

REVIEW: *HELICOBACTER PYLORI* AND NON-MALIGNANT UPPER GASTROINTESTINAL DISEASES

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Abstract: This review covers publications on the associations between *Helicobacter pylori* (*H. pylori*) infection and non-malignant diseases of the upper gastrointestinal (GI) tract published between April 2021 and March 2022. Data on the influence of *H. pylori* on gastroesophageal reflux disease (GERD) remained controversial, showing a protective or no effect. An increase in the GERD prevalence was observed as the consequence of *H. pylori* eradication. The analyses of the association between *H. pylori* and Barrett's esophagus (BE) showed opposite results: an inverse effect on BE, especially for the CagA-positive *H. pylori* strain, and no effect in patients with GERD complications. The impact of *H. pylori* on the expression of non-coding RNAs and different signalling pathways of inflammation was demonstrated. The colonisation by *H. pylori* significantly decreased the α -diversity of the gastric microbiota. After successful eradication of *H. pylori*, the bacterial diversity index increased, and *Rhodococcus*, *Lactobacillus*, and *Sphingomonas* genera were significantly enriched. The authors discussed the possibility that these bacteria might be involved in gastric cancer development after *H. pylori* eradication. The artificial intelligence system could be a good resource for easier diagnosis of gastric precancerous lesions and *H. pylori* infection. Calculation of the economic effect of *H. pylori* eradication strategy for the treatment of peptic ulcer disease revealed great cost savings compared with proton-pump inhibitor therapy alone. *H. pylori* infection was a potential risk factor for the formation of gastric polyps, and the eradication of *H. pylori* increased the polyp elimination rate. The prevalence of *H. pylori* infection was lower in patients with coeliac disease than in controls. In conclusion, *H. pylori* remains a crucial factor in the development of GI diseases. Further studies on understanding molecular mechanisms of pathogenesis of *H. pylori*-associated diseases and the effect on *H. pylori* eradication are needed.

Keywords: Gastroesophageal reflux disease, Barrett's esophagus, Gastritis, Peptic ulcer disease, Gastric polyp, Coeliac disease.

INTRODUCTION

The prevalence of *Helicobacter pylori* (*H. pylori*) is decreasing in many developed countries; however, it remains an important global problem causing a lot of serious diseases. *H. pylori* infection is the strongest risk factor for developing gastric cancer. Also, non-malignant gastrointestinal (GI) diseases, including chronic gastritis and peptic ulcer disease (PUD), are associated with this infection. Although scientific and clinical research made great progress in understanding pathogenesis, prevention and treatment of *H. pylori*-associated diseases, many unanswered questions and clinical challenges remain. The controversies concerning the potential impact of *H. pylori* eradication on gastroesophageal reflux disease (GERD) or Barrett's esophagus (BE) have not yet been resolved. New molecular and genetic mechanisms involved in the pathophy-



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biology of *H. pylori*-associated diseases have been studied. This review summarises the advances in basic and clinical research on *H. pylori* and non-malignant GI diseases published from April 2021 to March 2022.

GASTROESOPHAGAL REFLUX DISEASE

H. pylori infection can prevent the occurrence of GERD by inducing gastric mucosal atrophy. A study carried out in South Korea analysed the quantitative correlation between the extent of atrophic gastritis assessed by endoscopy and serology and the severity of GERD¹. The study found that seropositivity for *H. pylori* immunoglobulin G antibody reduced the risk of GERD. The extent of atrophic gastritis was inversely correlated with the occurrence and severity of GERD. The authors concluded that the atrophic gastritis following *H. pylori* infection could protect against GERD. A study performed among Vietnamese patients with upper gastrointestinal symptoms also demonstrated that *H. pylori* significantly lowered the risk for GERD (OR = 0.777; 95% CI: 0.620-0.973)². On the contrary, Niknam et al. did not show a significant difference in the frequency of *H. pylori* infection between the erosive GERD and non-GERD groups, nor between mild and severe GERD³.

