A meta-analysis of the association between the presence of *Helicobacter pylori* and periodontal diseases

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**Abstract**

**Background:** The objective of this meta-analysis is to evaluate the association between the presence of *Helicobacter pylori* (*H. pylori*) and periodontal disease (PD).

**Methods:** PubMed and EMBASE databases were searched to identify eligible articles published from inception up to April 2018. Further articles were retrieved through a manual search of recent reviews. Cross-sectional studies, case-control studies and cohort studies reporting the association between *H. pylori* and PD were included. The pooled odds ratio (OR) and their 95% confidence interval (CI) were calculated.

**Results:** Four case-control studies and nine cross-sectional studies were included. A total of 6800 patients were included in this review. The odds for oral *H. pylori* positivity was 2.31 times (95% CI: 1.99–2.68) greater than those without *H. pylori*. Subgroup analyses involving different study locations, designs, and types of study population showed the similar results. The pooled OR for the gastric disease patients was the largest (3.50, 95% CI: 2.22–5.53, five articles). Stomach *H. pylori* was also significantly associated with PD, with OR 2.90 (95% CI: 1.37–6.14, two articles).

**Conclusions:** This meta-analysis supports an association between *H. pylori* and PD. More well-designed studies, especially prospective cohort studies are necessary to confirm these results.

**Abbreviations:** CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, *H. pylori* = *Helicobacter pylori*, OR = odds ratio, PCR = polymerase chain reaction, PD = periodontal disease, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RUT = rapid urease test.

**Keywords:** *Helicobacter pylori*, meta-analysis, periodontal disease

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1. **Introduction**

Periodontal disease (PD) is a group of inflammatory pathologies involving tooth supporting tissues, the structures that make up the periodontium.[1–3] PD mainly includes gingivitis and periodontitis. PD is one of the most prevalent oral diseases worldwide.[2] *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans*, and *Bacteroides forsythus* have been reported as the major periodontal pathogens.[3,4]

*Helicobacter pylori* (*H. pylori*) has cohabited with humans for at least 100,000 years,[3] which is one of the most common bacterial infections in humans. *H. pylori* is a gram-negative bacteria which usually exists in the human stomach. *H. pylori* has been designated as a Group 1 Carcinogen by the International Agency for Research on Cancer of the World Health Organization.[5,6] It has been suggested that *H. pylori* may be transmitted orally and is detected in dental plaque and saliva.[6,7] There is a close relation between the infection of *H. pylori* in the oral cavity and stomach.[8–11] A number of articles reported that *H. pylori* was very common in oral cavity, including oral mucosa, and dental plaque.[8,9,12]

A number of studies focused on the association between the presence of oral or stomach *H. pylori* (positivity) and PD. Some researchers reported that there was a positive association between them,[9,13,14] while some did not show any association.[15–17] Thus, whether *H. pylori* is associated with PD remains controversial. No meta-analysis has yet been conducted to assess this association. Therefore, the aim of this study was examined the association...
between oral or stomach \textit{H. pylori} and PD by combining all the eligible articles. This meta-analysis was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.\textsuperscript{[18]} The PRISMA 2009 Checklist is reported in Appendix 1, http://links.lww.com/MD/D21.

2. Methods

2.1. Search strategies

The PubMed and EMBASE databases were searched to identify eligible articles published from inception up to April 2018. The search strategy was as follows: (periodontal disease OR periodontitis OR gingivitis) AND (Helicobacter pylori OR \textit{h. pylori}). The search strategies were shown in Appendix 2, http://links.lww.com/MD/D21. We restricted our searches to human studies published in English. In addition, further articles were retrieved through a manual search of recent reviews.

2.2. Inclusion criteria

Two authors independently read the titles and abstracts of the articles. When there was any inconsistency between the two authors, a third author was consulted to reach a consensus. The inclusion criteria were as follows:

1. subjects: there were two groups: oral or stomach \textit{H. pylori} positivity group, and oral or stomach \textit{H. pylori} negativity group.

Figure 1. Flow chart of the search strategy.
Rapid urease test (RUT), polymerase chain reaction (PCR), or enzyme-linked immunosorbent assay (ELISA) to confirm the presence of \textit{H pylori}.

2. outcomes: PD (including periodontitis and gingivitis). Each individual was tested whether to have PD. For the association of \textit{H pylori} and PD, articles eligible for inclusion should report odds ratio (OR) or relative risk (RR) and their 95% confidence interval (CI), or data to calculate them.

3. study design: cross-sectional studies, case-control studies and cohort studies. The article which did not report the data about association of \textit{H pylori} and PD was excluded.

