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PREDICTIVE VALUES OF SALIVARY IL-6 AND SFAS-DEPENDENT APOPTOSIS INHIBITOR IN PATHOGENESIS OF ORAL LICHEN PLANUS

Sarah Gamal Moussa*, Ramy Mubarak Hussien** *and* Sherif Abd El Rahman Amer*

ABSTRACT

Introduction: Oral lichen planus (OLP) is a familiar inflammatory disease commonly seen in dental practice. Oral lichen planus' pathophysiology is not fully understood.

Objectives: The current research was aimed to determine the level of IL-6 in the saliva and the apoptosis-related marker soluble Fas (sFas) in OLP patients versus healthy controls before and after triamcinolone acetonide 0.1% in orabase application and to explore their roles in the etiology of OLP and if there is any possible correlation between the two studied markers.

Subjects and methods: 30 subjects were allotted into two equal groups. **Group I (control):** included 15 healthy individuals. **Group II (OLP):** included 15 patients who were formerly diagnosed with OLP and showed acute exacerbation at time of 1st examination. Present pain intensity (PPI) and Thongprasom clinical sign scoring were used on group II patients before and 1 month following treatment. Salivary samples for detection of IL-6 and sFas were collected once from group I and twice in group II.

Results: OLP group had higher values of IL-6 and sFas in their salivary samples that were statistically superior to those in the control group. In group II, following treatment, a significant reduction of PPI, Thongprasom sign scoring, IL-6 and sFas values was noticed. A weak positive correlation was found between IL-6 and sFas before and after treatment.

Conclusion: Salivary IL-6 and sFas concentrations in OLP group were higher than their values in control group and considerably decreased following therapy, confirming their usefulness in OLP diagnosis.

KEYWORDS: Salivary biomarkers, Oral lichen planus, IL-6, sFas, triamcinolone acetonide

* Lecturer of Oral medicine, periodontology and diagnosis, Faculty of Oral and Dental medicine, Future University in Egypt.
** Assistant Lecturer of Oral medicine, periodontology and diagnosis, Faculty of Oral and Dental medicine, Future University in Egypt.

INTRODUCTION

Oral lichen planus (OLP) is a chronic immune mediated disorder of the oral mucosa that includes the appearance of white lace-like lesions termed Wickham's stria, with or without the presence of erosive or atrophic areas, in addition to a wide range of clinical manifestations [1, 2]. OLP commonly affects the buccal mucosa bilaterally, dorsal surface and the lateral borders of the tongue and the gingiva. On the other hand, the floor of the mouth, the lips, and the palate are infrequently involved [3].

Although the exact etiology of OLP is unclear, several factors have been implicated in its etiopathogenesis. These include but are not limited to psychological stress, infection, immune response (both systemic and local), and hypersensitivity. In addition, the affection of the basal layer of keratinocytes was demonstrated to be linked to dysregulation of both innate and required immune systems. [4, 5].

Interleukin IL-6 is considered as a multifunctional cytokine that is involved in both inflammatory and immune responses. The production of IL-6 originates from activated T and B cells, activated macrophages, monocytes, fibroblasts, endothelial cells, and keratinocytes and is controlled by nuclear factor–kB, which is stated to play a significant role in the aggravation of inflammatory processes [6]. Clinicians can detect IL-6 level in serum and saliva and suggest it to be a capable biomarker for monitoring the disease activity [7, 8]. In the past decade, IL-6 in the saliva and serum of OLP patients was investigated and compared to IL-6 levels in healthy individuals. However, within these studies, some researchers reported a significant difference in the levels of IL-6 between healthy controls and OLP patients, while other investigators found no significant differences [9, 10, 11].

The TNF family of type II transmembrane proteins includes Fas ligand (FasL, APO-1L, CD95L, and CD178). FasL was formerly thought to be an effector protein linked only to T cells, but over the previous years it was found to be present in and on a wide variety of different cell types and organs. By attaching to its default receptor Fas (APO-1 and CD95), it was discovered that FasL induces apoptosis [12]. The apoptosis induced by the Fas/FasL system may play a role in the pathophysiology of several autoimmune diseases. On the other hand, soluble Fas (sFas, sAPO-1) is formed as an alternative mRNA splice variant and as a proteolytically cleaved transmembrane molecule CD95 fragment [13].

