

From the stomach to other organs: *Helicobacter pylori* and the liver

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Abstract

Many recent studies have examined the importance of *Helicobacter pylori* (*H. pylori*) infection in the

pathogenesis of the diseases outside the stomach and explored the significance of this bacterium in the pathogenesis of some metabolic and cardiovascular diseases. Recent studies have provided evidence that *H. pylori* is also involved in the pathogenesis of some liver diseases. Many observations have proved that *H. pylori* infection is important in the development of insulin resistance, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, liver fibrosis and cirrhosis. The worsening of liver inflammation of different origins also occurs during *H. pylori* infection. Some studies have indicated that *H. pylori* infection induces autoimmunological diseases in the liver and biliary tract. The potential significance of this bacterium in carcinogenesis is unclear, but it is within the scope of interest of many studies. The proposed mechanisms through which *H. pylori* impacts the development of hepatobiliary diseases are complex and ambiguous. The importance of other *Helicobacter* species in the development of hepatobiliary diseases is also considered because they could lead to the development of inflammatory, fibrotic and necrotic injuries of the liver and, consequently, to hepatocellular carcinoma. However, many contrary viewpoints indicate that some evidence is not convincing, and further studies of the subject are needed. This review presents the current knowledge about the importance of *H. pylori* in the pathogenesis of liver and in biliary diseases.

Key words: *Helicobacter pylori*; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Liver cirrhosis; Liver fibrosis; Hepatic carcinoma

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Core tip: *Helicobacter pylori* (*H. pylori*) is generally regarded as the risk factor of the development of gastric diseases, including cancer. However, some authors suggest that *H. pylori* infection can cause other disorders, including liver diseases such as non-alcoholic fatty liver diseases, non-alcoholic steatohepatitis, liver

fibrosis, cirrhosis and hepatic carcinoma. The importance of other *Helicobacter* species in the development of hepatobiliary diseases is also considered. This review examines the current knowledge on the impact of *H. pylori* infection on the pathogenesis of liver and biliary diseases and considers various points of view.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium that was discovered in 1983 and was reported in 1984 in the *Lancet* by Warren and Marshall^[1], who were awarded the Noble prize in 2005. *H. pylori* infection is very common throughout the world but is particularly common in developing countries^[2]. This infection is also more common among elderly persons than adolescents^[3]. As indicated by the second part of its name (*pylori*), *H. pylori* colonizes the distal part of the stomach. In most cases, the infection occurs during childhood and persists throughout life. *H. pylori* infection is the cause of many diseases, such as chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer. According to the Correa theory, *H. pylori* infection causes sequential phenomena, leading from chronic gastritis through jejunal metaplasia and dysplasia to gastric cancer^[4]. Many pathophysiological mechanisms are involved in the phenomena leading to inflammation and carcinogenesis. The overexpression of cyclooxygenase-2 and inducible nitric oxide synthase results in the excessive generation of prostaglandin E2 (PGE2) and nitric oxide (NO). Recent data indicate that ERK activation induced by *H. pylori* infection plays very important role in up-regulation of PGE2 (prostaglandin E2) and NO generation in the gastric mucosa at the level of inhibitory κ B kinase- β and cytosolic phospholipase A2 activation. A peptide hormone, ghrelin, counters the proinflammatory consequence of the lipopolysaccharide (LPS) of *H. pylori* through Src/Act-dependent S-nitrosylation^[5]. Moreover, the ability of this hormone to counter the responses of the gastric mucosa to *H. pylori* LPS relies on phosphatidylinositol 3-kinase (PI3K) activation, which depends on the phospholipase C/protein kinase C signaling pathway. PI3K activity is required for the induction of cSrc/Act activation^[6]. More detailed data on these interesting phenomena have recently been published^[7].

These complicated pathophysiological mechanisms occur within the gastric mucosa. However, the chronic infection elicits not only chronic inflammatory but also immune responses on the local and systemic level^[8].

This review searches for a connection between *H. pylori* infection and certain liver diseases.

H. PYLORI AND NON-ALCOHOLIC FATTY LIVER DISEASE - DOES A LINK EXIST?

Many studies indicate that *H. pylori*, the risk factor for the development of gastric diseases such as cancer, is the cause of other disorders. Some authors suggest that *H. pylori* infection and chronic liver diseases are linked^[9-11]. Moreover, *H. pylori*-like DNA is more commonly found in liver samples from chronic liver disease patients than from controls^[4-12].

