INDONESIAN JOURNAL OF DENTISTRY
Faculty of Dentistry Universitas Muhammadiyah Semarang

CORRELATION BETWEEN SALIVARY CORTISOL LEVELS IN PATIENTS WITH PSYCHOLOGICAL STRESS AND INCIDENCE OF RECURRENT APHTHOUS STOMATITIS: A SCOPING REVIEW

Fiki Muhammad Ridho[1], Aufa Alma'as Nabila Maulidina[1], Bella Pardian Nur Allifiah[2]
[1]*Faculty of Dentistry, Universitas Airlangga, Surabaya, Indonesia*
[2]*Faculty of Dentistry, Universitas Muhammadiyah Yogyakarta, Yogyakarta, Indonesia*

Correspondence: fikimuhammadridho@gmail.com

Received February 5th, 2024; 1st revision March 27th, 2024; 2nd revision March 28th, 2024; Accepted March 29th, 2024; Published online April 2nd, 2024.

Keywords:

Aphthous, Cortisol, Recurrent Aphthous Stomatitis, Saliva, Stress

Indonesian Journal of Dentistry
Volume 4 No 1 Issue 3 Year 2024 Pages 22-33
URL https://jurnal.unimus.ac.id/index.php/IJD
DOI http://dx.doi.org/10.26714/ijd.v4i1.14026

ABSTRACT

Background: The etiology of recurrent aphthous stomatitis (RAS) is still unclear, but psychological stress is thought to contribute to the occurrence of RAS. One of the biomarkers for evaluating psychological stress levels is through measuring salivary cortisol levels. This scoping review aims to review and evaluate the correlation between salivary cortisol levels in individuals with psychological stress and an increased incidence of RAS.
Methods: A scoping review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines through databases on PubMed, ScienceDirect, Scopus, ProQuest, and Google Scholar until November 2023. All included studies discussed salivary cortisol levels in RAS patients and controls.
Results: Eleven of the twelve studies showed an increase in salivary cortisol levels in RAS patients compared with the control group, with eight of them having a statistically significant increase. In addition, eight studies evaluated the level of psychological stress in respondents, seven of which concluded that there was an increase in stress levels in RAS patients with five of them showing a statistically significant increase.
Conclusion: In conclusion, the present study concludes that there is a correlation between increased salivary cortisol levels in individuals with psychological stress and an increased incidence of RAS.

INTRODUCTION

Recurrent aphthous stomatitis (RAS), commonly referred to as canker sores, represents a persistent inflammatory ailment affecting oral cavity in the form of painful, recurring ulcers that can arise as a result of the disease process.[1] RAS affects between 8.3-47.2%,[2–4] but the prevalence of RAS varies between 5-60%.[5] Based on size, number and duration, RAS is categorized into three distinct types, namely minor RAS (70-85%), major RAS (10%), and herpetiform RAS (<10%).[6] Typically, RAS is characterized by the presence of a circular or oval-shaped ulcer, coated with a yellowish white fibro-membrane layer, surrounded by an erythema halo, and tends to cause pain.[7] The etiology of RAS

is still uncertain; however, several factors have been linked to the RAS occurrence, including genetic factors, local injury, bacteria and viruses, food hypersensitivity, vitamin and micronutrient deficiencies, systemic diseases, hormonal factors, smoking cessation, psychological stress, immune disorders, and drugs.[8,9]

Several studies reported that psychological stress is significantly correlated with the occurrence of RAS.[10,11] Psychological stress, both acute and chronic, can result in increased cortisol levels which have a bad influence on reduced immunity and have a negative impact on individual health.[12,13] Changes in cortisol levels in saliva serve as indicators of fluctuations in adrenal function that have an impact on an individual's energy levels, resistance to disease, emotional state, and overall sense of well-being,[14] and it is thought that elevated salivary cortisol concentrations can trigger the development of ulcers that lead to RAS.[15]

