



ORIGINAL RESEARCH



Evaluation of Factors Associated with the Onset or Aggravation of Oral Lichenoid Reactions in Isfahan City of Iran

Zahra Faraji¹, Amir Mansour Shirani^{2*}, Nazanin Rezaei Mirghayed³

Received: 2024-05-12/ Accepted: 2025-01-02 / First publication date: 2025-05-20

© The Author(s) 2025

Abstract

Background: Lichenoid reactions include a group of lesions with different etiology but with common clinical and histological appearance. This study aimed to determine the prevalence of factors associated with oral lichenoid reactions, including dietary influences. This is the first study to evaluate these factors collectively.

Materials and methods: In this descriptive-analytic study, 73 oral lichenoid reaction patients' files that were confirmed by biopsy and had complete recorded data in patients referred to IAU University and some oral medicine offices in Isfahan city were assessed for predisposing or aggravating factors. The data were analyzed by Chi-squared test and analysis of variance by SPSS 20 ($\alpha=0.05$)

Results: There were significant relationships between stress ($p=0.01$), some kinds of toothpaste (Pooneh, Sensodyne) ($p=0.04$), metal (amalgam filling, PFM crowns and bridge, chrome cobalt dentures) ($p<0.001$), some drugs (for hypertension, diabetes, hypothyroidism) ($p<0.001$), some foods (date and spices) ($p=0.04$) with oral lichenoid reactions.

Conclusion: Amalgam filling, PFM crown and bridge, chrome cobalt dentures and 3 groups of drugs were most related factors to oral lichenoid reactions but stress, some toothpastes and foods were also related.

Key words: Lichenoid eruptions, mouth, etiology, risk factors

Introduction

Lichenoid reactions encompass a group of lesions with different etiologies but with common clinical and histological features. Histopathological tests are unable to distinguish between different types of lichenoid reactions. Oral lichenoid reactions include lichen planus, contact lichenoid reactions, lichenoid drug eruptions, and graft-versus-host disease (GVHD) (1). Lichen planus is one of the most common chronic inflammatory skin diseases involving the oral cavity and can affect the skin, oral mucosa, genital mucosa, scalp, and nails. (2,3). Oral

lichen planus occurs in 2.2-5% of the population, with the highest prevalence occurring between the ages of 30 and 60, affecting women twice as much as men. Six clinical forms of oral lichenoid reactions have been reported, including reticular, papular, plaque-like, erythematous, erosive (ulcerative), and bullous (1).

The etiology of oral lichen planus is not well understood (4). In recent years, more evidence has emerged regarding the primary role of the immune system in causing this disease. This theory is supported by the histopathological characteristics of a band-like infiltration beneath the epithelium, consisting mainly of T lymphocytes and macrophages, as well as basal cell degeneration known as liquefaction degeneration (1). Factors related to the etiology of oral lichenoid reactions include genetic predisposition, dental restorative materials, drugs, contact allergies, food allergies,

Corresponding author: Dr. Amir Mansour Shirani

Department of Oral Medicine, Faculty of Dentistry, Isf.C, Islamic Azad University, Isfahan, Iran
Email: am.shirani@iau.ac.ir

1. Faculty of Dentistry, Isf.C, Islamic Azad University, Isfahan, Iran

2. Department of Oral Medicine, Faculty of Dentistry, Isf.C, Islamic Azad University, Isfahan, Iran

3. Department of Oral Medicine, Faculty of Dentistry, Isf.C, Islamic Azad University, Isfahan, Iran

stress, lifestyle, diabetes, hypertension trauma, and infectious agents (5,6).

Despite the importance of these factors, no study has been found in Iran that addresses all of these conditions. Iranian patients are using different foods as other counties thus this study was necessary to be done for better treatment of lichenoid patients.

Materials & Methods

The present study was a retrospective study. The study population consisted of patients with lichenoid reactions who had been referred to the Oral Medicine Department, Dental School of Isfahan (Khorasgan) branch of Islamic Azad University, and some Oral Medicine offices in Isfahan city for a period of 5 years (between 2010-2015).

