World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v7.i30.2968

World J Hepatol 2015 December 28; 7(30): 2968-2979
ISSN 1948-5182 (online)

REVIEW

Extragastric manifestations of *Helicobacter pylori* infection: Possible role of bacterium in liver and pancreas diseases

Elizabeth MA Rabelo-Gonçalves, Bruna M Roesler, José MR Zeitune

Elizabeth MA Rabelo-Gonçalves, Bruna M Roesler, Laboratory of Gastroenterology and Hepatology, Center of Diagnosis of Digestive Diseases, State University of Campinas, Campinas, São Paulo 13083-878, Brazil

José MR Zeitune, Department of Internal Medicine, Faculty of Medical Sciences, State University of Campinas, Campinas, São Paulo13083-887, Brazil

Author contributions: Rabelo-Gonçalves EMA contributed to the study idea, study design, literature search, manuscript writing and final revision of the article; Roesler BM contributed to the literature search, manuscript writing and final revision of the article; Zeitune JMR contributed to study design, manuscript writing and the final version of the article.

Conflict-of-interest statement: The authors declare no conflict of interests.

Correspondence to: Elizabeth MA Rabelo-Gonçalves, BSc, MSc, Laboratory of Gastroenterology and Hepatology, Center of Diagnosis of Digestive Diseases, State University of Campinas, Rua Carlos Chagas 420, Campinas, São Paulo 13083-878, Brazil. elizabeth.goncalves@gc.unicamp.br
Telephone: +55-19-35218557
Fax: +55-19-35218566

Received: April 27, 2015
Peer-review started: May 4, 2015
First decision: July 6, 2015
Revised: November 26, 2015
Accepted: December 13, 2015
Article in press: December 15, 2015
Published online: December 28, 2015

Abstract

Helicobacter pylori (*H. pylori*) is an ancient microorganism that has co-evolved with humans for over 60000 years. This bacterium typically colonizes the human stomach and it is currently recognized as the most common infectious pathogen of the gastroduodenal tract. Although its chronic infection is associated with gastritis, peptic ulcer, dysplasia, neoplasia, MALT lymphoma and gastric adenocarcinoma, it has been suggested the possible association of *H. pylori* infection with several extragastric effects including hepatobiliary and pancreatic diseases. Since a microorganism resembling *H. pylori* was detected in samples from patients with hepatobiliary disorders, several reports have been discussed the possible role of bacteria in hepatic diseases as hepatocellular carcinoma, cirrhosis and hepatic encephalopathy, nonalcoholic fatty liver disease and fibrosis. Additionally, studies have reported the possible association between *H. pylori* infection and pancreatic diseases, especially because it has been suggested that this infection could change the pancreatic physiology. Some of them have related a possible association between the microorganism and pancreatic cancer. *H. pylori* infection has also been suggested to play a role in the acute and chronic pancreatitis pathogenesis, autoimmune pancreatitis, diabetes mellitus and metabolic syndrome. Considering that association of *H. pylori* to liver and pancreas diseases needs further clarification, our work offers a review about the results of some investigations related to the potential pathogenicity of *H. pylori* in these extragastric diseases.

Key words: Hepatocellular carcinoma; Cirrhosis; Hepatic encephalopathy; *Helicobacter pylori*; Nonalcoholic fatty liver disease; Fibrosis; Pancreatitis; Pancreatic cancer; Diabetes mellitus; Metabolic syndrome

Core tip: *Helicobacter pylori* (*H. pylori*) has been

associated with several extragastric manifestations, including liver and pancreas diseases. Evidence for its role in the pathogenesis of chronic liver diseases and liver carcinoma is supported by several clinical and experimental studies. Furthermore, epidemiologic and serology-based works have reported a possible association between the microorganism and pancreatic cancer. *H. pylori* infection has also been linked to the acute and chronic pancreatitis pathogenesis and it could be related to the development of autoimmune pancreatitis, diabetes mellitus and metabolic syndrome. This review summarizes recent findings on the possible role of *H. pylori* infection in the etiology of liver and pancreas disorders.

Rabelo-Gonçalves EMA, Roesler BM, Zeitune JMR. Extragastric manifestations of *Helicobacter pylori* infection: Possible role of bacterium in liver and pancreas diseases. *World J Hepatol* 2015; 7(30): 2968-2979 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i30/2968.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i30.2968

INTRODUCTION

Helicobacter pylori (*H. pylori*) is an ancient organism that has co-evolved with humans for over 60000 years[1]. This bacterium typically colonizes the human stomach and it is currently recognized as the most common infectious pathogen of the gastroduodenal tract[2]. Most infected individuals do not develop disease, leading to the hypothesis that some *H. pylori* strains are harmless or even beneficial[3]. However, its chronic infection is associated with increased risk for several disease outcomes including gastritis, peptic ulcer, dysplasia, neoplasia, mucosa associated lymphoid tissue lymphoma and invasive gastric adenocarcinoma[4].

In recent years, it has been suggested the possible role of *H. pylori* infection with several extragastric effects including neurodegenerative, metabolic and cardiovascular conditions, as well as hepatobiliary, pancreatic and colorectal diseases[5-7]. Moreover, studies indicate that this bacterium may be related to the development of skin diseases such as urticaria as well as rheumatic disorders[8,9].

Since *Helicobacter* spp. have been isolated from the liver samples of a variety of mammals, it was suggested that bacteria may be involved in the pathogenesis of chronic liver diseases (CLD) and liver carcinoma[10-12]. Regarding to human studies, a microorganism resembling *H. pylori* was firstly detected in resected gallbladder mucosa of patient with gallstone[13]. Nilsson *et al*[14] reported the detection of *H. pylori* using molecular biology techniques such as polymerase chain reaction (PCR), hybridization and partial DNA sequencing in liver samples from patients with primary sclerosing cholangitis and primary biliary cirrhosis (PBC).

Subsequent studies have verified the possible association of *H. pylori* infection in the development of other liver diseases, particularly hepatocellular carcinoma (HCC), in different geographic areas. Some authors have reported a very high prevalence of antibodies to *H. pylori* and the prevalence of bacteria in patients with cirrhosis, compared with controls[15-18]. Although *Helicobacter* spp. DNA was successfully detected in liver samples of individuals with primary liver carcinoma[19-23], the remaining question was whether these findings corresponded to the true liver colonization by bacteria or whether *H. pylori* DNA could result from the retrograde transfer of this DNA from the duodenum to liver. Nevertheless, the isolation of *H. pylori* in culture medium using liver samples was crucial for supporting the true bacterial colonization[24,25].

Another extragastric digestive organ indicated as a possible target for *H. pylori* is the pancreas and some mechanisms by which *H. pylori* infection may influence pancreatic physiology have been object of several studies. It has been suggested that some aggressive factors produced by this microorganism such as ammonia and lypopolysaccharides (LPSs), as well as the production of inflammatory cytokines, could induce the pancreas damage. These conditions associated with the activation of leukocytes could be responsible for the clinical outcome of the pancreas diseases[26].

Considering these aspects, several epidemiologic and serology-based studies have reported a possible association between the microorganism and pancreatic cancer[27-30] and, in addition, epidemiological studies have examined if there could be any association between peptic ulcers development and risk of pancreatic cancer. Results from cohort studies with large number of pancreatic cancer cases and detailed information on type of peptic ulcers (*i.e.*, gastric *vs* duodenal) observed positive associations with gastric ulcers, but not duodenal ulcers[31,32]. *H. pylori* infection has also been suggested to play a role in the acute and chronic pancreatitis (CP) pathogenesis[33-35] and it has been reported that this infection could be related to autoimmune pancreatitis (AIP) mainly through induction of autoimmunity, by molecular mimicry, and apoptosis[36]. Finally, a possible role of *H. pylori* in diabetes mellitus (DM)[37,38] and metabolic syndrome have been investigated[39,40].

However, the interpretation of so different results obtained from the mentioned studies makes the interpretation of their relevance be inconclusive. *H. pylori* more virulent strains, such as the ones that harbor the CagA pathogenicity island, together with the host characteristics, could be important for the clinical expression of pancreatic diseases, and other systemic disorders. In some cases, *H. pylori* might be a minor factor contributing to disease development owing to the persistent inflammatory state of the gastric mucosa[41]. Considering these findings and that, the role of *H. pylori* infection in the liver and pancreatic diseases remains controversial, in the review we attempt to discuss about the results of some investigations related to the potential pathogenicity of *H. pylori* in these extra gastric diseases.

ROLE OF *H. PYLORI* IN LIVER DISEASES

HCC

The HCC is the main primary malignant tumor of the liver and the fifth most common type of cancer. It is estimated that more than 50000 cases are diagnosed annually and that the disease is the third leading cause of cancer-related death in the world population[42-47]. The cases of death due to HCC vary 250000-1 million individuals per year and its prevalence varies according to geographic location, gender, age and ethnicity[48].

The development of HCC is attributed to several factors such as alcoholism, exposure to mycotoxins (aflatoxins), hereditary hemochromatosis, PBC, deficiency of α-1-anti-trypsin, Wilson's disease and microcystin[21,49-51]. Chronic viral infections are considered the main risk factor of HCC in 75%-80% of cases[47], wherein hepatitis B virus (HBV) infection is responsible by 50%-55% of cases[52] and hepatitis C virus (HCV) infection occurs in 25%-30% of patients[53]. However, the detection of *H. pylori* in patients with HCC may suggest the role of bacteria in the pathogenesis of this disease.

