J Oral Med Oral Surg 2023;29:12
https://doi.org/10.1051/mbcb/2023009

https://www.jomos.org

JOMOS
Journal of Oral Medicine and Oral Surgery

Original Research Article

Comparative assessment of salivary level of cortisol, anxiety and depression in patients with oral lichen planus

Soudeh Jafari[1], Maryam Baharvand[2], Maryam Jarahzade[3], Mahshid Namdari[4], Pardis Hojjat[5] and Marzieh Alimohammadi[3,*]

[1] Department of Oral Medicine, Dental School, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Department of Oral and Maxillofacial Medicine, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Department of Oral Medicine, Dental Faculty, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4] Community Oral Health Department, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5] Department of Periodontics, Faculty of Dentistry, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

(Received: 21 October 2022, accepted: 1 February 2023)

Keywords: Anxiety / depression / scale / saliva

Abstract – Oral lichen planus (OLP) is an inflammatory condition of oral mucosa and skin. The present study compared salivary cortisol, depression and anxiety levels of patients with erosive and reticular OLP and healthy controls. In this case-control trial, 69 individuals (23 healthy, 23 erosive OLP and 23 reticular OLP patients) were selected. The participants completed the hospital anxiety and depression scale (HADS) and 5 mL of their unstimulated saliva were collected. Salivary cortisol levels were measured by enzyme-linked immunosorbent assay (ELISA). The comparison of anxiety and depression scores as well as salivary cortisol levels was done one-way analysis of variance (ANOVA) test while the paired comparisons were done by Turkey post hoc test. The mean anxiety score in erosive OLP patients was significantly higher than that in the control and reticular OLP groups. The reticular OLP and control groups had no significant difference in this respect. The three groups were not significantly different regarding the depression score or salivary level of cortisol. The correlation between depression and anxiety was significant but salivary level of cortisol had no correlation with anxiety or depression. This study showed that anxiety control may aid in control of erosive OLP, although further investigations are required.

Introduction

Lichen planus (LP) is a chronic, inflammatory and immune-mediated disease of unknown etiology that can affect the skin, hair, nail, and mucous membrane [1–3]. Oral lichen planus (OLP) is a relatively common disease in which, T lymphocytes invade the basal layer cells of oral mucosal epithelium [4,5]. OLP lesions are usually bilateral, symmetric or asymmetric, located on buccal mucosa, tongue, lips and/or gingiva, with different clinical manifestations and divided into: reticular (with fine white lines or Wickham's striae), plaque-like, papular, erosive (ulcerated), atrophic (erythematous) types [6]. Modified World Health Organization (WHO) diagnostic criteria propose diagnosing OLP both histologically and clinically [7]. Although the pathogenesis of OLP is still ambiguous, the role of immunological mechanisms in its initiation and progression has been confirmed [5].

Psychological conditions such as stress and anxiety have also been suggested as the etiologic factors for development of OLP [8,9]; however, this correlation is still a matter of controversy [5,10]. According to some evidence, psychological conditions can alter the immunological functions. Also, OLP patients have shown higher susceptibility to some psychological disorders, and stressful conditions have been reported prior to disease initiation in 10–68% of the patients [5]. Moreover, aggravation of disease has been observed in stressful or depressing situations [11]. Stress and some other psychological conditions can cause dysregulation of immunological responses and change the balance of Th1/Th2 cytokines and increase the Th2 response as such, which is associated with the occurrence of autoimmune conditions [12]. Interactions have been reported between the nervous system, immune system, and endocrine system in different autoimmune conditions. Stress induces the release of neuroendocrine hormones, and leads to immune dysregulation or increased/altered production of cytokines and development of autoimmune diseases [10]. Thus, stress has been suggested as an etiologic factor for development of OLP, while some others reported that it may be the outcome of OLP [13].

