



Is there a role of toothpastes in the development of recurrent aphthous stomatitis? A prospective controlled clinical trial with skin patch testing

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Objectives. The oral mucosa is exposed to a large number of antigenic agents contained in toothpastes. These agents are reported to stimulate recurrent aphthous stomatitis (RAS) pathogenesis, and toothpastes that do not contain probable allergenic substances reduced the number and frequency of aphthous ulcers. We aimed to determine whether the skin patch test (SPT) can be used to determine if toothpaste allergens play a role in the etiology of RAS.

Study Design. Sixty-three patients with RAS and 47 healthy volunteers were skin patch tested with sodium lauryl sulfate, cocamidopropyl betaine, propylene glycol, aluminum chloride hexahydrate, menthol, triclosan, and titanium dioxide, which are present in most of the toothpastes. Fisher's exact test and the Yates chi-square test were used to compare categorical variables and patch test results between 2 groups.

Results. The SPT was positive in 8 (22.2%) patients with RAS and 11 (23.4%) control subjects, and the difference between the groups was not statistically significant ($P < .05$). Sodium lauryl sulfate, titanium dioxide, and menthol were the most common positive allergens in both groups.

Conclusions. Allergens in toothpastes did not appear to stimulate the formation of RAS. However, in order to determine a clearer relationship, a study in a larger patient series employing intraoral patch testing with more toothpaste ingredients is suggested. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:43–48)

Recurrent aphthous stomatitis (RAS) is a frequently seen disorder of the oral mucosa, characterized by chronic ulcerations. It affects approximately 20% of the population.¹ RAS clinically presents with oval ulcers of different sizes, consisting of a yellowish white central fibrinous exudate surrounded by an erythematous halo. There are 3 clinical subtypes of RAS according to their size; approximately 85% of all cases of RAS have minor (<1 cm diameter), 10%-15% have major ulcers (>10 mm), and 5%-10% have herpetiform ulcers (1-2 mm, multiple ulcers) RAS. The ulcers are usually located in nonkeratinized regions, such as the buccal mucosa.² The etiopathogenesis is not clear. Researchers have reported genetic, hormonal, psychogenic, traumatic, infectious, autoimmune, and gastrointestinal conditions (celiac disease, Behçet disease); dietary factors; and hypersensitivity.^{2,3}

The oral mucosa is exposed to a wide variety of antigens.⁴ A number of studies have investigated the role of various agents, including food additives, benzoic acid,^{4,5} sodium lauryl sulfate (SLS), cocamidopropyl betaine (CAPB),⁶⁻⁸ nickel,⁹ potassium dichromate,¹⁰ fragrance mix 1, cinnamic alcohol,¹¹ triclosan, and propylene glycol¹² in the etiopathogenesis of aphthous lesions.⁴⁻¹⁵ Several histopathological studies demonstrated the role of type

IV hypersensitivity reactions in RAS related to exogenous antigens. These studies reported that cytotoxic CD8 T lymphocytes were increased in number in oral ulcers and injured oral epithelium by the release of various cytokines, and this was demonstrated with skin patch tests (SPTs).^{5,10} The SPT is the gold standard diagnostic method employed to detect the responsible exogenous antigens contacting skin and causing allergic skin reactions.¹⁰

Toothpastes are the most frequently consumed oral hygiene products by people in all age groups. They contain a number of chemicals, including abrasives, detergents, humectants, antibacterials, fluoride salts, coloring agents, flavors, and thickeners. SLS,⁶ CAPB, titanium dioxide, propylene glycol, aluminum chloride hexahydrate (ACH), menthol, and triclosan are the suspected allergens found in the toothpastes.¹²⁻¹⁵ No studies to date have investigated the role of toothpastes in the etiology of RAS using a wide SPT panel, after optimum elimination of the other potential factors in the etiology of the disorder. To our knowledge, our present study is the first in the literature to investigate the role of toothpaste allergens in RAS etiology employing SPT. In our study, to provide a homogeneous group, only patients with minor RAS were examined.

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Statement of Clinical Relevance

The role of toothpaste allergens in recurrent aphthous stomatitis etiology has been observed using a skin patch test, and haptens in the toothpastes do not play a role in type IV hypersensitivity reactions in the development of aphthous stomatitis.

