

Salivary IgA and IgG in oral lichen planus and oral lichenoid reactions diseases

Parichehr Ghaleyani, Farimah Sardari¹, Mojtaba Akbari²

Department of Oral Medicine and Torabinejad Dental Research Center, School of Dentistry, Isfahan University of Medical Sciences, ¹Department of School of Dentistry, Isfahan University of Medical Sciences, ²Epidemiologist, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: The objective of this study was to assess the level of salivary IgA and IgG in oral lichen planus (OLP) and oral lichenoid reactions (OLR) patients as diagnostic factors to the differential diagnosis of OLP, OLR diseases.

Materials and Methods: Saliva sample were obtained from 50 OLP, 50 OLR patients and 50 healthy subjects between April 2010 and October 2011. The clinical relevant data taken into account were: Demographical data, previous medication, and level of salivary IgA and IgG. Each sample was assessed to determine the level of salivary IgA by ELISA test and salivary IgG by radial immune diffusion.

Results: The mean of salivary IgA and IgG in patients were 119.01 ± 114.18 mic/ml and 3.25 ± 1.81 mic/ml, respectively. There were no significant differences for salivary IgA and IgG between OLP and OLR, but the mean of salivary IgA and IgG in OLP and OLR patients were significantly more than normal group (P -value < 0.05). The cut-off value was set at >72 mic/ml for salivary IgA in both OLP and OLR groups and set at >3.7 mic/ml for salivary IgG. On comparing the AUCs, there was no significant difference between AUCs for IgA (0.715 ± 0.05 vs. 0.69 ± 0.5 , for OLP and OLR patients, respectively, P -value = 0.7) and IgG (0.681 ± 0.05 vs. 0.548 ± 0.06 , for OLP and OLR patients, respectively, P -value = 0.1).

Conclusions: Our results showed that the level of salivary IgA and IgG in OLP and OLR patients is higher than healthy controls, but they cannot be used as diagnostic factors to the differential diagnosis of OLP and OLR.

Key Words: IgA, IgG, oral lichen planus, oral lichenoid reactions

Address for correspondence:

Dr. Farimah Sardari, Department of Oral Medicine, School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: drsardari_farimah@yahoo.com

Received: 13.02.2012, Accepted: 15.05.2012

INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory and autoimmune disease, affecting the skin, nails, scalp, and mucosal membranes. The reported prevalence

rates of OLP vary from 0.5% to 2.2% of the general population. It is more frequently observed, mainly in middle-aged women.^[1-4] Although OLP is relatively common, there is so controversy, mainly in relation to the possibility of it becoming a malignant condition.^[5-7] Also, the WHO considers OLP as a systemic disorder associated with a rise in the danger of cancer.^[8]

However, the etiology of OLP remains unknown with a multifactorial pathogenesis.^[1] There are many fundamental factors that have been associated, such as: Anxiety, diabetes, autoimmune diseases, intestinal diseases, stress, hypertension, infections, and genetic predisposition.^[9,10]

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| Quick Response Code: | Website: www.advbiores.net |
|  | DOI: 10.4103/2277-9175.102977 |

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How to cite this article: Ghaleyani P, Sardari F, Akbari M. Salivary IgA and IgG in oral lichen planus and oral lichenoid reactions diseases. Adv Biomed Res 2012;1:73.

The diagnosis of OLP is usually achieved by clinical and histological examination. The clinical appearance of the lesions is the first diagnosis of OLP. Then, it is subsequently confirmed by a biopsy and a histopathological study. Most of authors believed that a biopsy is necessary, given that it lets us to check the clinical diagnosis and mark the differential diagnosis with other lesions.^[11]

Based on clinical and histological standpoint, oral lichenoid reactions (OLR) are similar to oral lichen planus,^[12] while the etiology of OLRs is related to the contact with specific agents, such as dental materials^[13-16] drugs^[17,18] and flavoring agents.^[19,20] Whereas restorative dental materials play an important role in the appearance of OLR,^[21] and many studies have documented contact hypersensitivity to dental materials such as amalgam,^[22] composite^[23] and dental acrylics.^[24] Additionally, other conditions such as lupus erythematosus, erythroleukoplakia, leukoplakia, and proliferative verrucous leukoplakia may present clinical and histopathology characteristics similar to oral lichen planus.^[25]

The differential diagnosis between a lichen planus and a lichenoid reaction will be determined by a combination of clinical and histological criteria of the lichen planus itself. Cases of lichen planus must have had all of the clinical and histological criteria. On the other hand, lichenoid reaction includes: 1- patients with typical lichen planus clinically but not histologically, 2- patients with typical lichen planus histologically but not clinically, 3- patients who are both clinically and histologically only compatible with lichen planus.^[26]

