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## ***Helicobacter pylori* infection and liver diseases: Epidemiology and insights into pathogenesis**

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### **Abstract**

Both *Helicobacter pylori* (*H. pylori*) infection and liver diseases, including nonalcoholic fatty liver disease (NAFLD), viral hepatitis, and hepatocellular carcinoma (HCC), have high prevalences worldwide, and the relationship between *H. pylori* infection and liver disease has been discussed for many years. Although positive correlations between *H. pylori* and NAFLD have been identified in some clinical and experimental studies, negative correlations have also been obtained in high-quality clinical studies. Associations between *H. pylori* and the pathogenesis of chronic viral hepatitis, mainly disease progression with fibrosis, have also been suggested in some clinical studies. Concerning HCC, a possible role for *H. pylori* in hepatocarcinogenesis has been identified since *H. pylori* genes have frequently been detected in resected HCC specimens. However, no study has

revealed the direct involvement of *H. pylori* in promoting the development of HCC. Although findings regarding the correlations between *H. pylori* and liver disease pathogenesis have been accumulating, the existing data do not completely lead to an unequivocal conclusion. Further high-quality clinical and experimental analyses are necessary to evaluate the efficacy of *H. pylori* eradication in ameliorating the histopathological changes observed in each liver disease.

**Key words:** *Helicobacter pylori*; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Hepatitis C virus; Hepatitis B virus; Viral hepatitis; Hepatocellular carcinoma

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**Core tip:** Both *Helicobacter pylori* (*H. pylori*) infection and liver diseases have high prevalences worldwide, and their relationship has been discussed for a long time. In this review, we comprehensively summarize positive and negative correlations suggested in clinical and experimental studies, and conclude that existing data cannot fully lead us to make a decision. We also point out the necessity of further analyses evaluating the efficacy of *H. pylori* eradication on histopathological changes in each liver disease. We believe this paper would help readers to gain a better understanding of the relationship between *H. pylori* and liver diseases.

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## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is one of the most well-known microbes in the world. Warren and Marshall reported the possible virulence of *H. pylori* in patients with gastritis, gastric ulcer, and duodenal ulcer in 1984<sup>[1]</sup>. Approximately 50% of the global population is estimated to be infected with *H. pylori*<sup>[2]</sup>, and chronic infection with *H. pylori* is one cause of chronic atrophic gastritis, peptic ulcer diseases, and gastric cancer<sup>[3,4]</sup>. Recently, findings concerning the influence of *H. pylori* on various extra-alimentary organs have accumulated<sup>[5-12]</sup>. Among these putative extra-alimentary disorders caused by *H. pylori*, the relationship with metabolic disorders remains controversial<sup>[13-23]</sup>.

Liver diseases, including nonalcoholic fatty liver disease (NAFLD), chronic viral hepatitis, and hepatocellular carcinoma (HCC), also have high prevalences worldwide. Consequently, the relationship between *H. pylori* and liver diseases has been discussed and still

remains controversial<sup>[10]</sup>. Although the presence of *H. pylori* or *Helicobacter* species has been observed in liver samples from patients with various liver diseases<sup>[24-30]</sup> and findings regarding possible roles for *H. pylori* in the pathogenesis of liver diseases have been accumulating, few studies have reported a direct contribution of *H. pylori* to the pathogenesis of liver diseases. Additionally, negative correlations have been identified in high-quality clinical studies<sup>[31-34]</sup>.

Currently, *H. pylori* is efficiently eradicated by various short-term treatments with combinations of antibiotics<sup>[35]</sup>. On the other hand, despite the remarkable progress in research and therapy, curative treatments have not yet been established for almost all liver diseases. Therefore, a discussion of whether *H. pylori* has a possible role in the pathogenesis of liver diseases and a clarification of the efficacy of *H. pylori* eradication in treating liver diseases are important. In this review, we present current insights into the relationship between *H. pylori* and liver diseases, such as NAFLD, chronic viral hepatitis, and HCC.

## H. PYLORI AND NAFLD

NAFLD is an emerging liver disease worldwide, including in Asian countries<sup>[31,36,37]</sup>. NAFLD is a spectrum of diseases ranging from simple steatosis to nonalcoholic steatohepatitis (NASH). The latter is progressive and considered a causative factor of cirrhosis, HCC, and systemic metabolic disorders<sup>[38-40]</sup>.

The initial description of NASH pathogenesis, which was previously defined as the "two-hit" theory, was presented by Day *et al.*<sup>[41]</sup> in 1998 and has been discussed by other researchers. In addition to a "first-hit" of hepatic steatosis, a "second-hit," such as gut-derived endotoxins, proinflammatory cytokines, dysregulation of adipokines, oxidative stress, endoplasmic reticulum stress, and lipotoxicity, is necessary for NASH development. Considering the complicated mechanisms of NAFLD, however, the "two-hit" theory had been thought to be insufficient, and instead, the "multiple-parallel hits" hypothesis was proposed by Tilg *et al.*<sup>[42]</sup>. According to this hypothesis, inflammatory mediators derived from various tissues, including the gut and adipose tissue, play a central role in the inflammatory cascade. However, the detailed pathogenesis largely remains unclear.

The relationship between *H. pylori* and NAFLD in the context of gastrointestinal tract inflammation has been long discussed but remains controversial (Table 1)<sup>[10,31-34,43-51]</sup>. Some cross-sectional or retrospective studies have not identified correlations between NAFLD and *H. pylori*<sup>[31-34]</sup>. Previously, we examined the associations of causative background factors with NAFLD by analyzing 13737 subjects in a cross-sectional study in Japan, but no correlations were observed between NAFLD and *H. pylori*, regardless of gender<sup>[31]</sup>. On the other hand, opposite results have also been reported<sup>[45-48]</sup>. In a meta-analysis, Wijarnpreecha *et al.*<sup>[49]</sup> found a significantly increased risk of NAFLD among patients with *H. pylori* infection, with pooled odds ratios



**Table 1** Summary of relevant studies between *Helicobacter pylori* and nonalcoholic fatty liver disease

Ref.	Year	Country	Study design	Number of subjects	Conclusion
Okushin <i>et al.</i> <sup>[31]</sup>	2015	Japan	Cross-sectional study	13737	Negative
Baeg <i>et al.</i> <sup>[32]</sup>	2016	South Korea	Cross-sectional study	3663	Negative
Fan <i>et al.</i> <sup>[33]</sup>	2018	China	Cross-sectional study	21456	Negative
Cai <i>et al.</i> <sup>[34]</sup>	2018	China	Cross-sectional study	2051	Negative
Polyzos <i>et al.</i> <sup>[45]</sup>	2013	Greece	Cross-sectional study	53	Positive
Doğan <i>et al.</i> <sup>[46]</sup>	2013	Turkey	Cross-sectional study	174	Positive
Kim <i>et al.</i> <sup>[47]</sup>	2017	South Korea	Retrospective study	17028	Positive
Chen <i>et al.</i> <sup>[48]</sup>	2017	China	Cross-sectional study	2263	Positive
Wijarnpreecha <i>et al.</i> <sup>[49]</sup>	2016	Various countries	Meta-analysis	38622	Positive
Jamali <i>et al.</i> <sup>[50]</sup>	2013	Iran	Prospective study (RCT)	49	Negative
Polyzos <i>et al.</i> <sup>[51]</sup>	2014	Greece	Prospective study	12	Negative

RCT: Randomized controlled trial.

of 1.21 (95%CI: 1.07-1.37).