MATERIALS AND METHODS

This study was conducted in 63 patients with minor RAS admitted to a dermatology clinic between January 2015 and March 2018 and 47 healthy volunteers. The patients with RAS included in the study were older than 18 years of age; had more than 3 RAS attacks/year; did not have any positive family history or any chronic disorder that may lead to oral ulcerations such as Behçet disease or inflammatory bowel disease; did not have anemia due to iron, vitamin B₁₂, or folate deficiency; and were not pregnant or breastfeeding or diagnosed with allergic contact dermatitis or an atopic diathesis. SPT was performed in all patients and control subjects. The exclusion criteria were the presence of the factors that exacerbated patients' complaints (eg, stress, menstruation, food, use of medications, mucosal trauma), smoking, and dental treatment (tooth filling, implant) in the previous year. The control group consisted of 47 healthy volunteers older than 18 years of age and without any history of RAS, systemic disorders, or atopic diathesis. Sixteen patients who had active dermatitis and were using systemic antihistamines, nonsteroidal anti-inflammatory drugs, topical corticosteroids, systemic corticosteroids, or immunosuppressive agents for various reasons were not been tested were excluded from the study. The remaining 47 patients were included in the study. Nine were excluded due to the displacement of allergen patches owing to water contact, friction, or other reasons, and 2 patients were excluded because we learned that they were receiving antihistamines. The study was completed with 36 patients and 47 control subjects, and their results were included in the statistical analysis.

The study protocol was approved by the Cosmetic Ethics Committee (MU, 2018/8). Informed consent was obtained from all participants before beginning the study. The study was funded by the Scientific Research Project Fund of the University of Health Sciences.

The demographic data and the clinical findings (frequency, duration, number and localization of oral aphthous ulcers, and recovery time) of the patients diagnosed with RAS were recorded. Complete blood count; serum iron level; iron-binding capacity; and ferritin, zinc, folate, and vitamin B₁₂ levels were obtained. The ingredients of the toothpastes used by the participants were recorded. The SPT allergens covered all of the substances investigated in the toothpaste formulations.

Application of SPT

In our study, a total of 7 allergen haptens were used in SPTs (Chemotechnique MB Diagnostics AB, Vellinge, Sweden). They were SLS, CAPB, propylene glycol, ACH, menthol, triclosan, and titanium dioxide, which are the most common ingredients of toothpastes¹⁶ with high allergenic potential. The selected hapten concentrations

minimized the possible irritant reactions. The properties, concentrations, and functions of each hapten in toothpastes are presented in Table I. The haptens were placed on 1 cm² blotting paper, or the blotting paper was impregnated with the hapten with the help of a plastic syringe, and the paper was adhered to the participant's back using a hypoallergenic, watertight plaster (IQ Ultimate; Chemotechnique MB Diagnostics). The second author evaluated the SPT results 48 hours after the application in a single-blind way in accordance with the scheme proposed by the International Contact Dermatitis Research Group 30 minutes, 72 hours, and 96 hours after removal of the skin patches (Table II).¹⁷ All negative (–) and suspicious positive (? , +) reactions were regarded as negative, whereas all reactions with erythema and induration (+, ++, +++) were regarded as positive. The reactions that started at the 48th hour and regressed at the 72nd hour were considered as irritant reactions, and the reactions that remained the same or became more severe at the 72nd hour were considered as positive.

Statistical analysis

Statistical analysis was conducted using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). The minimum sample size was determined as 42 control subjects and 42 patients for the power analysis (α error = 0.05; effect size = 0.8; power = 0.95). The normality of the data distribution was analyzed with the Shapiro-Wilk test. Nonparametric continuous variables were presented as medians (25th–75th percentiles). Categorical variables were presented as frequency and percent. The difference between the groups was analyzed with the Mann-Whitney *U* test for

Table I. Haptens found in toothpastes, their functions, and their vehicles

Hapten	Function	%	Vehicle
SLS	Cleanser: Antiplaque; it foams, making it difficult for the dental plaque and other accumulated substances to attach to the tooth surface, and in this way it dissolves them.	0.25	Water
CAPB	Detergent: cleanser	1	Water
Titanium dioxide	White, opaque coloring agent	10	Petrolatum
Propylene glycol	Provides viscosity	5	Water
Aluminum chloride hexahydrate	Corrosive, antitartar property or polisher	2	Petrolatum
Menthol	Flavoring	2	Petrolatum
Triclosan	Antiseptic agent	2	Petrolatum

Abbreviations: CAPB, cocamidopropyl betaine; SLS, sodium lauryl sulfate.

