Section: Dentistry

Original Research Article

EVALUATION OF SERUM AND SALIVARY LEVELS OF NITRIC OXIDE AND C - REACTIVE PROTEIN IN PATIENTS WITH ORAL LICHEN PLANUS IN SOUTH KASHMIR POPULATION

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Received *: 30/10/2025*
Received in revised form *: 18/12/2025*
Accepted *: 05/01/2026*

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DOI: 10.70034/ijmedph.2026.1.131

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (1); 733-736

ABSTRACT

Background: The etiopathogenesis of oral lichen planus (OLP) has been the center of study since a long time and a variety of etiological factors such as autoimmunity, heredity, drugs, dental materials, psychological factors, especially stress and anxiety have been associated with this disease. The aim and objective are to evaluate serum and salivary level of nitric oxide (NOx) and C - reactive protein (CRP) in patients with oral lichen planus as well as to evaluate their significant role as a prognostic marker.

Materials and Methods: The study sample consisted of 40 patients and the subjects were divided into two groups. Group A included 20 cases of normal oral mucosa and Group B comprised 20 cases of oral lichen planus. Salivary and serum levels of NOx and CRP were determined.

Results: In this study, serum and salivary levels of NOx and CRP increased significantly from normal oral mucosa patients to oral lichen planus. A significant correlation was found between NOx and CRP values in serum and saliva.

Conclusion: Oxidative stress cause damage to a range of organs in the human body. The results of present study revealed that NOx and CRP play a very important role in the etiopathogenesis of oral lichen planus. Salivary and serum CRP and NOx may be used as a non-invasive and prognostic marker for OLP.

Keywords: Oral lichen planus, C-reactive protein, Nitric oxide, oral potentially malignant disorders.

INTRODUCTION

Lichen Planus was obtained from the Greek word leikhēn, meaning "a tree moss" and the Latin word planus, meaning "flat".[1] The term was first described by British physician Erasmus Wilson in 1869 and it is thought to affect 0.5-1 per cent of the world's population.[2] Oral lichen planus is a chronic inflammatory disease that affects the skin as well as mucous membrane and oral lichen planus is the mucosal counterpart of cutaneous lichen planus. It occurs most frequently in the fourth decade of life and affects women more often than men in a ratio of 1.4:1.[3-5] Clinically, it presents as reticular, papular, plaque-like, erosive, atrophic or bullous types. The buccal mucosa, tongue and gingiva are most commonly affected sites in the oral cavity and they may appear weeks or months before the appearance of cutaneous lesions. The skin lesions appear as violaceous, flat-topped papules in ankles, wrist and genitalia however typically, the facial skin is spared. [6,7] In the oral cavity, the lesion appears as a radiating white, grey, velvety, thread-like papules in a linear, annular and retiform pattern forming typical lacy, reticular patches, rings and streaks. A tiny white elevated dot is present at the intersection of white lines known as Wickham striae as compared to striae of Wickham seen in the skin. [2,8,9]

Both specific and non-specific mechanisms may play a vital role in the etiopathogenesis of oral lichen planus. Specific mechanisms comprised of antigen presentation by basement layer keratinocytes and cytotoxic T lymphocyte that resulted in death of antigen-specific keratinocytes, whereas non- specific

mechanisms may be involved in mast cell degranulation and matrix metalloproteinase activation. These combined mechanisms, then cause T lymphocytes accumulation in the lamina propria underlying the epithelium, intraepithelial T lymphocytes migration, breakdown of basement membrane and keratinocyte apoptosis, all of which are characteristic features of oral lichen planus.[3] Dendritic cells (DC) play an important role in these immunopathological features with respect to antigens presented to T-cell.[10]

