Correlation of Salivary Cortisol with Stress, Anxiety and Depression in Oral Lichen Planus: A Systematic Review and Meta-analysis

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ABSTRACT

Aim: The aim of this study was to evaluate and correlate the salivary cortisol levels with depression, anxiety and stress scores in patients with OLP.

Background: Oral lichen planus (OLP) is an immunopathological disease where patients often relate the onset and aggravation of symptoms to increased levels of depression/anxiety/stress. Research suggests that salivary cortisol can be considered as a biomarker of stress. Psychosomatic diseases such as OLP validate the role of depression/anxiety/stress so that they can be effectively and comprehensively treated. A comprehensive electronic literature search was performed by using scientific databases MEDLINE, PubMed Central, Directory of Open Access Journal, Cochrane and Google Scholar. Studies included case control/cross-sectional studies in which the detection of salivary cortisol levels of the OLP patients and controls was assessed along with assessment of DAS with questionnaire/scales. Quality assessment was done using modified Newcastle–Ottawa Quality assessment scale (NOS) and The Joanna Briggs Institute (JBI) Critical Appraisal tool.

Review results: Eleven studies comprising 260 OLP patients and 253 controls were included. The results suggest that the depression/anxiety/stress scores were higher in OLP patients than controls. The anxiety, depression and stress scores showed statistically non-significant correlation with salivary cortisol in OLP.

Conclusion: The psychological factors including stress, anxiety and depression plays a crucial role in pathogenesis of OLP. So, supportive psychological treatment also needs to be considered while treating OLP patients.

Clinical significance: Oral lichen planus (OLP) is a psychosomatic disorder and salivary cortisol is biomarker of stress. The psychological factors including stress, anxiety and depression play a crucial role in pathogenesis of OLP. We reported higher salivary levels of cortisol and higher scores of anxiety, depression and stress in OLP patients compared to controls. Similarly, no correlation between anxiety, depression and stress scores with salivary cortisol is established. Thus, we recommend supportive psychological treatment together with the conventional therapy could increase patients' capability to deal with psychological instabilities that can improve the OLP healing.

Keywords: Anxiety, Cortisol, Depression, Oral lichen planus, Saliva, Stress.

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INTRODUCTION

Oral lichen planus (OLP) is currently recognized as a multifactorial disease with a complex interplay of genetic and environmental factors including patients' lifestyle, stress as well as anxiety.^{1–5} The prevalence of OLP varies from 0.5 to 4%, seen predominantly in middle-aged and elderly women.^{6–9} It is postulated to result from an abnormal T-cell mediated immune response in which auto-cytotoxic CD8⁺ T cells trigger apoptosis of oral epithelial cells.^{7,8,10–12}

Chronic stress is associated with the activation of the hypothalamic–pituitary–adrenal (HPA) axis as well as with depressed immune function.^{1,3,7,13,14} Various studies have shown that stress and anxiety can be considered as etiological factors in OLP, but there is still controversy concerning the exact mechanism.^{3,4,8,15,16} Accumulating evidence supports clinically relevant interrelations between psychological stressors and onset and progression of chronic diseases. Furthermore, psychological stress and psychiatric illness modify the immunological response.^{1,15–18}

Cortisol is considered as a primary end product of the HPA axis because it is widely considered as a biological regulator of adaptation and maintenance to homeostasis in response to psychological and physiological challenges.^{4,8,17,19} The measurement of salivary cortisol is an indicator of free cortisol or biologically active

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cortisol. So quantification of salivary cortisol could help in analyzing the activity of HPA axis and thus evaluate the role of psychological factors in the etiopathogenesis of OLP.^{1,4,6,10,20}

OLP is associated with significantly increased levels of anxiety, depression, and stress, as well as the development or worsening of lesions during times of emotional stress.^{2–5,10,14,19–25} However, few authors point to controversies in the relationship between OLP and psychological factors.^{4,8,15,16}

