



The Role of Stress in Recurrent Aphthous Stomatitis

Nurdiana Nurdiana¹  Putri Welda Utami Ritonga²  Pitu Wulandari³ 

¹ Department of Oral Medicine, Universitas Sumatera Utara, Medan, Indonesia

² Department of Prosthodontics, Universitas Sumatera Utara, Medan, Indonesia

³ Department of Periodontics, Universitas Sumatera Utara, Medan, Indonesia

Address for correspondence Nurdiana Nurdiana, drg., Sp. PM, Department of Oral Medicine, Universitas Sumatera Utara, Abadi Palace B. 19, Tanjung Rejo, Medan, 20122, Indonesia (e-mail: nurdiana@usu.ac.id).

Eur J Gen Dent 2023;12:42–47.

Abstract

Objectives This study aimed to determine the role of stress in recurrent aphthous stomatitis. Stress was examined with the Perceived Stress Scale and cortisol levels; meanwhile, recurrent aphthous stomatitis was assessed with the duration of the lesion.

Materials and Methods This was a cross-sectional analytical study conducted at Oral Medicine Installation, Universitas Sumatera Utara Dental Hospital, and Prodia Laboratory, Medan. The subjects were 50 patients with minor recurrent aphthous stomatitis, without systemic disease, who did not take systemic drugs or use orthodontic appliances. The diagnosis of recurrent aphthous stomatitis was established with anamnesis and clinical examination. Stress was examined by filling out the Perceived Stress Scale questionnaire and blood tests for serum cortisol levels.

Statistical analysis The data were analyzed using the Fisher test and Mann–Whitney *U* test.

Results This study showed no significant relationship between the Perceived Stress Scale category and recurrent aphthous stomatitis, with a *p*-value of 0.392. This study also showed no significant relationship between blood cortisol level and recurrent aphthous stomatitis with a *p*-value of 1.000.

Conclusion Stress may play an important role in recurrent aphthous stomatitis. However, this study did not show any difference in stress examined through the Perceived Stress Scale and cortisol levels based on the duration of recurrent aphthous stomatitis.

Keywords

- ▶ recurrent aphthous stomatitis
- ▶ stress
- ▶ Perceived Stress Scale
- ▶ cortisol level

Introduction

Recurrent aphthous stomatitis is characterized by recurring ulcers confined to the oral mucosa in patients with no other signs of disease.¹ Recurrent aphthous stomatitis is the most common oral mucosal disease that negatively affects the quality of life.^{2,3} Recurrent aphthous stomatitis affects 10 to 30% of the population, and the prevalence in the general population varies from 5 to 66%.^{2,4} The onset of recurrent aphthous stomatitis usually begins in adolescence or as a child. This condition is most common in individuals in their 20s, and its frequency decreases with age.⁵

The exact etiology of recurrent aphthous stomatitis remains unknown.⁴ The main predisposing factors for recurrent aphthous stomatitis are nutritional deficiency, hypersensitivity, drugs, hormones, genetics, local trauma, and stress.^{6,7} Several studies have shown that stress can affect the oral mucosa and cause recurrent aphthous stomatitis. Stress is a complex biological reaction whose mechanism is not fully understood.⁸ Stress may play an essential role in causing recurrent aphthous stomatitis, but the relationship between stress and the occurrence of oral pathology is still unclear.⁹ Stress levels can be evaluated clinically using a

article published online
April 21, 2023

DOI <https://doi.org/10.1055/s-0043-1768062>.
ISSN 2320-4753.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

questionnaire, such as the Perceived Stress Scale, and a blood test by examining the cortisol level in the blood.⁷

Correct diagnosis of recurrent aphthous stomatitis is crucial to determining the treatment of recurrent aphthous stomatitis, which is based on a complete history and clinical findings of ulcers, as well as laboratory examination if suspected to be related to a systemic condition.^{2,10} Therefore, this study aimed to determine the role of stress in recurrent aphthous stomatitis, which was examined with the Perceived Stress Scale questionnaire and blood cortisol levels.