To the best of our knowledge, only two randomized prospective studies have attempted to reveal the direct correlation between *H. pylori* eradication and NAFLD. As shown in the study by Jamali *et al.*<sup>[50]</sup>, eradication does not exert significant effects on the liver fat content, liver function tests, lipid profiles, and homeostasis model assessment of insulin resistance (HOMA-IR) index in patients with NAFLD, although one limitation of this study was that it was conducted on dyspeptic patients with NAFLD. Polyzos *et al.*<sup>[51]</sup> performed a small-scale prospective study of *H. pylori* eradication in patients with biopsy-proven NASH. In this study, eradication had no long-term effect on hepatic steatosis but showed a trend toward improving the noninvasive NAFLD fibrosis score<sup>[52]</sup>. Namely, in the *H. pylori*-eradicated group, the fibrosis scores decreased from -0.34 at baseline to -0.24 at month 12 ( $P = 0.116$ ), whereas the scores increased in the control group from -0.38 at baseline to -0.56 at month 12 ( $P = 0.249$ ). Larger-scale randomized prospective studies focusing on *H. pylori* eradication are needed.

NAFLD is closely related to metabolic syndrome. The relationship between *H. pylori* and metabolic syndrome has also been discussed for many years. Recently, Refaeli *et al.*<sup>[53]</sup> analyzed 147936 individuals aged 25-95 years who performed the urea breath test during 2002-2012 using a large computerized database of a health maintenance organization in Israel. In this study, the prevalences of *H. pylori* infection and metabolic syndrome were 52.0% and 11.4%, respectively. Compared to noninfected patients, *H. pylori*-infected patients exhibited an increased likelihood of developing metabolic syndrome (adjusted OR: 1.15, 95%CI: 1.10-1.19). Similar results have been obtained in a meta-analysis<sup>[54]</sup>, middle-sized community-based studies<sup>[55,56]</sup>, and hospital-based studies<sup>[17,57,58]</sup>. On the other hand, Takeoka *et al.*<sup>[59]</sup> reported unique controversial results focusing on the quantification of *H. pylori*-specific IgG concentrations. Namely, the subjects were stratified into 4 groups according to the concentration of *H. pylori*-specific IgG as follows: *H. pylori* seronegative ( $< 10$  U/mL), low *H. pylori*-specific IgG levels (10-30 U/mL), moderate *H. pylori*-specific IgG

levels (30-50 U/mL), or high *H. pylori*-specific IgG levels ( $> 50$  U/mL). After stratification, patients with low IgG levels had the lowest risk of metabolic syndrome, after adjusting for age, sex, smoking, drinking, and physical activity status. Using patients with the low IgG levels as the reference, patients with negative, moderate, and high IgG levels had ORs (95%CI) of 2.15 (1.06-4.16), 3.69 (1.12-16.7), and 4.05 (1.05-26.8), respectively. Indeed, *H. pylori*-specific IgG levels do not always reflect disease severity; further discussion is needed to determine why the group with low IgG levels, but not negative for IgG, exhibited the lowest risk of metabolic syndrome. Another cross-sectional study in Japan, which analyzed 7394 cases, evaluated the correlations between *H. pylori* infection with the development of metabolic syndrome and each parameter<sup>[17]</sup>. In this study, *H. pylori* seropositivity was a significant and independent predictor of metabolic syndrome (OR: 1.39, 95%CI: 1.18-1.62,  $P < 0.001$ ), as determined by a multivariate logistic regression analysis. Furthermore, according to the multivariate linear regression analysis, *H. pylori* seropositivity was significantly correlated with metabolic syndrome-related variables, such as higher systolic blood pressure ( $\beta$  coefficient = 1.03,  $P = 0.014$ ), a lower high-density lipoprotein (HDL) cholesterol level ( $\beta$  coefficient = -2.00,  $P < 0.001$ ), and a higher LDL cholesterol level ( $\beta$  coefficient = 2.21,  $P = 0.005$ ). In addition, successful eradication of *H. pylori* significantly improves disturbances in these metabolic parameters<sup>[60-63]</sup>. However, some reports contradict an association between *H. pylori* and these metabolic risk factors<sup>[64-68]</sup>. Therefore, we are not able to reach a definitive conclusion, and the effect of *H. pylori* on metabolic factors may depend on the subjects examined, due to differences in factors such as country of residence, dietary habits, culture, and fitness habits.

Since obesity is closely linked to NAFLD, a relationship between *H. pylori* and obesity has also been hypothesized. A meta-analysis by Lender *et al.*<sup>[69]</sup> concluded that the rates of obesity and overweight were inversely and significantly correlated with the prevalence of *H. pylori* infection ( $r = 0.29$ ,  $P < 0.001$ ). However, this meta-analysis only selected studies conducted in developed countries [GDP  $> 25000$  USD/(person·year)].

Contradictory results were obtained in rather large-scale studies performed in other countries, such as China<sup>[70,71]</sup>. The reason for this discrepancy remains to be elucidated, but the difference in dietary habits and culture is probably responsible. In addition, the subjects' appetites and actual food intake levels will presumably be changed after successful eradication of *H. pylori* and may affect body weight. To determine whether the presence of *H. pylori* itself triggers body weight gain, detailed studies without exogenous factors are necessary to determine whether an *H. pylori* infection itself triggers body weight gain. Nwokolo *et al.*<sup>[72]</sup> presented interesting data in a study examining this point. In a small-scale pilot trial, plasma ghrelin, leptin, and gastrin levels were measured before and after the cure of *H. pylori* in 10 subjects. After *H. pylori* cure, plasma ghrelin levels increased significantly by 75% ( $P = 0.002$ ). On the other hand, leptin and gastrin levels have decreased by 11% and 30%, respectively, although the differences were not significant. Ghrelin is known to stimulate appetite and induce a positive energy balance, leading to body weight gain<sup>[73]</sup>; therefore, an increase in plasma ghrelin levels might be associated with the development of obesity following the eradication of *H. pylori*.

One of the important manifestations of NAFLD is insulin resistance (IR)<sup>[74]</sup>. Higher HOMA-IR scores were recorded for *H. pylori*-infected patients<sup>[55,75-78]</sup>, while opposite results have also been obtained in other studies<sup>[19,79]</sup>. Cytokine production was suggested as a mechanism by which *H. pylori* induced IR. *H. pylori* infection stimulates the release of proinflammatory cytokines, including tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1, IL-6 and IL-8<sup>[80,81]</sup>. TNF- $\alpha$  induces IR by suppressing insulin-induced tyrosine phosphorylation of insulin receptor and its substrate, insulin receptor substrate (IRS)-1, in a hepatoma cell line<sup>[82]</sup>. In fact, neutralization of increased TNF- $\alpha$  levels in obese fa/fa rats significantly increases the peripheral uptake of glucose in response to insulin<sup>[83]</sup>. Adiponectin and fetuin-A are also regarded as key factors contributing to IR. Adiponectin, an adipocyte-derived hormone, antagonizes excess lipid storage in the liver and protects against inflammation and fibrosis<sup>[84]</sup>. According to Ando *et al.*<sup>[85]</sup>, successful eradication of *H. pylori* significantly increases total adiponectin levels from 5.61  $\mu\text{g/mL}$  to 6.16  $\mu\text{g/mL}$  ( $P < 0.0001$ ) as well as the levels of each multimer form (high-, middle-, and low-molecular-weight) of adiponectin. Fetuin-A, a glycoprotein produced by the liver, is correlated with impaired insulin sensitivity, glucose metabolism, and the onset of diabetes mellitus<sup>[86,87]</sup>. *H. pylori*-positive subjects have higher fetuin-A levels and HOMA-IR scores than *H. pylori*-negative subjects. In a cross-sectional study, the mean fetuin-A values were 0.77 g/L and 0.58 g/L in *H. pylori*-positive and *H. pylori*-negative subjects, respectively. Mean HOMA-IR scores were 3.1 and 2.2 in *H. pylori*-positive and *H. pylori*-negative subjects, respectively. In addition, a significant positive correlation between fetuin-A and HOMA-IR was observed after adjusting for other factors (adjusted coefficient  $\beta = 0.23$ ,  $P < 0.01$ )<sup>[88]</sup>.

Based on these results, levels of inflammatory cytokines, adiponectin and fetuin-A may be associated with *H. pylori*-related IR, although that relationship has not been completely acknowledged.

