

# REVIEW: *HELICOBACTER PYLORI* AND EXTRAGASTRIC DISEASES

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**Abstract** – The role of *Helicobacter pylori* infection in the development of extra-gastric disorders has been largely investigated in recent years, and some interesting insights have come up in the last year. *H. pylori* was associated with hypertension, atherosclerosis, and major cardiovascular events, with a specifically increased risk for virulent strains. The same strong association cannot be found with strict metabolic disorders. Inversely, a clearly negative association between *H. pylori* and other extra-gastric digestive disorders, including inflammatory bowel disease, coeliac disease, or Barrett’s esophagus was shown. *H. pylori* was found to be more prevalent in patients with chronic urticaria, suggesting that this phenomenon can be triggered by the infection-related inflammation. Another mechanism, that is the reduction of drug absorption, may be the biological reason for the negative association between *H. pylori* and Parkinson’s disease outcomes.

**Keywords:** *Helicobacter pylori*, Atherosclerosis, Non-alcoholic-fatty liver disease, Diabetes, Urticaria, Parkinson’s disease.

## INTRODUCTION

The extra-gastric manifestations of *Helicobacter pylori* infection represent one of the most intriguing topics of this field. In an expanded view, *H. pylori*-related extradigestive disorders are the clinical corollary of the biological potential of bacteria to influence human health beyond the gut.

In this review article, we aim to paint the landscape of the most relevant studies published on extra-gastric manifestations of *H. pylori* infection during the last year, which focused on cardiovascular and metabolic disorders, intestinal disorders, and miscellaneous diseases.

## CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVD) represent a burdensome issue for healthcare systems and are the first cause of death in Europe<sup>1</sup>. An established body of evidence supports the association between *H. pylori* infection and different CVD, including coronary heart disease (CHD), hypertension, atherosclerosis and stroke has been even consolidated by several articles published in the last years.



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## Coronary Heart Disease

According to a Swedish cohort study of 310 patients with acute myocardial infarction, *H. pylori* was detected in 20% of subjects, and its presence was more common in those with ST-elevation myocardial infarction (STEMI) rather than in those with non-STEMI (26% vs. 15%;  $p = 0.02$ )<sup>2</sup>.

Moreover, a recent meta-analysis shows a positive correlation between the presence of IgG antibodies against *H. pylori* and the risk of CHD (OR, 1.58; 95% CI: 1.34–1.87)<sup>3</sup>.

## Hypertension

Hypertension is one of the most relevant risk factors for CVD, such as ischaemic heart disease or stroke, and in 2015 it caused almost 8.5 million deaths<sup>4</sup>.

*H. pylori* may increase the risk of hypertension through various pathways, including the activation of inflammasomes and the impairment of the endothelial barrier and functions<sup>5</sup>.

In a meta-analysis of six high-quality studies involving a total of 11,317 hypertensive patients and 12,765 controls, *H. pylori* was significantly associated with hypertension in populations from both Asia and developing countries, as assessed by a random effect model (OR 1.34, 95% CI: 1.10–1.63,  $p = 0.002$ )<sup>6</sup>. This finding was also confirmed in another meta-analysis of several cross-sectional and case-control studies from 1996 to 2019 (OR 2.07; 95% CI 1.46–2.94,  $p \leq 0.001$ )<sup>6</sup>.

Moreover, recent data from an Italian cohort of 7,152 patients showed that long-lasting *H. pylori* infection was associated with a slight increase in the risk for hypertension (OR 1.17, 95% CI 1.02–1.35)<sup>7</sup>.

## Atherosclerosis

Chronic *H. pylori* infection can promote the development of atherosclerosis through the ability to recruit pro-inflammatory cytokines and to damage the endothelium<sup>8</sup>.

In a meta-analysis of 18 studies, Wang et al<sup>9</sup> found a robust correlation (Begg test  $p=0.300$ , Egger test  $p = 0.083$ ), between *H. pylori* infection and carotid atherosclerosis, especially in the female population<sup>9</sup>. This finding was confirmed in another meta-analysis<sup>10</sup> that showed an increased risk in patients under 60 years of age ( $p \leq 0.001$ ) and in those without other cardiovascular risk factors ( $p \leq 0.001$ ).

In another meta-analysis of 13 studies and 2,298 patients, *H. pylori* infection was significantly associated with larger overall carotid intima-media thickness (weighted mean difference: 0.07 mm; 95% CI: 0.02–0.12;  $p = 0.004$ ;  $I^2=91.1\%$ ;  $p \leq 0.001$ )<sup>11</sup>.

Overall, these data suggest that *H. pylori* may promote indirectly major cardiovascular events, especially in younger and healthier populations, and with a specific risk for virulent strains.