Several studies have tried to correlate the *H. pylori* infection in the development of HCC. Avenaud *et al*[20] detected *H. pylori* in 100% (8/8) of the liver tissue employed in their study. In 2001, Swedish researchers identified *Helicobacter* spp. in patients with HCC and cholangiocarcinoma[54]. Evaluating patients with chronic hepatitis, cirrhosis and HCC, Dore *et al*[21] used the serology and PCR to verify the presence of *H. pylori* infection. The results showed that 54% of patients were positive for the bacteria, and the prevalence of infection was higher in patients with HCC (73%) compared with patients with cirrhosis (58%) and chronic hepatitis (39%). *Helicobacter* DNA was detected in 17% of liver cirrhosis patients and 55% of individuals with HCC.

Verhoef *et al*[55] revealed the presence of *Helicobacter* DNA in 45% of liver samples from patients with HCC in contrast to 10% positive samples in the control group. Sequence analysis indicated that fragments had similarity with DNA of *H. pylori*. In this study the authors also noted the similarity among three samples of gastric biopsies of patients with HCC who were positive for the liver culture, suggesting that gastric colonization with *H. pylori* strains may be associated with the induction of HCC.

In 2004, Pellicano *et al*[56] confirmed the presence of *Helicobacter* spp. DNA in 17 (85%) of 20 liver samples from patients with HCC compared with 33% of positive *Helicobacter* cases in the control samples. Recently, more studies emphasize the detection of bacteria in hepatic tissue from patients with HCC, even suggesting its possible role in the progression of CLD due to higher prevalence of *H. pylori* in more advanced stages of liver disease as cirrhosis and HCC[25,57].

In addition, several researchers have described the association between *H. pylori* and HBV or HCV in the development of HCC. In fact, the prevalence of anti-*H. pylori* antibodies in patients infected with HBV is significantly higher when compared to subjects without viral infection[17,18,58-63]. In an attempt to verify the role of *H. pylori* in the progression of CLD in patients infected with HCV, investigators have reported that *Helicobacter* spp. DNA was detected in 4.2% of controls and 3.5% of individuals with noncirrhotic chronic hepatitis, compared with 61%-68% in cirrhotic liver and 90% in HCC tumoral tissue[22]. These results reinforced that prevalence of *H. pylori* infection may be associated with later stages of CLD and suggested that disease increased with the severity of the cancer. Then, it may be possible that *H. pylori* co-infection with HBV or HCV results in the progression from cirrhosis to cancer, reinforcing the synergistic cooperation between *H. pylori* and hepatitis virus in the development of HCC[47].

The mechanism by which *H. pylori* colonizes the human liver is not fully understood. Some researchers hypothesized that *H. pylori* DNA detection in liver tissue can result from bacterial translocation from the stomach into the blood through the portal system, especially in the advanced stages of chronic liver disease, when occurs the portal hypertension[47,64]. Furthermore, bacteria can reach the liver *via* circulating phagocytes and macrophages or retrograde transfer from the duodenum[24]. However, reports that involved *H. pylori* culture from the liver samples of patients with HCC support a true hepatic colonization by bacteria, discarding the possibility of retrograde contamination[25,65]. Additionally, no other bacteria in the digestive tract are associated with human liver carcinogenesis[66,67].

The experimental murine models of *H. hepaticus* infection show that bacteria are able to induce chronic active hepatitis and HCC in various strains of animals[11,68]. Moreover, enteric *Helicobacter* species are capable of producing toxins which can cause hepatocellular injury *in vivo*[69]. Furthermore, *Helicobacter* spp. may induce the production of proinflammatory chemokines and cytokines which contributes to the development of liver cancer by DNA damage, growth stimulation, increase of survival, angiogenesis and invasion into host tissue[70].

In a report employing human hepatocytes culture infected with *H. pylori*, Ito *et al*[71] have shown that bacteria are able to adhere and penetrate into these cells. The authors suggest that the process of bacterial internalization can be an *H. pylori* strategy to avoid the host immune reaction and remain in the liver, resulting in morphological and physiological changes in the hepatocytes. Analyzing the *in vitro* proliferation, adhesion and invasion responses of the hepatic tumor cell lines to LPS authors demonstrated that these characteristics were increased in response to LPS, which may be related to increased gene expression of interleukin-8 (IL-8) and transforming growth factor-beta 1 (TGF-β1). Considering that *H. pylori* has LPS, they inferred that bacteria may be ignored by host immune system and directly promote adhesion and invasion of hepatoma cells mediated by LPS[72].

In addition to the host immune system evasion

mechanisms, *H. pylori* virulence factors detected in liver samples from patients with HCC, such as *vac*A and *cagA* genes, are supposed to be involved in liver carcinogenesis[21,63,73]. These findings were recently supported by Esmat *et al*[74] who found that the positivity of *cagA* gene was directly proportional to the severity of liver disease. They studied patients infected with HCV in the presence and absence of cirrhosis and HCC. The *cag*A positivity occurred in 75% of patients with cirrhosis and HCC, 52.9% of cirrhosis subjects without HCC and 32% of individuals with chronic hepatitis. The authors have also shown significant differences when compared METAVIR system among groups which confirmed *H. pylori* association with later stages of fibrosis.

Cirrhosis and hepatic encephalopathy

Cirrhosis is a major health problem with high incidence and prevalence worldwide[75]. Considering that patients with cirrhosis are more likely to develop gastrointestinal mucosal lesions, with increased risk for peptic ulcer disease (PUD)[76], it was suggested that *H. pylori* infection has an important role in the pathogenesis of PUD in cirrhotic patients and may be related to the development of hepatic encephalopathy (HE) and hyperammonemia[77]. In fact, a recent review has demonstrated that eradication of *H. pylori* infection in patients with cirrhosis may have a positive effect on the control of hyperammonemia and HE[78].

In a meta-analysis, researchers have described that prevalence of *H. pylori* infection in individuals with cirrhosis has increased significantly worldwide, especially in Europe and America, due to viral cirrhosis and PBC[79]. However, Pellicano *et al*[80] related that some papers which concluded that there was no association between the prevalence of bacteria and PBC[81,82] were not reported in this meta-analysis. Another report demonstrated that there is a significant association between *H. pylori* infection and portal hypertensive gastropathy (PHG) in cirrhotic patients which is also related to the severity of PHG, suggesting that eradication of *H. pylori* must be considered in cirrhotic patients with PHG[75].

HE is a frequent complication of liver cirrhosis and manifests itself as a wide variety of neuropsychiatric symptoms[83]. It is admitted that ammonia is the most relevant substance in the pathogenesis of HE. Then, reduction of ammonia production in the gastrointestinal tract is a current treatment strategy for HE[78]. Considering that *H. pylori* urease hydrolyses urea present in the gastric juice into ammonia and carbon dioxide, and the amount of ammonia produced in the gastric mucosa could increase blood ammonia levels in cirrhotic patients, the possible participation of *H. pylori* infection in the pathogenesis of HE has been studied.

The current data associating *H. pylori* infection to the pathophysiology of HE are inconclusive. Initially, some reports have demonstrated that *H. pylori* contributes to hyperammonemia in cirrhosis, and the eradication of bacteria may reduce the blood ammonia[84-86]. After that, other studies have not found a significant difference in the ammonia levels between cirrhotic patients with and without *H. pylori* infection[87,88]. In a review, Zullo *et al*[89] confirmed that gastric ammonia production by *H. pylori* urease appears to be inadequate to clinically affect ammonia levels in the majority if cirrhotic patients.

In a recent review, it was demonstrated that positivity of *H. pylori* infection was higher in HE patients compared to non-HE individuals, particularly in the older subjects. However, there are no strong evidences for an effect of bacteria on increasing blood ammonia level, nor there is strong evidence to support the hypothesis that *H. pylori* eradication can reduce blood ammonia level and improve HE symptoms[90].

However, authors have described that HE is not fully reversible and *H. pylori* might contribute to persistent cognitive impairment even after resolution of symptoms[91]. Furthermore, it is believed that inflammatory cytokines produced during *H. pylori* infection may cross the blood-brain barrier and contribute to the pathogenesis of cognitive dysfunction associated with cirrhosis[92].

Nonalcoholic fatty liver disease

The nonalcoholic fatty liver disease (NAFLD) is currently considered the most common liver disease in Western countries, affecting up to 25%-30% of subjects[93-95]. NAFLD includes a broad spectrum of liver disorders, which range from nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH) which may progress to cirrhosis and HCC without significant alcohol consumption[96-98].

Authors have shown the possible participation of *H. pylori* infection in the pathogenesis of insulin resistance (IR)[39]. Considering that IR is implicated in the etiology of NAFLD, the evaluation of *H. pylori* infection as a risk factor for IR may help clarify its effect on NAFLD[99].

In 2008, researchers have detected *H. pylori* 16S rDNA in hepatic tissue collected from a 44-year-old woman with NASH[100]. After that, in a study employing liver samples from patients with CLD, *H. pylori* DNA was amplified in 45.5% (5/11) of samples obtained from subjects with NAFLD[57].