Both in vitro and in vivo, the sFas may alter lymphocyte mediated cytotoxicity and modify lymphocyte proliferation and development in response to self-antigen, respectively. Apoptosis mediated by Fas has been thought to be prohibited by sFas release blocking the Fas/FasL interactions. The biological relevance of sFas has been extensively investigated, with most of the research focusing on autoimmune disorders in relation to T-cell activity, solid tumors, and hematological malignancies [14].

We found no prior research that analyzed the correlation between IL-6 and sFas-dependent apoptosis inhibitor in the saliva of OLP patients. The current research set out to assess the use of salivary IL-6 and sFas levels as indicators of disease activity and progression in OLP patients before and after therapy.

SUBJECTS AND METHODS:

Ethical approval

The present study was conducted in accordance with the ethical standards established by the World Medical Association (Declaration of Helsinki, 1978, as revised in 2008) for investigations involving human participants. The Ethical Committee of the Faculty of Oral ana Dental Medicine, Future University in Egypt voted to accept the proposed protocol, and it was subsequently recorded under

the code number FUE.REC [17]10-2021. Before initiating this research, each participant provided their signature on an informed consent form, which was followed by a detailed description of the procedures that would be followed.

For this study, thirty participants were recruited from the outpatient facility of the Oral Medicine and Periodontology Department at the Faculty of Oral and Dental Medicine at Future University in Egypt.

Inclusion criteria:

- Patients' age ranging from 40-60 years.
- Systemically free patients based on the modified Cornell Medical Index [15].
- Patients free of any visible oral lesion other than OLP.
- Only patients with mild atrophic &/or bullous erosive oral lichen planus were included in the study [16].

Exclusion criteria:

- Users of tobacco in any form & alcoholics.
- Patients who used any drugs inducing hyposalivation.
- Pregnant or lactating females.
- Patients who used any corticosteroids in the past 6 months.

Subjects were allocated into two groups:

Group I (Control group): consisted of 15 healthy participants and salivary sample was collected from each one.

Group II (OLP group): consisted of 15 patients who were formerly diagnosed with OLP and showed an acute exacerbation at time of salivary sample collection. For each patient salivary sample was collected during exacerbation period and after topical corticosteroid treatment.

Triamcinolone acetonide 0.1% in orabase (Kenalog in Orabase: Bristol-Myers, Squibb, Spain) was prescribed for the OLP group to be applied topically 4 times a day for four weeks. At the fourth week Daktarin 2% oral gel (Janssen Pharmaceutica NV - Belgium (JANSSEN-CILAG)) was prescribed twice a day for one week.

Clinical examination

A- Comprehensive oral diagnosis was done, and pain was assessed for the patients in group II during exacerbation by using the McGill Pain Questionnaire's present pain intensity (PPI) [17]. Pain score within the applied system ranges from 0-5 as shown in (Figure 1).