Stress is among the factors that increases the production of cortisol. Cortisol is released from the adrenal cortex following stimulation of the hypothalamus-pituitary-adrenal axis, and

* Correspondence: m.alimohamadi95@yahoo.com

has various effects on the human body. It regulates the metabolism of carbohydrates, proteins, lipids, and water, controls the vascular reactions, affects the sensitivity of the nervous system, regulates the number of blood cells, and controls the response to stress [14,15]. High levels of cortisol have been detected in patients with depression, periodontal disease, burning mouth syndrome, and recurrent aphthous ulcers [10]. Increased serum cortisol levels have been reported in response to stressful conditions. A correlation has been reported between psychological stress and erosive form of OLP; however, no such a correlation was noted between reticular OLP and psychological stress [14,16]. Some others found no correlation between psychological stress and erosive OLP [10,17]. However, another study reported higher serum levels of cortisol in patients with erosive OLP compared with controls [14].

Assessment of the salivary level of cortisol is more advantageous compared with serum cortisol since saliva collection is completely non-invasive and stress-free. It does not require any expertise, and environmental changes such as thermal alterations, movements, or microorganisms have no significant effect on salivary level of cortisol [11,18].

Hospital anxiety and depression scale (HADS) is a commonly used questionnaire for assessment of depression and anxiety in patients [14,19]. The reliability of this questionnaire has been previous confirmed [20].

Considering the existing controversy regarding the correlation of anxiety and depression with different types of OLP, and absence of studies comparing the salivary cortisol level of patients with erosive and reticular OLP, this study aimed to assess the salivary level of cortisol, and anxiety and depression in patients with erosive and reticular OLP in comparison with healthy controls.

Materials and Methods

This case–control study was conducted on erosive and reticular OLP patients and sex- and age-matched healthy controls, who were selected among those presenting to the Oral Medicine Department of Shahid Beheshti Dental School. The study was approved by the ethics committee of the university (1396.569. IR.SBMU.RIDS.REC) and written informed consent was obtained from all participants prior to their enrollment.

A total of 23 patients with clinical manifestations of erosive-ulcerative OLP, 23 patients with clinical manifestations of reticular OLP, and 23 healthy controls (a total of 69 participants) were enrolled. The diagnosis of OLP was made by an oral medicine specialist following clinical examination and based on the clinical manifestations of lesions (presence of papular or reticular lesions). For indefinite cases, pathological assessment was performed to reach a definite diagnosis. The controls matched the patients in terms of age and sex, and had no systemic condition or oral lesion. The exclusion criteria were systemic conditions such as diabetes mellitus [21], hyperthyroidism, adrenocortical hyperfunction, cancer, coronary artery disease, psychological diseases, corticosteroid intake, smoking [22,23], pregnancy [24], nursing [25], and xerostomia [5,14].

The sample size was calculated to be 23 in each group to find a minimum of 5-unit difference in the mean salivary level of cortisol between the groups according to a previous study [17], 3-unit standard deviation of the mean salivary level of cortisol, alpha=0.05, and beta=0.1 using the multiple comparisons feature of PASS 11. The participants were enrolled using convenience sampling.

The participants were requested to fill out the HADS (hospital anxiety and depression scale) questionnaire [21]. Next, 5 mL of unstimulated saliva was collected from patients and controls. For this purpose, they were requested to rinse their mouth with water, and saliva was collected as described by Navazesh *et al.* [22] in sterile centrifuge tubes. Since the salivary level of cortisol is the highest in the morning [23], saliva sampling was performed between 9 and 10 a.m. [4,14]. The participants were requested to refrain from eating, toothbrushing or use of mouthwash for 1 h prior to sampling. The collected saliva samples were centrifuged at 3000 rpm for 15 min and were then frozen at −20 °C. For assessment of salivary level of cortisol, the samples were warmed up to 37 °C, and the salivary level of cortisol was measured using ELISA as instructed in the respective kit. The reason for using ELISA is its high specificity and sensitivity [26]. The patients then received treatment and underwent follow-up.

