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REVIEW – *HELICOBACTER PYLORI:* AND EXTRAGASTRIC DISEASES

M. Gesualdo[1,2], S. Fagoonee[3], G.M. Saracco[1,2], R. Pellicano[1]

[1]Unit of Gastroenterology, Città della Salute e della Scienza-Molinette Hospital, Turin, Italy
[2]Chair of Gastroenterology, Department of Medical Sciences, University of Turin, Turin, Italy
[3]Institute of Biostructure and Bioimaging, National Research Council, Molecular Biotechnology Center, Turin, Italy

Corresponding Author: Rinaldo Pellicano; MD; email: rinaldo_pellican@hotmail.com

Abstract: The relationship between *Helicobacter pylori* infection and many extragastroduodenal manifestations remains a fascinating topic of investigation. Since the stomach is a large organ containing a potentially high bacterial load, *H. pylori* infection might elicit a spectrum of pathologic consequences beyond the gastroduodenal tract through either inflammatory mediator released into circulation or the host immune response. Currently, although for several proposed associations the potential pathogenic mechanism remains unclear, a bacterial involvement cannot be excluded. In the intestinal tract, an interaction between *H. pylori* and microbiota, with protective or aggressive outcome, could explain the features of several diseases. Inflammatory bowel disease (IBD), that comprises Crohn's disease and ulcerative colitis, originates from a dysregulation of the host's immune response to commensal bacteria in individuals with genetic predisposition. The reduction of biodiversity and other specific imbalances in the fecal microbiota composition of IBD patients compared to that of healthy controls support this hypothesis. In such a scenario, an inverse correlation between *H. pylori* infection and IBD prevalence has been confirmed worldwide. Growing interest in a potential role of *H. pylori* arises from studies investigating metabolic syndrome, a condition involved in the pathogenesis of cardiovascular diseases. Other reported fields of investigation are hepatology, with a particular focus on non-alcoholic fatty liver disease; neurology, including Parkinson's disease and Alzheimer's disease; and hematology as well as dermatology. The present narrative review highlights the main associations between *H. pylori* and extragastroduodenal manifestations published during the past year.

Keywords: *Helicobacter pylori*, IBD, IBS, Metabolic disorders, Cardiovascular disorders, Skin diseases.

INTRODUCTION

Since the early 1990s, when the first potential associations between *Helicobacter pylori* infection and extragastroduodenal manifestations were reported, a large number of studies have been carried out to investigate this topic[1]. While for some of these associations a causal role has been confirmed, for others the association remains inconclusive due to epidemiological limitations of the studies and multifactorial etiology of the investigated diseases.

In this review, we analyzed the main and well-designed studies including adults, on the relationship between *H. pylori* infection and extragastroduodenal manifestations, published between April 2020 and March 2021. A literature search was performed in the PubMed database. The keyword used was "*Helicobacter pylori*".

EXTRAGASTRODUODENAL DISORDERS OF THE GASTROINTESTINAL TRACT

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is one of the gastrointestinal (GI) functional disorders, along with dyspepsia. Since *H. pylori* plays a key role in functional dyspepsia[2], it might be involved in IBS too. Recently, Liang et al[3] conducted a nationwide population-based retrospective study in Taiwan, comparing subjects with *H. pylori* infection to uninfected individuals. The cumulative incidence risk of IBS was higher in the *H. pylori* group compared to controls; the overall hazard ratio (HR) was 3.1 (95% confidence interval [CI]: 1.9-4.9, $p<0.001$). Furthermore, those who received eradication therapy had a lower risk of IBS than untreated subjects. A meta-analysis based on controlled trials[4] showed that *H. pylori* eradication significantly improved the remission rate of IBS patients. Nevertheless, Li et al[5], in a systematic review with meta-analysis, including eight studies with a total of 1,861 patients, found that the *H. pylori* infection rate was not significantly different between IBS cases (53.8%) and controls (41.7%).

Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBD), that include ulcerative colitis (UC) and Crohn's disease (CD), are chronic GI disorders with unclear pathogenesis. An inverse association between IBD and *H. pylori* has been reported, supporting the hypothesis of a protective role of this bacterium[6]. A recent meta-analysis[7], comparing the prevalence of *H. pylori* infection in patients with IBD and in healthy controls, found a pooled relative risk (RR) of <1, and in the subgroup analysis, the RR was 28% greater for UC than CD. Ding et al[8], in a Chinese case-control study, reported a significantly lower prevalence of *H. pylori* infection in IBD patients (9.6%) than in healthy subjects (29.8%), with no difference between patients treated with previous medications versus naïve ones.