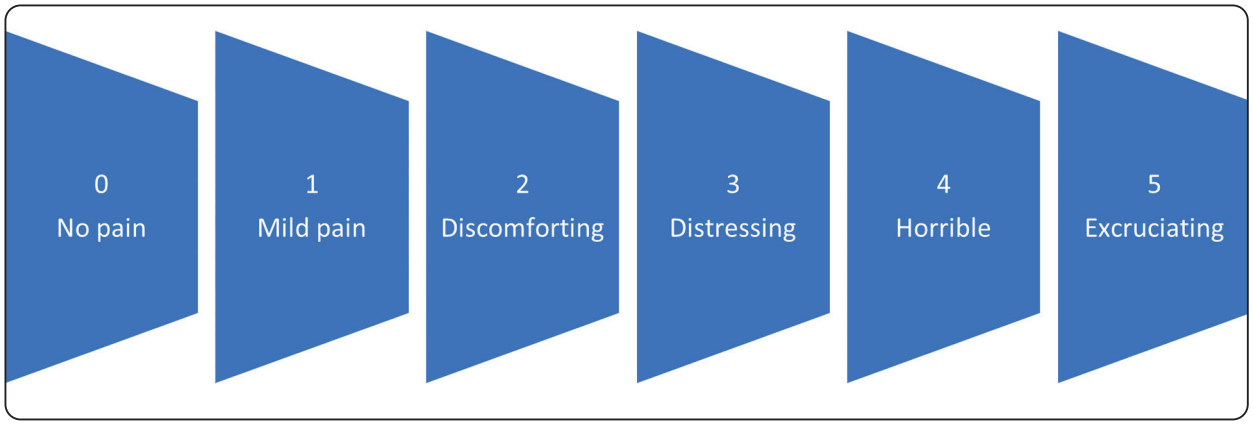
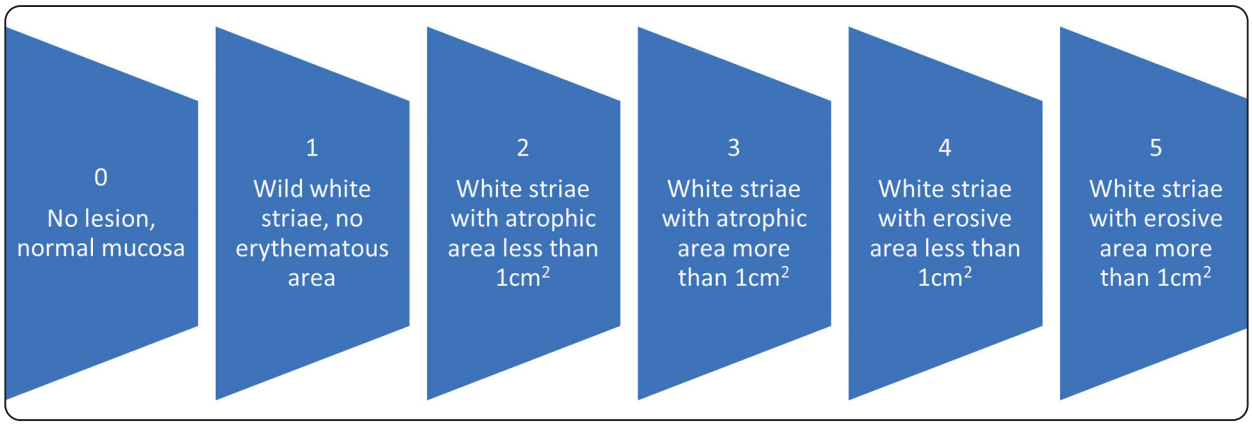


Fig. (1): Present pain intensity (PPI) of McGill Pain Questionnaire



Fig, (2): Thongprasom sign scoring.

B) Thongprasom et al. established a sign scoring system on a scale from 0 to 5 to rate the clinical severity of oral lesions, and this scale was used in a clinical assessment of all OLP patients at exacerbation time [16]. The patients' clinical scores were calculated by first scoring each lesion in the oral cavity independently, and then calculating the average scores. (Figure 2)

Salivary samples collection:

According to Navazesh's standard technique [18], whole unstimulated saliva (WUS) was collected once from the participants in the control group and twice from OLP group. In brief, the participants were instructed not to consume anything (water, food, chewing gum, etc.) for at least one and half hour before sample collection. The participants were given the instructions to first swallow, then tilt their head forward and to expectorate their saliva into a sterile tube for a period of five minutes while not swallowing. After the saliva samples were collected, they were immediately stored at a temperature of -80 degrees Celsius until analyzed.

Detection of IL-6 in salivary samples: Salivary concentrations of IL-6 were determined in duplicate for each participant using an enzyme linked immunosorbent test (ELISA) Human IL-6, assay kits (Human Quantikine IL-6 ELISA kit, R&D Systems, Minneapolis, MN). The assay recognizes both natural and recombinant human IL-6.

