

Evaluation of Serum Zonulin Levels in Patients with Recurrent Aphthous Stomatitis

© Gülsün Hazan Tabak¹, © Ayşen Karaduman¹, © Burçin Şener²

¹Department of Dermatology, Hacettepe University Faculty of Medicine, Ankara, Türkiye

²Department of Clinical Microbiology, Hacettepe University Faculty of Medicine, Ankara, Türkiye

Abstract

Aim: Recurrent aphthous stomatitis (RAS) is an inflammatory disease of the oral mucosa. Recently, it has been emphasized that an impaired intestinal barrier is involved in the development of inflammatory diseases. Zonulin, which reversibly increases intestinal permeability, may be involved in this process. We aimed to reveal the potential effect of intestinal permeability on the etiopathogenesis of RAS by measuring serum levels of zonulin.

Materials and Methods: This prospective case-control study included patients aged 18 to 65 years who were diagnosed with RAS, and a healthy control group. Serum zonulin levels in the groups were evaluated using the enzyme-linked immunosorbent assay.

Results: A total of 78 individuals were included: 27 diagnosed with RAS who had active ulcers, 25 diagnosed with RAS without ulcers, and 26 healthy controls. In the patient groups, serum zonulin levels were significantly higher than that in the healthy control group (127.32 ± 61.52 ng/mL, 121.04 ± 62.88 ng/mL, 89.22 ± 49.51 ng/mL, respectively; $P < 0.05$).

Conclusion: This study has demonstrated that serum zonulin levels are increased in patients with RAS. Increased serum zonulin levels suggest that leaky gut may be an etiological factor in the pathophysiology of RAS. The limitations of our study are the lack of prior research on the topic and the limited sample size.

Keywords: Aphthous ulcer, intestinal barrier function, microbiota, mouth mucosa, permeability

INTRODUCTION

Recurrent aphthous stomatitis (RAS), or RAS, is a chronic inflammatory disease characterized by painful, round ulcers of the non-keratinized oral mucosa that can cause difficulties in eating, swallowing, and speaking. Generally, RAS ulcers are covered by a pseudomembrane and surrounded by an erythematous halo.¹ RAS is slightly more common in children and adults of higher socioeconomic status and affects approximately 20% of the general population at any time.² Several factors have been proposed as possible causative agents. Trauma, psychosocial stress, hematinic deficiencies, microbial factors, and allergies to dietary ingredients are

possible causal agents of RAS in genetically susceptible individuals.^{3,4} Although the etiopathogenesis of the disease remains unclear, autoimmunity has been associated with RAS.^{5,6}

Alterations in intestinal barrier integrity and subsequent impairment of gut permeability have been implicated in various chronic inflammatory diseases, such as celiac disease, inflammatory bowel disease, irritable bowel syndrome, non-alcoholic fatty liver disease, type 1 and type 2 diabetes, obesity, and depression.⁷ Leaky gut increases antigen trafficking by allowing toxins, antigens, and bacteria

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to enter the bloodstream. The combination of immune dysregulation and environmental factors can trigger the onset of autoimmune disease in genetically susceptible individuals.⁸ Intestinal permeability and integrity can be measured in many ways, such as urinary excretion of marker molecules including monosaccharides, disaccharides, and chromium-51 EDTA (51Cr-EDTA), serum or fecal zonulin levels, and cell-culture models.^{8,9} Upregulation of zonulin, a putative physiological modulator of intestinal tract integrity, causes intestinal hyperpermeability and an uncontrolled influx of dietary and microbial antigens.^{7,10} Zonulin is the precursor of haptoglobin-2, and serum zonulin levels can be readily measured by enzyme-linked immunosorbent assay (ELISA).¹¹

In our study, we aimed to investigate the potential effect of intestinal permeability on the etiopathogenesis of RAS by measuring serum levels of zonulin.

