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Evaluation of interleukin-6 levels in saliva of patients with oral lichen planus

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ABSTRACT

Introduction: Oral lichen planus (OLP) is a chronic mucocutaneous inflammatory disorder with an unknown etiology. Although a considerable body of evidence suggests that immunologic factors are involved in the etiology of OLP, the involvement of cytokines in the pathogenesis of the disease is not fully understood yet. The aim of the present study was to assess interleukin-6 (IL-6) levels as a proinflammatory cytokine in the saliva of OLP patients compared to healthy controls.

Materials & Methods: This case-control study was conducted on 30 OLP patients (12 males and 18 females) and 30 healthy control subjects, selected from individuals who were referred to the Department of Oral and Maxillofacial Diseases in Faculty of Dentistry, Babol University of Medical Sciences. Samples of unstimulated saliva were collected. Salivary IL-6 levels were measured using an ELISA kit and compared between OLP patients and healthy controls. The collected data were analyzed by Chi-square, independent t-test, and receiver operating characteristic (ROC) curve using SPSS 18 Sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) were calculated. A value of $p<0.05$ was considered significant.

Results: Mean salivary IL-6 values in OLP patients and healthy controls were 24.68±9.90 ng/L and 13.76±9.27 ng/L, respectively. The difference was statistically significant ($P<0.001$). The mean IL-6 values in reticular and erosive forms of OLP clinically were 24.35±9.26 ng/L and 24.91±10.64 ng/L, respectively. This difference was not statistically significant ($P=0.87$).

Conclusion: Higher levels of IL-6 in saliva of OLP patients compared with healthy controls support the role of IL-6 in the pathogenesis of the disease.

Keywords: Lichen Planus, Cytokines, Interleukin-6.

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Introduction

Lichen planus (LP) with unknown etiology is a chronic inflammatory mucocutaneous disorder. [1] Some oral LP (OLP) OLP cases may become malignant. [2] OLP has been divided into two atrophic-erosive and reticular forms in different studies to better evaluate the disease. [3] OLP as a T-cell-mediated autoimmune disease is characterized through local overproduction of inflammatory cells, particularly T cells, in the basal cells of the oral epithelium. [4] Cytokines which are produced by T helper cells mediate and regulate through signaling pathways. Cytokine products from Th1 cells are involved in cell-mediated immunity, while cytokine products from Th2 cells mediate humoral immunity. Natural hosts maintain a certain level of cytokines at certain times. A cytokine imbalance triggers an inflammatory response and abnormal immune response because of local overproduction of cytokines.[5] Interleukin-6 (IL-6) as a type of cytokine is secreted by different cells like fibroblasts, osteoblasts, monocytes [6] and vascular endothelial cells in response to stimuli such as infection, inflammatory changes [7], and trauma. [8] L-6 as a type of pro-inflammatory cytokine is produced in OLP lesions and may be important in the pathogenesis of OLP. [9]

Cytokine storm syndrome (CSS) as a dysregulation of the synthesis of cytokines is a severe complication of inflammatory immune diseases.[10] IL-6 plays a role in autoimmune diseases, chronic inflammation, and cancer. In addition, it has a main role in the pathogenesis of CSS, [1, 2] observed in coronavirus disease 2019 (COVID-19).[11]

IL-6 could be a hopeful target for the treatment of severe COVID-19. [12] Human saliva is a complex mixture of electrolytes, proteins, hormones, antimicrobial particles, enzymes, and peptides. Almost 1400–2000 proteins have been found in saliva. Each of these proteins can be applied as a simple tool to evaluate infection, toxicity, and hormonal and immunological levels. [13] Saliva samples, increasingly used for disease diagnosis, are superior to blood samples in the laboratory. Saliva has several advantages over serum including a noninvasive collection method. The diagnostic accuracy of plasma and saliva is nearly identical as shown by the results of correlation coefficients and other statistical analyses. [1,14]

Since there is no agreement on the role of IL-6 in the pathogenesis of OLP, the aim of the present study was to assess and compare IL-6 levels in the saliva of OLP patients and healthy control subjects, and to determine the role of IL-6 in the pathogenesis of OLP. [1]