Non-alcoholic fatty liver disease (NAFLD) is a very common disease that affects 25%-30% of the population in western countries^[13,14]. Non-alcoholic steatohepatitis (NASH), liver fibrosis and cirrhosis are the consequences of NAFLD and influence the prevalence of morbidity and mortality. Fatty liver is significantly more often diagnosed in *H. pylori*-positive patients^[9]. According to another investigation, *H. pylori* infection may be one of the hits that contributes to the pathogenesis of NAFLD, and the eradication of *H. pylori* may be significant in the treatment of this disease^[11]. The pathogenic mechanism of this phenomenon is unclear.

The effect of the gut microbiota, including *H. pylori*, on liver damage has not been explored sufficiently. *Helicobacter* species may cause liver injury *via* specific toxins^[15]. Moreover, invasion of *Helicobacter* in the small bowel mucosa might increase gut permeability and facilitate the passage of bacterial endotoxins *via* the portal vein to the liver^[16].

H. pylori infection is positively correlated with developing metabolic syndrome and inversely correlated with morbid obesity^[2,17]. The rate of seropositivity is higher in patients with metabolic syndrome than in healthy subjects^[17]. However, other authors have claimed that the risk of obesity is increased after eradication of *H. pylori*. The source of this phenomenon is unclear. *H. pylori* eradication could cause an increased ghrelin concentration. Thereafter, improved appetite would lead to an increase in body mass^[2,18]. Jamali *et al.*^[19] did not find evidence that both the reduced amount of fat in the liver and the modified lipid profile are caused by eradication therapy. There are some doubtful approaches in the methodology of this study: NAFLD was diagnosed based on ultrasound methodology. Furthermore, dyspeptic patients were included, and the control group consisted of *H. pylori* (+) patients^[19]. Despite some important differences in methodology, including biopsy-proven diagnosis of NASH, selection of asymptomatic patients and *H. pylori* (-) patients in the control group, Polyzos's study obtained similar results^[20]. *H. pylori* infection may be the contributing factor for NAFLD to progress to NASH. Thus, *H. pylori* eradication may be important in NASH treatment^[21].

Other studies have shown that *H. pylori* infection co-exists with the development of NAFLD. The gut

microbiota may regulate insulin resistance (IR)^[22]; however, such an approach is controversial. IR could be one of the important pathogenic factors. *H. pylori* infection could be involved in the pathogenesis of IR. The accumulation of free fatty acids (FFAs) in the liver is caused by a decrease in their mitochondrial β -oxidation, which is one of the feature of IR^[23-25]. Whether *H. pylori* is important in the development of IR is not only unclear but also controversial. The homeostatic model of assessment IR (HOMA-IR) score is the most common method for assessing insulin sensitivity. A high HOMA-IR score indicates low insulin sensitivity. One study has shown that the HOMA-IR scores were higher in an *H. pylori*-positive group than in the negative group^[26]; however, other authors have a contrary opinion^[27]. *H. pylori* may be pathogenic and risk factors for obesity^[28] and type 2 diabetes mellitus (DM)^[29], which are components of metabolic syndrome (MS). *H. pylori* infection could explain why the pathogenesis of IR is complex^[21]. The trend exists toward a positive association between *H. pylori* infection and HOMA-IR^[30]. The potential association between *H. pylori* infection and IR may impact our understanding of the physiopathological mechanisms of MS, type 2 DM and NAFLD^[21].

However, the pathogenesis underlying the link among *H. pylori* infection, IR and MS is unclear. Many mechanisms must be considered^[31-33]. These mechanisms include the effect of fetuin-A, a glycoprotein produced by the liver^[34]. Fetuin A can be an anti-inflammatory factor^[35]. The level of fetuin-A is lower in *H. pylori*-infected patients compared with non-infected subjects^[36]. However, other findings have shown the opposite results, indicating that *H. pylori*-infected individuals have higher fetuin-A and insulin levels and HOMA-IR scores than non-infected individuals^[37]. According to other studies^[38], fetuin-A has proinflammatory properties, decreases glucose tolerance and inhibits insulin receptor tyrosine kinase in the liver^[33].