Hojo et al. examined the long-term (mean observation period 6.4 years) effects of eradication of *H. pylori* on reflux esophagitis⁴. Eradication treatment of *H. pylori* resulted in the improvement of atrophy in 30% of cases. This might lead to an increase in gastric acid secretion and GERD. The prevalence of reflux esophagitis was significantly higher after eradication than before eradication [7.0% (13/185) vs. 1.6% (3/185), $p=0.019$], even in patients who were taking an acid secretion inhibitor. In a similar study with a mean follow-up period of 2.8 years, GERD developed in 12% of the patients⁵. Being a current smoker, having functional dyspepsia, a hiatal hernia, and severe gastric atrophy were significant predictors of symptomatic GERD after *H. pylori* eradication, which was controlled by vonoprazan therapy. A systematic review with meta-analysis performed by Zamani et al⁶ confirmed that in cross-sectional surveys, *H. pylori* infection was associated with lower odds of GERD symptoms (OR = 0.74; 95% CI: 0.61-0.90) as well as of erosive esophagitis, in patients with GERD symptoms (OR = 0.70; 95% CI: 0.58-0.84).

BARRETT'S ESOPHAGUS

BE is a premalignant lesion associated with esophageal adenocarcinoma, with a prevalence that is increasing in both Western and Asian countries. The results of the studies⁶⁻⁸ on the role of *H. pylori* infection in the development of BE are inconsistent. Adachi et al⁷ analysed endoscopic findings of lymphoid hyperplasia in Barrett's epithelium. Lymphoid hyperplasia was not found in any patient without a current or prior *H. pylori* infection. Its prevalence was significantly higher in *H. pylori*-positive cases as compared to those post-eradicated (48.4% vs. 30.4%, respectively). Thus, lymphoid hyperplasia in Barrett's epithelium was associated with *H. pylori* infection.

Two recent meta-analyses^{6,8} published opposite results. Du et al⁸ showed an inverse association between the prevalence of *H. pylori* infection, especially those with a CagA-positive *H. pylori* strain, with BE (OR=0.70; 95% CI: 0.51-0.96); however, considerable heterogeneity was observed between the 36 studies. In the subgroup currently infected, *H. pylori* prevalence in BE was significantly lower than that of the controls. The difference disappeared in the subgroup indicating a history of infection. *H. pylori* was negatively correlated with long-segment BE but not with short-segment BE. Zamani et al⁶ did not find a significant association between *H. pylori* infection and either endoscopically-diagnosed (OR 1.84; 95% CI: 0.67-5.02) or histologically confirmed (OR 0.85; 95% CI: 0.60-1.20) BE in subjects with GERD complications.

GASTRITIS

Colonisation of *H. pylori* in the gastric mucosa induces an intense immune response and causes an inflammatory reaction, promoting the synthesis of cytokines and macrophages. The inflammatory reaction leads to lesions in the gastric mucosa and consequently ulcers,

gastritis, and gastric cancer. Important signalling pathways are activated, in which different microRNAs (miRNAs) are involved. *H. pylori* can deregulate miRNA expression and alter different signalling pathways. MiR-125a-5p is characterised as a tumour suppressor. Dos Santos et al⁹ assessed miR-125a-5p expression in samples from patients with normal gastric mucosa, gastritis, and gastric cancer correlating with the presence of *H. pylori* infection. This study found that the presence of *H. pylori* in the mucosa was associated with a significantly lower expression of miR-125a-5p in the control, gastritis and gastric cancer groups. Low expression of this miRNA seems to contribute to tumour invasion, dissemination, and metastasis.

The study by Vasapolli et al¹⁰ evaluated the influence of *H. pylori* eradication on inflammatory mucosal miRNAs miR-155 and miR-223. They found high levels of both miRNAs in the gastric mucosa from *H. pylori*-infected but otherwise healthy subjects. These miRNAs are frequently deregulated in *H. pylori*-positive subjects and are strongly associated with gastric preneoplastic conditions such as atrophic gastritis and intestinal metaplasia. The expression of miR-223 plays a role in the regulation of granulocytes and is directly linked to the degree of neutrophil infiltrate within the gastric mucosa. MiR-155 is a regulator of the immune response to *H. pylori* promoting Th1 and Th17 differentiation, which is necessary to control the infection but is related to the increased risk of preneoplastic gastric conditions. The study revealed that *H. pylori* eradication led to a significant reduction of miR-223 and a trend toward reduction of miR-155. Intake of proton-pump inhibitors (PPIs) was associated with a significant reduction of miR-155 but not miR-223 expression, which was more evident in *H. pylori*-infected mucosa and in the stomach antrum. Low-dose aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) did not change the expression of both miRNAs.

