# Saliva Levels of Adrenergic Receptors in Relation to Psychological Factors in Patients with Oral Lichen Planus

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**Objective:** *To evaluate the saliva level of α1 and β1 adrenergic receptors (ARs) in oral lichen planus (OLP) patients.*
**Methods:** *This case-control study included unstimulated saliva samples from 33 OLP patients (14 erosive, 19 non-erosive) and 33 healthy controls. All participants were evaluated on psychological conditions via the Depression, Anxiety and Stress Scale – 21 items (DASS 21). The saliva levels of α1 and β1 ARs was measured by enzyme-linked immunosorbent assay (ELISA). Data were analysed with a t test using SPSS 25 (IBM, Armonk, NY, USA).*
**Results:** *The saliva levels of α1 and β1 ARs of OLP patients (both erosive and non-erosive forms) were significantly higher than in healthy controls. Stress levels in patients with both forms of OLP were significantly higher than in the healthy group. There was a positive correlation between salivary α1 and β1 ARs and stress, and this positive correlation was also seen for saliva β1 ARs between anxiety or depression. The saliva level of α1 ARs was inversely correlated with unstimulated salivary flow rates ($r = -0.246$; $P = 0.046$).*
**Conclusion:** *This study indicated that OLP patients with both erosive and non-erosive forms have higher psychological stress and saliva levels of α1 and β1 ARs than healthy controls; however, the role of α1 and β1 ARs as salivary markers with regard to the development, severity of symptoms and outcome of OLP needs further investigation.*
**Key words:** *adrenergic receptors, oral lichen planus, saliva, stress*
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One of the most common, immune-mediated inflammatory diseases in the oral mucosa is oral lichen planus (OLP), which occurs as the result of autoreactivity of cytotoxic T lymphocytes attacking the basal keratinocytes[1]. Middle-aged women are the most commonly affected population, and the skin, vagina, oesophagus and larynx can also be affected[2].

The aetiology of OLP is not yet fully known; however, psychological disorders such as depression, anxiety and stress contribute towards its development and can exacerbate the lesions[3]. Previous studies established that OLP patients have higher levels of depression, anxiety and stress than the general population[4]. So far, researchers have used a variety of tools to investigate the relationship between psychological factors and lichen planus, such as standard questionnaires[5], examining the polymorphism of genes involved in the stress pathways[6], and measuring the level of biological markers such as cortisol, alpha-amylase and oxidative stress in various mediums[7].

Evaluation of psychological factors in lichen planus patients through self-reporting is unreliable, because patients can easily hide emotional changes or refuse to see a psychologist or psychiatrist for diagnosis or treatment due to embarrassment or side effects of medication[4]. Thus, the use of objective indicators with quan-

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titative measurement capability should be considered.

Activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis and their specific receptors following stress is one of the proposed hypotheses in OLP[8,9]. α and β adrenergic receptors (ARs) are from G protein-coupled receptors. The catecholamines that are released in response to stress bind to these receptors. In some autoimmune diseases, the quantitative and qualitative changes of ARs on the surface of different cells have been reported, although no such reports are available on OLP patients[10]. Also, α1 and β1 ARs may be involved in associated symptoms, such as xerostomia[3]. The association between OLP and hyposalivation and/or xerostomia has been documented[11,12].

In addition, OLP has been introduced as a potentially malignant disorder, but the exact underlying mechanism initiating malignant transformation in OLP is not clear[13,14]. Activation of the sympathoadrenal system by stress can have a role in cancer initiation, progression and metastases mainly via ARs, although this relationship is highly speculative[15].

Considering the possible role of psychological stress, the sympathetic nervous system and ARs in the aetiopathogenesis of immune-mediated inflammatory diseases such as OLP and its related symptoms, this study aimed to evaluate the level of α1 and β1 ARs in the saliva of OLP patients.