This assay employs an antibody specific for human IL-6 coated on 96-well plate. Standard samples and biotinylated anti-human IL-6 are pipetted into the wells and IL-6 present in a sample is captured by the antibody immobilized to the wells and by the biotinylated IL-6 specific detection antibody. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed. Following this second wash step, TMB substrate solution is added to the wells, resulting in color development proportional to the amount of IL-6 bound. The Stop Solution changes the color from blue to yellow and the intensity of the color is measured at 450nm.

Detection of sFas in salivary samples:

Samples were assayed for salivary levels of sFas by ELISA. In the lab, the salivary samples were thawed in ice followed by 15 minutes centrifuging at 3500 rpm (2600g) at 4°C to obtain the supernatant fluid phase. Supernatant were drawn off and used in the ELISA assays. sFas concentrations were determined in saliva samples from each patient using ELISA kits provided by DIAsource ImmunoAssays®, Belguim.

Statistical analysis:

Numerical data were expressed in terms of

range, mean ± standard deviation (±SD). Statistical analysis was performed by use of independent t-test to compare the two studied groups and Paired t-test to compare different time intervals in the same group. For non-parametric variables Wilcoxon test was used to compare the difference between before and after in the patients group. Pearson coefficient test was used to correlate between the two studied measures. A probability value (p) ≤ 0.05 was considered statistically significant. All statistical calculations were done using statistical package for social sciences (IBM SPSS statistics version 26).

RESULTS

A total of 30 subjects consented to take part in this study. The average age of the participants was 35.8 ±2.2 years for group I (control) and 38.9 ±11.2 for group II (OLP). There was a female predilection in both control group (66.6% females) and OLP group (80% females).

Pain and clinical scores were statistically significantly higher in patient`s group before treatment compared to their scores after treatment. (Table 1).

TABLE (1): Pain and clinical scores in Group II (OLP) before and after treatment.

Point of comparison		M	Min	Max
Pain score in OLP group	Before treatment	2	1	5
	After treatment	0	0	1
Wilcoxon Signed-Rank test	*P-value 0.00096**			
Clinical score in OLP group	Before treatment	3	3	5
	After treatment	0	0	2
Wilcoxon Signed-Rank test	*P-value 0.00064**			

M; median, Min; minimum, Max; maximum, Difference between medians of each 2-observation times measured by Wilcoxon signed ranks test, where p<.05 is significant.*

TABLE (2): The mean values of salivary IL-6 pg/ml & sFas (pg/ul) before treatment between the two groups and before and after treatment in Group II (OLP).

		Group I (Control)	Group II (OLP)	P value
Salivary IL-6				
X ±SD	**Before treatment**	5.1 ±11.5	19.8 ±20.7	0.02*
	After treatment		5.5 ± 11.4	
P value = *0.01**				
sFas				
X ±SD	**Before treatment**	3603.8 ±17.5	5271.5 ±19.2	< 0.05*
	After treatment		3833.8 ±9.5	
P value = < 0.0001*				

X; mean, SD; standard deviation.

: statistically significant at p≤ 0.05

TABLE (3): The mean values of salivary IL-6 pg/ml & sFas (pg/ul) between Group I (control) and Group II (OLP) after treatment.

	Control	OLP	P value
Salivary IL-6			
X ±SD	5.1 ±11.5	5.5 ±11.4	0.9245
sFas			
X ±SD	3603.8 ±17.5	3833.8 ±9.5	< 0.0001*

X; mean, SD; standard deviation.

: statistically significant at p≤ 0.05

The expression of salivary IL-6 and sFas was significantly higher in the OLP group compared to the control group. Following treatment and remission of the oral lichen planus lesions the values of the IL-6 and sFas decreased significantly. (Table 2). The reduction of the Il-6 values following treatment of OLP reached levels where no significant differences were noticed comparing it to the control values. On the contrary, following reduction salivary sFas values in OLP group following treatment, there was still a statistically significant difference compared to the control group. (Table 3) (Figure 3) (Figure 4).

