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Review Article

Effect of Casein-Phosphopeptide and Amorphous Calcium Phosphate on dental erosion- A systematic review

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ABSTRACT:

Background: Casein-Phosphopeptide and Amorphous Calcium phosphate (CPP-ACP) is a popularized remneralizing agent available in various formulations and is supposed to help in remineralization. The aim of this study is to systematically review the literature to study the re-mineralizing potential of CPP-ACP in treating dental erosion. **Materials &Methods:** An electronic search of the literature in various sources like Pub Med, Science Direct, Cochrane Register of Controlled Trials (CENTRAL), Wiley online library, Google scholars, Ovid medicine, and Grey literature. Through the initial search, 164 articles related to the subject were identified. Out of those, 155 articles were excluded after screening and removing duplicates. Nine RCT's were selected in which CPP-ACP were used as a treatment modality to treat or prevent dental erosion. **Results:** The results of these studies were not consistent as few trials claimed that the CPP-ACP has no significant effect on erosion. But recent studies show that there is increased precipitation of minerals and change in the surface hardness of enamel. **Conclusions:** The results of this review conclude that CPP-ACP is not a very potent re-mineralizing agent as it fails to reach the baseline hardness in the case of eroded enamel. Although it cannot repair dental erosion, CPP-ACP formulations can be used as a preventive measure or supplementary strategy in preventing dental erosion in susceptible individuals.

Key-words: Casein-Phosphopeptide and Amorphous Calcium phosphate (CPP-ACP); dental erosion; enamel hardness; re-mineralizing agent; a systematic review.

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INTRODUCTION

Dental erosion is a multi-factorial condition wherein there is a loss of the surface structure of teeth primarily due to an acid attack. Various factors like chemical, biological, intrinsic, occupational, and behavioral factors cause the erosion of teeth. The pH of soft drinks and food is the most common causative factor of erosion but not necessarily the initiator of dental erosion. Therefore acidity or buffering capacity of saliva and the general pH of the oral cavity plays a critical role in the etiology of these lesions [1]. Excessive consumption of acid-rich foods and carbonated drinks leads to generalized erosion. The biological component that contributes to the progression of erosion is saliva. Saliva is a vast entity of biological components that decide the pH of the oral cavity and the buffer capacity of saliva. One such component is a matrix metalloproteinase (MMP) which is implicated to aid in the erosive process [2].

Intrinsic factor resulting in dental erosion includes gastric acid which contains direct H+ ions. Though gastric acid reaching the oral cavity may seem trivial it occurs commonly where there is an increased frequency of vomiting or gastroesophageal reflux. Few examples of conditions in which this reflux is common are metabolic disorders, endocrinopathies, adverse effects of certain medications, and drug abuse [3]. Workers of industrial background like battery factory workers and those who work in highly hazardous conditions during which they are exposed

to acidic fumes of hydrochloric and sulphuric acid on a day-to-day basis have high scores of dental erosion, dentin hypersensitivity, and poor periodontal status [4]. This is due to the dissolution of hydroxyl apatite crystals and the subsequent release of calcium ions [5]. There was found to be a strong affiliation between eating behaviors and erosion. This phenomenon is more common in eating disorders which are of psychological origin. These disorders include bulimia nervosa, anorexia nervosa, and purging disorder. The first physical signs to appear in such disorders happen to be in the oral cavity. The erosion has a specific pattern in such patients and was seen on the palatal side of the anterior maxillary teeth [6]. Dental erosion accounts for certain other concerns like dentin hypersensitivity and aesthetics.

One of many strategies employed in the treatment of dental erosion is the use of a re-mineralizing agent to re-mineralize the surface structure. The most promising aspect of the mechanism seems to be the formation of a protective layer that is composed of different ions and is adherent to the surface or pellicle [7]. CPP is one such re-mineralizing agent which can be applied as a single component or with amorphous calcium fluoride phosphate (CPP-ACFP) and has been shown to reduce demineralization and promote re-mineralization of enamel subsurface [8].

