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Relationship between dietary factors and recurrent aphthous stomatitis in China: a cross-sectional study

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Abstract

Objective: Recurrent aphthous stomatitis (RAS), a common oral mucosal disorder characterized by chronic, inflammatory, and ovoid ulcers, has a complex etiology. The purpose of the study was to investigate the specific dietary factors influencing the prevalence of RAS.

Methods: A total of 754 participants aged 18 to 59 years were enrolled in this descriptive cross-sectional study. An anonymous questionnaire was adopted to investigate the distribution of RAS, dietary factors, self-reported trigger factors, and therapeutic methods.

Results: Among all participants, the prevalence rate of RAS was 21.4%. Univariable analysis showed that fruit, dairy products, vegetables, and water, but not fried foods, fermented foods, spicy foods, and eggs, were preventive factors against RAS. After adjusting for age and sex, multivariable regression analysis suggested that fruit (adjusted odds ratio [aOR] = 0.430, 95% confidence interval [CI] = 0.218–0.847) and water (aOR = 0.294, 95% CI = 0.119–0.726) were protective factors against RAS.

Conclusion: This study found that the consumption of fruit and water was negatively associated with RAS. These results imply a potential adjunctive and complementary role of food in RAS treatment and some feasible means of RAS prevention.

Keywords

Recurrent aphthous stomatitis, dietary habit, cross-sectional study, prevalence, preventive factor, treatment

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Introduction

Recurrent aphthous stomatitis (RAS), or recurrent oral ulceration, is one of the most common oral mucosal disorders, affecting 2% to 66% of the population, according to worldwide epidemiological data.[1] Characterized by multiple small, ovoid, and recurrent ulcers with circumscribed margins, yellowish white or gray floors, and erythematous haloes, RAS can greatly impact the functions of eating, speaking, and swallowing in severe cases.[2,3]

To elucidate the pathogenesis of RAS, researchers have suggested many influencing factors, including genetic factors, immune dysregulation, and stress,[3–6] as well as specific dietary factors.[7–19] It has been reported that cow's milk protein can induce RAS with an increase of anti-fresh cow's milk IgA, IgG, and IgE antibodies in the serum.[7,8] Other studies have suggested that some foods, such as tomatoes, oranges, lemons, and pineapple, can induce a proinflammatory cascade, leading to RAS.[11–13] Additionally, deficiencies of vitamin B12, vitamin D, folic acid, ferritin, and hemoglobin may be involved in keratinocyte proliferation and immune imbalance, thereby inducing RAS.[15–20] We designed this study to explore the potential associations between RAS and several dietary factors that have been suggested to be potential influence factors in the literature or in clinical settings.[7,14]

In this cross-sectional survey, we aimed to collect data regarding RAS incidence, dietary factors, self-reported trigger factors, and therapeutic methods to explore the relationships between RAS and dietary factors. This work can potentially encourage further study of the etiology of and prevention measures against RAS in the clinic.

Methods

Sample size, study design, and participants

A sample size of approximately 700 people was determined using the following formula:

$$N = \frac{U_\alpha^2 \times P_0 \times (1 - P_0)}{D^2}$$

in which N represents the sample size, U_α the Z-score for a given confidence interval ($\alpha = 0.05$, $U_\alpha = 1.96$), P_0 the estimated prevalence ($P_0 = 20\%$),[7] and D the permissible error ($D = 0.15 \times P_0$).

This cross-sectional study was conducted from June 2017 to September 2017. We used a multistage random sampling method to select five districts of Nanjing, China. Four neighborhood communities were randomly chosen from each district. Forty civilians who had resided in the city for at least 1 year were selected from each community. The inclusion criteria were being age 18 to 59 years and having no mental disorders, cognitive impairments, communication disabilities, or illiteracy. In line with previous studies,[7,21] RAS was diagnosed via self-report using a set of diagnostic criteria for RAS (Tables 1 and 2). Symptoms had to meet all major criteria and at least one minor criterion to be considered a definite diagnosis of RAS. Additionally, we excluded participants with oral local trauma factors and systemic disease (including hematinic deficiencies, Crohn disease, Behçet's disease, autoinflammatory disorders, hormonal conditions, diabetes, hypertension, or cardiovascular, renal, gastrointestinal, and liver disease).

Participants were asked to complete an anonymous questionnaire, which was developed on the basis of previous studies, with minor modifications. We collected data

Table 1. Major criteria for RAS

Major criteria	Description
1. Appearance	Multiple, small, ovoid, recurrent ulcers with erythematous haloes, circumscribed margins, and yellow or gray floors.
2. Recurrence	Average of at least one RAS occurrence yearly and recurrence does not affect the same site.
3. Mechanical hyperalgesia	Symptoms of painful lesions and contact with lesions can exacerbate pain.
4. Self-limitation	Ulcers can heal spontaneously without treatment.