Cortisol levels can be assessed by analyzing samples of serum, saliva, interstitial fluid, and urine, where measurements using saliva are non-invasive and very stable,[16] therefore, measurements using saliva samples can be carried out more easily compared to measurements using other methods. In addition, the examination of serum and/or saliva hormones, in this case including salivary cortisol, which is one of the biomarkers of chronic stress and anxiety, plays a crucial role in elucidating the correlation between psychological stress and the RAS occurrence.[17,18]

Saliva is a fluid that is easily available to patients and can be used as a biomarker to identify stress by examining cortisol levels in patients with oral diseases, in this case RAS. Some evidence shows a link between psychological stress and an increased incidence of RAS in individuals. Therefore, this scoping review aimed to review and evaluate the association between salivary cortisol levels in individuals with psychological stress and an increased incidence of RAS. So oral health professionals can identify stress factors in the occurrence of RAS by examining cortisol levels in saliva. In this manner, patients can be effectively managed, particularly in relation to their psychological stress conditions.

METHODS

Adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this scoping review was performed and the PICO (population, intervention, comparison, outcome) model was used in conducting this research, considering several aspects as follows: population (RAS patients), intervention (saliva collection), comparison (healthy controls), and outcome (salivary cortisol levels).

Information Sources

We conducted a comprehensive search until November 2023 in the following databases: PubMed, ScienceDirect, Scopus, ProQuest, and Google Scholar.

Search Strategy

In literature search in databases, we used several combinations of the following keywords: ("cortisol" OR "salivary cortisol") AND ("stress" OR "psychological stress" OR "anxiety" OR "depression") AND ("recurrent aphthous stomatitis" OR "RAS" OR "recurrent aphthous ulcer" OR "RAU"). In conducting literature search, we applied inclusion and exclusion criteria to limit the research articles we reviewed in this study.

Selection Process

After conducting a literature search in several databases, and all articles search results were input into the Mendeley reference manager, we then grouped them and all duplicates, if any, were removed. We then screened all the articles obtained by applying the inclusion criteria, including English-based articles, original research conducted on human subjects, research that tested cortisol levels in saliva, but limitation on the year of publication was not applied. Any articles failing to meet the specified inclusion criteria were eliminated. The remaining articles were filtered for initial review by evaluating the title and abstract, all articles that were not relevant to this research were excluded. In the final stage, we assessed the eligibility of the articles. All included articles were documented in Microsoft Excel 2019 for Windows.