Table II. Grading of patch test results according to International Contact Dermatitis Research Group recommendations¹⁷

Symbol	Morphology	Evaluation
–	No reaction	Negative reaction
?, +	Faint erythema only	Doubtful reaction
+	Erythema, infiltration, possibly papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction

numerical variables that do not have a normal distribution. Fisher's exact test and the Yates chi-square test were used to compare categorical variables and SPT results between 2 groups. Statistical significance was set at $P < .05$.

RESULTS

We included 36 patients with RAS (8 males, 28 females) and 47 healthy control subjects (18 males, 29 females). The mean ages of the patient and control groups were 26.6 ± 7.59 (18-43) and 24 ± 4.67 (18-35) years, respectively. The gender distributions of the study and control groups were 77.8% females/22.2% males and 61.7% females/38.3% males, respectively. Both groups showed homogeneous distributions in terms of age and gender ($P > .05$). The frequency and localization of aphthous ulcers and age of onset are presented in Table III. The study and control groups did not show any significant differences in terms of serum iron, total iron-binding capacity, ferritin, folic acid, or vitamin B₁₂ levels ($P > .05$).

Table III. Demographic characteristics and laboratory results of the participants

	Patients	Control subjects	P value
Number (N = 83) (%)	36 (43.4)	47 (56.6)	
Gender	8 M/28 F	18 M/29 F	0.11
Age, years, mean $\pm$ SD	26.6 ± 7.59	24 ± 4.67	0.10
Frequency of aphthous lesions, n (%)			
3-6 times/year	15 (41.7)		
>6/year	21 (58.3)		
Healing time, days, median (25th-75th percentiles)	8 (7-11.5)		
Location	Lower lip, 22.2%		
	Buccal mucosa, 13.9%		
	Tongue, 8.3%		
	At least 2 different locations, 55.8%		
Age of onset, years, median (25th-75th percentiles)	17.5 (15-22)		
Duration since onset, years, median (25th-75th percentiles)	6 (3-10)		
Serum iron level, median (25th-75th percentiles)	75 (50-98.7) μ g/dL	85 (57-108) μ g/dL	0.23
TIBC, median (25th-75th percentiles)	330 (307-376) μ g/dL	350 (304-380) μ g/dL	0.57
Ferritin, median (25th-75th percentiles)	31 (9-49.8) ng/mL	30.4 (10-52) ng/mL	0.46
Folic acid, median (25th-75th percentiles)	8.6 (5.3-9.9) ng/mL	7.7 (6-9.9) ng/mL	0.92
Vitamin B ₁₂ , median (25th-75th percentiles)	342 (292-424) pg/mL	356 (307-429) pg/mL	0.57

Abbreviations: N, number of the participants, M male, F female, TIBC: Total iron binding capacity.

Table IV. Patch test results of the participants

Haptens used in patch testing	Patients, n (%)	Control subjects, n (%)	P value
	8 (22.2)	11 (23.4)	0.899
SLS	2 (5.6)	4 (8.5)	0.606
CAPB	2 (5.6)	2 (4.3)	0.784
Titanium dioxide	2 (5.6)	4 (8.5)	0.606
Propylene glycol	1 (2.8)	2 (4.3)	0.721
Aluminum chloride hexahydrate	1 (2.8)	0	0.250
Menthol	2 (5.6)	4 (8.5)	0.606
Triclosan	2 (5.6)	2 (4.3)	0.784

Abbreviations: CAPB, cocamidopropyl betaine; SLS, sodium lauryl sulfate.

The results of SPT were positive in 8 (22.2%) patients with RAS and 11 (23.4%) control subjects, and the difference between the groups was not statistically significant ($P > .05$). The SPT results of the participants are summarized in Table IV. An irritant reaction was not detected in any of the participants.

