Frontiers in Dentistry

Effect of Casein Phosphopeptide Amorphous Calcium Phosphate and Xylitol Chewing Gums, and Probiotic Yogurt on Periodontal Parameters: A Randomized Clinical Trial

Maryam Mehrabkhani[1], Iman Parisay[1], Niayesh Mastoory[2], Vajihe Barati Doghai[1*]

1. Department of Pediatric Dentistry, Faculty of Dentistry Mashhad University of Medical Sciences, Mashhad, Iran
2. Private Practice, Mashhad, Iran

Article Info

Article type:
Original Article

Article History:
Received: 27 Mar 2021
Accepted: 23 Aug 2021
Published: 29 Sep 2021

**** Corresponding author:***
Department of Pediatric Dentistry, Faculty of Dentistry Mashhad University of Medical Sciences, Mashhad, Iran

Email: barativ891@gmail.com

A B S T R A C T

Objectives: This study aimed to assess the effect of casein phosphopeptide amorphous calcium phosphate (CPP-ACP) and xylitol chewing gums, and probiotic yogurt, as chemical plaque control strategies, on periodontal parameters.

Materials and Methods: This randomized clinical trial evaluated 120 eligible dental students that were randomly divided into four groups (n=30) for use of (I) CPP-ACP chewing gum, (II) xylitol chewing gum, (III) probiotic yogurt, and (IV) chlorhexidine (CHX) mouthwash. The oral hygiene index-simplified (OHI-S), Silness and Loe gingival index (GI), and Silness and Loe modified plaque index (PI) were measured before and on days 15 and 30 after using the products. Paired t-test or its non-parametric equivalent was used to analyze the parameters after the intervention compared with baseline. The study groups were compared using one-way ANOVA or its non-parametric equivalent.

Results: The OHI-S did not change over time, and most participants had a good OHI-S. The CHX group had the most favorable, and the probiotic yogurt group had the least favorable GI. Pairwise comparisons of the groups did not reveal a significant difference in GI between the CPP-ACP gum and CHX groups (P>0.05). CHX caused the greatest improvement in PI, with significant differences with other groups.

Conclusion: CHX was the most effective for improvement of periodontal parameters followed by CPP-ACP, which showed better results compared with other groups.

Keywords: Casein Phosphopeptide-Amorphous Calcium Phosphate Nanocomplex; Xylitol; Probiotics; Periodontal Diseases; Chlorhexidine

➢ **Cite this article as:** Mehrabkhani M, Parisay I, Mastoory N, Barati Doghai V. Effect of Casein Phosphopeptide Amorphous Calcium Phosphate and Xylitol Chewing Gums, and Probiotic Yogurt on Periodontal Parameters: A Randomized Clinical Trial. *Front Dent.* 2021:18:35.

INTRODUCTION

Gingivitis refers to inflammation of the gingiva, and is a common oral condition caused by the activity of bacteria and accumulation of dental plaque as the main etiologic factors [1-3]. Mechanical plaque removal is the most effective and most commonly practiced plaque control strategy. However, despite its optimal efficacy, its effectiveness depends on learning the correct technique of tooth brushing and patient motivation. Moreover, it is not sufficiently effective for removal of subgingival plaque. Thus, chemical agents in the form of mouthwashes, chewing gums, and toothpastes have been suggested as an adjunct to mechanical plaque removal [1-4]. Chlorhexidine mouthwash (0.2%; CHX) is currently the gold standard antibacterial agent for periodontal therapy [2,3,5]. Considering the side effects of CHX mouthwash such as alteration of the sense of

taste, tooth discoloration, and supragingival calculus formation, its usage should be limited to 2 weeks [2,3]. Thus, it is imperative to find a material with no or minimal side effects, favorable taste, and higher acceptance by patients for oral hygiene maintenance.

Chewing gums are highly popular among children and adults. Adolescents often spend more time chewing gums rather than toothbrushing, which can also increase the saliva flow and decrease the amount of dental plaque, and can be effective for improving the periodontal indexes [6,7]. Sugar-free gums exert their cariostatic effects by enhancing the mechanical flushing effect of the saliva that eliminates food residues, and raising the plaque pH following the increase in concentration of remineralizing ions and bicarbonate in stimulated saliva [6]. Use of sugar-free gums after each meal can decrease the count of *Streptococcus mutans* [8]. Polyol sweeteners are extensively used as an alternative to sucrose and fructose in sugar-free food products, and are among the low-calorie food products. Of polyols, xylitol and sorbitol have been more commonly studied [7-9].

Although sorbitol can be consumed by the bacteria in the long-term, compared with xylitol, it is still effective for caries prevention and is also cheaper than xylitol [10]. Xylitol is a natural five-carbon sugar, which is extensively used as a non-cariogenic sweetener; it cannot be fermented by most oral bacteria [8].

Casein, a milk phosphoprotein, is another natural compound used in the composition of chewing gums. It reacts with calcium and phosphate, and is used as a safe additive in the food industry [11]. This product is technically referred to as casein phosphopeptide amorphous calcium phosphate (CPP-ACP). CPP stabilizes the ACP, and also binds to biofilm macro-molecules on the tooth surface, serving as a reservoir for calcium phosphate ions [11]. It is also used as a remineralizing agent for incipient caries [11,12]. Moreover, in the recent years, it was shown that CPP-ACP has anti-cariogenic properties in both humans and laboratory animals and can decrease dental plaque and periodontal disease. Sugar-free gums containing CPP-ACP decrease the count of *Streptococcus mutans* in the oral environment, irrespective of the frequency and duration of use [13,14].