## Materials and methods

This case-control study was approved by the Ethics Committee of the School of Dentistry at Tehran University of Medical Sciences, Tehran, Iran (TUMS.DENTISTRY.REC.1396.4182). Thirty-three patients with definite clinical and histopathological diagnoses of OLP were selected among those referred to the Oral and Maxillofacial Medicine Department of School of Dentistry of TUMS from 5 April 2016 to 20 December 2017. A total of 33 age- and sex-matched healthy persons (Table 1) who did not have any clinical signs/symptoms of gingival inflammation or other type of oral lesion and were willing to participate in this study comprised the control group. All participants signed written informed consent forms before participating, and all research was conducted in accordance with the Declaration of Helsinki. Of all the OLP patients, 12 had erosive-atrophic, 18 had reticular, 2 had bullous and 1 had papular OLP. The authors evaluated AR levels in three groups: control, erosive OLP (erosive-atrophic and bullous, n =14), and non-erosive OLP (reticular and popular, n = 19). The inclusion criteria were definite clinical diagnosis of OLP based on the presence of bilateral reticular lesions in the oral mucosa, and fulfilment of the modified World Health Organisation histopathological criteria for OLP (well-defined band-like zones of inflammatory infiltration limited to the superficial part of the connective tissue, including mainly mature lymphocytes and vacuolar degeneration of the basal layer of the epithelium). The exclusion criteria were history of systemic or local treatments in the past 3 months, smokers, patients with systemic diseases such as cardiovascular diseases, hypertension, renal or hepatic diseases, diabetes mellitus, malignancies or neuromuscular disorders, with a history of medication intake, particularly medication affecting the ARs in the past 3 months, and pregnant or nursing women. In addition, all participants were evaluated for psychological conditions via the Depression, Anxiety and Stress Scale – 21 Items (DASS 21)[16]. Several previous studies had evaluated the psychological profile of OLP patients using DASS-2117-19, and this questionnaire has also been used in several previous studies to assess the psychological effects of drugs with an affinity to the ARs[20]. The scale can quantify the severity of depression, anxiety and stress. The validity and reliability of this questionnaire in the Persian language were examined by Samani and Jokar[21] in 2010.

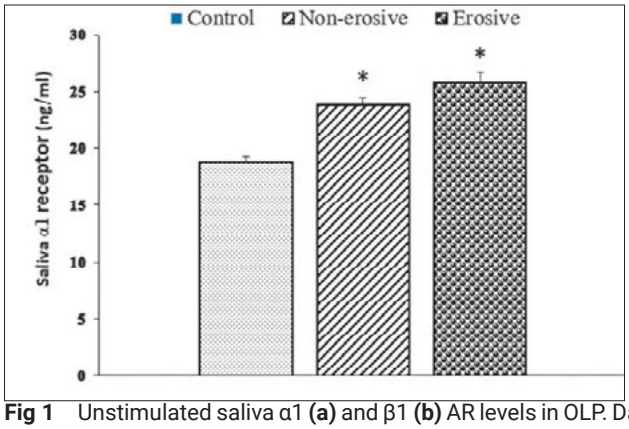
Each of the DASS subscales consists of seven questions, and the final score is obtained through the sum of the scores for the related questions. Each question is scored from 0 (“does not apply to me at all”) to 3 (“perfectly true for me”).

### *Saliva sample collection*

Unstimulated saliva samples were collected from all participants from 9 a.m. to 12 p.m. They were instructed to refrain from eating for 2 hours before saliva sampling, then sit on a chair and spit into a plastic vial as often as possible for 5 minutes. The salivary flow rate was calculated by dividing the saliva volume (in millilitres) by time (in minutes). Hyposalivation was diagnosed when the unstimulated salivary flow rate was less than 0.1 ml/min[22].