Recently, the gut microbiota has been the focus of studies on the pathogenesis of various diseases and has also been suggested to play key roles in NAFLD pathogenesis<sup>[89,90]</sup>. Cytotoxin-associated gene A antigen (CagA), the known virulence factor of *H. pylori*, has been reported to alter the gut microbiota, resulting in the exacerbation of cell proliferation and immune phenotypes<sup>[91]</sup>. Furthermore, increased mucosal permeability of the intestine induced by *H. pylori* infection was reported<sup>[92]</sup>. These alterations in the gut environment, such as the microbiota and mucosal barrier, by *H. pylori* may influence the pathogenesis of NAFLD.

In summary, positive correlations between *H. pylori* and NAFLD have been reported in some clinical and experimental studies, but other studies have presented contradictory data. Further analyses focusing on the effect of *H. pylori* eradication on histopathological changes in patients with biopsy-proven NAFLD are necessary.

## **H. PYLORI AND CHRONIC VIRAL HEPATITIS OR CIRRHOSIS**

The involvement of *H. pylori* in the pathogenesis of chronic viral hepatitis has been speculated (Table 2). Esmat *et al.*<sup>[30]</sup> evaluated the presence of the *H. pylori* CagA gene in liver samples from patients with hepatitis C virus (HCV)-related chronic hepatitis or cirrhosis by the polymerase chain reaction (PCR). In this study, the *H. pylori* gene was detected in 28.2% cases of late fibrosis (F3 + F4) and 5.9% cases of early fibrosis (F1 + F2) ( $P = 0.0001$ ) by PCR. The influence of *H. pylori* on the progression of HCV-related liver diseases has also been examined. Anti-*H. pylori* antibody positivity was significantly and independently associated with cirrhosis in patients with HCV-related chronic hepatitis or cirrhosis in multivariate analyses (OR: 2.42, 95%CI: 1.06-5.53,  $P = 0.037$ )<sup>[93]</sup>. Rocha *et al.*<sup>[94]</sup> examined liver tissues from *H. pylori*-infected patients and revealed that the *Helicobacter* 16S rDNA was only detected in 4.2% of liver samples from control patients and in 3.5% of samples from patients with noncirrhotic chronic hepatitis C. The *Helicobacter* 16S rDNA was detected in 68.0% of liver samples from patients with HCV-positive cirrhosis without HCC as well as in 61.3% of patients with HCC. In a meta-analysis, Wang *et al.*<sup>[95]</sup> analyzed the prevalence of *H. pylori* infection in a total of 1449 patients with chronic hepatitis C and 2377 control cases. The prevalence of *H. pylori* was significantly higher in patients with chronic hepatitis C than in those without chronic hepatitis C (pooled odds ratio 2.93). In a subgroup analysis, the odds ratios were 4.48 for HCV-related cirrhosis and 5.45 for HCC. These results suggest an association between *Helicobacter* species and HCV-related disease progression, but these findings only show the presence of *H. pylori*, not its pathogenicity.

**Table 2** Summary of relevant studies between *Helicobacter pylori* and chronic viral hepatitis, cirrhosis, and hepatocellular carcinoma

Ref.	Year	Country	Study design	Number of subjects	Conclusion
HCV					
Esmat <i>et al</i> <sup>[30]</sup>	2012	Egypt	Cross-sectional study	85	Positive
Queiroz <i>et al</i> <sup>[93]</sup>	2006	Argentina	Cross-sectional study	106	Positive
Rocha <i>et al</i> <sup>[94]</sup>	2005	France	Cross-sectional study	109	Positive
Wang <i>et al</i> <sup>[95]</sup>	2016	Various countries	Meta-analysis	3826	Positive
HBV					
Ponzetto <i>et al</i> <sup>[96]</sup>	2000	Italy	Case-control study	355	Positive
Huang <i>et al</i> <sup>[97]</sup>	2017	China	Cross-sectional study	608	Positive
Mohamed <i>et al</i> <sup>[98]</sup>	2018	Egypt	Cross-sectional study	170	Positive
Wang <i>et al</i> <sup>[99]</sup>	2011	China	Cross-sectional study	1872	Negative
Wang <i>et al</i> <sup>[100]</sup>	2016	China	Meta-analysis	4645	Positive
HCC					
Nilsson <i>et al</i> <sup>[24]</sup>	2001	Sweden	Cross-sectional study	36	Positive
Pellicano <i>et al</i> <sup>[25]</sup>	2004	Italy	Cross-sectional study	26	Positive
Huang <i>et al</i> <sup>[26]</sup>	2004	China	Cross-sectional study	36	Positive
Xuan <i>et al</i> <sup>[27]</sup>	2006	China	Cross-sectional study	50	Positive
Xuan <i>et al</i> <sup>[101]</sup>	2008	Various countries	Meta-analysis	522	Positive

HCV: Hepatitis C virus; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma.

in the liver. *H. pylori* may putatively flow into the liver via the portal vein and be caught and eliminated by intrahepatic immune cells such as Kupffer cells in the normal liver. Since the number of these cells decreases with the progression of fibrosis, *H. pylori* is speculated to be present in the liver as a result of immune escape. Accordingly, the prevalence of *H. pylori* might simply be high in patients with cirrhosis compared with that in control or noncirrhotic patients. Additional in-depth studies are required to confirm the actual involvement of *H. pylori* in the progression of liver fibrosis.

Clinical findings suggesting relationships between *H. pylori* and hepatitis B virus (HBV)-related liver diseases have also been reported<sup>[96-100]</sup>. A higher prevalence of *H. pylori* infection in HBV-infected patients has been reported in several studies<sup>[96-98]</sup>, but these findings may just reflect the hygienic environments in childhood. Actually, Wang *et al*<sup>[99]</sup> reported that the prevalence of *H. pylori* infection in asymptomatic HBV carriers was 38.67% in Shandong Province, China, which was not different than that in the normal adult population recruited from the same region (35.94%,  $P = 0.352$ ). Possible associations between the progression of HBV-related liver disease and liver-related complications, such as variceal bleeding, ascites, and encephalopathy, have also been reported<sup>[97]</sup>. In a meta-analysis of a Chinese population, the prevalence of *H. pylori* infection among patients with HBV-related liver diseases increased as the disease severity increased<sup>[100]</sup>. Namely, the *H. pylori*-positive rate in patients with chronic hepatitis B patients but not cirrhosis or HCC was 2.44-fold higher than that in healthy controls (pooled OR: 2.44, 95%CI: 1.85-3.24;  $P < 0.01$ ). Furthermore, the *H. pylori*-positive rate in patients with HBV-induced cirrhosis was 4.28-fold higher (pooled OR: 4.28, 95%CI: 2.99-6.13,  $P < 0.01$ ) than that in healthy controls, while it was 6.02-fold higher (pooled OR: 6.02, 95%CI: 4.33-8.37,  $P = 0.821$ ) in patients with HBV-related HCC. Therefore, the presence of *H. pylori* may accelerate the progression of HBV-related liver

pathogenesis, but the precise pathogenicity in the liver remains to be elucidated.

In summary, although *H. pylori* infection and chronic viral hepatitis seem to be associated in limited situations, further studies are necessary to obtain a final conclusion since researchers have not yet clearly determined whether *H. pylori* itself directly contributes to the progression of viral hepatitis.

## H. PYLORI AND HEPATOCARCINOGENESIS

Several clinical studies have reported an association between *H. pylori* and HCC (Table 2). *H. pylori* and similar species were detected in liver samples from patients with HCC<sup>[24-27]</sup>. Additionally, a positive association between *H. pylori* and the risk of HCC was reported in a meta-analysis<sup>[101]</sup>. The overall prevalence of *H. pylori* in the liver was 53.3% (129 of 242) in patients with HCC and 10.4% (29 of 280) in controls, and the odds ratio for the association between *H. pylori* infection and the risk of HCC was 13.63 (95%CI: 7.90-23.49). These observations, however, only showed the presence of *H. pylori* in liver tissues. HCC is usually accompanied by liver fibrosis, and in these circumstances, the intrahepatic immune status and hemodynamics may be changed to permit the inflow of *H. pylori* and escape from immunity in the liver, as noted above. Therefore, the presence of *H. pylori* only in HCC tissues does not provide strong support for an association with HCC.