On the other hand, probiotic bacteria are considered as safe bacteria that can contribute to periodontal health. If consumed in adequate amounts, they have positive effects on human health, and their safety has been confirmed by the World Health Organization and Food and Agriculture Organization [15]. Studies regarding the effects of probiotics on dental caries, halitosis, and periodontal disease are limited. However, evidence shows that probiotics can control gingivitis by controlling inflammation [16-19]. The bacteria present in yogurt and fermented dairy products are the main source of probiotics for humans. *Bifidobacterium* is commonly used in probiotic yogurt. According to an in vitro study, it can reduce the count of *Porphyromonas gingivalis* by adhering to the subgingival biofilm [20]. Probiotics may also be useful for treatment of chronic periodontitis [15,21]. According to a systematic review on the efficacy of probiotics for treatment of chronic periodontitis, and their confirmed efficacy when used along with scaling and root planing, further clinical studies are still warranted in this respect [22]. Thus, this study aimed to assess the effect of chewing gums containing CPP-ACP and xylitol, and probiotic yogurt on periodontal parameters.

MATERIALS AND METHODS

This single-blind randomized clinical trial was approved by the ethical committee of our university (IR.MUMS.sd.rec.1394.200, date approved: 2017-02-08) and registered in the Iranian Registry of Clinical Trials (IRCT2017020432380N1).

A total of 120 dental students who had not used any antibiotics or mouthwashes in the past 2 weeks [23], and met the following inclusion criteria were enrolled: Males and females with no systemic diseases such as diabetes mellitus or renal failure, no orthodontic appliances, no smoking, no pregnancy, and absence of active dental caries. Those allergic to the tested materials, and students who had to use antibiotics or anti-

inflammatory drugs during the study period were excluded. The participants were briefed about the study, and received oral hygiene instructions prior to measurement of their periodontal parameters.

Each participant received a package including an Oral-B toothbrush and an Oral-B toothpaste as well as the test material, which was determined after randomization. The participants were requested not to use any mouthwash or antibiotics during the study period.

According to a previous study [24], the sample size was calculated to be 30 in each group considering the mean debris index (DI) of the control and chewing gum groups, 95% confidence interval, and 80% study power. The outcome for calculation of sample size was the DI in this study.

After signing the informed consent forms, one operator not involved in the study performed block randomization using randomized.org to generate random numbers. The numbers were placed in sealed envelopes by an independent researcher, and randomly administered among the students to determine their group allocation. Accordingly, the students were divided into four groups as follows (n=30):

(I) CPP-ACP chewing gum
(II) Xylitol chewing gum
(III) Probiotic yogurt
(IV) CHX mouthwash

The students in the four groups were matched in terms of age (confirmed by ANOVA, P=0.57, F=0.67) and gender (Chi-square test, P=0.06).

All participants were dental students who had the same level of oral hygiene at baseline, which did not change in the first and second follow-ups; thus, they were standardized in this respect.

CPP-ACP gums (Recaldent, GC Co., Tokyo, Japan) containing xylitol, maltitol, aspartame, citric acid, and CPP-ACP (milk derivative) were used by the participants in group I.

Trident chewing gums (Mondelez International, East Hanover, USA) containing sorbitol, gum base, xylitol, natural and artificial flavors, glycerin, potassium, and mannitol were used by the participants in group II.

Probiotic yogurt (Kaleh, Tehran, Iran) containing fresh cow milk, concentrated fat-free milk, thermophilic starter, and *Bifidobacterium* probiotic was used by the participants in group III.

Group IV participants used 0.2% CHX mouthwash (Vi-One, Rojin Cosmetics, Tabriz, Iran) containing deionized water, sorbitol, glycerin, poloxamer 407, menthol, polyethylene glycol, CHX digluconate, xylitol, citric acid, thymol, and essence.

The participants in groups I and II were requested to use the chewing gums for 20 min three times a day after breakfast, lunch, and dinner for a total period of 30 days. The participants in group III consumed 200 g of probiotic yogurt once a day for a total period of 30 days. The participants in group IV used 10 mL CHX mouthwash every night after toothbrushing for 1 min for a period of 15 days [25]. A checklist was used to record the periodontal status of the patients. The oral hygiene index-simplified (OHI-S) was used for assessment of oral hygiene, which has two components of calculus index (CI) and debris index. Also, the gingival index (GI) of Silness and Loe [3], and the modified plaque index (PI) of Silness and Loe [4, 8] were calculated and recorded.

To calculate the OHI-S, first the DI was measured such that 2 anterior and 4 posterior teeth in the maxilla and mandible (buccal surface of the teeth #11, 16 and 26, and lingual surface of the teeth #46 and 36) were examined and scored 0 to 3 as follows:

0: No debris or stain present
1: Soft debris covering not more than one third of the tooth surface, or presence of extrinsic stains without other debris regardless of surface area covered
2: Soft debris covering more than one-third, but not more than two-thirds, of the exposed tooth surface.
3: Soft debris covering more than two-thirds of the exposed tooth surface.