The HADS questionnaire has 7 questions to assess the level of depression, and 7 questions to assess the level of anxiety. The questions were scored using a 5-point Likert scale (0–4). A total score between 0 and 7 indicated no anxiety/depression, scores 8–10 indicated suspected depression/anxiety, and scores 11–21 indicated the presence of anxiety/depression.

Data were analyzed using SPSS version 25. The Kolmogorov–Smirnov test was applied to analyze the normality of data distribution, which showed normal distribution of all data ($P > 0.05$). Thus, comparisons were made using parametric tests. The mean salivary level of cortisol and the mean scores of anxiety and depression were compared among the three groups using one-way ANOVA. Pairwise comparisons were made using the Tukey's test. The Student *t*-test was applied to compare males and females regarding the anxiety and depression scores and salivary level of cortisol. The non-parametric Kruskal-Wallis test was used to compare the three groups regarding the frequency of different levels of anxiety and depression. Three-way ANOVA with Wald correction was also applied to assess the effect of different variables on total depression/anxiety score and level of depression. Level of significance was set at 0.05.

Results

There were 15 females (65.2%) and 8 males (34.8%) in the control group, 12 females (52.2%) and 11 males (47.8%) in the reticular OLP, and 12 females (52.2%) and 11 males (47.8%) in

Table I. Measures of central dispersion regarding the salivary level of cortisol (μg/dL) in the three groups ($n = 23$).

Group	Mean	Std. deviation	Std. error	95% CI		Minimum	Maximum
				Lower bound	Upper bound		
Control	98.0	0.21	0.04	0.89	1.07	0.6	1.37
Reticular	1.01	0.19	0.04	0.93	1.09	0.63	1.72
Erosive	1.09	0.15	0.03	1.03	1.16	0.75	1.36

Table II. Measures of central dispersion for the depression score in the three groups ($n = 23$).

Group	Mean	Std. deviation	Std. error	95% CI		Minimum	Maximum
				Lower bound	Upper bound		
Control	5.22	1.83	0.38	4.42	6.01	2	8
Reticular	5.87	2.94	0.61	4.6	7.14	2	11
Erosive	6.35	3.46	0.72	4.85	7.84	2	14

Table III. Measures of central dispersion for the anxiety score in the three groups ($n = 23$).

Group	Mean	Std. deviation	Std. error	95% CI		Minimum	Maximum
				Lower bound	Upper bound		
Control	8.57	2.84	0.59	7.34	9.79	1	14
Reticular	9.3	3.23	0.67	7.91	10.7	4	15
Erosive	11.57	3.12	0.67	10.22	12.91	5	16

Table IV. Measures of central dispersion for the mean anxiety and depression scores and salivary level of cortisol separately in males and females.

Variable	Group	Number	Mean	Std. deviation	Std. error	Mean difference	*P* value
Anxiety	Females	39	9.9	3.44	0.55	0.197	0.81
	Males	30	7.9	3.12	0.57		
Depression	Females	39	5.97	2.94	0.47	0.374	0.59
	Males	30	5.6	2.69	0.49		
Salivary cortisol (μg/dL)	Females	39	1.05	0.21	0.03	0.057	0.22
	Males	30	0.99	0.16	0.03		

the erosive OLP group. The Chi-square test showed no significant difference among the three groups regarding the frequency of males and females ($P = 0.59$).

Table I presents the measures of central dispersion regarding the salivary level of cortisol in the three groups. ANOVA showed no significant difference in the salivary level of cortisol among the three groups ($P = 0.09$).

Table II presents the measures of central dispersion for the depression score in the three groups. One-way ANOVA revealed no significant difference in the depression score among the three groups ($P = 0.4$).

Table III indicates the measures of central dispersion for the anxiety score in the three groups. One-way ANOVA revealed a significant difference in the mean anxiety score among the three groups ($P < 0.004$). Pairwise comparisons by the Tukey's test revealed that the mean anxiety score in erosive OLP patients was significantly higher than control ($P < 0.004$) and reticular OLP ($P < 0.039$) groups. No significant difference was noted between the control and reticular OLP groups ($P = 0.69$).

