Review

Reviews of Research on the Relationship between Oral *Helicobacter pylori* and *H. pylori* Infection

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Abstract

Helicobacter pylori is one of the most common pathogens among humans, and it is also closely related to stomach diseases. Spread of its diseases must be understood to properly control *H. pylori*. Oral *H. pylori* may also play an important role in the spread of the bacterium. This study provides an overview on the role of oral *H. pylori* in spread, diagnosis, and prevention of this organism. The present work also determines difficulties encountered in current studies and progress of research on the relationship between oral *H. pylori* and oral diseases.

Helicobacter pylori is a unipolar, flagellose, spiral-shaped Gram-negative bacterium measuring 0.3–1.0 μm × 2.0–5.0 μm. *H. pylori* in epithelial cell surface of gastric mucosa often show typical spiral or arc shape and become rod-shaped or spherical in adverse circumstances. *H. pylori* is microaerobic, requiring 5% to 8% of environmental oxygen [1]. Humans serve as primary hosts of *H. pylori* [2]. *H. pylori* is also a unique microorganism that can be cultured and isolated from the human stomach [3].

In 1983, Warren *et al*. [4] reported that approximately half of gastric ulcer patients feature tiny, curved bacteria attached to their stomach cavity; these bacteria were later cultured and isolated by Marshall *et al*. [5]. Later studies discovered that this bacterium, that is, *H. pylori*, causes most of duodenal ulcer and gastric ulcers [6]. *H. pylori* also primarily results in development of gastric cancer [7]. Discovery of *H. pylori* infection was considered an important factor that affected people's health worldwide; however, the manner of its spread among humans remains controversial. In 1989, Krajden *et al*. [8] observed *H. pylori* strains in membranes of oral plaque organisms and saliva. In recent years, most research focused on whether *H. pylori* can settle in the mouth, and whether oral cavity serves as source of *H. pylori* spread.

Detection method and detection rate of *H. pylori* in oral cavity

Using different methods to detect *H. pylori* in plaque biofilm, saliva, and oral mucosa result in large differences in detection rates [9]. Early research [8] mostly utilized culture method because of harsh survival conditions and presence of other oral bacteria. *H. pylori* yields low detection rate. Some scholars [10] used urease test to detect oral *H. pylori* and noted high detection rates. However, these experimental methods cannot rule out the presence of other oral urease bacteria, thus causing false positive rates and unclear results. Reliable detection methods include molecular biological tests (such as polymerase chain reaction and gene sequencing), which feature high specificity and sensitivity and are suitable for detection of oral *H. pylori*.

Molecular biological techniques also present differing detection rates for oral *H. pylori*. Such findings are attributed to differences in ethnic, dietary, educational, economic conditions [11], and different laboratory tests used by researchers. Although polymerase chain reaction generally presents high sensitivity, it shows strong specificity; primers used also affect detection results. The most commonly used polymerase chain reaction amplification primers include

H. pylori urease (HPU)-based and cytotoxin-related gene (cag) A-based primers. However, these tests exhibit certain defects as follows: 1) HPU exists in many bacteria, features high homology, and possibly results in false positives when amplified; 2) cagA gene is only expressed in some parts of *H. pylori* and is therefore susceptible to false negative results. Therefore, studies should develop a unified and effective detection method or standard for oral *H. pylori*.

