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

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Abstract – The article considers the role of *Helicobacter pylori* (*H. pylori*) in the formation and progression of non-malignant diseases of the upper gastrointestinal tract and reviews the results of studies published in the period from April 2023 to May 2024. The association of *H. pylori* with gastroesophageal reflux disease remains controversial. However, eradication therapy has no significant effect on the formation of Barrett's esophagus. There is an inverse relationship between *H. pylori* infection and the prevalence of eosinophilic esophagitis. *H. pylori* is still the main cause of chronic gastritis, which in some patients is accompanied by dyspepsia syndrome. Eradication of *H. pylori* can significantly improve morphologic features of atrophic gastritis and the severity of intestinal metaplasia at an early stage. The increased risk of gastric cancer in patients with autoimmune gastritis may be the result of previously unrecognized *H. pylori* infection. Against the background of a general trend towards a decrease in the prevalence of *H. pylori*-associated peptic ulcer disease, there is an increase in the proportion of drug-induced peptic ulcer disease, particularly among the older age group.

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

BACKGROUND

This review summarizes research findings of studies related to *Helicobacter pylori* and non-malignant diseases published between April 2023 and May 2024.

The PubMed/MEDLINE, EMBASE, Cochrane Central, and Google Scholar databases were searched using the keyword "*Helicobacter pylori*". Selection criteria were full-text articles published in English, including original studies, systematic reviews, and meta-analyses. Articles related to epidemiology and diagnosis of *Helicobacter pylori* (*H. pylori*) infection, tumor, and rare *H. pylori*-associated diseases, extragastric manifestations of infection, *H. pylori* infection in pediatric practice, and other *Helicobacter* types were excluded from the analysis. All authors independently reviewed and analyzed the articles. Any disagreements were resolved through consensus.

ESOPHAGEAL DISEASES

Gastroesophageal Reflux Disease

There are still discussions about possible associations between the development and course of gastroesophageal reflux disease (GERD) and *H. pylori*, as evidenced by the rising prevalence of

GERD alongside decreasing rates of *H. pylori* infection in the population. This can be attributed to the realization of the acid-dependent mechanism of esophageal mucosal damage in conditions of excessive acid secretion in certain *H. pylori*-associated diseases. Additionally, the importance of evaluating the prognosis of GERD in the context of *H. pylori* eradication cannot be overstated.

Chen et al[1] analyzed the occurrence of GERD in individuals (16,404 people of European origin) with different levels of antibodies to *H. pylori* in the serum based on the IEU GWAS database (https://gwas.mrcieu.ac.uk/). The findings revealed that there was no association between the detection of antibodies to *H. pylori* antigens and the incidence of GERD. Another study was conducted on 219 patients with GERD, of whom 49.3% were diagnosed with *H. pylori* infection. The conclusion revealed that there was no significant association between the GERD course (peculiarities of clinical manifestations, the stage of reflux esophagitis) and *H. pylori*. A similar result was obtained in the study carried out in Boho Village, Sianjur Mulamula District, Sumatra Province. Despite the small sample size, the findings of this study are considered important due to its implementation in a unique geographical area[2]. Of the 100 participants involved in the study, GERD was diagnosed in 20% of the examined individuals, and 17% of them had positive *H. pylori* status in the fecal test, with no statistically significant association between *H. pylori* infection and GERD.