The case report described by Abenavoli *et al*[101] related the improvement in IR and fatty liver indices after *H. pylori* eradication therapy, reinforcing the possible association among *H. pylori* infection, IR and NAFLD. In the same year, another study revealed that prevalence of anti-*H. pylori* IgG titers, together with lower circulating adiponectin and higher tumor necrosis factor-α levels, was higher in individuals with NAFLD compared with control group[102]. Moreover, using logistic regression analysis model, researchers mentioned that both *H. pylori* infection and Homeostasis Model of Assessment-Insulin Resistance which is the marker of the metabolic syndrome, were considered independent variables to predict NAFLD. In addition, no correlation was found between *H. pylori* infection and progression to NASH. Then, it was suggested that presence of *H. pylori* may be involved to early-stage NAFLD.

However, Sumida *et al*[103] performed a recent study

which was the first one to show that NASH is more prevalent in *H. pylori*-positive patients than in non-infected individuals. Histopathologic analysis revealed that bacteria was associated with hepatocyte ballooning; however, there was no association of *H. pylori* with steatosis or liver fibrosis. Authors still mentioned that although the exact pathogenic mechanisms involved in hepatocyte ballooning as well as its role in NAFLD remain unclear, it is considered as a key histologic feature of NASH.

Considering that the prevalence of NAFLD is increasing worldwide and that *H. pylori* infection may present a role in its pathogenesis, further studies on this area are needed, in order to provide better understanding of the role of *H. pylori* infection in NAFLD. However, once this association is confirmed, it is possible that *H. pylori* eradication regimens might have therapeutic implications on NAFLD[39].

Fibrosis

As mentioned before, *Helicobacter* spp. infection is more prevalent in advanced stages of liver diseases, reinforcing the possible association of bacteria with the progression of chronic hepatitis to cirrhosis and HCC[49].

In order to elucidate these findings, researchers have induced experimental hepatic fibrosis with carbon tetrachloride (CCl4) administration in mice and rats orally challenged with *H. pylori*. Authors verified a significant increase in the fibrotic score in *H. pylori*-positive animals treated with CCl4 when compared with non-infected animals treated with CCl4. Furthermore, they observed that alpha-smooth muscle actin and TGF-β1 also enhanced in *H. pylori* infected animals[104].

After that, authors have suggested that increased liver fibrosis in *H. pylori* infection may occur through increased TGF-β1 induced pro-inflammatory signaling pathways in hepatic stellate cell line (HSC). They still mentioned that *H. pylori* infection may be involved in increased risk TGF-β1-mediated tumorigenesis by disturbing the balance between apoptosis and proliferation of hepatocytes[105]. Another group has also described an increase in activated kupffer cells and hydrogen peroxide levels in *H. pylori* infection which might result in activation of HSC alone or in combination with TGF-β1, amplifying hepatic inflammation *via* release of proinflammatory cytokines[106,107].

More recently, Esmat *et al*[74] studied liver samples from patients with HCV-related chronic hepatitis and cirrhosis in the presence or absence of HCC in order to verify the possible role of *H. pylori* infection in the disease progression. They showed that prevalence of *cag*A gene was directly proportional to severity of liver disease and was more positive in advanced stages of fibrosis (28.2%) compared to early stages (5.9%); it was still suggested by authors that *H. pylori* can produce toxins that may interfere with hepatic cells.

One aspect that deserves further analysis of hepatology experts is the analysis of a possible role of *H. pylori* infection in the liver fibrosis determined by schistosomiasis.

Therefore, these findings confirm that hepatocytes can be stimulated by *H. pylori* infection, resulting in collagen accumulation and, consequently, in hepatic fibrosis[108].

ROLE OF *H. PYLORI* IN PANCREAS DISEASES

Acute and CP

In the last decades, acute pancreatitis, defined as an acute inflammatory response from unregulated activation of pancreatic enzymes, has demonstrated an increase in its incidence[109,110]. This disorder, which can present a persistent hypovolemia, besides a decreased intravascular volume, can lead to extrapancreatic complications[111]. In 2007, a publication revealed an important frequency of patients with acute pancreatitis that also presented acute gastrointestinal mucosal damage[112] and it suggests that this bacterium infection could somewhat influence the acute pancreatitis progression.

Two important mechanisms-hypergastrinemia and duodenal acidification-together with the translocation of the microorganism or its toxins into the pancreas, have been cited as important mechanisms by which *H. pylori* infection could have an effect on the acute pancreatitis progression[26]. Warzecha *et al*[33] observed the effect of *H. pylori* infection of the gastric mucosa on the clinical evaluation of the disease in a model of ischaemia/reperfusion-induced in rats. Their results have suggested an evidence of damage effect of *H. pylori* infection of the stomach in patients diagnosed with acute pancreatitis. Lee *et al*[113] trying to evaluate the relationship between PUD and acute pancreatitis, studied 78 patients with acute pancreatitis, and 41 of them suffered from peptic ulcer disease, but only 31.7% of these 41 patients were infected by *H. pylori*. They concluded that PUD is associated with severe acute pancreatitis and the treatment for PUD should be considered for patients with that disease.

As regards to the possible association between CP and *H. pylori* infection, different hypothesis have been suggested. According to Manes *et al*[26], there are three possible roles of this infection and the evolution of CP: The influence of this microorganism infection in the pathogenesis and evolution in idiopathic forms of CP, the influence of this infection on the exocrine pancreatic secretion in individuals with CP, and the possibility of CP influences the gastrointestinal physiology and, consequently, the pathogen colonization.

Besides, important alterations in the gastric function found in CP could demonstrate the presence of *H. pylori* infection in the stomach rather than changes induced by the pancreatic disease. Study developed by Manes *et al*[35] reported that the prevalence of *H. pylori* infection in patients with CP is similar that of two other studied groups of individuals, one with patients with alcoholic liver cirrhosis and other with healthy subjects, but the

frequency and severity of *H. pylori* negative chronic gastritis in the antrum was significantly higher in individuals with CP than in the other groups. Similar results were found by Niemann *et al*[34]. In their study, the prevalence of *H. pylori* infection was investigated in individuals with CP, with and without duodenal ulcers, in comparison to a control group which only included patients with duodenal ulcer. The results suggested that the bacterium infection can contribute to the CP development, but no as the main cause for the disease development.

Pancreatic cancer

The potential role of *H. pylori* infection in pancreatic cancer (exocrine pancreatic carcinoma or pancreatic ductal adenocarcinoma) has also been suggested. This cancer is the fifth leading cause of cancer related death worldwide. Its high degree of death incidence is especially due to the diagnosis generally done in the advanced stage and to the poor responses to current treatments[114-117].

Lowenfels *et al*[118] considered that similarly pathologic consequences of gastric tissue due to *H. pylori* chronic infection could be observed in CP and consequently in pancreatic cancer.

A meta-analysis of six cohort studies and one case-control study found that the pooled relative risk estimate for pancreatic cancer among patients with CP is 13.3[119]. Duell *et al*[120] analyzed 5048 patients with pancreatic cancer in ten case-control studies and found only a small association between pancreatic cancer and antecedent CP, although this study presented some limitations. Despite of these findings, it has been considered that CP is a rare cause of pancreatic cancer[121].

Other possible mechanisms for the association between *H. pylori* and pancreatic cancer include changes in gastrin (increased secretion) and somatostatin (low number of antral somatostatin cells) resulting from *H. pylori* gastritis[28,122-124], increased DNA synthesis, increased formation of N-nitroso components (due to bacterial overgrowth), and chronic inflammation properly, aspect that can be responsible by itself for initiating the carcinogenesis process[125-127].

In addition, *H. pylori* chronic infection, as responsible for the production of proinflammatory cytokines and reactive oxygen species, as well as of other inflammatory mediators, may induce the tissue inflammation. In consequence, the increase on genomic DNA damage and cell proliferation (aspects that may lead to an inactivation of tumor-suppressor genes), are factors which may contribute the malignant transformation of pancreatic cells[128]. Considering it, Takayama *et al*[129] reported that activities of nuclear factor-κb, activator protein-1, and serum response element of human pancreatic cancer cells were shown to be increased by *H. pylori* infection, as well as serum levels of IL-8, suggesting that the development of pancreatic cancer could be similar to the gastric carcinogenesis. Consequently, environmental aspects such as dietary habits, smoking and alcohol consumption can contribute for the development of pancreatic cancer[130], as well as they contribute in gastric cancer.

