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Original Research

Salivary Cortisol as a Diagnostic Marker in Oral Lichen Planus

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Abstract:

Background: Lichen planus (LP) is a common chronic inflammatory diseases of oral mucous membrane and skin. Cortisol, also known as "stress hormone" released by the adrenal gland, has been used as an indicator in various studies related to stress evaluation. The aim and objective of the study were to evaluate salivary cortisol levels and psychological factors and to find a correlation between the two in patients with oral LP (OLP) and control group.

Materials and Methods: This study was comprised of 50 patients, 25 OLP patients (clinically and histopathologically proved), along with 25 subjects with the age and sex-matched healthy controls were included in the study. Stimulated saliva samples were collected, centrifuged at 800 rpm and analyzed for the level of cortisol by using cortisol enzyme linked immunosorbent assay. Psychosocial factors of study and control groups were measured by using depression anxiety and stress scale. Student's *t*-test was used for comparison of psychological factors and salivary cortisol levels between OLP patients and the control group.

Results: Significantly higher depression, anxiety, and stress, (18.16 ± 2.62, 13.08 ± 2.15, 20.80 ± 3.34, respectively) scores were observed in patients with OLP compared to controls, irrespective of sex. Increased salivary cortisol levels were observed among 14 OLP patients in the study group. A correlation that was found between psychological factors and salivary cortisol levels in the OLP patients was positive. The Pearson's correlation coefficient "*r*" values, between depression, anxiety, and stress with salivary cortisol was: +0.21, +0.24, +0.23, respectively among the study group.

Conclusion: The present study concluded that OLP is closely related to stress. Hence, in the investigations of OLP estimation of the salivary cortisol levels should be considered. OLP patients should be provided with proper psychological counseling, which will increase their ability to cope with stress together with traditional treatment modalities.

Key Words: Anxiety, depression, oral lichen planus, salivary cortisol, stress

Introduction

Oral lichen planus (OLP) is an immunopathological disease that involves the cell-mediated arm of the immune system.[1] It is believed to result from an abnormal T-cell mediated immune response in which basal epithelial cells are recognized as foreign because of changes in the antigenicity of their cell surface. The cause of this immune-mediated basal cell damage is unknown.[2] LP affect primarily middle-aged adults, and prevalence is greater among women. Children are only rarely affected. The classic skin lesion of the cutaneous form of the LP can be described as purplish, polygonal, planar, pruritic, papules, and plaques. These skin lesions commonly involve the flexor surfaces of the legs and arms, especially the wrists.[2] White papules that usually coalesce, forming a network of lines (Wickhan's striae) are the characteristic OLP.[3]

Patient with OLP often relate the onset and aggravates of oral symptoms to an increase in negative and stressful events. Several studies have reported a relationship between OLP and various forms of disorders related to stress, although the results have not been consistent. It is possible that the activity of symptoms of OLP in many patients may involve an impaired capacity to suppress an increased immune response following a stressful event. Evidence accumulated during the last few decades supported that psychological stress and psychiatric illness can modify the immunological response. Investigators examining patients with dental fear have revealed elevated concentrations of salivary – Free cortisol following stress in conjunction with dental treatment.[1]

Cortisol, also known as "stress hormone" released by the adrenal gland, has been used as an indicator in various studies related to stress evaluation. Cortisol is the main glucocorticoid in humans and has a large range of influences on metabolism, vascular responsiveness, immunoregulation, cognition, and behavior. It also has an impact on various pathological diseases including inflammatory autoimmune disorders. The measurement of salivary cortisol is an indicator of free cortisol or biologically active cortisol in human serum and provides easy and non-invasive technique.[4]

The aim of the study was to evaluate psychological factors and salivary cortisol levels in OLP patients and compare it with the control group. The objectives of the study were to find

a correlation between the psychological factors and salivary cortisol levels in OLP patients with the control group.

Materials and Methods

The study was conducted in the Department of Oral Medicine and Radiology, Guru Nanak Dev Dental College and Research Institute, Sunam, Punjab. All the patients were included in the study were not suffering from any systematic diseases such as diabetes, cardiovascular disease, renal dysfunction, and liver disorder, etc., or any other mucosal diseases and free of adverse habit of chewing tobacco, gutka, and habits of smoking.

This study is comprised of 50 patients including 25 OLP patients (Group A), and 25 patients as control (Group B). Patients were informed about regarding the study and their written consent were obtained after recording detailed case history as per performa. Clinically diagnosed cases of OLP were subjected to incisional biopsy. The histopathologically diagnosed OLP cases were included in the study. An informed consent was obtained from each patient for the further diagnostic procedure.