RAS, recurrent aphthous stomatitis.

Table 2. Minor criteria for RAS

Minor criteria	Description
1. Family history of RAS	Presence of RAS in at least one first-degree relative
2. Location of ulcers	Non-keratinized oral mucosa
3. Duration	Several days to 2 weeks
4. Precipitating factors	Stress, local trauma, and infections
5. Smoking	Non-smoker

RAS, recurrent aphthous stomatitis.

including demographic information, dietary factors, self-reported trigger factors, and therapeutic methods.[22–28] According to *Dietary Guidelines for Chinese Residents*,[29] daily consumption of fruit, dairy, water, and vegetables was estimated and classified into different levels. Consumption frequencies of other dietary factors were classified into three categories: often (at least 4 times per week), sometimes (1–3 times per week), never, or seldom. Consumption frequencies of eggs were classified into sometimes or often (at least 1 time per week), never, or seldom. In line with *Dietary Guidelines for Chinese Residents*,[29] fruit included drupe, berry, melon, pome, and citrus fruit; dairy included skim/low-fat and whole milk, condensed milk, milk powder, milk tablets, liquid yogurt, curd yogurt, ice cream, cheese, and butter; water included plain water (bottled water and tap water) and beverages (soft drinks, energy drinks, alcoholic drinks, milk, coffee, juice, tea, and other beverages), but not moisture in foods; vegetables included Cruciferae, Umbelliferae, Leguminosae, Solanum, Chenopodiaceae, and Cucurbitaceae. We excluded those participants who did not complete all questions on the questionnaire.

Statistical analysis

The original data from the pencil-and-paper questionnaire were processed and transcribed in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and IBM SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used to set up a database of the results. All categorical variables are described using frequency and percentage. We assessed the validity and reliability of the questionnaire using Cronbach's α, the Kaiser–Meyer–Olkin (KMO) test, and Bartlett's test of sphericity. The difference in sex or age among participants with and without RAS was assessed using chi-square

analysis. Univariable analysis was performed using the crosstab function in SPSS to obtain preliminary results and screen out variables with little evidence of an association. Variables with a p value < 0.05 in the univariable analysis were included in multivariable regression analysis to evaluate the connection between dietary factors and RAS. Multivariable logistic regression was adjusted for age and sex, and statistical significance was defined as $p < 0.05$.

Ethics approval

This study followed the STROBE statement guidelines (Text S1) and was approved by the Ethics Committee of Nanjing Stomatological Hospital (2014NL-002 (KS)).

Results

Reliability and validity of the questionnaire

Cronbach's α for the questionnaire was 0.797, indicating good reliability. The KMO value was 0.883, and the χ^2 value in Bartlett's test of sphericity was 70.598 ($p < 0.05$), suggesting good validity.

Participant characteristics

A total of 754 participants (336 men and 418 women) aged 18 to 59 years were enrolled in this study, with a RAS prevalence of 21.4% (n = 161). The demographics of the participants are summarized in Table 3. There was no significant difference in sex or age among participants with and without RAS in chi-square analysis.

Self-reported trigger factors and therapeutic methods in the RAS group are summarized in Table 4. A total 53.4%, 56.5%, 69.6%, 69.6%, and 78.9% of the RAS group self-reported stress, reduced immune function, irregular life schedule, and unhealthy diet as trigger factors, respectively. The distribution of trigger factors in the various age groups is shown in Figure 1. Nearly half (n = 89, 55.3%) of participants were not undergoing treatment for RAS; 29.2% and 15.5% of participants in the RAS group were using conventional medicine or alternative treatment (AT), respectively.

Associations of dietary factors with RAS

The distribution of RAS prevalence in the groups according to different dietary habits is shown in Figure 2. Table 5 presents preliminary results regarding the relationship between RAS and putative dietary factors in univariable analysis. The findings revealed that RAS was negatively associated with the consumption of fruit (OR = 0.402), dairy (OR = 0.470), water (OR = 0.224), and vegetables (OR = 0.619) ($p < 0.05$). RAS was not significantly associated with other factors, including fried foods, fermented foods, spicy foods, eggs, sex, or age. The significant variables were all included in the multivariable logistic regression, which was adjusted for age and sex (Table 6 and Figure 3). After adjustment for confounders, multivariable logistic regression revealed that RAS was negatively associated with fruit (adjusted odds ratio [aOR] = 0.430, 95% confidence interval [CI] = 0.218–0.847, $p = 0.015$) and water (aOR = 0.294, 95% CI = 0.119–0.726, $p = 0.008$).