H. pylori infection stimulates the release of pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-6 and IL-8^[39]. TNF- α is the important pathogenic factor in the pathogenesis of IR, NAFLD and NASH. The mechanism of TNF- α activity is complicated and includes up-regulated Ser phosphorylation^[40] or inhibition of the autophosphorylation of the tyrosyl of IRS-1^[41]. The downregulation of GLUT4^[42] and the acceleration of lipolysis, which increases the concentration of FFAs, is also possible. Then, these reactions evoke oxidative stress^[43] and lead to detrimental effects in hepatic endoplasmic reticulum^[44] and the activation of nuclear factor κ B (NF- κ B)^[45].

Adipokines are important factors that are involved in the pathogenesis of NAFLD and NASH. They can have pro- or anti-inflammatory properties. Adiponectin is one of the first discovered adipokines. This important fat-derived compound has anti-inflammatory properties and many other ones^[46], including the suppression of macrophage function, antilipogenic effects^[47] and the inhibition of NF- κ B activation^[48]. The adiponectin level is

lower in *H. pylori*-positive patients with NAFLD than in *H. pylori* negative patients^[11]. Thus, *H. pylori* infection increases the risk of NAFLD development by reducing the concentration of adiponectin.

Abnormal serum lipid compositions and lipid metabolism are very common in patients with MS and NASH. However, the impact of *H. pylori* infection on lipid metabolism is controversial. Some authors have found that the serum triglyceride level is higher in *H. pylori*-positive patients but that the high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) and total cholesterol levels do not differ between *H. pylori*-positive and *H. pylori*-negative patients^[49]. Others have found that *H. pylori* infection is an important factor that negatively modifies serum lipids such as increasing LDL-C and decreasing HDL-C level^[36,50].

It is unclear whether the influence of *H. pylori* infection on liver steatosis and NASH has a similar pathogenesis as other species that colonizes the digestive tract. Qualitative and quantitative changes in the microbial system of the small bowel impair the intestinal barrier and bacterial translocation^[51]. The increased level of endotoxin-mediated cytokines observed in patients with the portal hypertension underlies the enhanced degree of inflammation and fibrosis of the liver^[52]. Small intestinal bacterial overgrowth is correlated with the severity of steatosis but not with NASH^[53].

As stated above, many studies suggest that *H. pylori* infection is correlated with the spectrum of fatty liver diseases. This influence on the liver is at least partially associated with metabolic disturbances. However, the systemic recruitment of the inflammatory factors that are present at the time of *H. pylori* infection^[54] could be responsible for a larger spectrum of extra-gastric manifestations, including other forms of liver damage.

H. PYLORI INFECTION AND LIVER FIBROSIS

Goo *et al*^[55] showed a significant increase in the fibrotic score and aminotransferase activity in a group inoculated with *H. pylori* and CCl₄ (carbon tetrachloride) compared with a CCl₄-treated group in an animal model of fibrosis. Transforming growth factor- β 1 (TGF- β 1) and smooth muscle actin (α -SMA) levels were also enhanced in the co-treated group^[55]. TGF- β 1 is a key profibrogenic cytokine and is crucial in the production of extracellular matrix by activated hepatic stellate cells (HSCs)^[56]. TGF- β 1 promotes HSC differentiation into myofibroblasts^[56] and facilitates the formation of α -SMA positive fibers in this cell type^[57].

Carbohydrate metabolism within the liver is probably disturbed in animals inoculated with *H. pylori*. The decreased amount of hepatic glycogen is very likely result of increased glucose utilization and increased energy production from glycolysis because of mitochondrial impairment and a depletion of the hepatic ATP

stores. Endotoxins may cause hydropic degeneration in hepatocytes^[55]. Hepatocellular injury increases the serum aminotransferase activity, hydroxyproline content and extent of fibrotic area^[55].

The influence of *H. pylori* infection on hepatic fibrogenesis in the absence or presence of TGF- β 1 was examined in an animal model^[58]. *H. pylori* strongly promoted a HSC line only if TGF- β 1 was added. HSCs play pivotal roles in the progression of liver fibrosis^[59]. However, TGF- β 1 is essential as a fibrogenic growth factor that activates HSCs through the SMAD2/3-mediated pathway^[60]. Additionally, the activation of TGF- β 1 correlates with injuring factors such as oxidative stress, aging and inflammation^[61].