The inclusion criteria were patients with clinical features of oral lichenoid reaction, biopsied and confirmed by pathologist. Etiologic factors for each patient were recorded. The exclusion criteria were files with missing data about age, gender duration of involvement, clinical oral forms (reticular, papular, plaque-like, erythematous. As, erosive (ulcerative), and bullous), location, skin or genital involvement, proximity of lesions to amalgam filling or PFM crown or bridge or chrome cobalt partial denture (contact lichenoid reaction), medicines (for lichenoid drug eruption), history of bone marrow transplantation (for GVHD), family history (other persons in near relative had similar lichenoid reaction), foods that were related to burning sensation or aggravation of the oral lesion (to prepare a list of causative Iranian foods), sign of mouth breathing and xerostomia in clinical evaluation, history of virus hepatitis B and C. The study was approved by the University (23810201931006) and the Ethic Committee of the University (1402-04-14-21731).

The data were analyzed by Chi-squared test and analysis of variance with the SPSS 20.0 software and the statistical significance p value was considered as 0.05.

Results

In this study, data of 73 patients with lichenoid reaction according to inclusion and exclusion criteria were considered. Of whom 44 patients (60.3%) were female and 29 (39.7%) were male. The age of the patients ranged from 20 to 76 years, with a mean age of 45.6 years. The duration of involvement ranged from 1 month to 17 years, with a mean of 3.8 years. The highest percentage of lichenoid reactions was

lichen planus (34 patients), followed by drug-induced lichenoid reaction (24 patients) and contact lichenoid reaction (15 patients) lichenoid reactions. Graft-versus-host disease (GVHD) was not seen among the patients in this study. The highest age prevalence of lichenoid reaction was observed among individuals aged 41-50 years.

The most affected area in mouth was the buccal mucosa (90%), then gingiva, tongue, skin, palate and genital mucosa (Table 1). The most clinical form was reticular then erythematous (Table 2).

Table 1. Frequency of the involved area (some patients had different areas of involvement, and each area was considered separately).

Involved areas	Number	Percentage
Cheek	65	90
Gum	30	41
Tongue	24	32.8
Skin	12	16.4
Palate	4	5.4
Genital mucosa	1	1.36

Table 2. Frequency of clinical forms (some patients had different clinical forms, and each clinical form considered separately)

Clinical forms	Number	Percentage
papule	7	9.5
plaque	15	20.5
reticular	67	91.7
erythematous	54	73.9
Ulcerative (erosive)	31	42.4
vesicular	13	17.8
Post-inflammatory pigmentation	6	8.2

17 lichen planus patients (from 34 patients) ,4 lichenoid drug eruption patients (from 24 patients) and 1 contact lichenoid patients (from 15 patients) had history of stressful life situation before lesions appearance. There was a meaningful relation between stress and type of lichenoid reaction ($P=0.01$) by Chi-square test. Stress showed relation to incidence of lichen planus.

The most commonly used medicine among the patients was antihypertensive medication. By one-way ANOVA analysis, there was a significant difference between the number of patients in each lichenoid type that used drugs. It was significantly higher in the drug-induced lichenoid group than other

groups ($p < 0.001$). The chi-square test showed a significant relationship between this type of disease and hypertension, diabetes, and hypothyroidism ($p < 0.001$).

Some patients said foods such as melon, walnut, Khoresh Fesajjan, cola, Arden, Halva Ardeh, date, spices like pepper and cinnamon, grenadine, aubergine, jujube, and tomato paste were related to exacerbation or relapse of oral lichenoid reaction. Considering the chi-square test, there was a significant relationship between the type of lichenoid and the consumption of dates and spices ($p = 0.04$), and it was more common in lichen planus patients.

The chi-square test showed that there was a significant relationship between the type of lichenoid contact reactions and toothpaste usage (Pooneh and Sensodyne), ($p = 0.04$). No cases of mouthwash sensitivity were observed among the patients.

The chi-square test showed a significant association between the type of lichenoid (contact lichenoid reactions) and proximity to metal restoration and prosthesis ($p < 0.001$). The most observed lesions were adjacent to amalgam (80.76%), followed by Porcelain-fused-to-metal (PFM) crowns and bridges (11.53%), and finally, adjacent to chrome cobalt prostheses (7.69%).

The chi-square test showed a significant relationship between the type of disease and xerostomia ($p = 0.04$), with more dryness observed in drug-induced lichenoid reactions. It seemed related to drugs side effects. However, no significant relationship was found between the type of disease and mouth breathing ($p = 0.25$).