To measure the CI, each surface was scored from 0 to 3 as follows:

0: No calculus present
1: Supragingival calculus covering not more than one-third of the exposed tooth surface.

2: Supragingival calculus covering more than one-third but not more than two-thirds of the exposed tooth surface, or the presence of individual flecks of subgingival calculus around the cervical portion of the tooth or both.
3: Supragingival calculus covering more than two-thirds of the exposed tooth surface or a continuous heavy band of subgingival calculus around the cervical portion of the tooth or both.
In this study, the CI of all individuals was zero. Thus, only DI was considered. Accordingly, the OHI-S of each participant ranged from 0 to 3. All the obtained DI scores were divided by the number of surfaces (which was 6) to obtain the OHI-S.
In Silness and Loe modified PI, six areas of mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual and distolingual of the Ramfjord teeth (#16, 21, 24, 36, 41, and 44) were evaluated instead of four surfaces. For determination of PI, first, the teeth were dried and then examined visually under adequate lighting with a periodontal probe or a dental explorer. Each surface was scored as follows by visual inspection or examination by a periodontal probe:
Score 0: No plaque present
Score 1: A film of plaque adhering to the free gingival margin detectable by a probe
Score 2: Moderate amount of soft debris in the gingival pocket visible to the naked eye
Score 3: Abundant soft debris in the gingival pocket or gingival margin
In order to determine the GI, the four-point Silness and Loe GI was used. Score 0 indicated normal gingiva, score 1 indicated mild inflammation (slight change in color and mild edema along with bleeding on probing), score 2 indicated moderate inflammation along with redness, edema, and bleeding on probing, and score 3 indicated severe inflammation along with severe redness, edema, ulceration, and spontaneous bleeding. The participants were recalled at 15 and 30 days for measurement of their periodontal parameters. In this study, the participants could not be blinded to the intervention due to different types of materials used.
However, the measurements were made by an examiner (Dr. Mastoory) whose optimal intra-observer agreement was confirmed by calculating the kappa value (which was found to be >80%), and was blinded to the group allocation of the participants. The statistician who analyzed the data was also blinded to the group allocation of the participants. The difference between the primary and secondary measurements was analyzed to assess the efficacy of chewing gums, probiotic yogurt, and CHX. Paired t-test or its non-parametric equivalent was used to compare the data before and after the interventions. One-way ANOVA or its non-parametric equivalent was used to compare the groups. $P<0.05$ was considered statistically significant.

RESULTS

A total of 120 dental students with no systemic disease, orthodontic appliances, or active dental caries participated in this study (Figure 1); out of which, 43 (35.83%) were males and 77 (64.16%) were females. The mean age of the participants was 23.88±2.86 years (range 20-36 years). The OHI-S, which included CI and DI, was found to be zero for all participants. No significant change was noted in this respect in the first and second recall sessions compared with baseline. Thus, no statistical analysis was carried out in this respect (Figure 2). Figure 3 shows the Silness and Loe GI of the study groups at different time points. The generalized estimating equation (GEE) model was used to assess the correlation of GI and different time points, which showed that the odds ratio of a poorer GI in the xylitol gum, probiotic yogurt, and CPP-ACP gum groups, compared with the CHX group, was 1.77, 2.78, and 1.034, respectively. This ratio was significantly higher in the probiotic yogurt group compared with the CHX group (P=0.004). The least significant difference method was used for pairwise comparisons of the groups regarding GI (Table 1). Pairwise comparisons of the groups showed that the GI in the probiotic yogurt group had significant differences with that in CPP-ACP gum and CHX groups (P=0.005, and P=0.002, respectively). Figure 4 shows the PI of the study groups at different time points.