MATERIALS AND METHODS

Study Participants

The present prospective case-control study, conducted between November 2021 and January 2022, included patients aged 18–65 years who were diagnosed clinically with RAS and had no chronic systemic or dermatologic disease; RAS patients were divided into two groups according to the presence or absence of an active aphthous ulcer, and a healthy control group without any chronic systemic or dermatologic disease was also included. The minimum sample size was calculated by power analysis to be 19 participants per group, and 75 participants, planned to be grouped as follows, were included in the study.

Group IA: 25 Patients with clinically diagnosed RAS with an active oral ulcer.

Group IB: 25 Patients with clinically diagnosed RAS but without an active oral ulcer.

The healthy control group: A control group of 25 healthy participants without chronic skin disease.

Patients with a 3-year or longer history of regularly recurring episodes of oral aphthous ulceration and at least three ulcers per year for the previous 12 months were included, while those with a history of systemic disease in which oral ulceration may be a feature (such as Behçet's syndrome, coeliac disease, Crohn's disease, or ulcerative colitis); those receiving concurrent systemic steroids, immunomodulatory drugs, or cytotoxic medications; those who used systemic antibiotics, probiotics, or prebiotics in the last 3 months; those on a current specific diet (vegan, vegetarian, or gluten-free);

those with previous gastrointestinal tract surgery; those with malignancy; and those who were pregnant were excluded.

Age, gender, smoking status, duration of breastfeeding, mode of delivery, disease duration, age of onset, and attacks per year were recorded. Disease duration, age at onset, and attacks per year were referred to as the "activity parameters of RAS".

Blood Sample Collection and Laboratory Analysis

Ethical approval for the study was obtained from the Hacettepe University Ethics Committee (approval number: 2021/10-50, date: 04.05.2021). After obtaining written informed consent, blood samples were collected from each participant. One gel vacuum biochemistry tube of blood was collected from each participant. Following coagulation for 45-60 min at room temperature, the serum was separated by cold centrifugation (+4 °C) at 4000 rpm for 10 minutes and then stored at -80 °C until analysis. Serum zonulin level was quantified using a commercial kit (Catalog No. E-EL-H5560, Elabscience) employing a sandwich ELISA with a 3-fold dilution. The measurement range of the kit was 0.78-50 ng/mL, and the sensitivity was 0.47 ng/mL. Serum zonulin values outside the detection range were calculated using a continuous parabolic equation whose R-squared value was closest to 1 in Excel.

Also, hemoglobin, serum ferritin, serum vitamin B12, and serum folate levels were measured in each patient. The normal values accepted for hemoglobin were > 12 g/dL for women and > 13 g/dL for men; serum ferritin, > 9 µg for women and > 18 µg/L for men; serum B12, > 200 ng/L; and folate, 3 µg/L.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences, version 20.0, for Windows. Continuous variables were expressed as mean [\pm standard deviation (SD)], ordinal variables as median (interquartile range), and as numbers and percentages for categorical variables. The normality of the numerical variables was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Independent two-group comparisons for numerical that are normally distributed were performed using independent samples t-test, and one-way ANOVA was used for comparisons of more than two groups. For numerical data that were not normally distributed, the Mann–Whitney U test and the Kruskal–Wallis H test were used. If the conditions for the "chi-square" test were met, the "chi-square" test statistic was used to analyze the categorical variables; otherwise, "Fisher's exact test" was used. Correlation analysis between the two numeric variables was performed using a Pearson or Spearman test, depending on data normality. The "paired samples statistics" or "Wilcoxon" test was used for binary comparisons between dependent

groups. For all analyses, a *P*-value < 0.05 was considered statistically significant, and 95% confidence intervals were reported.