Oral *H. pylori* and *H. pylori*

Correlation between oral H. pylori and H. pylori infection

H. pylori can be detected in the oral cavity; however, studies must still determine the association of oral *H. pylori* with *H. pylori* infection, and whether such conditions are homological. Scholars performed analyses based on two aspects: 1) detection rate of oral *H. pylori* in *H. pylori* infectors. Most studies indicated that positive carriers of *H. pylori* show higher detection rates for oral *H. pylori* than negative carriers. Recent studies showed close relation of *H. pylori* infection with oral *H. pylori* [12–14]. Zou *et al.* [9] analyzed detection rates of oral *H. pylori* among *H. pylori*-positive and *H. pylori*-negative populations. These researchers also observed higher detection rate of oral *H. pylori* among positive carriers than negative carriers [odds ratio (OR) = 3.61, 95% confidence interval (CI)=1.91–6.82), confirming the correlation between oral *H. pylori* and *H. pylori* infection. These findings also showed that regardless of method used, oral *H. pylori* and *H. pylori* infection display correlation. (2) In view of homology of stomach and oral *H. pylori* genotype of the same individual, numerous studies showed high homology of oral *H. pylori* with *H. pylori* infection. Cai *et al.* [15] used polymerase chain reaction to detect genotypes of *H. pylori* and oral *H. pylori* in patients with stomach diseases and discovered high homology in the same individual. At 89% probability, the same type of *H. pylori* was detected in different *in vivo* loci [14]. Momtaz *et al.* [16] suggested that *H. pylori* in saliva exhibit homology with strains of gastric specimens and those isolated from feces. Silva *et al.* [17] observed high detection rate of oral *H. pylori* cytotoxic genes in *H. pylori* infectors. This evidence suggests correlation of oral *H. pylori* with *H. pylori* infection. However, these studies still cannot explain whether oral *H. pylori* causes *H. pylori* infection, or whether *H. pylori* results in development of oral *H. pylori*.

Role of oral cavity in spread of H. pylori

An epidemiological survey [18] showed that human population features high rate of *H. pylori* infection in crowded living conditions, suggesting that *H. pylori* is possibly spread directly from one person to another. Oral–oral and fecal–oral routes are considered the most possible routes of spread of *H. pylori*. As *H. pylori* may also be present in the mouth, oral *H. pylori* may also cause infection and spread of *H. pylori* in humans. In this regard, supporters of oral–oral and fecal–oral route theories provide different answers.

Oral–oral theory supporters suggest that *H. pylori* can settle in the mouth and spread through media, such as saliva. Mégraud [19] argued that in developed countries, owing to improved hygienic conditions, *H. pylori* is unlikely to be spread by feces. Thus, *H. pylori* may be spread by oral–oral route. Fernández-Tilapa *et al.* [20] used polymerase chain reaction and observed high detection rates of *H. pylori* among positive carriers of serum antibody for *H. pylori*; this result was possibly caused by *H. pylori* spread through saliva. For oral–oral theory supporters, if *H. pylori* can spread through saliva, then dentists face high risks of *H. pylori* infection because of their frequent exposure to this medium. However, the current number of infected dentists is low, and such conclusion shows inconsistency. Honda *et al.* [21] reported that Japanese dentists face higher risk of infection with *H. pylori* than the same-aged control group, and this risk inclines toward young dental practitioners. Loster *et al.* [22] showed that before clinical practice, dentists do not present higher detection rates of *H. pylori* than dental students.

Supporters of fecal–oral spread theory suggest that *H. pylori* is a passing bacterium in the oral cavity and cannot directly cause *H. pylori* infection. Spread of *H. pylori* in populations may be mediated by drinking water contaminated with *H. pylori* from feces [23]. The main evidence that disprove the theory of fecal spread is low detection rates of *H. pylori* in feces; these values are even lower than those of oral specimens [24]. However, such findings may also be associated with reaction of fecal contaminants in agents of polymerase chain reaction.

To date, some evidence support oral–oral spread or fecal–oral spread, but determining specific route of spread remains improbable. Controversies also surround the assumption of

whether *H. pylori* can settle and reproduce in the oral cavity for long periods. Scholars [25] suggested that small numbers of oral *H. pylori* can be detected through polymerase chain reaction, and this finding may be due to low activity of spherical *H. pylori*. Thus, oral *H. pylori* may not directly lead to *H. pylori* infection.