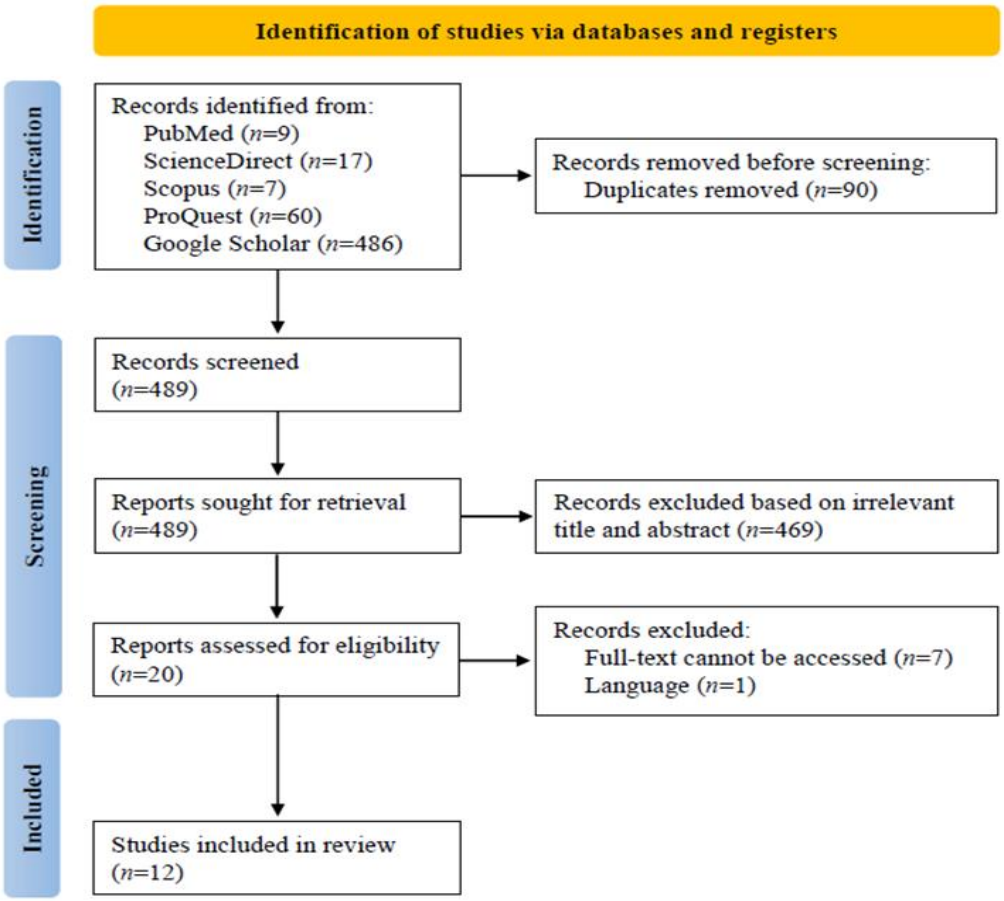

Figure 1. The process of selecting studies using PRISMA diagram.

RESULTS

This scoping review incorporated twelve studies addressing salivary cortisol levels among individuals diagnosed with RAS, comprising ten cross-sectional studies and two case-control studies.

Table 1. Summary of the included articles.

Reference	Country	Design	Participant	Results
McCartan et al.[19]	UK	Cross-sectional	12 RAS patients and 12 normal patients	Salivary cortisol levels in RAS patients were 7.3 nmol/l and in normal patients were 3.2 nmol/l (p<0.01)
Albanidou-Farmaki et al.[20]	Greece	Cross-sectional	38 RAS patients and 38 controls	Salivary cortisol levels in RAS patients were 1.44 (±0.58) µg/dl and in controls were 0.91 (±0.56) µg/dl (p=0.001)
Nadendla et al.[21]	India	Cross-sectional	30 RAS patients and 30 controls	Salivary cortisol levels in RAS patients were 47.73±8.80 nmol/l and in controls were 13.90±3.55 nmol/l (p=0.000)
Michel et	Brazil	Cross-sectional	30 RAS	In samples before breakfast, the

Reference	Country	Design	Participant	Results
al.[22]			patients and 30 controls	average concentrations of salivary cortisol in RAS patients with active lesions were 15.80 nmol/l and in controls were 14.50 nmol/l (p=0.258), Meanwhile, in samples before lunch, the average concentrations of salivary cortisol in RAS patients with active lesions were 8.05 nmol/l and in controls were 7.25 nmol/l (p=0.083).
Kunikullaya et al.[23]	India	Case-control	34 cases and 34 controls	The average levels of salivary cortisol in patients with RAS were 3.35±1.8 ng/dl and in controls were 3.65±2.5 ng/dl (p=0.78)
Madkour & El Refaie[24]	Egypt	Cross-sectional	25 RAS patients and 25 healthy controls	Salivary cortisol levels in RAS patients were 1.53±0.69 µg/dl and in controls were 1.02±0.48 µg/dl (p=0.0039)
Polat et al.[25]	Turkey	Cross-sectional	39 RAS patients and 25 healthy controls	The average levels of salivary cortisol in patients with RAS were 0,15377 µg/dl and in controls were 0,111804 µg/dl (p=0.127)
Zakaria et al.[26]	Egypt	Cross-sectional	35 RAS patients and 35 healthy controls	The average levels of salivary cortisol in patients with RAS were 1.70±0.34 µg/dl and in controls were 0.47±0.05 µg/dl (p=0.00; 95% CI=0.99-1.47)
Vandana et al.[27]	India	Cross-sectional	30 RAS patients and 30 controls	Salivary cortisol levels in RAS patients were >3 ng/ml (83.3%) and normal salivary cortisol, 1.2-3 ng/ml (16.7%). The controls exhibited normal salivary cortisol levels, with an average value of 1.96 pg/ml (p<0.001)
Mirzaei et al.[28]	Iran	Case-control	30 RAS patients and 30 controls	Salivary cortisol levels in RAS patients were 5.35±3.71 ng/ml and in controls were 4.73±2.91 ng/ml (p=0.67)
Aijaz et al.[29]	India	Cross-sectional	26 RAS patients and 26 healthy controls	Salivary cortisol levels in 85% of all RAS patients were >3 ng/ml, while 15% were 1.2-3 ng/ml. Meanwhile, in controls, 26% had