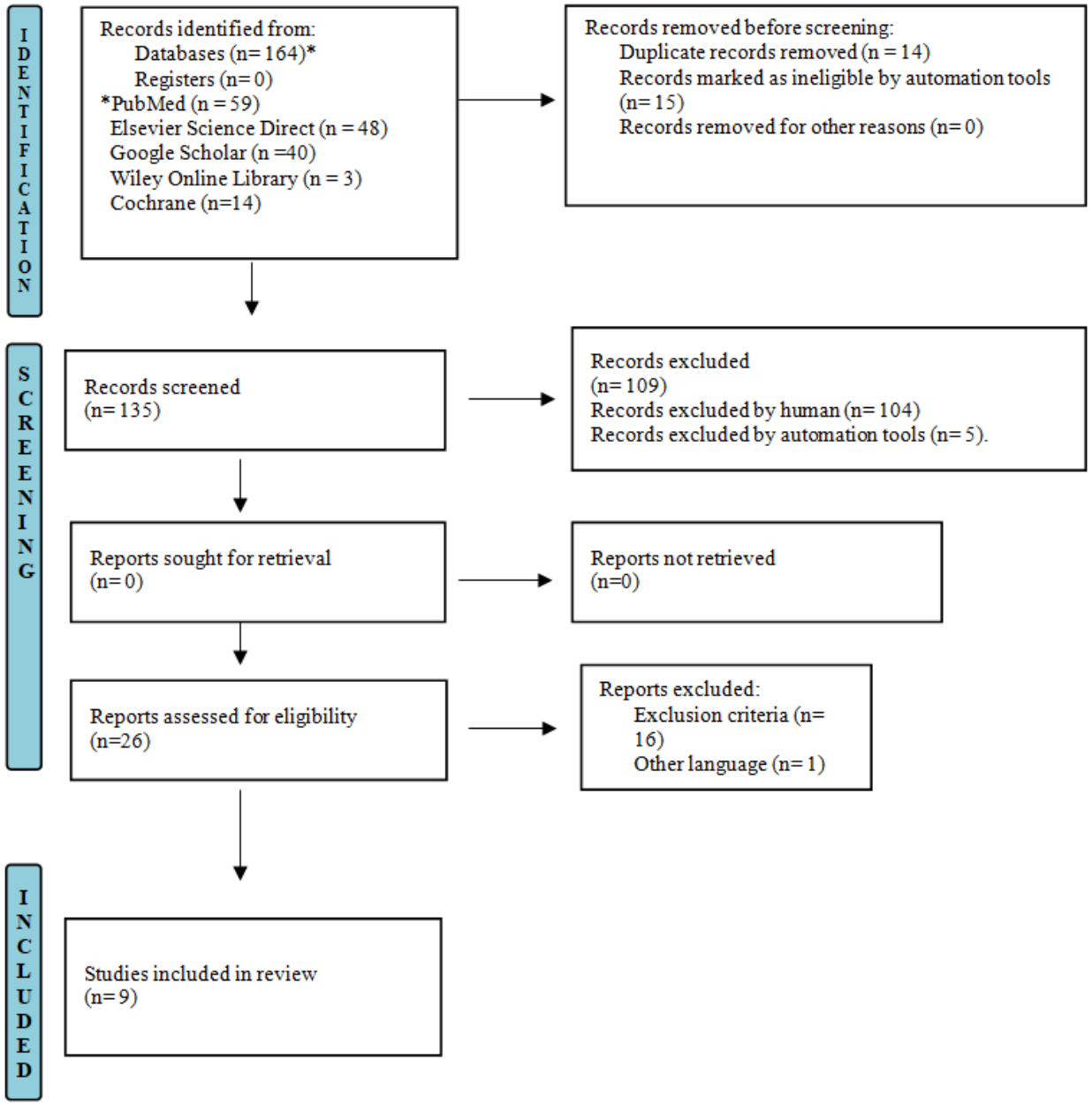
The mechanism of action of casein phosphopeptides is to alter the bio-availability of calcium phosphate levels by maintaining ionic phosphate and calcium up to the point where the ions are in super saturated condition super to increase re-mineralization [9][10]. The use of ACP also has an added advantage as it controls the precipitation of CPP alongside calcium and phosphate ions [11]. CPP-ACP is available in many forms such as gels, solutions, chewing gums, dentifrice, topical creams, and tooth mousse. Studies show that CPP-ACP along with Tricalcium phosphate increases the micro-hardness of teeth [12].

