings urged the manufacturers to release the calcium phosphate remineralizing agents. Casein phosphopeptides amorphous calcium phosphate (CPP-ACP) products are considered the base in the calcium phosphate compounds. Their remineralizing potential was documented in the literature [5]. Regarding the vital role of fluoride for the remineralization process, it was included in these compounds and found to have a synergistic effect [6].

Regenerative medicine-based dental approaches are being assumed and denote an ongoing transition from reparative to regenerative biomimetic dentistry. These biomimetics introduced in the dental market were based on the use of SAP. Those SAP are claimed to be triggered to form fibrillar scaffolds with negative terminal domains. This, in turn, attracts calcium phosphate ions and induces the production of de novo hydroxyapatite crystals [7].

The remineralizing potential of SAP was already tickled in the literature [2,7]. In addition, the effect of the usage of fluoride and CPP-ACP compounds with this product was not extensively addressed. Consequently, this study was performed to explain the effect of combining fluoride or CPP-ACPF with SAP in comparison to the remineralizing potential of SAP on its own.

Current research aimed to investigate the difference in the remineralizing potential between SAP, fluorides, and CPP-ACPF, in addition to the efficiency of combination between fluoride, CPP-ACPF, and SAP on the remineralization of artificial carious (lesions).

MATERIALS AND METHODS

I. Teeth Selection:

Sixty sound, recently pulled-out molar teeth were collected from patients with compromised periodontal conditions. The research was waived from Research Ethics Committee, Faculty of Dentistry, Suez Canal University as the research carried on unidentified samples. The previously extracted teeth were examined by the aid of a stereomicroscope at 40x to remove all teeth that had any enamel defaults [8]. The selected teeth were carefully cleaned with tap water; then stored in distilled water at room temperature till usage [9].

II. Teeth Preparation:

Selected molars were split by 2 mm under the cementoenamel junction in a horizontal manner by using a microtome (Leica 1600 saw microtome, Wetzlar, Germany). The crowns were implanted in a pink tube-shaped self-cured acrylic gum molds with the buccal surfaces facing directed upwards [1] Finishing and polishing disks were used (Sof-Lex Pop-On Disks 3M ESPE, St Paul, MN, USA) in successively finer grit of different sizes at a slow speed, so that the buccal surfaces became wet, ground and flat [11]. The buccal surface of each sample was fixed by using a square-shaped adhesive tape (4 x4 mm), while the whole surface of the remaining enamel was coated by an acid-resistant, blue nail polish). After aeration, the adhesive tape was removed leaving a square area on the enamel surface, obtaining a window of standardized area of exposed enamel surface on all enamel specimens[12].

III. Specimens Grouping:

Specimens were randomly divided into two identical groups of 30 samples each. (Samples did not receive a biomimetic material in control one (B0); while in the second group (B1): a biomimetic material was applied "Curodont Repair™/or Regenamel" (Credentis AG, Windisch, Switzerland). Every group was additionally subdivided randomly into 3 subgroups, 10 each (N=10) depending on the remineralizing material used; either (R0): artificial saliva, (R1): fluoride "Bifluorid 10" (VOCO, Cuxhaven, Germany), or (R2): CPP-ACPF "MI Varnish" (GC Corporation, Tokyo, Japan).

IV. Creation of Artificial Caries-like Enamel Lesions:

Enamel Lesions (artificial caries-like) were performed to the exposed window in the specimens. The solution composed of 2.2 mM $CaCl_2$, 2.2 mM NaH_2PO_4 (Sodium dihydrogen orthophosphate dehydrate), and 0.05 M acetic acid; (1 M KOH (potassium hydroxide) was used to adjust pH at 4.4. 10ml of demineralization solution was used per 1 mm^2 of enamel. Each Enamel Specimen was immersed separately in 160 ml demineralizing solution in a tightly sealed glass container, which was stored at room temperature about four consecutive days to the time that a uniform white spot wound appeared on the surface of the enamel window [13]. The solution was renewed every day and its pH was verified using a pH meter. After that, samples were rinsed using tap water for 30 seconds and saved in distilled deionized water [14].

V. Remineralizing Regimens:

Specimens of the group (B1) received a biomimetic material (Curodont Repair™) which was used depending on the manufacturer's instructions as follows, it was applied by pushing the two parts of its plastic applicator for the applicator attached sponge to be soaked in the solution. The sponge was then squeezed and the material was applied. It was then left to be absorbed by the lesion for 30 minutes at room temperature. Each of the fore-mentioned two groups (B0 and B1) was further divided into three equal subgroups of ten specimens each according to the remineralizing agents used which were applied according to the manufacturer's instructions: artificial saliva (control group), fluoride-base varnish (Bifluorid 10) was applied as follows: specimens were dried, and a disposable brush was used to apply the varnish in circular movements. The surfaces were thinly and uniformly coated with the varnish in a single hit. The varnish was left 20 seconds to be absorbed, and then air dried; CPP-ACPF-base varnish (MI Varnish) was applied as follows: firstly, samples were allowed to be dried, secondly, application of a thin uniform varnish layer by using of a single hit painting motion, using a disposable brush. It was also left undisturbed about 20 seconds.

