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ORIGINAL ARTICLE

A Systematic Review on the Impact of *Helicobacter Pylori* Eradication on Gastrointestinal and Extra-Gastrointestinal Diseases

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ABSTRACT

Background: *Helicobacter pylori* (*H. pylori*) is a major cause of peptic ulcer disease (PUD) and gastric cancer, with emerging associations with metabolic, cardiovascular, neurological, and autoimmune diseases. This systematic review evaluates the impact of *H. pylori* infection and its eradication on these conditions.

Methods: A systematic search was conducted across different databases from January 2000 to June 2023. Eligible studies included clinical trials, cohort studies, and meta-analyses that assessed disease progression or symptom improvement post-eradication.

Results: Eradication significantly reduces PUD recurrence (from 85.3% to 6.8%) and lowers gastric cancer risk by 36%, though its effect on intestinal metaplasia remains unclear. The impact on GERD is inconclusive. *H. pylori* increases insulin resistance by 54% and metabolic syndrome risk by 31%, with eradication improving lipid profiles and glucose metabolism. The infection is linked to atherosclerosis, hypertension, and systemic inflammation, with eradication reducing CIMT and inflammatory markers. *H. pylori* is also associated with Alzheimer's and Parkinson's diseases, likely via gut-brain axis disruption, and may impair levodopa absorption in Parkinson's disease. Autoimmune links include rheumatoid arthritis and Hashimoto's thyroiditis through molecular mimicry and immune activation.

Conclusion: While eradication is essential for GI diseases, its role in extra-GI conditions remains under investigation. Targeted eradication in high-risk populations may offer therapeutic benefits, but broad eradication requires further study.

Keywords: *Helicobacter pylori,* peptic ulcer, gastric cancer, metabolic syndrome, cardiovascular disease, neurodegenerative disorders, autoimmune diseases, eradication therapy.

INTRODUCTION

H. pylori is a Gram-negative, spiral bacterium that colonizes gastric mucosa and is associated with gastrointestinal diseases. It affects almost half of the population worldwide, particularly in developing countries, where poor sanitation and overcrowding favor the disease[1]. In contrast, *H. pylori* infection is less common in developed countries[2].

Transmission primarily occurs through oral-fecal routes within communities[3]. In addition, contaminated food and water can also transmit *H. pylori*, particularly in areas of inadequate sanitation[4]. Urease produced by the bacterium neutralizes stomach acids, which results in chronic infection, while adhesins allow adhesion to gastric cells and help induce inflammation[5].

H. pylori causes chronic gastritis, peptic ulcer, and gastric cancer; it has been classified as a class I carcinogen by WHO[6,7]. It can also lead to iron deficiency and neurodegenerative diseases, including Parkinson's disease[8].

Invasive diagnosis includes histology, while noninvasive methods are stool antigen and serology tests[9]. Antibiotics combined with proton pump inhibitors are used to treat the infection, but increasing rates of antibiotic resistance can be a challenge[10]. Vaccines are currently not available, and preventive strategies are based on hygiene, sanitation, and access to clean water[1].

METHODS

Study Design: This systematic review was performed according to guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This review mainly focused on the correlation between *H. pylori* eradication and various diseases.

Search Strategy: A systematic search was conducted within four major databases: Cochrane Library, Web of Science, Scopus, and PubMed to find the most relevant studies available. The research incorporated the following terms: ("*H. pylori* eradication" OR "*Helicobacter pylori* treatment") AND ("gastric cancer" OR "peptic ulcer" OR "GERD" OR "diabetes" OR "cardiovascular diseases" OR "neurological disorders" OR "autoimmune diseases") as search terms. The research results were limited to studies specifically on *H. pylori* eradication through the implementation of Boolean operators.

Inclusion Criteria: We considered only clinical trials based on RCTs, prospective and retrospective cohort studies, as well as meta-analyses or systematic reviews. For this purpose, studies had to evaluate disease progression, symptom improvement, or clinical outcome after *H. pylori* eradication for the purpose of comparing interventions. The studies were selected based on their potential to assess the impact of eradication therapy on one or more of the following diseases: gastric cancer, peptic ulcer disease, gastroesophageal reflux disease (GERD), diabetes, cardiovascular diseases, neurological disorders, and autoimmune diseases. All age groups were included in the studies involving human participants. Additionally, only the studies published between Januray 2000 and June 2023 were included.

Exclusion Criteria: Case reports, animal studies, and studies published in languages other than English were not included. Additionally, studies failing to clearly define the eradication intervention of *H. pylor*i and that did not evaluate the progression or relapse of disease were also excluded.

Data Extraction and Analysis: A standardized form was used for data extraction for consistency and accuracy of the data. The outcome measures were disease progression, symptom relief, and time till the recurrence of the disease after *H. pylori* eradication.