The total score (the sum of depression and anxiety scores) was 10.52 ± 4.12 in the control group, 12.17 ± 4.42 in reticular OLP group and 14.65 ± 4.66 in the erosive OLP group. One-way ANOVA showed a significant difference in the mean total score among the three groups ($P = 0.009$). Pairwise comparisons by the Tukey's test revealed that the mean total score in the erosive OLP group was significantly higher than that in the control group ($P < 0.006$). However, the difference between the reticular OLP and control groups ($P = 0.42$), and erosive and reticular OLP groups ($P = 0.14$) was not significant.

Table V. Frequency of different levels of anxiety in the three groups.

Group	Level of anxiety			
	No anxiety	Suspected for anxiety	Anxious	Total
Control	7 (30.4%)	11 (47.8%)	5 (21.7%)	23 (100%)
Reticular OLP	7 (30.4%)	7 (30.4%)	9 (39.1%)	23 (100%)
Erosive OLP	4 (17.4%)	4 (17.4%)	15 (65.2%)	23 (100%)
Total	18 (26.1%)	22 (31.9%)	29 (42%)	69 (100%)

Table VI. Frequency of different levels of depression in the three groups.

	No depression	Suspected for depression	Depressed	Total
Control	21 (91.3%)	2 (8.7%)	0	23 (100%)
Reticular OLP	17 (73.9%)	3 (13%)	3 (13%)	23 (100%)
Erosive OLP	16 (69.6%)	5 (21.7%)	2 (8.7%)	23 (100%)
Total	54 (3.78%)	10 (14.5%)	5 (7.2%)	69 (100%)

Table IV presents the measures of central dispersion for the mean anxiety and depression scores and salivary level of cortisol separately in males and females. The Student *t*-test found no significant difference between males and females in any of the measured variables ($P > 0.05$).

The Pearson's correlation test found no significant correlation between the anxiety score and age ($P = 0.12$, $r = 0.191$), depression score and age ($P = 0.11$, $r = 0.195$), or salivary cortisol level and age ($P = 0.60$, $r = 0.231$). However, the correlation between depression and anxiety scores was significant ($P < 0.001$, $r = 0.382$). The correlation of anxiety score and salivary level of cortisol ($P = 0.78$, $r = 0.034$), and salivary level of cortisol and depression ($P = 0.19$, $r = 0.161$) was not significant.

Tables V and VI present the frequency of different levels of anxiety and depression in each group, respectively. The non-parametric Kruskal-Wallis test found no significant difference among the three groups regarding the frequency of different levels of depression ($P = 0.15$). However, the three groups were significantly different regarding the frequency of different levels of anxiety ($P = 0.04$).

Three-way ANOVA with Wald correction was then applied considering the total score as dependent variable, and age and salivary level of cortisol as covariant factors, which showed that the effect of erosive OLP on total score was significant ($P = 0.026$); while reticular OLP ($P = 0.32$), gender ($P = 0.85$), age ($P = 0.94$) and salivary level of cortisol ($P = 0.71$) had no significant effect on the total score of depression and anxiety. Three-way ANOVA with Wald correction by considering the level of depression as dependent variable and age and salivary level of cortisol as covariant factors indicated that the effect of erosive OLP on level of depression was significant ($P = 0.027$); while reticular OLP ($P = 0.23$), gender ($P = 0.77$), age ($P = 0.32$) and salivary level of cortisol ($P = 0.16$) had no significant effect on the level of depression.

Discussion

Considering the suggested role of stress as an etiologic factor in pathogenesis of OLP [27], this study assessed the salivary level of cortisol, and anxiety and depression of patients with erosive and reticular OLP in comparison with healthy controls.