## Stroke

Stroke is currently the second most frequent cause of death worldwide<sup>12</sup>. In a cohort study of 273,135 patients, IgG antibodies for *H. pylori* or positive C13 urea breath test were associated with the development of stroke (OR 1.43; 95% CI: 1.25–1.64 and OR 2.209; 95% CI: 1.33–3.66, respectively)<sup>13</sup>.

The association of *H. pylori* and specific stroke aetiologies was also confirmed in this study, as *H. pylori* was associated with atherothrombotic stroke (OR 1.97; 95% CI: 1.46–2.67) and with stroke caused by small artery disease (OR 2.61; 95% CI: 1.53–4.44), but not with cardioembolic stroke<sup>13</sup>. Moreover, as found for atherosclerosis, the association with CagA-positive strains was also strong for strokes (OR 1.76; 95% CI: 1.25–2.49)<sup>13</sup>.

These data are coherent with the evidence of a possible role of chronic *H. pylori* infection in the atherosclerosis process and endothelial dysfunction. as shown in a large cohort of nearly 14,000 subjects, where *H. pylori* was associated with intracranial atherosclerosis in women  $\leq 60$  years of age (OR 2.261; 95% CI: 1.839–2.780,  $p \leq 0.001$ )<sup>14</sup>.

In a meta-analysis of 50 case-control studies and 33,978 patients, even other bacterial infections significantly increased the risk of ischaemic stroke (OR 1.704; 95% CI: 1.57–1.84;  $p = 0.01$ ), potentially because of cross-reaction phenomena and metabolic alterations<sup>15</sup>. In particular, *H. pylori* was more present in the population with non-embolic ischaemic stroke than in healthy individuals (OR: 1.6; 95% CI: 1.4–1.8)<sup>15</sup>.

## METABOLIC DISEASES

### Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is often considered the hepatic manifestation of metabolic syndrome<sup>16</sup>. Given the growing diffusion of this syndrome worldwide, the prevalence of NAFLD has reached up to 25% globally, representing the most common liver disease<sup>17</sup>.

NAFLD is an “umbrella” term used to describe a spectrum of pathologies, encompassing a continuum from steatosis (with or without inflammation) to non-alcoholic steatohepatitis (NASH), to cirrhosis and hepatocellular carcinoma (HCC)<sup>18</sup>.

As the exact pathogenesis remains unknown, the relationship between the development of NAFLD and *H. pylori* infection has been a topic of interest in both previous and recent literature.

Insulin resistance, which is highly common in most patients with NAFLD, has a considerable impact on the liver, and makes hepatocytes more vulnerable to oxidative stress and lipid peroxidation<sup>19</sup>. *H. pylori* exerts both a direct effect on the hepatobiliary tract by promoting toxin circulation in the portal system<sup>19</sup> and an indirect effect through the enhancement of insulin resistance, specifically by increasing the release of pro-inflammatory cytokines, eicosanoids, acute phase proteins and reactive oxygen species (ROS)<sup>20</sup>.

When a controlled attenuation parameter, including elastography and other more sensitive metabolic factors for NAFLD diagnosis was used, *H. pylori* seropositivity was not found to be associated with an increased risk of NAFLD<sup>21</sup>. In another meta-analysis including studies where NAFLD was diagnosed mainly with US, Wei et al reported a significant increase in the risk of NAFLD prevalence (OR 1.38, 95% CI: 1.23–1.55,  $I^2 = 86.8\%$ ,  $p \leq 0.001$ ) and incidence (OR 1.21, 95% CI: 1.01–1.44,  $I^2 = 6.5\%$ ,  $p = 0.301$ )<sup>22</sup>.

In a recent meta-analysis of 18 studies with populations from different geographical areas<sup>23</sup>, it was demonstrated that the risk of developing NAFLD, diagnosed by liver biopsy and ultrasound imaging (US), was increased by 22% in patients infected with *H. pylori* (adjusted OR: 1.22, 95% CI 1.09–1.35).

Taking all these mechanisms into consideration, the likely involvement of *H. pylori* in the development of NAFLD remains a concept to be further deepened and elaborated. Based on the influence of *H. pylori* on insulin resistance, its role in diabetes has also been investigated.

### Diabetes

Even though the interplay between type 2 diabetes mellitus (T2DM) and *H. pylori* has been investigated in many studies, this association still remains controversial. If on one hand, hyperglycaemia is involved in the mechanisms of gastric cancer promotion<sup>24,25</sup> in concert with *H. pylori*, on the other, patients with T2DM had a higher risk of *H. pylori* eradication failure than non-diabetic patients (OR 2.59, 95% CI: 1.82–3.70)<sup>26</sup>.

In detail, the body mass index (BMI) was identified as a major determinant of the efficacy of *H. pylori* eradication in diabetic patients<sup>26</sup>.