Discussion

In this cross-sectional study, we explored the distribution of RAS, dietary factors, self-reported trigger factors, and therapeutic methods among our study population and found a prevalence of 21.4%, in accordance with the literature.[14,30,31] Moreover, fewer than half (72, 44.7%) of participants with RAS had ever received treatment,

Table 3. Participant demographics

		RAS				
	N	Yes (%)	No (%)	OR	95% CI	*p*
Sex						
Male	336	72 (45)	264 (45)	1.000		
Female	418	89 (55)	329 (55)	0.992	0.699–1.408	0.964
Age, years						
18–29	576	117 (73)	459 (77)	1.000		
30–44	114	29 (18)	85 (14)	1.338	0.838–2.137	0.222
45–59	64	15 (9)	49 (8)	1.201	0.651–2.217	0.558

RAS, recurrent aphthous stomatitis; OR, odds ratio; CI, confidence interval.

Table 4. Self-reported trigger factors and the main therapeutic methods in different age groups

	n (%)			
	18–29 (N=117)	30–45 (N=29)	46–59 (N=15)	%
Self-reported trigger factors (multiple answers)				
Stress	64 (55)	14 (48)	8 (53)	53.4
Reduced immune function	61 (52)	19 (66)	11 (73)	56.5
Irregular life schedule	84 (72)	19 (66)	9 (60)	69.6
Unhealthy diet	99 (85)	17 (59)	11 (73)	78.9
Other or none	22 (19)	6 (21)	3 (20)	19.3
Therapeutic methods				
Conventional medicines	30 (26)	10 (35)	7 (47)	29.2
Alternative treatments	14 (12)	7 (24)	4 (27)	15.5
No treatment	73 (62)	12 (41)	4 (27)	55.3

Unhealthy diet: Experienced RAS several hours after consuming high-temperature food, spicy food, fried food, or fermented food.
RAS, recurrent aphthous stomatitis.

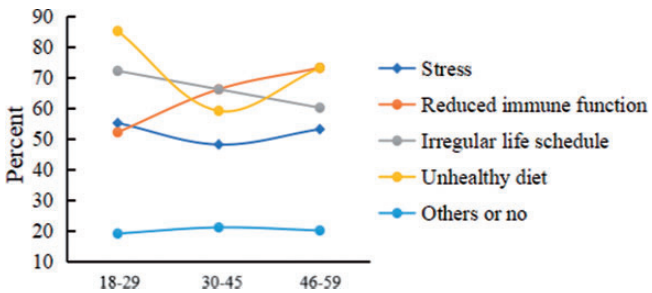

Figure 1. Distribution of trigger factors in the different age groups

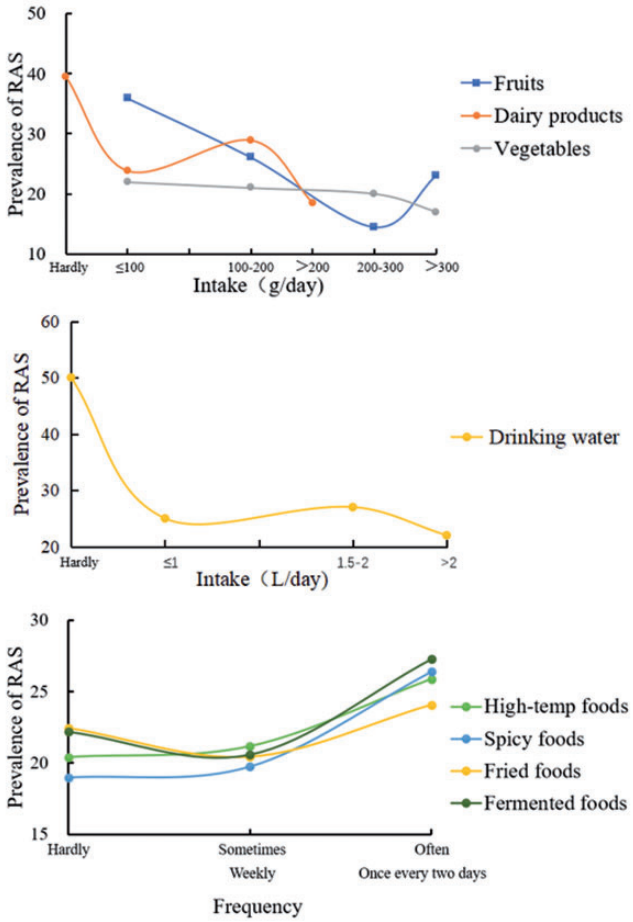

Figure 2. Distribution of rates of recurrent aphthous stomatitis (RAS) in groups with different dietary habits, including consumption of fruit, dairy products, and vegetables (A), water (B), and spicy foods, high-temperature foods, fried foods, and fermented foods (C)