Finally, other important meta-analysis concluded that *H. pylori* infection can be considered a significantly factor to the pancreatic cancer development, also considering that regional aspects can be important for this. Xiao *et al*[29] reported countries regional aspects reporting that the association between *H. pylori* infection and pancreatic cancer development is more evident in Europe and East Asia, and decreases in North America. They also suggested that *H. pylori* CagA positive strains are not possibly associated with pancreatic cancer development. Despite of it, meta-analysis conducted by Wang *et al*[30] concluded that *H. pylori* infection and CagA positive strains are associated with a decreased risk of pancreatic cancer in Eastern populations but have no significant associations in Western countries. Lindkvist *et al*[131], in a prospective study, also concluded that no association between this pathogen infection and the risk for pancreatic cancer was found in their nested case-control study within a population based cohort. Nevertheless, recent study with 56 cases of pancreatic cancer analyzed anti-Hp IgG (*H. pylori*-specific antibodies), Hp IgM (*H. pylori* antibodies) and CagA-Hp-IgG (*H. pylori* serotoxin-associated protein A antibody), comparing the results with a control group. The results obtained demonstrated that *H. pylori* infection rate in the patients group was significantly higher than that in the control group ($P < 0.01$). Besides, the positive rate of CagA-Hp in the observation group was 38.88%, and 21.53% in the control group ($P < 0.05$). The researchers concluded that *H. pylori* infection, especially with CagA positive strains, besides smoking history and the history of CP, is one of the risk factors for pancreatic cancer development[132].

AIP

AIP has been recognized as a form of CP, which is always associated with autoimmune manifestations[133]. It is defined as an inflammatory process of the pancreas characterized by hypergammaglobulinemia, enlargement of the organ, fibrotic changes with lymphocytic infiltrations and presence of autoantibodies, among other alterations, all of them contributing to the tissue destruction possibly by apoptosis[36].

The coexistence of AIP with other autoimmune diseases has been reported in the literature. Among them, they can be cited Sjögren's syndrome, PBC, autoimmune hepatitis, Hashimoto's thyroiditis and gastric ulcer, among others[134-136].

As regards to the mechanisms by which *H. pylori* infection could trigger AIP, the molecular mimicry between bacterial antigens and human ones has been reported as the most plausible hypothesis, based on epidemiological studies[137,138].

According to Kountouras *et al*[36], bacterial heat shock proteins (Hsps), particularly Hsp-60 or Hsp-70 of *H. pylori*, may represent major target antigens

responsible for molecular mimicry causing autoreactivity between this microorganism and the host's immune gastric tissue, being probably responsible for the humoral and/or cellular (T-cell) response against these proteins and consequently influencing the pathogenesis of autoimmune diseases such as AIP[139,140].

Guarneri *et al*[141] reported the existence of two molecules possibly involved in the molecular mimicry (CA-Ⅱ and α-HpCA), that are homologous to the HLA molecule DRB1*0405, reported as a risk factor for the development of AIP[142]. Considering it, and the importance of α-HpCA for gastric colonization, the host immune response against this molecule could turn against the autoantigen CA-Ⅱ, promoting the appearance of AIP in genetically predisposed individuals[142,143].

Besides, HLA-DR antigens are expressed on the pancreatic duct cells as well as on $CD4^+$ suggesting an autoimmune mechanism involved in inflammation[134,144], event that, in conjunction with epithelial cells apoptosis, can be upregulated by *H. pylori* infection and, consequently, be important to the development of AIP[140].

Besides, important researches have indicate that apoptosis is a mechanism of cell death in several important *H. pylori*-associated upper gastrointestinal damages and in extradigestive disorders. These studies hypothesized that *H. pylori* could change the expression of some genes including that ones encoding growth factors, transcription factors, and apoptosis proteins, among others, consequently contributing to the development both of gastrointestinal and extradigestive diseases. In addition, some virulence factors of *H. pylori*, such as urease, could contribute to cell apoptosis probably to activation of T cells[36]. Finally, in addition, microcirculatory changes promoted by *H. pylori* infection through platelet and platelet-leukocyte aggregation could promote the amplification of the pancreatic injury[142,145,146].

Obviously the relationship between *H. pylori* infection and AIP development has to better studied, but it can be considered that various autoimmune and apoptotic sequelae induced by this chronic and long-term infection appear to influence the pathophysiology of AIP.

DM and metabolic disorders

Type 1 or type 2 DM development have also been reported to a high prevalence of *H. pylori* positive individuals[147]. In a meta-analysis, Zhou *et al*[148] found a high prevalence of this microorganism infection in individuals with DM, particularly type 2. Jeon *et al*[149] reported similar results and concluded in their sampling that individuals who were seropositive for *H. pylori* were 2.7 times more at risk to develop DM than seronegative patients. Nevertheless, this association remains controversial[150].

Gunji *et al*[151] evaluated the association between IR and *H. pylori* infection and suggested that this infection could really contribute even in an independent way to promoting this condition. Besides, study developed by So *et al*[152] in China concluded that *H. pylori* infection could be an independent predictor for hyperglycemia and reduced insulin sensitivity and this fact has shown to be important for the high prevalence of type 2 DM in this country population.

Metabolic syndrome, one of the most prevalent global health problems that predisposes to type 2 DM and it is linked to IR, has also be proposed to be associated to *H. pylori* infection[153,154]. Polyzos *et al*[39], through a quantitative homeostatic model, studied this possible association, but data concerning this relationship remain contradictory. In anyway, the eradication of the infection appears to prevent negative metabolic effects in the pathogenesis of DM[155].

CONCLUSION

The higher prevalence of *H. pylori* infection in subjects with hepatitis, cirrhosis, HE, NAFLD and HCC may suggest its possible role in the pathogenesis of CLD. Moreover, many studies have found a synergistic association between this bacterium and hepatitis viruses, mainly HCV, suggesting that *H. pylori* may represent a co-risk factor in the progression of liver diseases, especially HCC. However, high quality prospective studies in non-cirrhotic HCC patients co-infected with HCV are needed to confirm these findings.

Another important fact to consider is that patients with severe CLD are more likely to develop bacterial infection. Then, *H. pylori* infection could be related to immunological and inflammatory changes in the liver. In this context, bacterium would not be considered a risk factor for HCC and the colonization of hepatic tissue could result from tumor process.

Complex interactions in the gastric mucosal changes determined by the pathogen infection could contribute to the pancreatic cancer development, especially by N-nitrosamine exposure of the host, added by dietary and smoking habits. Important meta-analyses have reported an increased risk for pancreatic cancer development in subjects contaminated by *H. pylori*. In addition, it has also been suggested that *H. pylori* causes AIP due to molecular mimicry between bacterium and enzymes that are highly expressed in the pancreatic ductal and pancreatic cells, in addiction of apoptosis process. Finally, *H. pylori* infection has been associated to both type 1 and type 2 DM development, as well as metabolic syndrome, interaction that has not been determined. Despite some of these studies present some limitations, including a small number of patients and only hypothesis which have not been elucidated yet, the role played by *H. pylori* in the pathogenesis of such conditions have a substantial impact of healthcare and obviously its infection and the relationship with all the conditions described above has to be subject for further investigation.

Considering the worldwide liver and pancreatic diseases burden, as well as the possible association between *H. pylori* infection, which is commonly chronic and reported to poor sanitary conditions, besides the

widespread use of some medicines that can mask the real condition of the infection, a complete elucidation of the role played by *H. pylori* in the pathogenesis of such conditions have certainly a substantial impact of healthcare.

REFERENCES

1 **Moodley Y**, Linz B, Bond RP, Nieuwoudt M, Soodyall H, Schlebusch CM, Bernhöft S, Hale J, Suerbaum S, Mugisha L, van der Merwe SW, Achtman M. Age of the association between Helicobacter pylori and man. *PLoS Pathog* 2012; **8**: e1002693 [PMID: 22589724 DOI: 10.1371/journal.ppat.1002693]

2 **Roubaud Baudron C**, Franceschi F, Salles N, Gasbarrini A. Extragastric diseases and Helicobacter pylori. *Helicobacter* 2013; **18** Suppl 1: 44-51 [PMID: 24011245 DOI: 10.1111/hel.12077]

3 **Mishra S**. Is Helicobacter pylori good or bad? *Eur J Clin Microbiol Infect Dis* 2013; **32**: 301-304 [PMID: 23132690 DOI: 10.1007/s10096-012-1773-9]

4 **Makola D**, Peura DA, Crowe SE. Helicobacter pylori infection and related gastrointestinal diseases. *J Clin Gastroenterol* 2007; **41**: 548-558 [PMID: 17577110]

5 **Franceschi F**, Gasbarrini A. Helicobacter pylori and extragastric diseases. *Best Pract Res Clin Gastroenterol* 2007; **21**: 325-334 [PMID: 17382280]

6 **Roubaud-Baudron C**, Krolak-Salmon P, Quadrio I, Mégraud F, Salles N. Impact of chronic Helicobacter pylori infection on Alzheimer's disease: preliminary results. *Neurobiol Aging* 2012; **33**: 1009.e11-1009.e19 [PMID: 22133280 DOI: 10.1016/j.neurobiolaging.2011.10.021]

7 **Venerito M**, Selgrad M, Malfertheiner P. Helicobacter pylori: gastric cancer and extragastric malignancies - clinical aspects. *Helicobacter* 2013; **18** Suppl 1: 39-43 [PMID: 24011244 DOI: 10.1111/hel.12078]

8 **Tebbe B**, Geilen CC, Schulzke JD, Bojarski C, Radenhausen M, Orfanos CE. Helicobacter pylori infection and chronic urticaria. *J Am Acad Dermatol* 1996; **34**: 685-686 [PMID: 8601663]