Materials and Methods

This was an analytical study with a cross-sectional approach conducted at the Oral Medicine Installation at the Universitas Sumatera Utara Dental Hospital and Prodia Clinical Laboratory Medan. Diagnosis of recurrent aphthous stomatitis and Perceived Stress Scale examination was carried out at the Oral Medicine Installation at the Universitas Sumatera Utara Dental Hospital, and cortisol level examination was carried out at the Prodia Clinical Laboratory.

The study involved 50 individuals with recurrent aphthous stomatitis. The sampling method in this study was nonprobability sampling with the purposive sampling method. All subjects who met the inclusion and exclusion criteria were included. The inclusion criteria include individuals with minor type recurrent aphthous stomatitis, individuals who do not have a systemic disease or take any drug, individuals who do not use orthodontic appliances, and individuals who volunteered to be a study subject.

Recurrent aphthous stomatitis is diagnosed with anamnesis and clinical examination. Anamnesis was done to determine the recurrence of recurrent aphthous stomatitis, and a clinical examination was done to examine the ulcer. The Perceived Stress Scale was analyzed using a questionnaire consisting of 10 questions to assess stress levels and was compiled using a rating scale. The answers used a 5-point Likert scale interval value: 0 = never, 1 = rarely, 2 = sometimes, 3 = quite often, and 4 = very often. Questions stating negative responses (question numbers 4, 5, 7, and 8) were scored in reverse with a score of 0 = 4, 1 = 3, 2 = 2, 3 = 1, and 4 = 0. The overall score obtained was the total score of 10 questions with scores ranging from 0 to 40. A score of 0 to 13 indicated mild stress, a score of 14 to 26 indicated moderate stress, and a score of 27 to 40 indicated severe stress.^{11,12} After that, blood samples of all the patients were taken. A blood (serum) sample was obtained early morning (7–9 a. m.). Professional analysts in the laboratory then analyzed the blood sample.

The data obtained were then analyzed. The relationship between the Perceived Stress Scale scores and the duration of recurrent aphthous stomatitis was analyzed with the Mann–Whitney *U* test. Meanwhile, the relationship between serum cortisol levels and the duration of recurrent aphthous stomatitis was analyzed with Fisher's tests. Data analysis was done with IBM SPSS Statistics Software, version 22.

Results

The results of this study indicated that most of the patients (37 [74%]) were in late adolescence (17–25 years). Five (10%) patients were in their early adolescence (12–16 years). Meanwhile, early adulthood (26–35 years) and late adulthood (36–45 years) accounted for 4 (8%) patients each (►Fig. 1).

This study also showed that 35 (70%) patients with recurrent aphthous stomatitis were females and 15 (30%) patients were males (►Fig. 2).

►Fig. 3 shows the duration of recurrent aphthous stomatitis. Forty (80%) patients experienced recurrent aphthous stomatitis for less than 7 days, and 7 (20%) patients experienced recurrent aphthous stomatitis for more than 7 days.

In this study, the highest percentage of patients' Perceived Stress Scale category was moderate, consisting of 37 (74%) patients. Meanwhile, 11 (22%) patients were in the mild category and 2 (4%) patients were in the severe category (►Fig. 4).

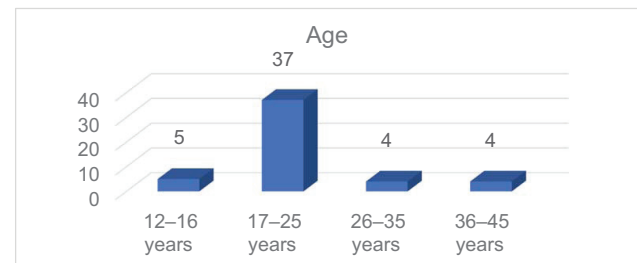


Fig. 1 Distribution of the patients according to age.

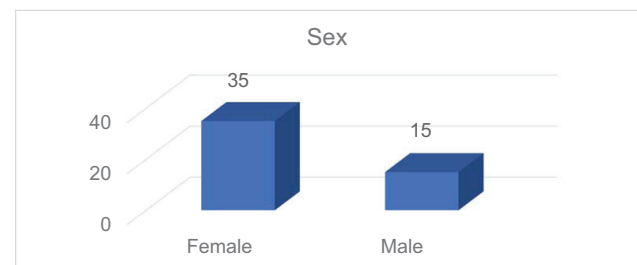


Fig. 2 Distribution of the patients according to sex.