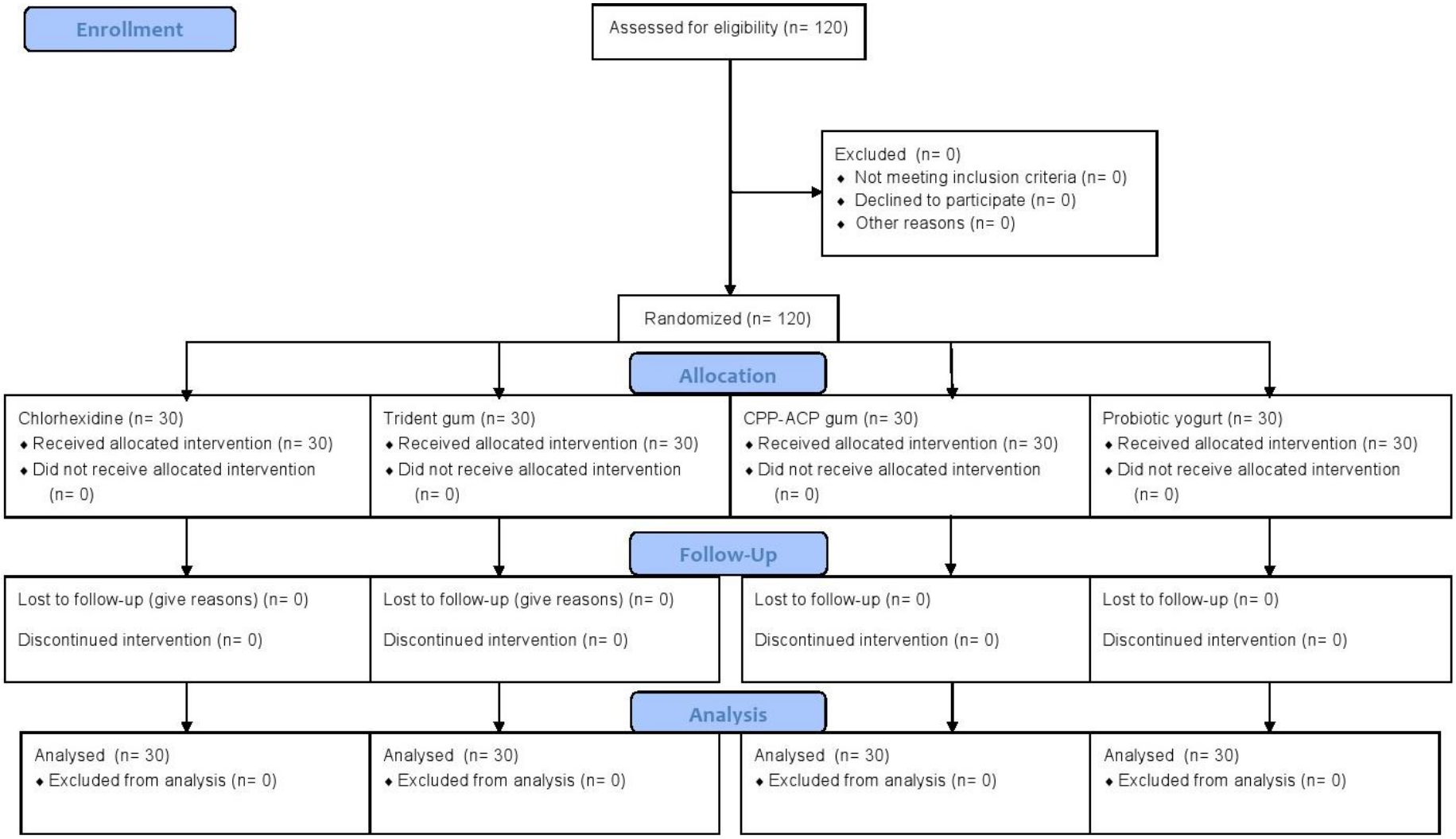

Fig. 1. Flowchart of the study

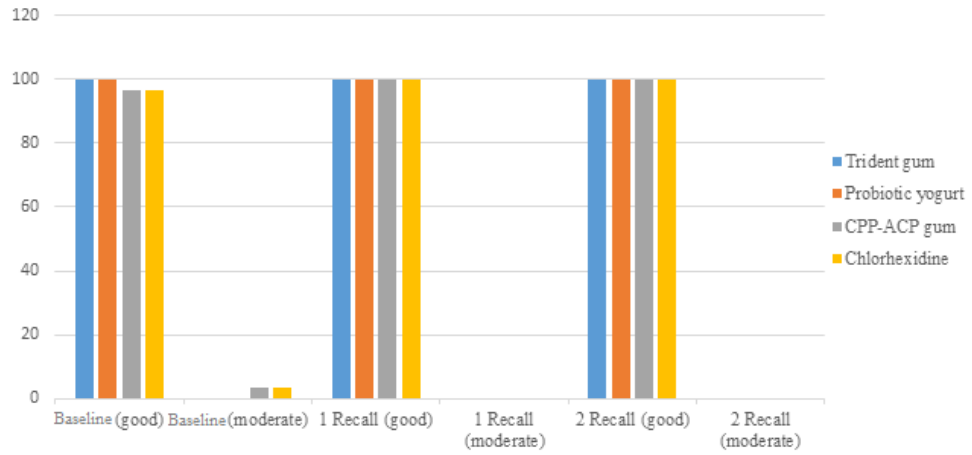

Fig. 2. Frequency distribution of oral hygiene index-simplified scores of the study groups at different time points

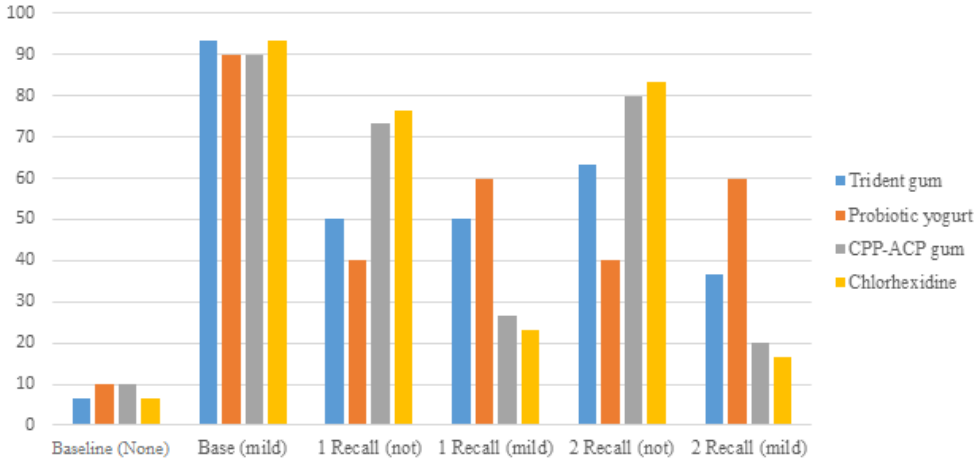

Fig. 3. Silness and Loe gingival index of the study groups at different time points