TABLE (4): Correlation between Il-6 and sFas in both groups before treatment and in OLP group after treatment

Groups	Pearson correlation (r)	P value
Control group	0.432	0.107
OLP group	0.060	0.832
After treatment		
OLP group	0.494	0.061

r: Pearson coefficient.

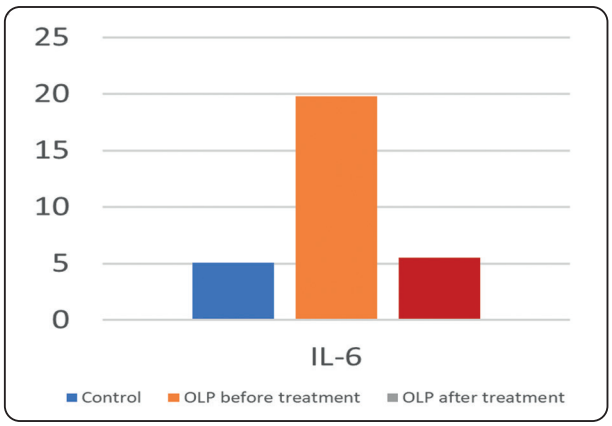


Fig. (3): The mean difference of Il-6 values between control group and OLP group before and after treatment

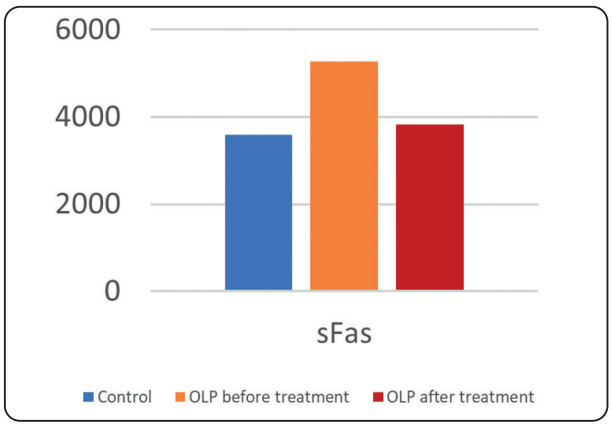


Fig. (4): The mean difference of sFas values between control group and OLP group before and after treatment

By using Pearson correlation coefficient, the (r) value was less than 0.5 in Group I and in Group II before and after treatment which reflects a week correlation Il-6 and sFas in saliva. (Table 4)

DISCUSSION

Lichen planus is a complex mucocutaneous chronic inflammatory condition affecting stratified squamous epithelium and may persist up to more than twenty years with periods of remission and exacerbation[19].

In the present study, the pain was assessed by the present pain intensity (PPI) of McGill Pain Questionnaire [17] and the concluded results were in accordance with Hegarty et al., who reported that using fluticasone gave rise to significant improvement in the painful symptoms experienced by OLP patients [20]. The clinical signs were assessed using the sign scoring measures set by Thongprasom et al., which has been used in other multiple studies[21,22,23,24]. Following treatment there was a significant reduction in the scored values which goes in accordance with Arash et al., who reported a significant reduction in Thongprasom score after treatment and after 2 months of discontinuation of the triamcinolone acetonide 0.1% [25].

The detection of disease-related cytokines in saliva as a noninvasive diagnostic technique has been considered in several studies [26, 27, 28]. Hence, the aim of the present study was to assess the levels of IL-6 and sFas in the saliva of OLP patients before and after treatment and versus healthy controls and to investigate if there is a possible correlation between them.

Additionally, it was discovered that the pathogenesis of the premalignant and malignant forms of oral lichen planus is influenced by IL-6, IL-8, and tumor necrosis factor-α (TNF-α) representing the NF-kB-dependent pro-inflammatory cytokines[29,30]. TNF-α and IL-6 are more monitored in the saliva[31,32], while IL-8 are better detected in the serum[33].