9 **Zentilin P**, Seriolo B, Dulbecco P, Caratto E, Iiritano E, Fasciolo D, Bilardi C, Mansi C, Testa E, Savarino V. Eradication of Helicobacter pylori may reduce disease severity in rheumatoid arthritis. *Aliment Pharmacol Ther* 2002; **16**: 1291-1299 [PMID: 12144579]

10 **Fox JG**, Yan LL, Dewhirst FE, Paster BJ, Shames B, Murphy JC, Hayward A, Belcher JC, Mendes EN. Helicobacter bilis sp. nov., a novel Helicobacter species isolated from bile, livers, and intestines of aged, inbred mice. *J Clin Microbiol* 1995; **33**: 445-454 [PMID: 7536217]

11 **Fox JG**, Yan L, Shames B, Campbell J, Murphy JC, Li X. Persistent hepatitis and enterocolitis in germfree mice infected with Helicobacter hepaticus. *Infect Immun* 1996; **64**: 3673-3681 [PMID: 8751916]

12 **Franklin CL**, Beckwith CS, Livingston RS, Riley LK, Gibson SV, Besch-Williford CL, Hook RR. Isolation of a novel Helicobacter species, Helicobacter cholecystus sp. nov., from the gallbladders of Syrian hamsters with cholangiofibrosis and centrilobular pancreatitis. *J Clin Microbiol* 1996; **34**: 2952-2958 [PMID: 8940429]

13 **Kawaguchi M**, Saito T, Ohno H, Midorikawa S, Sanji T, Handa Y, Morita S, Yoshida H, Tsurui M, Misaka R, Hirota T, Saito M, Minami K. Bacteria closely resembling Helicobacter pylori detected immunohistologically and genetically in resected gallbladder mucosa. *J Gastroenterol* 1996; **31**: 294-298 [PMID: 8680555]

14 **Nilsson HO**, Taneera J, Castedal M, Glatz E, Olsson R, Wadström T. Identification of Helicobacter pylori and other Helicobacter species by PCR, hybridization, and partial DNA sequencing in human liver samples from patients with primary sclerosing cholangitis or primary biliary cirrhosis. *J Clin Microbiol* 2000; **38**: 1072-1076 [PMID: 10698999]

15 **Schmulson MJ**, De León G, Kershenovich A, Vargas-Vorackova F, Kershenobich D. Helicobacter pylori infection among patients with alcoholic and nonalcoholic cirrhosis. *Helicobacter* 1997; **2**: 149-151 [PMID: 9432344]

16 **Siringo S**, Vaira D, Menegatti M, Piscaglia F, Sofia S, Gaetani M, Miglioli M, Corinaldesi R, Bolondi L. High prevalence of Helicobacter pylori in liver cirrhosis: relationship with clinical and endoscopic features and the risk of peptic ulcer. *Dig Dis Sci* 1997; **42**: 2024-2030 [PMID: 9365129]

17 **Fan XG**, Zou YY, Wu AH, Li TG, Hu GL, Zhang Z. Seroprevalence of Helicobacter pylori infection in patients with hepatitis B. *Br J Biomed Sci* 1998; **55**: 176-178 [PMID: 10367401]

18 **Pellicano R**, Leone N, Berrutti M, Cutufia MA, Fiorentino M, Rizzetto M, Ponzetto A. Helicobacter pylori seroprevalence in hepatitis C virus positive patients with cirrhosis. *J Hepatol* 2000; **33**: 648-650 [PMID: 11059871]

19 **Ponzetto A**, Cutufia MA, D'Errico A, Angelino R, Pellicano R, Leone N. Demonstration of Helicobacter spp by PCR in liver of patients with liver cirrhosis and hepatocellular carcinoma. *Gut* 1999; **45**: A88

20 **Avenaud P**, Marais A, Monteiro L, Le Bail B, Bioulac Sage P, Balabaud C, Mégraud F. Detection of Helicobacter species in the liver of patients with and without primary liver carcinoma. *Cancer* 2000; **89**: 1431-1439 [PMID: 11013355]

21 **Dore MP**, Realdi G, Mura D, Graham DY, Sepulveda AR. Helicobacter infection in patients with HCV-related chronic hepatitis, cirrhosis, and hepatocellular carcinoma. *Dig Dis Sci* 2002; **47**: 1638-1643 [PMID: 12141829]

22 **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]

23 **Rabelo-Gonçalves EM**, Sgardioli IC, Lopes-Cendes I, Escanhoela CA, Almeida JR, Zeitune JM. Improved detection of Helicobacter pylori DNA in formalin-fixed paraffin-embedded (FFPE) tissue of patients with hepatocellular carcinoma using laser capture microdissection (LCM). *Helicobacter* 2013; **18**: 244-245 [PMID: 23350684 DOI: 10.1111/hel.12040]

24 **de Magalhães Queiroz DM**, Santos A. Isolation of a Helicobacter strain from the human liver. *Gastroenterology* 2001; **121**: 1023-1024 [PMID: 11665691]

25 **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]

26 **Manes G**, Balzano A, Vaira D. Helicobacter pylori and pancreatic disease. *JOP* 2003; **4**: 111-116 [PMID: 12743416]

27 **Raderer M**, Wrba F, Kornek G, Maca T, Koller DY, Weinlaender G, Hejna M, Scheithauer W. Association between Helicobacter pylori infection and pancreatic cancer. *Oncology* 1998; **55**: 16-19 [PMID: 9428370]

28 **Stolzenberg-Solomon RZ**, Blaser MJ, Limburg PJ, Perez-Perez G, Taylor PR, Virtamo J, Albanes D. Helicobacter pylori seropositivity as a risk factor for pancreatic cancer. *J Natl Cancer Inst* 2001; **93**: 937-941 [PMID: 11416115 DOI: 10.1093/jnci/93.12.937]

29 **Xiao M**, Wang Y, Gao Y. Association between Helicobacter pylori infection and pancreatic cancer development: a meta-analysis. *PLoS One* 2013; **8**: e75559 [PMID: 24086571 DOI: 10.1371/journal.pone.0075559]

30 **Wang Y**, Zhang FC, Wang YJ. Helicobacter pylori and pancreatic cancer risk: a meta- analysis based on 2,049 cases and 2,861 controls. *Asian Pac J Cancer Prev* 2014; **15**: 4449-4454 [PMID: 24969867]

31 **Luo J**, Nordenvall C, Nyrén O, Adami HO, Permert J, Ye W. The risk of pancreatic cancer in patients with gastric or duodenal ulcer disease. *Int J Cancer* 2007; **120**: 368-372 [PMID: 17044024 DOI: 10.1002/ijc.22123]

32 **Bao Y**, Spiegelman D, Li R, Giovannucci E, Fuchs CS, Michaud DS. History of peptic ulcer disease and pancreatic cancer risk in men. *Gastroenterology* 2010; **138**: 541-549 [PMID: 19818786 DOI: 10.1053/j.gastro.2009.09.059]

33 **Warzecha Z**, Dembiński A, Ceranowicz P, Dembiński M, Sendur R, Pawlik WW, Konturek SJ. Deleterious effect of Helicobacter pylori infection on the course of acute pancreatitis in