OLP can be aggravated by stressful events, and the role of psychological counseling in treatment of OLP has been previously confirmed [28]. The present results showed that the three groups had no significant difference regarding the salivary level of cortisol ($P = 0.09$). Also, salivary level of cortisol had no correlation with anxiety ($P = 0.78$, $r = 0.034$) or depression ($P = 0.19$, $r = 0.161$). Lopez-Jornet *et al.* found significantly higher serum level of cortisol in OLP patients compared with controls, which was different from the present results [5]. This difference may be due to the fact that they measured the salivary level of cortisol using the chemiluminescent enzyme immunoassay. Evidence shows that this assay is different from the ELISA used in the present study in quantitative analyses [5]. Ivanovski *et al.* reported higher cortisol level in erosive OLP patients but found no significant difference between the reticular OLP and control groups in this respect [29]. Although the present study found no significant difference in salivary level of cortisol among the three groups, this value was the highest in the erosive OLP group, compared with the control group (1.09 vs. 0.98 μg/dL). Vassandacoumara

and Daniel reported that salivary level of cortisol in OLP patients was insignificantly higher than that in healthy controls, which was similar to the present findings [19]. Shetty *et al.* found significantly higher serum level of cortisol in erosive OLP patients compared with controls while the difference in this regard was not significant between reticular OLP patients and controls [14]. Their results cannot be directly compared with the present findings since they evaluated the serum level of cortisol. However, a strong association has been reported between the salivary and serum levels of cortisol.

Almost any type of physical or psychological stress can cause an immediate increase in adrenocorticotropic hormone, and a subsequent rise in serum cortisol within a couple of minutes [30]. Cortisol has a half-life of 1–1.5 hours; thus, high serum or saliva level of cortisol is not necessarily an indicator of anxiety, and may simply indicate high stress level around the time of measurement [30]. Cortisol has a regulatory effect on the immune system, and its high levels can inhibit the activity of the immune system. Since one suggested etiology of OLP is the hyperactivity of Langerhans cells, T-cells, and lymphocytes, and their cytotoxicity against the epithelial cells [27,31], and considering the role of cortisol in decreasing the count of lymphocytes and other immune cells and inhibition of cytotoxicity reactions against the epithelial cells [30], it may be concluded that low salivary level of cortisol may induce autoimmune conditions such as OLP [17].

The results regarding the correlation of salivary level of cortisol and OLP have been controversial [10,32,33]. Variations in the cortisol levels can be due to sexual differences, time of saliva collection, medication intake, diet, and technique of saliva collection, which may affect precise assessment of the correlation of stress and cortisol level [34].

Regarding the level of depression and anxiety, the present results showed that the mean anxiety score in erosive OLP patients was significantly higher than control ($P < 0.004$) and reticular OLP ($P < 0.039$) groups. The reticular OLP and control groups had no significant difference in this respect ($P = 0.69$). The three groups were not significantly different regarding the depression score ($P = 0.4$). Also, the total anxiety/depression score in patients with erosive OLP was significantly higher than that in the control group. The correlation between depression and anxiety was significant ($P < 0.001$, $r = 0.382$)

Hirota *et al.* reported comparable levels of depression and anxiety in OLP patients and controls, which was different from the present results [35]. This difference may be due to the use of different tools for assessment of depression and anxiety since they used the State-Trait Anxiety Inventory and the Center for Epidemiological Studies Depression Scale for this purpose while we used the HADS questionnaire in the present study. Valter *et al.* showed that OLP patients had higher scores of anxiety, depression and stress than healthy controls, using the Beck's Depression Inventory [36]. Vallejo *et al.* reported higher levels of anxiety and depression in OLP patients than healthy controls using the Hamilton Anxiety Scale for assessment of anxiety, and the Montgomery-Asberg Depression Rating Scale for assessment of stress [37]. Vassandacoumara and Daniel used the HADS questionnaire and reported significantly lower anxiety and depression scores in the control group compared with OLP patients [19]. Similarly, Shah *et al.* demonstrated higher levels of depression, anxiety and stress in OLP patients compared with controls [4]. The results of the abovementioned studies were generally in line with the present findings, except for the results regarding depression. Although no significant difference was noted in depression score among the three groups in the present study, the total anxiety/depression score in the erosive OLP group was significantly higher than that in the control group. This finding may indicate the role of depression in development of OLP through hormonal mechanisms, and stress can serve as an aggravating factor in this process [38]. However, considering the available reports regarding higher level of anxiety in OLP patients, anxiety control should be considered as part of treatment in OLP patients. Variable effects of stress on the immune system may be related to psychological status of the host. Also, factors such as nutrition, sleep quality, association of depression and anxiety disorders, smoking, alcohol consumption, and chronic and acute stresses can affect the relationship of depression and the immune system [39].