Because psychological disorders are not easily measurable, studies have used psychometric testing to quantify and establish a relationship between OLP and behavioral changes. In recent years, the mental health of patients with OLP has been clinically assessed both with and without psychological questionnaires that are acceptable to patients and have enough sensitivity and specificity in their ability to diagnose such diseases.^{9,26}

Numerous studies have postulated the role of psychological factors like stress, anxiety and depression in OLP, but with conflicting results.^{2,4,8,15,17,19} Further, previous systematic reviews have reported higher salivary cortisol levels in OLP patients.^{9,27} However, there was no emphasis on the correlation of salivary cortisol levels with depression, anxiety and stress (DAS) scores. Thus, the aim of this systematic review is to evaluate and correlate the salivary cortisol levels with the DAS scores in OLP patients.

METHODOLOGY

This systematic review and meta-analysis was developed and registered in PROSPERO (registration number: CRD42021226601). The research question was "Is there any correlation between salivary cortisol levels and Depression, Anxiety and Stress scores in patients with oral lichen planus."

- Patient (P): Patients diagnosed with oral lichen planus clinically and/or histopathologically.
- Intervention (I): Analysis of salivary cortisol with assessment of anxiety, depression and stress levels in patients diagnosed with oral lichen planus.
- Comparator (C): Healthy subjects not suffering with any diseases/conditions, without other skin lesions and/or not on any drugs.
- Outcome (O): Estimation of salivary cortisol levels and assessment of anxiety, depression and stress scores in oral lichen planus and controls.

Inclusion Criteria

Case-control/cross-sectional studies in which the detection of salivary cortisol levels in OLP patients and controls was assessed along with assessment of DAS with questionnaire/scales were included. Also, publications written in English language and available as full text were included.

Exclusion Criteria

Case series/case reports, animal studies, *in vitro* studies and studies in unpublished formats and articles not available as full text were excluded.

Search Strategy

Databases including PubMed/MEDLINE, PubMed central (PMC), Google Scholar, Cochrane and Directory of Open Access Journal (DOAJ) were searched from 1st January 2010 to 21st January 2021. The following MeSH terms were searched in PubMed/MEDLINE, PubMed central (PMC) including: "oral," "lichen," "planus," "psychological factors," "stress," "anxiety," "salivary," and "cortisol." In Google scholar and DOAJ the terms used were "oral lichen planus," and "cortisol."

Data Extraction

The search and screening process were carried out by 2 independent reviewers (MW, MM). The titles and abstracts of all retrieved articles were screened and irrelevant studies were

excluded. Full text of the eligible studies were obtained and thoroughly analyzed as per eligibility criteria (inclusion/exclusion) for future data extraction.

Two examiners (MW and RM) evaluated titles, abstracts and full text and if there was a diverging opinion, the disagreement among examiners was reexamined and decisions were made unanimously. Each reviewer first decided on a study's eligibility for inclusion in the systematic review, based on the reported parameters. It was performed using a customized data extraction form, which included following contents: year of publication, study design, study population, mean age, laboratory method of detecting salivary cortisol, tools for measuring the stress/anxiety/depression and outcomes. Inconsistencies were discussed and resolved between the two authors. Missing or unclear information was sought from the authors of the selected papers.

Risk of Bias Assessment

Two authors (MW and RM) independently estimated the quality/risk of bias of each included study. Case-control studies were evaluated by modified Newcastle–Ottawa Quality assessment scale (NOS).²⁸ Risk of bias was assessed domain wise. The studies were considered as good quality/low risk of bias when for the selection domain ≥ 3 stars; for comparability domain ≥ 1 star; and for outcome/exposure domain ≥ 2 stars were obtained. The studies were considered as fair quality/some concern when for the selection domain ≥ 2 stars; comparability domain ≥ 1 star; outcome/exposure domain ≥ 2 stars were obtained. The studies were considered as poor quality/high risk of bias when for the selection domain ≥ 0 or 1 star; comparability domain 0 star; outcome/exposure domain 0 or 1 star were obtained.