Role of oral H. pylori in diagnosis of H. pylori infection

Oral *H. pylori* and its genotype identification and immunological detection may play important roles in identifying types of *H. pylori* infection and diagnosing types of diseases resulting from the correlation between oral *H. pylori* and *H. pylori* infection.

Confirming possible existence of oral *H. pylori* may bear significance in identification of varying degrees of gastritis and precancerous lesions. Jun *et al*. [26] observed higher detection rates of oral *H. pylori* among patients with chronic atrophic gastritis than patients with digestibility ulcers and superficial gastritis. Considering that oral *H. pylori* features high homology with *H. pylori*, Tiwari *et al*. [27] suggested that saliva can be used for reliable noninvasive specimen examination for *H. pylori* infection. Such method analyzes genotypes of *H. pylori* cag pathogens, which are isolated from saliva, to assess the type of *H. pylori* infection among patients.

In addition to direct detection of *H. pylori*, detection of *H. pylori* antigens and antibodies in saliva may also provide basis for diagnosis of stomach diseases. Yingying *et al*. [28] detected oral *H. pylori* antigen on different types of stomach diseases and discovered the association of oral *H. pylori* with degree of gastritis activity and precancerous lesions of gastric mucosa. Oral *H. pylori* antigen in patients with chronic active gastritis or with moderate to severe intestinal or atypical hyperplasia also present significantly high detection rates. Results showed higher light density of *H. pylori* IgG in the gastric cancer group than chronic atrophic gastritis and gastric ulcer groups. Higher sensitivity was also observed in gastric cancer screened for *H. pylori* IgG (72.0%, OD>0.5), providing a new mode of thinking for primary screening of gastric cancer.

To date, research on the role of oral *H. pylori* in diagnosis and identification of gastropathy are still in exploratory stages. One challenge involves clarification of the relationship between oral *H. pylori* and *H. pylori* infection and role of oral *H. pylori* in development of diseases. Saliva and plaque biofilm can be used as non-invasive specimens of *H. pylori* infection; these specimens may pose certain prospects in diagnosis of stomach diseases.

Role of eradicating oral H. pylori in prevention of H. pylori infection

Conventional triple therapy is the most commonly used and most effective treatment for *H. pylori* eradication; it comprises one proton pump inhibitor plus two antibiotics. However, probability of recurrence after treatment is high considering that *H. pylori* exists in the mouth and is swallowed into the stomach along with saliva. Zou *et al*. [9] observed patients with upper gastrointestinal diseases and who received anti-*H. pylori* treatment. Results indicated that despite eradication of *H. pylori* in the stomach, *H. pylori* still existed in the mouth; this result may be associated with the presence of *H. pylori* in unique biofilm plaques that were unaffected by medicine.

Considering that oral *H. pylori* is a potential cause of recurrence or reinfection of *H. pylori* infection, some scholars suggested using drugs with periodontal basic therapy to reduce recurrence rate of *H. pylori* infection. However, experimental results showed inconsistency. Namiot *et al*. [30] studied the relationship between oral cleaning behavior and *H. pylori* eradication rate in patients with peptic ulcer after triple antibacterial treatment and observed that habit of maintaining cleanliness of oral cavity (such as brushing of teeth every day, cleaning dentures after meal, or removing dentures before sleeping every night) poses no effect on eradication rate of *H. pylori*, indicating that maintaining cleanliness of oral cavity cannot improve eradication rate of *H. pylori*. Presenting different findings, Song *et al*. [31] discovered significantly higher eradication rate of *H. pylori* in patients with periodontal nonsurgical treatment and who use mouthwash than those without periodontal nonsurgical treatment and do not use mouthwash. These results suggest that eradication rate of *H. pylori* with drug treatment is associated with patient's periodontal status and oral hygiene, agreeing with findings of Jia *et al*. [32]. Bouziane *et al*. [33] analyzed the effects of periodontal treatment on eradication rate of *H. pylori* before 2012 and noted that periodontal treatment can reduce recurrence rate of *H. pylori* infection in the stomach. These

results should be treated with caution because of small amount of raw data. In short, several studies reported that reduction of oral *H. pylori* can reduce recurrence rate of *H. pylori* infection, but significant evidence are still needed to support such conclusion.