Some *in vitro* studies have presented the possible mechanism underlying the association between *H. pylori* and hepatocarcinogenesis. As shown in the study by Zhang *et al*<sup>[102]</sup>, *H. pylori* causes pathological effects on HepG2 hepatoma cells by upregulating the expression of some proteins related to gene transcription and signal transduction. Virulent type *H. pylori* cause cell cycle arrest and apoptosis of Huh7 cells, another hepatoma cell line<sup>[103]</sup>. According to Liu *et al*<sup>[104]</sup>, histidine-rich protein



(Hpn), a small histidine-rich cytoplasmic protein from *H. pylori*, induces apoptosis by suppressing ubiquitin-specific peptidase 5 (USP5) expressions and activating the P14-P53 signaling pathway. However, these data are only indirect findings obtained from *in vitro* studies using cancer cell lines. Indeed, to the best of our knowledge, direct evidence for the tumorigenic effect of *H. pylori* on the liver has not been obtained. Ki *et al.*<sup>[105]</sup> postulated that *H. pylori* infection might promote the transforming growth factor (TGF)- $\beta$ 1-dependent oncogenic pathway, disturbing the balance between hepatocyte apoptosis and proliferation in a murine model of CCl<sub>4</sub>-induced fibrosis, but in this study, the development of HCC itself was not observed. Furthermore, in transgenic mice expressing HCV proteins, *H. pylori* infection did not promote the development of HCC<sup>[106]</sup>. Based on these findings, *H. pylori* infection is currently presumed to be unlikely to contribute to HCC development.

In summary, although *H. pylori* genes are frequently detected in HCC samples, possible correlations between *H. pylori* and hepatocarcinogenesis seem to be doubtful. Further studies showing the direct contribution *in vivo* using infectious animal models or mice transgenic for *H. pylori* genes are necessary to confirm this relationship.

## CONCLUSION

*H. pylori* have a high prevalence, and its roles in liver diseases, as well as its well-known contribution to the pathogenesis of gastric disorders, have been discussed. As described in this review, several correlations between *H. pylori* and liver diseases, particularly NAFLD, have been reported in some clinical and experimental studies, but these correlations remain controversial. Further analyses are required to elucidate the associations. In addition, since only a few studies have examined the effect of *H. pylori* eradication on the pathogenesis of NAFLD, histopathological confirmation that *H. pylori* eradication specifically prevents or improves disease progression is necessary. Concerning chronic viral hepatitis and HCC, some observational studies suggested positive correlations. But, we have to recognize possibilities of the publication bias and confounding factors such as hygienic environments and contaminations resulting from the presence of cirrhosis. Actually, few studies have definitively confirmed the pathogenic contribution of *H. pylori* to increase of inflammation, progression of fibrosis, or acceleration of hepatocarcinogenesis. *H. pylori* infection and liver diseases still have high prevalences worldwide and significant impact on patients' prognosis. There is a room to discuss whether *H. pylori* are really involved in pathogenesis of each liver disease. To demonstrate the actual involvement of *H. pylori* in these processes, *H. pylori* itself or its gene product must be shown to accelerate the pathogenesis of these diseases using well-established animal models.

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## REFERENCES

- 1 Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **1**: 1311-1315 [PMID: 6145023 DOI: 10.1016/S0140-6736(84)91816-6]
- 2 Cover TL, Blaser MJ. Helicobacter pylori in health and disease. *Gastroenterology* 2009; **136**: 1863-1873 [PMID: 19457415 DOI: 10.1053/j.gastro.2009.01.073]
- 3 Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ; European Helicobacter Study Group. Management of Helicobacter pylori infection—the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]
- 4 Matsuhisa T, Aftab H. Observation of gastric mucosa in Bangladesh, the country with the lowest incidence of gastric cancer, and Japan, the country with the highest incidence. *Helicobacter* 2012; **17**: 396-401 [PMID: 22967124 DOI: 10.1111/j.1523-5378.2012.00967.x]
- 5 Patel P, Mendall MA, Carrington D, Strachan DP, Leatham E, Molineaux N, Levy J, Blakeston C, Seymour CA, Camm AJ. Association of Helicobacter pylori and Chlamydia pneumoniae infections with coronary heart disease and cardiovascular risk factors. *BMJ* 1995; **311**: 711-714 [PMID: 7549683 DOI: 10.1136/bmj.311.7007.711]
- 6 Federman DG, Kirsner RS, Moriarty JP, Concato J. The effect of antibiotic therapy for patients infected with Helicobacter pylori who have chronic urticaria. *J Am Acad Dermatol* 2003; **49**: 861-864 [PMID: 14576665 DOI: 10.1016/S0190-9622(03)00846-6]
- 7 Maurer KJ, Ihrig MM, Rogers AB, Ng V, Bouchard G, Leonard MR, Carey MC, Fox JG. Identification of cholelithogenic enterohepatic helicobacter species and their role in murine cholesterol gallstone formation. *Gastroenterology* 2005; **128**: 1023-1033 [PMID: 15825083 DOI: 10.1053/j.gastro.2005.01.008]
- 8 Takahashi Y, Yamamichi N, Shimamoto T, Mochizuki S, Fujishiro M, Takeuchi C, Sakaguchi Y, Niimi K, Ono S, Kodashima S, Mitsushima T, Koike K. Helicobacter pylori infection is positively associated with gallstones: a large-scale cross-sectional study in Japan. *J Gastroenterol* 2014; **49**: 882-889 [PMID: 23736795 DOI: 10.1007/s00535-013-0832-z]
- 9 Franceschi F, Zuccalà G, Roccarina D, Gasbarrini A. Clinical effects of Helicobacter pylori outside the stomach. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 234-242 [PMID: 24345888 DOI: 10.1038/nrgastro.2013.243]
- 10 Waluga M, Kukla M, Żorniak M, Bacik A, Kotulski R. From the stomach to other organs: Helicobacter pylori and the liver. *World J Hepatol* 2015; **7**: 2136-2146 [PMID: 26328025 DOI: 10.4254/wjh.v7.i18.2136]
- 11 Rabelo-Gonçalves EM, Roesler BM, Zeitune JM. Extragastric manifestations of Helicobacter pylori infection: Possible role of bacterium in liver and pancreas diseases. *World J Hepatol* 2015; **7**: 2968-2979 [PMID: 26730276 DOI: 10.4254/wjh.v7.i30.2968]
- 12 de Korwin JD, Ianiro G, Gibiino G, Gasbarrini A. Helicobacter pylori infection and extragastric diseases in 2017. *Helicobacter* 2017; **22** Suppl 1 [PMID: 28891133 DOI: 10.1111/hel.12411]
- 13 Pietroiusti A, Diomedì M, Silvestrini M, Cupini LM, Luzzi I, Gomez-Miguel MJ, Bergamaschi A, Magrini A, Carrabs T, Vellini M, Galante A. Cytotoxin-associated gene-A--positive Helicobacter pylori strains are associated with atherosclerotic stroke. *Circulation* 2002; **106**: 580-584 [PMID: 12147540 DOI: 10.1161/01.CIR.0000023894.10871.2F]
- 14 Diomedì M, Pietroiusti A, Silvestrini M, Rizzato B, Cupini LM, Ferrante F, Magrini A, Bergamaschi A, Galante A, Bernardi G. CagA-positive Helicobacter pylori strains may influence the natural history of atherosclerotic stroke. *Neurology* 2004; **63**: 800-804 [PMID: 15365126 DOI: 10.1212/01.WNL.0000138025.82419.80]
- 15 Cho I, Blaser MJ, François F, Mathew JP, Ye XY, Goldberg JD, Bini EJ. Helicobacter pylori and overweight status in the United States: data from the Third National Health and Nutrition Examination Survey. *Am*