The study conducted on children with gastritis found that *H. pylori*-infected gastric tissue showed many differentially expressed genes associated with an active immune response¹¹. Tyrosine-protein phosphatase nonreceptor type 11 (PTPN11), which encodes SHP2, was significantly increased in macrophages of *H. pylori*-infected tissue. SHP2 could activate the glycolytic function of macrophages to promote *H. pylori*-induced inflammation. The transcription factor SPI1 could be responsible for the regulation of metabolism-associated gene expression and inflammation. The authors concluded that the SHP2/SPI1 axis could be a novel therapeutic target in *H. pylori*-induced paediatric gastritis. The study on children with digestive symptoms evaluated the role of TLR9 rs352140 in inflammation associated with *H. pylori* infection¹². Significantly higher values of leukocytes and neutrophils in the peripheral blood were found in children with *H. pylori* chronic gastritis. A TT variant genotype of TLR9 rs352140 polymorphism was associated with the increase in leucocytes and neutrophils. Thus, TT genotype carriers might have a more severe degree of inflammation.

A recent review highlighted the possible involvement of miRNAs in modulating host immune response and the genesis of acute, chronic, and pre-malignant lesions of the gastric mucosa caused by *H. pylori* gastric inflammation¹³. The review focused upon several miRNAs, including the let-7 family, miRNA-155, miRNA-146, miRNA-125, miRNA-21, and miRNA-221, which regulate interactions between toll-like receptors (TLRs) and lipopolysaccharide (LPS). TLRs recognise surface and molecular patterns of the bacterium, especially LPS, and act upon pathways, leading to activation of the nuclear factor-kappa B (NF- κ B), which stimulates the release of inflammatory cytokines. The expression alterations of miRNAs can modulate TLR-LPS interactions and activate their afferent pathways¹³. The study, which analysed the expression of long non-coding RNA HOTAIR in preneoplastic gastric conditions, demonstrated the highest prevalence of HOTAIR positivity in *H. pylori*-infected patients with intestinal metaplasia¹⁴.

Anti-inflammatory cytokines can influence inflammatory responses during infections. The expression of interleukin (IL)-35 and IL-37 was studied in *H. pylori*-infected patients with gastritis and gastric ulcer as well as in non-infected patients¹⁵. IL-35 inhibits the development of T-effector cells such as Th1, and Th17. IL-37 suppress the inflammatory cytokines. The study found that the mean expression of IL-35 and IL-37 in patients with *H. pylori* infection was significantly lower than in non-infected subjects.

H. pylori colonisation has a significant effect on the host gut microbiota. In the study performed using metagenomic sequencing in 96 patients from the Chinese population, the gastric microbial community structure between *H. pylori*-positive and *H. pylori*-negative individuals was

compared¹⁶. The colonisation of *H. pylori* in the stomach significantly decreased the α -diversity of the gastric microbiota. The relative abundance of *Stenotrophomonas maltophilia*, *Stenotrophomonas* spp, *Variovorax* spp, *Chryseobacterium* spp, *Comamonas* spp, and *Pseudomonas stutzeri* was decreased in the stomach of *H. pylori*-positive individuals. Even 55 gastric microbial metabolic pathways were enriched in the *H. pylori*-positive group, whereas only 2 pathways were observed in the *H. pylori*-negative group. Another study, which simultaneously examined the bacteria of gastric mucosa, juice, and faeces in different stages of gastric precancerous lesions, revealed changes in microbial diversity across the progression of gastritis¹⁷. The diversity and interactions of gastric mucosal bacteria significantly decreased in the intraepithelial neoplastic stage. *Gemella*, *Streptococcus*, *Actinobacillus*, *Hemophilus*, and *Acinetobacter* genera were associated with the development of gastric precancerous lesions.

