

## Clinical evaluation of serum transaminases and plasma glucose levels in patients with oral lichen planus: A hospital based study

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### Abstract

**Introduction:** The association of lichen planus with chronic liver disease and diabetes mellitus has been extensively studied, but the conclusions are often controversial. Aim of the study was to assess the relationship of lichen planus with liver function status and diabetes mellitus in patients from Malabar region of Kerala.

**Materials and Method:** The study was performed on 50 patients with oral lichen planus (OLP) as study group and 50 control group cases. Routine blood test was carried out in all the patients and analyzed for ALT(Alanine transaminase), AST(Aspartate transaminase) levels, fasting plasma glucose(FPG) and random plasma glucose levels (RPG). The values of ALT and AST levels  $\geq 40$  IU/l were categorized as impaired liver function. Subjects with FPG  $\geq 126$  mg/dl and/or RPG  $\geq 200$  mg/dl were considered as having diabetes mellitus.

**Results:** FPG/RPG levels were elevated in 17 cases with OLP while only 10 control group cases had increased levels ( $p > 0.05$ ). Regarding AST and ALT levels, it was elevated in 23 cases (46 %) and in 10 cases (20 %) of the study group and control group, respectively. These differences were statistically significant ( $P < 0.006$ ). Out of 16 erosive forms, 11 cases showed elevated AST/ALT levels and among 34 non-erosive cases, only 12 patients showed elevated AST/ALT levels ( $p < 0.05$ ).

**Conclusion:** Elevated transaminases and plasma glucose levels can be associated with oral lichen planus according to this study. However, larger sample size studies, evaluating different parameters are required to establish the hepatic changes and impaired glucose function in OLP.

**Keywords:** AST, ALT levels, Diabetes mellitus, Oral lichen planus

### Introduction

Lichen planus (LP) is a chronic autoimmune mucocutaneous disease that may affect the oral mucosa, skin, genital mucosa, scalp and nails.<sup>(1)</sup> The prevalence of oral lichen planus in general population varies from 0.2–4%.<sup>(2)</sup> Mucous membrane involvement may occur in addition to cutaneous disease, or may be the only manifestation of lichen planus; however, it is estimated that, about 50% of the patients with skin lesions have oral lesions. Unlike self-limiting cutaneous lesions, oral lichen planus (OLP) is often chronic and rarely undergoes spontaneous remission.<sup>(3)</sup>

Malignant transformation of oral lichen planus, especially the erosive variety, has been documented, and about 0.4% - 5% transformation has been suggested.<sup>(3)</sup> Oral lichen planus can predispose to opportunistic infection by fungal microbes. A high prevalence of *Candida albicans* with oral lichen planus is thought to be related to impairment of cellular immunity.

Many investigators have reported a correlation between lichen planus and liver diseases.<sup>(4,5)</sup> The prevalence of this association varies widely in the literature, ranging from 0.1% to 35% in series based on occasional determinations of serum transaminase activity.<sup>(6)</sup> Erosive lichen planus is particularly stated to appear in association with chronic liver diseases.<sup>(5,7,8)</sup> It is important to look for any impairment in liver function tests in case of erosive oral lichen planus as

elevation of serum transaminase levels were reported in many studies conducted earlier. Aspartate transaminase (AST) and Alanine transaminase (ALT) are considered as sensitive indicators of liver damage or injury from different types of diseases. A number of authors have suggested that patients with oral lichen planus have been associated with diabetes mellitus more often than the general population. Diabetes mellitus (DM) and lichen planus are considered to be associated with immunological changes, thus making a possible relationship between them of special interest. The relationship between lichen planus and diabetes has been extensively studied, but conclusions are often controversial.<sup>(9,10,11)</sup> This variability in previous results motivates further investigations concerning the association of OLP with DM.

The present study was taken up to evaluate serum transaminases and plasma glucose levels in oral lichen planus and whether there is any association between them and occurrence of OLP. The literature showing relation of oral lichen planus with transaminase levels and diabetes in our population are few, and hence the relevance of the study.

### Materials and Method

The study was conducted in the Department of Oral Medicine and Radiology, Government Dental College, Kozhikode, in association with, the Department of Biochemistry, Govt. Medical College,

Kozhikode, over a period of six months. One hundred subjects were included in the study, who were subdivided into two groups:

- a. Study group
- b. Control group.

