

WJGP 5th Anniversary Special Issues (1): *Helicobacter pylori****Helicobacter pylori* and pancreatic diseases**

Milutin Bulajic, Nikola Panic, Johannes Matthias Löhr

Milutin Bulajic, University Clinical Hospital "Santa Maria della Misericordia", Piazzale S Maria della Misericordia 15, 33100 Udine, Italy

Milutin Bulajic, Faculty of Medicine, University of Belgrade, 11000 Belgrade, Serbia

Milutin Bulajic, Nikola Panic, University Clinical-Hospital Center "Dr Dragisa Misovic-Dedinje", 11000 Belgrade, Serbia

Johannes Matthias Löhr, Karolinska Institute, SE-171 77 Stockholm, Sweden

Johannes Matthias Löhr, Department of Medicine II, Molecular Gastroenterology Unit, Medical Faculty Mannheim, University of Heidelberg, D-68135 Mannheim, Germany

Author contributions: Bulajic M and Panic N drafted the manuscript; Löhr JM reviewed the manuscript.

Correspondence to: Nikola Panic, MD, University Clinical-Hospital Center "Dr Dragisa Misovic-Dedinje", Milana Tepica 1, 11000 Belgrade, Serbia. nikola.panicmail@gmail.com

Telephone: +381-11-3672025 Fax: +381-11-3672025

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Abstract

A possible role for *Helicobacter pylori* (*H. pylori*) infection in pancreatic diseases remains controversial. *H. pylori* infection with antral predominance leading to an increase in pancreatic bicarbonate output and inducing ductal epithelial cell proliferation could contribute to the development of pancreatic cancer *via* complex interactions with the ABO genotype, dietary and smoking habits and N-nitrosamine exposure of the host. Although the individual study data available so far is inconsistent, several meta-analyses have reported an increased risk for pancreatic cancer among *H. pylori* seropositive individuals. It has been suggested that *H. pylori* causes autoimmune pancreatitis due to molecular mimicry between *H. pylori* α -carbonic anhydrase (α -CA) and human CA type II, and between *H. pylori* plasminogen-binding protein and human ubiquitin-protein ligase E3 component n-recogin 2, enzymes that are highly expressed in the pancreatic ductal and

acinar cells, respectively. Future studies involving large numbers of cases are needed in order to examine the role of *H. pylori* in autoimmune pancreatitis more fully. Considering the worldwide pancreatic cancer burden, as well as the association between autoimmune pancreatitis and other autoimmune conditions, a complete elucidation of the role played by *H. pylori* in the genesis of such conditions could have a substantial impact on healthcare.

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Key words: *Helicobacter pylori*; Pancreatic cancer; Pancreatitis; Autoimmune pancreatitis; Molecular mimicry

Core tip: *Helicobacter pylori* (*H. pylori*) infection with antral predominance could contribute to the development of pancreatic cancer through complex interactions with ABO genotypes, dietary and smoking habits and N-nitrosamine exposure of the host. It has been suggested that *H. pylori* causes autoimmune pancreatitis due to molecular mimicry between *H. pylori* α -carbonic anhydrase (α -CA) and human CA type II, and between *H. pylori* plasminogen-binding protein and human ubiquitin-protein ligase E3 component n-recogin 2. Considering the worldwide burden of pancreatic diseases, complete elucidation of *H. pylori* role in their genesis could have substantial healthcare impact.

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INTRODUCTION

Helicobacter pylori (*H. pylori*), the ubiquitous bacterium that colonizes the human stomach, has been the subject of increased attention in the last 30 years. It has been sug-

gested that modern humans were infected with *H. pylori* before their migration from Africa over 58000 years ago and that *H. pylori* strains have been intimately associated with their human host populations ever since^[1]. Over half the modern human population is infected with *H. pylori*, and its prevalence varies from 60%-90% in Japan, China, Russia and most of Central and Eastern Europe to 30%-40% in Western Europe and the United States^[2]. *H. pylori* is proven to be associated with an increased risk for gastric cancer^[3], peptic ulcer disease^[4] and lymphoma^[5]; however, a possible role for *H. pylori* infection in pancreatic disease remains controversial.

Previous studies have examined the association between *H. pylori* infection and diseases of the pancreas, including pancreatic carcinoma^[6-12] and autoimmune pancreatitis^[13-15], but with inconsistent results. Nevertheless, there is a solid theoretical basis for explaining the potential role for *H. pylori* in the development of these conditions. It has been proposed that *H. pylori* causes autoimmune pancreatitis due to molecular mimicry between *H. pylori* α -carbonic anhydrase (α -CA) and human CA type II^[14], and it is known that the homologous CA segments contain the binding motif of the HLA molecule DRB1*0405, which confers a risk of developing autoimmune pancreatitis. Furthermore, it has been suggested that *H. pylori* infection contributes to the development of pancreatic cancer *via* complex interactions with the ABO genotype, dietary and smoking habits and N-nitrosamine exposure of the host^[16].

Pancreatic cancer is the eighth leading cause of cancer-related deaths worldwide^[17] with the five year survival rate as low as 6%^[18]. Autoimmune pancreatitis is a relatively novel clinical entity defined as a chronic inflammation of the pancreas due to an autoimmune mechanism^[19]. Although autoimmune pancreatitis accounts for a relatively small proportion of chronic pancreatitis cases it can be associated with other autoimmune conditions, suggesting a possible involvement of the entire gastrointestinal system. With this in mind, elucidating the role of *H. pylori* in the development of pancreatic diseases could have a substantial impact on health care.