RESULTS

The Role of *H. pylori* in Gastrointestinal Diseases

Peptic Ulcer Disease (PUD): Peptic ulcer disease (PUD) is well recognized as being caused by *H. pylori* infection. Systematic reviews of a number of studies demonstrate the tremendous impact of *H. pylori* eradication on preventing ulcer recurrence, reducing symptom severity, and decreasing the need for long-term proton pump inhibitors. After successful eradication, gastric ulcer recurrence was 11.4%, compared to 64.5% in the group that was unsuccessfully treated, and 6.8% versus 85.3% for duodenal ulcer recurrence[11]. In addition, eradication is considered the best way to prevent PUD complications, such as bleeding ulcers. In a study of 422 patients, the rates of rebleeding after successful eradication

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were reduced to 0.22% per patient year[12]. Another study demonstrated that dyspepsia declined from 79% to 18%, and the need for acid suppressive therapy decreased from 54% to 13% in *H. pylori*-treated patients who were successfully treated. In several studies, it has been reported that *H. pylori*-negative patients have a greater role in chronic liver disease in the ulcer pathogenesis[13]. NSAID use is also considered to be an independent risk factor for recurrence, even after eradication[14].

Gastric Cancer & Precancerous Conditions: Successful eradication of *H. pylori* infection can lower the risk of gastric cancer; successful eradication helps to reverse precancerous conditions such as atrophic gastritis. A meta-analysis found that after successful eradication, the risk of gastric cancer reduced by 36% (RRR 0.64, 95% CI 0.48–0.85)[15]. For patients with gastritis, the benefit of successful eradication was significant, but it was less promising for patients with intestinal metaplasia or dysplasia. One study showed that *H. pylori* eradication improves atrophic gastritis, as histological scores were improved within 8.6 years[16]. Atrophic gastritis was resolved in 61% of patients[17]. Some studies have also reported a reduction in intestinal metaplasia after six years of successful eradication[16], while other studies have rationalized it as the 'point of no return'[18]. Gastric disease is considered a risk for metachronous tumors, but a decrease of up to 53% was observed among those who underwent endoscopic mucosal resection[17]. Nonetheless, eradication therapy drastically reduces the incidence of cancer in patients with gastritis and atrophic gastritis, though the effect is less considerable in those with more advanced precancerous changes[19].

Gastroesophageal Reflux Disease (GERD): There is an ongoing debate regarding the relationship between *H. pylori* eradication and gastroesophageal reflux disease (GERD). According to some studies, eradication increases the risk of GERD, while other studies find no relationship between GERD and *H. pylori* eradication. These inconsistencies can be attributed to variations in host factors, microbiome composition, and gastric acid. A retrospective study revealed increased incidence of GERD symptoms (37% vs. 13%, p=0.04) after eradication[20]. Another study found a strong link between higher levels of acid exposure in GERD patients[21]. Some studies also reported esophagitis recurrence, but there is a lack of evidence regarding the recurrence rate in treated and non-treated groups[22]. In antral gastritis, gastric acid secretion may increase after eradication and may decrease in corpus gastritis[23].

Corpus gastritis caused by *H. pylori* influences acid regulation, potentially increasing the risk of hypochlorhydria, which in turn lowers the risk of GERD. Acid secretion may be restored or increased with eradication[24]. Finally, the alteration of gastric microbiota after eradication can also be a contributing factor in the development of GERD[25].

Functional Dyspepsia (FD): Upper abdominal pain with no clear origin is a common symptom of functional dyspepsia (FD). *H. pylori* eradication and its correlation with FD symptoms are debatable with inconsistent results reported in the studies. One study shows that FD patients who were successfully treated experienced symptom resolution in 30-50% of cases, along with a 10% relative risk reduction[26]. Another study found that patients with ulcer-like FD showed greater improvements compared to those with dysmotility-like FD[27]. However, researchers have not identified the specific mechanisms through which symptom relief happens after successful *H. pylori* eradication[28]. Additionally, it has been observed that ghrelin levels increase after *H. pylori* eradication[29].

Impact of *H. pylori* on Extra-Gastrointestinal Diseases

Metabolic Disorders: The possible link between *H. pylori* infection and metabolic disorders (insulin resistance, type 2 diabetes (T2DM), obesity, and metabolic syndrome) is not completely understood. Some studies suggest that *H. pylori* contributes to these metabolic disorders through chronic inflammation, gut hormone changes, and altered lipid metabolism. Similarly, a meta-analysis found that *H. pylori* infection increases the risk of insulin resistance by 54% (OR = 1.54, 95% CI = 1.19–1.98) and melanoma by 31% (RR = 1.31, 95% CI = 1.13–1.51)[30]. Additionally, elevated pro-inflammatory cytokines, TNF-α and IL-6, have been observed in *H. pylori*-infected patients[31]. Although BMI slightly increases in certain cases, eradication did not significantly influence insulin resistance and fasting glucose levels[32].