Ethical clearance from the human ethical committee, Government Dental College, Kozhikode, was obtained prior to the study. Patients who reported to the outpatient clinic of the Department of Oral Medicine and Radiology, Government Dental College, Kozhikode were screened for cases of oral lichen planus. Fifty consecutive patients of either gender aged above 18 years, fulfilling the diagnostic criteria for OLP<sup>(2)</sup> (clinically and histopathologically) were enrolled for the study after getting informed consent. The control group consisted of fifty age and sex matched subjects, selected from the outpatient department of Oral Medicine and Radiology with clinically appearing normal mucosa and who required blood examination as a part of their treatment. Patients having severe systemic problem and thus rendered unfit for biopsy, patients unwilling for biopsy, those with clinical presentation of lichenoid contact reaction, lichenoid drug eruptions and Discoid Lupus Erythematosus, patients with clinical diagnosis of oral lichen planus, but histopathological report as lichenoid reaction or lichenoid dysplasia were excluded from the study.

Patients with oral lichen planus were examined in detail and findings were recorded in a proforma specially designed for the study. The patient details regarding age, gender, occupation and socioeconomic status were obtained. A detailed history with importance to chief complaint and its duration, general health, past medical and family history, previous drug therapy, deleterious habits like tobacco chewing, cigarette smoking and alcohol consumption, dietary habits, oral hygiene status and brushing habits were recorded.

A detailed clinical examination was carried out and the sites, distribution, type of lichen planus and the presence of any associated skin lesions were recorded in the proforma. The clinical evaluation of OLP was based on the classification that was proposed by Andreasen who described six clinical forms of OLP.<sup>19</sup> When more than one clinical type of lesions was found in the same patient such as reticular and erosive; the most severe form of the disease (i.e. erosive) was used to classify the lesions. All the subjects in the study group were subjected to histopathological examination for confirmation of the lesions.

Routine blood test was carried out in all the patients. The samples were then analyzed for ALT, AST levels (ERBA SGOT and SGPT kits) and fasting and random plasma glucose levels (Glucose kit, Agappe diagnostics) by fully automated clinical wet biochemistry analyzer, Cobas C-311 (Roche Diagnostics, USA). The values of ALT and AST levels

$\geq 40$  IU/l were categorized as impaired liver function. Subjects with fasting blood glucose  $\geq 126$  mg/dl and/or random plasma glucose  $\geq 200$  mg/dl were considered as having diabetes mellitus. Patients with raised ALT and/or AST levels were subjected to qualitative detection of Antibodies to Hepatitis C Virus. The kit used was fourth generation ELISA containing HCV Antigens for core, NS3, NS4 and NS5 (HCV TRI-DOT, Diagnostic Enterprises).

The results of lab investigations were analyzed and the patients were classified according to the standardized criteria. All the collected data were interpreted using the statistical software SPSS<sup>®</sup> version 11, for Microsoft<sup>®</sup> Windows<sup>®</sup>. A descriptive study was made for clinically relevant variables. The associations between the different qualitative variables were examined using Pearson's chi square test. The Student's t-test in turn was used to compare the different quantitative variables. P-value  $\leq 0.05$  were considered statistically significant.

## Results

Our hospital belongs to tertiary level and is the only Govt. Dental College in this area which drains patients from the all over the Malabar region of Kerala. Among the 27505 patients who attended the outpatient clinic in the Department of Oral Medicine and Radiology during the study period, 80 patients (0.29%) had oral lichen planus. The age of OLP patients ranged from 22-60 years, with a mean age of  $44.78 \pm 9.83$  years. Majority of the patients were above 40 years of age with the peak age group being 41-50 years.

The most common chief complaint of the OLP patients was burning sensation (86%) followed by mucosal discoloration (8%) and pain (6%). There were 9 patients who were known cases of diabetes mellitus in the study group and 3 known cases in the control group. Family history of LP was positive only in one patient. Out of the 50 patients, 48 (96%) patients did not have any deleterious habits. Of the remaining two patients, one patient had smoking and the other had tobacco chewing habit. In the control group, there were five patients (10%) with deleterious habits of smoking (2 subjects) and tobacco chewing (3 subjects).

Reticular form was the most common clinical type seen in 24 patients (48%), followed by erosive in 16 (32%), atrophic in 6 (12%), plaque type in 3(6%) and bullous type in one patient (2%). Out of 50 OLP patients, ten (20%) had extra oral manifestations of which, seven had skin involvement, one had genital and two had involvement of other sites (scalp). Among the ten cases, five were reticular type, one had atrophic type and four had erosive form of oral lichen planus.

All the patients in study group (100%) had LP on the buccal mucosa. The next most common site was the gingiva (70%). Distribution of sites involved by each type of OLP is shown in Table 1. Statistical analysis performed for each of the three most prevalent sites

(buccal mucosa, gingiva and tongue) showed no significant association between the site and the clinical

form of the disease, except for the palate ( $P < 0.05$ ) in which erosive form was predominantly observed.