H. pylori eradication affects the gastric microbiota. The study conducted by Mao et al¹⁸ showed that, after successful eradication of *H. pylori*, the bacterial diversity index increased, and the composition of the gastric microflora was restored to levels close to those of *H. pylori*-negative subjects. However, this effect was incomplete and might contribute to the long-term risks. The eradication treatment itself had little effect on the gastric microflora. Nonetheless, the study by Niu et al¹⁹ showed that gastric microbiota could influence the result of *H. pylori* eradication therapy. Patients who did not respond to the treatment were compared to those whose treatment was successful. In the failure group, the microbial diversity and the species abundance were significantly lower compared to that of the success group. In patients with successful *H. pylori* eradication, *Rhodococcus*, *Lactobacillus*, and *Sphingomonas* genera were significantly enriched. Sitkin et al²⁰ proposed that these bacteria might be involved in gastric cancer development after the eradication of *H. pylori* infection. Evidence suggests that eradication of *H. pylori* can alter the gut microbiota, leading to short-term or long-term dysbiosis, and can also change the metabolism of gastric and intestinal bacteria. Furthermore, eradication therapy with antibiotics and PPIs can lead to serious adverse effects, including severe *Clostridioides difficile*-associated diarrhoea. The authors argue that eradication cannot be an unconditional recommendation in every case of *H. pylori* infection, and the decision should be based on an assessment of the benefit-risk ratio for the individual patient²⁰. Over recent years, the eradication of *H. pylori* infection has also become much more difficult because of the widespread acquisition of antibiotic resistance. Dargenio et al²¹ suggested using *Limosilactobacillus reuteri* as an adjuvant of standard *H. pylori* eradication with antibiotics and PPIs. *L. reuteri* can survive in the gastric acid environment and colonise the gastric mucosa. It inhibits the growth of *H. pylori* and, at higher concentrations could kill it. Routine assessment of the success of eradication is recommended.

Assessment of *H. pylori* infection may give false-negative biopsy results, especially in patients who are hypochlorhydric because of atrophic gastritis or PPI consumption²². Advances in endoscopy, including magnifying narrow-band imaging endoscopy, significantly improved the diagnostic capability of *H. pylori* gastritis. The diagnostic accuracy reached more than 90%. The presence of regular arrangement of collecting venules (RAC) was highly predictive of *H. pylori*-negative status²³⁻²⁵. An artificial intelligence system seems to be a good resource for an easier diagnosis of *H. pylori* infection. Computer-aided detection systems in GI endoscopy are machine learning methods specifically developed to assist endoscopists to improve the accurate detection of pathologies. The study by Franklin et al²⁶ applied a convolutional neural network (CNN) to determine whether a CNN can differentiate autoimmune gastritis and *H. pylori* gastritis. Gold standard diagnoses were blindly established by two GI pathologists. The CNN distinguished between cases of two types of gastritis with an accuracy equal to that of the GI pathologists²⁶. The review article by Tokat et al²⁷ revealed that the CNN system showed a high performance in the detection of gastric precancerous lesions and *H. pylori* infection with an accuracy of more than 90%. Systematic review and meta-analysis²⁸ of the use of artificial intelligence for the diagnosis of *H. pylori* infection demonstrated a pooled-diagnostic accuracy of 80% with a high heterogeneity between the studies.

PEPTIC ULCER DISEASE

A high proportion of peptic ulcer cases is associated with *H. pylori* infection. However, there are several causes of peptic ulceration in addition to *H. pylori* infection. Accurate testing of *H. pylori*

status is therefore encouraged in all patients with PUD²². The eradication therapy is recommended for the treatment of *H. pylori*-positive peptic ulcers. The study assessed the cumulative economic and health effects of the *H. pylori* eradication strategy for the treatment of PUD compared with PPI therapy²⁹. The *H. pylori* eradication strategy has not only made a significant contribution to quality-adjusted life years (QALYs), preventing ulcer recurrence and reducing ulcer-associated deaths, but has also resulted in great cost savings.

