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Research Article

L-Arginine Toothpaste Protects Ph in Caries-Free Patients: A Pilot Study

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Introduction

Oral Microbiota is essential for the balance between oral health and the occurrence of the main oral disorders: caries and periodontal diseases. While most treatments focus straightforwardly on the reduction of pathological microorganisms, the promotion of a healthy oral microbiome through probiotics and prebiotics is an increasingly used alternative therapeutic approach, although the evidence on its efficacy is not always consistent [1-3]. Frequent exposure to dietary sugars, such as sweetened foods, causes continuous pH declines in the oral cavity, leading to a sharp fall in biofilm pH values, which has been described to be involved in the origin of caries. Continuous acidogenic fluctuations, when perpetuated, produce disbalance of oral homeostasis inducing frequent pH falls that disrupts the balance between tooth mineralization and demineralization causing a net mineral loss within the tooth's hard tissues [4,5].

Some bacteria belonging to the *Streptococcus* genus (i.e. *S. mutans or S. sobrinus*) have been identified as cariogenic agents by inducing pH decreases that can disrupt the balance between tooth mineralization and demineralization. However, the necessary interaction with other components of the microbiota, including other bacteria, virus, fungi, and even protozoa, underscores the complexity of the cariogenic process [6,7].

In recent years, several studies have explored the use of toothpastes containing ingredients with the potential to improve health of the oral microbiota and thus preserve the acid-base balance. One widely studied component has been L-arginine, an amino acid that has a prebiotic effect with documented benefits on oral health, ranging from acid-base balance to modulation of biofilm development [7,8]. For instance, toothpaste supplemented with L-arginine and fluoride exhibited significantly higher effectiveness in preventing oral caries formation than fluoride-only supplemented toothpaste [9]. Another study observed that a toothpaste containing 8% arginine modulated the composition of the oral flora, reducing sucrose metabolism, and this effect was reversed when its use was discontinued [10]. In contrast, a similar study found that supplementation with an arginine concentration of 2% (but not 4% nor 8%) increased the remineralization of enamel caries-like lesions [11]. Moreover, a combination of 2% L-arginine supplemented toothpaste with *L. rhamnosus*, besides biofilm reduction, effectively regulated acid-base balance [12]. In the same line, a recent study described that L-arginine supplemented toothpaste had a significant effect in caries reduction and oral microbiome balance [13].

Dental caries occurrence has been consistently associated with the balance of oral flora and oral microbiome composition has been reported to differ significantly between subjects with and without caries [14,15]. Since caries formation is related to a low pH environment, the presence of acidogenic bacteria is necessary for caries etiology [16,17]. All these findings point to a synergistic effect of prebiotic supplemented toothpaste with bacteria present in healthy oral microbiome to preserve acid-base equilibrium.

Therefore, it was hypothesized that L-arginine supplemented toothpaste effect in pH regulation would be more marked in those patients with a healthy oral microbiome, manifested by the absence of caries record. For that purpose, the effect on pH fluctuation of L-arginine supplemented toothpaste in five patients that have developed caries in the past was studied and compared with five patients that have not presented caries.

Materials and Methods

All participants were enrolled in the same private clinic. The exclusion criteria was: (i) patients that received antibiotic treatment within the preceding 3 months, (ii) were currently using antibiotics, (iii) had already been using a toothpaste with arginine. Consecutive patients were offered to participate in the study until there were five patients enrolled in each group. Caries lesions were considered according to the International Caries Detection and Assessment System (ICDAS) score of 5 or 6 (dentinal, cavitated lesions).

The Caries-Free group comprised individuals with no reported or clinical evidence of caries experience [decayed, missing, and filled teeth (DMFT = 0)]. The Caries-Not-Free group encompassed both, individuals that had caries/restorations and individuals with current active/unrestored lesions (DMFT>0). Informed consent was approved by the Institutional Review Board of the Universidad Europea de Madrid and obtained from all the participants (see suppl. materials). The study received approval by the ethical committee of Hospital Universitario Severo Ochoa (Código CI 2023-360).

All patients were assessed before L-arginine treatment and after one week of daily (at least twice a day) L-arginine treatment. Participants were instructed to abstain from oral hygiene procedures for at least 8 hours prior to the collection of salivary samples. Additionally, individuals were requested to refrain from food or beverage consumption for at least 1 hour prior to sample collection.