RESULTS

Study Participants

A total of 78 participants, comprising 27 patients with RAS and an active oral ulcer (6 females, 21 males; group IA), 25 patients with RAS without an active oral ulcer (4 females, 21 males; group IB), and 26 healthy controls (6 females, 20 males) were enrolled in the study. In the active oral ulcer group, 15 (56%) patients had only minor aphthae, and 7 (26%) patients had only major aphthae. The remaining 5 patients had both types of oral aphthae. In both patient groups, no history of herpetiform aphthae was reported, and no active herpetiform lesions were observed. The mean age was 36 ± 11.8 (mean ± SD) and 36 ± 13.2 years, respectively, for the patient groups and 33.4 ± 9.4 years for the control group. There were no significant differences between the groups in age and gender (*P* = 0.798 and *P* = 0.792, respectively) (Table 1).

Three patients in group IA, seven in group IB, and nine participants in the control group were current smokers; there was no significant difference in smoking habits between the groups (*P* = 0.120). Other descriptive features of RAS patients are shown in Table 2.

In groups IA and IB, twelve (23.1%) patients were delivered by Caesarean section and 40 (76.9%) by normal vaginal delivery. Four participants in the control group (15.4%) were

delivered by Caesarean section and 22 (84.6%) by normal vaginal delivery. There was no difference in mode of delivery between the groups (*P* = 0.428). The proportion of patients who received breast milk for less than six months was higher in the control group [6 patients (11.5%) in the patient group; 4 patients (15.6%) in the control group]. However, there was no significant difference in the duration of breast milk intake between the groups (*P* = 0.486).

Hematinic Deficiencies in RAS Patients and Healthy Controls

Blood hemoglobin levels were below normal in 2 patients (7.4%) in group IA, 3 patients (12%) in group IB, and 3 patients (11.5%) in the control group (*P* = 0.809). Ferritin levels were below normal in 5 patients (18.5%) in group IA, 6 patients (24%) in group IB, and 5 patients (19.2%) in the control group (*P* = 0.870). Vitamin B12 levels were below normal in group IA (12 patients, 44.4%), group IB (5 patients, 20%), and the control group (10 participants, 18.5%) (*P* = 0.159). Serum folic acid levels were within normal limits in all participants.

Serum Zonulin Levels in RAS Patients and Healthy Controls

The serum zonulin levels of groups IA and IB were found to be significantly higher compared to that in the control group (127.3 ± 61.5 ng/mL, 121 ± 62.9 ng/mL, and 89.2 ± 49.5 ng/mL, respectively; *P* = 0.017 and *P* = 0.049, respectively) (Figure 1). In contrast, there was no significant difference between groups IA and IB (*P* = 0.718).

Table 1. Age and gender of the study participants

	Age (years) Mean ± SD (min-max)	Gender n (%)	
		Female	Male
Group IA	36 ± 11.8 (21-63)	21 (77.8%)	6 (22.2%)
Group IB	36 ± 13.2 (19-61)	21 (84%)	4 (16%)
Control group	33.4 ± 9.4 (20-56)	20 (76.9%)	6 (23.1%)
P-value	0.798	0.792	

SD: Standard deviation, min: Minimum, max: Maximum

Table 2. Descriptive features of RAS patients

	All patients (n = 52)	Group IA (n = 27)	Group IB (n = 25)	P-value
Disease duration (years) median (IQR)	15 (10-25)	15 (10-25)	19 (10-27.5)	0.600
Age of onset (years) median (IQR)	15 (10-22)	16 (9-27)	15 (10-19.5)	0.653
Attacks/per year median (IQR)	7 (4-12)	10 (4-15)	6 (4-10)	0.106