Cardiovascular Diseases: *H. pylori* infection can cause different cardiovascular complications due to systemic inflammation and oxidative stress phenomena. Several studies reported that *H. pylori* infection can cause atherosclerosis and hypertension. Carotid intima-media thickness (CIMT), a major risk indicator of subclinical atherosclerosis, has been linked with *H. pylori* infection in many studies. Neutrophil gelatinase-associated lipocalin (NGAL) and high-sensitivity C-reactive protein (hs-CRP), a major vascular inflammatory marker, are elevated in different chronic infections, including *H. pylori*[33]. Many studies have also reported that eradication therapy can reduce systemic inflammation and improve endothelial function[34].

Neurological & Neurodegenerative Disorders: *H. pylori* infection has been linked to neurodegenerative diseases. The infection causes chronic inflammation, alters the gut microbiome, and disrupts the gut-brain axis, which may contribute to the development of neurodegenerative diseases. Emerging evidence links *H. pylori* infection to neurodegenerative diseases like Alzheimer's (AD) and Parkinson's (PD). However, it has been reported that eradication therapy leads to cognitive improvement and slow disease progression[35].

Autoimmune Diseases: *H. pylori* infection is a risk factor for the development of autoimmune diseases. It can produce autoantibodies against thyroid peroxidase in Hashimoto's thyroiditis[36]. In rheumatoid arthritis (RA), *H. pylori* is linked to an increased number of rheumatoid factors and anti-citrullinated protein antibodies (ACPAs), which are markers of the autoimmunity. Eradication therapy leads to a decrease in inflammatory markers in RA patients[37].

DISCUSSION

This systematic review focuses on how *H. pylori* infection plays a role in both gastrointestinal (GI) and extra-GI diseases. Through eradication, the recurrence of peptic ulcers and the risk of gastric cancer is significantly reduced, particularly before the development of advanced lesions[11]. Some studies suggest that intestinal metaplasia may reverse after eradication, though more research is needed on atrophic gastritis[16].

The link between *H. pylori* eradication and GERD remains open for discussion; although some studies showed worsening symptoms[20], others reported no significant effect [22].

In addition to GI diseases, *H. pylori* can also contribute to metabolic disorders, increasing the risk of insulin resistance by 54% and metabolic syndrome by 31%[30]. However, the effect of eradication on metabolism remains inconsistent[38].

Through inflammation and oxidative stress, *H. pylori* can lead to cardiovascular implications, such as atherosclerosis and endothelial dysfunction[33]. Eradication can reduce systemic inflammation and improve endothelial function[34].

Certain studies showcase the role of *H. pylori* in the development of neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, with impaired levodopa absorption and systemic inflammation worsening PD symptoms[8].

H. pylori is also linked with autoimmune diseases, including RA and Hashimoto's thyroiditis, likely through molecular mimicry. Eradication may lower the inflammatory markers present in RA, though findings are mixed[37].

Clinical Implications: Given the strong association between *H. pylori* infection and GI diseases, current guidelines universally recommend eradication therapy for PUD, gastric cancer prevention, and MALT lymphoma. However, with an increasing body of research showing its involvement in the pathogenesis of metabolic, cardiovascular, neurological, and autoimmune diseases, the question arises as to whether *H. pylori* eradication should be considered beyond GI diseases.

Selective eradication may be more beneficial, especially for those with evidence of insulin resistance. Similarly, in patients with cardiovascular diseases, eradication may help reduce inflammation, improve endothelial function, and lower the risk of atherosclerosis[39].

In neurological disorders, screening and eradication may be considered for PD patients experiencing worsening symptoms or poor levodopa absorption. However, universal eradication for these conditions is premature and requires further validation through clinical trials[32].

Limitations & Future Directions: The extra-gastrointestinal effects of *H. pylori* remain a major gap for further research, aside from its successful eradication and treatment. The evaluation of cardiovascular diseases and neurodegenerative impacts requires extended follow-up periods, as current studies have insufficient tracking duration. Targeted eradication in those individuals with components of metabolic syndrome or Parkinson's disease should be explored in randomized trials. Moreover, further study of host-microbe interactions, changes in the gut microbiome, and genetic predisposition will help elucidate the systemic effects of *H. pylori*[40].

CONCLUSION

The results from this systematic review demonstrate that *H. pylori* eradication plays an essential part in sustaining long-term treatment of GI diseases. Eradication therapy improved PUD treatment because it successfully prevents ulcer recurrence and simultaneously improves symptoms, as well as reduces the dependency on PPI usage. The recurrence risks for treated patients should be evaluated against possible influencing factors such as NSAID intake and existing medical conditions. The need for eradication therapy proves vital for GI diseases. The eradication of *H. pylori* in high-risk environments could improve therapy outcomes, yet scientists need to investigate complete eradication approaches for all patients.

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