The Joanna Briggs Institute (JBI) Critical Appraisal tool was used to estimate quality of analytical cross sectional studies.²⁹ The positive answers of $\leq 49\%$ were considered as high risk of bias, whereas 50–69% for moderate risk and low risk of bias was considered when the positive answers were $>70\%$. The disagreements between two reviewers were resolved with discussion with third reviewer.

Statistical Analysis

The Review Manager 5.4 (RevMan 5.4, The Cochrane Collaboration, Oxford, United Kingdom) applying the mean difference (MD) and 95% confidence intervals (CIs) was used with a random/fixed-effects analysis. Forest plots and funnel plots were created to visualize the differences between groups and publication bias. The MD was calculated to estimate the salivary cortisol levels in OLP patients versus controls. The I^2 statistics were applied to evaluate heterogeneity between the studies. High heterogeneity was determined if $I^2 > 50\%$ and low heterogeneity when $I^2 < 50\%$. The random or fixed model was used depending upon high or low heterogeneity found, respectively. The Medcalc meta-analysis software was used to evaluate the correlation between the DAS scores and salivary cortisol. Also, publication bias was assessed among the studies using funnel plot and by Begg's and Egger's tests. The $p < 0.05$ was considered statistically significant.

RESULTS

Literature Search

Figure 1 depicts the study search process conducted according to the PRISMA guidelines. The initial online database (PubMed/MEDLINE, PMC, Cochrane, DOAJ and Google Scholar) and manual reference of included studies search yielded a total of 122 articles. After initial

Fig.1: PRISMA flow diagram (2009)

screening and applying the inclusion and exclusion criteria, eleven studies were included in the qualitative and quantitative analysis of salivary cortisol levels in OLP and healthy subjects.^{1-4,7,8,16,21-24}

Study Characteristics

The studies included 260 OLP patients and 253 controls. In all the included studies, ELISA was the most commonly used method of estimation for salivary cortisol level^{3,4,8,16,18,20,21} followed by the chemiluminescence immunoassay in two studies^{2,7} and radioimmunoassay in study by Girardi C et al.¹

Seven studies had case-control design^{1,4,8,16,19,20,22} and four studies had comparative cross-sectional design.^{2,3,7,21} Data of all included studies are shown in Table 1.

The scales/questionnaires used for scoring the DAS in various studies were Beck Depression Inventory, Beck Anxiety inventory, Lipps inventory of stress symptoms for adults (LISS) Hamilton anxiety scale, Holms and Rahe's stress scale, the state and trait anxiety inventory, and Percieved stress scale.^{1-4,7,8,16,18,20-22}

Girardi et al.,¹ Pires et al.,⁴ Pippi R et al.,⁸ Gaur B et al.,¹⁸ Gupta and Ahuja,²¹ and Kaur et al.²⁰ assessed the DAS scores. Lopez-Jornet et al.² and Vassandacoumara and Daniel² assessed anxiety and depression scores. Nadendla et al.³ assessed only the anxiety scores. Zenouz et al.¹⁶ assessed only stress scores.

The Weighted Kappa^a inter-examiner agreement rating was 0.87 with standard error 0.19 and 95% CI 0.64–1.00.

Results of Quality Assessment

All studies showed good and low risk of bias and were rated as high quality. The detail scores of the studies are given in Tables 2A and B.