VI. pH-cycling Protocol:

Enamel samples were put in a pH-cycling model about 8 days. The blocks were stored for 2 hours in the demineralizing solution, and about 22 hours in artificial saliva. Demineralizing (6.25 mL/mm^2) and remineralizing (3.12 $mL/mm^{2)}$ solutions were used per area of enamel. Which means 56ml/tooth of demineralizing solution and 28 ml/tooth of remineralizing solution. On the 4^{th} day, the demineralizing and remineralizing solutions were substituted by fresh ones [15].

VII. Surface Microhardness Test:

Assessment of SMH was estimated by a Vickers Microhardness Tester (Buehler Wilson Hardness Tester, Lake Bluff, USA) through a Vickers diamond indenter for all the tested six sub-groups. The SMH was assessed before demineralization of the specimens as a baseline, after demineralization,

after remineralization, and after pH cycling. Each measurement was performed for 5 seconds with a 100 g load, while the load was perpendicular to the enamel surface. The SMH value was performed by calculating the mean value of three measurements of three different indentations at approximately 0.5 mm from each other. The same examiner used the same device to conduct each reading. Microhardness calculation was estimated by this equation [16]:

$$HV = 1854.4L/d^2$$

VIII. Statistical Analysis:

The percentage of surface microhardness recovery (%SMHR) was (evaluated) after remineralization as follows [15]:

$$\frac{\text{Baseline SMH - After demineralization}}{\text{After remineralization - After demineralization}} \times 100$$

= Percentage of SMH changes

Data distribution and normality tests using Kolmogorov-Smirnov and Shapiro-Wilk tests, data were found numerical (i.e. parametric). Parametric distribution was obvious in the data. The mean and standard deviation (SD) values of the data were presented.

Repeated measures Analysis of Variance (ANOVA) was used to study the effect of biomimetic material, remineralizing agent, pH-cycling process, and their interactions on mean microhardness. The influence of biomimetic material was evaluated using two-way ANOVA), remineralizing agent, and their interaction on the mean percentage change in SMH after remineralization.

Pair-wise comparisons were made using Bonferroni's post-hoc test when the ANOVA test was significant whenever ANOVA was significant. The significance level was adjusted at $P \leq 0.05$. Statistical analysis was estimated using IBM® (IBM® Corporation, NY, USA) SPSS® (SPSS® Inc., an IBM Company) Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

RESULTS

Influence of various Interactions on SMH:

Table (1) showed a significant difference between the mean microhardness of remineralizing agents in the B1 group, which received biomimetic material ($p<0.001$, effect size =0.632). Pair-wise comparisons between remineralizing agents (reported that CPP-ACPF (B1R2 group had the highest significant mean microhardness) The fluoride varnish group (B1R1) reported a significantly less mean value. No remineralizing agent group (artificial saliva) (B1R0) showed the statistically significantly lowest mean microhardness value (The lowest average for microhardness value was reported in the non-remineralizing group) (B1R0).

Percentage Change in Surface Microhardness after Remineralization (%SMHR)

Two-way ANOVA Results:

Regardless of the remineralizing agent, biomimetic material had a significant influence on the average percentage change for SMH after the remineralization process ($P<0.001$, effect size=0.987). As well as remineralizing agents had a significant influence on the average percentage change for SMH after the remineralization process ($p<0.001$, effect size=0.987). The interaction between the two variables had a statistically significant effect on the average percentage change in SMH after remineralization ($P <0.001$, effect size =0.604) was significantly affected by the interaction between the two variables. As a result, the two variables are dependent on each other (Table 2).

Table (1) *The Mean and Standard Deviation (SD) Values and Results of Repeated Measures ANOVA Test for Comparison between Microhardness Values of Remineralizing Agents:*

Mineralization Process	Biomimetic Material	No Remineralization		Fluoride Varnish		CPP-ACPF		P-value	Effect Size (Partial eta Squared)
		Mean	SD	Mean	SD	Mean	SD		
Base Line	No Biomimetic Material	365.6	20.8	361.9	12.4	365.9	22.7	0.879	0.006
	Biomimetic Material	372.2	5.3	362.5	23.1	364.7	12.3	0.533	0.029
After Demineralization	No Biomimetic Material	186.8	8.6	185.8	7.9	185.6	16.2	0.56	0.082
	Biomimetic Material	192.3	4.6	182.5	16.4	190.7	8.8	0.188	0.076
After Remineralization	No Biomimetic Material	190.1 ^{B}	8.8	217.4 ^{A}	9.3	235.7 ^{A}	20.5	<0.001*	0.625
	Biomimetic Material	262.3 ^{C}	6.4	295.6 ^{B}	26.5	335.7 ^{A}	15.5	<0.001*	0.632

Table (2) *Two-way ANOVA Results for the Effect of Different Variables on Mean %SMHR after Remineralization:*