The intervention of eroded teeth depends on the magnitude of the lost tooth structure. The best treatment option for teeth with loss of structure greater than two-thirds of the whole tooth is restoration as there is secondary dentin exposure [13]. But when the erosion is mild or moderate without structure loss the option of further prevention is abided by. Early diagnosis and re-mineralizing agents come to the save. Fluoride helps in this case as it hardens enamel and resists dissolution further. For patients with extensive tooth wear, applying a dentine bonding agent to the exposed dentine to prevent further damage and reduce sensitivity is a practical option [14].This study is aimed to systematically review the randomized control trials that involve CPP-ACP as a treatment modality for dental erosion.

MATERIALS &METHODS

Inclusion criteria for this study includes RCT's on the use of CPP-ACP in dental erosion to date, Studies that study the effect of CPP and/or ACP formulations on dental erosion, Full-text articles available in various search engine. Published articles including original articles and research papers on the role of CPP-ACP on dental erosion were searched in the various databases like Pub Med, Central, Cochrane Register of Controlled Trials (CENTRAL), Elsevier Science Direct, Google scholar, Wiley online library. In Google scholar, advanced search option was used to search articles in which the words "Casein phospopeptide" and "Amorphous calcium phosphate" were included. Full-text and relevant articles were selected using the Mesh representations "Casein Phosphopeptide (CPP)" AND "Amorphous Calcium Phosphate (ACP)" AND "dental erosion" in all the databases. Through initial search 164 articles were found to be relevant out of which 139 Non-randomized studies and studies published in languages other than English were excluded using automated filter tools given in the databases like PubMed and Chochrane. Studies that used CPP and/or ACP for treating or preventing dental abnormalities other than dental erosion were also excluded by the author after screening the eligible studies. The methodology of the selected studies was carefully read to check if the trial meets all the inclusion criteria. The results of the studies which use CPP-ACP as study along with other remineralizing agent as control for treating dental erosion and the statistical analysis for the same was collected and tabulated. The tool used to assess the bias was Cochrane risk of bias assessment and the results were tabulated.

Figure 1: Flow diagram showing the number of studies identified, screened and included in this systematic review



RESULTS

Table 1 shows the characteristics of the interventions in the included studies.

S. no	Author name	Year	Sample size	Specimen Characteristics	Duration	Intervention
1.	Wegehaupt, Florian J et al[15]	2012	200	Enamel samples from freshly extracted bovine lower and ten volunteers (four male, six female, aged 23–52 years) were recruited to participate in this study	Seven days	**Series 1**: 250 ppm of fluoride in the form of AmF/SnF2, Meridol, GABA, Therwil, Switzerland **Series 2**: CPP-ACP in crème formulation **Series 3:** Meridol **Series 4:** CPP-ACP in Tooth Mousse formulation After five minutes of intraoral wear, the appliance containing CPP-ACP was removed from the mouth. Then the teeth were rinsed with a fluoride-containing mouth rinse for three minutes.