2.3. Data extraction

The relevant data were independently extracted by two authors, and were further checked by a third author to reach a consensus when there was inconsistence. The following data were extracted: the first author, year of publication, country, research design, source of the patients, types of study population, \textit{H pylori} diagnostic method, sample size, the number of patient with \textit{H pylori}-positive and \textit{H pylori}-negative, age, sex, smoking habits, alcohol consumption, and the outcomes. The outcomes mainly included PD, periodontitis, and gingivitis. There were two types of study population: gastric disease, and general population. Some articles enrolled the patients who had dyspepsia or complaints regarding the upper digestive tract (gastric disease). Some articles enrolled the general population with or without PD (general population).

2.4. Statistical analysis

A $\chi^2$ test of homogeneity was conducted, and inconsistency index ($I^2$) statistics were calculated. If heterogeneity did not exist among articles, a fixed-effects model was performed. Otherwise, a random-effects model was performed. The association between oral \textit{H pylori} or stomach \textit{H pylori} and PD were analysed separately.

For pooled estimate of binary data, OR with its corresponding 95% CI were calculated. Subgroup analyses in terms of different study locations (developed countries and developing countries), designs (cross-sectional studies and case-control studies), and types of study population (gastric disease and general population)
were performed. A two-sided $P$ value $\leq .05$ was considered as statistical significance. Sensitivity analysis was performed using the leave-one-out approach. All analyses were performed using the STATA software (version 14.0).

3. Results

3.1. Characteristics of eligible studies

Figure 1 showed the article selection procedure. The search yielded 411 articles. After exclusion, a total of 13 eligible articles were included for analysis.[13–16,19–27]

Among these articles, three were conducted in developed countries (the USA,[13] the UK,[22] and Japan[26]), and others in developing countries. Four articles were case-control studies, and nine were cross-sectional studies. Eleven articles were performed in a hospital setting, while only two were performed in a community setting. The sample sizes of the selected studies ranged from 28 to 4474. A total of 6200 patients were included in this review. The proportion of the patients with *H pylori* positivity ranged from 5.0% to 70.0%, with a median of 28.6%. The characteristics of the selected studies were summarized in Table 1.

3.2. Meta-analysis of PD

There was no heterogeneity among the thirteen articles ($I^2 = 35.6\%, P = .098$), thus a fixed-effects model was performed. The combined OR was 2.31 (95% CI: 1.99–2.68; Table 2, Fig. 2), which indicated that the patients with *H pylori* positivity was positively associated with PD.

Subgroup analyses were performed to evaluate the association between oral *H pylori* and PD (Table 2). The pooled OR in developing countries was 2.47 (95% CI: 1.95–3.13), and that in developed countries was 2.20 (95% CI: 1.82–2.66). The summarized ORs for articles based on cross-sectional studies and case-control studies were 2.37 (95% CI: 2.02–2.77) and 2.01 (95% CI: 1.35–2.99), respectively. For the patients with gastric disease, the pooled OR was 3.50 (95% CI: 2.22–5.53). For general population, the pooled OR was 2.19 (95% CI: 1.99–2.68).

A sensitivity analysis was conducted to identify potential heterogeneity. Almost all pooled OR and 95% CI from the included articles were within the estimated ranges, expect the article conducted by Dye et al (Table 3).[13]

Two articles also reported the association between stomach *H pylori* and PD. The pooled OR was 2.90 (95% CI: 1.37–6.14; Fig. 3).

4. Discussion

*H pylori* is a gram-negative microaerophilic bacterium that colonizes gastrointestinal mucosa and is considered to be an influencing factor for many oral diseases. In this meta-analysis, risk of PD in the patients with *H pylori* positivity was 2.31 times higher than those with *H pylori* negativity. Although five eligible articles reported that there was no significant association between *H pylori* and PD,[15,16,21,22,26] the result indicated that high expression of *H pylori* positivity was associated with a higher prevalence of PD. The association between oral *H pylori* and PD may be related with the following mechanisms.

1. There is a close relation between *H pylori* positivity in the oral cavity and the stomach. Some researches indicated that *H
Pylori could transmit through oral-oral or fecal-oral routes.\textsuperscript{28–30} The oral cavity is the first extra-gastric reservoir of H pylori.\textsuperscript{9,11,31} The oral mucosa (especially the gingival sulcus) and dental plaque are places for bacterial colonization.\textsuperscript{12} Based on the result of a meta-analysis, the prevalence of co-infection of gastric and dental plaque H pylori was 49.7%.\textsuperscript{32} Some experiment demonstrated that H pylori existed in the gingiva plaque, and might played a role in the development of PD.\textsuperscript{27,33,34} As gram-negative and anaerobic bacteria in biofilms went up, the inflammation of periodontium deteriorated and cytokines secretion increased.\textsuperscript{33,34}