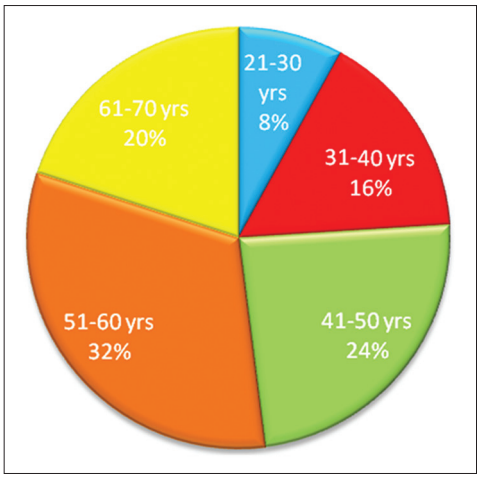
Intensity of burning sensation was assessed by using a visual analog scale (VAS) which is from 0 to 10 (with 1 cm divisions, where "0" is considered as no burning sensation and "10" is worst possible burning sensation). These patients were asked to mark VAS scale at a point which best represented the symptoms. After the histopathological approval, these patients were subjected to the collection of saliva and psychological evaluation. Saliva was collected in the morning hours between 9 and 10 am to prevent diurnal variations. In each patient, approximately 2.0 ml of stimulated saliva was collected from by drawing it with a disposable syringe and centrifuged at 800 rpm and analyzed for levels of cortisol by using cortisol enzyme linked immunosorbent assay. After that, patients were subjected for a psychological evaluation to estimate depression, anxiety, and stress scale (DASS). This scale comprises of a self-assessment questionnaire of 42 questions. Each component of depression, anxiety, and stress contain 14 questions. The questionnaire was translated into the regional language of Punjabi for the purpose of benefit to the patient.

Statistical analysis was presented as number and percentages for categorical data and mean ± standard deviation for quantitative/continuous data. Student's *t*-test was used to compare the means of both the groups. Categorical data were analyzed by using Chi-square test. Pearson's correlation coefficient was used to analyze the relationship between different parameters. $P = 0.05$, or less was considered for statistical significance for all the tests.

Results

The present study comprised of 50 subjects, out of which 25 patients were histopathologically proved OLP group (Group A) and 25 patients were with the control group (Group B). A total of 25 patients of OLP group, out of which 9 patients (36%) were males and 16 (64%) were female patients in each group. The average age of patients between 21 and 70 years. Maximum, i.e., 32% patient were present in the age group between 51 and 60 years (Graph 1). Three types of clinical pattern were observed in the present study, reticular in 13 (52%) patients, in erosive form of OLP in 11 (44%) patients, and plaque only in one patient 1 (4%) (Graph 2 and Table 1); and all the patient were symptomatic (Table 2). 2 (8%) patients were presented with skin involvement.

In this study, we found increased values of depression, anxiety, and stress with mean values (18.16 ± 2.62, 13.08 ± 2.15, 20.80 ± 3.34, respectively) among the OLP group (Group A) (Graphs 3 and 4) which was significant. The salivary cortisol levels were found to be increased in 14 patients and 11 patients had normal levels, i.e., 3-10 ng/ml with mean value of 10.29 ± 1.25 as compared to the control group with mean value of 4.58 ± 1.30) (Graph 5 and Table 3) we found significantly higher levels of salivary cortisol levels in OLP group patients. We also found a positive correlation between psychological factor depression, anxiety, stress, and salivary cortisol levels in patients with OLP (Group A) and it was statistically significant ($P < 0.05$) (Graph 5 and Table 4) and in control group (Group B) it was positive correlation, which was non-significant (Graph 6 and Table 5).



Graph 1: Distribution of oral lichen planus patients according to age.

Table 1: Distribution of OLP patients according to gender.