Oral *H. pylori* and oral diseases

Oral H. pylori and periodontal diseases

Patients with periodontal diseases may feature suitable conditions for survival of *H. pylori* because of the presence of oxidation–reduction potential microenvironment with low-oxygen partial pressure in deep periodontal pockets. Studies showed association of oral *H. pylori* with periodontal diseases. For example, Li *et al*. [34] observed high detection rates for oral *H. pylori* in patients with periodontal diseases, whereas the study of Silva *et al*. [35] supported the above results. Differently, Silva *et al*. were unable to detect *H. pylori* in subgingival plaque.

Oral H. pylori and oral ulcer

Oral mucosa and gastric mucosa are all gastrointestinal mucosa and derive from the ectoderm; they present similar development and structure. *H. pylori* is one of the causes of gastric ulcer; thus, studies should explore whether oral *H. pylori* is associated with oral ulcer. Riggio *et al*. [36] and Richter *et al*. [37] discovered the relationship of *H. pylori* with recurrent aphthous ulcer. Considering that these early studies focused on urease A gene-based primers, detection results showed high false positive rates. Minhai *et al*. [38] further used nested polymerase chain reaction with high specificity and sensitivity to detect *H. pylori* and observed absence of correlation between *H. pylori* and recurrent aphthous ulcer. Thus, pathogenesis of oral ulcer from oral *H. pylori* infection requires further explanation.

A small number of studies centered on the correlation between oral *H. pylori*, caries [39,40], lichen planus [41], and bad breath [42]. However, to date, controversies still surround oral *H. pylori*, caries, periodontal disease, and recurrent aphthous ulcer. Further research should determine biological mechanism of *H. pylori*.

Summaries

Different detection rates of *H. pylori* were observed in the oral cavity; these results may be related to imperfection of detection methods. Therefore, a unified detection method for *H. pylori* must be developed for its accurate detection. A large number of studies showed correlation of oral *H. pylori* with *H. pylori* infection. However, their causal relationship requires additional research. Oral *H. pylori* may act as "repository" to cause oral–oral spread of *H. pylori* among populations and infection and recurrence of *H. pylori*. Further studies on colonization conditions of *H. pylori* in oral cavity and its relationship with other oral microbes also aid in verifying this theory, providing a new mode of thinking regarding diagnosis and prevention of gastric diseases. Oral *H. pylori* and periodontal and other oral diseases may also possess a certain correlation. In-depth studies on oral *H. pylori* will aid in prevention and control of *H. pylori* infection.

Declarations

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No.

Competing interests

The author declares that she has no competing interest.

Authors' contributions

LL Zu made the literature analysis and wrote, discussed and revised the manuscript of this review.

References

1 Cover TL. Perspectives on methodology for in vitro culture of *Helicobacter pylori*. Methods Mol Biol, 2012, 921:11-15.

2 Noto JM, Peek RM Jr. *Helicobacter pylori*: an overview. Methods Mol Biol, 2012, 921:7-10.

3 Engstrand L, Lindberg M. *Helicobacter pylori* and the gastric microbiota. Best Pract Res Clin Gastroenterol, 2013,27(1):39-45.

4 Warren J, Marshall B. Unidentifi ed curved bacilli on gastric epithelium in active chronic gastritis. Lancet, 1983, 1(8336):1273-1275.

5 Marshall BJ, Warren JR. Unidentifi ed curved bacilli in the stomach of patients with gastritis and peptic ulceration.Lancet, 1984, 1(8390):1311-1315.

6 Alakkari A, Zullo A, O'Connor HJ. *Helicobacter pylori* and nonmalignant diseases. Helicobacter, 2011, 16 (Suppl1):33-37.