rats. *Pancreatology* 2002; **2**: 386-395 [PMID: 12138227 DOI: 10.1159/000065086]
34 **Niemann T**, Larsen S, Mouritsen EA, Thorsgaard N. Helicobacter pylori infection in patients with chronic pancreatitis and duodenal ulcer. *Scand J Gastroenterol* 1997; **32**: 1201-1203 [PMID: 9438316]
35 **Manes G**, Dominguez-Muñoz JE, Hackelsberger A, Leodolter A, Rössner A, Malfertheiner P. Prevalence of Helicobacter pylori infection and gastric mucosal abnormalities in chronic pancreatitis. *Am J Gastroenterol* 1998; **93**: 1097-1100 [PMID: 9672337]
36 **Kountouras J**, Zavos C, Chatzopoulos D. A concept on the role of Helicobacter pylori infection in autoimmune pancreatitis. *J Cell Mol Med* 2005; **9**: 196-207 [PMID: 15784177 DOI: 10.1111/j.1582-4934.2005.tb00349x]
37 **Marietti M**, Gasbarrini A, Saracco G, Pellicano R. Helicobacter pylori infection and diabetes mellitus: the 2013 state of art. *Panminerva Med* 2013; **55**: 277-281 [PMID: 24088801]
38 **Franceschi F**, Tortora A, Gasbarrini G, Gasbarrini A. Helicobacter pylori and extragastric diseases. *Helicobacter* 2014; **19** Suppl 1: 52-58 [PMID: 25167946 DOI: 10.1111/hel.12159]
39 **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]
40 **Franceschi F**, Annalisa T, Teresa DR, Giovanna D, Ianiro G, Franco S, Viviana G, Valentina T, Riccardo LL, Antonio G. Role of Helicobacter pylori infection on nutrition and metabolism. *World J Gastroenterol* 2014; **20**: 12809-12817 [PMID: 25278679 DOI: 10.3748/wjg.v20.i36.12809]
41 **Malfertheiner P**, Link A, Selgrad M. Helicobacter pylori: perspectives and time trends. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 628-638 [PMID: 25001975 DOI: 10.1038/nrgastro.2014.99]
42 **Lau WY**. Primary liver tumors. *Semin Surg Oncol* 2000; **19**: 135-144 [PMID: 11126378]
43 **Lau WY**. Management of hepatocellular carcinoma. *J R Coll Surg Edinb* 2002; **47**: 389-399 [PMID: 11874260]
44 **Llovet JM**, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907-1917 [PMID: 14667750]
45 **Lai EC**, Lau WY. The continuing challenge of hepatic cancer in Asia. *Surgeon* 2005; **3**: 210-215 [PMID: 16076007]
46 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108 [PMID: 15761078]
47 **Tu QV**, Okoli AS, Kovach Z, Mendz GL. Hepatocellular carcinoma: prevalence and molecular pathogenesis of Helicobacter spp. *Future Microbiol* 2009; **4**: 1283-1301 [PMID: 19995189 DOI: 10.2217/fmb.09.90]
48 **Hall AJ**, Wild CP. Liver cancer in low and middle income countries. *BMJ* 2003; **326**: 994-995 [PMID: 12742895]
49 **Pellicano R**, Ménard A, Rizzetto M, Mégraud F. Helicobacter species and liver diseases: association or causation? *Lancet Infect Dis* 2008; **8**: 254-260 [PMID: 18353266 DOI: 10.1016/S1473-3099(08)70066-5]
50 **Bosch FX**, Ribes J, Cléries R, Díaz M. Epidemiology of hepatocellular carcinoma. *Clin Liver Dis* 2005; **9**: 191-211, v [PMID: 15831268]
51 **Humpage AR**, Falconer IR. Mycrocystin-LR and liver tumor promotion: effects on cytokinesis, ploidy, and apoptosis in cultured hepatocytes. *Env Toxicol* 1999; **14**: 61-75
52 **Liu CJ**, Kao JH. Hepatitis B virus-related hepatocellular carcinoma: epidemiology and pathogenic role of viral factors. *J Chin Med Assoc* 2007; **70**: 141-145 [PMID: 17475593]
53 **Farinati F**, Cardin R, Bortolami M, Burra P, Russo FP, Rugge M, Guido M, Sergio A, Naccarato R. Hepatitis C virus: from oxygen free radicals to hepatocellular carcinoma. *J Viral Hepat* 2007; **14**: 821-829 [PMID: 18070284]
54 **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]
55 **Verhoef C**, Pot RG, de Man RA, Zondervan PE, Kuipers EJ, IJzermans JN, Kusters JG. Detection of identical Helicobacter DNA in the stomach and in the non-cirrhotic liver of patients with hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2003; **15**: 1171-1174 [PMID: 14560149]
56 **Pellicano R**, Mazzaferro V, Grigioni WF, Cutufia 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]
57 **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]
58 **Ponzetto 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]
59 **Ponzetto A**, Pellicano R, Leone N, Cutufia MA, Turrini F, Grigioni WF, D'Errico A, Mortimer P, Rizzetto M, Silengo L. Helicobacter infection and cirrhosis in hepatitis C virus carriage: is it an innocent bystander or a troublemaker? *Med Hypotheses* 2000; **54**: 275-277 [PMID: 10790764]
60 **Spinzi G**, Pellicano R, Minoli G, Terreni N, Cutufia MA, Fagoonee S, Rizzetto M, Ponzetto A. Helicobacter pylori seroprevalence in hepatitis C virus positive patients with cirrhosis. The Como cross-sectional study. *Panminerva Med* 2001; **43**: 85-87 [PMID: 11449177]
61 **Leone N**, Pellicano R, Brunello F, Cutufia MA, Berrutti M, Fagoonee S, Rizzetto M, Ponzetto A. Helicobacter pylori seroprevalence in patients with cirrhosis of the liver and hepatocellular carcinoma. *Cancer Detect Prev* 2003; **27**: 494-497 [PMID: 14642558]
62 **Ponzetto A**, Pellicano R, Redaelli A, Rizzetto M, Roffi L. Helicobacter pylori infection in patients with Hepatitis C Virus positive chronic liver diseases. *New Microbiol* 2003; **26**: 321-328 [PMID: 14596342]
63 **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]
64 **Tsuneyama K**, Harada K, Kono N, Hiramatsu K, Zen Y, Sudo Y, Gershwin ME, Ikemoto M, Arai H, Nakanuma Y. Scavenger cells with gram-positive bacterial lipoteichoic acid infiltrate around the damaged interlobular bile ducts of primary biliary cirrhosis. *J Hepatol* 2001; **35**: 156-163 [PMID: 11580136]
65 **Leelawat K**, Suksumek N, Leelawat S, Lek-Uthai U. Detection of VacA gene specific for Helicobactor pylori in hepatocellular carcinoma and cholangiocarcinoma specimens of Thai patients. *Southeast Asian J Trop Med Public Health* 2007; **38**: 881-885 [PMID: 18041306]
66 **Ito K**, Nakamura M, Toda G, Negishi M, Torii A, Ohno T. Potential role of Helicobacter pylori in hepatocarcinogenesis. *Int J Mol Med* 2004; **13**: 221-227 [PMID: 14719127]
67 **Abu Al-Soud W**, Stenram U, Ljungh A, Tranberg KG, Nilsson HO, Wadström T. DNA of Helicobacter spp. and common gut bacteria in primary liver carcinoma. *Dig Liver Dis* 2008; **40**: 126-131 [PMID: 18083084]
68 **Ihrig M**, Schrenzel MD, Fox JG. Differential susceptibility to hepatic inflammation and proliferation in AXB recombinant inbred mice chronically infected with Helicobacter hepaticus. *Am J Pathol* 1999; **155**: 571-582 [PMID: 10433949]
69 **Taylor NS**, Fox JG, Yan L. In-vitro hepatotoxic factor in Helicobacter hepaticus, H. pylori and other Helicobacter species. *J Med Microbiol* 1995; **42**: 48-52 [PMID: 7739025]
70 **Balkwill F**, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001; **357**: 539-545 [PMID: 11229684]
71 **Ito K**, Yamaoka Y, Ota H, El-Zimaity H, Graham DY. Adherence, internalization, and persistence of Helicobacter pylori in hepatocytes. *Dig Dis Sci* 2008; **53**: 2541-2549 [PMID: 18320323 DOI: 10.1007/s10620-007-0164-z]
72 **Liu X**, Liang J, Li G. Lipopolysaccharide promotes adhesion and