The pooled OR in the gastric disease patients was 3.50 (95\% CI: 2.22–5.53), which was higher than that in general population, according to the results of subgroup analyses. Two articles also reported the association between stomach H pylori and PD. The combined OR was 2.90, which was higher than that in oral H pylori positivity (OR=2.31). These results showed that gastric disease had a positive impact on PD. A meta-analysis reported that the prevalence of co-infection of gastric and dental plaque H pylori was 49.7%.\textsuperscript{32} Bouziane et al performed a meta-analysis of randomized controlled trials, and reported that the adjunction of periodontal treatment to eradication therapy appeared to reduce gastric H pylori recurrence compared with eradication therapy alone.\textsuperscript{33} This result provides some useful information for periodontists, that periodontists should ask the patients about history of gastric disease, and examine the oral and stomach H pylori. If the patient has symptoms of gastric disease, the periodontist should suggest relevant treatments to maintain the effect of periodontal therapy.

Some limitations should be addressed.

1. This meta-analysis only enrolled cross-sectional studies and case-control studies; therefore we could not confirm the association between H pylori and PD. Whether PD existed and then created an environment for H pylori or whether H pylori played a role in the onset and development of PD could not be differentiated. Therefore, prospective cohort studies should be performed to solve this question.

2. Lots of factors can have an effect on PD, such as age, sex, smoking, poorly controlled diabetes, possibly obesity, stress and osteopenia.\textsuperscript{3,12} In order to understand whether H pylori was an independent predictor for PD, the above factors should be controlled. This meta-analysis was based on the unadjusted data, which did not control those factors. Therefore, our results may be confounded by other factors.

3. This meta-analysis did not consider the effects of other bacteria to PD. Some studies demonstrated that P gingivalis, A actinomycetaceae, and B furosae were associated with PD.\textsuperscript{4,12,36}
5. Conclusions

In conclusion, this meta-analysis based on the eligible articles supports an association between *H* pylori positivity and PD. The pooled OR in the gastric disease patients was 3.50 (95% CI: 2.22–5.53), which was higher than that in general population. More well-designed studies, especially prospective cohort studies are necessary to confirm these results. The periodontists should ask the patients with PD about history of gastric disease, and examine the oral and stomach *H* pylori.

Author contributions

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References

[1] Botero JE, Rosing CK, Duque A, et al. Periodontal disease in children and adolescents of Latin America. Periodontol 2000 2015;67:34–57.

[2] Petersen PE, Ogawa H. The global burden of periodontal disease: towards integration with chronic disease prevention and control. Periodontol 2000 2012;60:15–39.

[3] Genco RJ, Borgnakke WS. Risk factors for periodontal disease. Periodontol 2000 2013;62:59–94.

[4] Ambili R, Preeja C, Archana V, et al. Viruses: are they really culprits for periodontal disease? A critical review. J Investig Clin Dent 2014;5:179–87.

[5] Moodley Y, Linz B, Bond RP, et al. Age of the association between Helicobacter pylori and oral mucosa. PLoS Pathog 2012;8:e1002693.

[6] Schistosomes . liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7–14 June 1994. IARC Monogr Eval Carcinog Risks Hum 1994;61:1–241.

[7] Handa O, Naito Y, Yoshikawa T. Redox biology and gastric carcinogenesis: the role of Helicobacter pylori. Redox Rep 2011;16:1–7.

[8] Anand PS, Nandakumar K, Shenoy KT. Are dental plaque, poor oral hygiene, and periodontal disease associated with Helicobacter pylori infection? J Periodontol 2006;77:692–8.

[9] Adler I, Muino A, Aguas S, et al. Helicobacter pylori and oral pathology: a meta-analysis. J Physiol Pharmacol 2014;65:559–66.

[10] Zou QH, Li RQ. Helicobacter pylori in the oral cavity and stomach. Eur J Oral Sci 2008;116:297–304.

[11] Al Asqah M, Al Hamoudi N, Anil S, et al. Is the presence of Helicobacter pylori in dental plaque of patients with chronic periodontitis a risk factor for gastric infection? Can J Gastroenterol 2009;23:177–9.

[12] Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2003;361:1809–20.

[13] Dye BA, Kruseon-Moran D, McCullan G. The relationship between periodontal disease attributes and Helicobacter pylori infection among adults in the United States. Am J Public Health 2002;92:1809–15.

[14] Nisha KJ, Nandakumar K, Shenoy KT, et al. Periodontal disease and Helicobacter pylori infection: a community-based study using serology and rapid urease test. J Investig Clin Dent 2016;7:37–45.