- J Epidemiol* 2005; **162**: 579-584 [PMID: 16093294 DOI: 10.1093/aje/kwi237]
- 16 **Longo-Mbenza B**, Nkondi Nsenga J, Vangu Ngoma D. Prevention of the metabolic syndrome insulin resistance and the atherosclerotic diseases in Africans infected by *Helicobacter pylori* infection and treated by antibiotics. *Int J Cardiol* 2007; **121**: 229-238 [PMID: 17368586 DOI: 10.1016/j.ijcard.2006.12.003]
  - 17 **Gunji T**, Matsuhashi N, Sato H, Fujibayashi K, Okumura M, Sasabe N, Urabe A. *Helicobacter pylori* infection is significantly associated with metabolic syndrome in the Japanese population. *Am J Gastroenterol* 2008; **103**: 3005-3010 [PMID: 19086952 DOI: 10.1111/j.1572-0241.2008.02151.x]
  - 18 **Satoh H**, Saijo Y, Yoshioka E, Tsutsui H. *Helicobacter Pylori* infection is a significant risk for modified lipid profile in Japanese male subjects. *J Atheroscler Thromb* 2010; **17**: 1041-1048 [PMID: 20610892 DOI: 10.5551/jat.5157]
  - 19 **Naja F**, Nasreddine L, Hwalla N, Moghames P, Shoaib H, Fatfat M, Sibai A, Gali-Muhtasib H. Association of *H. pylori* infection with insulin resistance and metabolic syndrome among Lebanese adults. *Helicobacter* 2012; **17**: 444-451 [PMID: 23066847 DOI: 10.1111/j.1523-5378.2012.00970.x]
  - 20 **Stergiopoulos C**, Kountouras J, Daskalopoulou-Vlachoyianni E, Polyzos SA, Zavos C, Vlachoyiannis E, Kokkali S, Deretzi G, Kapetanakis N, Katsinelos P, Gavalas E. *Helicobacter pylori* may play a role in both obstructive sleep apnea and metabolic syndrome. *Sleep Med* 2012; **13**: 212-213 [PMID: 22137108 DOI: 10.1016/j.sleep.2011.04.016]
  - 21 **Shin DW**, Kwon HT, Kang JM, Park JH, Choi HC, Park MS, Park SM, Son KY, Cho B. Association between metabolic syndrome and *Helicobacter pylori* infection diagnosed by histologic status and serological status. *J Clin Gastroenterol* 2012; **46**: 840-845 [PMID: 23064216 DOI: 10.1097/MCG.0b013e3182522477]
  - 22 **Buzás GM**. Metabolic consequences of *Helicobacter pylori* infection and eradication. *World J Gastroenterol* 2014; **20**: 5226-5234 [PMID: 24833852 DOI: 10.3748/wjg.v20.i18.5226]
  - 23 **Lee M**, Baek H, Park JS, Kim S, Kyung C, Baik SJ, Lee BK, Kim JH, Ahn CW, Kim KR, Kang S. Current *Helicobacter pylori* infection is significantly associated with subclinical coronary atherosclerosis in healthy subjects: A cross-sectional study. *PLoS One* 2018; **13**: e0193646 [PMID: 29499055 DOI: 10.1371/journal.pone.0193646]
  - 24 **Nilsson HO**, Mulchandani R, Tranberg KG, Stenram U, Wadström T. *Helicobacter* species identified in liver from patients with cholangiocarcinoma and hepatocellular carcinoma. *Gastroenterology* 2001; **120**: 323-324 [PMID: 11246512 DOI: 10.1053/gast.2001.21382]
  - 25 **Pellicano R**, Mazzaferro V, Grigioni WF, Cutufo MA, Fagoonee S, Silengo L, Rizzetto M, Ponzetto A. *Helicobacter* species sequences in liver samples from patients with and without hepatocellular carcinoma. *World J Gastroenterol* 2004; **10**: 598-601 [PMID: 14966925 DOI: 10.3748/wjg.v10.i4.598]
  - 26 **Huang Y**, Fan XG, Wang ZM, Zhou JH, Tian XF, Li N. Identification of *Helicobacter* species in human liver samples from patients with primary hepatocellular carcinoma. *J Clin Pathol* 2004; **57**: 1273-1277 [PMID: 15563667 DOI: 10.1136/jcp.2004.018556]
  - 27 **Xuan SY**, Li N, Qiang X, Zhou RR, Shi YX, Jiang WJ. *Helicobacter* infection in hepatocellular carcinoma tissue. *World J Gastroenterol* 2006; **12**: 2335-2340 [PMID: 16688821 DOI: 10.3748/wjg.v12.i15.2335]
  - 28 **Cindoruk M**, Cirak MY, Unal S, Karakan T, Erkan G, Engin D, Dumlu S, Turet S. Identification of *Helicobacter* species by 16S rDNA PCR and sequence analysis in human liver samples from patients with various etiologies of benign liver diseases. *Eur J Gastroenterol Hepatol* 2008; **20**: 33-36 [PMID: 18090988 DOI: 10.1097/MEG.0b013e3282efa4f2]
  - 29 **Pirouz T**, Zounubi L, Keivani H, Rakhshani N, Hormazdi M. Detection of *Helicobacter pylori* in paraffin-embedded specimens from patients with chronic liver diseases, using the amplification method. *Dig Dis Sci* 2009; **54**: 1456-1459 [PMID: 18975076 DOI: 10.1007/s10620-008-0522-5]