which was lower than the percentage reported in another study.[28,32] Nearly one-third of participants who ever received treatment for RAS mainly used AT versus conventional medicine, despite a lack of randomized controlled trials to prove the effectiveness and safety of AT. Many factors, including the frequency of RAS, can greatly influence patients' choice of therapeutic methods. Further investigation is needed to explore which factors influence therapeutic method choices and the clinical effects achieved among patients with RAS who use AT.

Univariable analysis revealed that RAS was negatively associated with the consumption of fruit, dairy, water, and vegetables ($p < 0.05$). RAS was not significantly associated with other factors, including fried foods, fermented foods, spicy foods, and eggs. Zinc, vitamin B12, and probiotics in dairy products may explain the preventive mechanisms of dairy against RAS.[17,33–40] Several studies reported that

Table 5. Univariable analysis of the relationship between dietary factors and RAS

Variables	RAS (%)	Control (%)	OR	95% CI	*p*
Fruit					
≤100 g	64 (40)	178 (30)	1.000		
>100 g and ≤ 200 g	78 (48)	299 (50)	0.726	0.497–1.060	0.097
>200 g and ≤ 300 g	13 (8)	90 (15)	0.402	0.210–0.768	**0.006**
>300 g	6 (4)	26 (4)	0.642	0.253–1.631	0.351
Dairy					
Hardly ever or never	28 (17)	71 (12)	1.000		
≤100 g	44 (27)	185 (31)	0.603	0.349–1.042	0.070
>100 g and ≤ 200 g	74 (46)	256 (43)	0.733	0.441–1.218	0.231
>200 g	15 (9)	81 (14)	0.470	0.232–0.949	**0.035**
Water					
Hardly ever or never	11 (7)	11 (2)			
≤1000 mL	50 (31)	198 (33)	0.253	0.104–0.616	**0.002**
>1000 mL and ≤ 2000 mL	85 (53)	317 (53)	0.268	0.122–0.640	**0.003**
>2000 mL	15 (9)	67 (11)	0.224	0.082–0.612	**0.004**
Vegetables					
≤100 g	29 (29)	132 (12)	1.000		
>100 g	71 (71)	522 (88)	0.619	0.386–0.993	**0.047**
High-temperature foods					
Never or seldom	70 (43)	273 (46)	1.000		
Sometimes	69 (43)	257 (43)	1.047	0.721–1.521	0.809
Often	22 (14)	63 (11)	1.362	0.784–2.365	0.273
Spicy foods					
Never or seldom	22 (14)	94 (16)	1.000		
Sometimes	87 (54)	354 (60)	1.050	0.624–1.766	0.854
Often	52 (32)	145 (24)	1.532	0.874–2.688	0.137
Fried foods					
Never or seldom	33 (20)	114 (19)	1.000		
Sometimes	102 (63)	397 (67)	0.888	0.569–1.384	0.599
Often	26 (16)	82 (14)	1.095	0.609–1.970	0.761
Fermented foods					
Never or seldom	61 (38)	214 (36)	1.000		
Sometimes	94 (58)	363 (61)	0.908	0.631–1.307	0.605
Often	6 (4)	16 (3)	1.316	0.494–3.507	0.583
Eggs					
Sometimes or often	158 (98)	568 (96)	1.000		
Never or seldom	3 (2)	25 (4)	2.318	0.691–7.777	0.173

Hardly ever or never: less than once a week and the consumption is hard to quantify. Never or seldom: less than once a week. Sometimes: 1–3 times per week. Often: at least 4 times per week.

Boldface values are statistically significant with $p < 0.05$.