Upper GI bleeding is the most prevalent complication of PUD that markedly increases mortality. Hypersecretion of gastric acid increased the bleeding risk. Secretion is associated with the serum level of gastrin 17, pepsinogen I, and pepsinogen II. The study on PUD caused by *H. pylori* infection estimated that serum gastrin-17 > 9.86 pmol/L distinguished bleeding from non-bleeding patients with 90.2% sensitivity and 68.2% specificity³⁰. Thus, an elevated level of gastrin 17 may be an effective early predictor of peptic ulcer bleeding. Another study evaluated the five-year recurrence rate for patients with PUD and risk factors contributing to PUD relapses³¹. The recurrence rate of PUD was 30.9%. Patients who had a complicated PUD were associated with a higher rate of recurrence (45.9%). Three risk factors were identified as risk factors for recurrence: *H. pylori* infection, NSAIDs, and steroid use.

GASTRIC POLYPS

Gastric polyps are usually asymptomatic lesions of the upper GI. The study by Gao et al³² analyzed the gastric juice microenvironment in patients with polyps. The prevalence of gastric fundic gland polyps was significantly higher than that of the gastric hyperplastic polyps. PPIs, *H. pylori* infection, and bile reflux were the potential risk factors for the formation of gastric polyps³². The retrospective 10-year analysis of upper GI endoscopies in a hospital in Tunis found a 0.46% prevalence of polyps³³. Hyperplastic polyps were the most common. The highest proportion of polyps was located in the fundus, with smaller than 5 mm. The most prevalent indications for endoscopy in patients with polyps were epigastric pain and anemia. The authors associated the prevalence of gastric polyps with the high frequency of *H. pylori* infection in the country. A meta-analysis³⁴ revealed that after the successful eradication of *H. pylori*, most gastric polyps were eliminated (-79%) (95% CI: 72%-86%), which was significantly more compared to the control group.

COELIAC DISEASE

There are controversies about the associations between *H. pylori* colonization and coeliac disease. Some studies^{35,36} reported no association; whereas others stated that *H. pylori* can protect against disease. The study carried out in Northwest China did not find a statistically significant difference in *H. pylori* infection prevalence between patients with coeliac disease and controls³⁵. However, *H. pylori*-positive patients with coeliac disease demonstrated more severe mucosal damage than *H. pylori*-negative patients (Marsh grades 2 and 3). The meta-analysis, which analyzed the association between *H. pylori* and coeliac disease, demonstrated that *H. pylori* infection was lower in patients than in controls (OR = 0.57; 95% CI: 0.44-0.75)³⁶. The same association was shown in children and adults. On the other hand, *H. pylori*-infected patients with coeliac disease were more likely to have symptoms of abdominal pain, diarrhea, and distension.

An anti-tissue transglutaminase (anti-tTG) IgA test is recommended for coeliac disease screening. However, a low serum titer of anti-tTG has been described in various conditions without coeliac disease. There is some evidence that infectious agents can play a role in the production of anti-tTG antibodies independent of gluten. The study examined the link between a positive coeliac serology and *H. pylori* infection in children³⁷. The data demonstrated that the serum level of anti-tTG IgA in *H. pylori*-infected patients was comparable to that of non-infected patients. After *H. pylori* eradication, serum anti-tTG IgA level dropped below the cutoff value in 81% of previously infected patients, while only in 20% of non-infected patients. The authors concluded that *H. pylori* infection may cause a false or transient positive coeliac serology; therefore, a positive serology should be carefully interpreted in the presence of *H. pylori* infection before confirming the diagnosis of coeliac disease.

CONCLUSIONS

The extent of atrophic gastritis following *H. pylori* infection was inversely associated with the occurrence and severity of GERD. The prevalence of reflux esophagitis was significantly higher after *H. pylori* eradication than before. The data on the role of *H. pylori* infection in the development of BE remain inconsistent, showing an inverse effect on BE, especially for the CagA-positive *H. pylori* strain, and no effect in patients with GERD complications. *H. pylori* can deregulate miRNA expression and alter different signalling pathways, which are related to inflammatory reactions, preneoplastic conditions and gastric cancer. The colonisation of *H. pylori* in the stomach significantly decreases the α -diversity of the gastric microbiota, which can be restored after *H. pylori* eradication. However, this effect might contribute to the long-term risks. Machine learning methods show a high performance in the detection of *H. pylori* infection and gastric precancerous lesions.

Conflict of interest

The authors have no competing interests.

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