H. PYLORI, OXIDATIVE STRESS AND LIVER CELL DAMAGE

An immunohistochemical study showed the presence of *H. pylori* antigen fragments in the liver of infected animals. A histological analysis showed that the hepatic cell architecture was disrupted, which was accompanied by slight necrosis, inflammation and ballooning of liver cells. These alterations could explain the higher vulnerability of mildly degenerated, infected liver tissue to injuring factors such as toxins, alcohol or the accumulation of fat^[54-62].

The increased number of binucleated hepatocytes described by Jeong *et al.*^[63] indicates that *H. pylori* infection has additional pathological effects. The authors suggested that this phenomenon could be caused by the fusion of two hepatocytes with injured cell membranes or by regenerative processes against damage of the liver^[63].

Senescence marker protein-30 (SMP30) is a multi-functional protein that prevents oxidative stress and cellular apoptosis^[64,65]. Lipopolysaccharide (LPS) originating from *H. pylori* cells may underlie the oxidative stress^[55]. The reduction in SMP30 in CCl₄-treated livers was enhanced by *H. pylori* infection in experimental study and *H. pylori* LPS is probably its cause^[55]. One of the virulence factors, vacuolating cytotoxin A (Vicar), was detected in the hepatocytes of patients with mild hypertransaminasemia and *H. pylori* infection. This finding supports the hypothesis that aminotransferase activity may be slightly elevated by cytotoxic strains of *H. pylori*^[66]. According to another study, *H. pylori* is an independent factor that causes liver damage^[67]. Its effective eradication leads to a decrease in aminotransferase activity in dyspeptic patients with unexplained mild hypertransaminasemia and concomitant *H. pylori* infection. This finding suggests that *H. pylori* infection is important in increasing the activity of aminotransferases^[68].

H. PYLORI AND AUTOIMMUNOLOGIC LIVER DISEASES

One study has indicated that *H. pylori* infection parti-

cipates in inducing autoimmunological diseases^[69]. The mitochondrial autoepitopic region of pyruvate dehydrogenase complex E2 (PDC-E2) is similar to urease beta of *H. pylori*^[70]. This similarity suggests that *H. pylori* infection is related to the risk of primary biliary cirrhosis (PBC). *H. pylori* DNA was detected in the livers of PBC patients^[71]. However, evidence of immunological cross-activity at the CD4 T-cell and β -cell level was not found, and the importance of cross-reactive antibodies against *H. pylori* VacA antigen and human PDC-E2 was not established^[69]. Moreover, the prevalence of *H. pylori* infection did not differ between PBC patients and controls^[69].

Both supportive and contradictory data exist concerning a possible link between *H. pylori* infection and primary sclerosing cholangitis (PSC). Some studies detected *H. pylori* DNA in the livers of patients with PSC^[72,73]. Nilsson *et al.*^[72] identified *H. pylori* and other *Helicobacter* species from patients with PSC and PBC.

PSC is often accompanied by ulcerative colitis. The hypothesis that inflammation-induced alterations in the gut flora may promote *Helicobacter* translocation from the gut to the liver in ulcerative colitis patients is very interesting. This translocation of pathogens can cause liver autoimmunity^[74,75]. The prevalence of antibodies against non-gastric *H. pylori* in patients with autoimmune liver diseases is increased^[69]. However, the prevalence of *H. pylori* in PSC patients did not differ compared with the prevalence in controls^[69].

Evidence in support of a relationship between the prevalence of autoimmune hepatitis (AIH) and *H. pylori* infection is also insufficient^[69]. A clear association between *H. pylori* seroprevalence and AIH was not confirmed in a previous study^[76]. Dzierzanowska-Fangrat *et al.*^[77] evaluated pediatric patients and observed no association between *Helicobacter* infection and AIH in children. Thus, relationship between *H. pylori* colonization of gastric tissue and liver disease is controversial.