RAS, recurrent aphthous stomatitis; CI, confidence interval; OR, odds ratio.

patients with RAS had lower levels of serum zinc as compared with health controls, suggesting a role of zinc in ulcer healing and free-radical scavenging in treating RAS.[36–38] Additionally, vitamin B12 has important roles in DNA synthesis and cell division, and vitamin B12 deficiency may induce oral epithelial atrophy in RAS

Table 6. Multivariable logistic regression of the relationship between dietary factors and RAS

Variable	RAS (%)	Control (%)	Unadjusted OR (95% CI, *p*)	Adjusted OR (95% CI, *p*) [a]
Fruit				
≤100 g	64 (40)	178 (30)	1	1
>100 g and ≤ 200 g	78 (48)	299 (50)	0.756 (0.505–1.132, 0.175)	0.740 (0.491–1.114, 0.149)
>200 g and ≤ 300 g	13 (8)	90 (15)	**0.435 (0.222–0.852, 0.015)**	**0.430 (0.218–0.847, 0.015)**
>300 g	6 (4)	26 (4)	0.755 (0.289–1.970, 0.566)	0.715 (0.269–1.903, 0.502)
Dairy				
Hardly ever or never	28 (17)	71 (12)	1	1
≤100 g	44 (27)	185 (31)	0.682 (0.389–1.197, 0.183)	0.716 (0.403–1.269, 0.252)
>100 g and ≤ 200 g	74 (46)	256 (43)	0.922 (0.539–1.577, 0.765)	0.996 (0.565–1.756, 0.990)
>200 g	15 (9)	81 (14)	0.573 (0.276–1.187, 0.134)	0.632 (0.294–1.358, 0.240)
Water				
Hardly ever or never	11 (7)	11 (2)	1	1
≤1000 mL	50 (31)	198 (33)	**0.290 (0.117–0.717, 0.007)**	**0.294 (0.119–0.726, 0.008)**
>1000 mL and <2000 mL	85 (53)	317 (53)	**0.338 (0.138–0.826, 0.017)**	**0.343 (0.140–0.843, 0.020)**
>2000 mL	15 (9)	67 (11)	**0.277 (0.099–0.773, 0.014)**	**0.276 (0.098–0.777, 0.015)**
Vegetables				
≤100 g	29 (18)	132 (12)	1	1
>100 g	132 (82)	522 (88)	0.697 (0.421–1.152, 0.159)	0.683 (0.412–1.131, 0.138)

Hardly ever or never: food is consumed less than once a week and the consumption is hard to quantify.

[a]Adjusted for age, sex.

Boldface values are statistically significant with $p < 0.05$.

RAS, recurrent aphthous stomatitis; CI, confidence interval; OR, odds ratio.

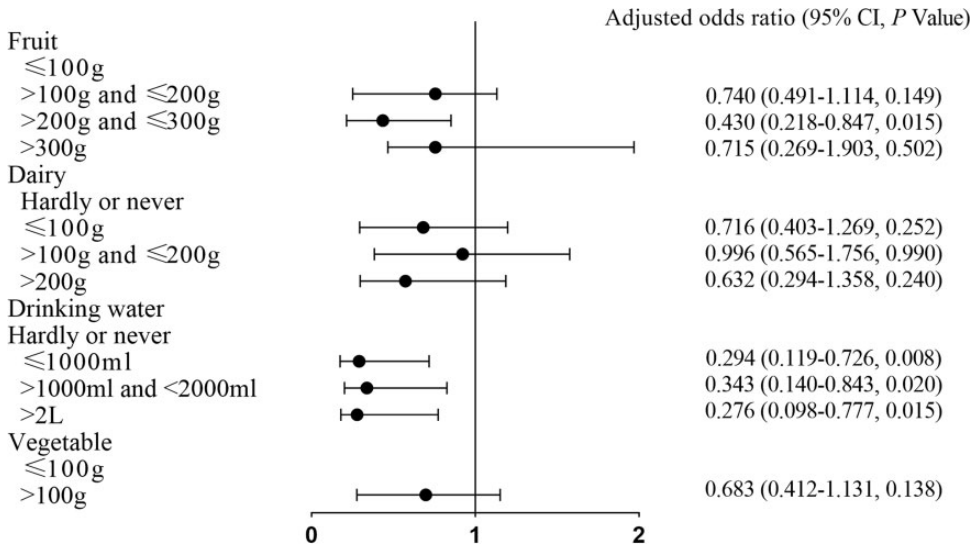

Figure 3. Multivariable logistic regression of the relationship between dietary factors and recurrent aphthous stomatitis
[a]Adjusted for age and sex.

development.[20] Other studies have reported a change in the microbiome in RAS and a treatment effect of a *Lactobacillus* and *Bifidobacterium* composition on RAS.[39,40] Zinc and selenium in vegetables may explain the preventive mechanisms of consuming vegetables in RAS.[40–44] Zinc has been suggested to be involved in the synthesis of protein and collagen, which contribute to wound healing, and selenium supplementation has been associated with a decrement of lipid peroxidation and incidence of infectious complications, as well as better wound healing.[10,41–44]