7 Cover T, Peek RM. Diet, microbial virulence, and *Helicobacter pylori*-induced gastric cancer. Gut Microbes, 2013,4(6):482-493.

8 Krajden S, Fuksa M, Anderson J, *et al*. Examination of human stomach biopsies, saliva, and dental plaque for Campylobacterpylori. J Clin Microbiol, 1989, 27(6):1397-1398.

9 Zou QH, Li RQ. *Helicobacter pylori* in the oral cavity and gastric mucosa: a meta-analysis. J Oral Pathol Med, 2011,40(4):317-324.

10 Esfahanizadeh N, Modanlou R. Correlation between oral hygiene and *Helicobacter pylori* infection. Acta Med Iran,2010, 48(1):42-46.

11 Goh KL, Chan WK, Shiota S, *et al*. Epidemiology of *Helicobacter pylori* infection and public health implications. Helicobacter, 2011, 16 (Suppl 1):1-9.

12 Rasmussen LT, Labio RW, Gatti LL, et al. *Helicobacter pylori* detection in gastric biopsies, saliva and dental plaque of Brazilian dyspeptic patients. Mem Inst Oswaldo Cruz, 2010, 105(3): 326-330.

13 Silva DG, Tinoco EM, Rocha GA, *et al*. *Helicobacter pylori* transiently in the mouth may participate in the transmission of infection. Mem Inst Oswaldo Cruz, 2010, 105(5):657-660.

14 Assumpção MB, Martins LC, Melo Barbosa HP, *et al*. *Helicobacter pylori* in dental plaque and stomach of patients from Northern Brazil. World J Gastroenterol, 2010, 16(24):3033-3039.

15 Cai H, Li W, Shu X, *et al*. Genetic variation of *Helicobacter pylori* in the oral cavity and stomach detected using thymine adenine cloning in children with chronic gastritis. Pediatr Infect Dis J, 2014, 33(1): e1-e6.

16 Momtaz H, Souod N, Dabiri H, *et al*. Study of *Helicobacter pylori* genotype status in saliva, dental plaques, stool and gastric biopsy samples. World J Gastroenterol, 2012, 18(17):2105-2111.

17 Silva DG, Stevens RH, Macedo JM, *et al*. Detection of cytotoxin genotypes of *Helicobacter pylori* in stomach, saliva and dental plaque. Arch Oral Biol, 2009, 54(7):684-688.

18 Dattoli VC, Veiga RV, da Cunha SS, *et al*. Seroprevalence and potential risk factors for *Helicobacter pylori* infection in Brazilian children. Helicobacter, 2010, 15(4):273-278.

19 Mégraud F. When and how does *Helicobacter pylori* infection occur. Gastroenterol Clin Biol, 2003, 27(3 Pt 2):374-379.

20 Fernández-Tilapa G, Axinecuilteco-Hilera J, Giono-Cerezo S, *et al*. vacA genotypes in oral cavity and *Helicobacter pylori* seropositivity among adults without dyspepsia. Med Oral Patol Oral Cir Bucal, 2011, 16(2): e175-e180.

21 Honda K, Ohkusa T, Takashimizu I, *et al*. High risk of *Helicobacter pylori* infection in young Japanese dentists. JGastroenterol Hepatol, 2001, 16(8):862-865.

22 Loster BW, Czesnikiewicz-Guzik M, Bielanski W, *et al*. Prevalence and characterization of *Helicobacter pylori* (H.pylori) infection and colonization in dentists. J Physiol Pharmacol, 2009, 60 (Suppl 8):13-18.

23 Dorji D, Dendup T, Malaty HM, *et al*. Epidemiology of *Helicobacter pylori* in Bhutan: the role of environment and Geographic location. Helicobacter, 2014, 19(1):69-73.