Reference	Country	Design	Participant	Results
				salivary cortisol levels >3 ng/ml and 74% had 1.2-3 ng/ml, this difference was significant (p<0.05)
Shakeel et al.[14]	India	Cross-sectional	41 RAS patients and 41 healthy controls	In RAS patients, 83% had salivary cortisol levels >3 ng/ml and 17% had 1,2-3 ng/ml. Meanwhile, in controls, 28% had salivary cortisol levels of >3 ng/ml and 72% had 1,2-3 ng/ml, with a significant difference (p<0.05)

DISCUSSION

Psychologically, stress stimulates cortisol secretion. The hypothalamus is stimulated by activation of the hypothalamic-pituitary-adrenal (HPA) axis to secrete corticotropin releasing hormone (CRH), subsequently prompting the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. This cascade ultimately results in the release of glucocorticoids, such as cortisol, from the adrenal glands. In addition, the HPA axis operates on a diurnal rhythm. The cortisol awakening response (CAR) refers to the first cortisol spike that occurs upon awakening in the morning, which is then followed by a gradual decrease in cortisol levels during the day.[30,31] Thus, those who are continuously exposed to psychological stress factors are more likely to suffer from stress which may make it easier for diseases related to the body's immune system, including RAS, to develop.[32]

Of the twelve articles included, eight studies showed a significant elevation in salivary cortisol levels among individuals with RAS in comparison to the levels of salivary cortisol observed in healthy individuals, three studies showed a non-significant increase, and one article had results where salivary cortisol levels were higher in control individuals, as indicated by the results of measuring salivary cortisol levels in RAS patients and healthy controls with statistically significant differences in research conducted by McCarten et al. (p<0.01),[19] Albanidou-Farmaki et al. (p=0.001),[20] Nadendla et al. (p=0.000),[21] Madkour et al. (p=0.0039),[24] Zakaria et al. (p=0.00; 95% CI=0.99-1.47),[26] Vandana et al. (p<0.001),[27] Aijaz et al. (p<0.05),[29] and Shakeel et al. (p<0.05).[14] There are several studies that, although there is an increase in salivary cortisol levels in RAS patients with active lesions compared to salivary cortisol levels in controls, the differences are not significant, as shown in the results of studies conducted by Michel et al. on active lesions before breakfast (p=0.258) and before lunch (p=0.083),[22] Polat et al. (p=0.127),[25] and Mirzaei et al. (p=0.67).[28] As well as study carried out by Kunikullaya et al. which showed results that salivary cortisol levels were higher in the control group (p=0.78).[23]

Several methods of testing salivary cortisol levels were used, such as using radioimmunoassay,[19,22] luminescent immunoassay method,[20] enzyme-linked immunosorbent assay (ELISA) method,[14,21,23,24,26–29] and electrochemiluminescence.[25] All studies analyzed salivary cortisol levels in RAS patients and in the control group, which resulted in eleven studies (91.67%) having salivary cortisol levels higher than controls with eight of them increasing significantly, three of them increasing insignificantly, and another one producing high salivary cortisol levels in the control group. The reason for the difference in the significance of the results of measuring salivary cortisol levels in samples of RAS patients and the control group is possibly due to differences in measurement methods used in several of the included studies. However, the findings remain dominated by the results of increased salivary cortisol levels in RAS patients.

