

# Cortisol And Psychological Factors in Etiology of Lichen Planus

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## Abstract

**Background and Objectives:** Lichen planus is a common chronic inflammatory disease of oral mucosa and skin, whose exact pathogenic mechanisms have not been understood. Cortisol, has been used as an indicator in various psychological evaluation studies. Salivary cortisol measurement is an indicator of free cortisol in human serum and provides noninvasive and easy technique.

**Aims,** evaluation of cortisol levels and psycho-immunity profile in lichen planus patients was done. Using case-control method.

**Materials and Method:** 145 participants were admitted which had been done at dermatological outpatient clinic at Al-Yarmook Teaching Hospital. 32 patients were clinically proven cases of LP, 113 subjects along with age and sex-matched healthy controls. DASS Score questionnaire was administered to evaluate the psychiatric status (depression, anxiety and stress), Saliva samples were collected, and analyzed for cortisol level by using **ELISA** in study group and 46 of control group. The serum test were examined in 32 for each group using enhanced lanthanide fluoroimmunoassay technique for cortisol.

**Results:** The mean serum and Salivary cortisol level of the LP group showed a very highly significant difference ( $p=0.001$ ) from the controls in multivariate statistic. The mean of DASS scores and the depression derangement specifically showed a very highly significant difference ( $p=0.001$ ) from the controls. The stress and anxiety derangement showed high difference but it failed to reach to significant difference from the controls. There is an important association between serum and salivary cortisol concentration.

**Conclusion:** the cortisol and psychiatric factors play a vital role in the pathogenesis of LP and saliva cortisol could be a possible indicator instead of serum cortisol

**Key Words:** *Lichen Planus, Cortisol, DASS, Stress, Depression, Anxiety*

## Introduction

Lichen planus is a chronic inflammatory mucocutaneous disorder, which can manifest in the oral mucosa. Oral lichen planus affects 0.1-4% of various populations. The disease usually affects middle-aged to elderly females. Currently the precise cause of lichen planus is unclear. Stress, depression and anxiety are the most common psychological factors, which causes alteration of the body tissues in general and oral in specific<sup>(1)</sup>. The world health organization classified OLP into several clinical forms: Reticular, papular, plaque – like, atrophic, erosive, ulcerative and bullous. The most

often affected areas are the posterior buccal mucosa and tongue, the non-erosive form is often asymptomatic. The erosive forms are commonly sensitive or painful and affect the quality of life<sup>(2)</sup>.

Stress alters the regulation of both sympathetic and parasympathetic branches of autonomic nervous system, with consequential alteration in hypothalamic control of endocrine response controlled by the pituitary gland, autonomic activation and elevation of hormones, including those produced by hypothalamic-pituitary – adrenal axis, play pivotal roles in regulation immune surveillance mechanism, including production of

cytokines that control the inflammatory process (3).

Cortisol is a 21-carbon glucocorticoid secreted by the adrenal cortex that regulates carbohydrate, protein, fat and water metabolism, maintains vascular reactivity, affects the sensitivity of the nervous system, regulates blood cell numbers, and affects the human stress response (4). Cortisol levels can be measured in urine, and saliva. This approach has several methodological advantages, including the noninvasive collection of samples, reduced stress and repeatable sampling unlike blood. Cortisol in saliva is a useful index for investigations of chronic and acute stress reflected in HPA axis activity (5).

**The objectives of this study are:** Estimate serum and unbounded salivary cortisol level in Lichen Planus patient, evaluate the psychological disorders (depression, anxiety and stress) levels using Depression Anxiety Stress scale in Lichen Planus patient. and evaluate correlation between serum and salivary unbounded cortisol in Lichen Planus patient.

**Patient selections:** A total of thirty-two patient with Lichen Planus seen in the dermatological clinic at Al Yarmook Hospital., **Questionnaires:** is including name, complete history , *Depression Anxiety Stress Scales - DASS21* (the DASS is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety, and stress), **Salivary cortisol :** A-Reagents supplied in unbounded salivary cortisol kit ,and **Serum cortisol kit:** Vidas cortisol kit: Is used to determine cortisol on serum.

**Method**

**DASS questionnaires:** All case-control subjects are asked to use 4-point severity/frequency scales to rate the extent to which they have experienced each state over the past week.