H. PYLORI INFECTION AS THE CAUSE OF LIVER CIRRHOSIS?

The prevalence of ulcers of the stomach and/or duodenum caused by *H. pylori* is higher in patients suffering from hepatic cirrhosis^[78,79]. A recent meta-analysis suggests that there is also a significantly high prevalence of *H. pylori* infection among patients with cirrhosis^[80]. Eradication therapy may be beneficial for cirrhotic patients because it diminishes the risk of recurrent peptic ulcers and bleeding^[81,82]. However, Stalke *et al.*^[83] demonstrated a positive correlation between the degree of gastric colonization by this bacterium and parenchymatous liver damage in a group of hospitalized patients without liver cirrhosis.

H. pylori infection contributes to the development of hepatic encephalopathy and hyperammonemia^[84]. In a meta-analysis of six cohort studies that involved 632 *H. pylori*-positive and 396 negative cirrhotic patients, infection was associated with elevated blood ammonia

levels^[85]. Whether the *H. pylori* eradication is effective in the treatment of hepatic encephalopathy has not been fully examined.

Most data suggesting a relationship between *H. pylori* and liver complications comes from studies on viral hepatitis patients. Indeed, there have been some attempts to estimate the influence of *H. pylori* infection on the progression of fibrosis in patients with HCV-related chronic hepatitis. Esmat *et al.*^[86] revealed that *H. pylori* polymerase chain reaction (PCR) [cytotoxic-associated gene A (CagA)] was positive in a significantly higher percentage of patients with late fibrosis (F3 + F4 based on METAVIR staging) than with early fibrosis. In another study concerning HCV(+) patients, Queiroz *et al.*^[87] noted that cirrhosis in this group was associated with both age and *H. pylori*-positive status, which was confirmed by ELISA and PCR tests.

HCV patients who are coinfecting with *H. pylori* have more advanced fibrosis than HCV patients without infection^[88]. Decreased glycogen and total proteins in hepatocytes and cirrhotic nodules are frequently observed in HCV patients who are coinfecting with *H. pylori*^[88]. Additionally, *H. pylori* infection facilitates the progression to cirrhosis in patients with HCV infection^[9].

In contrast, Castéra *et al.*^[89] did not confirm that the presence of *Helicobacter* species DNA is associated with advanced liver diseases. The lack of correlation between the presence of *H. pylori*-like DNA in the liver and positive *H. pylori* serology was also proved^[89].

H. PYLORI AS AN ONCOGENIC FACTOR FOR THE LIVER?

Over-expression of hepatitis B virus (HBV) antigen (HBsAg and HBcAg) is present in the gastric mucosa of patients infected with *H. pylori* who are also suffering from hepatitis B^[90]. Because both pathogens confer oncologic risk [gastric MALT-lymphoma and hepatocellular carcinoma (HCC), respectively], the authors suggest that early treatment of *H. pylori* infection could be beneficial in this group of patients^[90,91].

H. pylori may be important in the development of HCC. Nilsson *et al.*^[92] identified *H. pylori* and similar species in liver samples from patients with HCC and cholangiocarcinoma (CCA). The presence of *H. pylori* in the bile was associated with a higher risk of CCA^[93]. Additionally, *H. pylori* was detected in hepatic tissue of patients who underwent resection because of primary HCC^[94,95]. Some *in vitro* studies may support the hypothesis that this bacterium may promote liver carcinogenesis. CagA *H. pylori* has an *in vitro* cytotoxic effect on HepG2 hepatocarcinoma cells^[96]. Moreover, Ito *et al.*^[97] observed a disturbed balance between hepatic cell proliferation and apoptosis and disrupted hepatocyte replication related with persistence of intracellular *H. pylori*. However, a recent study using an animal model of hepatitis C virus-induced hepatocellular cancer showed that *H. pylori* infection does not promote the

development of HCC^[98].

Zhang *et al.*^[99] indicated that *H. pylori* exerts a pathological effect on HepG2 cells by up-regulating the expression of integrin β -1, protein kinase C α , LIM/homeobox protein Lhx1, eIF-2-beta, MAP kinase kinase 3, PINCH protein and Ras-related protein Rab-37, which are involved in transcription, signal transduction and metabolism. This study provides indirect evidence that *H. pylori* is important for carcinogenesis in hepatic cells^[99].

Xuan *et al.*^[100] performed a systematic review of relevant studies. Only 10 of 103 clinical trials fulfilled the very strict selection criteria and were involved in the analysis^[100]. Based on this meta-analysis, the authors determined that the association of *H. pylori* infection and HCC is described by an OR of 13.63. However, these results should be interpreted with caution. *Helicobacter* DNA was detected and identified in some of the included studies as *H. pylori*-like organisms.