Stephan curve kinetics were determined by instructing participants to expectorate saliva specimens into sterile plastic tubes. An electric pH meter was used to record the pH value of the salivary samples. At the end of each measurement, the pH meter was immersed under sterile water for cleaning purposes. For each visit, the resting salivary pH (Basal) was initially recorded prior to sucrose exposure. Then, participants were instructed to rinse with Coca-Cola® (Atlanta, GA, USA) for 1 minute. After expelling the sucrose source, salivary samples were collected and pH measurements were performed at the specified intervals: 1 minute, 5 minutes, 15 minutes and 25 minutes. After rinsing mouth with water and a 30 min resting period, the same protocol was repeated with Orange Juice Auchan® (Compiègne, France).

At the end of the pre-arginine phase/1st visit, participants were provided with ELMEX PRO ARGIN toothpaste (Colgate-Palmolive, New York City, NY, USA), accompanied by a flyer outlining the recommended oral hygiene procedures for the following week (see Supplementary material). Participants returned to the clinic after 1 week of arginine exposure. During the post-arginine phase/2nd visit, the identical procedure was replicated, under the same protocol as in the pre-arginine phase/1st visit.

The normal distribution of the data obtained was evaluated by Shapiro-Wilk analysis. ($P > 0.05$). Hence, parametric tests were selected. One-way analysis of variance (ANOVA) followed by the post-hoc Bonferroni pairwise comparison test was run (see supplementary material).

The differences in the maximum of the pH decrease were analyzed for each group before and after L-arginine treatment. Moreover, differences in the magnitude of change over time were assessed by calculating the area under the line for both variables (pH fall, time in minutes) of the Stephan curve, which was plotted as change in the pH over time vs basal values. Also in this case, differences were analyzed for each group before and after L-arginine treatment. In both analyses, paired one-tailed T-Student test was conducted, considering a significance level of $\alpha = 0.05$.

Results

The basal salivary pH values were homogeneous for patients in both groups, 7.14±0.41 for patients in the DMFT=0 group (caries free) and 7.18±0.43 in the DMFT>0 group (caries record). Before L-arginine treatment, the pH fall was more pronounced when orange juice was used as a sucrose source (0.99 in the first minute) than when Coca-Cola® was used (0.61 in the first minute) (Table 1).

Table 1: pH values for each patient and sucrose source. DMFT=0 means absence of caries (decayed, missing, and filled teeth = 0). DMFT>0 means caries record (decayed, missing, and filled teeth > 0).

	SUCROSE SOURCE COCA-COLA									
	BEFORE L-ARGININE TREATMENT					AFTER L-ARGININE TREATMENT				
	BASAL	1 MIN	5 MIN	15 MIN	25 MIN	BASAL	1 MIN	5 MIN	15 MIN	25 MIN
PATIENT 1 DMFT=0	0	-0,6	-0,5	-0,2	-0,1	0	-0,8	-1,3	-0,4	0
PATIENT 2 DMFT=0	0	-0,2	-0,1	0,1	0	0	0,2	-0,3	0	0
PATIENT 3 DMFT=0	0	-0,8	-1,2	-0,5	-0,2	0	0,3	0,8	0	0,2

PATIENT 4 DMFT=0	0	-0,7	-1,5	-0,7	-0,3	0	-0,4	-0,4	-0,3	0
PATIENT 5 DMFT=0	0	-0,9	-1	-0,9	-0,7	0	-0,7	-0,7	-0,6	-0,1
PATIENT 1 DMFT>0	0	-0,5	-0,9	-0,4	0	0	-0,3	-0,3	-0,2	0
PATIENT 2 DMFT>0	0	-1	-0,8	-0,5	-0,5	0	-0,4	-1	-0,5	0
PATIENT 3 DMFT>0	0	-0,1	0,3	0,2	0,2	0	0,2	-0,5	-0,3	0,1
PATIENT 4 DMFT>0	0	-1,3	-1,9	-1,4	-0,5	0	-1,6	-1,9	-1,7	-1,2
PATIENT 5 DMFT>0	0	0	-0,4	-0,1	0	0	-0,2	-0,8	-0,5	-0,3