**Table 1 case-control difference in Serum and Salivary cortisol, the differences failed to reach the level of statistical significant 0.1{NS}**

parameters	group	range	mean	SD	SE	n	p(t-test)
Serum cortisol	Control	(1.8-192.9)	171.4	60.9	11.13	30	0.23 {NS}
	Cases	(40.1-194)	194.4	85.1	15.04	32	
	Cohen’s effect size of being a case compared to control =0.43						
Salivary unbounded cortisol	Control	(1.8-192.9)	171.4	60.9	11.13	30	0.82 {NS}
	Cases	(40.1-194)	194.4	85.1	15.04	32	
	Cohen’s effect size of being a case compared to control =0.34						

**Salivary and Serological laboratory tests:** Collecting Saliva: The participants gave 5 minutes to collect saliva in the plain tube. The time of collection was between (9:30 am-12:00 pm) to pool saliva and refrigerate samples within 30 minutes and freeze at or below -20°C within 4 hours after collection. The Serological measurements were done in Teaching Laboratories at Al Yarmook Hospital for each group.

**Statistical Analysis:** Data were translated into a computerized database structure. A multiple linear regression model was used to study the net and independent effect of a set of explanatory variable on a quantitative outcome (dependent) variable like salivary cortisol concentration. The model provides the following parameters: P (model), Unstandardized partial regression coefficient, P for regression coefficient, and R<sup>2</sup>. A multiple logistic regression model was used to assess the net role of a set of explanatory variables in predicting Lichen Planus cases differentiating them from healthy controls, the model provides the following parameters: P-value for the model, The overall predictive power, Adjusted OR, and P-value for OR.

**Cases Distribution:** 32 patient included in the study were distributed into 21 females and 11 males, the female to male ratio was 1.9:1. While the control group consisted of 113 divided into 57 females and 56 males. The female ratio was almost 1:1. For the Lichen Planus group their ages were ranged between (16-60) with a mean ±SD 41.6 ±13.2 years. Compare to (19-67) years in control groups with a mean± SD are 41.8 ± 11.4years. The differences failed to reach the level of statistical significant 0.1 {NS}. The age difference between study groups is not an important confounder.

**Asses the magnitude the case-control difference in DASS scale**

**The anxiety Score (/100)** showed obviously higher 7 in comparison with healthy controls. The effect of the disease on the **anxiety Score** was moderate (Cohen's =0.38).

**The depression score (/100)** showed obviously higher 11.1 in comparison with healthy controls (27.9). The effect of the disease on the depression score was moderate (Cohen's =**0.58**).

**The stress Score (/100)** showed obviously higher 6.5 in comparison with healthy controls (42.6). The effect of the disease on the **stress Score** was moderate (Cohen's =0.31).

**The DAS Score (/100)** showed obviously higher 8.2 in comparison with healthy controls (33.3), the effect of the disease on the depression score was moderate (Cohen's =**0.48**).

**Table 2 Asses the magnitude the case-control difference in DASS scale**

DASS scale		range	mean	SD	SE	n	p(t-test)
anxiety Score (/100)	Cases	(4.8 - 71.4)	36.4	17	3.01	32	0.06[NS]
	Control	(0 - 81)	29.4	18.7	1.76	113	
	Cohen's effect size of being a case compared to control 0.38						
depression Score (/100)	Cases	(0 - 85.7)	39	21.3	3.76	32	0.004
	Control	(4.8 - 85.7)	27.9	18.5	1.74	113	
	Cohen's effect size of being a case compared to control = 0.58						
stress Score (/100)	Cases	(14.3 - 90.5)	49.1	17.5	3.1	32	0.13[NS]
	Control	(4.8 - 90.5)	42.6	22.2	2.09	113	
	Cohen's effect size of being a case compared to control = 0.31						
DAS Score (/100)	Cases	(12.7 - 76.2)	41.5	16.3	2.88	32	0.017
	Control	(6.3 - 76.2)	33.3	17.3	1.63	113	
	Cohen's effect size of being a case compared to control = 0.48						

**Table 3 a multiple logistic regression model was used. After adjusting for the confounding effect of age, gender, magnitude of psychiatric derangement and serum immunoglobulins, it was found that serum cortisol concentration was significantly higher among cases with Lichen Planus. Depression score was the most affected among the 3 measures of psychiatric derangement.**

	OR	P
Anxiety score (/100)	1.04	0.28[NS]
Depression score (/100)	1.05	0.079
Stress score (/100)	1.0	0.92[NS]
Serum Cortisol	1.02	0.023
Age in years	0.97	0.34[NS]
female gender compared to male	7.07	0.022

P (Model) < 0.001

Overall prediction accuracy = 82.3%

**Table 4** A multiple logistic regression model was used. After adjusting for the confounding effect of age, gender and magnitude of psychiatric derangement. It was found that salivary cortisol concentration was significantly higher among cases with Lichen Planus.