IQR: Interquartile range, RAS: Recurrent aphthous stomatitis

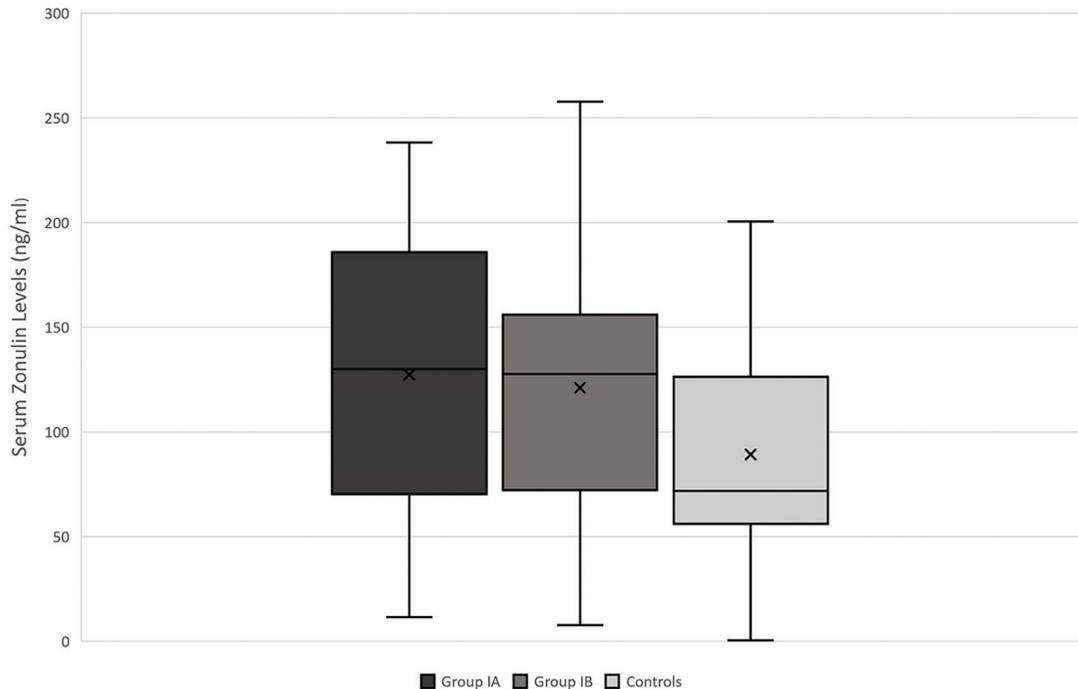


Figure 1. Serum levels of zonulin were significantly higher in the patient groups compared with the healthy controls ($P = 0.046$)

Age ($r_s = -0.028$, $P = 0.805$), smoking status ($P = 0.141$), disease duration ($r_s = -0.108$, $P = 0.444$), age of onset ($r_s = 0.141$, $P = 0.320$), and attacks/per year ($r_s = 0.061$, $P = 0.670$) were not correlated with serum zonulin levels. The results show a significant difference in the serum zonulin levels of females and males, with values of 125.4 ± 61.5 ng/mL and 63.1 ± 58 ng/mL, respectively ($P < 0.001$).

While the mode of delivery and duration of breast milk intake separately did not have an effect on the serum zonulin levels ($P = 0.128$ and $P = 0.830$, respectively), the serum zonulin levels of those who were delivered by vaginal delivery and received breast milk for longer than 6 months were significantly lower than that of those who were delivered by Caesarean section and received breast milk for less than 6 months (101.7 ± 58.8 ng/mL and 154.5 ± 56.6 ng/mL, respectively; $P = 0.045$).

DISCUSSION

Our findings demonstrated that serum zonulin levels were significantly increased in patients with RAS compared with healthy controls, supporting the hypothesis that impaired gut barrier function may be involved in the pathogenesis of RAS.

The tightly packed single-cell-thick epithelial layer of the intestinal mucosa serves an essential role as a “gatekeeper” against large microbial communities and potentially harmful antigens in the lumen. Zonulin, the physiological modulator of intercellular tight junction competence, has been the subject of numerous clinical studies because it may play

a role in the pathogenesis of many chronic inflammatory diseases, including celiac disease, type I diabetes, ankylosing spondylitis, and inflammatory bowel disease, due to its triggering effect on the immune response.¹²⁻¹⁴

Celiac disease is a gluten-sensitive autoimmune enteropathy accompanied by progressive mucosal damage. Lammers et al.¹⁵ conducted an *in vitro* physiological study and identified that gliadin binds to chemokine receptor CXCR3 on intestinal epithelial cells and consequently permits aberrant passage of the possible antigens from the lumen to the mucosa by releasing of zonulin. Drago et al.¹⁶ found that intestinal exposure to gliadin leads to intestinal hyperpermeability in both individuals with and without celiac disease but revealed that the patients with celiac disease exhibit an exaggerated and persistent intestinal zonulin releasing.