HEPATOBILIARY DISEASES

Zhao et al[9] assessed the association between *H. pylori* infection and liver damage in 60 patients with hepatitis B virus (HBV) cirrhosis. The levels of HBV DNA and transaminases were higher in patients with *H. pylori* infection than in uninfected subjects. Furthermore, inflammatory factors and the mRNA levels of retinoic acid receptor-related orphan receptor gamma-t (ROR γt) and fork- head box P3 (FoxP3) in liver and serum samples were higher in patients with *H. pylori* compared to others; overall, this condition was associated with more severe hepatic damage.

Abid et al[10], in a case-control study, assessed the impact of *H. pylori* eradication and small intestine bacterial overgrowth (SIBO) treatment on minimal hepatic encephalopathy (MHE). *H. pylori* eradication did not improve MHE while the resolution of SIBO induced a significant amelioration of MHE.

In recent years, non-alcoholic fatty liver disease (NAFLD) has become the most important cause of cirrhosis. In a Chinese retrospective study[11], the authors found a positive correlation between *H. pylori* infection and NAFLD and its severity; in particular, male and younger NAFLD patients were more likely to have an *H. pylori* infection compared to others. In a Guatemalan cross-sectional study[12], no overall association was found, but some bacterial antigens (VacA, CagA and *Helicobacter hepaticus* antigen HH0713) were correlated to NAFLD.

In a systematic review with meta-analysis[13], the authors found a positive correlation between the gallbladder and *H. pylori* infection, concerning both chronic cholecystitis and cholelithiasis (OR: 3.05, 95%CI: 1.81-5.14). Makkar et al[14], in a case-control study, observed a correlation between more virulent strains (CagA positive) and the risk of biliary tract cancer, but the results were not statistically significant after correction for multiple comparisons.

NEUROLOGICAL DISORDERS

Multiple sclerosis is a chronic disorder with unclear physiopathology. On the basis of immunological mechanisms induced by *H. pylori*, the potential role of this bacterium has been investigated. In contrast with previously published data, an endoscopic-based study[15] showed that *H. pylori* infection rate was significantly higher in multiple sclerosis patients versus controls (p=0.002). Hence, the authors hypothesized that molecular mimicry, caused by *H. pylori*, could induce a cross reaction with ganglioside surface components.

Guillain-Barré syndrome (GBS) is an autoimmune disorder arising after an infectious episode, the main causal agent being *Campylobacter jejuni*. Dardiotis et al[16] performed a meta-analysis and found a higher positivity to IgG antibodies for *H. pylori* in GBS patients compared to controls, both in serum (OR: 2.31, 95%CI: 1.30-4.11) and in cerebrospinal fluid (OR: 42.45, 95%CI: 9.66-186.56).

Beydoun et al[17] assessed the relationship between Alzheimer's disease (AD), *H. pylori* seropositivity, periodontal disease and periodontal infections. The authors found that 55% of the patients were *H. pylori* positive, and selected periodontal pathogens titers, factors and clusters interacted synergistically with *H. pylori* seropositivity to increase the risk of AD and all-cause dementia. Doulberis et al[18], in a systematic review, highlighted that the changes in the GI microbiota, including *H. pylori*, as a component of the "gut-brain axis", might be involved in the physiopathology of AD.

CARDIOVASCULAR AND CEREBROVASCULAR DISEASES

Considering the global impact of cardiovascular and cerebrovascular diseases, intensive research has been carried out on the possible role of *H. pylori* infection in this particular pathogenesis.

In a cross-sectional Chinese study[19], the authors included 17,100 participants and observed that the prevalence of hypertension was higher in subjects positive for *H. pylori* infection, with an OR: 1.117 (95%CI: 1.029-1.213, p=0.008).

In an Iranian systemic review and meta-analysis[20], based on 145 serological and molecular studies involving patients with coronary artery disease, *H. pylori* prevalence was higher in the case of serological tests (OR: 63.3%, 95%CI: 60-66.5) and lower in the case of molecular tests (OR: 12.8%, 95%CI: 4-22). In a multicenter Swedish study[21], including 310 patients with acute myocardial infarction (AMI), the overall prevalence of *H. pylori* infection was 20% (95%CI: 15.5-24.7); interestingly, *H. pylori* was more common in patients with ST-elevation MI (STEMI) than in those with the non-STEMI type (26% and 15%, respectively). Wang et al[22], in a meta-analysis including case-control and cohort studies, found that *H. pylori* infection significantly increased the risk of cardiovascular events, especially MI (OR: 1.80, 95%CI: 1.42-2.26).

In another meta-analysis[23], including 40 studies with a total of 273,135 patients, the authors showed that both anti-CagA antibody and urea breath test (UBT) positivity were associated with increased risk of stroke with an OR: 1.77 (95%CI: 1.25-2.49) and OR: 2.21 (95%CI: 1.33-3.66), respectively.