Among the patients under study, one case of hepatitis B, one case of dysplastic changes, and two cases of other near family involvement were observed.

Discussion

Studies from the past to the present have always sought to investigate the etiological factors of oral lichenoid reactions and lichen planus. Various factors such as stress, medications, genetic predisposition, infectious agents, dental materials, autoimmunity, food allergies, lifestyle, diabetes, and hepatitis have been proposed as etiological factors (5,7). However, the prevalence of each of these factors has received less attention. The aim of this study was to better understand the etiological factors of lichenoid reactions in Isfahan city of Iran, determine the prevalence of these factors, and establish their relationship. The most common age of involvement

in oral lichen planus is reported to be in middle age (55 years) and the fifth decade of life (8). In the present study, the highest prevalence of these lesions was also observed in the fourth decade, which is similar to the results obtained by Shirani et al. in Isfahan (9). Regarding the results of this study, the studies by Pakfetrat et al. (10), Esmaeili et al. (11), and Khalili et al. (12) have reported the highest prevalence in the fourth decade. In contrast to the results of this study, the study by Bokor-Bratić and Pícurić (8) reported the most common age of involvement to be in the fifth decade, and a study by Mathew et al. (13) reported it to be in the fourth and fifth decades.

The most common site of involvement in this study was the buccal mucosa, which is similar to other studies conducted inside and outside the Iran (6,8,10).

Sandhu et al. (14), Ivanovski et al. (15), and Ebrahimi et al. (16) have shown a relationship between lichen planus and stress, which is consistent with the present study, where a significant relationship between stress and lichen planus was found in the patients studied.

The study by Kaomongkolgit (17) demonstrated an association between antihypertensive and hypoglycemic drugs and oral lichenoid lesions, such that replacing the drug led to improvement in oral lesions in the patient. Also, Guijarro Guijarro and López Sánchez (18) showed a relationship between anticoagulant drugs and oral lichenoid lesions, and after replacing the drug, the lesions improved. In this study, a relationship between some drugs and lichenoid reaction was identified, and a significant relationship was found between antihypertensive drugs, diabetes drugs, and hypothyroidism drugs with lichenoid drug eruption. A significant relationship was found between xerostomia and lichenoid drug reactions. In this study, drug usage, especially antihypertensive drugs and diabetes drugs, may be the causative factor for xerostomia in studied individuals, and it is necessary to control the signs and symptoms of xerostomia for these patients (19).

In the studies by Mårell et al. (20), Montebugnoli et al. (21) and Grossman et al. (22), it was shown that after replacing amalgam restorations, adjacent lichenoid lesions showed considerable improvement. In this study, the highest percentage was related to contact lichenoid reaction adjacent to amalgam fillings. Improvement of lesions after replacing the

restoration was observed in most of them (about 70% of patients).

There was a significant relationship between some toothpaste usage and oral lichenoid reaction. It was similar to Serrano-Sánchez (23) et al. showed, a relationship between toothpaste flavorings and oral lichenoid lesions.

Various viral and microbial factors related to lichen planus have been mentioned in various studies (24, 25), but in the present study, no relationship between these infectious agents and lichen planus was observed. Only one case of hepatitis B was observed. In study of Michele et al. (26), the authors did not find a clear relationship between the hepatitis virus and lichen planus. Also, the results of Garg et al. (27) showed no relationship between hepatitis and this disease. But in some other studies, like Birkenfeld et al., this relation was seen (28). Perhaps if the sample size had been larger, the possibility of a relationship between the hepatitis virus and the type of disease could have been determined.

In this study, the effect of family history was seen in only two cases of patients. Adami et al. (29) showed that the upregulation of innate immune genes in patients' epithelium plays an important role in the stages of lichen planus.

In this study, according to patients, some foods like spices could exacerbate the oral lesions in these patients. A significant relationship was found between the consumption of two food substances, spices and dates, with lichenoid reactions, which is consistent with the results of Pakfetrat et al. (30), suggesting that the consumption of spices exacerbates the symptoms of lesions.

