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REVIEW – *H. PYLORI* & NON-MALIGNANT DISEASES

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Abstract – The role of *Helicobacter pylori* in several non-malignant diseases affecting the upper gastrointestinal tract has been reviewed. The effects of *H. pylori* eradication on gastroesophageal reflux disease (GERD) and reflux laryngopharyngitis (RLP) remain controversial. Esophageal physiology tests and symptom score studies have suggested that *H. pylori* eradication may increase esophageal acid exposure and enhance symptoms. Regarding RLP, a retrospective study showed that compared to PPI treatment alone, *H. pylori* eradication yielded additional benefits in improving both the reflux symptom index and reflux finding score.
Novel data have been presented for *H. pylori* and gastroduodenal diseases. The relationship between *H. pylori* infection and autoimmune gastritis (AIG) has been highlighted as a diagnostic marker for differentiating AIG from *H. pylori*-associated gastritis. A long-term study on the natural history of AIG, in which previous *H. pylori* infection was excluded, showed no association between AIG and excess of gastric cancer risk, and this finding has been extensively discussed. The link between duodenal eosinophils and mast cells in the pathogenesis of both functional-dyspepsia and *H. pylori*-associated dyspepsia has been investigated. Global studies have shown that the incidence of peptic ulcer disease continues to decline in the 21st century. A possible protective role of *H. pylori* eradication in reducing peptic ulcer bleeding in older patients using aspirin is presented. Finally, studies have analyzed the role of *H. pylori* eradication in early and long-term complications of bariatric surgery.

Keywords: Gastroesophageal reflux disease, Eosinophilic esophagitis, Autoimmune gastritis, Peptic ulcer, Dyspepsia, Bariatric surgery.

INTRODUCTION

Helicobacter pylori infection causes chronic gastritis, which can progress to severe gastroduodenal pathologies, including peptic ulcers, gastric cancer, and gastric MALT lymphoma. Other non-malignant upper gastrointestinal diseases are associated with this infection and are increasingly being studied in basic and clinical research. This review summarizes recent advances related to *H. pylori* infection in nonmalignant gastrointestinal diseases, including gastroesophageal reflux disease (GERD), eosinophilic esophagitis, autoimmune gastritis, peptic ulcer disease, dyspepsia, functional dyspepsia, nonsteroidal anti-inflammatory drug consumption, and bariatric surgery, published from April 2022 to March 2023.

ESOPHAGEAL DISEASES

Gastroesophageal Reflux Disease

The effects of *H. pylori* eradication on GERD have not been completely elucidated. A study conducted in China using high-resolution esophageal manometry, 24-h esophageal pH mon-

itoring, and the Gastroesophageal Reflux Disease Questionnaire before and after successful *H. pylori* eradication analyzed 68 patients diagnosed with both GERD and *H. pylori*[1]. After eradication, the median distal contractile integral was significantly decreased, and inefficient esophageal motility was significantly increased compared with that before *H. pylori* eradication, suggesting that eradication reduced esophageal peristalsis. The 24-h esophageal pH monitoring showed significantly different scores before and after *H. pylori* eradication, indicating that eradication increased esophageal acid exposure. Furthermore, after eradication, the group had higher symptom scores than before *H. pylori* treatment. The lack of control groups (without any treatment and/or proton pump inhibitor (PPI) use only) and no report of the time point of the second HRM, pH metry, or questionnaire constitute important limitations of this study.

The stomach microbiome and the role of *H. pylori* infection were evaluated in 197 patients with erosive reflux disease (ERD), non-erosive reflux disease (NERD), and gastritis using the rRNA approach on gastric biopsy specimens[2]. A negative correlation between *H. pylori* and microbial diversity was observed in ERD, but not in patients with NERD. Although *H. pylori* dominates the gastric microbiota and induces significant inflammation, the relationship between ERD and *H. pylori* infection remains unclear. Other factors, such as smoking habits and alcohol consumption, can also affect ERD.

The relationship between *H. pylori* infection and reflux laryngopharyngitis (RLP) also is still unclear. A study aimed to evaluate the outcomes of the anti-*H. pylori* therapy (omeprazole 40 mg/day, mosapride citrate 15 mg/day, amoxicillin 1 g BID, and clarithromycin 500 mg BID for 4 weeks) or omeprazole 40 mg/day alone (control group) for 4 weeks to improve RLP symptoms in 410 patients[3]. The authors concluded that the overall response rate was significantly higher in *the H. pylori-treated* group, whereas the reflux symptom index and reflux finding score were significantly lower (p <0.05). However, the study has severe limitations related to tests to confirm eradication, as well as the time point at which post-treatment tests were performed.