	SUCROSE SOURCE: ORANGE JUICE									
	BEFORE L-ARGININE TREATMENT					**AFTER L-ARGININE TREATMENT**				
	BASAL	1 MIN	5 MIN	15 MIN	25 MIN	BASAL	1 MIN	5 MIN	15 MIN	25 MIN
PATIENT 1 DMFT=0	0	-2,4	-0,5	-0,2	0	0	-1,1	-0,9	-0,2	0
PATIENT 2 DMFT=0	0	-0,2	0,1	-0,1	-0,1	0	0,5	0,2	0,3	0,3
PATIENT 3 DMFT=0	0	-1,1	-0,8	-0,6	-0,3	0	0,6	-0,3	-0,2	0
PATIENT 4 DMFT=0	0	-1,5	-1,4	-0,4	0	0	-0,7	-0,8	-0,6	-0,3
PATIENT 5 DMFT=0	0	-0,6	-0,8	-0,5	-0,1	0	-0,9	-0,5	-0,2	0
PATIENT 1 DMFT>0	0	0,1	-0,2	-0,1	-0,1	0	0,1	-0,2	-0,1	0
PATIENT 2 DMFT>0	0	-1,1	-0,4	-0,4	-0,2	0	0	-0,7	-0,4	0
PATIENT 3 DMFT>0	0	-0,4	-0,1	-0,2	-0,2	0	-0,2	-0,2	-0,1	0,2
PATIENT 4 DMFT>0	0	-2,7	-2,1	-1,3	-0,5	0	-3	-2,5	-2	-1,2
PATIENT 5 DMFT>0	0	0	0	-0,1	0,1	0	-1	-0,7	-0,2	0

Note*: Supplementary Material: ANOVA, informed consent and informative sheet.

The maximum decrease in pH values for each patient at any time was analyzed. In the DMFT>0 group, there were no statistically significant differences in the maximum decrease in pH when comparing either sucrose source before or after L-arginine treatment. For Coca-Cola®, the pH fall was 0.9 both before and after treatment, while for orange juice the pH fall was 0.9 before treatment and 1.04 afterwards. On the other hand, in the DMFT=0 group, there was an important reduction in the maximum decrease after L-arginine treatment: upon Coca-Cola® exposure, there was a 40% reduction, from 0.9 to 0.54 (P = 0.187) while, upon orange juice exposure, there was a 48% reduction (P = 0.038) (Figure 1).

In order to assess differences in the magnitude of change over time up to 25 minutes, Stephan curve was plotted for the pH variation vs basal over time, and the area under the line was calculated. After this period, most patients recovered basal pH values. Before the L-arginine treatment, there were no differences in the magnitude of change in pH over time when comparing DMFT=0 group with DMFT>0 group (P = 0.43 for Coca-Cola®, p = 0.46 for orange juice).

Following L-arginine exposure for 1 week, there were important differences in the magnitude of change over the 25 minutes period post-sucrose source challenge between DMFT=0 group and DMFT>0 group. While in the DMFT>0 group there was no reduction but a small increase (around 30%) in the pH fall sustained over time after administration of any of the sucrose sources, the caries free patients (DMFT=0) showed a dramatic reduction in the pH fall sustained over time: After L-arginine treatment, the reduction in the area under the line of the Stephan curve when Coca-Cola® was used as sucrose source was a 56% (P = 0.125) while, when orange juice was used as sucrose source, it was a 50.5% (P= 0.029) (Figure 2).

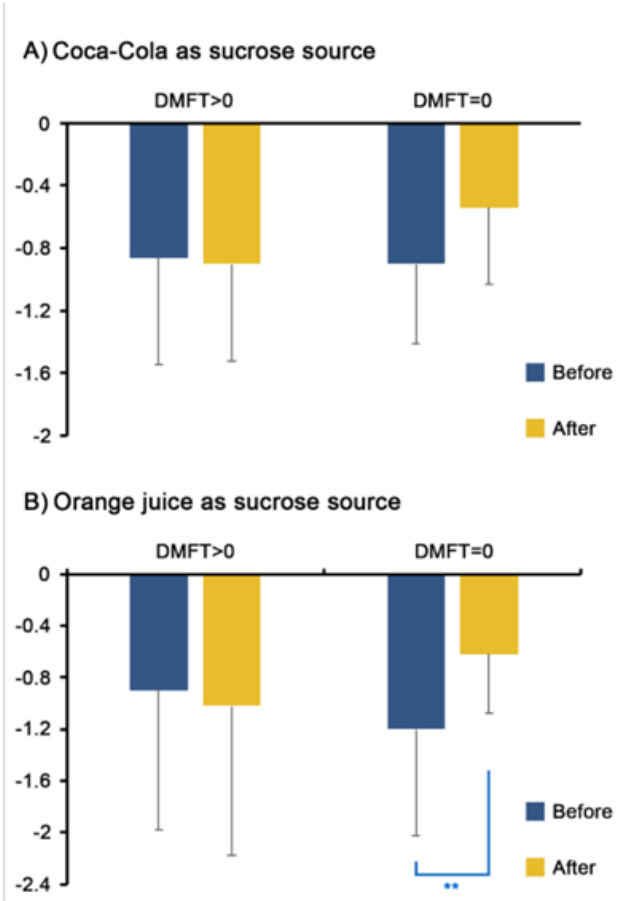

Figure 1: Maximum of the pH decrease for each group and sucrose source before (blue) and after (yellow) L-arginine treatment. DMFT=0 means absence of caries (decayed, missing, and filled teeth = 0). DMFT>0 means caries record (decayed, missing, and filled teeth > 0). ** = P value < 0.05.