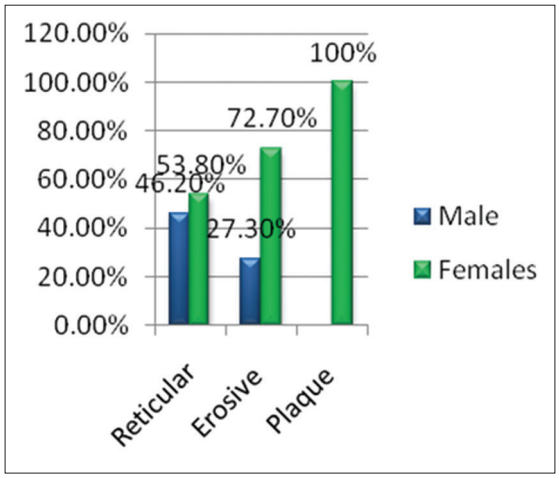
Type of LP	Gender		Total *n* (%)
	Male	Female	
Reticular	06	07	13 (52)
Erosive	03	08	11 (44)
Plaque	-	1	1 (4)
Total	9	16	25 (100)

OLP: Oral lichen planus, LP: Lichen planus

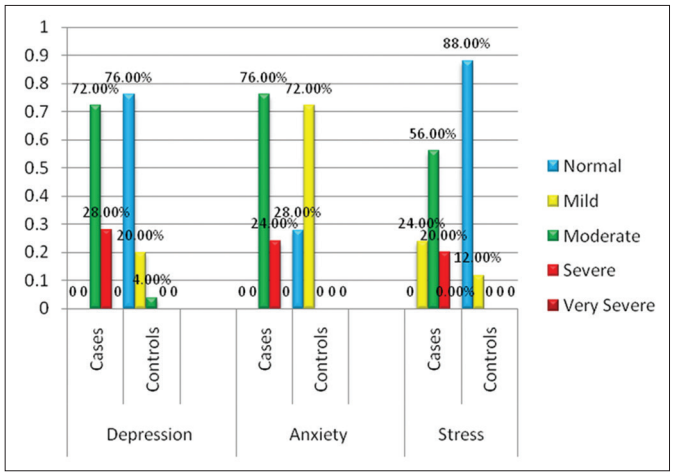
Table 2: Severity of burning sensation in patients with different types of OLP.

Type of LP	VAS score		
	Mild (5-44 mm)	Moderate (45-74 mm)	Severe (75-100 mm)
Reticular (13)	1 (7.75%)	12 (92.3%)	-
Erosive (11)	-	07 (63.6%)	04 (36.4%)
Plaque (1)	-	-	01 (100%)
Total	01	19	05

OLP: Oral lichen planus, VAS: Visual analogue scale, LP: Lichen planus



Graph 2: Distribution of patients according to the type of oral lichen planus and gender.



Graph 3: Depression, anxiety and stress in patients with and without oral lichen planus.

Table 3: Salivary cortisol levels in patients with and without OLP.

Salivary cortisol levels ng/ml	Cases	Controls	*t* value	df	*P* value
3-10	11	25	15.723	48	0.001
>10	14	-			
Mean±SD	10.29±1.25	4.58±1.30			

OLP: Oral lichen planus, SD: Standard deviation

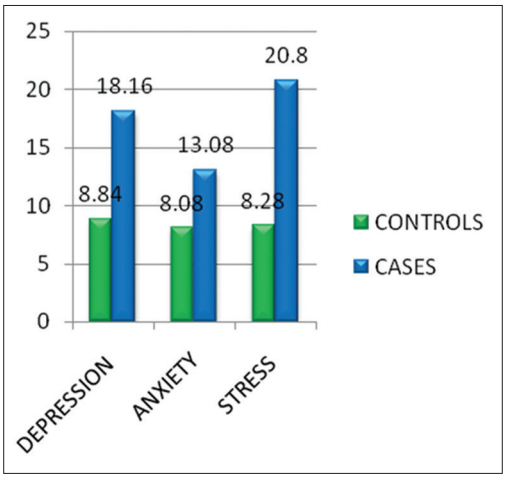
Table 4: Correlation between salivary cortisol and psychological factors in control group.

Salivary cortisol and psychological factors	*R* value	*P* value
Depression and salivary cortisol	+0.21	0.04 significant
Anxiety and salivary cortisol	+0.24	0.04 significant
Stress and salivary cortisol	+0.23	0.04 significant

Table 5: Correlation between salivary cortisol and psychological factors in OLP patients.