2.	Prestes, Letícia et al[16]	2013	12	Twelve healthy adult subjects (nine females and three males, aged 19–30 years were enrolled following the CONSORT guidelines	15 days	They chewed a type of Sugar-free gum according to the **Phase 1:** with CPP–ACP **Phase 2:** without CPP–ACP **Phase 3:** no chewing gum (control)
3.	de Alencar, Catarina Ribeiro Barros et al[17]	2014	72	Enamel blocks from unerupted recently extracted human third molars and twelve healthy adult subjects (ten females and two males) with an average age of 27.2 years (range 23–38 years)	Three weeks	**Group I** – Sugar-free chewing gum containing CPP-ACP **Group II** – Sugar-free chewing gum without CPP-ACP **Group III** – negative control group, without chewing gum In phases of GI and GII volunteers chewed the gum for 30 minutes, four times with an interval of four hours.
4.	Wiegand, Annette et al[18]	2014	15	Fifteen healthy adult volunteers (mean age: 33.2 7.6 years, 3 males, 12 females)	35 days	Specimens were extra orally eroded and brushed using non-fluoridated toothpaste (negative control). The study groups included I. milk II. CPP-ACP paste CPP-ACP paste and 900 ppm of Fluoride in a mouth rinse. This was applied using appliance immediately after erosion.
5.	Andressa Feitosa Bezerra de Oliveira et al[19]	2016	10	Ten healthy adult volunteers (7 females and 3 males), aged 22– 38 years old, from different ethnic origins and socioeconomic status, participated in this study	21 days	A three-way crossover study with study groups as: **Group 1:** sugar-free chewing gum containing CPP-ACP **Group 2:** regular sugar-free chewing gum without CPP-ACP **Group 3:** saliva—no chewing gum. An abrasion test was done in each phase. A 3D measurement of lesion depth and surface roughness of sound and eroded surfaces were measured. A salivary calcium concentration was also determined.
6.	Jordão, M.C et al[20]	2016	120	Enamel blocks whose overall average initial surface hardness was 342.89 (±15.30) KPa/mm 2 were selected and randomly assigned to Twenty healthy adult volunteers (14 female, 6 male, aged 18–29 years).	Three weeks	Treatment levels: **phase I (PI)** – Sugar-free chewing gum with CPP- **phase II (PII)** – conventional sugar-free chewing gum without CPP **phase III (PIII)** – negative control phase, without chewing gum. Volunteers wore intraoral palatal appliances for two hours and the study group chewed gum for 30 min whereas control group did not. Then the appliances were treated in a cola drink for five minutes to promote demineralization and surface hardness loss percentage was calculated.
7.	Eda Arat Maden et al[21]	2017	60	Crown sections of human primary molars were embedded in acrylic resin blocks thus leaving the enamel surfaces exposed	-	Three treatment groups with 20 sections in each group: **Group 1:** artificial saliva **Group 2:** CPP-ACP **Group 3:** 1.23% APF gel. All specimens were exposed to the Demineralization-remineralization cycle. This was repeated

						twice at eight-hour intervals and then roughness values were measured and then treated with artificial saliva, CPP-ACP and APF gel applied for ten minutes.
8.	Hao Yu et al[22]	2018	12	4 human enamel specimens were placed on the tooth surfaces of volunteers' maxillary central incisors and first molars	Seven days	The upper and lower arch appliances containing CPP-ACP were worn and the in situ trials were performed under supervision during the daytime in the Research institute. The patients were allowed to remove appliances for one hour during lunch.
9.	Fernandes et al[23]	2019	192	Enamel blocks with initial surface hardness differing from 324 to 379 HV were chosen and randomized	-	The groups assigned were: **Group I:** CPP-ACP paste **Group II**: CPP-ACPF Paste **Group III:** Fluoridated paste **Group IV**: Placebo Paste Various agents were applied intra-orally and maintained in the mouth for three hours. Then, to promote erosion, the appliances were removed and immersed in hydrochloric acid. The final surface hardness and hardness loss were evaluated.