During recent years, it has become more evident that the immune system has a primary role in the development of the oral lichen planus. It was theorized that serum level of immunoglobulin may play a role in the pathogenesis of oral mucosal diseases, or reflect clinical changes in these conditions.^[27] Increased levels of serum IgA and IgG in patients with OLP were reported previously.^[28,29] Ghaliani *et al.*^[30] showed significant differences in distribution of IgG+ cells among different locations in oral lichen planus and oral lichenoid lesions separately; but the differences between distribution of IgG+ cells between the two groups of oral lichen planus and oral lichenoid lesions were not significant. Sisti *et al.*^[27] showed increasing levels of salivary IgA and IgG in these patients. Since the role of immunofluorescence and immunohistochemical stains in the establishment of a diagnosis of OLP is limited^[31] and also little is known about the levels of salivary IgA and IgG in OLP and OLR patients, salivary IgA and IgG levels have not

yet been comprehensively studied among OLP and OLR patients. Treatments for both conditions, on the other hand, are different and because of the possibility of malignant transformation, one of them should be carefully followed. Therefore, present study was designed to assess the level of salivary IgA and IgG in OLP and OLR patients and also in healthy controls as diagnostic factors for the differential diagnosis of OLP and OLR diseases.

MATERIALS AND METHODS

The study population consisted of 100 patients (50 OLP patients and 50 OLR patients) who referred to Dental Clinic of the University of Isfahan, Iran between April 2010 and October 2011. Also, 50 healthy subjects without any oral and systemic disease were recruited as control group. Patients of any age and gender with clinically- and histopathologically-confirmed diagnosis of OLP and OLR were eligible if they had no history of smoking, diabetes, hepatitis, and any systemic or infection diseases. The definitive clinical and histopathological criteria used to distinguish and categorize the lesions were based on the WHO criteria.^[12] OLP patients with history of any systemic or topical medication for their oral disease 2 months prior to study were not eligible for the trial. This study was approved by the Ethics Committee of the Isfahan University School of Dental Medicine, and written informed consent was obtained from the participants in this study.

The clinical relevant data taken into account were: Demographical data, previous medication, and level of salivary IgA and IgG. ELISA test was used to determine salivary IgA (Human IgA Saliva Diametra kit, the binding Site, Italy), and salivary IgG was determined by radial immuno-diffusion (Human IgG kit, binding site group ltd., Birmingham, UK).

Saliva samples were obtained from all patients and healthy controls. Saliva collection was performed as described previously by Wu-Wang *et al.*^[32]. To avoid circadian variations, the saliva samples were collected between 10 a.m. and 1 p.m. Participants were instructed to collect saliva in their mouth for 5 min without swallowing and to spit into a clean glass tube. Then, pooled samples were immediately placed in a -20°C freezer until required.

Statistical analyzes were done using SPSS-18. Data are presented as means \pm 1SD, number (%) or median [IQR] as appropriate. Statistical analysis diagnostic parameters of IgA and IgG were optimized by using the ROC analysis. Receiver-operating-characteristic (ROC) analysis was performed by plotting on the X-axis

the 1-specificity and on the Y-axis the sensitivity. The diagnostic sensitivity and specificity are a function of the selected cut-off value. The area under the curves (AUC) was calculated for IgA and IgG for both OLP and OLR patients in comparison with healthy controls, and were compared using the method of Hanley and McNeil.^[33] Results were regarded as significant at or below the 5% probability level.

RESULTS

Of 150 subjects enrolled in this study, 14 subjects (OLP group, 6; OLR group, 2 and control group 6 subjects) refused informed consent and were excluded. Finally, 136 subjects were included in the analysis. The mean age of the subjects was 44.13 ± 9.79 years, 50 subjects (36.8 %) were male, and 86 subjects (63.2 %) were female. The mean of IgA and IgG in patients were 119.01 ± 114.18 and 3.25 ± 1.81 , respectively. Table 1 showed characteristics and clinical findings in studied groups. Age and sex were not statistically significant among groups (P -value > 0.05), but the mean of IgA and IgG in OLP and OLR groups were significantly more than in normal group (P -value < 0.05). Bonferroni test showed that differences in mean of IgA between OLP group with normal group (P -value = 0.004) and OLR group with normal group (P -value = 0.014) were statistically significant. Also, mean of IgG in OLP group was higher in compared with normal group (P -value = 0.014).