Synthesis of Results

A quantitative synthesis (meta-analysis) was performed on the selected 11 studies for salivary cortisol levels in OLP and healthy subjects. Four cross sectional studies and seven case control studies were included for assessing the correlation of salivary cortisol levels with anxiety, depression and stress in OLP.^{1-4,7,8,16,21-24}

Meta-analysis

Salivary Cortisol Levels in OLP

Meta-analysis of cross-sectional and case-control studies showed no difference in the salivary cortisol in OLP and controls (Fig. 2)

using random model analysis. The pooled mean difference in cross-sectional studies of the salivary cortisol levels in OLP patients compared with controls was 5.19 ng/mL (95% CI: -0.72, 11.10) with $I^2 = 97\%$ which was statistically non-significant. ($Z = 1.72$; $p = 0.09$). Similarly, the pooled mean difference of the salivary cortisol levels in case-control studies was 0.55 ng/mL (95% CI: -2.53, 3.63) with $I^2 = 98\%$ which was statistically non-significant. ($Z = 0.35$; $p = 0.73$).

Stress, Anxiety and Depression Scores in OLP and Controls

Meta-analysis of cross-sectional studies (Fig. 3) in OLP patients compared to controls showed higher anxiety and depression scores which was statistically significant (MD: 7.58; 95% CI: 3.06–12.06; $p = 0.0009$ and MD: 5.39; 95% CI: 2.38–8.40; $p = 0.0005$ respectively). However, high heterogeneity was found in both anxiety ($I^2 = 94\%$) and depression ($I^2 = 85\%$) scores. The stress scores in OLP patients as compared to controls were statistically significant. Quantitative analysis between stress and OLP could not be performed as only one study has been reported.

Case-control studies (Fig. 4) showed higher stress and anxiety scores in OLP as compared to controls which was statistically significant. (MD: 9.04; 95% CI: 1.31–16.77; $p = 0.02$ and MD: 4.15; 95% CI: 3.11–5.19; $p < 0.00001$ respectively). No significant differences were observed for depression scores in OLP and controls. (MD: 5.72; 95% CI: -1.14 to 12.57; $p = 0.10$).

Correlation of Anxiety, Depression and Stress Scores with Salivary Cortisol Levels

In the two cross-sectional studies (Fig. 5) there was no correlation of anxiety and depression scores with salivary cortisol levels in OLP ($r = 0.0127$, $p = 0.931$, 95% CI: -0.267 to 0.290; and $r = 0.0888$, $p = 0.687$, 95% CI: -0.331 to 0.479 respectively) (Fig. 5). The Egger's test was significant ($p < 0.0001$) indicating possibility of publication bias. But Begg's test was non-significant ($p = 0.3173$).

In the three case-control studies (Fig. 6), there was no correlation of anxiety, depression and stress scores with salivary cortisol levels in OLP. ($r = 0.123$, $p = 0.313$, 95% CI: -0.116 to 0.348; $r = 0.136$, $p = 0.263$, 95% CI: -0.102 to 0.359; $r = 0.160$, $p = 0.117$, 95% CI: -0.0403 to 0.349, respectively). The Begg's and Egger's test ($p > 0.05$) indicated minimal or nil publication bias across the studies.

