

Association of helicobacter pylori and oral lichen planus: A systematic review and meta-analysis

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Review Article

Abstract

BACKGROUND AND AIM: Oral lichen planus (OLP) has been known as an inflammatory disease and might have an association with helicobacter pylori (*H. pylori*) infection. The main purpose of this study is to evaluate the role of *H. pylori* in patients with OLP.

METHODS: In this review study, all articles with English abstracts were searched in the Google Scholar, PubMed, Web of Science, Cochrane Library, and Scopus databases up to May 2020. The searches were performed using the Medical Subject Headings (MeSH) terms and keywords of "oral lichen planus" or "oral lichenoid reaction" or "OLP" and "Helicobacter pylori" or "H. pylori". The heterogeneity percentage obtained during different studies was evaluated by the Cochrane (Q) test and I² statistic. The analyses were performed by the Comprehensive Meta-Analysis (CMA) software version 2.0.

RESULTS: Amongst the 16 articles obtained after the abstract review, 7 proper articles fitted to our study were included in this meta-analysis. The meta-analysis results showed that the incidence of *H. pylori* in patients with OLP was 2.9 times greater than that in the control group ($P < 0.05$).

CONCLUSION: Based on the results of previous studies, *H. pylori* increases the risk of OLP lesions. Therefore, testing for *H. pylori* infection in these patients before starting routine treatment is recommended.

KEYWORDS: Lichen Planus; Oral; Helicobacter Pylori; Meta-Analysis

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Oral lichenoid reactions characterize a family of lesions with different causes and similar clinical and histologic forms, which include the following disorders: Oral lichen planus (OLP), lichenoid drug reaction, lichenoid amalgam reactions, and lichenoid graft versus host disease.¹ OLP is a chronic inflammatory disease, which is commonly seen as bilateral lesions in different areas of the oral cavity and affect most middle-aged women.²⁻⁴ An important issue in OLP is the possibility of malignant changes, which has

been debated for years. Although extensive research has been carried out in this area, it is still doubtful whether the lesion is benign or prone to malignancy. OLP has a variety of clinical symptoms seen in the mouth, can be distressing by burning and pain, and have periods of recovery and recurrence.¹⁻⁵ It should be noted that the main effective factors of the disease are not yet well recognized. Similar lesions could be created when different systemic conditions and autoimmune diseases are considered, but the exact relationship between all these

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factors and the cause of the lesion has not yet been determined.⁶

In recent decades, the role of bacteria and viruses associated with OLP has been studied. Among the bacterial infections that may initiate OLP, the helicobacter pylori (*H. pylori*) infection is illustrated to be a main factor.⁷ *H. pylori* is a gram-negative bacterium with a spiral shape that is the most prevalent and well-known bacteria with high impact on the human stomach and causes chronic gastritis and gastrointestinal ulcers, and has recently been known as a risk factor for gastric adenocarcinoma.⁸⁻¹⁰

While *H. pylori* bacteria colonize the stomach and upper duodenum, their natural reservoir has not been confirmed. Oral cavity is one of the possible options. In addition, histological similarities among gastric and oral ulcers may suggest a probable role of *H. pylori* in the development of oral lesions.¹¹

Numerous studies have been performed on the role of *H. pylori* infection in pathogenesis of OLP. In some of these studies, the rate of this bacterium was high in patients with OLP,¹²⁻¹⁴ and in others there was no significant difference with the healthy group.¹⁵⁻¹⁸ Given the differences, the aim of the current study is to systematically review and analyze the relationship between OLP and *H. pylori* infection. A similar study was conducted and published in China in 2017,¹⁹ however in that study, only the association of oral *H. pylori* with OLP was assessed and the search resources were limited and mostly related to Chinese databases. Therefore, we decided to conduct a study with a search in international databases and newer and high-quality articles in English.