Of the 19 participants with positive SPT results, 11 (57.9%) were males and 8 (42.1%) were females, and there was a statistically significant difference between the genders ($P = .01$). When aphthous ulcer frequency was grouped as 3-6 and >6 per year, no difference was found between the 2 groups in terms of patch test results ($P > .05$). SLS, titanium dioxide, and menthol were the most common positive allergens in both groups.

DISCUSSION

Toothpastes are the most frequently used oral hygiene products in all age groups. They contain a number of chemicals, including abrasives, detergents, humectants,

antibacterials, flavors, and thickeners.^{6,7} Those substances, which are frequently used in daily life, may cause allergic sensitization. Histopathological studies revealing the role of type IV allergic reactions against exogenous antigens in RAS etiology reported that cytotoxic CD8 T lymphocytes were increased in ulcerated lesions, and these lymphocytes injured the oral epithelium, as demonstrated with SPT.^{5,10,14} However, only a few evidence-based studies reported that some substances in toothpastes stimulated RAS pathogenesis, and toothpastes that do not contain probable allergenic substances reduced the number and/or frequency of aphthous ulcers.¹⁸

Some vitamins and hematological parameters have important roles in epithelial keratinization and collagen synthesis, and the relationship between RAS and their deficiencies is well known. Sun et al¹⁹ found significantly lower folic acid, vitamin B₁₂, iron, and hemoglobin levels in patients with RAS than in healthy individuals. Porter et al²⁰ reported that 40% of patients with RAS had low levels of serum ferritin; the cause in half of them was not investigated, and those patients were not directed to the relevant specialist(s). It was also stated that vitamin B₁₂ and ferritin levels should be checked routinely in patients with RAS.²⁰ Therefore, to evaluate the effect of toothpastes on RAS in our study, the study and control groups were analyzed in terms of all aforementioned hematological parameters. Levels of these parameters were within the normal limits, and they were distributed homogeneously.

In a study in which 85 allergens were examined with SPTs in 331 patients with multiple oral mucosal disorders, including RAS, the most common allergens reported were preservatives, metals, and fragrances.¹⁴ Zirwas et al¹¹ examined 80 toothpaste formulations and reported that the most noticeable allergens were menthol among the fragrances; CAPB used as a surfactant and antimicrobial; and triclosan, SLS, and propylene glycol used as preservative agents. SLS is an anionic detergent that has been used as an antibacterial surfactant for many years, providing easy dispersion of toothpaste in the mouth. However, it may lead to the development of ulcers by disrupting the intercellular junctions in the oral mucosa, decreasing the keratinization index, or disrupting the protective mucin barrier with glycoprotein denaturation when used in high concentrations and repetitively.⁶ Shim et al⁶ compared toothpastes containing 1.5% SLS and no SLS and reported that those without SLS significantly reduced ulcer duration and pain score; however, they did not affect the number and frequency of the ulcers. Healy et al¹⁵ performed a double-blind cross-sectional study and reported that use of toothpastes without SLS did not result in any significant change in ulcer patterns, including frequency, duration, and pain. A review

published in 2019 reported that there were not enough data to determine whether SLS-free toothpastes reduced ulcer duration, frequency (episode), pain, or number.¹⁸ In our study, no statistically significant difference was found between the RAS and control groups in terms of positive skin patch reactions for SLS ($P > .05$). The difference of our study from previous studies is that it is the first study to investigate allergen sensitivity at a standardized SPT concentration of SLS 0.25% in patients with RAS.

Lawrence et al¹³ and Zirwas et al¹¹ have emphasized the importance of antibacterial and antiplaque effects of triclosan, SLS, and propylene glycol in the tartar-protective toothpastes, and they reported that those substances might cause ulceration in the mucosa with a type IV hypersensitization. Skaare et al²¹ examined 19 healthy individuals, applied a toothpaste containing triclosan/SLS and zinc and another one containing triclosan/SLS and propylene glycol directly to the skin with occlusion, and reported that the latter was a greater irritant. In our study, no statistically significant difference was found between the RAS and control groups in terms of SPT results of propylene glycol and triclosan ($P > .05$). This may be due to differences in test methods and different concentrations of allergens among studies. In other studies, irritant effects were caused by the application of toothpastes to the skin with direct occlusion. However, the type IV hypersensitivity reaction that seemed to occur with the application of standardized allergens at certain concentrations in the form of SPT was evaluated in our study.