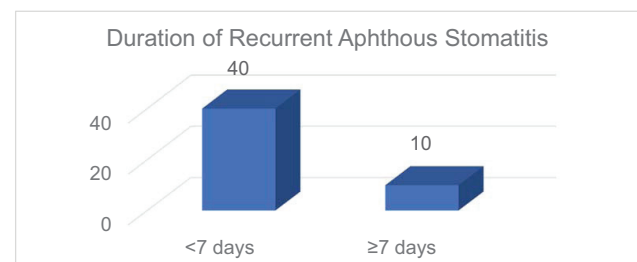


Fig. 3 Distribution of the patients according to the duration of recurrent aphthous stomatitis.

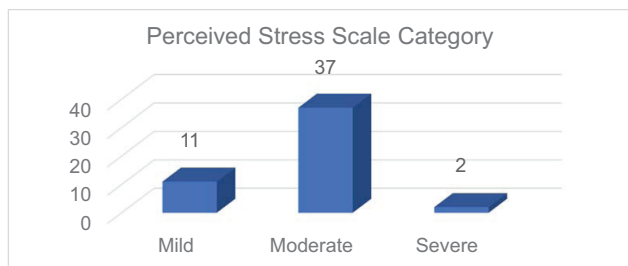


Fig. 4 Distribution of the Perceived Stress Scale category in recurrent aphthous stomatitis patients.

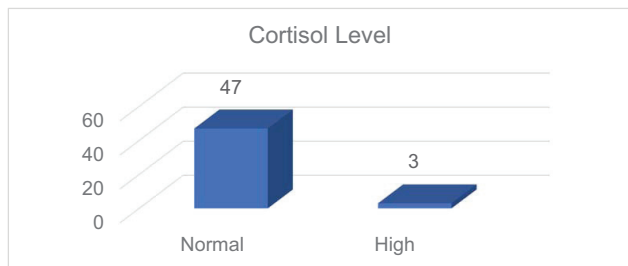


Fig. 5 Distribution of cortisol level in recurrent aphthous stomatitis patients.

► **Fig. 5** shows the distribution of cortisol levels of patients in this study. It was found that 47 (94%) patients had normal cortisol levels and 3 (6%) had high cortisol levels.

► **Table 1** shows the relationship between stress measured with the Perceived Stress Scale questionnaire and the duration of recurrent aphthous stomatitis. There was no significant relationship between the Perceived Stress Scale category and recurrent aphthous stomatitis, with a *p*-value of 0.392 (*p* > 0.05).

► **Table 2** shows the relationship between stress measured with blood cortisol level and the duration of recurrent

aphthous stomatitis. There was no significant relationship between blood cortisol level and recurrent aphthous stomatitis with a *p*-value of 1.000 (*p* > 0.05).

Discussion

Recurrent aphthous stomatitis can occur in adolescence or even during childhood. Taheri et al revealed that 87% of recurrent aphthous stomatitis patients were in the age group of 22 to 25 years.¹¹ The results of this study indicate that the most of the patients with recurrent aphthous stomatitis were in late adolescence (17–25 years), and the incidence decreases with age. This study was in accordance with the finding of Rajmane et al, which showed that the most commonly affected age group with recurrent aphthous stomatitis was 20 to 29 years (56.9%), and the prevalence decreased with age.¹² Kaur et al assessed the prevalence of recurrent aphthous stomatitis in the North Indian population; the study showed that 60% of the patients with recurrent aphthous stomatitis were in the age group of 20 to 30 years.¹³ Studies showed that 80% of recurrent aphthous stomatitis patients experienced this disorder for the first time before the age of 30 years; the peak is in their 20s. The frequency will decrease with increasing age.^{5,14} The percentage of affected patients decreases after the third decade of life.¹⁵

Studies have shown that in children and adults affected by recurrent aphthous stomatitis, the incidence of this disorder is higher in females than in males.^{15–17} In relation to the female predisposition to recurrent aphthous stomatitis, some authors have suggested that this association is related to hormonal rates. The study by Hedge et al, which investigated the prevalence of recurrent aphthous stomatitis, shows females had a slight predominance compared to males, with females at 51.6% and males at 48.4%.¹⁸ This result is consistent with the results of this study, where there