invasion of hepatoma cell lines HepG2 and HepG2.2.15. *Mol Biol Rep* 2010; **37**: 2235-2239 [PMID: 19680784 DOI: 10.1007/s11033-009-9710-4]
73 **Huang Y**, Fan XG, Zhou JH. [Immunohistochemistry of Helicobacter pylori in primary liver carcinoma tissues]. *Zhongnan Daxue Xuebao Yixueban* 2004; **29**: 15-17 [PMID: 16136995]
74 **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]
75 **Sathar SA**, Kunnathuparambil SG, Sreesh S, Narayanan P, Vinayakumar KR. Helicobacter pylori infection in patients with liver cirrhosis: prevalence and association with portal hypertensive gastropathy. *Ann Gastroenterol* 2014; **27**: 48-52 [PMID: 24714519]
76 **Rabinovitz M**, Yoo YK, Schade RR, Dindzans VJ, Van Thiel DH, Gavaler JS. Prevalence of endoscopic findings in 510 consecutive individuals with cirrhosis evaluated prospectively. *Dig Dis Sci* 1990; **35**: 705-710 [PMID: 2344804]
77 **Abdel-Hady H**, Zaki A, Badra G, Lotfy M, Selmi C, Giorgini A, El-Sayed M, Badr R. Helicobacter pylori infection in hepatic encephalopathy: Relationship to plasma endotoxins and blood ammonia. *Hepatol Res* 2007; **37**: 1026-1033 [PMID: 17610507]
78 **Schulz C**, Schütte K, Malfertheiner P. Does H. pylori eradication therapy benefit patients with hepatic encephalopathy?: systematic review. *J Clin Gastroenterol* 2014; **48**: 491-499 [PMID: 24583758 DOI: 10.1097/MCG.0000000000000108]
79 **Feng H**, Zhou X, Zhang G. Association between cirrhosis and Helicobacter pylori infection: a meta-analysis. *Eur J Gastroenterol Hepatol* 2014; **26**: 1309-1319 [PMID: 25304251 DOI: 10.1097/MEG0000000000000220]
80 **Pellicano R**, Fagoonee S. Helicobacter pylori and cirrhosis: any missing data in the meta-analysis? *Eur J Gastroenterol Hepatol* 2015; **27**: 182-183 [PMID: 25533432 DOI: 10.097/MEG.0000000000000243]
81 **Floreani A**, Biagini MR, Zappalà F, Farinati F, Plebani M, Rugge M, Surrenti C, Naccarato R. Chronic atrophic gastritis and Helicobacter pylori infection in primary biliary cirrhosis: a cross-sectional study with matching. *Ital J Gastroenterol Hepatol* 1997; **29**: 13-17 [PMID: 9265572]
82 **Durazzo M**, Rosina F, Premoli A, Morello E, Fagoonee S, Innarella R, Solerio E, Pellicano R, Rizzetto M. Lack of association between seroprevalence of Helicobacter pylori infection and primary biliary cirrhosis. *World J Gastroenterol* 2004; **10**: 3179-3181 [PMID: 15457568]
83 **Amodio P**, Montagnese S, Gatta A, Morgan MY. Characteristics of minimal hepatic encephalopathy. *Metab Brain Dis* 2004; **19**: 253-267 [PMID: 15554421]
84 **Shimamoto C**, Hirata I, Katsu K. Breath and blood ammonia in liver cirrhosis. *Hepatogastroenterology* 2000; **47**: 443-445 [PMID: 10791209]
85 **Demirtürk L**, Yazgan Y, zci O, Ozel M, Toğrol E, Gültepe M, Gürbüz AK, Yildirim S. The effect of Helicobacter pylori eradication on gastric juice and blood ammonia concentrations and on visual evoked potentials in cirrhotics. *Helicobacter* 2001; **6**: 325-330 [PMID: 11843965]
86 **Nandakumar R**, Naik AS, Pandit B, Kamat R, Bhatia SJ. Effect of Helicobacter pylori eradication on serum ammonia levels in patients with chronic liver disease. *Indian J Gastroenterol* 2003; **22**: 221-223 [PMID: 15030034]
87 **Miquel J**, Barcena R, Boixeda D, Fernández J, SanRoman AL, Martín-de-Argila C, Ramosa F. Role of Helicobacter pylori infection and its eradication in patients with subclinical hepatic encephalopathy. *Eur J Gastroenterol Hepatol* 2001; **13**: 1067-1072 [PMID: 11564957]
88 **Huber M**, Rössle M, Siegerstetter V, Ochs A, Haag K, Kist M, Blum HE. Helicobacter pylori infection does not correlate with plasma ammonia concentration and hepatic encephalopathy in patients with cirrhosis. *Hepatogastroenterology* 2001; **48**: 541-544 [PMID: 11379349]
89 **Zullo A**, Hassan C, Morini S. Hepatic encephalopathy and Helicobacter pylori: a critical reappraisal. *J Clin Gastroenterol* 2003; **37**: 164-168 [PMID: 12869889]
90 **Hu BL**, Wang HY, Yang GY. Association of Helicobacter pylori infection with hepatic encephalopathy risk: a systematic review. *Clin Res Hepatol Gastroenterol* 2013; **37**: 619-625 [PMID: 23830279 DOI: 10.1016/jclinre.2013.05.004]
91 **Kountouras J**, Zavos C, Deretzi G. Helicobacter pylori might contribute to persistent cognitive impairment after resolution of overt hepatic encephalopathy. *Clin Gastroenterol Hepatol* 2011; **9**: 624; author reply 624-625 [PMID: 21334456 DOI: 10.1016/j.cgh.2011.02.011]
92 **Kountouras J**, Zavos C, Deretzi G, Vardaka E, Boziki M, Gavalas E, Kouklakis G, Katsinelos P, Venizelos I, Nikolaidou C, Polyzos SA, Giartza-Taxidou E. Helicobacter pylori induced cognitive dysfunction might be associated with falls and fractures in cirrhosis. *Hepatology* 2013; **57**: 1284 [PMID: 22745033 DOI: 10.1002/hep.25926]
93 **de Alwis NM**, Day CP. Non-alcoholic fatty liver disease: the mist gradually clears. *J Hepatol* 2008; **48** Suppl 1: S104-S112 [PMID: 18304679 DOI: 10.16/jjhep.2008.01.009]
94 **Bellentani S**, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. *Dig Dis* 2010; **28**: 155-161 [PMID: 20460905 DOI: 10.1159/000282080]
95 **Bhala N**, Jouness RI, Bugianesi E. Epidemiology and natural history of patients with NAFLD. *Curr Pharm Des* 2013; **19**: 5169-5176 [PMID: 23394091]
96 **Ludwig J**, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980; **55**: 434-438 [PMID: 7382552]
97 **Matteoni CA**, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999; **116**: 1413-1419 [PMID: 10348825]
98 **Rafiq N**, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, Younossi ZM. Long-term follow-up of patients with nonalcoholic fatty liver. *Clin Gastroenterol Hepatol* 2009; **7**: 234-238 [PMID: 19049831 DOI: 10.1016/j.cgh.2008.11.005]
99 **Li M**, Shen Z, Li YM. Potential role of Helicobacter pylori infection in nonalcoholic fatty liver disease. *World J Gastroenterol* 2013; **19**: 7024-7031 [PMID: 24222944 DOI: 10.3748/wjg.v19.i41.7024]
100 **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: 10.197/MEG.0b013e3282efa4f2]
101 **Abenavoli L**, Milic N, Masarone M, Persico M. Association between non-alcoholic fatty liver disease, insulin resistance and Helicobacter pylori. *Med Hypotheses* 2013; **81**: 913-915 [PMID: 24011768 DOI: 10.1016/j.mehy.2013.08.011]
102 **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/jmetabol.2012.06.007]
103 **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]
104 **Goo MJ**, Ki MR, Lee HR, Yang HJ, Yuan DW, Hong IH, Park JK, Hong KS, Han JY, Hwang OK, Kim DH, Do SH, Cohn RD, Jeong KS. Helicobacter pylori promotes hepatic fibrosis in the animal model. *Lab Invest* 2009; **89**: 1291-1303 [PMID: 19736546 DOI: 10.138/labinvest.2009.90]

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-β1-induced inflammatory signaling. *Lab Invest* 2010; **90**: 1507-1516 [PMID: 20531291 DOI: 10.138/labinvest.2010.109]

106 **García-Trevijano ER**, Iraburu MJ, Fontana L, Domínguez-Rosales JA, Auster A, Covarrubias-Pinedo A, Rojkind M. Transforming growth factor beta1 induces the expression of alpha1(I) procollagen mRNA by a hydrogen peroxide-C/EBPbeta-dependent mechanism in rat hepatic stellate cells. *Hepatology* 1999; **29**: 960-970 [PMID: 10051504]

107 **Wheeler MD**, Kono H, Yin M, Nakagami M, Uesugi T, Arteel GE, Gäbele E, Rusyn I, Yamashina S, Froh M, Adachi Y, Iimuro Y, Bradford BU, Smutney OM, Connor HD, Mason RP, Goyert SM, Peters JM, Gonzalez FJ, Samulski RJ, Thurman RG. The role of Kupffer cell oxidant production in early ethanol-induced liver disease. *Free Radic Biol Med* 2001; **31**: 1544-1549 [PMID: 11744328]

108 **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]

109 **Imrie CW**. Acute pancreatitis: overview. *Eur J Gastroenterol Hepatol* 1997; **9**: 103-105 [PMID: 9058618]

110 **Whitcomb DC**. Clinical practice. Acute pancreatitis. *N Engl J Med* 2006; **354**: 2142-2150 [PMID: 16707751 DOI: 10.1056/NEJMc054958]

111 **Frossard JL**, Steer ML, Pastor CM. Acute pancreatitis. *Lancet* 2008; **371**: 143-152 [PMID: 18191686 DOI: 10.1016/S0140-6736(08)60107-5]

112 **Chen TA**, Lo GH, Lin CK, Lai KH, Wong HY, Yu HC, Hsu PI, Chen HH, Tsai WL, Chen WC. Acute pancreatitis-associated acute gastrointestinal mucosal lesions: incidence, characteristics, and clinical significance. *J Clin Gastroenterol* 2007; **41**: 630-634 [PMID: 17577121 DOI: 10.1097/01.mcg.0000225638.37533.8c]

113 **Lee KM**, Paik CN, Chung WC, Yang JM. Association between acute pancreatitis and peptic ulcer disease. *World J Gastroenterol* 2011; **17**: 1058-1062 [PMID: 21448359 DOI: 10.3748/wjg.v17j8.1058]

114 **Hassan MM**, Bondy ML, Wolff RA, Abbruzzese JL, Vauthey JN, Pisters PW, Evans DB, Khan R, Chou TH, Lenzi R, Jiao L, Li D. Risk factors for pancreatic cancer: case-control study. *Am J Gastroenterol* 2007; **102**: 2696-2707 [PMID: 17764494 DOI: 10.1111/j.1572-0241.2007.01510.x]

115 **Hidalgo M**. Pancreatic cancer. *N Engl J Med* 2010; **362**: 1605-1617 [PMID: 20427809 DOI: 10.1056/NEJMra0901557]

116 **Maisonneuve P**, Lowenfels AB. Epidemiology of pancreatic cancer: an update. *Dig Dis* 2010; **28**: 645-656 [PMID: 21088417 DOI: 10.1159/000320068]

117 **Kang R**, Tang D. Autophagy in pancreatic cancer pathogenesis and treatment. *Am J Cancer Res* 2012; **2**: 383-396 [PMID: 22860230]

118 **Lowenfels AB**, Maisonneuve P, Lankisch PG. Chronic pancreatitis and other risk factors for pancreatic cancer. *Gastroenterol Clin North Am* 1999; **28**: 673-685, x [PMID: 10503143]

119 **Raimondi S**, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. *Best Pract Res Clin Gastroenterol* 2010; **24**: 349-358 [PMID: 20510834 DOI: 10.1016/j.bpg.2010.02.007]