In our study, multivariable logistic regression showed that RAS was negatively associated with fruit (aOR = 0.430) and water (aOR = 0.294) ($p < 0.05$). It is noteworthy that RAS was first found to be associated with the total consumption of fruit and water in this study. Considering the significant decrease in folate levels among patients with RAS compared with health controls reported in several studies, and the capacity of vitamin C to reduce outbreaks and pain levels in cases of minor-type RAS,[1,5,18,19] fruit may prevent RAS by supplementing folate and vitamin C. Considering the capacity of calcium to protect the oral mucosa and regulate immune capacity by maintaining tissue polarity,[45,46] as well as the capacity of magnesium to reduce both serum nitric oxide and lipid peroxidation to treat ulcers in a mouse model,[47] water may prevent RAS by supplementing calcium and magnesium. Thus, the consumption of certain foods, especially fruit and water, may indirectly influence the risk of RAS by changing the composition of oral microbiota and the blood concentration of nutrients, including vitamin B12, folate, vitamin C, zinc, selenium, calcium, and magnesium.[36–47]

We acknowledge a bias toward a younger population in our study, which might result from a high percentage of students residing in the chosen neighborhood communities. However, considering that no significant association was found between age

and RAS in this study, this bias should not affect the generalizability of our results. Nevertheless, despite our attempts to choose districts representative of different demographic characteristics, our inclusion of participants from only one city leads to some inevitable limitations in terms of generalizability and extrapolation of the results to other urban and rural areas. Additionally, our findings were generated using self-reports, which also led to a lack of the clinical type of RAS. Finally, the variables in this study were general and can be misleading. As nutrients vary greatly among different foods, the effect of these variables on RAS could result from the consumption of certain species of plant foods. Therefore, our results should be interpreted with caution.

Conclusion

The present study findings indicated that consuming fruit and drinking water might be potentially protective against RAS and might be valuable daily preventive measures against RAS. These results could provide new insights into the prevention and treatment of RAS.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Availability of data and materials

The data supporting this study are available from the corresponding author on reasonable request.

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References

1. Yasui K, Kurata T, Yashiro M, et al. The effect of ascorbate on minor recurrent aphthous stomatitis. *Acta Paediatr* 2010; 99: 442–445. DOI: 10.1111/j.1651-2227.2009.01628.x.
2. Giannetti L, Murri Dello Diago A and Lo Muzio L. Recurrent aphtous stomatitis. *Minerva Stomatol* 2018; 67: 125–128. DOI: 10.23736/s0026-4970.18.04137-7.
3. Bilodeau EA and Lalla RV. Recurrent oral ulceration: Etiology, classification, management, and diagnostic algorithm. *Periodontol 2000* 2019; 80: 49–60. DOI: 10.1111/prd.12262.
4. Queiroz S, Silva M, Medeiros AMC, et al. Recurrent aphthous ulceration: an epidemiological study of etiological factors, treatment and differential diagnosis. *An Bras Dermatol* 2018; 93: 341–346. DOI: 10.1590/abd1806-4841.20186228.
5. Chiang CP, Yu-Fong Chang J, Wang YP, et al. Recurrent aphthous stomatitis - Etiology, serum autoantibodies, anemia, hematinic deficiencies, and management. *J Formos Med Assoc* 2019; 118: 1279–1289. DOI: 10.1016/j.jfma.2018.10.023.
6. Saikaly SK, Saikaly TS and Saikaly LE. Recurrent aphthous ulceration: a review of potential causes and novel treatments. *J Dermatolog Treat* 2018; 29: 542–552. DOI: 10.1080/09546634.2017.1422079.
7. Chainani-Wu N and Nayudu A. Resolution of recurrent aphthous ulcers after discontinuation of cow's milk protein intake. *J Am*