Table 1 Relationship between Perceived Stress Scale category and duration of recurrent aphthous stomatitis

Duration of recurrent aphthous stomatitis	Perceived Stress Scale category						<i>p</i> value
	Mild		Moderate		Severe		
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
<7 d	8	72.7	30	81.1	2	100	0.392
≥7 d	3	27.3	7	18.9	0	0	

Table 2 Relationship between cortisol level and duration of recurrent aphthous stomatitis

Duration of recurrent aphthous stomatitis	Cortisol level				<i>p</i> value
	Normal		High		
	<i>n</i>	%	<i>n</i>	%	
<7 d	37	78.7	3	100	1.000
≥7 d	10	21.3	0	0	

were more female patients than male patients. Moreover, the study by Rathod et al also showed that the prevalence of recurrent aphthous stomatitis was higher in females (85.9%) than in males (14.09%).¹⁹ Queiroz et al also showed that out of 68 recurrent aphthous stomatitis cases, 59.2% were females and 40.8% were males.²⁰

In this study, the duration of recurrent aphthous stomatitis was mostly less than 7 days. This finding is consistent with that in the study by Kamil et al, according to which the duration of ulcers was most commonly 2 to 5 days (73.7%), followed by more than 5 days (21.9%), and more than 7 days (4.4%).²¹ These findings are similar to a study conducted by Rathod et al, which concluded that the ulcers healed within 2 to 5 days in most patients (96.36%).¹⁹ Meanwhile, this study is slightly different from the study by Hedge et al¹⁸ and Rodriguez-Archilla et al.²² Hedge et al recorded that ulcers healed in less than 1 week in 46.2% of patients, in 1 to 2 weeks in 38% of patients, and in more than 2 weeks in 15.8% of patients.¹⁸ In the study by Rodriguez-Archilla et al comprising 200 individuals with recurrent aphthous stomatitis, 49% of lesions healed in less than 7 days and 51% in more than 7 days.²² The duration required for healing of the ulcer depends on the type of ulcer. The process of oral ulcer healing involves four phases: hemostasis, inflammation, proliferation, and remodeling.²³ In the hemostasis stage, blood vessels restrict blood flow, and platelets stick together to seal the wound. Then, threads of fibrin reinforce the seal through a process called coagulation.²⁴ At the inflammation stage, cytokine proinflammatory and reactive oxygen species persistently increase, causing elevated oxidative and inflammatory stress.²³ The repair process starts by removing damaged cells and bacteria.²⁴ During the proliferation stage, a process of re-epithelialization strongly correlated to angiogenesis occurs, which supports epithelial layer contraction in wounds.²³ Cells from the wound's edges move across the opening to close the wound. In the remodeling (maturation) stage, maturation occurs when collagen is remodeled, and the wound fully closes. Any cells used to repair the wound that is no longer needed are removed by a process called apoptosis.²⁴ In minor recurrent aphthous stomatitis, ulcers heal within 7 to 14 days and may last up to 21 days in each episode.²⁵

The etiology and pathogenesis of recurrent aphthous stomatitis so far have remained elusive.²⁶ Stress can be defined as a person's psychological and mental reactions that various situations can cause. Stress is part of the human lifestyle. Stress can help achieve one's goals, but on the other hand, prolonged stress can negatively impact one's physical and mental health and performance. Stress can also increase the incidence of systemic diseases and affect oral health.^{9,27}

This study assessed the stress level using the Perceived Stress Scale. It is one of the most widely used psychological instruments for measuring the perception of stress. It measures the degree to which situations in one's life are appraised as stressful. The assessment instrument shows adequate reliability and validity in assessing a person's psychological stress condition.³ The results in this study align with the study conducted by Purnami et al, which showed that most

patients had moderate stress levels. The results showed that 75.8% of subjects had moderate stress levels, 22.9% had mild stress levels, and only 3% had severe stress levels.²⁸

Stress levels can also be evaluated through blood tests, such as the level of cortisol in the blood.⁷ Cortisol is a critical hormone in reaction to stress.²⁹ Stress can cause an increase in salivary cortisol levels and affect immunoregulatory activity causing inflammation by increasing the number and activity of leukocytes, causing various changes in the oral cavity.³⁰ In humans, stress and anxiety levels can be identified with free blood and salivary cortisol.³