Lowental and Pisanti in 1977 introduced a biopsychosocial model to assess the interactions of the biological outcome (disease), psychological outcome (illness) and social outcome (sickness) [16]. Accordingly, anxiety may be the outcome of OLP [16]. On the other hand, due to the susceptibility of oral mucosa, OLP may be considered a psychological disease, or psychological factors may serve as a risk factor for it [29].

In the present study, the correlation between depression and anxiety was significant ($P < 0.001$, $r = 0.382$) but salivary level of cortisol had no correlation with anxiety ($P = 0.78$, $r = 0.034$) or depression ($P = 0.19$, $r = 0.161$). Some studies reported significant correlations between OLP and level of depression, anxiety and stress [29,40–42]; while, some others refuted such correlations [17,43–45]. Variations in the results may be due to the use of different questionnaires, subjective nature of the questions, and absence of a standard methodology [43].

In total, the role of stress as a factor that impairs the immune system, affects the production and release of cytokines, and leads to destructive activity of cytotoxic T cells has been suggested in development of OLP [39]. Thus, stress reduction should be included in the treatment protocol of OLP patients [45]. Considering all the above, the present results highlighted the significance of the assessment of psychological profile of patients with erosive and atrophic OLP.

The existing ambiguity regarding the role of stress and anxiety as the etiology or outcome of OLP was a limitation of this study, which calls for further studies on a larger sample size. Also, future studies are recommended to assess the effect of treatment of anxiety and depression on the course and signs and symptoms of OLP.

Conclusion

Considering the significantly higher level of anxiety in erosive OLP patients compared with reticular OLP and control groups, anxiety control may aid in control of erosive OLP, although further case-control trials are required.

Conflict of interest

There was no conflict of interest.

Funding

The authors did not have any financial donors and all the expenses were covered by the authors of the study manuscript.

Ethical approval

This study was approved by research deputy of Shahid Beheshti Dental School with the code of ethics IR.SBMU.RIDS.REC.1396.569.

Informed consent

Written informed consent was obtained from all the patients in Persian language that they could understand.

Author contributions

Soudeh Jafari and Maryam Baharvand designed the method and edited the manuscript. Marzieh Alimohammadi performed an oral examination, searched for related articles and designed tables. Mahshid Namdari performed the data analysis. Maryam Jarahzadeh got the information and set up the database. Pardis Hojjat drafted manuscript.