The role of oxidative stress in pathophysiologic changes of basal cells of epidermis in lichen planus has also been considered in the literature.[11] Nitric oxide is a short living product of nitrogen metabolism produced by several cells in the organism with very significant physiological function. Endothelial cells and neural cells produce NOx, macrophages and other inflammatory cells can induce its synthesis and release. The most important inductors of NOx synthesis are bacterial products. The biological function of NOx can be demonstrated into two types. First, it acts as an endothelial-derived relaxer of vascular smooth muscle, an inhibitor of platelet aggregation and adhesion, and a neuronal messenger. Secondly, the NOx synthesized in huge amounts by activated macrophage is a cytotoxic molecule influencing the ability of cells to kill bacteria, viruses and protozoa along with tumour cells. However, NOx secreted by macrophages has damaging effects against cellular proteins, DNA and lipids leading to periodontitis.[12-14] C-reactive protein (CRP), a systemic marker of chronic inflammation, is an acute phase protein, the levels of which vary on daily basis, rises with aging, increased blood pressure, smoking, coffee and alcohol consumption, decreased physical activity, raised levels of triglycerides, insulin resistance and diabetes, high protein diet, chronic tiredness and suffering from sleep disturbances, and depression.[15] CRP belongs to pentraxins protein family; pentraxins are the ancient proteins having cyclic pentameric arrangement of five non-covalently bound identical subunits,[16] placed in a symmetric cyclic design around a central pore, determining a pentameric, discoid, and flattened configuration.[17] CRP is also considered as a prognostic factor for various malignancies and the risk of cancer is increased when pre-diagnostic CRP levels are high. The aim of the present study was to determine serum and salivary level of nitric oxide (NOx) and C - reactive protein (CRP) as oxidative stress and inflammation status in patients with oral lichen planus as well as to review their considerable function as a prognostic marker.

MATERIALS AND METHODS

A cross-sectional study was conducted on 40 subjects in GMC, Anantnag and the study group was divided into two groups: -

Group A- 20 subjects of normal oral mucosa

Group B- 20 subjects of oral lichen planus

The histopathological confirmation was done on all cases of oral lichen planus and normal oral mucosa. The study was approved by the ethical committee of the institution and an informed consent was obtained from all study subjects. The patients who were receiving therapy or suffering from any systemic condition like hepatic or renal disorders, patients who were pregnant or taking antibiotics or NSAIDS within a month of sample collection, patients with underlying systemic diseases, oral cancer or previously treated oral lichen planus, chronic alcoholics were excluded from the study to rule out altered liver function that could lead to variations in CRP and NOx levels.

Sample collection was done in the morning from the study subjects so as to prevent diurnal variation. Blood samples were taken from cubital vein and left to clot at 40C in a sterile, clean, dry tube and kept inside the refrigerator. Serum was collected by centrifuge the blood at 3,000rpm for 5 to 10 minutes in 10cc sterile tubes and stored at -20°C until the time of analysis.

In this study, 10 ml of unstimulated whole saliva was collected from each patient into a sterile centrifuge tube. After centrifugation, the separated clear salivary fluid was stored in disposable storage vials at -80°C until the test day.

Serum and salivary NOx determination was based on the Griess reaction in which a chromophore with a strong absorbance at 545nm is formed by the reaction of nitrite with a mixture of N-naphthyl ethylenediamine and sulphanilamide. For NOx detection, aliquots of the sample were mixed with cadmium in glycine buffer at pH 9.7 to reduce nitrate to nitrite, which was then mixed with fresh reagent. The absorbance was measured by spectrophotometer. Salivary and serum levels of CRP were determined using immunoturbidimetry based on agglutination. CRP causes agglutination of the latex particles coated with anti-human CRP. The agglutination of the latex particles is proportional to the CRP concentration and is measured by turbidimetry. The test specimen is mixed with activation buffer and latex reagent which was then allowed to react. CRP in the test specimen causes the formation of an insoluble complex that produces turbidity, which is measured at 546 nm. The increased turbidity corresponds to increased concentration of CRP in the test specimen. All the data was analysed using statistical software (SPSS version 21.0). Mean and standard deviation were calculated for each individual group. A probability value (p) of ≤ 0.05 was considered to be statistically significance.

RESULTS

In the present study, 60.00% and 40.00% of the subjects in Group A were males and females respectively. In Group B, 40.00% and 60.00% were males and females respectively. [Table 1].

In the present study, the mean age of the patients in Group A and Group B were 26.75±6.08 years and 32.50±7.32 years respectively [Table 2].

In the present study, the mean serum level of CRP in Group A and Group B were 1.62±1.07 and 4.36±2.91 mg/l respectively. The mean serum level of CRP increased from normal oral mucosa to oral lichen planus with a statistically significant difference. In the present study, the mean serum level of NOx in Group A and Group B were 36.65±6.85 and 60.55±17.45 µmol/l respectively. The mean serum level of NOx was found to be significantly higher in oral lichen planus as compared to normal oral mucosa [Table 3].