Sapone et al.¹⁷ reported that patients with type I diabetes and their first-degree relatives without celiac disease have significantly higher serum zonulin levels compared to age and sex-matched healthy controls and detected that participants’ serum zonulin levels have a positive correlation with intestinal permeability by using lactulose/mannitol urine test.

RAS is one of several chronic, inflammatory, ulcerative diseases of the oral mucosa. Susceptibility to RAS is determined by various DNA polymorphisms, particularly those related to alterations in cytokine metabolism; these cytokines [e.g., interleukin (IL)-1, IL-2, IL-10, IL-12, interferon- γ , and tumor necrosis factor- α] elicit abnormal antigen-presenting

cell function and T-cell activity, and susceptibility is modified by environmental factors.¹⁸⁻²¹ Manthiram et al.²² proposed to define RAS as the mildest form of Behçet's spectrum disorders due to the similarities within pathogenesis and genetic architecture. Fresko et al.²³ demonstrated intestinal hyperpermeability in patients with Behçet's disease without known gastrointestinal manifestations by the determination of ⁵¹Cr-EDTA excretion rate. Increased intestinal permeability in Behçet's disease, independent of gastrointestinal tract involvement, was demonstrated by a sugar absorption test in another study.²⁴ We found that serum zonulin levels were significantly higher in the patient groups, consistent with other studies in several chronic inflammatory disorders. To our knowledge, the present study is the first to investigate the role of intestinal hyperpermeability in patients with RAS.

Our study showed significant differences in serum zonulin levels between females and males. Sex-based immunological differences contribute to variations in the incidence of autoimmune diseases. It is now well established that 80% of autoimmune diseases occur in females, which is compatible with our results. The biallelic overexpression of pseudoautosomal immunomodulatory genes on the X chromosome in females and the effects of sex hormones on innate and adaptive immunity could explain females' susceptibility to autoimmune diseases.^{25,26}

The mode of delivery and diet during infancy (breast milk or formula) play a major role in shaping the healthy gut microbiota that supports intestinal integrity by maintaining its structure and function.²⁷ We demonstrated that vaginal delivery and receiving breast milk for more than 6 months positively affect intestinal permeability.

Sapone et al.¹⁷ demonstrated that serum zonulin levels don't correlate with indicators of glycemic control such as hemoglobin A1c, serum glucose levels, and the age at diagnosis of type 1 diabetes. On the contrary, Szymanska et al.²⁸ revealed that elevation in fecal zonulin is associated with Crohn disease activity, and significantly correlate with fecal calprotectin level. Singh et al.²⁹ observed a correlation between serum zonulin levels and diarrhea severity in patients with diarrhea-predominant irritable bowel syndrome. We did not find a correlation between serum zonulin levels and RAS activity parameters.

Study Limitations

The primary limitation of this study was the small sample size. Although this did not prevent achieving statistically significant results, a larger sample size in future studies will provide more robust evidence regarding the relationship between intestinal hyperpermeability and the activity parameters of RAS.

CONCLUSION

In this study, serum zonulin levels in patients with RAS were significantly higher than those in the control group. The results of the study suggest that leaky gut may play a role in the etiopathogenesis of RAS. Given the paucity of published findings, our findings should prompt further investigations into the role of zonulin in the development of RAS.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Hacettepe University Ethics Committee (approval number: 2021/10-50, date: 04.05.2021).

Informed Consent: After obtaining written informed consent, blood samples were collected from each participant.