IL-6 is a pleiotropic pro-inflammatory mediator playing variable roles in acute phase reactions, hematopoiesis, and immunological responses. In cases of injuries and infections, IL-6 is secreted as an adaptive response [34]. Yet, the uncontrolled or the increased expression of Il-6 significantly impacts the pathogenesis of several human disorders including OLP. In addition, The angiogenic process in OLP was amplified by IL-6 [35], which supports its role in the disease pathogenesis [36]. The pathological roles of IL-6 in autoimmunity, inflammation and cancer have been reported in multiple preclinical and clinical studies [37].

The results of the present study showed that IL-6 in the salivary samples of OLP patients was significantly higher than that in controls before treatment with a mean value of 19.8 pg/ml. This is in agreement with Mozaffari et al., who stated that IL-6 is considered an important biomarker of OLP and confirms the role of this cytokine in the pathogenesis of OLP[32]. The same was noticed by Metwalli et al., who found a strong correlation between OLP and IL-6 levels in Egyptian population in addition to a statistically significant correlation between IL-6 levels and the severity of OLP [38].

In accordance with the present study Zhu et al., agreed that salivary levels of IL-6 were positively associated with OLP severity and should be used as a potential biomarkers in OLP diagnosis and prognosis of OLP[39].

Topical steroids are considered as the first-line treatment for symptomatic OLP [40] and in our study following the usage of topical triamcinolone acetonide 0.1% in orabase, the IL-6 values in the salivary samples were dropped significantly reaching a mean of 5.5 ± 11.4 pg/ml. Rhodus et al., treated their OLP patients using 0.1% dexamethasone oral rinse for 6 weeks and reported a significant decrease in TNF-a, IL-1-α, IL-6, and IL-8 following treatment. Unlike our study, they found a statistically significant difference between OLP patients after treatment and controls [28].

The elevated sFas levels in OLP group may be implicated in the escape of T cells from apoptosis[14]. In the present study OLP group showed high levels of sFas in saliva when compared to controls, similarly Aliev et al., mentioned that the mean salivary sFas level in OLP patients is the same as it in patients with squamous cell carcinoma and significantly higher than that in healthy subjects. Unlike Sklavounou et al., who didn't detect any differences in sFas serum levels between atrophic-erosive and reticular OLP [14], Aliev et al., reported that the salivary levels of sFas depend on the clinical form and severity of the disease[41].

In accordance with the present study Neppelberg et al., reported high levels of sFas in saliva of OLP patients when compared to normal oral mucosa which may be due to the putative dysfunction in the Fas/FasL mediated apoptosis which involved in the pathogenesis of OLP[42]

On the contrary, Mashhadiabbas et al., showed no significant difference between sFas level in OLP patients and healthy subjects and no significant role of Fas proteins in apoptosis of OLP but the difference in results may be related to differences in assay characteristics[43].

During remission of the OLP lesion, the sFas showed a significant reduction when compared with the pre-treatment values, however this reduction was still significantly higher than that of the controls. A similar result was reported when serum levels of sFas were analyzed before and after treatment of psoriasis and the post treatments values were still significantly higher than that of control persons [44]. Habibagahi et al., evaluated sFas concentrations in head and neck carcinoma patients and reported a significantly higher levels in patients with different tumor stages compared to healthy individuals. Following surgical removal of the tumors, sFas values decreased significantly, though the values were still significantly higher than that of controls [45].

A weak positive correlation was found between IL-6 and sFas before and after treatment of OLP

patients. Unluckily we found no studies correlating them except one study that reported an inverse correlation between Il-6 and sFas in semen qualities of infertile men [46].

CONCLUSIONS

Il-6 and sFas levels in saliva were significantly higher in OLP patients compared to controls which suggest their use as diagnostic markers. Topical treatment of the OLP lesions resulted in a significant reduction in Il-6 and sFas values in addition to significant improvement of pain and clinical scores.

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