Persistent infection with *H. pylori* can modulate hepatocyte replication and may be important for the pathogenesis of liver diseases. Increased apoptosis could result from the release of virulent factors, which are inside the hepatocytes^[97]. The virulent strain can likely arrest cell proliferation. *H. pylori* might increase the risk of TGF- β 1-dependent tumorigenesis by disturbing the balance between hepatocyte apoptosis and proliferation^[58]. This result is probably strain- and species-dependent^[97]. Infection by *H. pylori* leads to the induction of TNF- α which also can be involved in carcinogenic processes in the liver^[101].

An analysis of HCC patients indicates that 60.7% of cases are infected by *Helicobacter* species (based on PCR), and this rate is much higher ($P < 0.01$) than in control group. This finding suggests that colonization of the liver tissues by *Helicobacter* spp. could be significant for the carcinogenesis that occurs in HCC patients^[100]. However, a hypothesis that explains the importance of *H. pylori* in the pathogenesis of HCC is currently lacking and requires further exploration.

The importance of *H. pylori* in the development of CCA is unclear. However, Boonyanugomol *et al.*^[102] found that the prevalence of *H. pylori* infection is significantly higher in patients with CCA than in patients with cholelithiasis and the control group. The authors concluded that the CagA-positive strains in particular could be involved in CCA carcinogenesis^[102]. The inflammatory grade at the portal zone around the bile ducts was significantly higher in patients with CCA and *H. pylori* PCR-positive liver tissue specimens than in non-infected liver samples. Moreover, the mononuclear cell infiltration in *H. pylori* PCR-positive samples was significantly higher^[102]. Inflammation leads to the production of several cytokines that can induce cell proliferation and oxidative DNA damage and decrease cell survival^[103]. These phenomena could underlie the development of bile duct cancer^[102]. The authors concluded that *H. pylori*, especially CagA-positive *H. pylori*, can be involved in the development of CCA. Furthermore, its importance is probably greater than that of other bacteria^[102]. Fukuda

et al.^[104] obtained the opposite results and stated that *H. pylori* was detected in a small number of hepatobiliary cancer patients in Japan. These contradictory results suggest that *H. pylori* prevalence varies across regions^[105].

The possible importance of *H. pylori* in the pathogenesis of bile duct cancer is unclear. Boonyanugomol *et al.*^[106] showed that the factors that were involved in *H. pylori* internalization in CCA cells were encoded by cagPAI. The polymerization of actin and $\alpha 5\beta 1$ -integrin is also probably important. *H. pylori* attaches to β -1 integrin receptors and can promote phosphotyrosine signaling, which activates the tyrosine phosphorylation cascade and leads to internalization of the bacterium into the hepatocytes^[97]. *H. pylori* infection is also associated with proliferation, apoptosis^[97,100-107] and inflammation with a concomitant increase in IL-8 in the bile ducts^[106]. *H. pylori* up-regulates *NOD1* gene expression in biliary cell lines in a cagPAI-dependent manner, which is similar to the mechanism in gastric cells^[106]. Moreover, increased expression levels of toll like receptor 4 (*TLR4*) and *TLR5* genes were observed in biliary cells after stimulation with *H. pylori*.

OTHER *HELICOBACTER* SPECIES AS RISK FACTORS FOR LIVER DISEASES

Based on the above observations, exploring the association between *H. pylori* infection and the course of chronic liver diseases and carcinogenesis is of interest, especially in patients with a risk of severe liver disease. Nevertheless, some evidence suggests that other *Helicobacter* species are important in certain liver pathologies. *Helicobacter hepaticus* (*H. hepaticus*) is associated with the induction of hepatic inflammation and the pathogenesis of cholestatic diseases such as PBC and PSC^[108,109].

H. hepaticus was discovered in 1992. This bacterium could be crucial in the development of cholelithiasis, cholecystitis, and liver and gallbladder cancer^[110]. *H. hepaticus* is similar to *H. pylori*, but it lacks virulence factors VacA and CagA. The adhesion proteins SabA, AlpA, and Bab A are also absent. However, many genes are related to *H. pylori*, including urease structural subunits, 16S rRNA, and 18 kDa immunogenic protein^[110].