Materials & Methods

This study was approved by the Ethics Committee of Babol University of Medical Sciences, Babol, Iran (with code IR.MUBABOL.HRI.REC.1397.257). In this case-control study, a sample of 30 OLP patients with clinical and histopathological manifestations and 30 healthy control subjects volunteered to participate. They were matched for gender and age and referred to the Department of Oral and Maxillofacial Diseases in Faculty of Dentistry, Babol University of Medical Sciences. The demographic data of both case and control groups were recorded. The sample size was calculated using previous studies with 60 subjects. [1]

Pregnant women, women taking contraceptives, alcoholics, people with liver and kidney diseases, psoriasis, diabetes mellitus, Sjogren's syndrome, systemic lupus erythematosus (people with the known systemic disease) and infectious diseases and rheumatoid arthritis, [14] people with active periodontal disease and active severe cavities [5], people with maxillofacial trauma in the last six months, people treated with corticosteroids, and OLP patients treated in the last three months [15] were excluded from the study.

Healthy control subjects did not correspond to any of the above eight categories. They also had no symptoms of mucocutaneous diseases. OLP patients were selected as a simple random sample without considering the severity of the disease and were divided into two groups according to histopathological and clinical examinations before sampling: reticular and atrophic-erosive OLP.

Saliva collection method

Demographic, histopathologic, and clinical data were recorded in a checklist prepared by the investigator under the supervision of a specialist in oral and maxillofacial diseases and an oral and maxillofacial pathologist.

To collect unstimulated saliva samples, patients were asked to sit relaxed and upright for 5 to 10 minutes at least two hours after meals between 8 and 11 a.m. to allow saliva to accumulate in the mouth and not to do anything to stimulate salivation during this time. Two milliliters of unstimulated saliva was collected by continuous monitoring of saliva using the drooling collection (pitting) method in a plastic container with a lid. Saliva samples were immediately placed in ice-cooled flasks and taken to the laboratory to determine the IL-6 concentrations in the saliva. Samples were centrifuged at 3000 rpm for 15 minutes at 4°C. The upper aqueous phase was transferred to an Eppendorf tube. The tubes were stored in a freezer at -80°C prior to analysis.

ELISA kits (supplied by Bioassay Technology Laboratory, China, with 1.03 ng/L sensitivity) were used to determine IL-6 concentrations. The collected data were analyzed by Chi-square, independent t-test, and receiver operating characteristic (ROC) curve using SPSS 18. Specificity, sensitivity, negative predictive values (NPVs), and positive predictive values (PPVs) were calculated. A value of $p<0.05$ was considered significant

Results

Totally, 60 persons participated in the current study (30=OLP patients and 30=healthy control subjects). Among them, 12 (40%) and 18 (60%) persons were men and women in each group, respectively. The two groups were similar in terms of gender (P = 0.99). The demographic characteristics of the two groups are shown in Table 1.

Table 1. Demographic characteristics of the two groups

Group Variables	OLP patients' Frequency (%)	Healthy controls' Frequency (%)	P-value
Male	12 (40)	12 (40)	
Female	18 (60)	18 (60)	
Age (mean ± SD)	48.13±67.83	48.33±14.47	0.92**

* Chi-square test ** Independent t-test

Mean IL-6 values in saliva of OLP patients (24.68±9.90) were higher than those in saliva of healthy control subjects (13.76±9.27). The results of the independent t-test indicated a statistically significant difference between the two groups (P<0.001). IL-6 levels were also measured in two forms of OLP, and the mean IL-6 values in the reticular (n=13) and erosive (n=17) forms were 24.35±9.26 and 24.91±10.64, respectively (Figures 1, 2). No significant difference was found in the mean IL-6 values between reticular and erosive forms (P=0.87). The level of IL-6 in saliva was measured using a kit purchased from Bioassay Technology Laboratory (Figures 3, 4).

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ROC curves were used to determine the most useful cut-off point for the diagnostic value of IL-6 (Figure5). The area under the curve (AUC) was 78.4% (P=0.001), which was acceptable for distinguishing OLP patients from healthy subjects. The cutoff point for IL-6 was set at 17.5 (sensitivity = 76.7% and specificity = 70%). PPV and NPV were calculated to be 72% and 75%, respectively (Table 2).