References

1. Alharbi A, Khobrani A, Noor A, Alghamdi W, Alotaibi A, Alnuhait M, *et al.* Risk of lichen sclerosus and lichen planus in patients receiving immune checkpoint inhibitors. Int J Environ Res Public Health 2023;20:580.
2. De Porras-Carrique T, Ramos-García P, Aguilar-Diosdado M, Warnakulasuriya S, González-Moles MÁ. Autoimmune disorders in oral lichen planus: a systematic review and meta-analysis. Oral Diseases 2022;00:1–13.
3. Górski B. Dental implant treatment in patients suffering from oral lichen planus: a narrative review. Int J Environ Res Public Health 2022;19:8397.
4. Shah B, Ashok L, Sujatha G. Evaluation of salivary cortisol and psychological factors in patients with oral lichen planus. Indian J Dent Res 2009;20:288.
5. Lopez-Jornet P, Cayuela CA, Tvarijonaviciute A, Parra-Perez F, Escribano D, Ceron J. Oral lichen planus: salival biomarkers cortisol, immunoglobulin A, adiponectin. J Oral Pathol Med 2016;45:211–217.
6. Rotaru DI, Sofineti D, Bolboac SD, Bulboac AE. Diagnostic criteria of oral lichen planus: a narrative review. Acta Clin Croat 2020;59:513.
7. Zotti F, Nocini R, Capocasale G, Bertossi D, Fior A, Peretti M, *et al.* Oral Lichen Planus: risk factors of malignant transformation and follow up. Ten years retrospective study. J Clin Exp Dent 2021;13:e630.
8. Lugovi -Mihi L, Špiljak B, Blagec T, Delaš Aždaji M, Franceschi N, Gaši A, *et al.* Factors participating in the occurrence of inflammation of the lips (cheilitis) and perioral skin. Cosmetics 2023;10:9.
9. Hong S, Fan R, Cohen JM. Lichen planus is associated with depression and anxiety: a cross-sectional study in the All of Us research program. Arch Dermatolog Res 2022;314:1-3.
10. Girardi C, Luz C, Cherubini K, de Figueiredo MAZ, Nunes MLT, Salum FG. Salivary cortisol and dehydroepiandrosterone (DHEA) levels, psychological factors in patients with oral lichen planus. Arch Oral Biol 2011;56:864–868.
11. Nadendla LK, Meduri V, Paramkusam G, Pachava KR. Association of salivary cortisol and anxiety levels in lichen planus patients. J Clin Diagn Res 2014;8:ZC01.
12. Marshall GD. The adverse effects of psychological stress on immunoregulatory balance: applications to human inflammatory diseases. Immunol Allergy Clin 2011;31:133–140.
13. Sandhu SV, Sandhu JS, Bansal H, Dua V. Oral lichen planus and stress: An appraisal. Contemp Clin Dent 2014;5:352.
14. Shetty S, Thomas P, Chatra L, Shenai P, Rao P, Babu S. An association between serum cortisol levels in erosive and nonerosive oral lichen planus patients 2010;1.
15. Subhash S, Bindu R, Nair PS, George AE. A study of serum cortisol levels in patients with lichen planus. J Skin Sexually Trans Dis 2022;4:57–62.
16. Lowental U, Pisanti S. Oral lichen planus according to the modern medical model. J Oral Med 1984;39:224–226.
17. Rödström PO, Jontell M, Hakeberg M, Berggren U, Lindstedt G. Erosive oral lichen planus and salivary cortisol. J Oral Pathol Med 2001;30:257–263.
18. Safarzadeh E, Mostafavi F, Ashtiani MH. Determination of salivary cortisol in healthy children and adolescents. Acta Med Iranica 2005;43:32–36.
19. Vassandacoumara V, Daniel JM. Correlation between salivary cortisol levels and hospital anxiety and depression scores in oral lichen planus and recurrent aphthous stomatitis. Stomatolog Disease Sci 2017;1:103–108.
20. Lamey P, Lamb A. The usefulness of the HAD scale in assessing anxiety and depression in patients with burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1989;67:390–392.
21. Chiodini I, Adda G, Scillitani A, Coletti F, Morelli V, Di Lembo S, *et al.* Cortisol secretion in patients with type 2 diabetes: relationship with chronic complications. Diabetes Care 2007;30:83–88.
22. Navazesh M, Kumar SK. Measuring salivary flow: challenges and opportunities. J Am Dental Assoc 2008;139:35S–40S.
23. Steptoe A, Ussher M. Smoking, cortisol and nicotine. Int J Psychophysiol 2006;59:228–235.
24. Akinloye O, Obikoya O, Jegede A, Oparinde D, Arowojolu A. Cortisol plays central role in biochemical changes during pregnancy. Int J Med Biomed Res 2013;2:3–12.
25. Amico JA, Johnston JM, Vagnucci AH. Suckling-induced attenuation of plasma cortisol concentrations in postpartum lactating women. Endocrine Res 1994;20:79–87.
26. Sakamoto S, Putalun W, Vimolmangkang S, Phoolcharoen W, Shoyama Y, Tanaka H, *et al.* Enzyme-linked immunosorbent assay for the quantitative/qualitative analysis of plant secondary metabolites. J Natl Med 2018;72:32–42.