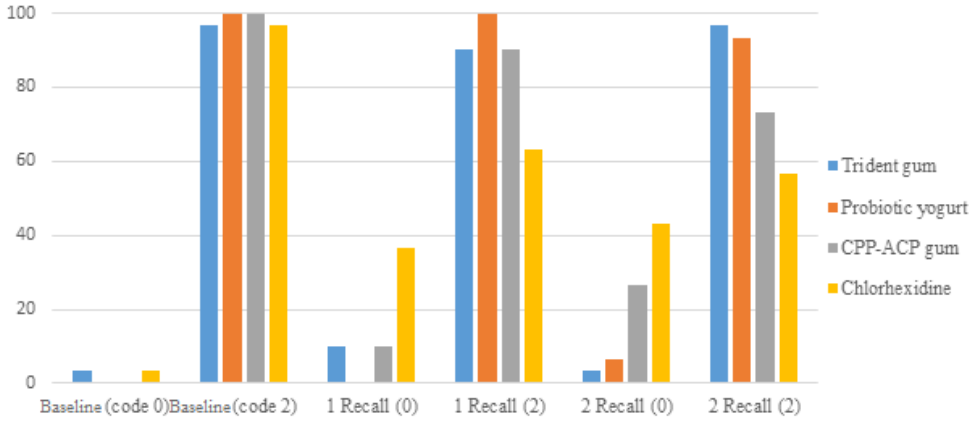

Fig. 4. Plaque index of the study groups at different time points

Table 1. Pairwise comparisons of gingival index among the study groups

Study groups	Xylitol gum	Probiotic yogurt	CPP-ACP* gum	Chlorhexidine
Xylitol gum	-	0.25	0.094	0.054
Probiotic yogurt	0.25	-	0.005	0.002
CPP-ACP gum	0.094	0.005	-	0.904
Chlorhexidine	0.054	0.002	0.904	-

* Casein phosphopeptide amorphous calcium phosphate

The GEE model was used to analyze thecorrelation of PI with the assessment time points since the time of assessment was a linear variable (Table 2). The results of the GEE model indicated that the odds of visible PI in the xylitol gum, probiotic yogurt, and CPP-ACP gum groups, compared with the CHX, were 6.65, 15.91, and 2.68, respectively; all three values were significantly higher than that in the CHX group (P=0.001, P<0.001, and P=0.014, respectively). The least significant difference method was used for pairwise comparisons of the groups (Table 3). Pairwise comparisons of the groups revealed that the PI in the CHX group was significantly different from that in the remaining three groups (P<0.001, P<0.001 and P=0.014, respectively). Also, the probiotic yogurt group had a significant difference with the CPP-ACP group in this respect (P=0.007).

DISCUSSION

This study evaluated the effect of CPP-ACP and xylitol chewing gums and probiotic yogurt on periodontal parameters [4].

The OHI-S, which included CI and DI, was found to be zero for all participants since they were all dental students and had good oral hygiene.

Of different antibacterial agents locally used for prevention and treatment of periodontal disease, anti-septic agents have the highest application; among which, 0.2% CHX is more commonly used due to its wide-spectrum antimicrobial activity and optimal substantivity in the oral environment. CHX has bacteriostatic activity against periopathogenic microorganisms (for more than 12 h) and is therefore recognized as the gold standard for this purpose [2,3].

Rindom Schiott et al, [18] in 1970 showed that daily rinse of 10 mL of 0.2% CHX for 1 min (as used in the present study) decreased plaque accumulation by 60% and the severity of gingivitis by 50-80%. Rindom Schiott et al, [18] in 1970 showed that daily rinse of 10 mL of 0.2% CHX for 1 min (as used in the present study) decreased plaque accumulation by 60% and the severity of gingivitis by 50-80%.

Table 2. Effect of type of treatment on plaque index

Study groups	Model coefficient	P	Odds ratio	Confidence interval of odds ratio
Xylitol gum	1.89	0.001	6.65	2.1-21.06
Probiotic yogurt	2.76	<0.001	15.91	3.69-68.68
CPP-ACP gum	0.989	0.014	2.68	1.21-5.91
Chlorhexidine	0*	-	1	-

* Reference group

Table 3. Pairwise comparisons of plaque index among the study groups

Study groups	Xylitol gum	Probiotic yogurt	CPP-ACP* gum	Chlorhexidine
Xylitol gum	-	0.327	0.104	<0.001
Probiotic yogurt	0.327	-	0.007	<0.001
CPP-ACP gum	0.104	0.007	-	0.014
Chlorhexidine	<0.001	<0.001	0.014	-

* Casein phosphopeptide amorphous calcium phosphate

Also, according to a systematic review, CHX can be used as an adjunct to control gingivitis and decrease the GI [25]. In our study, CHX was used as a standard mouthwash in the control group to serve as a reference for the purpose of comparison. Similar to the abovementioned studies, our results indicated a reduction in PI and GI of the participants who used CHX at both the first and second recall sessions compared with baseline; these reductions were significantly greater in the CHX group compared with other groups.

In our study, chewing gums containing xylitol and CPP-ACP were used, which are considered as chemical plaque-control substances.