Table 1: Characteristics of included studies

Sr.no	Author/year	Study design	No. of OLP patients and controls	Mean age of patients/controls (years)	Salivary cortisol measurement method	Sampling time	Questionnaire used for assessment of depression/anxiety/stress	Outcome
1.	Girardi C et al. ¹	Case-control	31/31	53.8/55.5	Radio-immunoassay	8-10 am	Beck Depression Inventory, Beck Anxiety inventory, Lipps inventory of stress symptoms for adults (LISS)	Non-significant difference between the OLP and controls with respect to depression, anxiety or stress, or with respect to morning and night salivary levels of dehydroepiandrosterone and cortisol.
2.	Pippi R et al. ⁸	Case-control	20/14	57/53	ELISA	Morning, noon, & evening (7.30 am, 12.00 Noon and 19.30 pm)	The state and trait anxiety inventory Beck Depression Inventory Perceived stress scale	OLP patients showed a significantly lower capability of active coping that was associated with higher scores in stress perception and loneliness and significant reduction of diurnal salivary cortisol production (morning). Salivary cortisol level in patient with OLP significantly less than healthy persons. Statistically significant increase in salivary cortisol and stress scores in OLP patients.
3.	Nosratzahi T et al. ²⁴	Case-control	20/20	45.8/42.8	ELISA	9-10 am	Depression Anxiety Stress (SCL-90)	Salivary cortisol level in patient with OLP significantly less than healthy persons.
4.	Zenouz AT et al. ¹⁶	Case-control	30/30	48.6/47.3	ELISA	9-10 am	Holms and Rahe's stress scale	Statistically significant increase in salivary cortisol and stress scores in OLP patients.
5.	Kaur B et al. ²¹	Case-control	25/25	Matched	ELISA	9-10 am	Depression Anxiety Stress scale	Significantly higher depression, anxiety, and stress scores in OLP. Salivary cortisol levels were increased and correlated with psychological factors in OLP.
6.	Gaur A et al. ²²	Case-control	30/30	46.50±28.99 / 46.50±28.99	ELISA	9-10 am	Depression Anxiety Stress scale	Highly significant increase in salivary cortisol levels in OLP subjects. A significantly higher stress anxiety and depression levels in OLP.
7.	Pires ALPV et al. ⁴	Case-control	21/21	49.19/48.10	ELISA	Awakening, 30-minute post-awakening, bedtime	Beck Depression Inventory, Beck Anxiety inventory, Perceived stress scale	Oral lichen planus was associated with anxiety, depression and stress scores through psychological tests, but not in relation to the pattern of salivary cortisol secretion.
8.	Nadendla LK et al. ³	Cross-sectional	20/20	Matched	ELISA	9-9:15 am	Hamilton anxiety scale	The mean salivary cortisol level and anxiety score in OLP group showed highly significant difference (p < 0.001) Positive correlation between anxiety and salivary cortisol.
9.	Lopez-Jornet P et al. ²⁷	Cross-sectional	33/32	57 ± 15.8 / 53 ± 12	Chemiluminescent enzyme immunoassay	Before 10 am	Hospital anxiety and Depression scale	Significantly higher Hospital anxiety and depression scale (HADA) and Pittsburgh sleep quality scores in OLP. Significant increase in cortisol in OLP.
10.	Vassandacoumara V & Daniel JM. ²	Cross-sectional	20/20	42.3/34.1	Chemiluminescent immunoassay	8-9 am	Hospital anxiety and Depression scale	Non-significant increase in salivary cortisol level in the OLP compared to controls. Anxiety and depression scores showed strong positive correlation in both groups.
11.	Gupta & Ahuja. ²³	Cross-sectional	10/10	39.51/23.75	ELISA	9-10 am	Depression Anxiety Stress scale	Depression, anxiety and stress along with salivary cortisol levels were higher in oral lichen planus. Salivary cortisol levels were correlated with psychological factors.

Table 2A: Quality assessment of case-control studies using the modified Newcastle-Ottawa Quality assessment scale

Studies	Selection		Comparability			Exposure		Non-response rate	Total quality score
	Is the case definition adequate?	Representative-ness of the cases	Selection of controls	Definition of controls	Comparability of cases & controls	Ascertainment of exposure	Same method of ascertain-ment for cases & controls		
Girardi et al. ¹	1	0	1	1	1	1	1	1	Good
Pippi et al. ⁸	1	0	1	1	1	1	1	1	Good
Nosratzahi et al. ²⁴	1	1	1	1	1	1	1	1	Good
Zenouz et al. ¹⁶	1	1	0	1	1	1	1	1	Good
Kaur et al. ²¹	1	1	0	1	1	1	1	1	Good
Gaur et al. ²²	1	1	0	1	1	1	1	1	Good
Pires et al. ⁴	1	1	1	1	1	1	1	1	Good

Table 2B: Quality assessment of cross-sectional studies using Joanna Briggs Institute (JBI) critical appraisal tool

Studies	Response options*								Overall appraisal	Risk of bias
	1	2	3	4	5	6	7	8		
Nadendla et al. ³	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Include	Low
Lopez-Jornet et al. ²⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include	Low
Vassandacoumara and Daniel ²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include	Low
Gupta and Ahuja ²³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include	Low

* 1 - Were the criteria for inclusion in the sample clearly defined?; 2 - Were the study subjects and the setting described in detail?; 3 - Was the exposure measured in a valid and reliable way?; 4 - Were objective, standard criteria used for measurement of the condition?; 5 - Were confounding factors identified?; 6 - Were strategies to deal with confounding factors stated? 7 - Were the outcomes measured in a valid and reliable way?; 8 - Was appropriate statistical analysis used?