Dent Assoc 2017; 148: 614–617. DOI: 10.1016/j.adaj.2017.02.028.
8. Besu I, Jankovic L, Konic-Ristic A, et al. Good tolerance to goat's milk in patients with recurrent aphthous ulcers with increased immunoreactivity to cow's milk proteins. *J Oral Pathol Med* 2013; 42: 523–527. DOI: 10.1111/jop.12052.
9. Shi L, Wan K, Tan M, et al. Risk factors of recurrent aphthous ulceration among university students. *Int J Clin Exp Med* 2015; 8: 6218–6223.
10. Lin KC, Tsai LL, Ko EC, et al. Comorbidity profiles among patients with recurrent aphthous stomatitis: A case-control study. *J Formos Med Assoc* 2019; 118: 664–670. DOI: 10.1016/j.jfma.2018.10.002.
11. Shakeri R, Zamani F, Sotoudehmanesh R, et al. Gluten sensitivity enteropathy in patients with recurrent aphthous stomatitis. *BMC Gastroenterol* 2009; 9: 44. DOI: 10.1186/1471-230x-9-44.
12. Slebioda Z, Szponar E and Kowalska A. Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: literature review. *Arch Immunol Ther Exp (Warsz)* 2014; 62: 205–215. DOI: 10.1007/s00005-013-0261-y.
13. Tarakji B, Baroudi K and Kharma Y. The effect of dietary habits on the development of the recurrent aphthous stomatitis. *Niger Med J* 2012; 53: 9–11. DOI: 10.4103/0300-1652.99822.
14. Du Q, Ni S, Fu Y, et al. Analysis of Dietary Related Factors of Recurrent Aphthous Stomatitis among College Students. *Evid Based Complement Alternat Med* 2018; 2018: 2907812. DOI: 10.1155/2018/2907812.
15. Al-Maweri SA, Halboub E, Al-Sufyani G, et al. Is vitamin D deficiency a risk factor for recurrent aphthous stomatitis? A systematic review and meta-analysis. *Oral Dis* 2019. DOI: 10.1111/odi.13189.
16. Chen H, Sui Q, Chen Y, et al. Impact of haematologic deficiencies on recurrent aphthous ulceration: a meta-analysis. *Br Dent J* 2015; 218: E8. DOI: 10.1038/sj.bdj.2015.100.
17. Al-Amad SH and Hasan H. Vitamin D and hematinic deficiencies in patients with recurrent aphthous stomatitis. *Clin Oral Investig* 2020; 24: 2427–2432. DOI: 10.1007/s00784-019-03102-9.
18. Bao ZX, Shi J, Yang XW, et al. Hematinic deficiencies in patients with recurrent aphthous stomatitis: variations by gender and age. *Med Oral Patol Oral Cir Bucal* 2018; 23: e161–e167. DOI: 10.4317/medoral.21885.
19. Wu YC, Wu YH, Wang YP, et al. Hematinic deficiencies and anemia statuses in recurrent aphthous stomatitis patients with or without atrophic glossitis. *J Formos Med Assoc* 2016; 115: 1061–1068. DOI: 10.1016/j.jfma.2016.10.007.
20. Ozyurt K, Celik A, Sayarlıoglu M, et al. Serum Th1, Th2 and Th17 cytokine profiles and alpha-enolase levels in recurrent aphthous stomatitis. *J Oral Pathol Med* 2014; 43: 691–695. DOI: 10.1111/jop.12182.
21. Al-Omiri MK, Karasneh J, Alhijawi MM, et al. Recurrent aphthous stomatitis (RAS): a preliminary within-subject study of quality of life, oral health impacts and personality profiles. *J Oral Pathol Med* 2015; 44: 278–283. DOI: 10.1111/jop.12232.
22. Nanri H, Yamada Y, Itoi A, et al. Frequency of Fruit and Vegetable Consumption and the Oral Health-Related Quality of Life among Japanese Elderly: A Cross-Sectional Study from the Kyoto-Kameoka Study. *Nutrients* 2017; 9: 1362. DOI: 10.3390/nu9121362.
23. Bradshaw PT, Siega-Riz AM, Campbell M, et al. Associations between dietary patterns and head and neck cancer: the Carolina Head and Neck Cancer Epidemiology Study. *Am J Epidemiol* 2012; 175: 1225–1233. DOI: 10.1093/aje/kwr468.
24. Ma R, Chen H, Zhou T, et al. Effect of bedtime on recurrent aphthous stomatitis in college students. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015; 119: 196–201. DOI: 10.1016/j.oooo.2014.10.014.
25. Gallus S, Bosetti C, Franceschi S, et al. Laryngeal cancer in women: tobacco, alcohol, nutritional, and hormonal factors. *Cancer Epidemiol Biomarkers Prev* 2003; 12: 514–517.
26. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional,