### *Evaluation of the severity of OLP lesions and disease activity*

To evaluate the severity of oral lichen planus lesions (severity score), the Thongprasom scoring system, as referenced in Thongprasom et al[23], was used. In this system, 0 indicates the absence of lesions, 1 denotes mild white lesions without erythematous areas, 2 indicates white striae with atrophic lesions smaller than 1 cm, 3



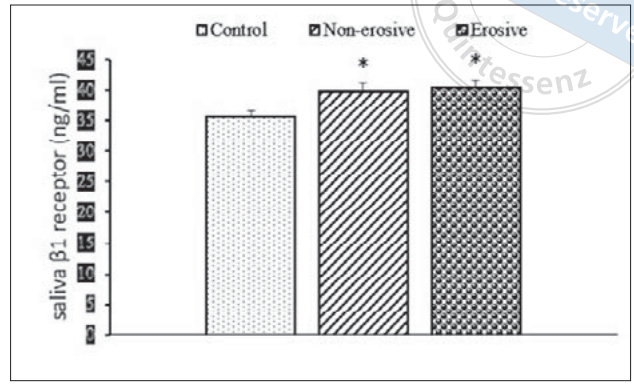




**Fig 1** Unstimulated saliva α1 **(a)** and β1 **(b)** AR levels in OLP. Data are expressed as mean ± standard error of the mean and analysed using a one-way analysis of variance (ANOVA) followed by a Student-Newman-Keuls post hoc test. *$P < 0.05$ compared with healthy controls and non-erosive OLP, respectively.

corresponds to white striae with atrophic lesions larger than 1 cm, 4 denotes lesions with ulcerated areas less than 1 cm and 5 indicates lesions with ulcerated areas above 1 cm. The pain intensity (pain score) of OLP patients was also measured using a visual analogue scale (VAS), from 0 to 10.

### *Laboratory procedures*

After centrifuging the samples for 10 minutes at 2000 rpm, the purified saliva (supernatant) was poured into 1-ml microtubes, kept at −20°C (as frozen) and sent to a laboratory to measure the level of α1 and β1 ARs within 24 hours. The measurements were made using the enzyme-linked immunosorbent assay (ELISA) kit for β1 and α1 ARs respectively (USCN Life Science, Wuhan, China) according to the manufacturer's protocol to determine the exact level of ARs in each individual.

### *Statistical analysis*

The collected data were analysed using SPSS version 25.0 (SPSS, IBM, Armonk, NY, USA). A Shapiro-Wilk test was used to check normality and the level of significance was $P > 0.05$, thus they had normal distribution. The results were presented as mean ± standard error or median ± interquartile range and analysed using a *t* test, chi-square test and one-way analysis of variance (ANOVA) followed by a Student-Newman-Keuls as post hoc test, Kruskal-Wallis test, and Spearman and Pearson correlation coefficient. The level of significance was $P < 0.05$.

## Results

There was no significant difference in age between the OLP (46.2 ± 2.2 years) and control (45.5 ± 2.2 years) groups ($P = 0.808$).

The level of α1 and β1 ARs in unstimulated saliva were significantly higher in OLP patients compared with the healthy controls ($P < 0.05$), but there were no significant differences in saliva levels of α1 and β1 ARs between erosive and non-erosive forms of OLP (Fig 1). Statistical analysis of the results showed that unstimulated salivary flow rates were significantly lower in OLP patients with the erosive form than in healthy controls ($P = 0.005$); however, there was no significant difference between patients with the non-erosive form of OLP and healthy controls (Fig 1). The stress score was significantly higher in both forms of OLP than in the control group, and was also higher in patients with the erosive form than those with the non-erosive form (Table 2). There was no significant difference in anxiety and depression between the three groups (Table 2).

The level of α1 and β1 ARs in saliva had no significant association with sex ($P > 0.05$). The level of α1 and β1 ARs in saliva had no significant correlation with age either ($P > 0.05$).

Saliva concentrations of β1 ARs were significantly correlated with pain, severity, stress, anxiety and depression. The saliva level of α1 ARs was significantly correlated with stress, pain and severity, but not with anxiety and depression (Table 3).

The unstimulated salivary flow rate was inversely correlated with the saliva level of α1 ARs ($r = −0.246$; $P = 0.046$) but not with the level of β1 ARs ($r = −0.099$; $P = 0.433$)

**Table 1** Age and sex of participants in the two study groups

| Variable | Control | OLP |
|---|---|---|
| N | 33 | 33 |
| Age (y) | 45.5 ± 2.2 | 46.2 ± 2.2 |
| Sex (M/F) | 12/21 | 12/21 |

F, female; M, male.