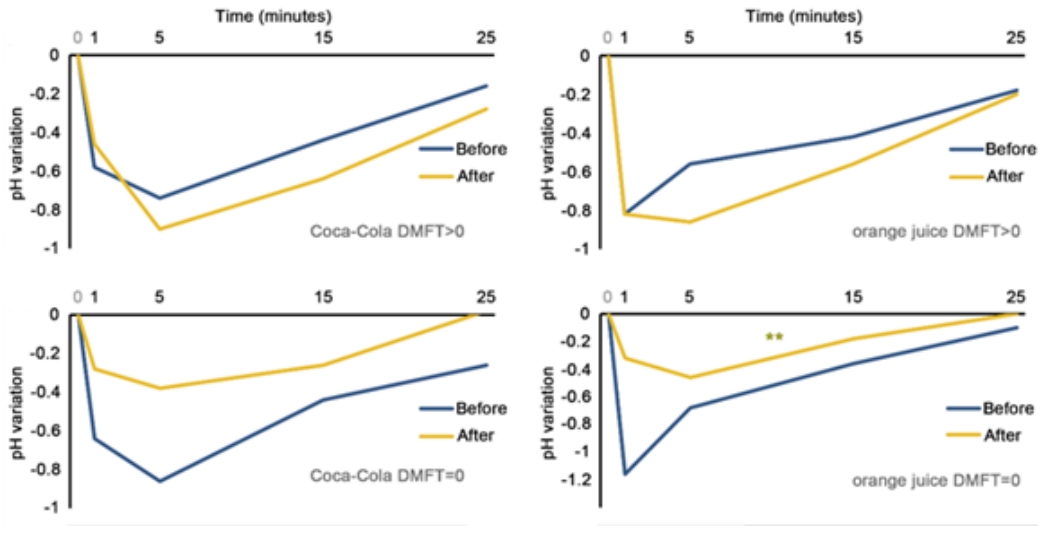

Figure 2: Stephan curve was plotted for the pH variation vs basal up to 25 minutes for each group and sucrose source before (blue) and after (yellow) L-arginine treatment. DMFT=0 means absence of caries (decayed, missing, and filled teeth = 0). DMFT>0 means caries record (decayed, missing, and filled teeth > 0). Area under the line was calculated to estimate magnitude of change: ** = P value < 0.05.

Discussion

It was observed a protective effect of L-arginine supplemented toothpaste against salivary pH fall in patients without dental caries (DMFT=0), while it was not observed in those patients with a record of dental caries (DMFT>0). Our results suggest a higher effectivity of L-arginine treatment in individuals without dental caries than in individuals with a caries record.

The pH fall was more pronounced when orange juice was used as a sucrose source than when Coca-Cola® was used. Moreover, despite the maximum decrease and the magnitude change over time in the pH were similarly reduced by L-arginine treatment in caries-free patients challenged with both sucrose sources, it only reached statistical significance for orange juice due to a higher variance when Coca-Cola® was used as sucrose source. These differences among sucrose sources might be caused by either orange juice higher acidity or Coca-Cola ®'s carbonate content, which might have a buffering effect. If this would be the case, it is unlikely that Coca-Cola® carbonate content might have affected the orange juice treatment, as there was a mouth water rinsing and a pause period between sucrose challenges.

Occurrence of caries depends on the oral microbiota balance, which is the result of a complex interaction between the host, diet and microorganisms [18,19]. Our results point to a lack of prebiotic effectivity in patients with unbalanced oral microbiota, which is manifested as a record of dental caries. A symbiotic microbial community enables quick pH recovery after sucrose exposure [20,21] For example, *L. rhamnosus*, a widely studied probiotic bacteria, was combined with collagen peptides and found to significantly increase the pH of the oral environment in the initial stages of biofilm formation, thereby preventing the cariogenic process [22].