A descriptive study of 535 patients with GERD (375 men and 160 women; mean age 42.90±14.73 years) found different results. *H. pylori* was identified in 145 (27.1%) patients[3]. The authors found a strong correlation between the stage of reflux esophagitis and *H. pylori* infection (χ^2=25.180, p<0.001) and statistically significant differences in the average of GERDq score between patients with and without *H. pylori* infection (t =-4.503, p<0.001). This allowed the conclusion about an association between *H. pylori* infection and the GERD course. Also, in September 2023, meta-analysis results of the risk factors assessment of erosive GERD based on 114 studies with a total of 759,100 participants were presented[4]. Of the 29 factors analyzed, age ≥60 years [odds ratio (OR) 2.03 (1.81-2.28)], Caucasian race [OR 1.67 (1.40-1.99)], unmarried status [OR 1.08 (1.03-1.14)], duration of GERD ≥ 5 years [OR 1.27 (1.14-1.42)], obesity [OR 1.78 (1.61-1.98)], central obesity [OR 1, 29 (1.18-1.42)], diabetes mellitus [OR 1.24 (1.17-1.32)], arterial hypertension [OR 1.16 (1.09-1.23)], dyslipidemia [OR 1.15 (1.06-1.24)], hypertriglyceridemia [OR 1.42 (1.29-1.57)], esophageal diaphragmatic hernia [OR 4.07 (3.21-5.17)], and nonalcoholic fatty liver disease [OR 1.26 (1.18-1.34)] were significant factors. However, *H. pylori* infection [OR 0.56 (0.48-0.66)] and atrophic gastritis [OR 0.51 (0.31-0.86)] were associated with a decreased risk of erosive reflux esophagitis.

A meta-analysis of 6 studies conducted between 1988 and June 2023 demonstrated that *H. pylori* infection was associated with a lower risk of GERD (OR 0.68), Barrett's esophagus (OR 0.59), or esophageal adenocarcinoma (OR 0.54). However, infection was not associated with an increased risk of esophageal adenocarcinoma in patients with Barrett's esophagus [OR 0.91; 95% confidence interval (CI) 0.68-1.21][5].

Special attention should be paid to evaluating the effect of eradication therapy on the course of GERD. In a study of 340 patients (mean age: 66.9 ± 12.9 years) with a median follow-up of 55 months (interquartile range: 29.8-89.3), endoscopic images of the esophageal mucosa obtained before and after eradication therapy were evaluated. At initial endoscopic evaluation, 187 patients (55%) were found to have esophageal diaphragmatic hernia, and all patients had gastric atrophy. Reflux esophagitis was detected in 7 patients (2%) before eradication and in 21 patients (6%) after it, which represented a significant increase (p=0.007). Only 0.6% of patients had Barrett's esophagus elongation after eradication of the infection, suggesting that there was no significant effect of treatment on the development or elongation of Barrett's esophagus[6].

In the current year, the results of a study were published, and the authors assessed the risk of developing esophageal adenocarcinoma following *H. pylori* eradication. The population-based multinational cohort, named the Nordic *Helicobacter Pylori* Elimination Project (NordHePEP), comprised all adults (>18 years of age) who received *H. pylori* eradication therapy between 1995 and 2018 in any of the 5 Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) with follow-up throughout 2019. Among 661,987 participants who participated during 5,495,552 person-years after eradication (median follow-up period 7.8 years; range 1-24 years), 550 cases of esophageal adenocarcinoma occurred. The overall standardized incidence ratio (SIR) of esophageal adenocarcinoma was not increased (SIR 1/4 0.89; 95% CI 0.82-0.97). The SIR did not increase over time after eradication but rather decreased and was 0.73 (95% CI, 0.61-0.86) 11-24 years after treatment. No significant differences were found in the stratified analysis. The overall

SIR of esophageal squamous cell carcinoma, calculated for comparison, showed no association (SIR 1/4 0.99; 95% CI 0.89-1.11). The absence of an increased risk of esophageal adenocarcinoma after *H. pylori* eradication suggests that eradication is safe in terms of esophageal cancer risk[7].

The results of a systematic review comprising 15 studies with a higher prevalence of laryngopharyngeal reflux disease (LPRD) in *H. pylori*-positive patients compared to *H. pylori*-negative patients (OR 1.19; 95% CI 1.07-1.3; *p*=0.001) are also noteworthy in the context of this relationship. The authors emphasize the need for further well-designed studies to evaluate the efficacy of *H. pylori* eradication in LPRD treatment[8].