A total of eight studies conducted evaluations to assess the level of stress and/or depression in subjects. Research conducted by McCartan et al. using the Hospital Anxiety and Depression scale,[19] Albanidou-Farmaki et al. and Kunikullaya et al. evaluated anxiety levels using Spielberger's State-Trait Anxiety Inventory (STAI-T and STAI-S),[20,23] Nadendla et al. and Zakaria et al. measured the level of anxiety using the Hamilton's anxiety scale,[21,26] Michel et al. measured stress levels using Lipp's Adult Stress Symptom Inventory and measured anxiety using Beck's anxiety inventory,[22] Polat et al. evaluated anxiety levels using the Hamilton anxiety rating scale and evaluated depression using the Hamilton depression rating scale,[25] and Mirzaei et al. assessed levels of anxiety and depression by employing Beck's anxiety inventory and Beck's depression inventory, respectively.[28]

Total of eight studies that evaluated levels of stress and/or depression, five studies demonstrated a statistically significant elevation in stress and/or depression levels within the RAS patient group in comparison to the control group, as shown by the results of study conducted by McCartan et al. ($p<0.05$),[19] Albanidou-Farmaki et al. ($p=0.001$ for STAI-T and $p=0.001$ for STAI-S),[20] Nadendla et al. ($p=0.000$),[21] Michel et al. ($p=0.001$ for stress levels and $p=0.004$ for anxiety levels),[22] and Zakaria et al. ($p=0.00$).[26] A total of two studies showed a non-significant increase in stress and/or depression levels in patients with RAS in comparison to the control group, as shown by research conducted by Kunikullaya et al. ($p=0.127$)[23] and Mirzaei et al. ($p=0.95$ for anxiety levels and $p=0.44$ for depression levels).[28] As well as one study that had different significance values for the levels of anxiety ($p=0.686$) and depression ($p=0.001$).[25] Most of the results of measuring the level of psychological stress of respondents showed an increase in levels of anxiety and depression in patients experiencing with RAS compared to healthy individuals, this shows that there is a correlation between increased psychological stress and an increase in the incidence of RAS. However, there are some results that are not significant or there is no significant difference between the level of psychological stress in RAS patients and controls, this is possible due to the heterogeneity of the samples included in the study, differences in

degrees of severity, and differences in methods or scales for measuring levels of psychological stress used.

In research conducted by Kunikullaya et al. concluded that there was an increase in the level of psychological stress in RAS patients, although it was not statistically significant, but the results of measuring salivary cortisol levels indicated no significant change within the RAS patient group. The presence of a reactive increase in salivary rate during active RAS lesions may contribute to the discrepancy with the hypothesis in the study. In addition, variations in the severity of RAS in patients may also influence the results of measuring salivary cortisol levels.[23] Mirzaei et al. observed elevated salivary cortisol levels in the group of patients with RAS compared to the control group. Nevertheless, this difference did not achieve a level of statistical significance. Apart from that, the results of measuring levels of stress and depression in the two groups did not show significant differences, so this study concluded that anxiety and depression were probably not factors that caused RAS in the sample in this study.[28]

Nonetheless, there exists a positive correlation between increasing salivary cortisol levels and the prevalence of psychological stress among individuals with RAS.[19–22,26] This is because increasing levels of psychological stress in individuals can increase serum cortisol levels.[33] Because cortisol has a small structure and is fat soluble, cortisol is capable of undergoing passive diffusion where it migrates from the capillaries to the main cells and be distributed to parts of the body, one of which is saliva.[34] In saliva, sampling is easier, non-invasive, painless, and can be done by individuals themselves. Thus, saliva is effectively used to measure cortisol levels in individuals to measure the presence or absence of psychological stress factors in patients with RAS. This is corroborated by the statement which states that the translocation of cortisol from the bloodstream to saliva occurs rapidly, typically within a timeframe of less than 2-3 minutes.[35]