The described L-arginine path for alkali generation is the Arginine Deiminase System (ADS), which generates ATP and ammonia [23,24]. This alkalinizing effect leads to a reduction in biofilm formation and mitigation of enamel demineralization [25]. Indeed, it has been reported that there is a higher ADS activity in plaque rather than saliva samples and this may be due to the difference in abundance of arginolytic bacteria between these two sites [26]. Most of the ADS positive bacteria are commensal to the oral cavity, including *Streptococcus sanguinis*, *S. parasanguinis*, *S. gordonii*, *S. mitis*, some Lactobacillus and Actinomyces species, and certain Spirochetes [27,28].

This generation of ammonia has been proven to increase directly the pH of dental biofilm and saliva, which tilts the equilibrium in favor of remineralization rather than demineralization. Furthermore, by increasing the oral pH, ammonia may alter the structure of the biofilm, boost the proliferation of commensal species and reduce the accumulation of aciduric and acidogenic bacteria that rely on low pH to gain an ecological advantage, thus enhancing the alkaline production of arginine-solubilizing bacteria, such as *Streptococcus sanguinis* and *S. Gordonii* [23,29,30].

Therefore, L-arginine has the potential to prevent pH falls but, unlike bicarbonate, its effect is not immediate. A certain time is required for arginine to be metabolized by arginolytic bacteria, generate ammonia and increase the pH, which will then slow down the proliferation of aciduric bacteria, alter the composition of oral microflora and halt further acidification.

The findings of the present study are consistent with the pivotal work by Nascimento et al, which illustrated notably elevated levels of salivary ADS activity among individuals with DMFT=0 compared to those with DMFT>0.24 Specifically, the mean ADS activity of salivary samples from caries-free individuals was five-fold higher compared to caries-active individuals (P=0.0004). Additionally, Nascimento's subsequent research in children revealed a tendency of a higher ADS salivary activity among children with DMFT=0 compared to DMFT>0 in permanent dentition [26]. Overall, these findings suggest that caries free individuals may harbor a more favorable oral microbial composition, characterized by an increase in abundance of arginolytic bacteria, which would enhance production of ammonia and consequently, raise salivary and plaque pH levels.

Conversely, individuals with caries exhibit a reduced prevalence of arginolytic bacteria and a tendency towards acidogenic bacterial species, leading to diminished levels of ammonia, and thus lower salivary and oral biofilm pH [27,31]Results presented here are in line with those of *Koopman*, et al. involving nine individuals with DMFT=0, which revealed a positive correlation between the duration of arginine usage and salivary arginolytic potential, as well as a change in the microbial composition of saliva [10]. The results suggest fast increase in salivary ammonia levels after the utilization of 8% arginine toothpaste, with the peak production and concentration of ammonia observed at the final check-up visit after 8 weeks of usage. On the other hand, in line with the observations described in the present work, a study on 20 individuals with active caries lesions (ICDAS scores between 2-3) did not observe any significant improvement in salivary pH levels after 14 days of L-arginine gel utilization [32].

Recent studies indicate that the use of L-arginine has the capacity to modify biofilm biomass, thickness and architecture, as well as to influence the species abundance within a microbial community. This reduction in biofilm thickness, biomass, and bacterial viability is dependent upon the salivary concentration of arginine. Furthermore, studies have shown that high salivary concentrations of arginine (millimolar) present a 15 -fold reduction in biofilms mass and a 35-fold reduction in thickness [33,34] Moreover, a meta-analysis demonstrated that dairy products containing probiotics have a positive effect on increasing salivary pH through oral microbiota modulation [35].

This study has several limitations. First, the absence of the composition of patients' oral microbiota as well as the ADS activity.

Second, sample size was not calculated and might be underpowered to detect any effects in the DMFT>0 population. Third, the observed pH falls even before treatment are small and transitory, as decreases below pH 5.5 are considered to be the ones involved in caries [36]. It must be considered that the scope of this work is to study the L-arginine supplementation buffering effect on the pH, not the caries formation. Another aspect to consider is the possible buffering effect of carbonate present in Coca-Cola®, which might be a confounder to avoid in future research. Last, it would have been quite interesting to study the effect of probiotics supplementation in those patients with a caries record and whether it changes their response to L-arginine supplementation. Future research should explore this potential synergistic effect.

Toothpaste supplementation with L-arginine has a protective effect against salivary pH fall in patients that are not prone to caries. This differential effect of L-arginine supplemented toothpaste on acid-base regulation in patients with or without a record of caries, underscores the importance of a healthy oral microbiome for prebiotic therapy efficacy. Further work will be necessary to define the potential synergistic effect of prebiotics such as L-arginine with probiotic supplementation to enhance pH stability and reduce caries occurrence.

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Conflict of Interest

The authors declare no conflict of interest.

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