  - 30 **Esmat G**, El-Bendary M, Zakarya S, Ela MA, Zalata K. Role of *Helicobacter pylori* in patients with HCV-related chronic hepatitis and cirrhosis with or without hepatocellular carcinoma: possible association with disease progression. *J Viral Hepat* 2012; **19**: 473-479 [PMID: 22676359 DOI: 10.1111/j.1365-2893.2011.01567.x]
  - 31 **Okushin K**, Takahashi Y, Yamamichi N, Shimamoto T, Enooku K, Fujinaga H, Tsutsumi T, Shintani Y, Sakaguchi Y, Ono S, Kodashima S, Fujishiro M, Moriya K, Yotsuyanagi H, Mitsushima T, Koike K. *Helicobacter pylori* infection is not associated with fatty liver disease including non-alcoholic fatty liver disease: a large-scale cross-sectional study in Japan. *BMC Gastroenterol* 2015; **15**: 25 [PMID: 25880912 DOI: 10.1186/s12876-015-0247-9]
  - 32 **Baeg MK**, Yoon SK, Ko SH, Noh YS, Lee IS, Choi MG. *Helicobacter pylori* infection is not associated with nonalcoholic fatty liver disease. *World J Gastroenterol* 2016; **22**: 2592-2600 [PMID: 26937147 DOI: 10.3748/wjg.v22.i8.2592]
  - 33 **Fan N**, Peng L, Xia Z, Zhang L, Wang Y, Peng Y. *Helicobacter pylori* Infection Is Not Associated with Non-alcoholic Fatty Liver Disease: A Cross-Sectional Study in China. *Front Microbiol* 2018; **9**: 73 [PMID: 29445363 DOI: 10.3389/fmicb.2018.00073]
  - 34 **Cai O**, Huang Z, Li M, Zhang C, Xi F, Tan S. Association between *Helicobacter pylori* Infection and Nonalcoholic Fatty Liver Disease: A Single-Center Clinical Study. *Gastroenterol Res Pract* 2018; **2018**: 8040262 [PMID: 29527224 DOI: 10.1155/2018/8040262]
  - 35 **Suzuki H**, Mori H. World trends for *H. pylori* eradication therapy and gastric cancer prevention strategy by *H. pylori* test-and-treat. *J Gastroenterol* 2018; **53**: 354-361 [PMID: 29138921 DOI: 10.1007/s00535-017-1407-1]
  - 36 **Kojima S**, Watanabe N, Numata M, Ogawa T, Matsuzaki S. Increase in the prevalence of fatty liver in Japan over the past 12 years: analysis of clinical background. *J Gastroenterol* 2003; **38**: 954-961 [PMID: 14614602 DOI: 10.1007/s00535-003-1178-8]
  - 37 **Satapathy SK**, Sanyal AJ. Epidemiology and Natural History of Nonalcoholic Fatty Liver Disease. *Semin Liver Dis* 2015; **35**: 221-235 [PMID: 26378640 DOI: 10.1055/s-0035-1562943]
  - 38 **Marrero JA**, Fontana RJ, Su GL, Conjeevaram HS, Emick DM, Lok AS. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. *Hepatology* 2002; **36**: 1349-1354 [PMID: 12447858 DOI: 10.1053/jhep.2002.36939]
  - 39 **Rubinstein E**, Lavine JE, Schwimmer JB. Hepatic, cardiovascular, and endocrine outcomes of the histological subphenotypes of nonalcoholic fatty liver disease. *Semin Liver Dis* 2008; **28**: 380-385 [PMID: 18956294 DOI: 10.1055/s-0028-1091982]
  - 40 **Baffy G**, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. *J Hepatol* 2012; **56**: 1384-1391 [PMID: 22326465 DOI: 10.1016/j.jhep.2011.10.027]
  - 41 **Day CP**, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology* 1998; **114**: 842-845 [PMID: 9547102 DOI: 10.1016/S0016-5085(98)70599-2]
  - 42 **Tilg H**, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology* 2010; **52**: 1836-1846 [PMID: 21038418 DOI: 10.1002/hep.24001]
  - 43 **Tang DM**, Kumar S. The Association Between *Helicobacter pylori* Infection and Nonalcoholic Fatty Liver Disease. *Curr Gastroenterol Rep* 2017; **19**: 5 [PMID: 28155087 DOI: 10.1007/s11894-017-0545-1]
  - 44 **Cheng DD**, He C, Ai HH, Huang Y, Lu NH. The Possible Role of *Helicobacter pylori* Infection in Non-alcoholic Fatty Liver Disease. *Front Microbiol* 2017; **8**: 743 [PMID: 28539915 DOI: 10.3389/fmicb.2017.00743]
  - 45 **Polyzos SA**, Kountouras J, Papatheodorou A, Patsiaoura K, Katsiki E, Zafeiriadou E, Zavos C, Anastasiadou K, Terpos E. *Helicobacter pylori* infection in patients with nonalcoholic fatty liver disease. *Metabolism* 2013; **62**: 121-126 [PMID: 22841522 DOI: 10.1016/j.metabol.2012.06.007]
  - 46 **Doğan Z**, Filik L, Ergül B, Sarıkaya M, Akbal E. Association between *Helicobacter pylori* and liver-to-spleen ratio: a randomized-controlled single-blind study. *Eur J Gastroenterol Hepatol* 2013; **25**: 107-110 [PMID: 23013624 DOI: 10.1097/MEG.0b013e3283590c10]
  - 47 **Kim TJ**, Sinn DH, Min YW, Son HJ, Kim JJ, Chang Y, Baek SY, Ahn SH, Lee H, Ryu S. A cohort study on *Helicobacter pylori* infection associated with nonalcoholic fatty liver disease. *J Gastroenterol* 2017; **52**: 1201-1210 [PMID: 28382402 DOI: 10.1007/s00535-017-1337-y]