27. Alajbeg I, Challacombe SJ, Holmstrup P, Jontell M. Red and white lesions of the oral mucosa. Burket's Oral Med 2021:85–138.
28. Dhabhar FS, Mcewen BS. Acute stress enhances while chronic stress suppresses cell-mediated immunityin vivo: a potential role for leukocyte trafficking. Brain Behav Immun 1997;11:286–306.
29. Ivanovski K, Nakova M, Warburton G, Pesevska S, Filipovska A, Nares S, *et al.* Psychological profile in oral lichen planus. J Clin Periodontol 2005;32:1034–1040.
30. Guyton AC, Hall JE. Textbook of Medical Physiology 11 th ed. Philadelphia: Saunders 2006. 944–960
31. Khaled AR. Measurement and correlation of salivary and serum cortisol levels in recurrent aphthous stomatitis 2006;52:921-930.
32. Prolo P, Chiappelli F, Cajulis E, Bauer J, Spackman S, Romeo H, *et al.* Psychoneuroimmunology in oral biology and medicine: the model of oral lichen planus. Ann NY Acad Sci 2002;966:429–440.
33. Koray M, Dülger O, Ak G, Horasanli S, Üçok A, Tanyeri H, *et al.* The evaluation of anxiety and salivary cortisol levels in patients with oral lichen planus. Oral Diseases 2003;9:298–301.
34. Vedhara K, Miles J, Bennett P, Plummer S, Tallon D, Brooks E, *et al.* An investigation into the relationship between salivary cortisol, stress, anxiety and depression. Biol Psychol 2003;62:89–96.
35. Hirota S, Moreno R, Dos Santos C, Seo J, Migliari D. Psychological profile (anxiety and depression) in patients with oral lichen planus: a controlled study. Minerva Stomatolog 2013;62:51–56.
36. Valter K, Vu i evi Boras V, Buljan D, Vidovi Juras D, Suši M, Gabri Panduri D, *et al.* The influence of psychological state on oral lichen planus. Acta Clin Croat 2013; 52(2.): 145–149.
37. Vallejo MG-P, Huerta G, Cerero R, Seoane J. Anxiety and depression as risk factors for oral lichen planus. Dermatology 2001;203:303–307.
38. Xiao-hong W, Xu-dong H, Song-hong W, Hua X. Study of association between oral lichen planus and depression in female patients. Shanghai J Stomatol 2011;20:548-552.
39. Ader R, Felten DL, Cohen NC. Psychoneuroimmunology 23th ed. New York: Academic Press 2001. 191, 383, 472 p.
40. Rojo-Moreno J, Bagán J, Rojo-Moreno J, Donat JS, Milián MA, Jiménez Y. Psychologic factors and oral lichen planus: a psychometric evaluation of 100 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol 1998;86:687–691.
41. Vallejo M, Zarabozo G. Anxiety as an etiologic factor in oral lichen planus (OLP). Med Oral 2000;5:7–13.
42. Chaudhary S. Psychosocial stressors in oral lichen planus. Aust Dental J. 2004;49:192–195.
43. Macleod R. Psychological factors in oral lichen planus. Br Dent J. 1992;173:88.
44. McCartan BE. Psychological factors associated with oral lichen planus. J Oral Pathol Med 1995;24:273–275.
45. M.Allen C, Beck FM, Rossie KM, Kaul TJ. Relation of stress and anxiety to oral lichen planus. Oral Surg Oral Med Oral Pathol 1986;61:44–46.