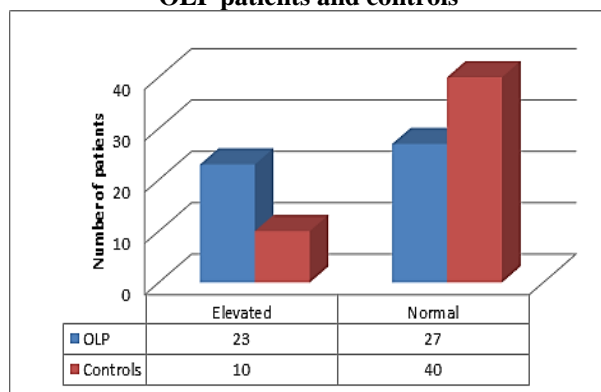
**Table 1: Distribution of sites involved by each type of OLP**

Type of OLP	Buccal mucosa	Gingiva	Palate	Tongue (Lateral/ventral / Dorsum)	Upper/Lower lip	Floor of mouth
Reticular	24	17	5	12	2	1
Plaque	3	1	0	2	0	0
Bullous	1	0	0	0	0	0
Atrophic	6	5	0	5	0	0
Erosive	16	12	11	13	4	0
Total	50(100%)	35(70%)	16(32%)	32(64%)	6 (12%)	1(2%)

The mean distribution of AST levels in OLP patients and control group were  $38.88 \pm 17.89$  and  $30.82 \pm 13.70$  respectively. There was statistically significant difference for the mean AST levels between the study and control group ( $P < 0.01$ ). The mean distribution of ALT levels ( $42.12 \pm 28.32$ ) was higher in OLP patients than that in the control group ( $36.02 \pm 18.35$ ) though it was not statistically significant.

Regarding AST and ALT levels, it was elevated in 23 cases (46%) and in 10 cases (20%) of the study group and control group, respectively. These differences were statistically significant ( $P < 0.006$ ) (Table 2). Considering the ALT/AST levels and type of OLP, it was observed that, they were raised in 8 cases of reticular, 4 cases of atrophic (Fig. 1) and 11 cases of erosive LP though no statistically significant differences were observed.

**Table 2: Comparison of AST/ALT levels between OLP patients and controls**



**Fig. 1: Atrophic lichen planus**

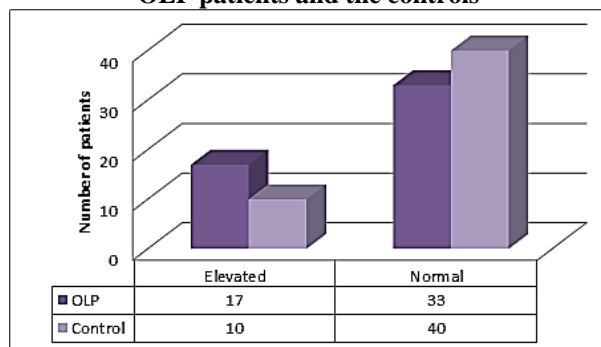
For the ease of comparing the AST/ALT levels between the erosive and non-erosive types, reticular, plaque and atrophic types of LP were grouped together as non-erosive types. Out of the 16 erosive cases, 11 cases (68.8%) showed elevated AST/ALT levels. However, out of the 34 non-erosive cases, only 12 patients (28%) showed elevated AST/ALT levels which showed that the results were statistically significant ( $P < 0.05$ ).

Correlating the elevation of ALT/AST levels and site wise distribution in OLP patients, of the 23 patients, 3 had lesion on the upper/lower lips, 17 had gingival involvement, 8 had OLP on the palate, 16 patients with the lesion on tongue, all the patients had involvement of buccal mucosa and 6 of them had extraoral form of lichen planus. Patients with raised ALT/AST levels of study and control groups were subjected to detection of Hepatitis C Virus. Anti-HCV titre was negative in all the cases.

The mean fasting plasma glucose (FPG) value of the study group was  $112.42 \pm 32.56$  mg/100ml whereas that of controls was  $103.84 \pm 20.32$  mg/100ml. The FPG value of study group appeared higher than that of the control group. The mean random plasma glucose (RPG) value of study group was  $155.92 \pm 60.86$  whereas that of control group was  $140.56 \pm 38.03$  mg/100ml. Regarding FPG and RPG levels, the FPG and RPG values of study group appeared higher than that of the control group. There were 9 patients (3 males and 6 females) who were known cases of diabetes mellitus in the study group and 3 known cases (2 males and 1 female) in the

control group. As per the ADA criteria, FPG/RPG levels were elevated in 17 cases (34%) and 10 cases (20%) of the study group and control group respectively as seen in Table 3. However, when subjected to statistical analysis, it was not statistically significant.