Eosinophilic Esophagitis

A low prevalence of extraesophageal gastrointestinal pathology in patients with eosinophilic esophagitis (EoE) was shown[4]. In 1,668 adults studied in Los Angeles, they demonstrated *H. pylori* infection in 4.6% of the patients. In another study conducted in Mexico, a region with a high prevalence of *H. pylori* infection, 38 cases and 152 controls were evaluated[5]. Cases had a lower prevalence of *H. pylori* than controls (36.8% *vs.* 70.4%, OR: 0.21; 95% CI: 0.08-0.69; p = 0.001), an inverse relationship between *H. pylori* and EoE, as described in other reports. This conclusion reinforces the hygiene hypothesis, which proposes the alteration of the gut microbiome in allergic and autoimmune disease pathogenesis as an evolutionary hypothesis[6].

GASTRODUODENAL DISEASES

Autoimmune Gastritis

According to the current evidence, the causes of oxyntic gastric atrophy are *H. pylori* infection, autoimmune gastritis (AIG), and a combined *H. pylori*-autoimmune etiology. Considering the pathological features used to identify AIG in a background of *H. pylori* infection with gastric premalignant lesions, a small retrospective study suggested that enterochromaffin-like cell (ECL) hyperplasia remains a reliable marker for this disorder[7]. To identify the diagnostic markers for differentiating AIG from *H. pylori*-associated gastritis, Japanese investigators performed a comprehensive flow cytometric characterization of T lymphocytes in patients with AIG, current *H. pylori*-associated gastritis (active gastritis), and atrophic gastritis after *H. pylori* eradication (inactive gastritis)[8]. Lymphocytes were isolated from the greater curvature of the gastric antrum and the lesser curvature of the body. It was shown that CD4+/CD3+ and CD8+/CD3+ ratios in the greater curvature of the gastric antrum and lesser curvature of the body were different in autoimmune, active, and inactive gastritis. An antrum CD8+/CD4+ > 4.0 was proposed as a potential diagnostic marker for AIG, with a sensitivity of 71.4% and a specificity of 93.3%.

To assess whether *H. pylori* infection and AIG are associated with the risk of early onset stomach cancers (EOSCs; < 50 years of age), a nested case-control study was performed within the prospective Finnish Maternity Cohort. Study participants were recruited during their first and subsequent pregnancies between 1983 and 2016[9]. Seropositivity to *H. pylori* and AIG was assessed using multiplex serology in samples from 507 stomach cancer patients [297 EOSCs, 210 traditional-onset stomach cancers (TOSCs; >50 years of age), and 907 age-matched control subjects]. Among the overall study population, 23% of control subjects and 68% of patients were seropositive for *H. pylori*. *H. pylori*-seropositive individuals had a statistically significant 7-fold higher odds of developing either EOSC or TOSC (OR, 7.00; 95% CI, 4.93-9.94 and OR, 7.12; 95% CI, 4.60-11.01, respectively). Seropositivity for AIG was rare, with 2% seropositivity in control subjects and 11% in patients. AIG seropositivity was strongly associated with carcinoid tumors (OR, 100.84; 95% CI, 17.22-590.35).

Studies have been conducted to clarify the relationship among AIG, gastric adenocarcinoma, and type 1 neuroendocrine tumors. In a prospective study, 211 adult patients with AIG and naïve *H. pylori-negative* infection (histological, serological, and molecular methods) were followed up by endoscopic, histological and immunohistochemical tests for an average period of 7.5 years[10]. The findings showed that when *H. pylori* infection was rigorously excluded, AIG did not constitute a risk factor for the development of gastric cancer. Both in the initial biopsies and in the follow-up, the histological staging of gastritis using the OLGA system showed around 95% prevalence in stages 0, I, and II, < 5% in stage III, and 0% in stage IV. It should be considered that as AIG predominantly affects the gastric corpus, OLGA stage IV would not be reached due to the absence of moderate/intense atrophy in the gastric antrum/incisura angularis. Regarding ECL hyperplasia, a fundamental characteristic of AIG, a progression from the diffuse to adenomatoid presentation was observed, with type 1 neuroendocrine tumors (carcinoids) being identified in 10/211 (4.7%) of the patients. The authors concluded that, in isolation, AIG does not represent an increased risk of gastric cancer, and it is likely that the increased risk described in previous studies is due to a previous and unrecognized co-infection with *H. pylori*. This study raised challenging considerations by other experts who were properly replied to by the authors in the Gut's PostScript section regarding other etiologic factors possibly linked to corpus-restricted atrophy[11,12] and *H. pylori* and gastric cancer risk in patients[13-16]. Moreover, Goldenring[17], in a commentary on the same issue of this article, analyzing why patients with *H. pylori*-negative AIG fail to demonstrate increases in adenocarcinoma, speculates that the answers may lie in the preneoplastic environment and its influence on the gastric lineages, including the pattern of process inflammation and the predominant type of metaplasia observed (pyloric, pseudopyloric, intestinal metaplasia [IM] type complete or incomplete)[17]. To assess the prevalence of complete *vs.* incomplete IM in gastric conditions with different gastric cancer risks (AIG, *H. pylori* chronic active gastritis, reactive gastropathy, and patients with IM in an otherwise normal stomach), 386 patients with IM *+ve* gastric biopsy sets were studied[18]. Incomplete IM, known to carry a higher risk of GC and strongly associated with its progression, was significantly more prevalent in *H. pylori* gastritis (37.7%). The low prevalence of incomplete IM in AIG (8.3%) and reactive gastropathy (5.2%) was in keeping with the low GC risk associated with these conditions. Further studies in this area may establish whether the presence of autoimmune alterations and *H. pylori* infection can become a stand-alone entity.