The PI and GI of the participants in the CPP-ACP gum group were superior to other groups after the CHX group. Previous studies [11,12,26] on this topic mainly focused on enhancement of remineralization and treatment of white spot lesions by CPP-ACP, and this effect was also confirmed in a meta-analysis [27]; however, in the present study, we showed its positive effect on improvement of periodontal parameters. This effect can be attributed to the binding of CPP-ACP to dental plaque, which significantly increases the calcium content of the plaque, confers a buffering capacity, prevents tooth demineralization, and exerts bacteriostatic effects as well [13,28]. Also, CPP-ACP creates a negative charge on the tooth surface and exerts antibacterial effects as such. Previous studies [14,28] have shown that CPP-ACP chewing gum increases the salivary flow rate and subsequently improves its washing effect, which can prevent plaque accumulation and improve gingival and periodontal parameters.

Regarding the use of xylitol gum, it should be noted that xylitol is an immobile molecule that cannot remain for long in the oral cavity. Its penetration into the dental plaque only occurs through the dissemination phenomenon. This mechanism is probably responsible for plaque reduction by the effect of xylitol, and eradication of bacteria in absence of substrate [10,29]. Our results confirmed those of Keukenmeester et al, [9] who reported that use of xylitol by patients with regular oral hygiene did not cause a significant reduction in PI and GI.

This finding in our study was due to the fact that our study population was comprised of dental students who already had good oral hygiene prior to the study. Kaur et al. [30] found no significant difference in PI and GI of the two groups using xylitol and probiotic chewing gums. Similarly, we found no significant difference between the two groups, with the difference that they reported a significant reduction in parameters in both groups. Difference between their results and ours in this respect may be due to the use of different types of bacteria in the chewing gums and probiotic yogurt, and difference in type of products. Also, Saheer et al. [7] showed that use of xylitol chewing gum decreased the PI and GI, which was in agreement with our results. On the other hand, a significant difference was noted between the xylitol chewing gum and CHX in our study, which was in line with the results of Simons et al, [31] who compared xylitol chewing gum and CHX.

The efficacy of probiotic yogurt containing *Bifidobacterium*, as an easily available product, was also evaluated in this study as a chemical plaque-control substance. In this study, consumption of probiotic yogurt caused a reduction in GI and PI at both recall sessions similar to a previous study [32]. However, these reductions were significantly lower than those in the CHX group (gold standard). This result was the same as the findings of a clinical trial comparing a placebo yogurt and a probiotic yogurt containing *Bifidobacterium*, which showed that the latter had a positive effect on gingival inflammatory parameters and PI [33]. Moreover, Kohar et al. [34] reported that use of probiotic products such as drinks and lozenges decreased PI and bleeding index, but not significantly. Insignificant results in their study were explained to be due to the duration of usage and study population. Also, our results were in line with a systematic review [35] that showed small positive effect of probiotics on improvement of clinical parameters related to gingival health. Due to high heterogeneity of the reviewed studies, they called for clinical trials in this respect.

According to the literature, the positive efficacy of probiotics for improvement of periodontal status can be attributed to the reduction in

Porphyromonas gingivalis count. Also, optimal microbial balance is another reason for improvement of periodontal condition [15]. Evidence shows reduction of the number of binding sites for periopathogens on the biofilm following the possible coaggregation of *Bifidobacterium* and *Fusobacterium nucleatum* [36]. Several mechanisms have been suggested for the action of probiotics. For example, some bacteria release antimicrobial agents. Moreover, probiotic bacteria compete with pathogens for adhesion to surfaces [16,37]. In our study, participants used probiotic yogurt once a day with meal (lunch or dinner). The authors believe that the efficacy of probiotic yogurt may increase if the frequency of consumption increases to two or three times a day, or if it is consumed after meals and the patients are requested to refrain from drinking or rinsing their mouth for some time after its consumption. However, further investigations are warranted in this respect. Also, more accurate results could have been obtained after a longer follow-up period. A previous study reported a greater increase in the *Bifidobacterium* count at 90 days compared with 30 days, which suggests the possibility of delayed colonization of the bacteria [15]. By doing so, the local effects of probiotics may last for a longer period of time in the oral cavity, and result in a greater reduction in PI and GI. This study had some limitations. For instance, the duration of usage of CHX was not the same as the duration of usage of other products since use of CHX for more than 2 weeks is contraindicated. Also, consumption of probiotics in yogurt has a different local effect compared with its consumption in the form of chewing gum. When used in the form of yogurt, its duration of contact with the teeth is shorter, which can affect the outcome. Thus, use of probiotics in the form of products enabling longer contact with the teeth may yield more favorable results.

CONCLUSION

CHX was the most effective for reduction of GI and PI. Probiotic yogurt decreased the GI and PI, but the magnitude of reduction was smaller than that in other groups. CPP-ACP gum yielded superior results compared with the xylitol gum and probiotic yogurt.