In this study, the mean saliva level of CRP in Group A and Group B were 08.42±1.8 and 15.40±5.2µg/l respectively. The mean saliva level of CRP in oral lichen planus was more as compared to normal oral mucosa. The p-value was found to be statistically significant. The mean saliva level of NOx in Group A and Group B was 63.65±23.44 and 84.04±32.62µmol/l respectively. The mean salivary level of NOx increased from normal oral mucosa to oral lichen planus with a statistically significant p-value [Table 4].

Table 1: Gender wise distribution in normal oral mucosa and oral lichen planus

Group	No. of cases	Gender	
		Male	Female
Group A	20	12(60.00%)	08 (40.00%)
Group B	20	08(40.00%)	12(60.00%)

Group A- Normal oral mucosa, Group B-Oral lichen planus

Table 2: Age wise distribution in normal oral mucosa and oral lichen planus

Group	No. of cases	Mean ± Standard deviation
A	20	26.75±6.08
B	20	32.50±7.32

Group A- Normal oral mucosa, Group B-Oral lichen planus

Table 3: Serum C- reactive protein (mg/l) and NOx (µmol/l) in normal oral mucosa and oral lichen planus

Parameter	Group	No. of cases	Mean ± Standard deviation	P-value
Serum C- reactive protein	A	20	1.62±1.07	0.001
	B	20	4.36±2.91	
Serum NOx	A	20	36.65±6.85	0.001
	B	20	60.55±17.45	

Group A- Normal oral mucosa, Group B-Oral lichen planus

Table 4: Salivary C- reactive protein (µg/l) and NOx (µmol/l) in normal oral mucosa and oral lichen planus

Parameter	Group	No. of cases	Mean ± Standard deviation	P-value
Salivary C- reactive protein	A	20	08.42±1.8	< 0.001
	B	20	15.40±5.2	
Salivary NOx	A	20	63.65±23.44	0.001
	B	20	84.04±32.62	

Group A- Normal oral mucosa, Group B-Oral lichen planus

DISCUSSION

The Oral Lichen Planus (OLP) is a chronic inflammatory disease that involves skin and oral mucosa. It is a T-cell mediated autoimmune disease in which the cytotoxic CD8+ T cells trigger apoptosis of the basal cells of the oral epithelium. The oral lesions appear as white furrows or linear, papules, plaques, erythema, erosions or ulcers in the mouth and mostly affect the buccal mucosa, tongue, and gingiva. Currently, six clinical types of OLP have been reported including reticular, erosive, atrophic, papular, plaque-like and bullous. C-reactive protein is an acute phase protein and also considered as a marker of chronic inflammation which is synthesized in liver and has been identified as an important biomarker of wide range of spectrum of conditions like systemic infection, rheumatoid arthritis, vasculitis etc. Adipocytes secrete adipokines such as IL-6/TNF-alpha that are closely related with CRP.[18]

In the current study, serum and salivary CRP levels were evaluated in oral lichen planus patients to evaluate whether CRP could be used as a prognostic indicator for oral lichen planus. In this study, serum and salivary CRP levels were found to be significantly higher in oral lichen planus patients as compared to normal oral mucosa. These results were in agreement with the study done by Shiva et al in 2019.[19] The findings of the current study put forth that the potential use of salivary and serum CRP act as a parameter for systemic levels of inflammation. The correlation of increased CRP and chronic inflammation associated with OLP indicate CRP as a potential biomarker for disease activity and also act as a definitive predictor for determining the malignant transformation in OLP. The results of the study done by Atas et al,[20] evaluated high levels of CRP and ESR with high neutrophil count which may support the systemic inflammatory process in oral lichen planus patients. Santiago et al,[21] revealed patients with oral lichen planus showed higher lipid

peroxidation levels and CRP, hence chronic inflammation may elucidate these findings. Besides, increased CRP levels determine an increased predisposition to oral lichen planus due to chronic inflammation.

CONCLUSION

The present study concluded that there were increased levels of serum and salivary CRP as well as NOx in oral lichen planus patients as compared to patients with normal oral mucosa. Salivary and serum CRP as well as NOx may be used as a non-invasive, diagnostic and prognostic marker for OLP and it would be more helpful, if baseline values of both these parameters could be determined during treatment and follow-up visits of patients, which would further develop its importance in the clinical management of the disease.

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