Anxiety and stress are widely accepted as important etiological factors in recurrent aphthous stomatitis since patients often associate personal problems related to their work or home circumstances with the onset of periods of ulceration.¹⁴ When stress factors occur continuously, a person will easily experience stress, making it easier to experience chronic diseases related to the immune system, such as recurrent aphthous stomatitis.²⁸ Stress always leads to decreased immunity, characterized by increased glucocorticoid secretion.³¹ Physiologically, stress triggers the stimulation of two main systems: the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Activation of the HPA axis leads to the secretion of cortisol. Cortisol is a well-known stress hormone released from the cortex of the adrenal gland. It mediates several vital functions, such as regulating carbohydrates, protein, and fat metabolism, maintaining vascular reactivity, and regulating blood cell numbers.²⁹ Although the pathogenesis is unclear, the continuous increases in cortisol levels under stressful conditions may lead to increased inflammatory activity by inducing immune dysfunction, which in turn triggers recurrent aphthous stomatitis with a higher chance of recurrence.² Epidemiological studies have suggested that emotional stress may be a precipitating factor for recurrent aphthous stomatitis. Still, stress is unlikely to be the direct cause of ulceration and, in any event, is very difficult to quantify.³²

This study showed no significant relationship between the Perceived Stress Scale category and recurrent aphthous stomatitis. The results were in line with Bilal et al's study regarding the examination of anxiety and depression levels in 50 recurrent aphthous stomatitis patients and 50 patients without recurrent aphthous stomatitis using the Spielberger Perceived Stress Scale and Spielberger State-Trait Anxiety Inventory, which showed there was no significant difference in the Spielberger Perceived Stress Scale scores of the study subjects.³⁰ Stressful situations can cause a transitory increase of salivary cortisol and stimulate immunoregulatory activity by increasing the number of leukocytes in inflammatory sites, which are often observed during the pathogenesis of mouth ulcers. However, the exact mechanism of how stress-related mood instability and subjective well-being triggers mouth ulcers remains to be elucidated.³³ Thus, further study needs to be done because this study also showed no significant relationship between cortisol levels and recurrent aphthous stomatitis.

The role of stress in recurrent aphthous stomatitis episodes is still unclear.³⁴ Although the literature mentions

anxiety and stress as potential etiologic factors for developing recurrent aphthous stomatitis, this association remains controversial.²⁶ Stress has also been documented as a triggering factor for the development of recurrent aphthous stomatitis, but the exact underlying mechanism remains unclear and controversial.²⁹ Onset of the ulcer may be attributed to elevated salivary cortisol levels in the saliva.³⁴ A more recent study showed that stressful life events were significantly associated with the onset of recurrent aphthous stomatitis episodes but not with the duration of the episodes.³¹ Huling et al assessed the effect of stressful life events on the onset and duration of recurrent aphthous stomatitis. They found that stressful life events did not affect the duration of recurrent aphthous stomatitis episodes ($p=0.73$). Their finding indicates that stress is involved with the initiation of a recurrent aphthous stomatitis episode.³⁵

Conclusions

Stress is one of the etiologic factors of recurrent aphthous stomatitis, but the exact mechanism remains unclear. This study showed no significant relationship between the Perceived Stress Scale category and cortisol levels with recurrent aphthous stomatitis. Therefore, the dentist must always examine all the etiological factors that can cause recurrent aphthous stomatitis.

Consent

Informed consent was obtained from the subjects after explaining the research objective, voluntary participation, the right to autonomy and confidentiality, and the right to withdraw from the study.

Ethical Approval

The Research Ethics Committee of Universitas Sumatera Utara approved the study for health research (No. 732/KEP/US/2021) in 2021. The ethics committee also ensured the ethical conduct of the study.

Author Contributions

N.N. conceived, designed, provided materials, conducted the study, and collected and organized the data. P.W.U.R. provided logistic support and collected data. N.N. and P.W. collected, analyzed, and interpreted the data. All the authors were involved in writing the initial and final draft of the manuscript. All the authors have critically reviewed and approved the final draft and are responsible for the manuscript's content and similarity index.