Fig. 2: Forest plot – salivary cortisol levels in the OLP patients vs. controls [cross-sectional studies and case-control studies]

Fig. 3: Forest plot – anxiety and depression scores in the OLP patients vs. controls [cross-sectional studies]

Fig. 4: Forest plot – anxiety and depression and stress scores in the OLP patients vs. controls [case-control studies]

DISCUSSION

The evidence from this research suggests salivary cortisol levels were not significantly elevated in OLP compared to controls. The anxiety scores in OLP patients were significantly higher in OLP patients as shown in both cross-sectional and case control studies. The depression scores were shown to be higher in OLP patients in cross-sectional studies. The stress scores were also

significantly higher in OLP patients as reported in case-control studies. Quantitative evaluation of anxiety, depression and stress scores were statistically not correlated with salivary cortisol levels in OLP patients.

The studies by Gaur et al.¹⁸ Kaur et al.²⁰ and Pires et al.⁴ found a positive correlation between DAS scores with salivary cortisol levels in OLP. Zenouz et al.¹⁶ found no correlation between stress scores and salivary cortisol. Also, Lopez et al.⁷ and Vassandacoumara et al.²

Fig. 5: Forest plot and funnel plot – correlation of anxiety and depression scores with salivary cortisol in OLP patients [cross-sectional studies]

found no correlation between anxiety and depression scores with salivary cortisol levels in OLP. In a study by Nadendla et al.,³ the outcomes measured were not clearly mentioned as published data was not available although it was stated that cortisol levels were statistically not correlated with anxiety. Hence, it was not included in the meta-analysis. It is evident in the present systematic review that although anxiety, depression and stress score are significantly higher in OLP patients than controls, no correlation between these factors with salivary cortisol levels was observed.

Evidence suggests the role of psychological stress on the immune function that results in the development of psychosomatic disorders.^{5,18,25,30,31} Psychological stress acts as initiating or precipitating factor which causes an imbalance in the Th1/Th2 cytokines primarily. As the repeated episodes of stress continue there is a change or amplification of cytokine production including IL-2, IL-12, IFN- γ , TNF- α , IL-4, IL-5, IL-6, IL-10 and IL-13 that modify the immune response and initiate the inflammatory process which eventually results in the immune dysregulation. Neuroendocrine immune system primarily the catecholamines further this process by increasing the function of cytotoxic T cells that result in keratinocyte apoptosis which is the hallmark of OLP.^{5,32-36}

This psychological stress leads to activation of HPA axis which leads to increased production of glucocorticoids and

catecholamines followed by increased levels of cortisol in the serum and saliva. Many authors have suggested that the salivary cortisol levels indicate the free cortisol that can be used as a non-invasive and simple method for estimation of psychological instabilities.^{2,5,7,10,20,25,35}

This meta-analysis has included studies with good study design and analysis indicating high internal and external validity. The risk of bias was performed by two independent examiners for each study. The inter observer agreement was found more than 80% for studies being assessed.

High heterogeneity was evident in the included studies. This may be attributed to assessment of the DAS scores or variants of OLP in clinical diagnosis. Such variability does not allow creating a standard protocol for assessment of DAS scores in OLP. Since there is no 'standard scale' for measurement of DAS score. Further, the reliability of one scale over another is not estimated. However, the publication bias was observed in this study as evident from the results of Begg's and Egger's test.