24 Oztürk Y, Ozen H, Pehlivanoğlu E. Preventive approaches for intrafamilial *H. pylori* transmission as an efficient target strategy to decrease the prevalence of the infection in developing countries. Turk J Gastroenterol, 2013, 24(3):297-298.

25 Duś I, Dobosz T, Manzin A, *et al*. Role of PCR in *Helicobacter pylori* diagnostics and research—new approaches for study of coccoid and spiral forms of the bacteria. Postepy Hig Med Dosw: Online, 2013, 67:261-268.

26 Chen Jun, He Xiangyi, Wu Lingli, etc. Study on the Correlation between *Helicobacter Pylori* Oral Colonization and Gastrointestinal Diseases. West China Journal of Stomatology, 2011, 29 (4): 351-354.

27 Tiwari SK, Khan AA, Ahmed KS, *et al*. Polymerase chain reaction based analysis of the cytotoxin associated gene pathogenicity island of *Helicobacter pylori* from saliva: an approach for rapid molecular genotyping in relation to disease status. J Gastroenterol Hepatol, 2005, 20(10):1560-1566.

28 Yu Y, Wu Q, Xu K, *et al*. Study on the Relationship between the Detection of Saliva *Helicobacter Pylori* Antigen, Activity of Chronic Gastritis and Precancerous Lesions. Chinese Journal of Practical Internal Medicine, 2006, 26 (18): 1421-1423

29 Wang Y, Xu H, Sun Y, *et al*. The Value of Saliva *Helicobacter Pylori* IgG in the Preliminary Screening of Gastric Cancer. Chinese Journal of Practical Internal Medicine, 2009, 29 (3): 266-267.

30 Namiot DB, Namiot Z, Kemona A, *et al*. Oral health status and oral hygiene practices of patients with peptic ulcer and how these affect *Helicobacter pylori* eradication from the stomach. Helicobacter, 2007, 12(1):63-67.

31 Song HY, Li Y. Can eradication rate of gastric *Helicobacter pylori* be improved by killing oral *Helicobacter pylori*. World J Gastroenterol, 2013, 19(39):6645-6650.

32 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(10):1606-1609.

33 Bouziane A, Ahid S, Abouqal 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(12):1166-1173.

34 Li F, Jiang B, Zhang J, *et al*. Study on the Relationship between Periodontal Diseases and *Helicobacter Pylori* Infection. Guangdong Dental Disease Prevention and Control, 2011, 19 (3): 124-126.

35 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(11):896-901.

36 Riggio MP, Lennon A, Wray D. Detection of *Helicobacter pylori* DNA in recurrent aphthous stomatitis tissue by PCR. J Oral Pathol Med, 2000, 29(10):507-513.

37 Richter J, Grimmová M, Stiborová I, *et al*. Detection of *Helicobacter pylori* in the saliva of patients with recurrent aphthous stomatitis. Cas Lek Cesk, 2003, 142(11):665-669.

38 Nie M, Zhang T, Hu J, *et al*. Study on the Relationship between *Helicobacter Pylori* and RAU in Oral Cavity. Journal of Clinical Stomatology, 2006, 21 (9): 560-562.

39 Liu P, Yue J, Han S, *et al*. A cross-sectional survey of dental caries, oral hygiene, and *Helicobacter pylori* infection in adults. Asia Pac J Public Health, 2013, 25(4 Suppl):49S-56S.

40 Liu Y, Lin H, Bai Y, *et al*. Study on the relationship between *Helicobacter pylori* in the dental plaque and the occurrence of dental caries or oral hygiene index. Helicobacter, 2008,13(4):256-260.

41 Song Q, Spahr A, Schmid RM, *et al*. *Helicobacter pylori* in the oral cavity: high prevalence and great DNA diversity. Dig Dis Sci, 2000, 45(11):2162-2167.

42 Lee H, Kho HS, Chung JW, *et al*. Volatile sulfur compounds produced by *Helicobacter pylori*. J Clin Gastroenterol, 2006, 40(5):421-426.