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Review Article

Impact of *Helicobacter pylori* Infection on the Pathogenesis and Management of Nonalcoholic Fatty Liver Disease

Marianna G. Mavilia-Scranton, George Y. Wu and Murali Dharan*

Department of Medicine, Division of Gastroenterology and Hepatology, University of Connecticut, Farmington CT, USA

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Abstract

Helicobacter pylori (*H. pylori*) infection is widely prevalent worldwide. *H. pylori* infection has been reported to be a risk factor for the development of insulin resistance, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver fibrosis, and cirrhosis. Because treatment for NAFLD, other than weight loss is limited, the treatment for *H. pylori* infection is well established. It is important to determine whether screening and treatment for H. pylori infection should be considered in patients with no gastrointestinal symptoms. The aim of this mini-review is to evaluate the association between *H. pylori* infection and NAFLD including epidemiology, pathogenesis, and the evidence for *H. pylori* infection as a modifiable risk factor for preventing or treating NAFLD.

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Introduction

NAFLD is a spectrum of diseases ranging from bland hepatic steatosis to nonalcoholic steatohepatitis (NASH) to cirrhosis. The pathogenesis, particularly the drivers of progression in NAFLD are incompletely understood. While there are probably many contributing factors, one proposed mechanism underlying this progression is the influence of *Helicobacter pylori* (*H. pylori*) infection. *H. pylori* is thought to contribute to the development of NASH in many ways that range from influencing changes of metabolic risk factors, in the gut microbiome, of the inflammatory state, and other metabolically active hormones. Due to the rapidly growing population with NAFLD, there is a demand for identification of treatable targets and modifiable risk factors in this population. The objective of this report is to critically evaluate the evidence supporting and denying the association between *H. pylori* infection and NAFLD and to review the available literature on mechanisms underlying this association.

Keywords: *Helicobacter pylori*; Hepatic fibrosis; Hepatic steatosis; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis.

Abbreviations: CAP, controlled attenuation parameter; HOMA-IR, homeostatic model of assessment of insulin resistance; HPI, *Helicobacter pylori* infection; HIS, hepatic steatosis index; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; NAFLD-LFS, NAFLD liver fat score; NASH, nonalcoholic steatohepatitis; TE, transient elastography.

***Correspondence to:** Murali Dharan, Department of Medicine, Division of Gastroenterology and Hepatology, University of Connecticut Health Center, 263 Farmington Avenue, Farmington CT 06030, USA. ORCID: https://orcid.org/0000-002-9764-0068. Tel: +1-860-679-4124, Fax: +1-860-679-3159, E-mail: dharan@uchc.edu

Epidemiology

H. pylori infection has an extremely high prevalence. It is estimated that greater than half of the world's population has been infected with *H. pylori*.[1,2] Although the prevalence in developing nations may be as high as 70%,[3] it is decreasing in many developed countries. The prevalence of *H. pylori* in the US decreased from 11% to 9% between 2009 and 2018.[4]

NAFLD has a global prevalence of about 25%,[5,6] estimated at 882.1 million people affected in 2017, which has more than doubled since 1990.[7] Prevalence rates of up to 40% have been reported in Western countries.[8] NASH occurs in about 20–30% of NAFLD patients and of those, fibrosis develops in 32–37% of cases.[6,8,9] Much research is being conducted to better understand the factors driving the rapidly increasing incidence and progression along this continuum of the disease.

Association between *H. pylori* infection and NAFLD

In 2008, Cindoruk *et al*.[10] isolated *H. pylori* DNA from liver tissue of a patient with NASH. In this study, 75 liver biopsies were evaluated, and *H. pylori* was identified in two patients, one with NASH. Interestingly, among the 75 patients in the study, 52 had *H. pylori* gastritis and 27 had a histological diagnosis of NASH.[10] Although only one NASH patient was found to have *H. pylori* DNA in the liver, this finding fueled further investigation of the potential relationship between *H. pylori* infection and NAFLD. Since then, other studies have replicated the findings of *H. pylori* DNA the liver tissue of NAFLD patients.[11]

Several high-quality meta-analyses have demonstrated an association between NAFLD and *H. pylori* infection. Three meta-analyses showed an increased risk of NAFLD in *H. pylori*-positive patients compared to *H. pylori*-negative patients, with odds ratios (ORs) ranging from 1.19 to 1.27.[12–14] Two additional meta-analyses reported ORs of 1.36 to 1.38 for *H. pylori* infection in NAFLD patients.[1,15] The most recent of these meta-analyses by Heydari *et al*.,[12] published in 2022, included 22 studies and over 117,000 patients, had a 27% increased risk of developing NAFLD in patients with *H. pylori* infection.