Eosinophilic Esophagitis

The incidence of eosinophilic esophagitis (EoE) is increasing in some regions of the world, and previous retrospective studies have found an inverse association of disease prevalence with *H. pylori* infection. A study conducted in Mexico comprised adult patients without previous *H. pylori* eradication. The prevalence of *H. pylori* in patients with EoE was significantly lower than in those of the control group: 36.8% *vs.* 70.4% (OR 0.21; 95% CI 0.08-0.69; *p*=0.001). The authors emphasize the necessity of further research on other factors (socioeconomic, cultural, microbiota, etc.) as assessment parameters to clarify this relationship[9].

The protective role of *H. pylori* infection in the development of EoE was also confirmed in a case-control study conducted at Bundang Hospital, Seoul National University[10]. 45 patients with EoE were included in the retrospective analysis, and for each patient, 2 healthy individuals from the control group of the same sex and age were randomly selected. 17 out of 90 individuals (18.9%) of the control group had *H. pylori* infection, whereas only 2 patients with EoE out of 45 (4.4%) had *H. pylori* infection. Thus, EoE was inversely associated with *H. pylori* infection (OR 0.20; 95% CI 0.04-0.91; *p*=0.044).

A two-step Mendelian randomization analysis with genome-wide association study (GWAS) datasets demonstrated a correlation between anti- *H. pylori* IgG antibody levels and a reduced risk of EoE (OR 0.325; 95% CI 0.165-0.643; *p*=0.004)[11]. No cause-and-effect relationship was found between other antibodies against *H. pylori* and EoE. However, the authors demonstrated that the protective effect of *H. pylori* infection against EoE appears to be unrelated to inflammatory factors (IL-4, IL-5, IL-13, IL-17, and IFN-γ) as previously thought. Thus, it was hypothesized that *H. pylori* infection induces the expression of IFN-γ and IL-17, stimulating Th1 and Th17 cells while suppressing Th2 cells associated with allergic reactions. EoE is known to belong to a group of diseases with a Th2 immune response, which manifests itself as an over-release of inflammatory cytokines, such as IL-4, IL-5, and IL-13. The authors conclude that alternative inflammatory factors or pathways may influence the causal relationship between *H. pylori* infection and EoE.

GASTRODUODENAL DISEASES

Chronic Gastritis

A landmark event in the study of gastric diseases was the publication of the main provisions of the international consensus on the study of gastritis in clinical practice – Real-World Gastritis Initiative (RE.GA.IN.)[12]. The RE.GA.IN. interdisciplinary consensus brought together recognized gastritis experts from five continents. After debates on the most controversial aspects, the RE.GA.IN. consensus summarized the existing scientific data to develop patient-centered, evidence-based guidelines to assist clinicians in their daily clinical practice.

The consensus results include 8 sections: definitions and classification of the gastritis spectrum, spectrum of gastritis caused by *H. pylori*, key issues in the diagnosis of *H. pylori*-associated gastritis, *H. pylori*-associated gastritis: clinical outcomes, autoimmune gastritis, rare forms of gastritis, gastritis, and gastric microbiota, epidemiology of gastritis and related pre-tumor and tumor changes.

Regarding this topic, it should be noted that *H. pylori* is still the leading known cause of chronic gastritis worldwide[13-16], although its prevalence is decreasing in many parts of the world, especially among the young population. Non-atrophic gastritis is a potentially reversible inflammatory disease with minimal risk of gastric cancer. Diagnosis of atrophic gastritis should include data from endoscopic, morphologic studies, and serologic analysis[17]. Both the phenotype and topography of

atrophic changes should be reported and classified according to validated endoscopic and morphologic staging systems. The OLGA and OLGIM staging systems can be used for predictive risk assessment of both intestinal and diffuse gastric cancers.