Peptic Ulcer

Most peptic ulcer cases are associated with *H. pylori* infection or the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Secondary data analysis of the prevalence, mortality, and disability-adjusted life years (DALYs) due to peptic ulcer disease by sex, age group, and sociodemographic index (SDI) at the global level in 21 regions, 204 countries, and territories between 1990 and 2019 were performed using the Global Burden of Diseases, Injuries, and Risk Factors Study 2019[19]. The peptic ulcer age-standardized prevalence rate decreased from 143.4 (120.5 to 170.2) per 100,000 population in 1990 to 99.4 (83.9 to 117.5) per 100,000 population in 2019. Moreover, the age-standardized mortality rate decreased by 59.4% (55.3 to 63.1) and the DALYs rate fell by 60.6% (56.8 to 63.9) from 1990 to 2019. Across the SDI quintiles, the low-middle and low SDI quintiles had the highest age-standardized prevalence, mortality, and

DALYs rates from 1990 to 2019. More efforts are needed for the prevention, early diagnosis, and treatment of peptic ulcer disease in countries with low and low-middle SDI scores. Similarly, to assess the variation in peptic ulcer incidence trends since the turn of the 21st century, hospitalization data for peptic ulcers from 36 countries belonging to the Organization for Economic Co-operation and Development (OECD) were analyzed[20]. A decrease of 3.7% per year in hospitalizations and 4.7% in mortality from peptic ulcer between 2000-2019 was consistently observed. A Japanese study developed a cohort state-transition model for *H. pylori* eradication and PPI therapy strategies over a lifetime horizon from the healthcare payer's perspective[21]. The main outcomes were cost, quality-adjusted life-years (QALYs), life expectancy life-years (LYs), incremental cost-effectiveness ratios, ulcer recurrence, and ulcer-associated deaths. It was shown that from 2000 to 2020, *H. pylori* eradication strategy saved US$14.07 billion over a lifetime, increased 8.65 million QALYs and 1.23 million LYs over a lifetime, and prevented 551,298 ulcer recurrence cases and 59,465 ulcer-associated deaths, compared with PPI therapy strategy.

Following the decline in *H. pylori* infection and the exclusion of NSAIDS use or unusual causes of peptic ulcer disease, the diagnosis of idiopathic peptic ulcers has become more frequent and difficult to manage. A Belgian study analyzed the eventual role of gastric non-*H. pylori Helicobacter* (NHPH) species in large (n=529) and well-defined *H. pylori*-negative patients with chronic gastritis (n=454), peptic ulcer disease (n=63), and gastric MALT lymphoma, without an identified etiology (n=12)[22]. Patients were retrospectively (n = 464) and prospectively (n = 65) included, and asymptomatic gastric bypass patients (n = 38) were included as controls. Helicobacter species-specific Polymerase Chain Reaction (PCR) and sequencing assays were performed on several zoonotic gastric NHPHs. The prevalence of gastric NHPHs was 29.1% and 27.7% in retrospective and prospective cohorts, respectively, whereas no gastric NHPHs were detected in control biopsies. The eradication of gastric NHPHs has resulted in clinical and histological improvements, highlighting the pathophysiological role of these bacteria. Patients presenting with gastric complaints may benefit from routine PCR testing for zoonotic gastric NHPHs.