Authorship Contributions

Surgical and Medical Practices: G.H.T., A.K., Concept: G.H.T., A.K., Design: G.H.T., A.K., Data Collection or Processing: G.H.T., B.Ş., Analysis or Interpretation: G.H.T., B.Ş., Literature Search: G.H.T., A.K., Writing: G.H.T.

Footnotes

Conflict of Interest: The authors declared that they have no conflict of interest.

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REFERENCES

1. Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. *J Am Dent Assoc.* 2003;134(2):200-207.
2. Natah SS, Kontinen YT, Enattah NS, Ashammakhi N, Sharkey KA, Häyrynen-Immonen R. Recurrent aphthous ulcers today: a review of the growing knowledge. *Int J Oral Maxillofac Surg.* 2004;33(3):221-234.
3. Lau CB, Smith GP. Recurrent aphthous stomatitis: a comprehensive review and recommendations on therapeutic options. *Dermatol Ther.* 2022;35(6):e15500.
4. Slebioda Z, Szponar E, Kowalska A. Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: literature review. *Arch Immunol Ther Exp (Warsz).* 2014;62(3):205-215.
5. Lee YC, Jeong SJ, Eun YG, Song R, Oh IH. Risk of autoimmune diseases in recurrent aphthous ulcer patients: a nationwide population study. *Oral Dis.* 2021;27(6):1443-1450.
6. Lin KC, Tsai LL, Ko EC, Sheng-Po Yuan K, Wu SY. Comorbidity profiles among patients with recurrent aphthous stomatitis: a case-control study. *J Formos Med Assoc.* 2019;118(3):664-670.
7. Fasano A. All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. *F1000Res.* 2020;9:F1000 Faculty Rev-69.