and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1211–1259. DOI: 10.1016/s0140-6736(17)32154-2.
27. Wang H, Dwyer-Lindgren L, Lofgren KT, et al. Age-specific and sex-specific mortality in 187 countries, 1970-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2071–2094. DOI: 10.1016/s0140-6736(12)61719-x.
28. Sawair FA. Recurrent aphthous stomatitis: do we know what patients are using to treat the ulcers? *J Altern Complement Med* 2010; 16: 651–655. DOI: 10.1089/acm.2009.0555.
29. Wang SS, Lay S, Yu HN, et al. Dietary Guidelines for Chinese Residents (2016): comments and comparisons. *J Zhejiang Univ Sci B* 2016; 17: 649–656. DOI: 10.1631/jzus.B1600341.
30. Souza PRM, Duquia RP, Breunig JA, et al. Recurrent aphthous stomatitis in 18-year-old adolescents - Prevalence and associated factors: a population-based study. *An Bras Dermatol* 2017; 92: 626–629. DOI: 10.1590/abd1806-4841.20174692.
31. Ajmal M, Ibrahim L, Mohammed N, et al. Prevalence and psychological stress in recurrent aphthous stomatitis among female dental students in Saudi Arabia. *Clujul Med* 2018; 91: 216–221. DOI: 10.15386/cjmed-840.
32. Vucicevic Boras V and Savage NW. Recurrent aphthous ulcerative disease: presentation and management. *Aust Dent J* 2007; 52: 10–15; quiz 73. DOI: 10.1111/j.1834-7819.2007.tb00459.x.
33. Bahramian A, Falsafi P, Abbasi T, et al. Comparing Serum and Salivary Levels of Vitamin D in Patients with Recurrent Aphthous Stomatitis and Healthy Individuals. *J Dent (Shiraz)* 2018; 19: 295–300.
34. Pontes HA, Neto NC, Ferreira KB, et al. Oral manifestations of vitamin B12 deficiency: a case report. *J Can Dent Assoc* 2009; 75: 533–537.
35. Yıldırımyan N, Özalp Ö, Şatır S, et al. Recurrent Aphthous Stomatitis as a Result of Zinc Deficiency. *Oral Health Prev Dent* 2019; 17: 465–468.
36. Ozturk P, Belge Kurutas E and Ataseven A. Copper/zinc and copper/selenium ratios, and oxidative stress as biochemical markers in recurrent aphthous stomatitis. *J Trace Elem Med Biol* 2013; 27: 312–316. DOI: 10.1016/j.jtemb.2013.04.002.
37. Ozler GS. Zinc deficiency in patients with recurrent aphthous stomatitis: a pilot study. *J Laryngol Otol* 2014; 128: 531–533. DOI: 10.1017/s0022215114001078.
38. Bao ZX, Yang XW, Shi J, et al. Serum zinc levels in 368 patients with oral mucosal diseases: A preliminary study. *Med Oral Patol Oral Cir Bucal* 2016; 21: e335–e340. DOI: 10.4317/medoral.21079.
39. Mimura MAM, Borra RC, Hirata CHW, et al. Immune response of patients with recurrent aphthous stomatitis challenged with a symbiotic. *J Oral Pathol Med* 2017; 46: 821–828. DOI: 10.1111/jop.12621.
40. Yang Z, Cui Q, An R, et al. Comparison of microbiomes in ulcerative and normal mucosa of recurrent aphthous stomatitis (RAS)-affected patients. *BMC Oral Health* 2020; 20: 128. DOI: 10.1186/s12903-020-01115-5.
41. Lin Q, Xie YD, Xie QQ, et al. [Case-control study on risk factors of recurrent aphthous ulcer]. *Shanghai Kou Qiang Yi Xue* 2019; 28: 53–56.
42. Żwierełło W, Styburski D, Maruszewska A, et al. Bioelements in the treatment of burn injuries - The complex review of metabolism and supplementation (copper, selenium, zinc, iron, manganese, chromium and magnesium). *J Trace Elem Med Biol* 2020; 62: 126616. DOI: 10.1016/j.jtemb.2020.126616.
43. Prasad AS. Zinc: role in immunity, oxidative stress and chronic inflammation. *Curr Opin Clin Nutr Metab Care* 2009; 12: 646–652. DOI: 10.1097/MCO.0b013e3283312956.

44. Chasapis CT, Ntoupa PA, Spiliopoulou CA, et al. Recent aspects of the effects of zinc on human health. *Arch Toxicol* 2020; 94: 1443–1460. DOI: 10.1007/s00204-020-02702-9.
45. Lingyong J, Bing F, Lina H, et al. Calcium regulating the polarity: a new pathogenesis of aphthous ulcer. *Med Hypotheses* 2009; 73: 933–934. DOI: 10.1016/j.mehy.2009.06.037.
46. Nagai N, Takeda A, Itanami Y, et al. Co-administration of water containing magnesium ion prevents loxoprofen-induced lesions in gastric mucosa of adjuvant-induced arthritis rat. *Biol Pharm Bull* 2012; 35: 2230–2237. DOI: 10.1248/bpb.b12-00703.
47. Ige AO, Adewoye EO, Okwundu NC, et al. Oral magnesium reduces gastric mucosa susceptibility to injury in experimental diabetes mellitus. *Pathophysiology* 2016; 23: 87–93. DOI: 10.1016/j.pathophys.2016.04.003.