Kawaguchi *et al.*^[111] detected a microorganism that was similar to *H. pylori* in the resected gallbladder mucosa of a patient with gallstones in 1996. The possible routes of bile infection are ascending through the papillary sphincter and descending through the portal system. Thus, other bile-resistant *Helicobacter* species are found in bile juice and the gallbladder mucosa of patients with chronic cholecystitis. This phenomenon suggests that these bacterial agents could be important elements in some diseases of the biliary tract, including gallbladder cancer^[111]. Currently, several dozen *Helicobacter* species have been identified, and many of them are considered as the causative agents of

various diseases of the liver and biliary tract. However, *H. pylori* can also be considered as one of the precipitating factors in the formation of the gallstones^[112,113]. 16S rRNA amplification and DNA sequencing have been used to prove the presence of bacteria in gallstones. In another study, though, *Helicobacter* species were not found in bile juice. Consequently, the authors suggest that racial and demographic differences could explain these opposing results^[114].

H. hepaticus infection leads to oxidative stress in the liver by increasing the level of nitrogen and oxygen active substances. This phenomenon causes carcinogenesis in the liver^[115]. Particularly in patients with chronic hepatitis C virus infection, an additional infection by *H. hepaticus* may be a risk factor for the progression to liver cirrhosis or HCC^[94]. Krüttgen *et al.*^[116] did not identify *H. hepaticus* in HCC patients with concomitant chronic hepatitis B or hepatitis C. Moreover, they also did not disprove the importance of *H. hepaticus* in HCC cases caused by other carcinogens^[116].

Some experimental evidence indicates that *H. hepaticus* causes chronic liver diseases and HCC in mice. The long-term population of the liver by *H. hepaticus* leads to the development of inflammatory, fibrotic and necrotic injuries of the liver and, consequently, to HCC^[117]. Proliferation and apoptosis are increased in the hepatocytes of infected mice^[118].

H. hepaticus and other *Helicobacter* species, such as *H. pullorum*, *H. bilis*, may induce hepatocyte and biliary epithelia cell autoimmunity. These species can survive in low concentrations of human bile^[119]. Cytolethal-distending toxin (CDT) of *H. hepaticus* plays an important role in promoting the progression of hepatitis to premalignant or dysplastic lesions in the liver and biliary tract. CDT is a multimeric cytotoxin with nuclease activity. It exposes the immune system to endogenous antigens. The activation of proinflammatory NF- κ B and the increased proliferation of hepatocytes are crucial in promoting carcinogenesis^[120,121]. Patients with liver diseases had increased concentrations of anti-*H. hepaticus* antibodies compared with HBV- and/or HCV-infected patients^[122]. Based on a meta-analysis of 10 case-control studies in which 56% of subjects were positive for *Helicobacter* spp. infection compared with 20% in the control group, sufficient evidence supports the importance of *Helicobacter* spp. in hepatobiliary tract cancer development^[123,124]. The variability of the regional prevalence of the hepatobiliary tumors indicates that the prevalence of the risk factors for this disease (*e.g.*, geographical, environmental, and genetic factors and endemic infections) is meaningful for its pathogenesis^[125]. The infection rate of *Helicobacter* spp. (predominantly *H. pylori* and *H. bilis*) was significantly higher in the group with cancer of the biliary tract and in the benign biliary disease group than in the group without these diseases^[125]. The risk of carcinoma development is more probable in patients with hepatitis and steatosis who are also infected with *H. hepaticus*^[126].

CONCLUSION

In conclusion, *H. pylori*, which is a very important pathogenic factor in the stomach, is probably involved in the development of many other diseases. Recent studies describing its significance in cardiovascular, endocrine and metabolic diseases are complemented by investigations on its potential importance in benign or malignant diseases of other organs. Many studies indicate that *H. pylori* infection contributes to the pathogenesis of fatty liver, NAFLD and NASH. The importance of *H. pylori* in the exacerbation of inflammatory processes of different origins should also be considered. Finally, the potential importance of *H. pylori* in carcinogenic processes of the liver and biliary ducts was considered in this review. Furthermore, the significance of other *Helicobacter* species in hepatobiliary diseases was discussed. However, many opposing results indicate that some data are not convincing, and further studies are needed.

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