	OR	P
Anxiety score (/100)	1.02	0.39[NS]
Depression score (/100)	1.01	0.71[NS]
Stress score (/100)	1.04	0.15[NS]
Age in years	0.99	0.76[NS]
female gender compared to Male	3.96	0.025
Salivary cortisol	56.8	0.053

P (Model) < 0.001

Overall prediction accuracy = 77.2%

Table 5 The mean salivary cortisol was lowest (0.079) among cases with lowest concentration of serum cortisol (first tertile) and increase to reach its highest mean concentration (119) among cases with highest concentration of serum cortisol (third tertile). The differences observed in mean salivary cortisol were statistically significant. There was a moderately strong positive (direct) linear correlation between serum and salivary cortisol concentration ( $r=0.54$ ,  $P=0.001$ ).

**The mean salivary cortisol by 3 serum cortisol ordered categories (tertiles).**

	Serum Cortisol-tertile			P (ANOVA trend)
	First tertile (< 82.6)	Second tertile (82.6 - 118.9)	Third tertile (119.0+)	
Salivary cortisol				0.048
Range	(0.012 - 0.319)	(0.036 - 0.255)	(0.008 - 0.629)	
Mean	0.079	0.137	0.209	
SD	0.1	0.081	0.196	
SE	0.0353	0.0243	0.0544	
N	8	11	13	

**Table 6** a multiple linear regression model was used to assess the net and independent effect of a set of explanatory variables on the magnitude of salivary cortisol concentration. Only serum cortisol had a statistically significant association with salivary cortisol concentration after adjusting for age and gender, the 3 psychiatric scores and group membership (Lichen Planus Vs controls).

Conclusion: There is an important association between serum and salivary cortisol concentration.

	Partial regression coefficient	P
(Constant)	-0.25	0.46[NS]
Serum Cortisol	0.001	0.008
Age in years	0.002	0.13[NS]
female gender compared to male	0.008	0.85[NS]
Lichen Planus compared to healthy controls	0.028	0.51[NS]
Anxiety score (/100)	-0.002	0.3[NS]
Depression score (/100)	-0.001	0.26[NS]
Stress score (/100)	0.001	0.34[NS]

P (Model) = 0.06

R2=0.

Lichen Planus (LP) is a chronic inflammatory, autoimmune disease, affecting a wide variety of sites, including skin and mucous membranes. (6).

Anxiety, stress, depression and other psychological aspects of humans and their association with disease status were the domain of extensive research. Chronic conditions like Lichen Planus deserve special attention in this respect. (7).

Cortisol hormone is well established in medical literature as the stress hormone. Its direct relation to psychology is a known fact (8). The current study is the first of its kind in Iraq, its importance was reflected by exploring the association between psychology and cortisol both serum and salivary.

Three important domains of psychological abnormality in human were studied in the present work: stress, anxiety and depression.

Measurement of depression and its association with Lichen Planus was done by several scales. Wu XH, 2011 used self-rating depression scale (SDS), Hamilton depression scale(HAMD) (9).

Measurement of anxiety and its association with Lichen Planus was done by several scales. Two published articles by Maryam Rabiei (10), and Koray M, 2003 used spielbe rger’s State-Trait Anxiety Inventory. EL.Tawil M use Taylor manifest anxiety (11).

Measurement of stress and its association with Lichen Planus was done by several scales and indices in published articles. Farhad Mollashahi Leila, used Stress Life Event Questionnaires (12).

The current study used an updated psychology scale, which can measure the magnitude of anxiety, stress and depression as an independent entity with only 7 questions per domain.

DASS as a measure of psychology and its association with Lichen Planus or Cortisol Lichen Plan us Cortisol was used to a great extent in recently published articles. Singh R used DASS in measuring stress and its effect on cortisol level in medical students (13). Madhumita Premkumar also used DASS in measuring changes in mood and assessed the correlation with cortisol (14).

The current study showed a statistically significant positive association between psychiatric derangement and Lichen Planus. The mean DASS score was significantly higher in Lichen Planus cases compared to healthy control group. Depression was the almost affected to Lichen Planus.

The current study showed that the mean of serum and salivary cortisol was obviously higher with LP compared to control group.

A list of published case-control studies reported similar positive association between salivary cortisol and Lichen Planus. Maryam Rabiei (10), Carla Girardi (15), Sanjib kumar khataniar (16), and Bina Shah (17), measured

salivary cortisol detected by ELISA. They concluded that patients with oral Lichen Planus exhibited greater salivary cortisol than the controls.

The current study showed a strong direct correlation between serum and free unbound salivary cortisol in patients with Lichen Planus.

Published articles agreed with the previous conclusion. *Elisabeth Aardal* <sup>(18)</sup> and *Vining RF* <sup>(19)</sup>, studied the relation between free salivary cortisol and serum cortisol in healthy volunteers. They concluded that the relation between the cortisol concentrations in serum and saliva was positive.