[15] Valadan Tabhaz S, Yadegar A, Amimoorzafiri N, et al. Occurrence of Helicobacter pylori and its major virulence genotypes in dental plaque samples of patients with chronic periodontitis in Iran. Gastroenterol Hepatol Bed Bench 2017;10:S70–8.

[16] Salehi MR, Shah Aboei M, Naghsh N, et al. A Comparison in Prevalence of Helicobacter pylori in the Gingival Crevicular Fluid from Subjects with Periodontitis and Healthy Individuals using Polymerase Chain Reaction. J Dent Res Dent Clin Dent Prospects 2013;7:238–43.

[17] Burgers R, Schneider-Bracht W, Resch U, et al. Helicobacter pylori in human oral cavity and stomach. Eur J Oral Sci 2008;116:297–304.

[18] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

[19] Al Asqah M, Al Hamoudi N, Anil S, et al. Is the presence of Helicobacter pylori in dental plaque of patients with chronic periodontitis a risk factor for gastric infection? Can J Gastroenterol 2009;23:177–9.

[20] Anand PS, Nandakumar K, Shenoy KT. Are dental plaque, poor oral hygiene, and periodontal disease associated with Helicobacter pylori infection? J Periodontol 2006;77:692–8.

[21] Medina ML, Medina MG, Martin GT, et al. Molecular detection of Helicobacter pylori in oral samples from patients suffering digestive pathologies. Med Oral Patol Oral Cir Bucal 2010;15:e38–42.

[22] Riggio MP, Lennon A. Identification by PCR of Helicobacter pylori in subgingival plaque of adult periodontitis patients. J Med Microbiol 1999;48:317–22.

[23] Silva DG, Stevens RH, Macedo JM, et al. Presence of Helicobacter pylori in supragingival dental plaque of individuals with periodontal disease and upper gastric diseases. Arch Oral Biol 2010;55:896–901.

[24] Souto R, Colombo AP. Detection of Helicobacter pylori by polymerase chain reaction in the subgingival biofilm and saliva of non-dyspeptic periodontal patients. J Periodontol 2008;79:97–103.

[25] Sujaatha S, Jalihal UM, Sharma S. Association between periodontal disease and oral and gastric Helicobacter pylori infection. Indian J Gastroenterol 2015;34:343–4.

[26] Umeda M, Kobayashi H, Takeuchi Y, et al. High prevalence of Helicobacter pylori detected by PCR in the oral cavities of periodontitis patients. J Periodontol 2003;74:129–34.

[27] Yang J, Zhang Q, Chen M, et al. Association between Helicobacter pylori infection and risk of periodontal diseases in Han Chinese: a case-control study. Med Sci Monit 2016;22:121–6.

[28] Nguyen AM, Engrstrand L, Genta RM, et al. Detection of Helicobacter pylori in dental plaque by reverse transcription-polymerase chain reaction. J Clin Microbiol 1993;31:783–7.

[29] Brown LM. Helicobacter pylori: epidemiology and routes of transmission. Epidemiol Rev 2000;22:283–97.

[30] Wang XM, Yee KC, Hakseki-Taylor N, et al. Oral Helicobacter pylori infection: its relationship to successful eradication of gastric H. pylori and saliva culture confirmation. J Physiol Pharmacol 2014;65:559–66.

[31] Jia CL, Jiang GS, Li CH, et al. Effect of dental plaque control on infection of Helicobacter pylori in gastric mucosa. J Periodontol 2009;80:1606–9.

[32] Navabi N, Aramon M, Mirzazadeh A. Does the presence of the Helicobacter pylori in the dental plaque associate with its gastric infection? A meta-analysis and systematic review. Dent Res J (Isfahan) 2011;8:178–82.

[33] Bickel M, Axtelius B, Soloz C, et al. Cytokine gene expression in chronic periodontitis. J Clin Periodontol 2001;28:840–7.

[34] Ouhara K, Kawai T, Silva MJ, et al. Expression levels of novel cytokine IL-32 in periodontitis and its role in the suppression of IL-8 production by human gingival fibroblasts stimulated with Porphyromonas gingivalis. J Oral Microbiol 2012;4.

[35] Bouzanne A, Abuhd S, Aboufil R, et al. Effect of periodontal therapy on prevention of gastric Helicobacter pylori recurrence: a systematic review and meta-analysis. J Clin Periodontol 2012;39:1166–73.

[36] Norder Grusell E, Dahlen G, Reuth M, et al. Bacterial flora of the human oral cavity, and the upper and lower esophagus. Dis Esophagus 2013;26:84–90.