RESPIRATORY TRACT DISEASES

A Chinese observational study[24] found *H. pylori* infection in 61.2% of patients with a chronic cough versus 43.9% in the control group and, following bacterial eradication, 65.5% of the former group improved. Hence, the authors proposed that *H. pylori* could be a target in patients with a chronic unexplained cough.

In a retrospective Korean study[25], comparing patients with chronic obstructive pulmonary disease versus those without, no association was found between *H. pylori* infection and lung dysfunction.

HEMATOLOGICAL DISEASES

The correlation between immune thrombocytopenic purpura (ITP) and *H. pylori* infection has been supported by the Maastricht V/Florence Consensus Report[26]. Nevertheless, an international survey[27], assessing how hematologists approached the relationship between *H. pylori* infection and ITP, found that among those who completed the questionnaire, only 29% tested patients systematically for *H. pylori* infection.

Lee et al[28], in an analysis of the upside of eradication therapy in patients with ITP, reported that after *H. pylori* eradication, patients had a 2.78-fold increase in platelet count compared to baseline (p=0.016).

METABOLIC DISEASES

In the past year, several authors searched for a link between *H. pylori* infection and metabolic syndrome (MS), which includes dyslipidemia, hypertension, hyperglycemia and obesity.

Watanabe et al[29], in an analysis of the changes in lipid levels in patients who underwent *H. pylori* eradication, reported that high-density lipoprotein (HDL)-cholesterol levels were higher in cured patients compared to those with ongoing infection. Accordingly, Fallah et al[30] highlighted that patients with *H. pylori* infection not only had lower HDL-cholesterol levels, but they also had an impaired cholesterol efflux capacity. A Korean prospective cohort study[31], including 2,626 adults, confirmed the benefit of *H. pylori* eradication on dyslipidemia. Eradication therapy reduced the risk of incident dyslipidemia compared to persistent infection (HR: 0.85, 95%CI: 0.77-0.95, p=0.0004). In another Korean study[32] including 1,065 patients, total cholesterol levels in males and HDL in females were associated with *H. pylori* infection. Shimamoto et al[33], in a meta-analysis, confirmed that *H. pylori* had a negative influence on HDL levels and a positive correlation with low-density lipoprotein (LDL) and total cholesterol levels.

A case-control study carried out in China[34] found a positive link between obesity and *H. pylori* infection (OR: 1.07, 95%CI: 1.036-1.11).

In a community-based population study, conducted in a rural community of Bangladesh[35], *H. pylori* was found in 54.5% out of 767 subjects, with no relationship between *H. pylori* and MS. In a cross-sectional study, performed in an Ethiopian Hospital[36], *H. pylori*-positive patients had higher levels of total and LDL cholesterol compared to *H. pylori*-negative patients. Among 320 pregnant Chinese women, *H. pylori* was found to increase the risk of preeclampsia and gestational diabetes mellitus (DM)[37].

Diabetes Mellitus

Peng et al[38] reported that *H. pylori* infection induced alterations in glucose regulation in mice models. This event was associated with gut dysbiosis, with *H. pylori* being a possible causal agent. In a Chinese study[39], including patients with DM, arterial stiffness was lower in patients without *H. pylori* infection than in infected patients. In a systematic review with meta-analysis, Song et al[40] found that *H. pylori* eradication failure was higher in patients with type 2 DM compared to non-diabetics (OR: 2.59, 95%CI: 1.82-3.7). Nevertheless, eradication therapy improved glycemic control. Accordingly, in a Brazilian study[41], glycated hemoglobin levels (GHL) were higher in patients with *H. pylori*, but this association was also dependent on the activity of chronic gastritis and the degree of inflammation. In a retrospective Korean cohort study[42], 66,706 patients with type 2 DM were divided into two groups: those treated for *H. pylori* and those untreated. Antibiotic treatment was associated with a risk of overall mortality (HR: 0.74, 95%CI: 0.59-0.93, p=0.011). In an Iranian case-control study[43], including 302 healthy controls and 150 patients with *H. pylori* infection, a significant association among glycemic index, glycemic load and glycemic consumption, and *H. pylori* infection was found. A meta-analysis[44] including studies assessing the prevalence of *H. pylori* infection in diabetic patients reported a pooled prevalence of 54% (95%CI: 44-64). A study performed in Cameroon, enrolling dyspeptic patients with and without type 2 DM[45], showed a statistically significant *H. pylori* prevalence

in diabetics compared to non-diabetics (OR: 1.472, $p=0.02$); moreover, a body mass index (BMI) ≥25 kg/m^2, in combination with *H. pylori* infection, strongly favored the onset of DM. On the other hand, these findings were not confirmed in a cross-sectional study[46]. In fact, no correlation between *H. pylori* infection and DM (OR: 1.02; 95%CI: 0.88-1.18) was observed.