Table 2 shows the result and outcomes of the intended studies

S.no	Author name	Effect measure	Result	Outcome
1.	Wegehaupt, Florian J et al[15] (2012)	Knoop microhardness (KHN) measurement	Application of the CPP-ACP creme resulted in significantly higher surface microhardness (290.2 ± 31.4 KHN) compared to both the extra-oral application of the fluoride mouth rinse (series 1; 268.3 ± 25.9 KHN) and the untreated control (270.7 ± 29.0 KHN)	Intra-oral application of CPP-ACP provides no benefit related to the rehardening of softened enamel in erosion.
2.	Prestes, Letícia et al[16] (2013)	Knoop surface microhardness	Significant differences were found among the re-mineralizing treatments ($p < 0.0001$). Chewing gum (19% of micro-hardness recovery) improved the mineral precipitation compared to the control (10% recovery) and the addition of CPP–ACP into the gum promoted the best mineral precipitation effect (30% recovery).	CPP–ACP chewing gum improved the precipitation of minerals of eroded enamel.
3.	de Alencar, Catarina Ribeiro Barros et al[17] (2014)	Percentage of surface hardness recovery (%SHR)	Chewing gum with CPP-ACP (2 h = 50.0% < 24 h = 95.9%) showed higher hardness recovery than chewing gum without CPP-ACP (2 h = 30.0% < 24 h = 71.1%) and control (2 h = 15.7% < 24 h = 40.9%) ($p < 0.05$).	CPP-ACP can be used as an auxiliary strategy to potentiate the mineral precipitation of initial and mild erosive lesions.
4.	Wiegand, Annette et al[18] (2014)	Tissue loss determination.	Loss of tooth structure was significantly reduced by the use of fluoridated toothpaste	Milk and CPP-ACP were not the most effective agents in reducing structure loss.

			(enamel: 1.1 ± 1.0 mm; dentine: 2.4 ± 1.7 mm) and fluoride-containing mouth rinse (enamel: 1.5 ± 1.5 mm; dentine: 1.8 ± 1.9 mm)	
5.	Andressa Feitosa Bezerra de Oliveira et al[19] (2016)	3D non-contact profilometry	With CPP-ACP-containing chewing gum (G1), the mean value of erosion lesion depth with T1 treatment (5.3 ± 3.1 μm) significantly ($p < 0.05$) increased with immediate tooth brushing (T2). This difference was not evident while using conventional gum (G1)or during exposure to un-stimulated saliva (G2).	Incorporation of the CPP-ACP into a sugar-free gum significantly increased the re-mineralization/protection of eroded enamel surface.
6.	Jordão, M.C et al[20] (2016)	percentage of surface hardness loss	Both chewing gums significantly reduced surface hardness loss compared to the control phase (no chewing gum), whereas no statistically significant difference was found between chewing gums with and without CPP-ACP.	The presence of CPP-ACP in chewing gum does not significantly increase its protective effect.
7.	Eda Arat Maden et al[21] (2018)	surface roughness value	A statistically significant increase was found for surface roughness values measured after the erosion process in all groups. A statistically significant decrease in surface roughness was seen in all groups after re-mineralization treatment.	CPP-ACP and 1.23% APF treatments were able to reduce the erosive enamel loss produced by a carbonated soft drink. However, 1.23% APF gel showed the highest protective effect.
8.	Hao Yu et al[22] (2017)	Arithmetic average roughness (Ra)	Significant decreases in SMH were noted in both groups. Significant effects were found for surface treatment and specimen location (P = 0.007 and 0.033, respectively. Therefore, tooth Mousse containing CPP-ACP significantly enhanced the acid resistance of human enamel compared to that of the control group (%SMHl: 38.06 ± 5.68% vs. 52.39 ± 10.85%).	The application of CPP-ACP could be a suitable preventive strategy against enamel erosion.
9.	Freitas Fernandes et al[23] (2019)	percentage of surface hardness loss	The application of CPP-ACP paste, showed significantly lower enamel hardness loss (GI: 9.26% ±3.48 and GII: 9.14% ±1.73) compared to NaF (GIII: 15.5% ± 3.94) and placebo (GIV: 16.7% ± 4.07) pastes.	CPP-ACP pastes were capable of reducing initial erosive demineralization.