Over the past year, three new consensus conferences on the management of *H. pylori* infection in specific countries (China, Spain, and Italy) and one global conference (World Gastroenterology Organization) have been published, with special emphasis on the diagnostic and therapeutic aspects of *H. pylori-associated* peptic ulcer disease[23-26].

Dyspepsia and Functional Dyspepsia

Although *H. pylori* infection is classified as a separate entity from functional dyspepsia (FD), its role in the pathogenesis of FD remains unclear. To explore the link between duodenal eosinophils and mast cells in patients with FD, a systematic review and meta-analysis of 22 case-control studies with 1108 patients with FD and 893 controls was performed[27]. Duodenal eosinophils and mast cells are significantly increased in FD, and no association was found between duodenal immune cells and specific FD subtypes. *H. pylori*-negative FD patients had significantly higher duodenal eosinophils compared with controls (standardized mean difference, 3.98; 95% CI, 2.13-5.84; p = .0001). However, the authors concluded that the quality of evidence was very low, largely due to unexplained heterogeneity, with a serious risk of publication bias in all comparative analyses. Thus, causality remains uncertain, and further studies are required. Another important review on the role of gastric microbiota in FD patients discusses differences in microbiota in *H. pylori*-positive FD patients compared to *H. pylori*-negative FD and speculates that the benefit of long-term symptom relief after *H. pylori* eradication therapy in FD could not originate from the resolution of the infection, but possibly from the effects of antibiotics on the upper gut microbiota[28]. An Argentinian multicenter cross-sectional study evaluated the association between *H. pylori* virulence genes (*cag*A, *oip*A, and *vac*A) and low-grade duodenal eosinophilia in 301 patients with *H. pylori* related-dyspepsia (HpD), and 95 normal endoscopy and *H. pylori* positive gastric biopsy controls[29]. Low-grade duodenal eosinophilia was significantly associated with *cag*A strain 4.2 (95% CI, 1.78-9.93) but not with *oip*A and *vacA* genotypes, and remained significant after adjusting to age, gender, smoking, PPI and *vac*A *s1/m1* in HpD. To study the association between amino acid polymorphisms in

CagL, a component of the *H. pylori* type 4 secretion system, peptic ulcer disease (PUD) and non-ulcer dyspepsia (NUD), and 99 *H. pylori*-positive (PUD, n=46; NUD, n=53) patients were analyzed[0]. Three CagL amino acid polymorphism combinations were associated with PUD and NUD. Pattern 1 was only detected in PUD patient samples and was associated with a 1.35-fold increase in risk ($p = 0.02$). Patterns 2 and 3 were found only in NUD patient samples and were associated with a 1.26-fold increase in risk ($p = 0.03$). These patterns may help understand the course of *H. pylori* infection.

Nonsteroidal Anti-Inflammatory Drug Consumption

A large randomized, double-blind, placebo-controlled trial (Helicobacter Eradication Aspirin Trial [HEAT]) with patients aged 60 years or older receiving aspirin at a daily dose of 325 mg or less and with *H. pylori* positive ^{13}C-urea breath at screening was performed[31]. Patients (n=5352) were randomly assigned to receive active eradication (n=2677) or placebo (n=2675) and were followed up for a median of 5.0 years. There was a significant reduction in the time to hospitalization or death due to definite or probable peptic ulcer bleeding in the active eradication group in the first 2.5 years of follow-up compared with that in the control group, demonstrating that *H. pylori* eradication protects against aspirin-associated peptic ulcer bleeding. This paper deserves two interesting[32,33] comments and replies[34] through the Letter to the Editor section regarding possible explanations for the observed progressive loss of protection from ulcer bleeding after eradication over 2.5 years and methodological validity of the small percentage (10%) of participants retested to confirm *H. pylori* eradication. Finally, the permission for co-medication during the follow-up period, showing a significant increase in PPI prescriptions in the control group in the first 2.5 years might also be related to the observed results.