The synergistic carcinogenic effect of T2DM and *H. pylori* infection can be observed also in the colon. Hung-Ju Ko et al<sup>27</sup> reported that in a subgroup of 11,655 patients, in whom the

diabetes prevalence exceeded 6%, *H. pylori* infection significantly increased the risk of colorectal adenoma (pooled OR 2.16, 95% CI: 1.61–2.91) compared to the subgroup with a diabetes prevalence lower than 6%.

A recent meta-analysis<sup>28</sup> highlighted the biological background of this carcinogenesis process, studying the risk of gastric cancer among diabetic patients. Serum HbA1c levels higher than 6% were associated with an increased risk of gastric cancer (HR 1.36, 95% CI: 1.06–1.74). In this population, when a subgroup analysis was performed based on *H. pylori* infection status, an even stronger association between elevated HbA1c levels and gastric cancer was shown (HR 2.08, 95% CI: 1.46–2.98).

Considering that the incidence of both *H. pylori* and T2 DM is increasing globally, the appropriate control of both diseases may allow attenuation of associated cancer risk.

## EXTRA-GASTRIC DIGESTIVE DISORDERS

### Inflammatory Bowel Disease

Several studies have investigated the potential relationship between inflammatory bowel disease (IBD) and *H. pylori*, with inconclusive results. In a meta-analysis of 58 studies involving 13,549 patients with IBD and 50,654 controls, Shirzad-Aski et al<sup>29</sup> showed that the prevalence of *H. pylori* infection was 22.74% in patients with IBD and 36.30% in controls, finding a significant negative association (pooled OR 0.45, 95% CI: 0.39–0.53,  $p \leq 0.001$ ). Subgroup analysis revealed that the ORs were different when stratified by age and by study regions.

In another meta-analysis by Zhong et al<sup>30</sup>, IBDs were negatively correlated to *H. pylori* prevalence ( $p = <0.001$ ), and the odds of being colonized were 0.36 (95% CI: 0.26–0.49) for Crohn's disease and 0.54 (95% CI: 0.4–0.72) for ulcerative colitis. Interestingly, they observed that *H. pylori* eradication could lead to IBD flares (potentially because of antibiotic-related microbiome disruption) and found that the patients had a higher probability of relapse after the eradication (OR=1.41, 95% CI: 1.25–1.58).

### Coeliac Disease

Coeliac disease is an autoimmune disorder of the small intestine, that affects nearly 0.5–1% of the global population. Its pathogenesis is not well understood, and increasing evidence suggests that *H. pylori* could be involved<sup>31</sup>. A meta-analysis by Yue et al<sup>32</sup> identified 25 studies with a total of 141,355 participants and showed that the infection rate of *H. pylori* in patients affected by coeliac disease was about half of the controls (OR = 0.57, 95% CI 0.44–0.75).

### Esophageal Disorders

Gastro-esophageal reflux disease (GERD) is a common gastrointestinal disease that affects nearly 15% of the general population. The main complications that can develop are erosive esophagitis, in up to 30% of GERD patients, and Barrett's esophagus, found in 3–14% of patients<sup>33–35</sup>.

In a meta-analysis of 36 papers, Zamani et al<sup>36</sup> evaluated *H. pylori* as a potential risk factor in esophageal diseases, finding a negative association with gastroesophageal reflux symptoms (OR 0.74, 95% CI: 0.61–0.90) and erosive esophagitis among patients with symptoms (OR 0.70, 95% CI: 0.58–0.84). Notably, a meta-analysis by Du et al<sup>37</sup> observed an inverse relationship between *H. pylori* and Barrett's esophagus (OR=0.70; 95% CI: 0.51–0.96;  $p = 0.03$ ). The most likely mechanism to explain this observation is the corpus-predominant gastritis with decreased acid secretion caused by *H. pylori*.

## MISCELLANEOUS

### Chronic Urticaria

Chronic urticaria is a common histamine-mediated disease of the skin with a worldwide prevalence of approximately 0.5–1%<sup>38</sup>, characterised by wheals, angioedema, or both for more than 6 weeks<sup>39</sup>. Some studies have shown the potential involvement of *H. pylori* infection in chronic urticaria<sup>40</sup>, but a clear association has not yet been shown. A previous meta-analysis<sup>40</sup> reported a weaker but still significant association, reporting that the prevalence of *H. pylori* infection was higher in chronic urticaria than in controls (OR = 1.66; 95% CI: 1.12–2.45;  $p = 0.01$ ). A meta-analysis by Cui et al<sup>41</sup>, including six studies and 1,320 patients, found a significant correlation between *H. pylori* infection and chronic urticaria (OR = 3.00; 95% CI: 1.98–4.55;  $p < 0.00001$ ).

### Thyroid

Thyroid nodules are a common clinical disorder, with a prevalence of 20–70%, often found in elderly and female populations. Previous studies<sup>42,43</sup> have identified a positive association between *H. pylori* infection and the risk of thyroid nodules, and it could be interpreted as a risk factor both for benign and malignant nodules, almost 5–15% of all the thyroid nodules.