Figure 1. Reticular form

Figure 2. Erosive form

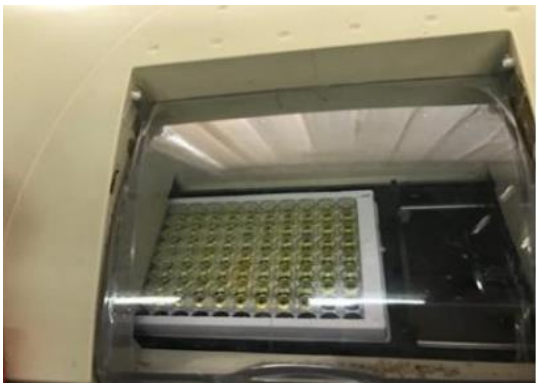

Figure 3. ELISA Plate Reader, in order to read the absorption of the wells

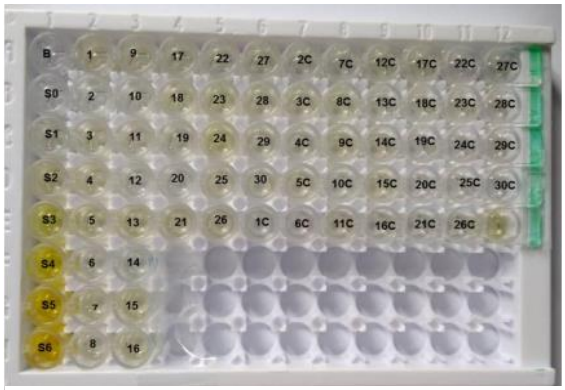

Figure 4. Rapid color change from blue to yellow after adding stop solution

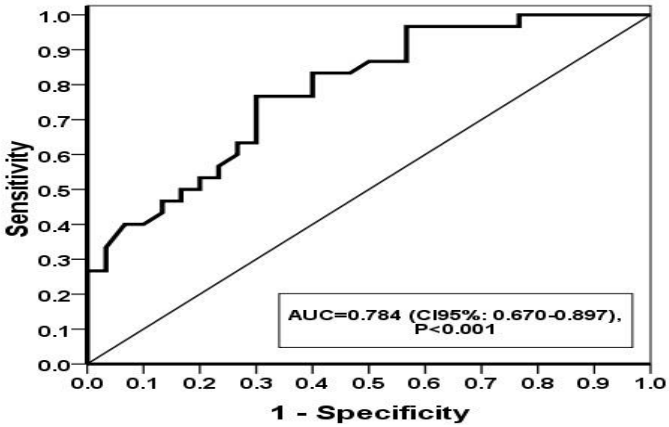

Figure 5. ROC curve of IL-6

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Table 2. Sensitivity, specificity, PPV, NPV, and cut-off point

Parameter	Value	Confidence interval
Sensitivity	77%	62-92
Specificity	70%	54-86
PPV	72%	56-87
NPV	75%	59-91

Discussion

In the ongoing study, salivary IL-6 levels in OLP lesions were assessed and compared with healthy control subjects. The results suggested that salivary IL-6 levels were significantly higher in the case group than the control group. Some studies [14, 16] also showed higher IL-6 levels in saliva and serum of OLP patients. Increased salivary concentrations of cytokines in OLP patients could be due to their increased release by the inflammatory cells or keratinocytes. Therefore, the injured oral mucosa may no longer act as a protective barrier (especially in the case of erosions LP). [14]

The etiology of OLP is not yet fully understood. Nevertheless, chronic inflammation is a major contributor to the progression of LP lesions. [5] Th1 cells promote cell-mediated immunity and produce cytokines (TNF-α and IL-2). Th2 cells enhance humoral immunity and produce IL-4-5-6-13 cytokines. Given the delicate balance between humoral and cell-mediated immunity, any change in immune balance triggers an inflammatory response. [5] Krausi [17] and Garlet [18, 19] suggest that inflammatory cytokines play an important role in tissue destruction in LP. Moudgil et al. [20] have revealed that anti-inflammatory cytokines facilitate recovery from the acute phase of the disease, and proinflammatory cytokines promote the spread of inflammation in autoimmune diseases, and Liu et al. [21] examined type I diabetes mellitus and salivary IL-6 levels in OLP patients using ELISA kits. The salivary IL-6 levels were significantly lower in the OLP group than the control group. These confounding results could be because of different study designs, including differences in the characteristics of the OLP patients. Diabetics were excluded from the current study because they suffer from a weakened immune system, which could act as a confounding factor. [15, 22]