Table 3 shows the assessment of the bias of the RCT's which were included in this review

S. no	Author and year	Random sequence generation	Allocation concealment	Selective reporting	Incomplete data outcome	Blinding of outcome	Blinding of participants and personal
1.	Wegehauptet al[15] (2012)	+	?	+	+	+	?
2.	Prestes, Letícia et al[16] (2013)	+	+	+	+	?	?
3.	de Alencar et al[17] (2014)	+	+	+	+	?	+
4.	Wiegand, Annette et al[18] (2014)	+	+	+	+	+	+
5.	Andressa Feitosa Bezerra et al[19] (2016)	+	+	+	+	+	+
6.	Jordão, M.C et al[20] (2016)	+	+	+	?	?	+
7.	Eda Arat Maden et al[21] (2018)	+	+	+	+	?	-
8.	Hao Yu et al[22] (2017)	+	+	+	+	+	+
9.	Freitas Fernandes et al[23] (2019)	+	+	+	+	?	+

DISCUSSION

The finding of the study by Wegehaupt et al [15] on the re-hardening by application of 250 ppm fluoride is similar to the findings by Wiegand et al[24]. However, Enamel re-hardening was not achieved by CPP-ACP crème. This can be due to many factors like decreased exposure time and lesser concentration of fluorides. The study concludes that the treatment of enamel softened by erosion shows no significant re-hardening.

Prestes, Letícia, et al [16] study showed that the in situ CPP-ACP induced a low surface microhardness recovery in the control phase. The presence of CPP-ACP had further enhanced the mineral precipitation, with about 1.5 and 3.0 folder increase compared to regular chewing gum and control, respectively. Still, the baseline microhardness was not achieved which was in line with the results of the study by Wegehaupt et al [15].

The results of the study by de Alencar et al [17] showed that after the application of 30 minutes of CPP-ACP 4 times and without any new erosive challenges there was an almost full recovery of enamel hardness, with baseline microhardness being achieved. The re-hardening ability of the CPP-ACP treatment was 25% and 58% higher than the effect of gum without CPP-ACP and saliva, respectively. This entirely contradicts the results and conclusion given by Jordão, M.C et al [20].

In summary, the results of a study by Wiegand et al [18] have shown that milk and CPP-ACP were ineffective in reducing erosive wear in enamel and dentine. The formulations of the CPP-ACP paste used in this study were ineffective in reducing the erosive wear significantly. This can be explained by the poor affinity of casein to eroded enamel as both casein and hydroxyapatite were positively charged under acidic conditions [15] [25].

In the current study by Andressa Feitosa Bezerra et al [19] even with the abrasion variable, the CPP-ACP treatment gum still had the lowest enamel lesion depth and surface roughness. These results were the same as the results of previous studies by Attin et al [26]. The lowest enamel depth is due to the supersaturation of calcium and phosphate ions on the enamel surface preventing the penetration of acid. The re-mineralizing potential can be backed up by the elevated presence of calcium in saliva even after two hours of chewing gum with CPP-ACP.

The null hypothesis of the study by Jordão M.C et al [20] was accepted as CPP-ACP chewing gum does not contribute to inhibiting enamel erosive demineralization, and therefore may not be considered an efficient preventive strategy for erosion. In conclusion, the results suggest that the use of chewing gum just before erosive demineralization can only reduce enamel hardness loss and does not participate in re-mineralization. The presence of CPP-ACP does not increase its protective effect. According to this

study, there is no scientific evidence to support the use of CPP-ACP in preventing tooth erosion.

In a study conducted by Eda Arat Maden et al [21], it was concluded that the treatment of dental erosion by using Tooth Mousse with CPP-ACP and 1.23% APF gel diminished the roughness of enamel and thus exhibited preventive properties. However, there was no complete repair of the erosion caused by acidic drinks in the primary teeth. However, the performance of 1.23% APF gel was superior to CPP-ACP. The protective mechanism is by the formation of the CaF2 layer under acidic conditions [27]. During an acidic attack, the fluoride is released from the calcium fluoride deposit. This results in the formation of Fluoroapatite resulting in increased resistance to further dissolution. The performance of CPP-ACP was not as significant as APF gel.

In the RCT's conducted by Hao Yu et al [22] the control group specimens exhibited a greater degree of demineralization, especially on the inter prism portion, compared with those treated with CPP-ACP. These findings were consistent with previous studies whose results were confirmed using Transmission Electron Microscopy (TEM). This provides proof that after the CPP-ACP application, the modified pellicle had greater electron density than the control [28]. A significant difference was present in the degree of demineralization between posterior and anterior teeth which can be explained by the rapid pH recovery in the posteriors after an attack by acidic drinks [29] [30].