Although the mechanism of psychological stress in the incidence of RAS in individuals is currently unclear, there are several possible relationships between psychological stress and an increase in the incidence of RAS. Psychological stress condition can unconsciously make individuals move their jaw, tongue, cheeks and/or lips, increasing the risk of trauma in the form of bites or movements that the individual is not aware of, causing RAS to occur on the oral mucosa.[36] Research suggests that patients with psychological stress unconsciously tend to actively move their tongues so that the tongue experiences trauma or friction on the teeth most often, resulting in ulcers that take longer to heal,[37] as well as bad habits such as lip and/or cheek biting due to stress contribute to ulceration, which continues to become RAS, in the oral cavity and daily activities will be disrupted, including eating and speaking.[38]

In addition, psychological stress also triggers immunoregulatory activity by augmenting the leukocyte count in RAS lesions, which is characteristic of RAS pathogenesis.[39] Increased cortisol in the body will also suppress interferon (INF)-γ and induce interleukin (IL)-10 and IL-4, thereby triggering dysregulation of the balance of these cytokines which play an important role in linking stress to the immune system.[40] Moreover, in situations of stress and continuous release of cortisol, there is an elevation in inflammatory activity due to the induction of immunological dysfunction, which in turn leads to the occurrence of RAS with a higher possibility of recurrence.[41]

According to the findings of this scoping review, it can be stated that a total of eleven studies (91.67%) reported higher levels of salivary cortisol compared to the control group with eight of them showed a statistically significant increase, three studies had insignificant results, and another concluded that salivary cortisol levels were high in healthy controls. Additionally, of the eight articles evaluated the level of psychological stress in respondents, seven studies stated that there was an increase in psychological stress levels in RAS patients compared to healthy controls with five articles showing a statistically significant increase. This scoping review has limitations due to the limited research included where the sample used cannot represent the population of all races, differences in methods for measuring salivary cortisol levels, sample heterogeneity, and the use of different scales or methods for measuring levels of psychological stress. However, this research can conclude that cortisol has increased in RAS patients and is possibly related to increased levels of psychological stress, so that examining salivary cortisol levels helps doctors and dentists in evaluating and carrying out appropriate management in RAS patients with psychological stress factors.

CONCLUSION

In conclusion, this study concludes that there is correlation between increased levels of salivary cortisol in individuals with psychological stress and an increased incidence of RAS. However, future research using more rigorous methods, with larger sample sizes, paying attention to occupational factors, education, and other factors related to stress exposure, may be warranted. Moreover, further studies into the mechanisms through which psychological stress contributes to the heightened occurrence of RAS need to be conducted.

ACKNOWLEDGMENT

Thank you to all the parties who have supported this research.

CONFLICT OF INTEREST

There is no conflict of interest in this research.