Salivary cortisol and psychological factors	*R* value	*P* value
Depression and salivary cortisol	+0.03	0.59 non-significant
Anxiety and salivary cortisol	+0.02	0.19 non-significant
Stress and salivary cortisol	+0.03	0.41 non-significant

OLP: Oral lichen planus

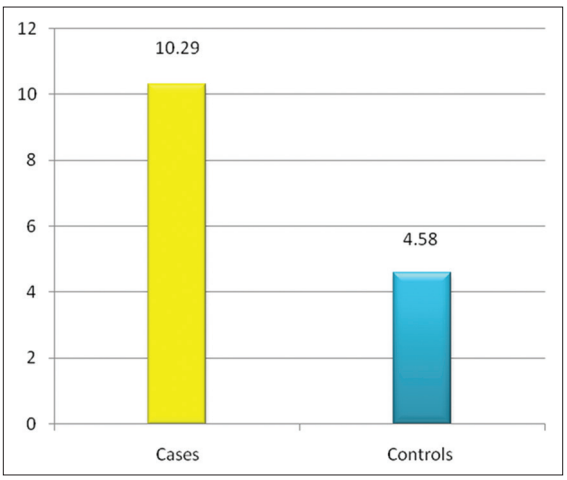


Graph 4: Mean disease activity score scores in patients with and without oral lichen planus.

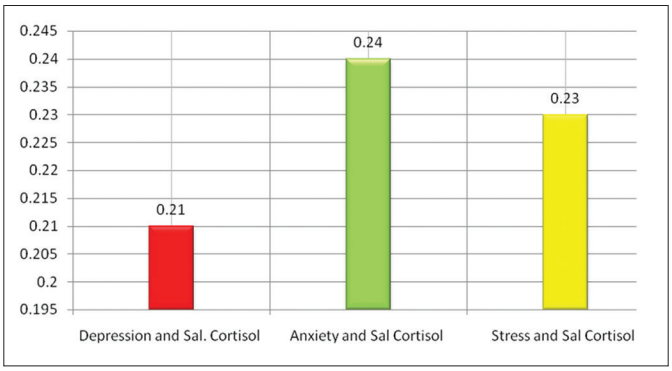
Discussion

OLP is a relatively common disease of adults and has a wide distribution in the world. The prevalence is found to be 0.02-0.22% among Indians, as per recorded in 30,000 dental outpatients.[5] The number of scales was used in the psychological evaluation of patients in previous studies, some of which were self-assessed and others reported by a psychiatrist. In the present study, we used a self-reported scale known as DASS, by which all the three parameters, i.e., depression, anxiety, and stress can be assessed.[4,6]

The increase in serum cortisol levels with psychological factors such as depression, anxiety, and stress, due to activation of hypothalamus pituitary adrenal (HPA) axis was very well established in the literature. Although, there are changes in the cortisol levels at different points of time during the whole day; a positive correlation was observed among the levels of salivary cortisol in the OLP patients.[7,8] Secretion of cortisol in saliva is a passive process, and it is a reliable indicator of serum levels also. Since, this is a non-invasive and easy procedure, for the measurement of salivary cortisol levels and psychological



Graph 5: Salivary cortisol levels in patients with and without oral lichen planus.



Graph 6: Correlation between salivary cortisol and psychological factors in oral lichen planus patients and control group.

factors in patients with OLP.[7,8] Cortisol by salivary sampling was evaluated in the current study. A total of 25 patients in a Group A, out of which 9 patients (36%) were males and 16 (64%) were female patients. Similarly, Group B comprised of 25 patients, out of which 9 patients (36%) were males and 16 (64%) were females. However, in our study, we found the female predominance in OLP group, which is accordance with the studies done by Xue *et al.*,[9] Shah in 2009,[4] Girardi *et al.*[10] The average age of patients between 21 and 70 years. The Maximum, i.e., 32% patient were present in the age group between 51 and 60 years (Graph 1).

It could be due to stress as one of the etiological factors for OLP. Stress occurs in middle age women because of poor socioeconomic status, financial strain, physical inactivity, low social support, and poor physical health. In our study,[7,11] we observed that the stress over the family concerns and hormonal imbalances were responsible for the etiopathogensis of OLP.

The present study included a total of three types of clinical pattern such as reticular in 13 (52%) patients, in erosive form of OLP in 11 (44%) patients, and plaque only in one patient 1 (4%) (Graph 2 and Table 1) and all the patient were symptomatics (Table 2). Totally, 2 (8%) patients were presented with skin involvement.