- 48 **Chen CX**, Mao YS, Foster P, Zhu ZW, Du J, Guo CY. Possible association between *Helicobacter pylori* infection and nonalcoholic fatty liver disease. *Appl Physiol Nutr Metab* 2017; **42**: 295-301 [PMID: 28177748 DOI: 10.1139/apnm-2016-0499]
- 49 **Wijarnpreecha K**, Thongprayoon C, Panjawatanan P, Manatsathit W, Jaruvongvanich V, Ungprasert P. *Helicobacter pylori* and Risk of Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis. *J Clin Gastroenterol* 2018; **52**: 386-391 [PMID: 28098578 DOI: 10.1097/MCG.0000000000000784]
- 50 **Jamali R**, Mofid A, Vahedi H, Farzaneh R, Dowlatsahi S. The effect of *Helicobacter pylori* eradication on liver fat content in subjects with non-alcoholic Fatty liver disease: a randomized open-label clinical trial. *Hepat Mon* 2013; **13**: e14679 [PMID: 24358044 DOI: 10.5812/hepatmon.14679]
- 51 **Polyzos SA**, Nikolopoulos P, Stogianni A, Romiopoulou I, Katsinelos P, Kountouras J. Effect of *Helicobacter pylori* eradication on hepatic steatosis, NAFLD fibrosis score and HSENSI in patients with nonalcoholic steatohepatitis: a MR imaging-based pilot open-label study. *Arq Gastroenterol* 2014; **51**: 261-268 [PMID: 25296089 DOI: 10.1590/S0004-28032014000300017]
- 52 **Angulo P**, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Sakseena S, Burt AD, Bida JP, Lindor K, Sanderson SO, Lenzi M, Adams LA, Kench J, Thorneau TM, Day CP. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology* 2007; **45**: 846-854 [PMID: 17393509 DOI: 10.1002/hep.21496]
- 53 **Refaeli R**, Chodick G, Haj S, Goren S, Shalev V, Muhsen K. Relationships of *H. pylori* infection and its related gastroduodenal morbidity with metabolic syndrome: a large cross-sectional study. *Sci Rep* 2018; **8**: 4088 [PMID: 29511278 DOI: 10.1038/s41598-018-22198-9]
- 54 **Upala S**, Jaruvongvanich V, Riangwiwat T, Jaruvongvanich S, Sanguankeo A. Association between *Helicobacter pylori* infection and metabolic syndrome: a systematic review and meta-analysis. *J Dig Dis* 2016; **17**: 433-440 [PMID: 27273478 DOI: 10.1111/1751-2980.12367]
- 55 **Chen LW**, Chien CY, Yang KJ, Kuo SF, Chen CH, Chien RN. *Helicobacter pylori* Infection Increases Insulin Resistance and Metabolic Syndrome in Residents Younger than 50 Years Old: A Community-Based Study. *PLoS One* 2015; **10**: e0128671 [PMID: 26020514 DOI: 10.1371/journal.pone.0128671]
- 56 **Chen LW**, Chien CY, Hsieh CW, Chang LC, Huang MH, Huang WY, Kuo SF, Chien CH, Lin CL, Chien RN. The Associations Between *Helicobacter pylori* Infection, Serum Vitamin D, and Metabolic Syndrome: A Community-Based Study. *Medicine (Baltimore)* 2016; **95**: e3616 [PMID: 27149497 DOI: 10.1097/MD.0000000000003616]
- 57 **Chen TP**, Hung HF, Chen MK, Lai HH, Hsu WF, Huang KC, Yang KC. *Helicobacter Pylori* Infection is Positively Associated with Metabolic Syndrome in Taiwanese Adults: a Cross-Sectional Study. *Helicobacter* 2015; **20**: 184-191 [PMID: 25582223 DOI: 10.1111/hel.12190]
- 58 **Yang W**, Xuan C. Influence of *Helicobacter pylori* Infection on Metabolic Syndrome in Old Chinese People. *Gastroenterol Res Pract* 2016; **2016**: 6951264 [PMID: 27429613 DOI: 10.1155/2016/6951264]
- 59 **Takeoka A**, Tayama J, Yamasaki H, Kobayashi M, Ogawa S, Saigo T, Hayashida M, Shirabe S. Impact of *Helicobacter pylori* Immunoglobulin G Levels and Atrophic Gastritis Status on Risk of Metabolic Syndrome. *PLoS One* 2016; **11**: e0166588 [PMID: 27851820 DOI: 10.1371/journal.pone.0166588]
- 60 **Scharnagl H**, Kist M, Grawitz AB, Koenig W, Wieland H, März W. Effect of *Helicobacter pylori* eradication on high-density lipoprotein cholesterol. *Am J Cardiol* 2004; **93**: 219-220 [PMID: 14715353 DOI: 10.1016/j.amjcard.2003.09.045]
- 61 **Ando T**, Minami M, Ishiguro K, Maeda O, Watanabe O, Mizuno T, Fujita T, Takahashi H, Noshiro M, Goto H. Changes in biochemical parameters related to atherosclerosis after *Helicobacter pylori* eradication. *Aliment Pharm Therap* 2006; **24**: 58-64 [DOI: 10.1111/j.1365-2036.2006.00026.x]
- 62 **Gen R**, Demir M, Ataseven H. Effect of *Helicobacter pylori* eradication on insulin resistance, serum lipids and low-grade inflammation. *South Med J* 2010; **103**: 190-196 [PMID: 20134372 DOI: 10.1097/SMJ.0b013e3181cf373f]
- 63 **Mokhtare M**, Mirfakhraee H, Arshad M, Samadani Fard SH, Bahardoust M, Movahed A, Masoodi M. The effects of *Helicobacter pylori* eradication on modification of metabolic syndrome parameters in patients with functional dyspepsia. *Diabetes Metab Syndr* 2017; **11** Suppl 2: S1031-S1035 [PMID: 28780229 DOI: 10.1016/j.dsx.2017.07.035]
- 64 **Woodward M**, Morrison C, McColl K. An investigation into factors associated with *Helicobacter pylori* infection. *J Clin Epidemiol* 2000; **53**: 175-181 [PMID: 10729690 DOI: 10.1016/S0895-4356(99)00171-7]
- 65 **Gillum RF**. Infection with *Helicobacter pylori*, coronary heart disease, cardiovascular risk factors, and systemic inflammation: the Third National Health and Nutrition Examination Survey. *J Natl Med Assoc* 2004; **96**: 1470-1476 [PMID: 15586651]
- 66 **Mostaza JM**, Camino N, Gerique JG, Peña R, Baquero M, Lahoz C. C-reactive protein levels and prevalence of chronic infections in subjects with hypoalbuminemia. *Metabolism* 2005; **54**: 33-37 [PMID: 15562377 DOI: 10.1016/j.metabol.2004.07.009]
- 67 **Sotiriopoulos A**, Gikas A, Skourtis S, Merkouris P, Pentzeridis P, Polydorou A, Pappas S. Seropositivity to *Chlamydia pneumoniae* or *Helicobacter pylori* and coronary artery disease. *Int J Cardiol* 2006; **109**: 420-421 [PMID: 15993502 DOI: 10.1016/j.ijcard.2005.05.039]
- 68 **Alzahrani S**, Nelson J, Moss SF, Paulus JK, Knowler WC, Pittas AG; Diabetes Prevention Program Research Group. *H. pylori* seroprevalence and risk of diabetes: An ancillary case-control study nested in the diabetes prevention program. *J Diabetes Complications* 2017; **31**: 1515-1520 [PMID: 28739267 DOI: 10.1016/j.jdiacomp.2017.05.015]
- 69 **Lender N**, Talley NJ, Enck P, Haag S, Zipfel S, Morrison M, Holtmann GJ. Review article: Associations between *Helicobacter pylori* and obesity—an ecological study. *Aliment Pharmacol Ther* 2014; **40**: 24-31 [PMID: 24832176 DOI: 10.1111/apt.12790]
- 70 **Xu C**, Yan M, Sun Y, Joo J, Wan X, Yu C, Wang Q, Shen C, Chen P, Li Y, Coleman WG Jr. Prevalence of *Helicobacter pylori* infection and its relation with body mass index in a Chinese population. *Helicobacter* 2014; **19**: 437-442 [PMID: 25256639 DOI: 10.1111/hel.12153]
- 71 **Zhang Y**, Du T, Chen X, Yu X, Tu L, Zhang C. Association between *Helicobacter pylori* infection and overweight or obesity in a Chinese population. *J Infect Dev Ctries* 2015; **9**: 945-953 [PMID: 26409735 DOI: 10.3855/jidc.6035]
- 72 **Nwokolo CU**, Freshwater DA, O'Hare P, Randeva HS. Plasma ghrelin following cure of *Helicobacter pylori*. *Gut* 2003; **52**: 637-640 [PMID: 12692045 DOI: 10.1136/gut.52.5.637]
- 73 **Inui A**, Asakawa A, Bowers CY, Mantovani G, Laviano A, Meguid MM, Fujimiya M. Ghrelin, appetite, and gastric motility: the emerging role of the stomach as an endocrine organ. *FASEB J* 2004; **18**: 439-456 [PMID: 15003990 DOI: 10.1096/fj.03-0641rev]
- 74 **Chitturi S**, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, Karim R, Lin R, Samarasinghe D, Liddle C, Weltman M, George J. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology* 2002; **35**: 373-379 [PMID: 11826411 DOI: 10.1053/jhep.2002.30692]
- 75 **Eshraghian A**, Hashemi SA, Hamidian Jahromi A, Eshraghian H, Masoompour SM, Davarpanah MA, Eshraghian K, Taghavi SA. *Helicobacter pylori* infection as a risk factor for insulin resistance. *Dig Dis Sci* 2009; **54**: 1966-1970 [PMID: 19009348 DOI: 10.1007/s10620-008-0557-7]
- 76 **Gunji T**, Matsuhashi N, Sato H, Fujibayashi K, Okumura M, Sasabe N, Urabe A. *Helicobacter pylori* infection significantly increases insulin resistance in the asymptomatic Japanese population. *Helicobacter* 2009; **14**: 144-150 [PMID: 19751440 DOI: 10.1111/j.1523-5378.2009.00705.x]
- 77 **Polyzos SA**, Kountouras J, Zavos C, Deretzi G. The association between *Helicobacter pylori* infection and insulin resistance: a systematic review. *Helicobacter* 2011; **16**: 79-88 [PMID: 21435084 DOI: 10.1111/j.1523-5378.2011.00822.x]
- 78 **Polyzos SA**, Kountouras J, Zavos C, Deretzi G. *Helicobacter pylori* Infection and insulin resistance. *Helicobacter* 2013; **18**: 165-166 [PMID: 23066701 DOI: 10.1111/hel.12019]