In a study performed in Kakoei et al (31) ,a city in Iran, dysplastic changes were observed in 6.2% of the patients. In more than half of the patients, dysplastic changes were present right from the start, and 2.20% of the patients experienced dysplastic changes on average within 2.05 years of the onset of lesions. Multiple logistic regression showed that the risk of dysplasia increases with aging, smoking, and thyroid disorders. In this study malignant transformation of lichenoid lesions was not evaluated. As the lichenoid reactions are premalignant lesions, the diagnosis and proper treatment of them are very important.

Triggers and exacerbating agents for OLP include psychological stress, medications, dental materials, EBV, VZV, HHV-6, HHV-7, HPV, hepatitis C, and liver dysfunction. OLP is also associated with systemic conditions of dyslipidemia, diabetes,

hypertension, and hypothyroidism (32). In this study, similar etiologic factors were found, but the effect of some viruses was not clear. Some kinds of foods and toothpaste were also related to lichenoid reactions

A small sample size was the limitation of this study because it was necessary to consider inclusion and exclusion criteria.

Conclusion

In conclusion, a significant relationship was found between stress and oral lichen planus disease in this study. Also, a significant relationship was found between contact lichenoid lesions and metal in dental filling and restoration. Some drugs were related to lichenoid drug eruption, like levothyroxine, which a lot of patients are using it in Iran. Other etiologic or exacerbating factors, like some Iranian food materials, seemed to be relevant to oral lichenoid reactions that had not been evaluated before in Iran. Some toothpaste, like Pooneh and Sensodyne, seems related to the exacerbation of lichenoid reactions that were not mentioned before in studies. It is necessary to control all related factors for the treatment of oral lichenoid reactions.

Conflict of Interests: The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial, or non-financial in this article

References

1. Glick M, Greenberg MS, Lockhart PB, Challacombe SJ. *Burket's Oral Medicine*. 13th ed. Hoboken: Wiley-Blackwell, 2021.p:85-138.
2. Agha-Hosseini F, Mirzaei-Dizgah I, Farmanbar N, Abdollahi M. Oxidative stress status and DNA damage in saliva of human subjects with oral lichen planus and oral squamous cell carcinoma. *J Oral Pathol Med*. 2012;41(10):736-740.
3. Sugerman PB, Savage NW, Walsh LJ, Zhao ZZ, Zhou XJ, Khan A, et al. The pathogenesis of oral lichen planus. *Crit Rev Oral Biol Med*. 2002;13(4):350-365.
4. van der Waal I. Oral lichen planus and oral lichenoid lesions; a critical appraisal with emphasis on the diagnostic aspects. *Med Oral Patol Oral Cir Bucal*. 2009;14(7):E310-E314.
5. Gupta S, Jawanda MK. Oral lichen planus: An update on etiology, pathogenesis, clinical presentation, diagnosis and management. *Indian J Dermatol*. 2015;60(3):222-229.
6. Scully C, Carrozzo M. Oral mucosal disease: Lichen planus. *Br J Oral Maxillofac Surg*. 2008;46(1):15-21
7. Ismail SB, Kumar SK, Zain RB. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis,