BONE DISEASES

Shafrir et al[47] reported that vitamin D levels were inversely associated with both *H. pylori* prevalence and successful eradication therapy.

In a cross-sectional Chinese study, *H. pylori*, BMI and homocysteine were associated with osteoporosis in premenopausal females[48], reinforcing the hypothesis that chronic inflammation due to *H. pylori* can induce bone damage. In a prospective study, Gennari et al[49] found that *H. pylori* infection, in particular with the more pathogenic strains, was a potential risk factor for osteoporosis. In a cohort of 1,149 adults followed up for eleven years, those infected by CagA-positive strains had a higher probability to have fractures (HR: 5.27, 95%CI: 2.23-12.63, $p<0.0001$). In a Korean cohort study[50] including 10,482 women, those with *H. pylori* infection had a higher risk of osteoporosis compared to those *H. pylori* negative (HR: 1.23, 95%CI: 1.03-1.45).

SKIN DISEASES

Chronic urticaria (CU) is a common skin disease characterized by erythematous lesions and angioedema, with unclear physiopathology. Guo et al[51], in a retrospective study including 522 patients with CU, reported that those with CU and *H. pylori* infection had clinical relief and a reduced rate of CU recurrence after bacterial eradication. In a randomized double-blind study performed in Egypt[52], 27 out of 72 patients with CU had an *H. pylori* stool antigen positivity. Patients with *H. pylori* infection were randomly assigned to receive eradication therapy or placebo. Those being actively treated showed more clinical benefit of CU compared to the placebo group. In a tertiary hospital in Tanzania[53], patients with CU had a significantly high rate of *H. pylori* infection compared to controls (OR: 5.5, 95%CI: 1.2-24.8, $p=0.02$). In a retrospective Taiwanese cohort study[54], including 23,802 patients with peptic ulcer disease (PUD) and 23,802 controls, the authors found that the risk of CU was related to PUD, independently of *H. pylori* infection, compared to controls, the HR was 1.45 (95%CI: 1.19-1.79) for patients with both PUD and *H. pylori* and 1.34 (95%CI: 1.09-1.64) for patients with only PUD.

In a Saudi study, Ahmed et al[55] reported that psoriatic patients treated for *H. pylori* infection had a significant reduction in the psoriasis area and severity index, compared to untreated patients. Wu et al[56], analyzing the National Health insurance Research Database in Taiwan, found no correlation between *H. pylori* and the risk of psoriasis (HR: 1.081, 95%CI: 0.9-1.28).

In an Egyptian cross-sectional study[57], including 100 patients with acne vulgaris (AV) and 100 healthy controls, those with severe AV presented higher levels of fecal *H. pylori* antigen compared to patients with a mild or moderate form of AV or healthy controls ($p<0.001$).

NON-GASTRIC CANCER

Several studies[58,59] reported an association between *H. pylori* infection and colorectal cancer (CRC)[5]. In a Sudanese cross-sectional study[59], the presence of *H. pylori* was detected in the colonic samples of 16 participants, 13 of whom with adenocarcinoma. The correlation between *H. pylori* infection and CRC was significant ($p=0.028$). In a Chinese study[60], 3,872 patients with CRC and 2,362 with normal colonic mucosa were compared by UBT as well as biopsies taken during gastroscopy. Patients with *H. pylori*-related atrophic gastritis had a higher risk of CRC (OR: 3.46, 95%CI: 2.63-4.55, $p<0.01$). Butt et al[61], in a prospective multicenter European study, found that 51% of CRC patients had an *H. pylori* seropositivity compared to 44% in the control group (OR: 1.36, 95%CI: 1.00-1.85). A positive link between *H. pylori* and CRC emerged in a meta-analysis performed by Zuo et al[58]. Forty-seven studies, with a total of 17,416 patients

with CRC and 55,811 healthy controls were included. Although the overall OR for the first group was 1.70 (95%CI: 1.64-1.76), the heterogeneity between the studies was high. In another Chinese study[62], the authors found no correlation between *H. pylori* infection and the risk of CRC after analyzing serology of 428 patients with CRC and 207 healthy controls.

In a Taiwanese study[63], 109,360 patients with PUD were compared with 218,720 controls. The cumulative risk of laryngeal cancer in cases with PUD was 2.27 (95%CI: 1.16-4.44), and *H. pylori* eradication may play a role in the prevention of this subtype of cancer. These data were confirmed in a Croatian prospective study[64] including 26 patients with chronic laryngitis and 51 patients with laryngeal cancer. The authors found that chronic gastritis and *H. pylori* were risks for laryngeal carcinoma.

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Conflict of interest

The authors declare to have no conflict of interests.

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