8. Bischoff SC, Barbara G, Buurman W, Ockhuizen T, Schulzke JD, Serino M, Tilg H, Watson A, Wells JM. Intestinal permeability—a new target for disease prevention and therapy. *BMC Gastroenterol.* 2014;14:189.
9. Camilleri M. Leaky gut: mechanisms, measurement and clinical implications in humans. *Gut.* 2019;68(8):1516-1526.
10. Sturgeon C, Fasano A. Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases. *Tissue Barriers.* 2016;4(4):e1251384.
11. Fasano A. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. *Physiol Rev.* 2011;91(1):151-175.
12. Ciccia F, Guggino G, Rizzo A, Alessandro R, Luchetti MM, Milling S, Saieva L, Cypers H, Stampone T, Di Benedetto P, Gabrielli A, Fasano A, Elewaut D, Triolo G. Dysbiosis and zonulin upregulation alter gut epithelial and vascular barriers in patients with ankylosing spondylitis. *Ann Rheum Dis.* 2017;76(6):1123-1132.
13. Wood Heickman LK, DeBoer MD, Fasano A. Zonulin as a potential putative biomarker of risk for shared type 1 diabetes and celiac disease autoimmunity. *Diabetes Metab Res Rev.* 2020;36(5):e3309.
14. Vanuytsel T, Vermeire S, Cleynen I. The role of Haptoglobin and its related protein, Zonulin, in inflammatory bowel disease. *Tissue Barriers.* 2013;1(5):e27321.
15. Lammers KM, Lu R, Brownley J, Lu B, Gerard C, Thomas K, Rallabhandi P, Shea-Donohue T, Tamiz A, Alkan S, Netzel-Arnett S, Antalis T, Vogel SN, Fasano A. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. *Gastroenterology.* 2008;135(1):194-204.e3.
16. Drago S, El Asmar R, Di Pierro M, Grazia Clemente M, Tripathi A, Sapone A, Thakar M, Iacono G, Carroccio A, D'Agate C, Not T, Zampini L, Catassi C, Fasano A. Gliadin, zonulin and gut permeability: effects on celiac and non-celiac intestinal mucosa and intestinal cell lines. *Scand J Gastroenterol.* 2006;41(4):408-419.
17. Sapone A, de Magistris L, Pietzak M, Clemente MG, Tripathi A, Cucca F, Lampis R, Kryszak D, Carteni M, Generoso M, Iafusco D, Prisco F, Laghi F, Riegler G, Carratu R, Counts D, Fasano A. Zonulin upregulation is associated with increased gut permeability in subjects with type 1 diabetes and their relatives. *Diabetes.* 2006;55(5):1443-1449.
18. Chen L, Ke Z, Zhou Z, Jiang X, Zhao Y, Zhang J. Associations of IL-1, 6, and 10 Gene polymorphisms with susceptibility to recurrent aphthous stomatitis: insights from a meta-analysis. *Genet Test Mol Biomarkers.* 2018;22(4):237-245.
19. Bhosale SS, Rajput BS, Takkar H, Bhagat SV, Vagger RM, Shaikh MIK. Establishment of role of IL-2, IL-10 and IL-12 in patients with recurrent aphthous stomatitis—a clinical study. *J Contemp Dent Pract.* 2018;19(10):1242-1245.
20. Najafi S, Yousefi H, Mohammadzadeh M, Bidoki AZ, Farhadi E, Rezaei N. Interleukin-2, interferon-gamma gene polymorphisms in recurrent aphthous stomatitis. *Prague Med Rep.* 2017;118(2-3):81-86.
21. Dalghous AM, Freysdottir J, Fortune F. Expression of cytokines, chemokines, and chemokine receptors in oral ulcers of patients with Behçet's disease (BD) and recurrent aphthous stomatitis is Th1-associated, although Th2-association is also observed in patients with BD. *Scand J Rheumatol.* 2006;35(6):472-475.
22. Manthiram K, Preite S, Dedeoglu F, Demir S, Ozen S, Edwards KM, Lapidus S, Katz AE; Genomic Ascertainment Cohort; Feder HM Jr, Lawton M, Licameli GR, Wright PF, Le J, Barron KS, Ombrello AK, Barham B, Romeo T, Jones A, Srinivasalu H, Mudd PA, DeBiasi RL, Gül A, Marshall GS, Jones OY, Chandrasekharappa SC, Stepanovskiy Y, Ferguson PJ, Schwartzberg PL, Remmers EF, Kastner DL. Common genetic susceptibility loci link PFAPA syndrome, Behçet's disease, and recurrent aphthous stomatitis. *Proc Natl Acad Sci U S A.* 2020;117(25):14405-14411.
23. Fresko I, Hamuryudan V, Demir M, Hizli N, Sayman H, Melikoğlu M, Tunç R, Yurdakul S, Yazici H. Intestinal permeability in Behçet's syndrome. *Ann Rheum Dis.* 2001;60(1):65-66.
24. Koc B, Aymelek S, Sonmez A, Yilmaz MI, Kocar H. Increased sucrose permeability in Behçet's disease. *Rheumatol Int.* 2004;24(6):347-350.
25. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol.* 2016;16(10):626-638.
26. Raza HA, Sen P, Bhatti OA, Gupta L. Sex hormones, autoimmunity and gender disparity in COVID-19. *Rheumatol Int.* 2021;41(8):1375-1386.
27. Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. *World J Gastroenterol.* 2015;21(29):8787-8803.
28. Szymanska E, Wierzbicka A, Dadalski M, Kierkus J. Fecal zonulin as a noninvasive biomarker of intestinal permeability in pediatric patients with inflammatory bowel diseases—correlation with disease activity and fecal calprotectin. *J Clin Med.* 2021;10(17):3905.
29. Singh P, Silvester J, Chen X, Xu H, Sawhney V, Rangan V, Iturrino J, Nee J, Duerksen DR, Lembo A. Serum zonulin is elevated in IBS and correlates with stool frequency in IBS-D. *United European Gastroenterol J.* 2019;7(5):709-715.