ACKNOWLEDGMENTS

The authors would like to thank the Research Council of Mashhad University of Medical Sciences, Mashhad, Iran. This study was supported by the Research Council of Mashhad University of Medical Sciences, Mashhad, Iran. The authors would like to thank the students for their participation and cooperation in this study.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Nozawa A, Oshima H, Togawa N, Nozaki T, Murakami S. Development of Oral Care Chip, a novel device for quantitative detection of the oral microbiota associated with periodontal disease. PLoS One. 2020 Feb;15(2):e0229485.
2. Mishra R, Chandrashekar KT, Tripathi VD, Hazari A, Sabu BS, Sahu A. Comparative evaluation of efficacy of 0.2% sodium hypochlorite (Hi Wash) mouthwash with 0.2% chlorhexidine mouthwash on plaque-induced gingivitis: A clinical trial. J Indian Soc Periodontol. 2019 Nov;23(6):534-8.
3. Badar SB, Zafar K, Ghafoor R, Khan FR. Comparative evaluation of Chlorhexidine, Metronidazole and combination gels on gingivitis: A randomized clinical trial. Int J Surg Protoc. 2019 Apr;14:30-3.
4. Abdulkareem AA, Al Marah ZA, Abdulbaqi HR, Alshaeli AJ, Milward MR. A randomized double-blind clinical trial to evaluate the efficacy of chlorhexidine, antioxidant, and hyaluronic acid mouthwashes in the management of biofilm-induced gingivitis. Int J Dent Hyg. 2020 Aug;18(3):268-77.
5. Khairnar MR, Karibasappa GN, Dodamani AS, Vishwakarma P, Naik RG, Deshmukh MA. Comparative assessment of Cranberry and Chlorhexidine mouthwash on streptococcal colonization among dental students: A randomized parallel clinical trial. Contemp Clin Dent. 2015 Jan;6(1):35-9.
6. Vantipalli UK, Avula SSJ, Enuganti S, Bandi S, Kakarla P, Kuravadi RV. Effect of three commercially available chewing gums on salivary flow rate and pH in caries-active and caries-free children: An in vivo study. J Indian Soc Pedod Prev Dent. 2017 Jul-Sep;35(3):254-9.

7. Saheer PA, Parmar P, Majid SA, Bashyam M, Kousalya PS, Marriette TM. Effect of sugar-free chewing gum on plaque and gingivitis among 14-15-year-old school children: A randomized controlled trial. Indian J Dent Res. 2019 Jan-Feb;30(1):61-6.
8. Meena Syed RC, Vandana Shrivastava, Vinod Sachdev. Comparative evaluation of 0.2% Chlorhexidine Mouthwash, Xylitol Chewing Gum, and Combination of 0.2% Chlorhexidine Mouthwash and Xylitol Chewing Gum on Salivary *Streptococcus mutans* and Biofilm Levels in 8- to 12-Year-Old Children. Int J Clin Pediatr Dent. 2016 Oct-Dec;9(4):313-9.
9. Keukenmeester RS, Slot DE, Rosema NA, Van Loveren C, Van der Weijden GA. Effects of sugar-free chewing gum sweetened with xylitol or maltitol on the development of gingivitis and plaque: a randomized clinical trial. Int J Dent Hyg. 2014 Nov;12(4):238-44.
10. Oza S, Patel K, Bhosale S, Mitra R, Gupta R, Choudhary D. To Determine the Effect of Chewing Gum Containing Xylitol and Sorbitol on *Mutans Streptococci* and *Lactobacilli* Count in Saliva, Plaque, and Gingival Health and to Compare the Efficacy of Chewing Gums. J Int Soc Prev Community Dent. 2018 Jul-Aug;8(4):354-60.
11. Guclu ZA, Alacam A, Coleman NJ. A 12-Week Assessment of the Treatment of White Spot Lesions with CPP-ACP Paste and/or Fluoride Varnish. Biomed Res Int. 2016 Oct;2016:8357621.
12. Sugiura M, Kitasako Y, Sadr A, Shimada Y, Sumi Y, Tagami J. White spot lesion remineralization by sugar-free chewing gum containing bio-available calcium and fluoride: A double-blind randomized controlled trial. J Dent. 2016 Nov;54:86-91.
13. Samuel V, Ramakrishnan M, Halawany HS, Abraham NB, Jacob V, Anil S. Comparative evaluation of the efficacy of tricalcium phosphate, calcium sodium phosphosilicate, and casein phosphopeptide - amorphous calcium phosphate in reducing *Streptococcus mutans* levels in saliva. Niger J Clin Pract. 2017 Nov;20(11):1404-10.
14. Padminee K, Poorni S, Diana D, Duraivel D, Srinivasan MR. Effectiveness of casein phosphopeptide-amorphous calcium phosphate and xylitol chewing gums on salivary pH, buffer capacity, and *Streptococcus mutans* levels: An interventional study. Indian J Dent Res. 2018 Sep-Oct;29(5):616-21.
15. Invernici MM, Salvador SL, Silva PHF, Soares MSM, Casarin R, Palioto DB, et al. Effects of *Bifidobacterium* probiotic on the treatment of chronic periodontitis: A randomized clinical trial. J Clin Periodontol. 2018 Oct;45(10):1198-210.
16. Hadj-Hamou R, Senok AC, Athanasiou AE, Kaklamanos EG. Do probiotics promote oral health during orthodontic treatment with fixed appliances? A systematic review. BMC Oral Health. 2020 Apr;20(1):126.
17. Akram Z, Shafqat S, Aati S, Kujan O, Fawzy A. Clinical efficacy of probiotics in the treatment of gingivitis: A systematic review and meta-analysis. Aust Dent J. 2020 Mar;65(1):12-20.
18. Rindom Schiott C, Loe H, Borglum Jensen S, Kilian M, Davies RM, Glavind K. The effect of chlorhexidine mouthrinses on the human oral flora. J Periodontal Res. 1970 Apr;5(2):84-9.
19. Schmitter T, Fiebich BL, Fischer JT, Gajfulin M, Larsson N, Rose T, et al. Ex vivo anti-inflammatory effects of probiotics for periodontal health. J Oral Microbiol. 2018 Jul;10(1):1502027.
20. Jasberg H, Soderling E, Endo A, Beighton D, Haukioja A. *Bifidobacteria* inhibit the growth of *Porphyromonas gingivalis* but not of *Streptococcus mutans* in an in vitro biofilm model. Eur J Oral Sci. 2016 Jun;124(3):251-8.
21. Vohra F, Bukhari IA, Sheikh SA, Albaijan R, Naseem M, Hussain M. Effectiveness of scaling and root planing with and without adjunct probiotic therapy in the treatment of chronic periodontitis among shamma users and non-users: A randomized controlled trial. J Periodontol. 2020 Sep;91(9):1177-85.
22. Vives-Soler A, Chimenos-Küstner E. Effect of probiotics as a complement to non-surgical periodontal therapy in chronic periodontitis: a systematic review. Med Oral Patol Oral Cir Bucal. 2020 Mar;25(2):e161-e7.
23. Lynch MC, Cortelli SC, McGuire JA, Zhang J, Ricci-Nittel D, Mordas CJ, et al. The effects of essential oil mouthrinses with or without alcohol on plaque and gingivitis: a randomized controlled clinical study. BMC Oral Health. 2018 Jan;18(1):6.
24. Kakodkar P, Mulay S. Effect of sugar-free gum in addition to tooth brushing on dental plaque and interdental debris. Dent Res J (Isfahan). 2010 Summer;7:64-9.
25. James P, Worthington HV, Parnell C, Harding M, Lamont T, Cheung A, et al. Chlorhexidine mouthrinse as an adjunctive treatment for gingival health. Cochrane Database Syst Rev. 2017 Mar;3(3):Cd008676.
26. Ahmadi Zenouz G, Ezoji F, Enderami SA, Khafri S. Effect of fluoride, casein phosphopeptide-amorphous calcium phosphate and casein phosphopeptide-amorphous calcium phosphate fluoride on enamel surface microhardness after microabrasion: An in vitro study. J Dent (Tehran). 2015 Oct;12(10):705-11.