Factors associated with accelerated progression of gastritis include the strain of *H. pylori* causing the infection, certain host genetic predispositions, family members with gastric cancer, as well as unhealthy lifestyle and social habits. It is recommended that patients with endoscopic findings suggesting a high risk of cancer or OLGA/OLGIM stage III-IV and/or advanced incomplete intestinal metaplasia (IM) should be under dynamic follow-up with endoscopic/morphologic examination at intervals of once every 3 years or according to local guidelines. *H. pylori* eradication stops the progression of mucosal damage and improves gastric structure and function.

Experts also suggest that in a certain group of patients, *H. pylori* may trigger an autoimmune process leading to atrophy of the gastric body mucosa.

Whether *H. pylori* eradication can reverse gastric mucosal precancerous lesions, including atrophy and intestinal metaplasia, remains controversial. Several studies have evaluated the effect of *H. pylori* eradication on the regression of precancerous changes in the gastric mucosa.

A meta-analysis of 20 studies with a total of 5,242 participants demonstrated that *H. pylori* eradication can significantly improve morphological signs of atrophic gastritis (AG) and the severity of intestinal metaplasia at an early stage. For example, *H. pylori* eradication significantly reduced the gland atrophy index in the antral region by comparing weighted mean differences (WMD) (WMD -0.36; 95% CI -0.52, -0.19; $p<0.01$), the atrophy index in the body (WMD -0.35; 95% CI -0.52, -0.19; $p<0.01$), IM index in the antral region (WMD -0.16; 95% CI -0.26, -0.07; $p<0.01$) and IM index in the body (WMD -0.20; 95% CI -0.37, -0.04; $p=0.01$). *H. pylori* eradication significantly improved AG (WMD 2.96; 95% CI 1.70, 5.14; $p<0.01$) and IM (WMD 2.41; 95% CI 1.24, 4.70; $p<0.01$). The association remained significant even when analyzing subgroups based on study design, sites of lesions, regions of residence, and observation periods[18].

A meta-analysis of 15 placebo-controlled studies showed that *H. pylori* eradication could prevent the progression of precancerous gastric lesions (OR 0.87; 95% CI 0.81-0.94; $p<0.01$) and even reverse their development (OR 1.32; 95% CI 1.17-1.50; $p<0.01$). *H. pylori* eradication significantly prevented the progression of intestinal metaplasia compared to placebo or no treatment (OR 0.80; 95% CI 0.69-0.94; $p<0.01$). Moreover, *H. pylori* eradication also improved the course of chronic atrophic gastritis (OR 1.84; 95% CI 1.30-2.61; $p<0.01$) and the severity of intestinal metaplasia (OR 1.41; 95% CI 1.15-1.73; $p<0.01$). However, in terms of preventing dysplasia progression (OR 0.86; 95% CI 0.37-2.00) and reducing dysplasia severity (OR 0.89; 95% CI 0.47-1.70), *H. pylori* eradication had no advantage[19].

Chronic gastritis is traditionally known as a disease etiologically related to environmental factors within the concept of so-called “environmental gastritis”. The opposite of *H. pylori*-associated gastritis is autoimmune gastritis (AIG), which is an inflammatory process limited to the body of the stomach. Damage to the acid-producing glands over a period of decades leads to loss of the original glands in the oxyntic mucosa of body and fundus, while the antrum remains virtually unaffected by the inflammatory process. As the body mucosa is destroyed, hypo- and then achlorhydria develops, and intrinsic factor production suffers, leading to pernicious anemia. These changes are accompanied by endoscopically and morphologically noticeable phenomena – hyperplasia and neoplasia of enterochromaffin-like cells.

Traditionally, AIG has been regarded as a precancerous condition of the stomach since it was first described. However, virtually all studies reporting an increased risk of cancer associated with AIG were conducted either in the era before the discovery of *H. pylori* or involved patients in whom *H. pylori*-associated gastritis was not excluded before atrophy and spontaneous eradication. The existence of such special cohorts in ongoing studies seems inadequate to accurately assess the risk of gastric cancer (GC) associated with the immune-mediated mechanism of gastric mucosal atrophy underlying AIG. It appears that the risk of developing neuroendocrine neoplasia of the gastric mucosa is well documented and proven, including in studies, but the risk of developing AIG-associated gastric cancer remains uncertain.