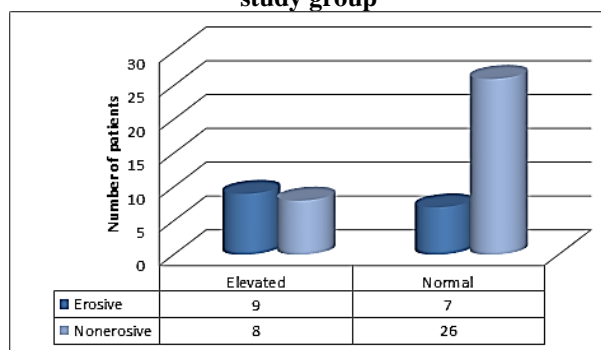
**Table 3: Comparison of FPG/RPG levels between OLP patients and the controls**



Of the 17 cases of elevated FPG/RPG levels, 9 cases were known diabetics (under treatment) and 8 cases were newly detected. Nevertheless, FPG/RPG levels were not raised in 2 of the known cases of diabetes mellitus (Controlled diabetes).

Among the 50 OLP subjects, the age range of the diabetics was 39-60 years with a mean of 47.3 years. The FPG/RPG levels were raised in seven cases of reticular LP, one case of atrophic and nine cases of erosive LP, although the levels were not elevated in plaque and bullous forms. For the ease of comparison, reticular, plaque and atrophic types of LP were grouped together as non-erosive types. The elevation of FPG/RPG levels between the erosive and non-erosive types was then compared. Among the 16 erosive cases, 9 cases (56.3%) showed elevated FPG/RPG levels. However, from Table 4 it is seen that, of the 34 non-erosive cases, only 8 patients (23.5%) showed elevated FPG/RPG levels which demonstrated that the results were statistically significant ( $P < 0.05$ ).

**Table 4: Comparison of FPG/RPG levels between the erosive and non-erosive forms of OLP in the study group**



## Discussion

Lichen planus is a chronic inflammatory mucocutaneous disease that affects skin and mucous membranes of squamous cell origin and with an uncertain etiology, although an autoimmune mechanism is known to be involved.<sup>(1)</sup> Current data suggest that OLP is a T cell-mediated autoimmune disease in which auto-cytotoxic CD8+ T cells trigger apoptosis of oral epithelial cells.<sup>(3)</sup>

Mehta et al<sup>(12)</sup> found 0.1% prevalence in rural Indian communities, while in Kerala, Pindborg et al<sup>(13)</sup> found a prevalence of 1.5%. In the present study, 80 out of 27505 patients had oral lichen planus which showed a prevalence of 0.29%. An analysis was carried out to evaluate whether any particular habit had an influence for the occurrence of oral lichen planus. It was observed that out of the 50 patients, 48 patients did not have any deleterious habits. In the control group, there were five patients with deleterious habits- smoking (2 subjects) and tobacco chewing habit (3 subjects). These results were not statistically significant indicating that habit may not be a contributing factor, although some of the previous studies have reported an association of oral lichen planus with deleterious habits.<sup>(8,14)</sup>

The clinical features of patients in the study share many similarities with those reported previously. The most common clinical type seen was reticular form in 24 patients (48%), followed by erosive in 16 (32%), atrophic in 6 (12%), plaque type in 3(6%) and bullous type in one patient (2%) which is in agreement with the results of other studies<sup>(8,14,15,16)</sup> although a few authors have reported a greater prevalence of atrophic-erosive forms than reticular lesions.<sup>(17,18)</sup> No cases of papular LP were observed in our study. This may be explained by the fact that, papular form is rare, and coexists with other forms. They are usually overlooked during the oral examination due to the small size of the lesion.<sup>(1)</sup>

Among the 50 OLP patients, 10 (20%) had extra oral manifestations. Several authors have observed that, patients with OLP also present or develop lesions on the skin.<sup>(15,17,19)</sup>

The most frequently affected sites in our group of patients coincide with those described by majority of the investigators. In this study, buccal mucosa was the single most common site of involvement in all the patients followed by the gingiva (70%), palate (32%), and dorsum of the tongue (28%). The most common location was the buccal mucosa, with a prevalence of 80–95%<sup>(15,20)</sup> followed by the tongue (30–50%) according to some authors.<sup>(15,20,21)</sup> Statistical analysis of the three most prevalent sites (buccal mucosa, gingiva and tongue) showed no significant association between the site and the clinical form of the disease, except for the palate ( $P < 0.05$ ) in which erosive form was predominantly observed. In our study, lichen planus confined to a single oral site was infrequent occurrence, though Eisen<sup>(20)</sup> had reported isolated lip lesions.