REFERENCES

1. Edgar NR, Saleh D, Miller RA. Recurrent Aphthous Stomatitis: A Review. The Journal of clinical and aesthetic dermatology. 2017 Mar;10(3):26–36.
2. Darjani A, Joukar F, Naghipour M, Asgharnezhad M, Mansour-Ghanaei F. Lifetime prevalence of recurrent aphthous stomatitis and its related factors in Northern Iranian population: The PERSIAN Guilan Cohort Study. Clinical Oral Investigations. 2021 Feb 8;25(2):711–8.
3. 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. Journal of pharmacy & bioallied sciences. 2021 Jun;13(Suppl 1):S363–6.
4. Manoj MA, Jain A, Madtha SA, Cherian TM. Prevalence and risk factors of recurrent aphthous stomatitis among college students at Mangalore, India. PeerJ. 2023;11:e14998.
5. Jurge S, Kuffer R, Scully C, Porter S. Number VI Recurrent aphthous stomatitis. Oral Diseases. 2006 Jan 23;12(1):1–21.
6. Belenguer-Guallar I, Jiménez-Soriano Y, Claramunt-Lozano A. Treatment of recurrent aphthous stomatitis. A literature review. Journal of clinical and experimental dentistry. 2014 Apr;6(2):e168-74.
7. Cui RZ, Bruce AJ, Rogers RS. Recurrent aphthous stomatitis. Clinics in Dermatology. 2016 Jul;34(4):475–81.
8. Rivera C. Essentials of recurrent aphthous stomatitis (Review). Biomedical Reports. 2019 Jun 11;
9. Sánchez J, Conejero C, Conejero R. Recurrent Aphthous Stomatitis. Actas Dermo-Sifiliográficas (English Edition). 2020 Jul;111(6):471–80.
10. Keenan AV, Spivakovksy S. Stress associated with onset of recurrent aphthous stomatitis. Evidence-Based Dentistry. 2013 Mar 12;14(1):25–25.
11. 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(4):455–8.
12. Prehananto H, Istiati, Zahro S. Correlation Between Stress and Recurrent Aphthous Stomatitis in Bank BRI Tulungagung Employees: An Observational Analytic. Dentika: Dental Journal. 2023 Jul 31;26(1):67–71.
13. Sherman GD, Mehta PH. Stress, cortisol, and social hierarchy. Current Opinion in Psychology. 2020 Jun;33:227–32.
14. Shakeel M, Sharma M, Iqbal A, Alisha, Mukherjee A, Bhattacharjee A. Assessment of salivary cortisol and dehydroepiandrosterone as oral biomarkers to assess stress in patients with recurrent aphthous stomatitis. International journal of health sciences. 2022 May 26;8080–5.
15. Bilal N. An Assessment of the Levels of Anxiety and Depression in Patients with Recurrent Aphthous Stomatitis. Archives of Otolaryngology and Rhinology. 2016 Jan 8;2(1):001–5.
16. Harrison RF, Debono M, Whitaker MJ, Keevil BG, Newell-Price J, Ross RJ. Salivary Cortisone to Estimate Cortisol Exposure and Sampling Frequency Required Based on Serum Cortisol Measurements. The Journal of Clinical Endocrinology & Metabolism. 2019 Mar 1;104(3):765–72.
17. Humberto JSM, Pavanin JV, Rocha MJAD, Motta ACF. Cytokines, cortisol, and nitric oxide as salivary biomarkers in oral lichen planus: a systematic review. Braz oral res. 2018 Aug 13;32.
18. Karaer I, Urhan A, Reyhani I. Stress and recurrent aphthous stomatitis. Med-Science. 2020;9(1):170–4.
19. McCartan BE, Lamey P -J., Wallace AM. Salivary cortisol and anxiety in recurrent aphthous stomatitis. Journal of Oral Pathology & Medicine. 1996 Aug 28;25(7):357–9.
20. Albanidou-Farmaki E, Poulopoulos AK, Epivatianos A, Farmakis K, Karamouzis M, Antoniades D. Increased Anxiety Level and High Salivary and Serum Cortisol Concentrations in Patients with Recurrent Aphthous Stomatitis. The Tohoku Journal of Experimental Medicine. 2008;214(4):291–6.
21. Nadendla LK, Meduri V, Paramkusam G, Pachava KR. Relationship of salivary cortisol and anxiety in recurrent aphthous stomatitis. Indian journal of endocrinology and metabolism. 2015;19(1):56–9.
22. Michel AR, Luz C, Wudarcki S, Cherubini K, Figueiredo MAZ de, Salum FG. Cortisol and dehydroepiandrosterone salivary levels, stress and anxiety in patients with recurrent aphthous stomatitis. Revista Odonto Ciência. 2016 Mar 21;30(4):120.
23. Kunikullaya U. K, Kumar M. A, Ananthakrishnan V, Jaisri G. Stress as a Cause of Recurrent Aphthous Stomatitis and Its Correlation with Salivary Stress Markers. The Chinese journal of physiology. 2017 Aug 31;60(4):226–30.
24. Madkour G, El Refaie I. Salivary Levels of α-Amylase & Cortisol In Patients With Recurrent Aphthous Ulceration. Egyptian Dental Journal. 2018 Jul 1;64(3):2391–7.
25. Polat C, Düzer S, Ayyıldız H, Seç S, Aksoy N, Sakallıoğlu Ö, et al. Association Between Anxiety, Depression, and Salivary Cortisol Levels in Patients with Recurrent Aphthous Stomatitis. Turkish archives of otorhinolaryngology. 2018 Sep;56(3):166–9.
26. Zakaria M, Hosny R. Relation between salivary cortisol and alpha amylase levels and anxiety in Egyptian patients with minor recurrent aphthous stomatitis. Egyptian Dental Journal. 2018 Apr 1;64(2):1235–43.