Rugge et al[20] evaluated the dynamics of morphologic changes in the gastric mucosa and made a comparative assessment during an 18-year observation period in order to establish a reliable link between the so-called ‘pure AIG’ (when excluding even an occasional, latent *H. pylori* infection) and the risk of cancer development in the prospective long-term study, based on strict clinical, serologic, and histological criteria. Previous or current *H. pylori* infection was

excluded in all patients according to the results of serologic, histologic, and molecular-biologic tests, and all underwent at least two paired endoscopies with biopsies. The revealed peculiarities of the inflammatory process, limited to the acid-producing compartment of the gastric body, with the dominance of pseudopyloric over intestinal metaplasia, and fixation of the dynamics of neuroendocrine hyperplasia development reflected the peculiarities of AIG. However, compared to the general population, no early and significant precancerous changes in the gastric mucosa were detected, such as progression of atrophy in the antrum or the presence of focal dysplasia (intraepithelial neoplasia). The study attracted a lot of interest and provoked a discussion about the possibility of a paradigm shift regarding the pre-cancerous conditions of the gastric mucosa on the pages of the journal Gut[21-25].

The authors' viewpoint is gaining popularity that the increased risk of gastric cancer previously reported in patients with AIG may be the result of unrecognized *H. pylori* infection. It is the latter circumstance and non-absolute criteria of the early onset (debut) of AIG that require more reliable criteria for assessing this condition and determination of its natural (isolated and independent) and *H. pylori*-associated dynamics[25-27]. In particular, such a combined dynamics of atrophic changes in the gastric mucosa when *H. pylori*-associated gastritis is combined with AIG is reported as more probable for the development of panatrophic gastritis in the RE.GA.IN.[12].

In a population-based study in the Fujian Province, the gut microbiota was investigated by sequencing 16S rRNA gene in fecal samples of patients with chronic non-atrophic gastritis (CNAG) and chronic atrophic gastritis (CAG) according to the presence of *H. pylori* infection. The study comprised 176 patients, including 126 patients with negative *H. pylori* test results (*H. pylori* –) and 50 patients with positive results (*H. pylori* +) using C14 breath test and histopathologic criteria. When analyzing the 16S rRNA gene sequencing results, there were no notable in alpha diversity, but differences in beta diversity were obtained. Specifically, the number of *Hungatella* (p=0.0003), *Acidaminococcus* (p=0.0148), *Megasphaera* (p=0.0066), *Eggerthella* (p=0.0288), *Lactobacillus* (p=0.0202), *Blautia* (p=0.0490) and *Lachnoclostridium* (p=0.0304) was much higher in patients with the *H. pylori* (–) compared to those with *H. pylori* (+) among patients with CNAG. The number of *Bilophila* (p=0.0089), *Bifidobacterium* (p=0.0371), *Blautia* (p=0.0040), *Erysipelotrichaceae_UCG_003* (p=0.0215), *Bacteroides* (p=0.0304), *Lachnospira* (p=0.0082), *Lachnospiraceae_UCG_003* (p=0.0281), *Eubacterium_eligens_group* (p=0.0077) and *Lachnospiraceae_UCG_010* (p=0.0293) was much higher in patients with the *H. pylori* (–) compared to those with *H. pylori* (+) among patients with CAG. The authors concluded that several genera of intestinal bacteria could potentially serve as diagnostic markers of the progression of *H. pylori*-associated chronic gastritis up to atrophy[28].