To determine the cut-off value, we performed a ROC analysis of the IgA and IgG from 44 OLP patients, 48 OLR patients, and 44 normal saliva cases as controls.

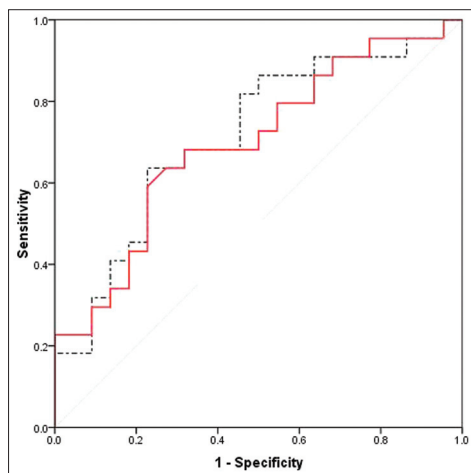


Figure 1: Receiver-operating-characteristic curve. Test performed for IgA with saliva sample from lichen planus patients (-----) ($n = 44$, $AUC=0.715$, P -value=0.0001) and lichenoid reaction patients; ($n = 48$, $AUC=0.69$, P -value=0.0005) and controls ($n = 44$). Based on the method of Hanley and McNeil,^[33] there was no significant difference between AUCs for IgA (0.715 ± 0.05 vs. 0.69 ± 0.5 , for lichen planus and lichenoid reaction patients, respectively, P -value=0.7). AUC = Area under the curve

AUC for IgA was 0.715 and 0.69 for OLP and OLR patients respectively, and the cut-off was set at >72 for both groups [Figure 1]. Also, AUC for IgG was 0.681 and 0.548 for both groups respectively, and the cut-off was set at >3.7 for both groups [Figure 2].

Cut-off value, AUC, sensitivity, and specificity of the IgA and IgG were shown in Table 2. Applying the cut-off value of >72 defined by ROC analysis for IgA showed that 28 of 44 OLP patients and 28 of 48 OLR patients were positive; also, based on the cut-off value of >3.7 for IgG, 28 of 44 OLP patients and 16 of 48 OLR patients were positive. On comparing the AUCs using the method of Hanley and McNeil,^[33] there was no significant difference between AUCs for IgA (0.715 ± 0.05 vs. 0.69 ± 0.5 , for OLP and OLR patients, respectively, P -value = 0.7) and AUCs for IgG (0.681 ± 0.05 vs. 0.548 ± 0.06 , for OLP and OLR patients, respectively, P -value = 0.1).

DISCUSSION

Attention should be given to the difficulty in founding the differential diagnosis by clinicians unaware of the two OLP and OLR diseases. Whereas, the high rate of microscopic finding of OLP compared with the low frequency of microscopic finding of OLR highlights this concern. Since that OLP should be more carefully followed because of the possibility of malignant transformation, the definitive diagnosis should be recognized as early as possible. Direct immunofluorescence detects immunoglobulins and complement components within biopsy specimens of

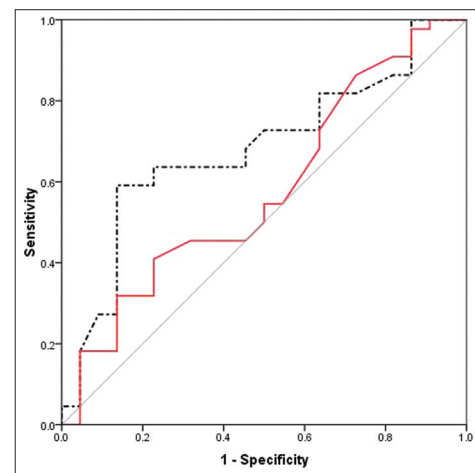


Figure 2: Receiver-operating-characteristic curve. Test performed for IgG with saliva sample from lichen planus patients (-----) ($n = 44$, $AUC=0.681$, P -value=0.0015) and lichenoid reaction patients; ($n = 48$, $AUC=0.548$, P -value=0.42) and controls ($n = 44$). Based on the method of Hanley and McNeil,^[33] there was no significant difference between AUCs for IgG (0.681 ± 0.05 vs. 0.548 ± 0.06 , for lichen planus and lichenoid reaction patients, respectively, P -value=0.1). AUC = Area under the curve