Bariatric Surgery

Most bariatric procedures involve some degree of gastric resection, which varies in type and extent between sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). The determination of *H. pylori* infection and its sequelae as preoperative risk factors for early and long-term complications of bariatric surgery has been studied. SG is one of the most common and effective surgical procedures for the treatment of morbid obesity. To examine *H. pylori* prevalence in SG specimens, its association with early (30-day) complications, and the impact of preoperative *H. pylori* eradication on outcomes, a retrospective observational study of a single Israeli tertiary bariatric center analyzed 1985 patients who underwent SG between January 2012 and December 2020[35]. They found a low prevalence (9%) of *H. pylori* among SG specimens and its presence did not seem to affect the early outcomes of SG. In addition, preoperative *H. pylori* eradication (n=111) did not change the early post-operative course, suggesting that routine preoperative *H. pylori* screening and eradication may be limited in patients undergoing SG. The authors suggested that eradication could be completed following SG, according to the *H. pylori* status of the specimen. Marginal ulcer (MU) is a common complication following RYGB, with an incidence rate of up to 25%. A meta-analysis involving 14 studies with 344,829 patients who underwent RYGB demonstrated that *H. pylori infection* (OR 4.97 [2.24-10.99]) was the most significant predictor of MU, followed by smoking (OR 2.50 [1.76-3.54]) and diabetes mellitus (OR 1.80 [1.15-2.80])[36]**.** A systematic review assessing the existing evidence on post-RYGB gastric cancer included 31 full-text articles presenting 35 cases from 1991 to 2022[37]. Post-bypass gastric cancer was described in 27 (77%) patients in the bypassed or excluded stomach and in 8 (23%) patients in the gastric pouch, and 47% of all patients presented with metastatic disease. In addition to known risk factors, such as *H. pylori* infection, tobacco smoking, and family history of gastric cancer, bile reflux was also considered. The authors suggested that gastric cancer risk assessment should be considered before gastric bypass surgery and that further investigation is needed to determine the value of post-operative gastric cancer surveillance. To determine whether a subgroup of US patients who underwent SG presented significant pathologic findings that could justify routine histopathologic evaluation of gastric

sleeve specimens, a retrospective electronic review of 3543 patients was performed[38]. A total of 1076 patients presented with abnormal pathologies, including gastritis (938), follicular gastritis (98), IM (25), gastrointestinal stromal tumors (12), leiomyoma (1), lymphoma (1), and other malignancies (1). In an editorial comment on this article, Love and Scott[39] emphasized the significant number of previously undiagnosed gastritis and *H. pylori* infections and reinforced the need for preoperative screening and treatment for gastritis and *H. pylori* detection by EGD or other methods. Pathological examination of sleeve gastrectomy specimens would be more appropriately reserved only for patients in whom abnormalities are noted on gross examination at the time of surgery.

Regarding the histological findings of IM as a known preneoplastic lesion, prior to the bariatric surgery, two studies were published. To assess the prevalence of IM and its associated factors in 753 patients who underwent primary SG or RYGB, a retrospective chart review was performed[40]. Baseline characteristics, preoperative endoscopic findings, and histopathological analysis of the SG specimens were analyzed. Procedures consisted of 411 (54.6%) gastric bypasses and 342 (45.4%) sleeve gastrectomies. Esophagitis and BE were found in 18.1% and 5.0% of patients, respectively. Preoperative gastric biopsy identified *H. pylori in* 6.4% and IM in 2.7%. Histopathological analysis of SG specimens identified *H. pylori* in 1.8% and IM in 0.9%. Older age and a Barrett esophagus were associated with IM on preoperative gastric biopsy. This association emphasizes the importance of diligent examination during preoperative endoscopy. To date, there is no consensus or position statement to address IM prior to bariatric surgery, and an international group of experts published a Letter to the Editor to suggest surgical procedures that allow full access for EGD evaluation (such as SG) in high-risk patients with gastric cancer with IM. Additionally, when deciding to perform gastric bypass procedures in these patients, resection of the remnant-inaccessible gastric tube must be considered because of the elevated risk of progression of IM to dysplasia or gastric cancer[41].

CONCLUSIONS

The effects of *H. pylori* eradication on GERD and RFP remain controversial. Global studies have shown that age-standardized prevalence and mortality estimates of peptic ulcer disease have decreased in the last 30 years and studies suggest that the *H. pylori* eradication strategy not only contributed significantly to preventing ulcer recurrence and reducing ulcer-associated deaths but also has resulted in great cost savings. The relationship between *H. pylori* and AIG, the two most important causes of corpus atrophic gastritis, has been extensively studied. An important long-term longitudinal study suggests that AIG without *H. pylori*-associated infection constitutes a continued increased risk of carcinoid tumor development but not of gastric adenocarcinoma. While *H. pylori* infection is now classified as a separate entity, its role in the pathogenesis of FD remains under scrutiny, and initial studies have been performed evaluating the link with duodenal eosinophils and mast cells. Finally, regarding *H. pylori* infection and bariatric surgery, an important meta-analysis involving patients who underwent RYGB demonstrated that *H. pylori* infection was the most significant predictor of MU. EGD with gastric biopsies is now considered essential in patients prior to bariatric surgery. However, clear recommendations are still missing for the management of IM before surgery.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contribution

Both authors equally contributed to the review.

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