Confounding factors that were addressed in most of the included studies are the cortisol awakening response (CAR), which is the rise in cortisol levels from wake time to 30 min post. In almost all the included studies the timing of salivary cortisol collection was followed as early morning sample to assess this response since

Fig. 6: Forest plot and funnel plot – anxiety and depression and stress scores in the OLP patients vs. controls [case-control studies]

timing of saliva sample collection is crucial in analyzing the results. Also, age and gender related changes associated with the cortisol levels were addressed by age and sex matching the controls in the included studies. Certain diseases and medications could change the cortisol production, so most studies designed strict exclusion criteria for this purpose. Similarly the intake of nicotine, alcohol and smoking could alter the cortisol levels; this issue was addressed by rigid inclusion criteria.³⁷

The use of language restriction is one of the inherent bias in this systematic review, providing prejudice in interpreting the evidence. There is currently no agreement on language limits in conducting systematic reviews. Non-English studies may be systematically different from English-language research, and limiting by these features may add a systematic bias as well. Because the review team does not have the ability to read other languages, the decision

to employ exclusively English-language publications may be made. Furthermore, the time and expense of translation are not viable given the time and financial constraints. To emphasise, the employment of non-restriction of language barrier would give high findings, and assessment of these studies may undermine the quality assessment in the absence of other inputs.³⁸ A recent study found no evidence of systematic bias from the use of language constraints in systematic review-based meta-analyses in conventional medicine.³⁹

There are certain limitations in the present systematic review that should be taken into consideration. The levels of cortisol secretion vary throughout the day depending on the stressful situations and the concentration of cortisol follows a normal circadian rhythm.³⁷ In the present analysis, only two studies have analyzed the diurnal variations of salivary cortisol in OLP

patients.^{4,8} Also, different scales of assessment of DAS were used in the included studies.^{3,4,7,8,18,21} The difficulty of establishing causality between OLP and psychological factors may be related to the use of different measurement instruments, as well as subjectivity, lack of a methodological standard and the low statistical power of the studies due to small sample size.^{4,9}

Nevertheless, the outcome of this meta-analysis should be interpreted carefully considering the high heterogeneity due to methods used to analyze DAS scores and limited number of studies involved for the meta-analysis. More research is required to understand the influence of language restrictions on systematic reviews in specific domains of Medicine. One feasible solution would be to make medical information available in widely accepted languages, preferably English. This will account for the evidence while reducing the potential bias of a language barrier. Future studies are needed with bigger cohorts in order to evaluate all the different variants of OLP. The assessment of stress and circadian rhythm of salivary cortisol also is a field of future research. Moreover, the standardized protocols and scales for assessing the stress, anxiety and depression need to be formulated for better comparison of results.

CONCLUSION

The current systematic review reported no difference in salivary cortisol levels in OLP patients. While higher scores of anxiety, depression and stress in OLP patients were reported compared to controls, but no correlation was seen between the anxiety, depression and stress scores with salivary cortisol levels. However, the results should be interpreted cautiously when correlating salivary cortisol levels with psychosocial factors in OLP since objectively quantifying a psychological disorder can often be difficult and inaccurate because of individuals' subjectivity and the difficulty of methodological standardization. Regardless, we recommend psychological counselling in conjunction with conventional management to help strengthen patients' ability to deal with psychological instabilities that may further improve healing of OLP.

CLINICAL SIGNIFICANCE

Oral lichen planus is a psychosomatic disorder and salivary cortisol is biomarker of stress. The psychological factors including stress, anxiety and depression plays a crucial role in pathogenesis of OLP. We reported higher levels of salivary cortisol and higher scores of anxiety, depression and stress in OLP patients compared to controls. Similarly, no correlation between anxiety, depression and stress score and salivary cortisol is established. Thus, we recommend psychological counseling in combination with conventional management to help increase patients' capability to deal with psychological instabilities that could further improve OLP healing.

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