Table 1: Characteristics, salivary IgA and IgG in study population

| | Lichen planus group (n = 44) | Lichenoid reaction group (n = 48) | Normal group (n = 44) | P-value |
|--------------|------------------------------|-----------------------------------|-----------------------|-------------------|
| Age (year) | 45.62 ± 9.45 | 43.9 ± 9.02 | 44.78 ± 10.9 | 0.37 |
| Sex | | | | |
| Male | 15 (34.1) | 18 (37.5) | 17 (38.6) | 0.57 [†] |
| Female | 29 (65.9) | 30 (62.5) | 27 (61.4) | |
| IgA (mic/ml) | 147.12 ± 137.24 | 137.24 ± 128.92 | 71.07 ± 59.86 | 0.002* |
| IgG (mic/ml) | 3.9 ± 1.92 | 3.05 ± 1.58 | 2.81 ± 1.78 | 0.01* |

Data presented as mean ± 1SD and number (Percent) P-values calculated with * One way ANOVA and [†] Chi-Square test. Post hoc test (Bonferroni) showed statistical significant differences between normal group with lichen planus group (P-value = 0.004) and normal group with lichenoid reaction group (P-value = 0.014) for IgA also, between normal group with lichen planus group (P-value = 0.014) for IgG

Table 2: Cut of value, AUC, Sensitivity and specificity of the IgA and IgG in patients with lichen planus and lichenoid reaction compared with normal saliva patients

| | AUC [95% CI] | Cut-off value | Positive (%) | Sensitivity [95% CI] | Specificity [95% CI] |
|-----------------------------------|----------------------|---------------|--------------|----------------------|----------------------|
| lichen planus group (n = 44) | | | | | |
| IgA (mic/ml) | 0.715 [0.61 to 0.81] | > 72 | 28 (63.6) | 63.64 [47.8 to 77.6] | 77.27 [62.2 to 88.5] |
| IgG (mic/ml) | 0.681 [0.57 to 0.77] | > 3.7 | 28 (63.6) | 59.09 [43.3 to 73.7] | 86.36 [72.6 to 94.8] |
| lichenoid reaction group (n = 48) | | | | | |
| IgA (mic/ml) | 0.690 [0.58 to 0.78] | > 72 | 28 (58.3) | 58.33 [43.2 to 72.4] | 77.27 [62.2 to 88.5] |
| IgG (mic/ml) | 0.548 [0.44 to 0.65] | > 3.7 | 16 (37.5) | 29.17 [17 to 44.1] | 86.36 [72.6 to 94.8] |

AUC = Area Under Curve Based on the method of Hanley and McNeil,^[33] there were no significant difference between AUCs for IgA (0.719 vs. 0.69, P-value = 0.7) and AUCs for IgG (0.681 vs. 0.548, P-value = 0.1)

patient's tissue and use in diagnosis of bullous diseases and other immune diseases, such as oral lichen planus, especially those in subepidermal bullous diseases that often have overlap in clinical and histological findings. Its use has assisted the understanding of the physiopathology of some bullous diseases, making possible new classifications and nosologic replacements.^[34] In present study, salivary IgA and IgG in OLP and OLR patients were compared with healthy controls and also compared between OLP and OLR patients as diagnostic factors to the differential diagnosis of diseases. Increased concentrations of both IgA and IgG, which were detected in the saliva of patients with OLP, compared with healthy controls. This is similar to the results obtained in previous studies, which reported increasing the level of serum IgA and IgG^[35-37] in OLP patients. Also, Sistiget *al.*^[27] found that in patients with OLP, all IgG and IgA subclasses were increased when compared with the healthy controls and concluded that this could implicate an important role of salivary immunoglobulin in pathogenesis of OLP.

CONCLUSION

Our results showed differences in the level of salivary IgA and IgG in OLR patients when compared with healthy controls. These results are difficult to compare because there are no data on salivary IgA and IgG in OLP patients.

To the best of our knowledge, this is the first report on comparing salivary IgA and IgG levels in patients with

OLP and OLR. The results of this study showed that no significant differences in the salivary IgA and IgG were found between OLP and OLR patients, whereas, the cut-off value for IgA was set at >72 and the cut-off value for IgG was set at >3.7 for both OLP and OLR patients. Therefore, these results suggest that the salivary IgA and IgG have low diagnostic value and do not play an important role in the differential diagnosis between a lichen planus and a lichenoid reaction; however, this should be confirmed by further studies.

In conclusion, our results showed that the level of salivary IgA and IgG in OLP and OLR patients is higher than healthy controls, but they cannot be used as diagnostic factors to the differential diagnosis of OLP and OLR. Though, both OLP and OLR diseases sound to be the same.

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