Freitas Fernandes et al [23] through his study suggested through his study that the use of CPP-ACP with or without fluoride to supplement it can be used as a preventive measure before an acid attack. The paste would interfere with the erosive demineralization of enamel. Although this contrasts all the results of previous studies the results cannot be compared as the other studies were conducted in laboratories under in situ protocols.

CONCLUSIONS

In summary, though CPP-ACP is a re-mineralizing agent, studies have shown that although it exhibits a certain degree of re-hardening, CPP-ACP fails to achieve baseline hardness. Therefore it is not a potent re-mineralizing agent. However, it can be used as a protective measure to prevent acid attacks in patients susceptible to dental erosion.

DECLARATION

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REFERENCES

1. Owens BM. The potential effects of pH and buffering capacity on dental erosion. 2007;55(6):527-31.
2. Buzalaf MA, Hannas AR, Kato MT. Saliva and dental erosion. Journal of Applied Oral Science. 2012;20(5):493–502.
3. Scheutzel P. Etiology of dental erosion ? intrinsic factors. European Journal of Oral Sciences. 1996;104(2):178–90.
4. Hattab FN. Oral and general health status of battery factory workers in Amman, jordan: Cases presentations and review. Journal of Interdisciplinary Dentistry. 2020;10(1):9.
5. Wiegand A, Attin T. Occupational dental erosion from exposure to acids--a review. Occupational Medicine. 2007;57(3):169–76.
6. Otsu M, Hamura A, Ishikawa Y, Karibe H, Ichijyo T, Yoshinaga Y. Factors affecting the dental erosion severity of patients with eating disorders. BioPsychoSocial Medicine. 2014;8(1):25.
7. Lussi A. Dental erosion—novel remineralizing agents in prevention or repair. Advances in Dental Research. 2009;21(1):13–6.
8. Aimutis WR. Bioactive properties of milk proteins with particular focus on anticariogenesis. The Journal of Nutrition. 2004;134(4).
9. Cross K, Huq N, Reynolds E. Casein phosphopeptides in oral health - chemistry and clinical applications. Current Pharmaceutical Design. 2007;13(8):793–800.
10. Schüpbach P, Neeser JR, Golliard M, Rouvet M, Guggenheim B. Incorporation of caseinoglycomacropeptide and caseinophosphopeptide into the salivary pellicle inhibits adherence of mutans streptococci. Journal of Dental Research. 1996;75(10):1779–88.
11. Cross KJ, Huq NL, Palamara JE, Perich JW, Reynolds EC. Physicochemical characterization of casein phosphopeptide-amorphous calcium phosphate Nanocomplexes. Journal of Biological Chemistry. 2005;280(15):15362–9.
12. Haghgou EHR, Haghgoo R, Roholahi MR, Ghorbani Z. Effect of casein phosphopeptide-amorphous calcium phosphate and three calcium phosphate on enamel microhardness. The Journal of Contemporary Dental Practice. 2017;18(7):583–6.
13. Bartlett DW. The role of erosion in tooth wear: Aetiology, prevention and management. International Dental Journal. 2005;55:277–84.
14. Azzopardi A, Bartlett DW, Watson TF, Sherriff M. The surface effects of erosion and abrasion on dentine with and without a protective layer. British Dental Journal. 2004;196(6):351–4.
15. Wegehaupt FJ, Tauböck TT, Stillhard A, Schmidlin PR, Attin T. Influence of extra- and intra-oral application of CPP-ACP and fluoride on re-hardening of eroded enamel. Acta Odontologica Scandinavica. 2011;70(3):177–83.
16. Prestes L, Souza BM, Comar LP, Salomão PA, Rios D, Magalhães AC. In situ effect of chewing gum containing CPP–ACP on the mineral precipitation of eroded bovine enamel—a surface hardness analysis. Journal of Dentistry. 2013;41(8):747–51.
17. de Alencar CR, Magalhães AC, de Andrade Moreira Machado MA, de Oliveira TM, Honório HM, Rios D. In situ effect of a commercial CPP-ACP chewing gum on the human enamel initial erosion. Journal of Dentistry. 2014;42(11):1502–7.
18. Wiegand A, Attin T. Randomised in situ trial on the effect of milk and CPP-ACP on dental erosion. Journal of Dentistry. 2014;42(9):1210–5.
19. de Oliveira AF, de Oliveira Diniz LV, Forte FD, Sampaio FC, Ccahuana-Vásquez RA, Tochukwu Amaechi B. In situ effect of a CPP-ACP chewing gum