Peptic Ulcer Disease

In 2024, the recommendations under the title "*Helicobacter pylori* and gastroduodenal ulcer disease" by the German Society of Gastroenterology were published[29]. The document states that the prevalence of infection among adults is decreasing. However, *H. pylori* continues to be one of the most common causes of peptic ulcer disease today. This underscores the importance of adhering to principles of effective diagnosis and utilizing the most efficient eradication therapy regimens, taking into account regional data and individual testing for bacterial susceptibility to treatment components. Eradication therapy is superior to other treatment methods for *H. pylori*-positive duodenal ulcers, but this has not been demonstrated for H. pylori-positive gastric ulcers. Compared to no treatment, eradication therapy effectively prevents recurrences of gastric and duodenal ulcers. In the presence of a gastric ulcer, a follow-up endoscopy with biopsy is necessary after 4-8 weeks to confirm ulcer healing and to take additional biopsies to rule out malignancy in case of incomplete healing. Monitoring of duodenal ulcers is still not recommended, but it may be considered in certain complicated cases of duodenal ulcers.

In a multicenter study in Korea, changing trends in the structure of peptic ulcer disease (PUD) were evaluated based on age and etiology from 2010 to 2019. A total of 26,785 patients from 7 databases were included, with the proportion of elderly individuals (≥ 65 years) accounting for 38.8%. Of the 19,601 patients, 41.8% had *H. pylori*-associated PUD, 36.1% had drug-induced PUD, and 22.1% had idiopathic PUD. Trends toward a decrease in the prevalence of *H. pylori*-associated PUD were demonstrated alongside an increase in drug-induced PUD. The prevalence of idiopathic

PUD showed an increasing trend in the elderly group (p=0.01). The authors concluded that further research is necessary to investigate the mechanisms of the influence of ulcerogenic drugs in the context of the ongoing population of aging[30].

In May 2023, the results of a retrospective analysis assessing the risk of gastroduodenal bleeding associated with anticoagulant use were published. The risk was found to be significantly higher with warfarin than with direct oral anticoagulants (DOACs). The study comprises 1,120 patients taking warfarin and 1,651 patients taking DOACs. The authors convincingly demonstrated that lower risks were observed among women who had no history of upper gastrointestinal bleeding, peptic ulcers, or ischemic heart disease, as well as those who did not take acid-suppressing medications or aspirin. Secondary analysis did not reveal a significant difference in the risk of upper gastrointestinal bleeding between those who underwent eradication and *H. pylori*-negative patients taking warfarin (OR 0.63; 95% CI 0.33-1.19) or DOAC (OR 1.37; 95% CI 0.45-4.22) for the first time[31].

A retrospective study, including 306 patients with *H. pylori*-associated peptic ulcer disease, presented data on primary treatment outcomes, including *H. pylori* eradication and ulcer healing, and analysis of factors influencing treatment outcomes. It was demonstrated that the sequence of *H. pylori* eradication and ulcer treatment did not significantly affect the results of infection eradication and ulcer scarring. In addition, patient age, type of peptic ulcer disease, type of clinic, and treatment regimen (including choice of proton pump inhibitor) did not significantly affect *H. pylori* eradication. However, patient gender and choice of antibiotic combination were key factors, as eradication rates were lower in female patients compared to males, and the combination of levofloxacin and clarithromycin was the least effective in *H. pylori* eradication. With regard to the treatment of peptic ulcers, gastric ulcers have been found to be more likely to be completely cured than duodenal ulcers[32].

H. Pylori and Dyspepsia

According to modern concepts, *H. pylori* obligatorily leads to the formation of chronic gastritis, which in some patients is accompanied by dyspepsia syndrome[12]. In patients without alarm symptoms, infection is diagnosed using non-invasive methods. If the test result is positive for *H. pylori*, the patient should receive eradication therapy. Dyspepsia associated with *H. pylori* should be considered in case of persistent relief of dyspepsia symptoms after eradication of *H. pylori* with a follow-up period of at least 6 months. Patients with dyspepsia and *H. pylori*-positive gastritis should be considered to have functional dyspepsia (FD) if symptoms persist 6 to 12 months after *H. pylori* eradication. Patients with dyspepsia and *H. pylori*-negative gastritis should be considered to have FD[33].