**Table 2** Comparison of variables between the OLP and control groups.

| Variable | Control (n = 33) | Non-erosive OLP (n = 19) | Erosive OLP (n = 14) | F | *P* value |
|---|---|---|---|---|---|
| Unstimulated flow rate (ml/min) | 0.43 ± 0.03 | 0.33 ± 0.04 | 0.28 ± 0.02* | 4.566 | 0.014[a] |
| Anxiety (score) | 4 ± 9 | 8 ± 5 | 9 ± 12 | NA | 0.137[b] |
| Depression (score) | 4 ± 8 | 8 ± 14 | 7 ± 10 | NA | 0.474[b] |
| Stress (score) | 0 ± 1 | 1 ± 3* | 2 ± 1*# | NA | 0.000[b] |

Data are expressed as **(a)** mean ± standard error of the mean or **(b)** median ± interquartile range and analysed using a **(a)** one-way ANOVA followed by a Student-Newman-Keuls post hoc test or **(b)** a Kruskal-Wallis test. * and # indicate $P < 0.05$ compared with the control and non-erosive OLP groups, respectively. The level of significance was $P < 0.05$. NA, not applicable.

**Table 3** Correlation between stress, anxiety and depression with saliva levels of α1 and β1 ARs. Data were analysed using a Spearman correlation test.

| Variable | Stress | Anxiety | Depression | Severity score | Pain score |
|---|---|---|---|---|---|
| Unstimulated saliva α1 AR (ng/ml) | r = 0.418; *P* = 0.001* | r = 0.188; *P* = 0.131 | r = 0.058; *P* = 0.645 | r = 0.706; *P* = 0.000* | r = 0.445; *P* = 0.000* |
| Unstimulated saliva β1 AR (ng/ml) | r = 0.526; *P* = 0.001* | r = 0.355; *P* = 0.003* | r = 0.464; *P* = 0.001* | r = 0.404; *P* = 0.001* | r = 0.395; *P* = 0.001* |

## Discussion

The present findings revealed the obviously higher saliva levels of α1 and β1 ARs in OLP patients compared with healthy controls. The main sources of the whole saliva content are from saliva secreted from the salivary glands, exfoliated oral mucosa cells and substances that enter the saliva from the bloodstream. The molecules that are expressed in different parts of salivary glands, either parenchyma or ducts, can be secreted in saliva[24]. Thus, the increased saliva levels of ARs in OLP patients can be caused by overexpression of ARs in the salivary gland cells and upregulation of ARs in the peripheral blood cells or tissue of OLP lesions. Determining the exact source of the AR in saliva requires further research across multiple mediums simultaneously.

Saliva as a diagnostic medium is superior to other mediums in several ways. Saliva sampling is non-invasive, safe, simple and inexpensive. It can also be repeated without causing discomfort to the patient[14]. Whole saliva is an accessible, valuable biofluid that contains components derived from various sources such as serum and mucosal surfaces[25].

OLP, as an immune-mediated inflammatory disease, has a complex, multifactorial pathogenesis. Physiological and psychological stressors are the major environmental aetiological factor involved in autoimmune diseases[26]. The present findings confirmed the results of previous studies regarding the substantial relationship between psychogenic stress and OLP[4]. We also demonstrated that unstimulated saliva levels of α1 and β1 ARs have a positive correlation with stress, whereas anxiety and depression had a positive correlation with β1 ARs only. The sympathoadrenal axes are the two main hormonal pathways that are activated alone or together in response to stress[27].

OLP is most common in middle-aged women. Most OLP patients have experienced several stressful events in their lifetime and have an elevated hypothalamic-pituitary-adrenal (HPA) response and cortisol levels similar to those under chronic stress[9,28,29], which can cause an imbalance in the autonomic nervous system (ANS)[30]. The sympathetic nervous system (SNS) is a part of the ANS in which there is a strong correlation between the ANS and the immune system. The binding of epinephrine to ARs alters the function of immune

cells and the secretion of inflammatory mediators such as TNF-α, IL-6 and IL-10. Several pieces of evidence confirm the role of these cytokines in the aetiopathogenesis of immune-mediated inflammatory diseases, including OLP[31]. Hence, these inflammatory factors can be considered as an intermediate link between the sympathetic nervous system and the development of autoimmune diseases[32].