Several other studies found histologic evidence of this association. A study of 64 morbidly obese patients undergoing bariatric surgery demonstrated that patients with active *H. pylori* infection had a higher rate of biopsy-proven NASH than *H. pylori*-negative patients (86.7% vs. 26.5%, $p<0.001$).[16] This study also showed more severe changes in steatosis grade, ballooning, lobular inflammation, and fibrosis stage in biopsies of *H. pylori*-positive patients.[16] The data showed that *H. pylori* infection was independently associated with NASH and fibrosis among obese patients. Another cross-sectional study by Sumida *et al*.[17] found similar results in a group of 130 patients with biopsy-proven NAFLD. This analysis found a higher prevalence of NASH among *H. pylori*-positive patients compared with *H. pylori*-negative patients (80.8% vs. 50.7%), independent of the presence of obesity and diabetes.[17,18] More specifically, the NAFLD activity score and grade of hepatocyte ballooning were significantly greater in *H. pylori*-positive patients. Although the fibrosis grade was higher among *H. pylori*-positive patients, with borderline statistical significance ($p=0.058$), perhaps due to a small sample size.[17]

A prospective cohort study by Kim *et al*.[19] followed more than 17,000 South Korean adults without NAFLD over 81,130 person-years found a higher incidence of NAFLD (as determined by ultrasonography) among *H. pylori*-seropositive patients. The incidence rate was 43.2 per 1,000 person-years in *H. pylori*-positive patients, compared with 37.2 per 1,000 person-years in those that were *H. pylori*-negative. This study is one of the only prospective analyses conducted on this topic. Authors conducted a multivariate analysis to control for confounders, such as body mass index (BMI) and alcohol intake, and excluded secondary causes of fatty liver disease during the follow-up period. The main limitation of this study was the use of *H. pylori* serology. Seropositivity for *H. pylori* includes all patients with *H. pylori* infection past or present and does not accurately characterize active infection. Data on *H. pylori* eradication, discussed later in this review, show that *H. pylori* infection-related risk is decreased after treatment. Therefore, only active *H. pylori* infection should be considered when assessing its relationship with NAFLD.

In a large study from southwest China, transient elastography (TE) was used to evaluate the relationship between NAFLD and *H. pylori* infection diagnosed by urea breath test.[20] In this study of 5,665 patients, the prevalence of NAFLD was greater in *H. pylori*-positive men (44.5 vs. 39.5%, $p<0.01$).[20] Although a positive correlation between *H. pylori* infection and NAFLD was not found, the presence of *H. pylori* infection was higher in patients with liver stiffness measurement (LSM) >7.4 kPa,[20] which indicates an association with fibrosis. Han *et al*.[21] performed a retrospective observational cohort study of 1,784 patients undergoing employer-based health screening incorporating TE and serology for *H. pylori* infection (Immunoglobulin G antibody testing). Their data showed no association between *H. pylori* seropositivity and NAFLD (defined as CAP ≥248 dB/m). Similar to previous studies, this was limited by the use of *H. pylori* serology rather than the gold standard for the diagnosis of *H. pylori* infection. Inclusion of all seropositive patients(presumably patients with eradicated infection as well) likely affected the relationship reported in this study. Although TE is also not the gold standard for diagnosis in NAFLD, it is increasingly being used as a noninvasive investigative tool making these data particularly relevant to clinical practice.

Similar to the data from Han *et al*.,[21] a study by Baeg *et al*.[22] also reported no significant relationship between *H. pylori* infection and NAFLD. In that study, 3,636 healthy adults underwent routine health screening in South Korea, including *H. pylori* breath testing and had calculations of hepatic steatosis index (HSI) and NAFLD liver fat score (NAFLD-LFS). There was no difference in the percentage of people with NAFLD between *H. pylori*-positive and negative groups (26.9% vs. 27.1%, $p=0.173$). Although this was a fairly large study conducted in an area with a high prevalence of *H. pylori* infection, the authors employed imperfect measures of NAFLD. HSI and NAFLD-LFS are scoring systems based on serologic parameters and medical history**.** While these measures are attractive as noninvasive markers of disease, they are not as reliable as liver biopsy for the diagnosis of NAFLD. In a large cohort of more than 5,000 patients screened for NAFLD with US in Central Europe, was no difference in the prevalence of NAFLD between *H. pylori*-positive versus negative patients.[23] Interestingly, when subgroup analysis was performed of patients screened for NAFLD with TE, there was a higher prevalence of NAFLD in *H. pylori*-positive patients (49% vs. 38%, $p=0.004$).[23] This again lends credence to the importance of the diagnostic tools used to evaluate this patient population. Although some studies dispute the association between *H. pylori* infection and NAFLD, the overwhelming majority of data supports a link between these entities.