- 79 **Sumida Y**, Kanemasa K, Imai S, Mori K, Tanaka S, Shimokobe H, Kitamura Y, Fukumoto K, Kakutani A, Ohno T, Taketani H, Seko Y, Ishiba H, Hara T, Okajima A, Yamaguchi K, Moriguchi M, Mitsuyoshi H, Yasui K, Minami M, Itoh Y. Helicobacter pylori infection might have a potential role in hepatocyte ballooning in nonalcoholic fatty liver disease. *J Gastroenterol* 2015; **50**: 996-1004 [PMID: 25622927 DOI: 10.1007/s00535-015-1039-2]
- 80 **Peek RM Jr**, Blaser MJ. Helicobacter pylori and gastrointestinal tract adenocarcinomas. *Nat Rev Cancer* 2002; **2**: 28-37 [PMID: 11902583 DOI: 10.1038/nrc703]
- 81 **Basso D**, Plebani M, Kusters JG. Pathogenesis of Helicobacter pylori infection. *Helicobacter* 2010; **15** Suppl 1: 14-20 [PMID: 21054648 DOI: 10.1111/j.1523-5378.2010.00781.x]
- 82 **Feinstein R**, Kanety H, Papa MZ, Lunenfeld B, Karasik A. Tumor necrosis factor-alpha suppresses insulin-induced tyrosine phosphorylation of insulin receptor and its substrates. *J Biol Chem* 1993; **268**: 26055-26058 [PMID: 8253716]
- 83 **Hotamisligil GS**, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 1993; **259**: 87-91 [PMID: 7678183 DOI: 10.1126/science.7678183]
- 84 **Buechler C**, Wanninger J, Neumeier M. Adiponectin, a key adipokine in obesity related liver diseases. *World J Gastroenterol* 2011; **17**: 2801-2811 [PMID: 21734787]
- 85 **Ando T**, Ishikawa T, Takagi T, Imamoto E, Kishimoto E, Okajima A, Uchiyama K, Handa O, Yagi N, Kokura S, Naito Y, Mizuno S, Asakawa A, Inui A, Yoshikawa T. Impact of Helicobacter pylori eradication on circulating adiponectin in humans. *Helicobacter* 2013; **18**: 158-164 [PMID: 23167259 DOI: 10.1111/hel.12028]
- 86 **Stefan N**, Fritsche A, Weikert C, Boeing H, Joost HG, Häring HU, Schulze MB. Plasma fetuin-A levels and the risk of type 2 diabetes. *Diabetes* 2008; **57**: 2762-2767 [PMID: 18633113 DOI: 10.2337/db08-0538]
- 87 **Kantartzis K**, Machann J, Schick F, Fritsche A, Häring HU, Stefan N. The impact of liver fat vs visceral fat in determining categories of prediabetes. *Diabetologia* 2010; **53**: 882-889 [PMID: 20099057 DOI: 10.1007/s00125-010-1663-6]
- 88 **Manolakis AC**, Tiaka EK, Kapsoritakis AN, Georgoulis P, Tsiopoulos F, Valotassiou V, Potamianos SP. Increased fetuin A levels in Helicobacter pylori infection: a missing link between H. pylori and insulin resistance? *Diabetologia* 2011; **54**: 472-474 [PMID: 21116603 DOI: 10.1007/s00125-010-1995-2]
- 89 **Henao-Mejia J**, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, Thaiss CA, Kau AL, Eisenbarth SC, Jurczak MJ, Camporez JP, Shulman GI, Gordon JI, Hoffman HM, Flavell RA. Inflammation-mediated dysbiosis regulates progression of NAFLD and obesity. *Nature* 2012; **482**: 179-185 [PMID: 22297845 DOI: 10.1038/nature10809]
- 90 **Quigley EM**, Abu-Shanab A, Murphy EF, Stanton C, Monsour HP Jr. The Metabolic Role of the Microbiome: Implications for NAFLD and the Metabolic Syndrome. *Semin Liver Dis* 2016; **36**: 312-316 [PMID: 27997970 DOI: 10.1055/s-0036-1593880]
- 91 **Jones TA**, Hernandez DZ, Wong ZC, Wandler AM, Guillemin K. The bacterial virulence factor CagA induces microbial dysbiosis that contributes to excessive epithelial cell proliferation in the Drosophila gut. *PLoS Pathog* 2017; **13**: e1006631 [PMID: 29049360 DOI: 10.1371/journal.ppat.1006631]
- 92 **Fukuda Y**, Bamba H, Okui M, Tamura K, Tanida N, Satomi M, Shimoyama T, Nishigami T. Helicobacter pylori infection increases mucosal permeability of the stomach and intestine. *Digestion* 2001; **63** Suppl 1: 93-96 [PMID: 11173917 DOI: 10.1159/000051918]
- 93 **Queiroz DM**, Rocha AM, Rocha GA, Cinque SM, Oliveira AG, Godoy A, Tanno H. Association between Helicobacter pylori infection and cirrhosis in patients with chronic hepatitis C virus. *Dig Dis Sci* 2006; **51**: 370-373 [PMID: 16534683 DOI: 10.1007/s10620-006-3150-y]
- 94 **Rocha M**, Avenaud P, Ménard A, Le Bail B, Balabaud C, Bioulac-Sage P, de Magalhães Queiroz DM, Mégraud F. Association of Helicobacter species with hepatitis C cirrhosis with or without hepatocellular carcinoma. *Gut* 2005; **54**: 396-401 [PMID: 15710989 DOI: 10.1136/gut.2004.042168]
- 95 **Wang J**, Li WT, Zheng YX, Zhao SS, Li N, Huang Y, Zhou RR, Huang ZB, Fan XG. The Association between Helicobacter pylori Infection and Chronic Hepatitis C: A Meta-Analysis and Trial Sequential Analysis. *Gastroenterol Res Pract* 2016; **2016**: 8780695 [PMID: 26904112 DOI: 10.1155/2016/8780695]
- 96 **Ponsetto A**, Pellicano R, Leone N, Berrutti M, Turrini F, Rizzetto M. Helicobacter pylori seroprevalence in cirrhotic patients with hepatitis B virus infection. *Neth J Med* 2000; **56**: 206-210 [PMID: 10821975 DOI: 10.1016/S0300-2977(00)00033-4]
- 97 **Huang J**, Cui J. Evaluation of Helicobacter pylori Infection in Patients with Chronic Hepatic Disease. *Chin Med J (Engl)* 2017; **130**: 149-154 [PMID: 28091405]
- 98 **Mohamed AA**, Elshimy AA, El Sadik AO, Ezzat E, Nasar M, Elshaer SSM, Sayed MM. Association between Severity of Liver Disease, Frequency of Helicobacter pylori Infection, and Degree of Gastric Lesion in Egyptian Patients with Hepatitis B Virus Infection. *Am J Trop Med Hyg* 2018; **98**: 221-226 [PMID: 29342404 DOI: 10.4269/ajtmh.17-0291]
- 99 **Wang MY**, Yue JY, Zhang YX, Liu XD, Gao XZ. Helicobacter pylori infection in asymptomatic HBV carriers, alcohol users and normal adult population in Shandong Province, China. *Clin Res Hepatol Gastroenterol* 2011; **35**: 560-562 [PMID: 21680277 DOI: 10.1016/j.clinre.2010.12.014]
- 100 **Wang J**, Chen RC, Zheng YX, Zhao SS, Li N, Zhou RR, Huang Y, Huang ZB, Fan XG. Helicobacter pylori infection may increase the risk of progression of chronic hepatitis B disease among the Chinese population: a meta-analysis. *Int J Infect Dis* 2016; **50**: 30-37 [PMID: 27457918 DOI: 10.1016/j.ijid.2016.07.014]
- 101 **Xuan SY**, Xin YN, Chen AJ, Dong QJ, Qiang X, Li N, Zheng MH, Guan HS. Association between the presence of H pylori in the liver and hepatocellular carcinoma: a meta-analysis. *World J Gastroenterol* 2008; **14**: 307-312 [PMID: 18186573 DOI: 10.3748/wjg.14.307]
- 102 **Zhang Y**, Fan XG, Chen R, Xiao ZQ, Feng XP, Tian XF, Chen ZH. Comparative proteome analysis of untreated and Helicobacter pylori-treated HepG2. *World J Gastroenterol* 2005; **11**: 3485-3489 [PMID: 15948260 DOI: 10.3748/wjg.v11.i22.3485]
- 103 **Ito K**, Yamaoka Y, Yoffe B, Graham DY. Disturbance of apoptosis and DNA synthesis by Helicobacter pylori infection of hepatocytes. *Dig Dis Sci* 2008; **53**: 2532-2540 [PMID: 18253829 DOI: 10.1007/s10620-007-0163-0]
- 104 **Liu Y**, Wang WM, Zou LY, Li L, Feng L, Pan MZ, Lv MY, Cao Y, Wang H, Kung HF, Pang JX, Fu WM, Zhang JF. Ubiquitin specific peptidase 5 mediates Histidine-rich protein Hpn induced cell apoptosis in hepatocellular carcinoma through P14-P53 signaling. *Proteomics* 2017; **17**: [PMID: 28523650 DOI: 10.1002/pmic.201600350]
- 105 **Ki MR**, Goo MJ, Park JK, Hong IH, Ji AR, Han SY, You SY, Lee EM, Kim AY, Park SJ, Lee HJ, Kim SY, Jeong KS. Helicobacter pylori accelerates hepatic fibrosis by sensitizing transforming growth factor- $\beta$ 1-induced inflammatory signaling. *Lab Invest* 2010; **90**: 1507-1516 [PMID: 20531291 DOI: 10.1038/labinvest.2010.109]
- 106 **García A**, Feng Y, Parry NM, McCabe A, Mobley MW, Lertpiriyapong K, Whary MT, Fox JG. Helicobacter pylori infection does not promote hepatocellular cancer in a transgenic mouse model of hepatitis C virus pathogenesis. *Gut Microbes* 2013; **4**: 577-590 [PMID: 23929035 DOI: 10.4161/gmic.26042]

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