Source of Variation	Type III Sum of Squares	df	Mean Square	F-value	P-value	Effect Size (Partial eta Squared)
Biomimetic Material	26304.693	1	26304.693	3273.572	<0.001*	0.987
Remineralizing Agent	9243.57	2	4621.785	575.173	<0.001*	0.965
Biomimetic Material × Remineralizing Agent Interaction	514.415	2	257.207	32.009	<0.001*	0.604

DISCUSSION

Remineralization of incipient carious lesions is one of the non-invasive approaches. These lesions consist mainly of an intact hypermineralized surface, overlying a lower mineral content demineralized subsurface zone. Despite the fact that the underlying lesion was protected by the surface layer, it may still hinder rapid remineralization. Because of this, the minimally invasive treatment options tend to remove a portion of this surface layer for increasing surface permeability, causing the intact, unaffected surface zone to be slightly permeable, in such a manner that will increase the surface permeability and allow the mineral ions easily access the wound through its underlying body, and thus activating the active lesions [7,12].

The SAP is regarded as the best approach to regenerate enamel. Its composition significantly influences the affinity of calcium ions, attracting these ions and depositing them on a de novo needle-

shaped hydroxyapatite meshwork, enabling deeper penetration remineralization of demineralized lesions [17].

The study aimed to measure the remineralizing effectiveness of SAP with the combination of two different remineralizing agents, sodium fluoride, and CPP-ACPF, and the outcome was in terms of change in SMH of carious enamel after being exposed to pH-cycling.

Several methods can be used to assess mineral gain or loss. Demineralization and remineralization changes of enamel were evaluated using SMH analysis [18]. SMH tests are quickly done, simple, and easy to obtain accurate results [8]. This technique makes it possible to measure the same specimen repeatedly over time. Thus, SMH evaluation is a reliable choice to estimate mineral changes with the advantage of reducing the experimental variations by a standardized source. Vickers hardness number was measured using 100 grams load for 5 seconds by the Vickers indenter, as it gives a proper size of the indentation for a precise measurement with the available equipment [16].

The present study's findings showed that compared to artificial saliva, all treatment plans significantly aided in the enamel wound remineralization, as well as, increasing enamel microhardness. More specifically, the application of SAP had a significant influence on the SMH, regardless of the type of the remineralizing agent applied; this observation complied with **Kirkham *et al.*** [19], **Kind *et al.*** [20], and **Schlee *et al.*** [21]; and contradicts those of **Golland *et al.*** [22] who found that the application of SAP didn't significantly increase the remineralization capacity of demineralized lesions due to the formation of irregular apatite crystals that didn't promote remineralization. Also, in comparison to groups that received artificial saliva, both remineralizing agents significantly increased enamel microhardness and helped the remineralization of enamel lesions.

Results documented that the highest %SMHR was observed in group B1R2 (SAP combined with CPP-ACPF), followed by group B1R1 (SAP combined with sodium fluoride varnish), and the lowest %SMHR was found in group B1R0 (SAP in combination with artificial saliva); the results were agreed with **Marinho *et al.*** findings [23].

On the contrary; there was a (-) significant difference when the remineralizing agents were compared regardless of the use of SAP; the highest %SMHR was found in group B0R2 (CPP-ACPF varnish), followed by group B0R1 (sodium fluoride varnish), and the lowest %SMHR was found in group B0R0 (artificial saliva); these results were in agreement with **Khoroushi and Kachuie** [24], **Benson, Shah and Willmot** [25].

CPP-ACPF (R2 group) remineralization activity was observed to be significantly higher in both groups (B0 and B1) compared to the other groups; this is because the two main proteins that makeup CPP-ACPF, casein, and statherin, stabilize calcium and phosphate ions and encourage their deposition as well as the remineralization of surfaces. The CPP-ACPF complex has an inherited affinity for hydroxyapatite; due to its small size nanoscopic, it can easily pass through the enamel's pores and diffuse under the concentration grade into the body of a demineralized enamel lesion. It then breaks down inside calcium and phosphate ions, which after that are used to replace the lost ions of the hydroxyapatite crystals of crystal spaces. It also had an inhibitory effect on mineral loss at demineralized sites; the previous results were agreed with **Hamba *et al.*** [26], and **Mehta *et al.*** [27]. Incorporation of fluoride within the CPP-ACP to give rise to CPP-ACPF result in easily deposition of fluoro-hydroxyapatite in the demineralized

places, which is more resistant to demineralization than hydroxyapatite leading to the reduction of the appearance of early incipient lesions. These positive actions of CPP-ACPF were of great boost to the remineralizing efficacy of SAP[28].

The observations of the present study rejected the first null hypothesis due to the presence of difference in the remineralizing potential between SAP, fluoride, and CPP-ACPF; as well as reject the second null hypothesis that revealed that the combination of SAP enhanced the remineralizing potential of both fluoride and CPP-ACPF.

CONCLUSION

Regardless of the present study's restrictions, it can be said that biomimetic, organic analogue in the form of self-assembly peptide showed superior remineralization potential in comparison to fluoride and CPP-ACPF-based remineralizing agents. Also, the self-assembly peptide showed a synergistic effect when mixed with both fluoride and CPP-ACPF. However. Its synergistic effect was superior with CPP-ACPF-based varnish.

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