Conversely, a recent case-control study<sup>9</sup> comparing 13,036 patients with thyroid nodules and 30,375 controls did not find any significant association, hypothesizing that the influence of confounding factors might explain the previously reported positive association.

### Growth Disorders

*H. pylori* is generally acquired during childhood, and the consequences of the infection during this age period remain controversial. Some studies suggest that *H. pylori* does not directly play a role in the growth and that the correlation described could be due to the lower socioeconomic condition associated with this infection<sup>44</sup>.

On the other hand, other studies suggest that it could affect the children's growth<sup>45</sup>, through mechanisms such as alteration in the appetite-regulating peptides<sup>46</sup> and iron deficiency anaemia<sup>47</sup>.

A recent meta-analysis by Xu et al<sup>48</sup>, including 29 studies and 9,384 subjects, showed a significant correlation between *H. pylori* infection and both linear growth disorders (OR = 1.76; 95% CI: 1.15–2.69,  $p = 0.01$ ) and ponderal growth disorders (OR: 2.47; 95% CI: 1.13–5.37;  $p = 0.02$ ). *H. pylori* was negatively correlated with children's height-for-age Z (HAZ) scores (SMD = -0.41; 95% CI: -0.69 – -0.13;  $p < 0.01$ ), but not significantly associated with other parameters such as weight, height, weight-for-age percentile scores, BMI, weight-for-age and BMI-for-age Z scores, linear and ponderal growth velocity.

### Parkinson's Disease

Nowadays, Parkinson's disease (PD), occurring after a progressive loss of dopaminergic neurons, represents the second most common neurodegenerative disorder<sup>49</sup>. Increasing lines of evidence suggest that infections and subsequent inflammation could play a role in the aetiology of PD<sup>50</sup>.

In a recent meta-analysis<sup>51</sup> *H. pylori* eradication reduced the units of levodopa equivalent daily dose (LEDD) (SMD -32.08; 95% CI: -87.88– -23.71,  $p = 0.26$ ;  $I^2 = 0\%$ ), and also positively affected the bradykinesia and myotonia, evaluating by the stride length and the torque to flex, and the Unified Parkinson's Disease Rating Scale (UPDRS)-III (pooled MD 6.27; 95% CI: 1.30–11.24,  $Z = 2.47$ ,  $p = 0.01$ ). Also, the absorption rate (onset time) became shorter after the eradication (pooled MD 14.91, 95% CI: 8.92–20.90,  $Z = 4.88$ ,  $p < 0.001$ )<sup>51</sup>.



This could be explained by a reduction of levodopa absorption and bioavailability caused by *H. pylori*, as several studies have hypothesized<sup>52</sup>.

Furthermore, in another meta-analysis of 13 studies and 826 patients, of which 383 with *H. pylori* infection<sup>53</sup>, positive patients recorded more units of levodopa equivalent daily dose (LEDD) (SMD = 0.178; 95% CI: 0.004–0.353;  $p = 0.046$ ) and an increased amount of time to achieve the 'ON' state (SMD = 0.778; 95% CI: 0.337–1.220;  $p = 0.001$ ;  $I^2 = 58.3\%$ ;  $p = 0.048$ )<sup>53</sup>. Conversely, the duration of "on" time of levodopa may be associated but the available data have not reached a statistically significance result yet (pooled MD -18.65; 95% CI: -38.66–1.36;  $Z = 1.83$ ,  $p = 0.07$ )<sup>51,53</sup>.

## CONCLUSIONS

The role of *H. pylori* infection in the development of extra-gastric disorders has been largely investigated in recent years, and some interesting insights have come up in the last year. Specifically, *H. pylori* was associated with hypertension, atherosclerosis, and major cardiovascular events including CHD and stroke, with a specifically increased risk for virulent strains. The same strong association could not be found with strict metabolic disorders, including NAFLD and T2DM, although the concomitant presence of *H. pylori* and T2DM appears to provide a synergistic cancer risk. Inversely, a clearly negative association was shown between *H. pylori* and other extra-gastric digestive disorders, including IBD, coeliac disease, GERD and Barrett's esophagus.

*H. pylori* was found to be more prevalent in patients with chronic urticaria, suggesting that this phenomenon can be triggered by the infection-related inflammation. Another mechanism, that is the reduction of drug absorption, may be the biological reason for the negative association between *H. pylori* and Parkinson's disease outcomes.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Contributions

Writing-original draft preparation: L.E. Del Vecchio, M. Fiorani E. Tohumcu, S. Porcari and G. Ianiro; Supervision and Conceptualization: G. Ianiro and G. Cammarota. All authors have read and agreed to the published version of the manuscript.

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