Proposed mechanisms of the pathogenetic role of *H. pylori* infection in NAFLD

In the current literature, several mechanisms have been proposed to explain the role of *H. pylori* infection in NAFLD related to inflammation, metabolic influence, changes to gut permeability and gut microbiome. Many authors have described *H. pylori* infection as one hit in a multiple hit model of progression from bland steatosis to NASH and fibrosis.[16,24]

The role of *H. pylori* infection in hepatic fibrogenesis was studied in a mouse model where *H. pylori* infection increased the development of liver fibrosis.[25] Mice were exposed to carbon tetrachloride to induce liver fibrosis with some mice also being orally inoculated with *H. pylori* organisms and followed for 4 months. Although there was liver fibrosis in both groups, *H. pylori*-infected mice had increased fibrosis scores, and ALT and AST levels compared with uninfected mice.[25] This suggests that *H. pylori* infection may act as a second hit and promote inflammatory/fibrotic processes when there are other risk factors at play.

In another mouse model, the impact of *H. pylori* infection was evaluated in diet-induced NAFLD.[26] A high fat diet was fed to both *H. pylori*-infected mice and *H. pylori*-negative controls. After 24 weeks, metabolic risk factors and liver histology were compared. *H. pylori*-positive mice had a greater abdominal circumference, fasting blood glucose, LDL, and ALT levels compared to controls. Histologically, *H. pylori*-positive mice had more steatosis in the liver as well as increased expression of inflammatory cytokines IL-1B and TNF-alpha. The authors concluded that *H. pylori* infection aggravated hepatic steatosis caused by the high fat diet.[18] Liver fibrosis was not evaluated in this study, which is a considerable weakness. additionally, the observation period was relatively short. A longer duration may have shed light on the development of fibrosis.

Chronic, low-grade inflammation caused by *H. pylori* infection can result in local and systemic effects. Local inflammation in the gastric mucosa may lead to release of proinflammatory cytokines that increase gut permeability and access to portal circulation.[27] *H. pylori* and other bacteria and toxins as well as cytokines may directly affect the hepatic parenchyma. This inflammatory milieu can activate stellate cells to generate fibrosis.[2]