Conflict of Interest

None declared.

References

- 1 Woo SB, Setterfield JF, Greenberg MS. Ulcerative, vesicular, and bullous lesions. In: Glick M, Greenberg MS, Lockhart PB, Challacombe SJ, eds. *Burket's Oral Medicine*. 13th ed. Hoboken, NJ: Wiley-Blackwell; 2021:52–57
- 2 Chiang CP, Yu-Fong Chang J, Wang YP, Wu YH, Wu YC, Sun A. Recurrent aphthous stomatitis - Etiology, serum autoantibodies, anemia, hematinic deficiencies, and management. *J Formos Med Assoc* 2019;118(09):1279–1289
- 3 Karaer IC, Urhan A, Reyhani I. Stress and recurrent aphthous stomatitis. *Med Sci (Turkey)* 2020;9(01):170–174
- 4 Laskaris G. *Pocket Atlas of Oral Diseases*. 3rd ed. Stuttgart: Georg Thieme; 2020:178–180
- 5 Ślebioda Z, Dorocka-Bobkowska B. Systemic and environmental risk factors for recurrent aphthous stomatitis in a Polish cohort of patients. *Postepy Dermatol Alergol* 2019;36(02):196–201
- 6 Ajmal M, Ibrahim L, Mohammed N, Al-Qarni H. Prevalence and psychological stress in recurrent aphthous stomatitis among female dental students in Saudi Arabia. *Clujul Med* 2018;91(02):216–221
- 7 Dalessandri D, Zotti F, Laffranchi L, et al. Treatment of recurrent aphthous stomatitis (RAS; aphthae; canker sores) with a barrier forming mouth rinse or topical gel formulation containing hyaluronic acid: a retrospective clinical study. *BMC Oral Health* 2019;19(01):153
- 8 Kunikullaya U K, Kumar M A, Ananthkrishnan V, Jaisri G. Stress as a cause of recurrent aphthous stomatitis and its correlation with salivary stress markers. *Chin J Physiol* 2017;60(04):226–230
- 9 Sharma M, Gupta R, Singh S. Correlation of psychological stress with recurrent aphthous stomatitis among dental students in an educational institution. *Int J Appl Dent Sci* 2017;3(04):455–458
- 10 Tarakji B, Gazal G, Al-Maweri SA, Azzeghaiby SN, Alaizari N. Guideline for the diagnosis and treatment of recurrent aphthous stomatitis for dental practitioners. *J Int Oral Health* 2015;7(05):74–80
- 11 Taheri MH, Eshraqi AM, Anwari A, Stanikzai AM. Prevalence of recurrent aphthous ulcers among dentistry students' in Kabul, Afghanistan: a questionnaire-based study. *Clin Cosmet Investig Dent* 2022;14:275–279
- 12 Rajmane YR, Ashwinirani SR, Suragimath G, Nayak A, Rajmane VS, Lohana M. Prevalence of recurrent aphthous stomatitis in western population of Maharashtra, India. *J Oral Res Rev* 2017;9:25–28
- 13 Kaur R, Behl AB, Punia RS, Nirav K, Singh KB, Kaur S. Assessment of prevalence of recurrent aphthous stomatitis in the North Indian Population: a cross-sectional study. *J Pharm Bioallied Sci* 2021;13(Suppl 1):S363–S366
- 14 Okoh M, Ikechukwu O. Presentation of recurrent aphthous ulcer among patients in a tertiary hospital. *African J Oral Health*. 2019;8(02):8–12
- 15 Mirowski GW. Aphthous stomatitis. Accessed July 22, 2022 at: <https://emedicine.medscape.com/article/1075570>
- 16 Ghom AG, Ghom SA, eds. *Textbook of Oral Medicine*. 3rd ed. New Delhi: Jaypee Brother Medical Publishers (P) Ltd; 2014:359–363, 858–859
- 17 Thoppay JR. Aphthous ulcers. Accessed July 22, 2022 at: <http://emedicine.medscape.com/article/867080>
- 18 Hedge S, Harini K, Ajila V, Babu S, Shetty SR. Prevalence of recurrent aphthous stomatitis: an institutional study. *Cumhuriyet Dent J* 2015;18(03):228–234
- 19 Rathod U, Kulkarni S, Agrawal V. Prevalence of recurrent aphthous ulcers in dental student: a questionnaire based study. *Int J Health Sci Res* 2017;12:80–83
- 20 Queiroz SIML, Silva MVAD, Medeiros AMC, Oliveira PT, Gurgel BCV, Silveira ÉJDD. Recurrent aphthous ulceration: an epidemiological study of etiological factors, treatment and differential diagnosis. *An Bras Dermatol* 2018;93(03):341–346
- 21 Kamil WNW, Amirham IQ, Omar MAH, Zainal M. Self-reported prevalence of recurrent aphthous stomatitis among UiTM dental students. *Compendium Oral Sci* 2022;9(02):54–62