At the same time, the leading structural changes associated with FD are recognized as low-degree inflammation in the duodenal mucosa due to infiltration by eosinophils and mast cells. A multicenter cross-sectional study was conducted to evaluate the association between variants of the nucleotide-binding domain of oligomerization 1 NOD1-796G>A and interleukin-1 beta IL-1B-511C>T genes and low-grade duodenal eosinophilia[34]. A total of 253 patients who met the Rome-IV criteria were selected before upper endoscopy, and 98 patients with *H. pylori*-related dyspepsia (HpD) were included after minimal (unremarkable) gastric mucosal changes on endoscopy and positive *H. pylori* in biopsies were assessed. 64 (65%) patients had epigastric pain syndrome (EPS), 24 (25%) had postprandial distress syndrome (PDS), and 10 (10%) had EPS/PDS intersect. FD subtypes were not associated with NOD1-796G>A or IL-1B-511C>T gene variants. Low-grade duodenal eosinophilia was significantly increased in NOD1-796 GG compared to the single A allele, but not in the single T allele or the CC allele of IL-1B-511. This association is dependent on CagA infection, as the presence of CagA strain was significantly associated with low-grade duodenal eosinophilia with isolated NOD1-796 GG variants and IL-1B-511 single T-allele, but not without CagA. After a combined polymorphism analysis with a single T allele of NOD1-796 GG/IL-1B-511, a synergistic effect on low-grade duodenal eosinophilia was found between these two loci, regardless of CagA strain status with HpD.

The pathogenesis of functional dyspepsia is multifactorial, and in our view, the consideration of the association between dyspeptic symptoms and *H. pylori*, including the period after eradication, is of interest. Tseng et al[35] provided compelling evidence of neuronal damage during *H. pylori* infection. Among these findings, MMP-9 showed a significant correlation with neuroinflammation and

was found to be highly expressed in macrophages. MMP-9 shows immunoreactivity that provokes macrophage-mediated neuronal apoptosis. These results open a new target point for preventing excessive neuroinflammation during *H. pylori* infection, which may be a major cause of persistent dyspeptic symptoms even after *H. pylori* eradication[35].

The incidence and patterns of gastric mucosal structural changes were studied in individuals with dyspepsia syndrome in a population-based study conducted in Esthammar, Sweden. In 2011, randomly selected adults completed a validated Abdominal Symptom Questionnaire (ASQ) (n=1,175). Patients under 80, who were eligible to participate in the study, were invited to undergo esophagogastroduodenoscopy (EGDS) (n=947); 402 individuals agreed, and 368 individuals underwent EGDS with biopsy of the antral and gastric body with serological testing for *H. pylori* (mean age – 54.1 years, 20-79 year-olds; 47.8% men). 40.2% had gastritis (148/368; 95% CI 35.2-45.2%). The most frequent histologic subtype was reactive (68/148; 45.9%), followed by *H. pylori* (44/148; 29.7%), chronic non- *H. pylori* (29/148; 19.6%), and autoimmune (4/148; 2.7%). Gastritis was significantly associated with older age and *H. pylori* status ($p<0.01$). Participants with gastritis were divided into three groups according to histologic categories: chronic inactive inflammation, AIG, and active inflammation. An important finding in this study is that there are no differences in clinical symptomatology with functional pathology (no signs of gastritis) and with histologic signs of gastritis[36].

In a study involving 138 patients with dyspeptic symptoms, an evaluation of changes in the gastric and duodenal mucosa was conducted. Each patient underwent histological and/or microbiological examination of ten biopsy samples (2 from the body, 3 from the antrum, 3 from the proximal duodenum, and 2 from the distal duodenum). Chronic gastritis (in the body and antrum) and duodenitis (proximal and distal) were significantly associated with the *H. pylori* infection. The patients with ulcers had a distinct pattern of gastro-duodenal inflammation compared to those without ulcers. Also, the patients with ulcers were characterized by a higher incidence of non-atrophic chronic gastritis in the body, chronic atrophic gastritis in the antrum, and a very high incidence of proximal duodenitis[37].