27. Ma X, Lin X, Zhong T, Xie F. Evaluation of the efficacy of casein phosphopeptide-amorphous calcium phosphate on remineralization of white spot lesions in vitro and clinical research: a systematic review and meta-analysis. BMC Oral Health. 2019 Dec;19(1):295.
28. Hegde RJ, Thakkar JB. Comparative evaluation of the effects of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and xylitol-containing chewing gum on salivary flow rate, pH and buffering capacity in children: An in vivo study. J Indian Soc Pedod Prev Dent. 2017 Oct-Dec;35(4):332-7.
29. Holgerson PL, Sjostrom I, Stecksen-Blicks C, Twetman S. Dental plaque formation and salivary mutans streptococci in schoolchildren after use of xylitol-containing chewing gum. Int J Paediatr Dent. 2007 Mar;17(2):79-85.
30. Kaur K, Nekkanti S, Madiyal M, Choudhary P. Effect of chewing gums containing probiotics and xylitol on oral health in children: A randomized controlled trial. J Int Oral Health. 2018 Sep;10:237.
31. Simons D, Beighton D, Kidd EA, Collier FI. The effect of xylitol and chlorhexidine acetate/xylitol chewing gums on plaque accumulation and gingival inflammation. J Clin Periodontol. 1999 Jun;26(6):388-91.
32. Benic GZ, Farella M, Morgan XC, Viswam J, Heng NC, Cannon RD, et al. Oral probiotics reduce halitosis in patients wearing orthodontic braces: a randomized, triple-blind, placebo-controlled trial. J Breath Res. 2019 May;13(3):036010.
33. Kuru BE, Laleman I, Yalnizoglu T, Kuru L, Teughels W. The Influence of a *Bifidobacterium animalis* Probiotic on Gingival Health: A Randomized Controlled Clinical Trial. J Periodontol. 2017 Nov;88(11):1115-23.
34. Kohar N, Emmanuel V, Astuti L. Comparison between probiotic lozenges and drinks towards periodontal status improvement of orthodontic patients. Dent J (Majalah Kedokteran Gigi). 2015 Sep;48:126.
35. Barboza EP, Arriaga PC, Luz DP, Montez C, Vianna KC. Systematic review of the effect of probiotics on experimental gingivitis in humans. Braz Oral Res. 2020 Mar;34:e031.
36. Haukioja A, Yli-Knuuttila H, Loimaranta V, Kari K, Ouwehand AC, Meurman JH, et al. Oral adhesion and survival of probiotic and other *lactobacilli* and bifidobacteria in vitro. Oral Microbiol Immunol. 2006 Oct;21(5):326-32.
37. Barzegari A, Kheyrolahzadeh K, Hosseiniyan Khatibi SM, Sharifi S, Memar MY, Zununi Vahed SA-O. The battle of probiotics and their derivatives against biofilms. Infect Drug Resist. 2020 Feb;13:659-72.