Methods

This systematic review study was approved by the ethics committee of Tabriz University of Medical Sciences, Tabriz, Iran (ethical code: IR.TBZMED.VCR.REC.1398.389) and was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for

reporting systematic reviews.²⁰ A focused question was produced according to the patient, intervention, comparison, outcome (PICO) principles.²¹ The main question for this study was "Is the incidence of *H. pylori* different in patients with OLP and healthy individuals"?

In this review study, all published articles with English abstracts were searched from Google Scholar, PubMed, Web of Science, Cochrane Library, and Scopus databases until May 2020. Additionally, the related sources in the selected studies were searched manually. The search was limited to human studies. The free and Medical Subject Headings (MeSH) terms were used in various combinations to obtain data. The search keywords included: 'lichen planus' OR 'erosive lichen planus' OR 'lichen planus, erosive' OR 'lichen planus, oral' OR 'lichen rubber planus' OR 'oral lichenoid reaction' OR 'OLP' OR 'oral lichen planus' AND 'helicobacter pylori' OR 'campylobacter pylori' OR 'campylobacter pyloris' OR *H. pylori* OR 'gram negative bacterium' OR 'gram negative bacillus' OR 'gram negative microbium' OR 'gram negative microorganism' OR 'gram negative organism' OR 'gram negative rod' OR 'gram-negative bacteria'.

After extracting the articles from the databases, they were screened by the subject expert in 3 steps. In the initial phase, the titles and abstracts of the articles were studied by two independent individuals based on the inclusion and exclusion criteria and the disagreements were resolved after consultation with the third author. Next, the full text of the selected articles was reviewed. The quality of the studies was assessed by the Newcastle-Ottawa Scale (NOS) method.²² Microsoft Excel (version 2010) was used to extract the characteristics of the studies. This form includes the author's name, year of publication, sample size, method of *H. pylori* detection, and the results of the studies.

The inclusion criteria were all the case-control studies that evaluated the

association of H. pylori infection with OLP. The reviews, case reports, letter to the editor, conference articles, non-English articles, and studies that investigated the relationship of H. pylori infection with cutaneous lichen planus were excluded from the review.

The heterogeneity percentage between the studies was evaluated by the Cochrane (Q) test and I² statistic; if I² > 50%, there was a heterogeneity. The analyses were performed by the Comprehensive Meta-Analysis (CMA) software version 2.0. Regarding the heterogeneity of studies, the random effects model was used. P < 0.05 was considered statistically significant. The publication bias was assessed through funnel plot analysis with the Egger's tests.

Results

Initial searches led to the extraction of 213 articles. Amongst the 16 article abstracts reviewed, 9 were included in this systematic review based on the inclusion and exclusion criteria, as presented in figure 1. The characteristics of these studies are shown in table 1.^{11-18,23}

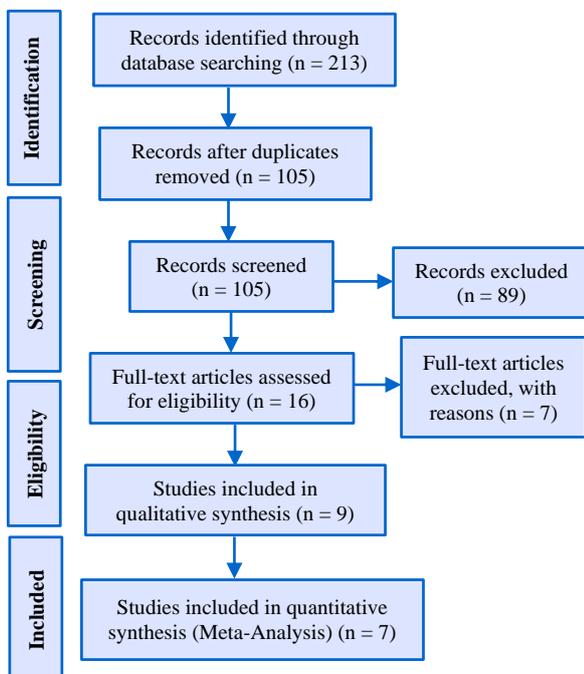


Figure 1. Flowchart of searching strategy based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

In two studies,^{11,17} the positive cases of H. pylori infection both in the case and the control groups were zero. For this reason, these two studies were excluded from the meta-analysis and finally, seven studies remained in the meta-analysis.