120 **Duell EJ**, Lucenteforte E, Olson SH, Bracci PM, Li D, Risch HA, Silverman DT, Ji BT, Gallinger S, Holly EA, Fontham EH, Maisonneuve P, Bueno-de-Mesquita HB, Ghadirian P, Kurtz RC, Ludwig E, Yu H, Lowenfels AB, Seminara D, Petersen GM, La Vecchia C, Boffetta P. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol* 2012; **23**: 2964-2970 [PMID: 22767586 DOI: 10.1093/annonc/mds140]

121 **Yadav D**, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013; **144**: 1252-1261 [PMID: 23622135 DOI: 10.1053/j.gastro.2013.01.068]

122 **Tham TC**, Chen L, Dennison N, Johnston CF, Collins JS, Ardill JE, Buchanan KD. Effect of Helicobacter pylori eradication on antral somatostatin cell density in humans. *Eur J Gastroenterol Hepatol* 1998; **10**: 289-291 [PMID: 9855043]

123 **Park SM**, Lee HR, Kim JG, Park JW, Jung G, Han SH, Cho JH, Kim MK. Effect of Helicobacter pylori infection on antral gastrin and somatostatin cells and on serum gastrin concentrations. *Korean J Intern Med* 1999; **14**: 15-20 [PMID: 10063309]

124 **Larsson LI**. Developmental biology of gastrin and somatostatin cells in the antropyloric mucosa of the stomach. *Microsc Res Tech* 2000; **48**: 272-281 [PMID: 10700044 DOI: 10.1002/(SICI)1097-0029]

125 **Risch HA**. Etiology of pancreatic cancer, with a hypothesis concerning the role of N-nitroso compounds and excess gastric acidity. *J Natl Cancer Inst* 2003; **95**: 948-960 [PMID: 12837831 DOI: 10.1093/jnci/95.13.948]

126 **Trikudanathan G**, Philip A, Dasanu CA, Baker WL. Association between Helicobacter pylori infection and pancreatic cancer. A cumulative meta-analysis. *JOP* 2011; **12**: 26-31 [PMID: 21206097]

127 **Dobrila-Dintinjana R**, Vanis N, Dintinjana M, Radić M. Etiology and oncogenesis of pancreatic carcinoma. *Coll Antropol* 2012; **36**: 1063-1067 [PMID: 23213974]

128 **Nilsson HO**, Stenram U, Ihse I, Wadstrom T. Helicobacter species ribosomal DNA in the pancreas, stomach and duodenum of pancreatic cancer patients. *World J Gastroenterol* 2006; **12**: 3038-3043 [PMID: 16718784 DOI: 10.3748/wjg.v12.i19.3038]

129 **Takayama S**, Takahashi H, Matsuo Y, Okada Y, Manabe T. Effects of Helicobacter pylori infection on human pancreatic cancer cell line. *Hepatogastroenterology* 2007; **54**: 2387-2391 [PMID: 18265671]

130 **Michaud DS**. Role of bacterial infections in pancreatic cancer. *Carcinogenesis* 2013; **34**: 2193-2197 [PMID: 23843038 DOI: 10.1093/carcin/bgt249]

131 **Lindkvist B**, Johansen D, Borgström A, Manjer J. A prospective study of Helicobacter pylori in relation to the risk for pancreatic cancer. *BMC Cancer* 2008; **8**: 321 [PMID: 18986545 DOI: 10.1186/1471-2407-8-321]

132 **Ai F**, Hua X, Liu Y, Lin J, Feng Z. Preliminary study of pancreatic cancer associated with Helicobacter pylori infection. *Cell Biochem Biophys* 2015; **71**: 397-400 [PMID: DOI: 10.1007/s12013-014-0211-2]

133 **Fan BG**, Andrén-Sandberg A. Autoimmune pancreatitis. *N Am J Med Sci* 2009; **1**: 148-151 [PMID: 22666688]

134 **Okazaki K**, Chiba T. Autoimmune related pancreatitis. *Gut* 2002; **51**: 1-4 [PMID: 12077078 DOI: 10.1136/gut51.1.1]

135 **Kim KP**, Kim MH, Song MH, Lee SS, Seo DW, Lee SK. Autoimmune chronic pancreatitis. *Am J Gastroenterol* 2004; **99**: 1605-1616 [PMID: 15307882 DOI: 10.1111/j.1572-0241.2004.30336x]

136 **Shinji A**, Sano K, Hamano H, Unno H, Fukushima M, Nakamura N, Akamatsu T, Kawa S, Kiyosawa K. Autoimmune pancreatitis is closely associated with gastric ulcer presenting with abundant IgG4-bearing plasma cell infiltration. *Gastrointest Endosc* 2004; **59**: 506-511 [PMID: 15044886 DOI: 10.1016/S0016-5107(03)02874-8]

137 **Persidis A**. Autoimmune disease drug discovery. *Nat Biotechnol* 1999; **17**: 1038 [PMID: 10504714 DOI: 10.1038/13748]

138 **Benvenga S**, Guarneri F, Vaccaro M, Santarpia L, Trimarchi F. Homologies between proteins of Borrelia burgdorferi and thyroid autoantigens. *Thyroid* 2004; **14**: 964-966 [PMID: 15671776 DOI: 10.1089/thy.2004.14.964]

139 **Spechler SJ.** Peptic ulcer disease and its complications. In: Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 7th ed. Philadelphia, PA: Saunders, 2002: 747-781

140 **Kountouras J**, Zavos C, Chatzopoulos D. Autoimmune pancreatitis, Helicobacter pylori infection and apoptosis: a proposed relationship. *Pancreas* 2005; **30**: 192-193

141 **Guarneri F**, Guarneri C, Benvenga S. Helicobacter pylori and autoimmune pancreatitis: role of carbonic anhydrase via molecular mimicry? *J Cell Mol Med* 2005; **9**: 741-744 [PMID: 16202223 DOI: 10.1111/j.1582-4934.2005.tb00506x]

142 **Klöppel G**, Lüttges J, Löhr M, Zamboni G, Longnecker D. Autoimmune pancreatitis: pathological, clinical, and immunological features. *Pancreas* 2003; **27**: 14-19 [PMID: 12826900]

143 **Chirica LC**, Petersson C, Hurtig M, Jonsson BH, Borén T, Lindskog S. Expression and localization of alpha- and beta-carbonic anhydrase in Helicobacter pylori. *Biochim Biophys Acta* 2002; **1601**: 192-199 [PMID: 12445482]

144 **Marcus EA**, Moshfegh AP, Sachs G, Scott DR. The periplasmic alpha-carbonic anhydrase activity of Helicobacter pylori is essential for acid acclimation. *J Bacteriol* 2005; **187**: 729-738 [PMID: 15629943]

145 **Okazaki K**, Uchida K, Chiba T. Recent concept of autoimmune-related pancreatitis. *J Gastroenterol* 2001; **36**: 293-302 [PMID: 11388391 DOI: 10.1007/s005350170094]

146 **DiMagno EP**, Chari S. Acute pancreatitis. In: Sleisenger & Fordtran's *Gastrointestinal and Liver Disease*. 7th Ed. Philadelphia, PA: Saunders, 2002: 913-941

147 **Kountouras J**, Zavos C, Chatzopoulos D. Induction of apoptosis as a proposed pathophysiological link between glaucoma and Helicobacter pylori infection. *Med Hypotheses* 2004; **62**: 378-381 [PMID: 14975507]

148 **Zhou X**, Zhang C, Wu J, Zhang G. Association between Helicobacter pylori infection and diabetes mellitus: a meta-analysis of observational studies. *Diabetes Res Clin Pract* 2013; **99**: 200-208 [PMID: 23395214 DOI: 10.1016/j.diabres.2012.11.012]

149 **Jeon CY**, Haan MN, Cheng C, Clayton ER, Mayeda ER, Miller JW, Aiello AE. Helicobacter pylori infection is associated with an increased rate of diabetes. *Diabetes Care* 2012; **35**: 520-525 [PMID: 22279028 DOI: 10.2337/dc11-1043]

150 **Albaker WI**. Helicobacter pylori infection and its relationship to metabolic syndrome: is it a myth or fact? *Saudi J Gastroenterol* 2011; **17**: 165-169 [PMID: 21546717 DOI: 10.4103/1319-3767.80377]

151 **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]

152 **So WY**, Tong PC, Ko GT, Ma RC, Ozaki R, Kong AP, Yang X, Ho CS, Lam CC, Chan JC. Low plasma adiponectin level, white blood cell count and Helicobacter pylori titre independently predict abnormal pancreatic beta-cell function. *Diabetes Res Clin Pract* 2009; **86**: 89-95 [PMID: 19747747 DOI: 10.1016/j.diabres.2009.08.010]

153 **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]

154 **Banić M**, Franceschi F, Babić Z, Gasbarrini A. Extragastric manifestations of Helicobacter pylori infection. *Helicobacter* 2012; **17** Suppl 1: 49-55 [PMID: 22958156]

155 **Malfertheiner P**, Selgrad M, Bornschein J. Helicobacter pylori: clinical management. *Curr Opin Gastroenterol* 2012; **28**: 608-614 [PMID: 23010682 DOI: 10.1097/MOG.0b013e32835918a7]

P- Reviewer: Manguso F **S- Editor**: Song XX
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com