CAPB is an amphoteric synthetic detergent, and it is one of the most commonly used agents in toothpastes owing to its antimicrobial and foaming effects and low potency for irritation.¹¹ However, in recent years, it has been reported that it results in contact hypersensitivity causing a delayed T-cell-mediated type IV hypersensitivity reaction.^{8,11} Herlofson and Barkvoll⁷ investigated the effect of 3 different toothpastes without SLS, CAPB, and detergent on aphthous ulcers in 30 patients with RAS. A much higher aphthous ulcer development frequency was reported in patients using toothpaste containing SLS than in the other 2 groups. In our study, a positive skin reaction for CAPB was found in only 4.8% of the participants, and there was no significant difference between the 2 groups. ($P > .05$).

Menthol is the most commonly used flavoring substance in toothpastes, and it has a potential for causing allergy.¹¹ Prasad et al²² reported that gums containing menthol resulted in cytotoxicity and cell membrane damage in the oral mucosa. Sainio et al²³ reported that among 48 allergens found in toothpaste formulations, menthol and cinnamic aldehyde caused hypersensitivity reactions most frequently. We did not find any statistically significant difference between the study and

control groups in terms of menthol hypersensitivity; however, menthol positivity detected by SPT was higher in the control group (5.6% vs 8.5%, respectively). A number of studies reported that some contents of toothpastes with whitening and antitartar properties, such as peroxide, pyrophosphate, titanium dioxide, and ACH, were highly associated with oral mucosal irritation.^{24,25} Inasmuch as those antitartar agents give a bitter taste to toothpastes, flavoring agents such as menthol are added at higher concentrations, and therefore these allergens are thought to have an increased irritant effect together.²⁶ The relationship between RAS and toothpaste allergens was investigated in our study with a much lower concentration, where the irritant potential was minimalized. There was no difference between 2 groups in terms of titanium dioxide and ACH positivity on the basis of SPT results, and no individuals in the control group had positive reactions for ACH.

Our study suggested that the type IV hypersensitivity reaction to allergens in toothpastes does not play a role in RAS pathogenesis. Various studies reported that intraoral patch tests yielded significant results regarding the relationship of oral mucosal diseases with orally exposed nickel or food additives.^{5,27} However, the oral mucosal patch test is not a standard method, and it has limited use due to difficulties in its application. It has been stated that it can be employed particularly in cases of allergic contact stomatitis when the SPT result is negative.²⁸ Therefore, in order to determine a clearer relationship, a study on a larger population employing an intraoral patch test including other components of the toothpastes is suggested. The allergens that are frequently used in toothpastes were studied as much as our budget allowed in this study. Some other important potential allergens, such as stannous fluoride, L-carvone, balsam of Peru, cinnamic aldehyde, and benzoic acid, were not assessed in the study. The absence of these allergens in the study may be a limitation of our study. We think that if the study had been conducted with a larger panel, we would have been able to find more meaningful values. In addition, rather than establishing a one-way relationship, individuals with positive SPT results may be followed up for clinical improvement for 1 year after recommending an allergen-free toothpaste.

CONCLUSION

RAS is a multifactorial condition, and it is an oral mucosal disease that occurs due to a combination of many factors. The relationship between RAS and toothpaste allergens was evaluated in our study using SPT, but it suggested that the type IV hypersensitivity reaction to allergens in toothpastes does not play a role in RAS pathogenesis.

The limitations of our study may be the inability to exclude some causative factors (eg, food allergy, infectious factors), although we tried our best to exclude major factors in the etiology of RAS. The diagnosis of RAS was established on the basis of clinical findings, and autoimmune or infectious causes were not investigated. In addition, we did not compare the aphthous ulcer subtypes (major, minor, and herpetiform), did not take the severity of SPT reactions into consideration, and performed the study on patients with minor aphthous ulcers. Future studies should consider those limitations in order to further enlighten the factors playing a role in RAS etiology.

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