Figure 2 shows the forest diagrams of the meta-analysis. Seven studies were included in the meta-analysis. In the OLP and control groups, 292 and 311 patients were studied, respectively. 160 patients from the OLP group and 130 controls were positive for H. pylori infection. Heterogeneity amongst the studies was significant [Q-value = 26.08, degree of freedom (df) = 6, I² = 77.002, P < 0.001].

The random-effects model was used to combine the results. The results of the meta-analysis illustrated that the H. pylori infection chance in the control group was 0.34 times that of the patients with OLP [odds ratio (OR) = 0.34, 95% confidence interval (CI) = 0.13-0.89, P = 0.290].

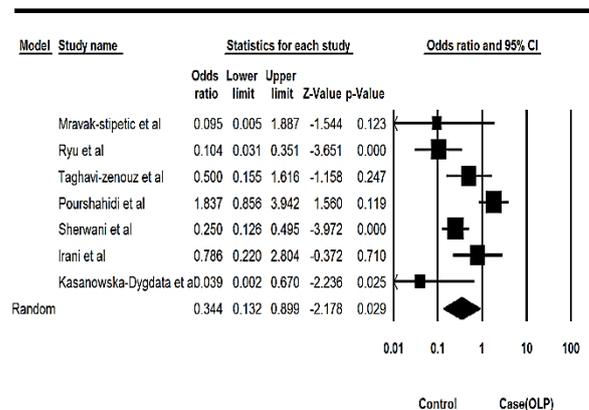


Figure 2. Forest diagrams from the meta-analysis

Egger's regression results showed that the publication bias was not significant among the studies (t-value = 0.98, df = 5, P = 0.370). Figure 3 shows a funnel diagram to verify the publication bias.

Discussion

In this meta-analysis, the results presented that the incidence of H. pylori in patients with OLP was 2.9 times higher than that of the control group, indicating that OLP might be associated with H. pylori infection.

Table 1. Summary of the data extracted from the studies included in this review

Authors	Country	Control group	Case group (OLP)	HP+ in control group	HP+ in OLP group	Sample	Method of H. pylori detection	Results (Significant relationship between OLP and H. pylori)
Mravak-Stipetic et al. ¹⁸	Croatia	20	21	0	4	Oral mucosa	PCR	No
Riggio et al. ¹¹	United Kingdom	13	20	0	0	Oral mucosa	PCR	No
Ryu et al. ¹²	Korea	44	21	11	16	Saliva	PCR	Yes
Taghavi et al. ¹⁶	Iran	30	30	20	24	Exhaled breath	Urea breath test	No
Pourshahidi et al. ²³	Iran	82	41	54	21	Serum	IgG ELISA test	No
Khan Sherwani et al. ¹³	Pakistan	80	80	37	62	Serum	IgG ELISA test	Yes
Hulimavu et al. ¹⁷	India	10	50	0	0	Oral mucosa	IHC	No
Irani et al. ¹⁵	Iran	15	27	8	16	Oral mucosa	IHC	No
Kazanowska-Dygdala et al. ¹⁴	Poland	40	72	0	17	Oral mucosa	PCR	Yes

OLP: Oral lichen planus; PCR: Polymerase Chain Reaction; IHC: Immunohistochemistry; IgG ELISA test: Immunoglobulin G enzyme-linked immunosorbent assay test