This factor might have influenced the results of Mozaffari et al. [15]'s study. In addition, numerous studies excluded patients who had undergone medical treatment 90 days before the study. Some medications can have long-term effects that may last longer than 90 days. This factor may have also influenced the results of the study by Mozaffari et al. [15], too. Kalogerakou et al. [23] examined peripheral blood samples from OLP patients and reported a decrease in the levels of Th1 and Th2 cytokines except for IL-4. These results are inconsistent with the results of the present study. This difference could be owing to the different sensitivity of the kits or the use of blood samples instead of saliva samples. Saliva analysis indicated the local release of cytokines involved in the pathogenesis of OLP. Therefore, saliva or tissue samples are efficient tools to evaluate cytokine levels. The main advantages of saliva include easy access, which provides a cost-effective screening, diagnostic, and treatment fluid. [24]

Furthermore, the results of the ongoing study demonstrated no significant difference in salivary IL-6 levels of erosive and reticular forms of OLP. Zhang et al. [14]and Yamamoto et al. [25] illustrated that serum IL-6 levels were

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not significantly different in OLP subtypes. However, salivary IL-6 levels were higher in patients with erosive or ulcerative lesions, suggesting that local release of cytokines increases salivary IL-6 levels in OLP patients.

Gu et al. [16] represented that IL-6 levels were significantly higher in oral exfoliated cells and serum of patients with ulcerative OLP than in patients with reticular OLP, which may be due to the local and systemic release of IL-6 by many cell types.

Rhodus et al. [26] and Kaur et al. [27] showed that IL-6 levels in serum and saliva were significantly higher in advanced stages of OLP lesions than in early stages. The discrepancy between studies might be due to the lack of a comprehensive tool to distinguish between the different clinical forms of OLP. Therefore, patients are often evaluated based on clinical and pathological presentations [14], which may increase the risk of errors and misdiagnosis of the LP subtype. The number of reticular and erosive subtypes of OLP was not matched in the case group of the current study, which may influence the results. Poor oral hygiene can also increase the risk of oral inflammation and elevate salivary IL-6 levels. [5] This aspect was neglected in the present study and should be investigated in future studies in a larger population. Therefore, it is recommended that saliva samples should be collected on a larger sample scale in future studies, taking oral hygiene into account, in order to accurately and efficiently explore the pathogenesis of LP. Different sensitivity of kits, small sample sizes, and mismatched samples in terms of age, gender, race, and geographic area could also affect the results of different studies. The cut-off point for IL-6 was set at 17.5 in the present study (sensitivity = 76.7% and specificity = 70%).

IL-6 monoclonal antibody has been used to effectively neutralize IL-6 activity in patients with multiple myeloma. [28] Moreover, Wang et al. [29] manifested that the production of inflammatory cytokines in OLP was inhibited by a bioactive compound called total glucosides of paeony (TGP) via suppressing the NF-κB signaling pathway. Davis et al. [30] Conclude that elevated levels of cytokines and their receptors in different organs play a key role in the pathogenesis of systemic lupus erythematosus (SLE). A better understanding of the regulation of the expression of important cytokines and their receptors may help to better understand the pathogenic mechanisms of the various types of SLE and their more effective treatments.

Therefore, cytokine concentration (cytokine therapy) determination can be used as a therapeutic approach for OLP. [5,31] Lowering IL-6 levels significantly alleviated the clinical symptoms of OLP. [26]Therefore, the IL-6 level is a useful marker in OLP patients. [32]Novel therapeutic strategies target the inhibition of IL-6 for the treatment of cancer as well as inflammatory and autoimmune diseases.[31,33]

Conclusion

Higher concentrations of IL-6 in saliva of OLP patients compared with healthy individuals in the present study support the hypothesis asserting a central role of IL-6 in the pathogenesis of OLP.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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Authors' Contribution

Motallebnejad M and Seyedmajidi M performed data collection, manuscript preparation, editing, and study supervision. Pouramir M and Ahmadian R performed data collection. Bijani A analyzed the data. Shokri Z performed data collection, manuscript preparation, editing, and study supervision, discovered the patient, and performed the patient examination.

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