Two published articles showed that salivary cortisol in critically ill patients may be a better laboratory indicator of cortisol levels than serum total cortisol. *Rômulo Carvalho* compared the performance of salivary and serum total cortisol in patients with severe sepsis <sup>(20)</sup>. *Aardal-Eriksson* showed that CRH stimulation induced a more pronounced cortisol response in saliva than in serum, having a closer correlation with ACTH hormone over serum cortisol. The study suggested that salivary cortisol measurement may be used as an alternative parameter in dynamic endocrine test <sup>(21)</sup>.

### Conclusion

1. The mean of salivary and serum cortisol was higher difference in LP than control subjects, the mean DASS and the special depression Derangement also higher in LP patient compared to control subjects ( $p < 0.001$ ).

2. The current study showed a strong direct correlation between serum and free unbound salivary cortisol in patients with lichen planus. Salivary cortisol in critically ill patients may be a better laboratory indicator of cortisol levels than serum total cortisol.

### Suggestion

1. As the present study is pioneering in Iraq, we recommend that further studies should be carried out with increasing the sample of patients for more accuracy and confirmation of results. Also we recommend for using psychiatric drug along with routine LP treatment to determine the efficacy of drug therapy of psychiatric disorders in lichen planus.

**Ethical Clearance** A consent form has been signed by each participant and the agreement of the ethical

committee at the Department of Oral Medicine was taken.

**Primary Founding source - Self**

**Conflict of Interest: Nil**

### References

1. Xia J LCHYYLea. Short-term clinical evaluation of intra lesional triamcnenoloneacetone injection for ulcerative oral lichen planus. *J Oral Pathol*; 35: 327-31; Med 2006.
2. Gu GM MM,DRea. Oral and serum IL-6 levels in oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 98:673-8. , editor.; 2004.
3. Francesco C OS. Psychologic views on stress-related oral ulcers. *Quintessence INT*; 2004.
4. Miller CS DJFDea. Salivarycortisol response to dental treatment of varying stress. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*; 1995.
5. Kirschbaum C, Sidney S, Seeman T. Socioeconomic Status, Race, and Diurnal Cortisol Decline in the Coronary Artery Risk Development in Young Adults (CARDIA) Study”. *Psychosomatic Medicine*; 2006.
6. Luis-Montoya P DSLVME. Lichen planus in 24 children with review of the literature. *Pediatr Dermatol*; 2005;22:295–8.
7. Folks DG WJ. *Psycocutaneous disorders*. Current Psychiatry Reports. 3219254th ed. Boston; 2001.
8. Djuric Z, Bird CE, Furumoto-Dawson A, Rauscher GH, Ruffin IV MT, Stowe RP, et al. Biomarkers of Psychological Stress in Health Disparities Research”. 13 October 2008.
9. Xiao-hong W, Xu-dong H, Song-hong W, Hua X. Study of association between oral lichen planus and depression in female patients. 2011.
10. Maryam Rabiei \* MSK,EKL,SK. The Comparison Between Anxiety, Level of Salivary Cortisol &SIgAIn Oral Lichen Planus. *JRDS*. JRDS 2012 Sep 3;: p. 125-131.
11. Koray M DOa. Oral medicine; behavioural science: The evaluation of anxiety and salivary cortisol levels in patients with oral lichen planus. *British Dental Journal*. 2004.
12. Leila Farhad Mollashahi KLMARLMH,HA. The Evaluation of Psychosocial Factors Associated with Oral Lichen Planus. 2009.

13. Singh OP KA. Lichen planus in India. An appraisal of 441 cases. *Int J Dermatol.* 1976;; p. 752–6.
14. Madhumita Premkumar ITSDDaRD. Clinical Study Circadian Levels of Serum Melatonin and Cortisol in relation to Changes in Mood, Sleep, and Neurocognitive Performance. .
15. Carla Girardi CLKCMAZdFMLTNFGS. Salivary cortisol and dehydroepiandrosterone (DHEA) levels, psychological factors in patients with oral lichen planus. 2011.
16. SKk. salivar cortisol levelestimationin patien with oral lichen planus. 2006.
17. Bina Shah LAGS. Evaluation of salivary cortisol and psychological factors in patients with oral lichen planus. 2009; 20(3): p. 288-292.
18. Holm. EAaAC. Cortisol in Saliva — Reference Ranges and Relation to Cortisol in Serum , *Eur J Clin Chem Clin Biochem.* 1995;(927-932.).
19. Vining RF MRMJHK. alivary cortisol: a better measure of adrenal cortical function than serum cortisol. *Ann Clin Biochem.* 1983 Nov; ;20 (Pt 6):329-35.
20. Rômulo Carvalho Vaz de Mello1 EFSBC. Serum and salivary cortisol in the diagnosis of adrenal. 2011.
21. Rômulo Carvalho Vaz de Mello1 EFSBCSPFN. Serum and salivary cortisol in the diagnosis of adrenal insufficiency and as a predictor of the outcome in patients with severe sepsis. 2011;55(7):445-9.