- 22 Rodríguez-Archilla A, Raissouni T. Clinical study of 200 patients with recurrent aphthous stomatitis. *Gac Med Mex* 2018;154(02):165–171
- 23 Surboyo MDC, Mahdani FY, Ernawati DS, Sarasati A, Rezkita F. The macrophage responses during diabetic oral ulcer healing by liquid coconut shell smoke: an immunohistochemical analysis. *Eur J Dent* 2020;14(03):410–414
- 24 Colgate. Granulation tissue and healing oral wounds. Accessed July 22, 2022 at: <https://www.colgate.com/en-us/oral-health/mouth-and-teeth-anatomy/granulation-tissue-and-wound-healing-in-the-mouth>
- 25 Susanto H, Kendarwati P, Imanusti K, Widyaningsih L, Budiarti S, Supriatno. Decreased salivary cortisol in recurrent aphthous stomatitis treated with topical steroids. *J Islamic Dent Assoc IRAN (JIDAI)* 2019;31(01):26–32
- 26 Vandana S, Kavitha B, Sivapathasundharam B. Salivary cortisol and dehydroepiandrosterone as oral biomarkers to determine stress in patients with recurrent aphthous stomatitis. *J Oral Maxillofac Pathol* 2019;23(02):213–217
- 27 Kristina SA, Widayanti AW, Sari IP. Investigating perceived stress among final-year pharmacy students in Indonesia. *Int J Pharma Res* 2020;12(02):439–444
- 28 Purnami CT, Ari S, Dian Ratna S, et al. Psychometric measurement of perceived stress among midwives at primary health care Province of Central Java Indonesia. *Indian J Public Health Res Dev* 2019;10(03):804–809
- 29 Madkour GG, El Refaie I. Salivary levels of α -amylase & cortisol in patients with recurrent aphthous ulceration. *Egypt Dent J* 2018;64:2391–2397
- 30 Bilal N, Karakus MF, Varkal MD, Boztepe OF, Bilal B, Sarıca S. An assessment of the levels of anxiety and depression in patients with recurrent aphthous stomatitis. *Arch Otolaryngol Rhinol*. 2016;2(01):1–5
- 31 Nur'aeny N, Gurnida DA, Suwarsa O, Sufiawati I. Serum level of IL-6, reactive oxygen species and cortisol in patients with recurrent aphthous stomatitis related imbalance nutrition intake and atopy. *J Math Fund Sci* 2020;53(03):286–296
- 32 Robinson M, Hunter K, Pemberton M, Sloan P. Soames'and Southam's Oral Pathology. 5th ed. Oxford: Oxford University Press; 2018:38–40
- 33 Wang K, Ding L, Yang C, Hao X, Wang C. Exploring the relationship between psychiatric traits and the risk of mouth ulcers using bi-directional Mendelian randomization. *Front Genet* 2020;11:608630
- 34 Thevara MC, Shilpashree KB, Murthy AK, Madhusudhan S, Khond M, Coutinho DA. Prevalence of recurrent aphthous stomatitis and its association with stress among undergraduate students in a dental institution: a cross sectional study. *Int J Appl Dent Sci* 2020;6(03):458–462
- 35 Huling LB, Baccaglioni L, Choquette L, Feinn RS, Lalla RV. Effect of stressful life events on the onset and duration of recurrent aphthous stomatitis. *J Oral Pathol Med* 2012;41(02):149–152