on enamel erosion associated or not with abrasion. Clinical Oral Investigations. 2016;21(1):339–46.
20. Jordão MC, Alencar CRB, Mesquita IM, Buzalaf MAR, Magalhães AC, Machado MAAM, et al. In situ effect of chewing gum with and without CPP-ACP on enamel surface hardness subsequent to ex vivo acid challenge. Caries Research. 2016;50(3):325–30.
21. Maden EA, Acar Ö, Altun C, Polat GG. The effect of casein phosphopeptide-AMORF calcium phosphate and acidulated phosphate fluoride gel on dental erosion in primary teeth: An in vitro study. Journal of Clinical Pediatric Dentistry. 2017;41(4):275–9.
22. Yu H, Jiang N-wu, Ye X-yi, Zheng H-yan, Attin T, Cheng H. In situ effect of Tooth Mousse containing CPP-ACP on human enamel subjected to in vivo acid attacks. Journal of Dentistry. 2018;76:40–5.
23. Fernandes LH, Alencar CR, Melo JB, Rios D, Honório HM, Cavalcanti AL. In situ effect of intra-oral application of pastes containing CPP-ACP or CPP-ACPF against initial enamel erosion. Pesquisa Brasileira em Odontopediatria e Clínica Integrada. 2019;19(1):1–9.
24. Wiegand A, Müller I, Schnapp JD, Werner C, Attin T. Impact of fluoride, milk and water rinsing on surface rehardening of acid softened enamel. An in situ study. 2008;21(2):113-8.
25. Barbour ME, Shellis RP, Parker DM, Allen GC, Addy M. Inhibition of hydroxyapatite dissolution by whole casein: The effects of ph, protein concentration, calcium, and Ionic strength. European Journal of Oral Sciences. 2008;116(5):473–8.
26. Attin T, Knöfel S, Buchalla W, Tütüncü R. In situ evaluation of different remineralization periods to decrease brushing abrasion of demineralized enamel. Caries Research. 2001;35(3):216–22.
27. Saxegaard Erik, Rölla Gunnar. Fluoride acquisition on and in human enamel during topical application in vitro. European Journal of Oral Sciences. 1988;96(6):523–35.
28. Kensche A, Pötschke S, Hannig C, Richter G, Hoth-Hannig W, Hannig M. Influence of calcium phosphate and apatite containing products on enamel erosion. The Scientific World Journal. 2016;2016:1–12.
29. Mendonça FL, Jordão MC, Ionta FQ, Buzalaf MA, Honório HM, Wang L, et al. In situ effect of enamel salivary exposure time and type of intraoral appliance before an erosive challenge. Clinical Oral Investigations. 2017;21(8):2465–71.
30. Lussi A, von Salis-Marincek M, Ganss C, Hellwig E, Cheaib Z, Jaeggi T. Clinical study monitoring the ph on tooth surfaces in patients with and without erosion. Caries Research. 2012;46(6):507–12.
31. Surya Rajeev Nair, S.Shree Lakshmi, B harathwaj.V.V, Sindhu.R , Raj Mohan, D. Prabu ,M.Dinesh Dhamodhar. Systematic Review on the Use of Indian Gooseberry in Improvement of Oral Hygiene. 2021;10(1):2611-20.
32. Ohri, A., Mohan, R., Prabu, D., Nagai, N., & Ogata, A. (2021). Effect Of Methamphetamine On The Oral Cavity-A Systematic Review. 2021; 32(3)