- management and malignant transformation. *J Oral Sci.* 2007;49(2):89-106.
8. Bokor-Bratić M, Pićurić I. The prevalence of precancerous oral lesions: Oral lichen planus. *Archive of Oncology.* 2001;9(2):107-9.
 9. Shirani AM, Razavi SM, Khazaei S, Khaleghi MA, Haerian A. Evaluation of oral lichen planus frequency in patients referred to the Oral Pathology Department of Isfahan School of Dentistry during the last two decades. *Journal of Isfahan Dental School* 2010; 6(4): 272-277
 10. Pakfetrat A, Basir Shabestari S, Falaki F. Five year clinical and epidemiologic findings of oral lichen planus patients referred to oral medicine department of Mashhad dental school-Iran. *Journal of mashhad dental school.* 2008;32(3):195-8.
 11. Esmaeili N, Barzegari M, Rezaei M. Clinical manifestations of Lichen Planus: A report of 120 cases. *Iranian Journal of Dermatology,* 2005; 8(2): 110-114.
 12. Khalili M, Shojaei M. A retrospective study of oral lichen planus in oral pathology department, Tehran University of Medical Sciences (1968-2002). *J Dent Med-tums* 2006; 19 (3) :45-52
 13. Mathew AL, Pai KM, Sholapurkar AA, Vengal M. The prevalence of oral mucosal lesions in patients visiting a dental school in Southern India. *Indian J Dent Res.* 2008;19(2):99-103
 14. Sandhu SV, Sandhu JS, Bansal H, Dua V. Oral lichen planus and stress: An appraisal. *Contemp Clin Dent.* 2014;5(3):352-356.
 15. Ivanovski K, Nakova M, Warburton G, Pesevska S, Filipovska A, Nares S, et al. Psychological profile in oral lichen planus. *J Clin Periodontol.* 2005; 32(10): 1034-1040
 16. Ebrahimi H, Pourshahidi S, Andisheh Tadbir A. Evaluation of the relationship between oral lichen planus and stress. *Journal of Dentistry.* 2011;12(1):43-7.
 17. Kaomongkolgit R. Oral lichenoid drug reaction associated with antihypertensive and hypoglycemic drugs. *J Drugs Dermatol.* 2010;9(1):73-75.
 18. Guijarro Guijarro B, López Sánchez AF. Lichenoid reaction caused by Clopidogrel, a new anti-platelet drug. *Med Oral.* 2003;8(1):33-37.
 19. Scully C. Oral and maxillofacial medicine: the basis of diagnosis and treatment. 4th ed. Elsevier Health Sciences; 2023,94-102
 20. Mårell L, Tillberg A, Widman L, Bergdahl J, Berglund A. Regression of oral lichenoid lesions after replacement of dental restorations. *J Oral Rehabil.* 2014;41(5):381-391
 21. Montebugnoli L, Venturi M, Gissi DB, Cervellati F. Clinical and histologic healing of lichenoid oral lesions following amalgam removal: a prospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2012;113(6):766-772.
 22. Grossman S, Garcia BG, Soares I, Monteiro L, Mesquita R. Amalgam-associated oral lichenoid reaction: case report and management. *Gen Dent.* 2008;56(2):e9-e11
 23. Serrano-Sánchez P, Bagán JV, Jiménez-Soriano, Sarrión G. Drug-induced oral lichenoid reactions: a literature review. *J Clin Exp Dent.* 2010;2(2):e71-5
 24. Scully C, Beyli M, Ferreiro MC, Ficarra G, Gill Y, Griffiths M, et al. Update on oral lichen planus: etiopathogenesis and management. *Critical Reviews in Oral Biology & Medicine.* 1998;9(1):86-122.
 25. Yildirim B, Sengüven B, Demir C. Prevalence of herpes simplex, Epstein Barr and human papilloma viruses in oral lichen planus. *Med Oral Patol Oral Cir Bucal.* 2011;16(2):e170-4
 26. Michele G, Carlo L, Mario MC, Giovanni L, Pasquale M, Alessandra M. Hepatitis C virus chronic infection and oral lichen planus: an Italian case-control study. *European journal of gastroenterology & hepatology.* 2007;19(8):647-52.
 27. Garg VK, Karki B, Agrawal S, Agarwalla A, Gupta R. A study from Nepal showing no correlation between lichen planus and hepatitis B and C viruses . *The Journal of Dermatology.* 2002;29(7):411-3.
 28. Birkenfeld S, Dreier J, Weitzman D, Cohen AD. A study on the association with hepatitis B and hepatitis C in 1557 patients with lichen planus *J Eur Acad Dermatol Venerol.* 2011;25(4):436-40.
 29. Adami GA, C F Yeung A, Stucki G, Kolokythas A, Sroussi HY, Cabay RJ, Kuzin I, Schwartz J. Gene expression based evidence of innate immune response activation in the epithelium with oral lichen planus. *Arch Oral Biol* 2014 ;59(3):354-61
 30. Pakfetrat A, Javadzadeh-Bolouri A, Basir-Shabestari S, Falaki F. Oral Lichen Planus: a retrospective study of 420 Iranian patients. *Med Oral Patol Oral Cir Bucal.* 2009;14(7):E315-E318.
 31. Kakoei S, Torabi M, Rad M, Karbasi N, Mafi S. Retrospective Study of Oral Lichen Planus and Oral Lichenoid Lesions: Clinical Profile and Malignant Transformation. *J Dent (Shiraz).* 2022;23(4):452-458
 32. Elenbaas A, Enciso R, Al-Eryani K. Oral lichen planus: a review of clinical features, etiologies, and treatment. *Dentistry Review.* 2022, 2(1),10000