Given these preconditions, in the present study, we showed the relation between the essential components of the SNS (ARs) and OLP.

A three-way association between psychological factors, the ANS and the immune system has been demonstrated in the development and severity of a variety of autoimmune diseases such as rheumatoid arthritis[32,33].

Psychosomatic disorder is a specific term to define clinical symptoms in a single organ system that are due to emotional factors, usually through autonomic nervous system innervation. In 2001, Bailoor and Nagesh[34] classified OLP as an oral psychosomatic disorder. Stress leads to the release of noradrenaline and adrenaline. This causes the activation of the SNS, both centrally and peripherally[35]. Several studies have demonstrated overactivity of SNS and higher levels of noradrenaline and adrenaline in OLP patients[36]. Activation of the sympathetic α/β-AR, mainly in innate immune cells, can result in either reduced or increased inflammatory cytokine production depending on timing and local noradrenaline concentration and influence the development and severity of inflammation[22]. Chronic stress can cause immune activation and suppresses immune-protective parameters that increase the risk of inflammatory/autoimmune disease such as OLP[37].

Along with this phenomenon, we also reported a significant relationship between the level of stress and the severity of lichen planus lesions. The higher incidence of major depression, anxiety and mood disorders by upregulating inflammatory cytokines such as IL-17 can be effective in the development and severity of inflammatory diseases[38]. The moderating role of immunosuppressive drugs and parasympathetic stimulation on psychological symptoms and autoimmunity confirms this[39]. In the present study, the positive correlation between stress, anxiety and depression with saliva levels of α1 and β1 ARs supports the above. Like in other immune-mediated inflammatory/autoimmune diseases, such as systemic sclerosis, an overactive SNS is associated with decreased parasympathetic system function[40]. Previous studies have shown downregulation of muscarinic receptors in OLP patients[41]. Overexpression of ARs may reflect increased SNS activity in OLP patients. Upregulating the activity of the SNS by increasing the production of salivary mucin via β1 ARs and proteins via ARs α1 and β1 and vasoconstriction can play a role in reducing the salivary flow rate in OLP patients[42]. The results of the present study also showed a negative correlation between salivary flow rate and AR levels.

In addition, changes in the levels of ARs can be effective in malignant transformation in OLP. Once the catecholamine neurotransmitter binds to an adrenoreceptor, it causes the initiation of signalling pathways that cause uncontrolled cell proliferation, invasion, migration and metastasis that play the main role in carcinogenesis[43]. Several studies have reported overexpression of α1 and β1 ARs in oral squamous cell carcinoma tissue compared with normal mucosa[44,45].

The results of the present study present an opportunity for better understanding of the interaction between the ANS, inflammation and the onset and severity of autoimmune diseases. Disruption of this three-way cycle through a variety of physiological and psychological therapies such as medications, stress reduction protocols and lifestyle changes can be considered in the treatment of immune-mediated inflammatory diseases, including OLP. Further studies with special attention paid to histological analysis are needed to confirm the overexpression of α1 and β1 ARs in OLP.

## Conclusion

This study indicated that OLP patients with both erosive and non-erosive forms have higher psychological stress and saliva levels of α1 and β1 ARs than healthy controls; however, the role of α1 and β1 ARs as a saliva marker in the development, severity of symptoms and outcome of OLP needs further investigation.

## Conflicts of interest

The authors declare no conflicts of interest related to this study.

## Author contribution

Drs Narges GHOLIZADEH and Nafiseh SHEYKHBAHAEI designed the study, collected and analysed the data and drafted the manuscript; Drs Arvin REZAYI and Iraj MIRZAII-DIZGAH collected and analysed the data. All authors reviewed and approved the manuscript.

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