Additionally, *H. pylori* infection is also thought to influence

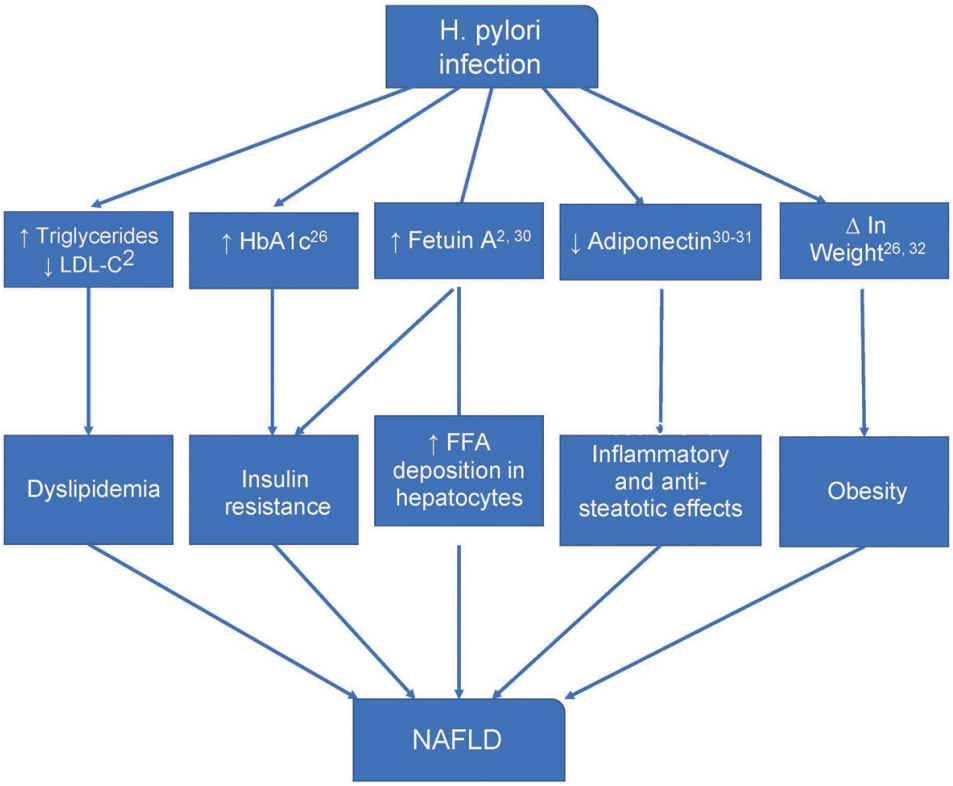

Fig. 1. Possible mechanisms of *H. pylori* infection on the development of NAFLD. FFA, free fatty acid; HbA1c, hemoglobin A1c; LDL-C, low density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease.

the development of NAFLD through changes to the gut microbiome.[28] Both *H. pylori* infection and its treatment can alter bacterial diversity and abundance within the GI tract.[27] Studies have shown that *H. pylori* infection specifically impacts *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Lactobacillus*, and *Proteobacteria* colonies and may generate a gut microbial profile similar to that seen in obese patients.[27,28] In humans, there are conflicting data regarding the impact of *H. pylori* infection on specific groups of bacteria. It is also unclear whether *H. pylori* infection, its treatment, or both impact changes in gut microbiome linked to NAFLD progression. It is proposed that changes in the microbiome may disrupt the gastrointestinal mucosa, allowing translocation of bacteria and other metabolites into the portal circulation and activation of inflammatory pathways.[16] A small study of 40 patients from rural China reported an increase in fecal Lactobacillus at 4 weeks post-treatment in subjects undergoing treatment for *H. pylori* infection, in patients with duodenal ulcers.[29] The findings may not be generalizable to other populations. It is also unclear if the increase in fecal Lactobacilli was sustained for long. In animal studies (Mongolian gerbils), *H. pylori* infection has been noted to be associated with higher gut concentrations of Lactobacillus species *H. pylori*-positive compared with *H. pylori*-negative controls.[30] However, the findings did not achieve statistical significance. A major limitation of that study was the use of bacterial cultures of intestinal aspirates to study the microbiome as opposed to gene sequencing. According to reviews on this topic, Lactobacillus is generally thought to promote a healthy microbiome,[8,27] but it remains unclear if the *H. pylori* infection-driven in Lactobacillus and other gut bacterial populations impact NAFLD development.

H. pylori infection as a risk factor for NAFLD

H. pylori infection has been directly linked to insulin resistance and dyslipidemia[1,2,26] which are currently accepted as contributors to the development of NAFLD. *H. pylori* infection is associated with lower HDL and higher triglyceride levels. Interestingly, following eradication of *H. pylori* infection, the lipid panel may become more favorable with increased HDL and lower LDL levels.[2] In a study of patients with diabetes, *H. pylori*-positive patients had higher HbA1c levels compared with *H. pylori*-negative patients.[26] Furthermore, patients with *H. pylori* infection and NAFLD may have an increased risk of cardio-cerebrovascular disease.[31]

H. pylori infection has also been associated with higher serum fetuin A levels.[2,32] Fetuin A is a glycoprotein, which transports free fatty acids and may lead to increased fat deposition in hepatocytes. This mechanism supports the histological finding of increased steatosis grade in liver biopsies of the *H. pylori*-positive patients compared to negative controls,[5] as described above. Fetuin A also influences insulin sensitivity by inhibition of insulin receptors in the liver, muscle and fat tissue.[32]

Several reviews have reported that *H. pylori* infection may also exert metabolic influence through adiponectin. Adiponectin, an anti-inflammatory adipokine, inhibits fat deposition in the liver under normal conditions.[32,33] Adiponectin levels are decreased in NAFLD patients.[30] Interestingly, following *H. pylori* infection eradication, adiponectin levels increased[2] which may have improved metabolic and inflammatory profiles in NAFLD patients. The association between *H. pylori* infection and metabolic risk factors for NAFLD is shown in Figure 1.