It is very well established in the literature that burning sensation was associated in patients with erosive lesions or is always related to the red component or non-keratotic variant of OLP. In majority of reported studies and surveys, OLP can be present at multiple oral sites with various clinical forms.[4]

The modern view of the etiopathogenesis of most of the diseases suggest them to be influenced by multiple factors, hence requiring a simultaneous evaluation of factors concerned with various etiology. The new biopsychosocial medical model, which comprises of biological findings (disease), psychological ones, and social correlatives were described by Engle. This concept holds true for OLP.[4]

Two of the conditions known to be intermediate factors leading to many somatic malfunctions, stress, and anxiety, are the combined results of psychological and environmental social factors. Each of these two factors have a potential effect on oral health.[4]

In the current study, we found increased levels of depression, anxiety, and stress with mean values (18.16 ± 2.62, 13.08 ± 2.15, 20.80 ± 3.34, respectively) among the OLP group (Group A), which was significant, and it is in accordance with the studies done by Koray *et al.* in 2003[3] Choudhary *et al.* in 2004,[14] Soto Araya *et al.* in 2004,[13] and Shah *et al.* in 2009[4] The salivary cortisol levels were found to be increased in 14 patients and 11 patients had normal levels, i.e., 3-10 ng/ml with mean value of 10.29 ± 1.25 as compared to the control group with mean value of 4.58 ± 1.30, we found significantly higher levels of salivary cortisol levels in OLP group patients which is in accordance with the studies done by Koray *et al.* in 2003[3] and Shah *et al.* in 2008.[4] We also found a positive correlation between psychological factor depression, anxiety, stress, and salivary cortisol levels in patients with OLP (Group A) and it was statistically significant ($P < 0.05$) and in control group (Group B) it was positive correlation, which was non-significant. The present study confirms that OLP is closely related to stress. Hence, in the investigations of OLP estimation of the salivary cortisol levels seems to be an important marker in diagnostic criteria.

It is accepted that the organization of the autonomic innervations is such that nerve fibers lie in close contact with lymphocytes, and that some noradrenergic terminals lie among the hematopoietic elements within bone marrow and terminate in the thymic parenchyma and in the T-cells of the lymph node paracortex. Evidence for a potential interaction between the central nervous system and the endocrine and immune system is derived from *in vivo* and *in vitro* observations that may bioactive molecules including corticosteroids can influence

immune function and that receptors for these molecules are present on mononuclear cells including lymphocytes and macrophages.[14]

Neuroendocrine and immune systems share many common signaling molecules and receptors supporting the notion that the brain has an immunoregulatory role while the immune system functions in a sensory capacity. Glucocorticoids can potentially affect immune function and, conversely, activated immune cells can release cytokines capable of affecting the HPA axis suggesting that an immune-HPA axis circuit operates during the immune response. The stimulation of the HPA axis will result in inhibition of the production of certain cytokines via the production of glucocorticoids. In turn, cytokines derived from activated immune cells including interleukin-1 (IL-1), tumor necrosis factor-alpha, interferon-alpha, and interferon can alter the function of the HPA axis.[14]

During stress mechanism, serum corticoid concentrations are significantly elevated potentially leading to an immunosuppressive milieu by their negative effects on mononuclear cells and the production of pro-inflammatory cytokines. This observation may reflect a compensatory upregulation of the HPA axis to control the immune and inflammatory response in these patients. However, the effects of glucocorticoids can be selective and depend on the stage and type of immune activity glucocorticoids can affect the lymphocyte subsets, and thus, induce a shift between Th1/Th2 cytokines while preferentially inhibiting non-activated lymphocytes, thus favoring IL-2 expression during clonal expansion.[14]

This may result in the suppression of cells having little or no affinity for an antigen and favor the clonal expansion of cells for antigen having high affinity. However, the major depression has been associated with activation of the inflammatory response as pro-inflammatory cytokines are potent stimulators of the HPA axis. In particular, IL-6 stimulates production of corticotrophin releasing hormone enhancing HPA activity, and hence, the increased levels of adrenocorticotropic hormone and cortisol levels. Paradoxically despite the hypersecretion of glucocorticoids, there is an increase in pro-inflammatory cytokine levels during chronic stress and depression suggesting a hypofunctional state of glucocorticoid receptors on immune cells that fail to suppress key components of cellular immunity.[14]

Cortisol and psychological status may play a role in the pathogenesis of OLP. Taken together, these may represent avenues by which the psychological status of an individual may impact on immune system homeostasis during onset and progression of LP.[13-15]

Conclusion

The present study confirms that OLP is closely related to stress. Hence, in the investigations of OLP estimation of the salivary cortisol levels seem to be an important marker in diagnostic criteria.

This psychological alteration forms a starting point for the initiation of various autoimmune reactions, which have been shown to be contributory to the pathogenesis of OLP. All the OLP patients should be provided with proper psychological counseling, which will increase their ability to cope with stress together with traditional treatment modalities. However, the estimation of the salivary cortisol levels seems to be a promising parameter in the investigation of OLP. Hence, our study necessitates further large sample size required with an improved protocol in order to improve that psychological state assessment in OLP patient, which could influence the better treatment plan.

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