27. Vandana S, Kavitha B, Sivapathasundharam B. Salivary cortisol and dehydroepiandrosterone as oral biomarkers to determine stress in patients with recurrent aphthous stomatitis. Journal of oral and maxillofacial pathology : JOMFP. 2019;23(2):213–7.
28. Mirzaei M, Zarabadipour M, Mirzadeh M. Evaluation the relationship between psychological profile and salivary cortisol in patients with recurrent aphthous stomatitis. Dental research journal. 2021;18:50.
29. Aijaz DrA, Vasundhara Dr, Patel DrP, Porwal B, Gupta DrP, Chandra DrA. Salivary cortisol and dehydroepiandrosterone in patients with recurrent aphthous stomatitis. International Journal of Applied Dental Sciences. 2022 Apr 1;8(2):210–2.
30. Corbett BA, Simon D. Adolescence, Stress and Cortisol in Autism Spectrum Disorders. OA autism. 2014 Feb 1;1(1):2.
31. Thau L, Gandhi J, Sharma S. Physiology, Cortisol [Internet]. StatPearls Publishing, Treasure Island (FL); 2022. Available from: http://europepmc.org/abstract/MED/30855827
32. Nurdiana N, Ritonga PWU, Wulandari P. The Role of Stress in Recurrent Aphthous Stomatitis. European Journal of General Dentistry. 2023 Jan 21;12(01):042–7.
33. Sushanthi LC, Ramani P, Ramasubramanian A, Gheena S, Krishnan RP. Serum Cortisol Levels in Lichen Planus: A Systematic Review with Meta-Analysis. Indian journal of dermatology. 2021;66(6):654–9.
34. Cay M, Ucar C, Senol D, Çevirgen F, Ozbag D, Altay Z, et al. Effect of increase in cortisol level due to stress in healthy young individuals on dynamic and static balance scores. Northern clinics of Istanbul. 2018;5(4):295–301.
35. Bozovic D, Racic M, Ivkovic N. Salivary cortisol levels as a biological marker of stress reaction. Med Arch. 2013;67(5):374–7.
36. Majid AA, Riolina A. Hubungan stomatitis aftosa rekuren (SAR) dan tingkat stres mahasiswa pada pembelajaran daring di Solo Raya. Padjadjaran Journal of Dental Researchers and Students. 2023;7(1):44–51.
37. Yuliana Y, Winias S, Hendarti HT, Soebadi B. Reccurent trauma-induced aphthous stomatitis in adjustment disorder patients. Dent J. 2019 Sep 30;52(3):163–7.
38. Hutajulu NA, Lubis WH. Stress Experienced during the COVID-19 Pandemic; Its Relationship with the Incidence of Recurrent Aphthous Stomatitis (RAS). Journal of International Dental and Medical Research. 2023;16(1):187–92.
39. de Barros Gallo C, Mimura MAM, Sugaya NN. Psychological Stress and Recurrent Aphthous Stomatitis. Clinics. 2009 Jul;64(7):645–8.
40. Sari RK, Ernawati DS, Soebadi B. Recurrent Aphthous Stomatitis Related to Psychological Stress, Food Allergy and GERD. ODONTO : Dental Journal. 2019 Jul 11;6(1):45.
41. 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. Journal of the Formosan Medical Association = Taiwan yi zhi. 2019 Sep;118(9):1279–89.