H. pylori infection has been associated with changes in body weight, although no direct causality has been confirmed.

It has been reported that *H. pylori*-positive patients have lower levels of ghrelin and higher levels of leptin, creating appetite suppression, particularly in children. These changes have been proposed as mechanisms for growth retardation and malnutrition.[27] However, a cross-sectional study of more than 2,600 adults in Taiwan showed *H. pylori* infection was associated with an increased BMI and increased risk of obesity with a OR of 1.836 (95% CI: 1.079–3.125, p=0.025).[34] Data on weight change following *H. pylori* infection eradication are conflicting. Some studies have shown that treatment of *H. pylori* infection relieved dyspeptic symptoms leading to increased appetite and weight gain. Other studies have demonstrated weight loss following *H. pylori* infection eradication although the reasons for this are not clear.[27] The influence of *H. pylori* infection on body weight appears to be different in adults and children possibly due to age-related phenomena on body weight.[27]

H. pylori infection eradication

To date, four studies have evaluated the relationship of *H. pylori* infection and NAFLD pre- and post- *H. pylori* eradication. In a study on 369 healthy, normal weight patients without NAFLD followed longitudinally over 2 years, 127 patients were *H. pylori*-positive and underwent treatment after the 2-year observation period, of whom 13.5% developed NAFLD during this period, whereas no *H. pylori*-negative patients developed NAFLD. Following *H. pylori* eradication, assessment for NAFLD 3 months post-therapy showed a decrease of NAFLD prevalence to 3.9% (p<0.001).[21] Although the study was reasonably powered, it was limited by its short post-treatment follow-up of only 3 months. In another small study of 13 patients with biopsy-proven NASH, which included six *H. pylori*-positive patients diagnosed by a positive urease breath test. The patients were followed for 12 months after eradication therapy. Noninvasive evaluation showed no change in hepatic steatosis, but there was a trend toward improvement in NAFLD fibrosis score 12 months after eradication.[35] Limitations of the study included assessment of fibrosis with a noninvasive method and a very small sample size. A third study by Jamali *et al*.[36] showed no difference in liver fat content as determined by NAFLD fat score, liver enzymes, and insulin resistance in 100 patients with *H. pylori* infection and NAFLD determined by steatosis on US at 24 weeks post-eradication. The study was limited by noninvasive measurement of steatosis and only dyspeptic patients were enrolled in the study. However, the restriction to dyspeptic patients may shed light on *H. pylori* infection causality in NAFLD.

A randomized controlled trial including 64 patients with both NAFLD and *H. pylori* infection compared treatment with lifestyle modification, and *H. pylori* infection eradication with clarithromycin-based triple therapy versus lifestyle modification alone.[37] The study used ultrasound and TE to diagnose NAFLD and endoscopic biopsy to diagnose *H. pylori* infection and followed patients for 24 weeks. Although both groups had significant reductions in the controlled attenuation parameter (CAP) score, the difference in LSM scores was not significant. Interestingly, there was a greater improvement in insulin resistance, measured by the homeostatic model of assessment of insulin resistance in patients with successfully eradicated *H. pylori* infection compared to untreated patients and patients who did not respond to therapy. The observed improvement in insulin resistance raises the possibility of further improvement in liver composition, or its surrogate CAP score, with longer follow-up. The main limitation of all four studies was differing follow-up, which ranged from 3 to 12 months. It is unclear what period is sufficient to see change following *H. pylori* infection eradication. More research is needed to clarify this period and the impact of *H. pylori* eradication on NAFLD.

Conclusion

The current first-line treatment of NAFLD is weight loss to modify known risk factors such as obesity and insulin resistance. *H. pylori* infection is an attractive potential target in treatment and risk factor modification for NAFLD given that there are effective ways to eradicate this pathogen. The data we has established a strong association between *H. pylori* infection and NAFLD and explored many potential mechanisms underlying this association. However, further research is warranted to better understand if this association is truly causal or at least contributory. A better understanding of the relationship between *H. pylori* infection and NAFLD may help clinicians identify patients who should be screened for NAFLD based on *H. pylori* infection status and patients with NAFLD who may benefit from *H. pylori* infection screening and eradication.

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Conflict of interest

GYW has been an editor-in-chief of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

MGMS is responsible for literature review, drafting manuscript and developing figure, GYW is responsible for major revisions, MD is responsible for topic conception, literature review, drafting manuscript and major revision.

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