The prevalence of liver diseases in lichen planus varies widely in the literature. In the present study, the number of OLP patients with elevated AST/ALT levels (46%) was significantly higher when compared with the controls (20%) ( $P < 0.006$ ). However, statistically significant differences were not observed between the elevation of ALT/AST levels and gender/age/site wise distribution of OLP in the study group, although Bagan et al<sup>(22)</sup> had observed that, the patients with oral lichen planus who had altered transaminase levels exhibited a higher percentage of tongue involvement. The mean AST/ALT levels of the study group showed statistically significant rise in comparison with the control group, in the present study ( $P < 0.01$ ). Thus, elevated transaminase levels can be associated with oral lichen planus, according to this study. Similar results were observed by Ali,<sup>(8)</sup> Chalkoo,<sup>(14)</sup> Bagan et al,<sup>(22)</sup> Korkij<sup>(23)</sup> and GISED.<sup>(24)</sup>

Regarding the relationship between serum transaminase levels and the type of oral lichen planus, 11 of 16 patients with elevated enzyme levels had erosive oral lichen planus and the remaining five had non-erosive oral lesions. The mean AST/ALT values were higher in patients with erosive oral lesions than those with non-erosive lesions in the present study. These findings may be an indication that, in the presence of hepatic changes, there is an equally greater predisposition toward development of aggressive oral lesions. Similar observation was reported earlier.<sup>(22)</sup> Analyzing these observations, it can be inferred that, the association of oral lichen planus with liver disorders is not coincidental.

A number of case reports worldwide have supported the possible link between HCV and lichen planus.<sup>(25,26,27,28,29)</sup> In the present study, attempts were also made to detect whether there was any correlation, between HCV and oral lichen planus. All studied cases with elevated AST/ALT levels were subjected to the estimation of Anti-HCV titre by highly sensitive fourth generation ELISA technique and, all were found to be seronegative. This result was in agreement with the observations of other studies from our country, South Asia and other parts of the world<sup>(25,28)</sup> although contrary results were also reported.<sup>(16,30)</sup> This may be due to the differences in the genetic, geographic, environmental or other host factors.<sup>(26)</sup> The seronegativity could be correlated to the fact that, these patients might be either in the early or chronic stage of HCV infection at the time of visit, or the patient may be really seronegative, and the elevation of transaminases may be caused by factor other than HCV, which might activate the progression of oral lichen planus.

An association between oral lichen planus and diabetes mellitus has been speculated for many years. Many authors have reported a strong association between lichen planus and DM.<sup>(9,10,18)</sup> However, this relationship could not always be established.<sup>(10,31)</sup>

All the subjects with elevated FPG/RPG levels were individuals within the age group of 38-60 years with a mean age of 47.3 years which are similar and comparable with the studies of Bagan et al<sup>(18)</sup> and Lowe et al.<sup>(32)</sup> In the present study, diabetes mellitus appeared more prevalent (34%) among patients with oral lichen planus, compared with that in the control group (10%). However, when we compared the correlation between diabetes mellitus in study and control group, the results were not found to be statistically significant. This might be either due to the small sample size or the methodology adopted for the study, as we had considered subjects with  $\geq 126$ mg/dl and/or  $\geq 200$  mg/dl for fasting plasma glucose and random plasma glucose levels respectively, while others considered  $\geq 100$ mg/dl and/or random plasma glucose of  $\geq 180$  mg/dl as having diabetes mellitus.

When OLP patients were grouped into erosive and non-erosive types, and the elevation of FPG/RPG levels were compared, among the 16 erosive cases, 9 cases (56.3%) showed elevated FPG/RPG levels. However, out of the 34 non-erosive cases, only 8 patients (23.5%) showed elevated FPG/RPG levels, which was statistically significant ( $P < 0.05$ ). Comparative studies of the erosive and non-erosive groups conducted earlier showed that, the diabetes mellitus was more common in the first group.<sup>(18,33)</sup> The high prevalence of DM in OLP patients showed in this study, suggests the need for incorporating FPG determination as a complementary test, for the diagnostic management of OLP patients.

## Conclusion

Elevated transaminases and plasma glucose levels can be associated with oral lichen planus and erosive forms in Malabar region of Kerala, according to this study. The small sample size and short duration of the present study are limitations in arriving at a definitive conclusion. However, further studies with larger sample size, evaluating different parameters for the evaluation of hepatic function are required to establish the hepatic changes and impaired glucose function occurring in oral lichen planus.

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