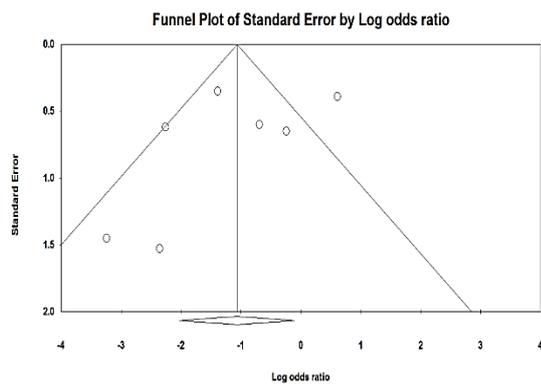


Figure 3. Funnel plot of random effect of studies of helicobacter pylori (H. pylori) infection in patients with Oral lichen planus (OLP) compared to healthy controls

In this meta-analysis, seven studies were reviewed. Although in four studies it was reported that there was no significant relationship between H. pylori infection and OLP,^{15,16,18,23} the results of the current meta-analysis indicated that the high incidence of H. pylori is positively correlated with high prevalence of OLP. All of the studies reviewed were case-controls in most of which, the cases and control groups were age and sex matched. As the most important limitation in the two studies,^{14,23} the diagnosis of OLP was only based on the clinical criteria

and not confirmed by histopathology, which may not indicate the true prevalence of H. pylori. The level of heterogeneity in this study was high ($I^2 = 77$) the most important source of which can be different methods of diagnosing H. pylori. In the present meta-analysis, Urea Breath Test (UBT), Polymerase Chain Reaction (PCR), immunohistochemistry, and Immunoglobulin G enzyme-linked immunosorbent assay test (IgG ELISA) were used to identify the H. pylori infection. Although UBT appears to be more specific, its specificity is questioned, given that other urease-producing bacteria can invade the gastric mucosa. It was shown that the histological method is very specific and sensitive, but accurate detection of H. pylori bacteria is difficult with a simple look at the morphology of the bacteria under a microscope. The IgG ELISA test does not show a current infection, and a negative antibody cannot rule out primary infection. The remaining option to diagnose H. pylori in different specimens is the PCR method, which has a high probability of false positive and negative, but with the design of very special primer, the PCR method can be

considered as the gold standard for diagnosis of *H. pylori*.^{24,25} Therefore, it is expected that uniform and accurate methods of diagnosing *H. pylori* will provide more evidence in the future.

Although bacterial pathogenesis or immune response against bacteria such as *H. pylori* can be considered as one of the causes of OLP, autoimmune mucosal damage due to the discharge of antigens from damaged cells following bacterial infection or antigenic similarity between *H. pylori* and antigens in the mucous membrane are another reasons that can be involved in the pathogenesis of this disease.²⁶ In such cases, it is not necessary to detect *H. pylori* in OLP lesions or gastric infection to prove the role of *pylori* in the development of OLP. As in many studies, no difference was found in the rate of *H. pylori* among healthy individuals and patients with OLP, which does not negate the probable role of *H. pylori* in the development of OLP lesions.

Studies have shown that local factors such as plaque and dental calculus can worsen gingival OLP, and plaque control can be effective in improving symptoms.^{27,28} These data could strengthen the role of microorganisms in the development of OLP. However, the results of some studies showed that there was no relationship between *H. pylori* infection and OLP. Another possible

reason for these results is that since most studies have been conducted in developing countries, more people in the control group have been infected with *H. pylori* infection.

The present study was along with some limitations: first, the sample size was limited for some groups. Second, the search was limited to articles in English, which might be considered a language bias. In the future, more studies with larger sample sizes and inclusion of non-English articles in meta-analysis are recommended.

Conclusion

According to the meta-analysis results, the chance of positive *H. pylori* infection in patients with OLP is higher than in healthy people. Therefore, testing for *H. pylori* infection in these patients before treatment is recommended that if the *H. pylori* infection is positive, antibiotic treatments along with routine OLP treatments may be a good option that in this regard, detailed clinical trial studies are needed in the future.

Conflict of Interests

Authors have no conflict of interest.

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