Bariatric Surgery

The impact of *H. pylori* on postoperative outcomes after sleeve gastrectomy remains controversial. A systematic review and meta-analysis of 13 studies involving 6,199 patients found that *H. pylori* infection correlates with a higher risk of overall postoperative complications (OR 1.56; 95% CI 1.13, 2.16; $p=0.007$), which emphasizes the need for prospective randomized research to evaluate the effect of preoperative screening and *H. pylori* eradication[38].

In contrast, a more recent meta-analysis of 8 retrospective comparative studies involving a total of 4,877 participants did not reveal statistically significant differences between *H. pylori*-positive and *H. pylori*-negative groups of patients who underwent sleeve gastrectomy in terms of overall complication rates (OR 1.46; 95% CI 0.95-2.23; $p=0.08$), including the risk of bleeding (OR 1.35; 95% CI 0.70-2.60; $p=0.38$)[39].

However, according to a survey of bariatric surgery experts (110 invited experts from 41 countries), most of them prescribe acid suppressants in the postoperative period after metabolic and bariatric surgery (MBS). Lifetime proton pump inhibitor prophylaxis is recommended by most experts for smokers who have discontinued non-steroidal anti-inflammatory drugs following any type of gastric bypass surgery. Two-thirds of experts (69%) perform *H. pylori* eradication prior to MBS. Two-thirds of experts (68%) regularly perform EGDS and biopsy before MBS. This expert survey emphasizes important perioperative interventions, which reached a consensus among two-thirds of international MBS experts. The variability in follow-up EGDS findings, complications treatment approaches, and threshold values for revision and conversion MBS highlights the need for further research and agreed recommendations[40].

In a retrospective cohort study conducted in Iran, the effectiveness of weight loss following Roux-en-Y gastric bypass (RYGB) over a 5-year observation period was compared between *H. pylori*-negative (HP-) patients and those who underwent eradication therapy (HPe). A total of 305 morbidly obese patients who underwent RYGB between February 2014 and November 2017 were included in the study. Among them, 27.2% were *H. pylori*-positive and received eradication therapy before surgery. Analysis of the results revealed no significant differences between HP- and HPe

patients in terms of total weight loss percentage 12-60 months later after RYGB. The excess weight loss percentage was higher in HPe patients compared to HP- patients 12 months later after RYGB (p=0.04); however, this difference did not exist after 36-60 months[41].

CONCLUSIONS

A landmark event of 2024 was the publication of the RE.GA.IN. consensus, which synthesized data from leading scientific studies for real clinical practice. Key provisions of the consensus address both *H. pylori* associated gastritis, highlighting the potential for reducing structural changes during *H. pylori* eradication, and other types of gastritis. Of particular interest is the ongoing debate regarding the absence of gastric cancer risk in cases of "pure" autoimmune gastritis, necessitating evaluation of both current *H. pylori* status and previous infection.

Well-known postulates about the association of *H. pylori* infection with peptic ulcer disease and dyspepsia also saw further development in the literature of the last year, exploring increased contributions of other etiological factors in gastrointestinal ulceration and mechanisms underlying dyspeptic symptoms.

Several studies have aimed to investigate the risk and course of GERD in the context of *H. pylori* infection and eradication, yielding conflicting results ranging from no effect to aggravation of GERD course. Nonetheless, compelling evidence exists regarding the absence of additional risk for esophageal adenocarcinoma following infection eradication.

Finally, the unification of screening approaches and the rationale for *H. pylori* eradication in individuals undergoing bariatric surgeries are deemed highly promising and crucial from a practical standpoint.

Conflict of Interest

The authors declare no conflicts of interest.

Ethics Statement

Not applicable due to the type of study.

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Authors' Contributions

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AI Statement

No artificial intelligence has been used for this article.

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