We have, therefore, conducted a comprehensive literature search in order to summarize the evidence for a role for *H. pylori* in the pathogenesis of pancreatic diseases with particular emphasis on pancreatic cancer and autoimmune pancreatitis.

H. PYLORI AND PANCREATIC CANCER

To date, no study has isolated *H. pylori* DNA in any pancreatic sample^[20,21]; however, although *H. pylori* appears not to colonize the pancreas it could have an effect on pancreatic carcinogenesis through pathophysiological action. *H. pylori* shows two different colonization behaviors: one associated with pangastritis leading to hypochlorhydria, atrophic gastritis, gastric ulcer and gastric cancer, and the other associated with antral-predominant gastritis leading to hyperchlorhydria, pyloric and duodenal ulcer and, potentially, pancreatic cancer. Colonization of the

antrum by *H. pylori* reduces the number of antral D-cells thus suppressing the production of somatostatin. This, in turn, leads to hyperacidity, which results in an increase in the secretion of secretin and pancreatic bicarbonate output. Secretin has been shown to have a positive effect on murine pancreatic growth as well as DNA synthesis in pancreatic ductal cells^[22], and it is possible that induced ductal epithelial cell proliferation could enhance the carcinogenic effect of known carcinogens, such as N-nitrosamines, in the pancreas, leading to the development of pancreatic cancer.

Although this assumption is hypothetical and needs to be proven there is indirect proof suggesting that *H. pylori* does play a role in pancreatic carcinogenesis. A number of serology-based studies have assessed the association between the presence of anti-*H. pylori* antibodies and pancreatic cancer^[6-12]. The first of these, conducted by Raderer *et al*^[6], reported a two-fold increase in the risk for pancreatic cancer among *H. pylori*-positive individuals [Odds ratio (OR) = 2.1, 95%CI: 1.09-4.05]. These findings were confirmed in the subsequent Alpha-Tocopherol, β -Carotene Cancer Prevention Study (ATBC Study), a prospective cohort study of male smokers that reported subjects positive for *H. pylori* antibodies or CagA-positive *H. pylori* strains to be at increased risk of developing pancreatic cancer (OR = 1.87, 95%CI: 1.05-3.34; OR = 2.01, 95%CI: 1.09-3.70, respectively)^[7].

In contrast, two succeeding studies^[8,9], each following patients for 20 years or more, reported no significant association between *H. pylori* infection and pancreatic cancer. In a nested case-control study of 104 pancreatic cancer cases and 262 matched controls, de Martel *et al*^[8] selected patients from among 128992 adult subscribers to the Kaiser Permanente Medical Care Program who had been enrolled from 1964 to 1969, and found no association between *H. pylori* (OR = 0.85, 95%CI: 0.49-1.48) or its CagA protein (OR = 0.96, 95%CI: 0.48-1.92) and the subsequent development of pancreatic cancer. In the second study, Lindkvist *et al*^[9] conducted a similar analysis on subjects from the Malmö Preventive Project cohort. After analysis of 87 cases and 263 matched controls the researchers reported that *H. pylori* seropositivity was not associated with pancreatic cancer (OR = 1.25, 95%CI: 0.75-2.09). Finally, a case-control study in a Polish population also reported that neither *H. pylori* (OR = 1.27, 95%CI: 0.64-2.61) nor CagA (OR = 0.90, 95%CI: 0.46-1.73) seropositivity were significant risk factors for pancreatic cancer^[10].

However, Risch *et al*^[11] were the first to suggest that infection with CagA-negative *H. pylori* could be a risk for pancreatic cancer. In a United States population-based case control study, conducted on 373 pancreatic cancer cases and 690 controls, the researchers reported that CagA-negative *H. pylori* seropositivity was a significant risk factor for pancreatic cancer (OR = 1.68, 95%CI: 1.07-2.66), while no significant association was reported for CagA-positive seropositivity (OR = 0.77, 95%CI: 0.52-1.16). Furthermore, the group observed the association between a pancreatic cancer risk and CagA-negative

H. pylori seropositivity only among individuals with a non-O blood type but not among those with O blood type (OR = 2.78, 95%CI: 1.49-5.20; OR = 1.28, 95%CI: 0.62-2.64, respectively), supporting a role for the ABO blood group system in mediating *H. pylori* carcinogenic potential in the pancreas. The same group conducted a similar study on the Chinese population of Shanghai and reported an increased, but not significant, risk of developing pancreatic cancer for CagA-negative *H. pylori* seropositive patients (OR = 1.28, 95%CI: 0.76-2.13)^[12]. In addition, CagA-positive seropositivity was shown to protect against pancreatic cancer when compared to *H. pylori* seronegative individuals (OR = 0.68, 95%CI: 0.54-0.84).

Several meta-analyses have attempted to summarize the existing data on the role of *H. pylori* in pancreatic carcinogenesis^[16,23,24] including different number of studies based on differences in inclusion criteria. All reported a significant increase in the risk of developing pancreatic cancer among *H. pylori*-positive individuals, with the summary OR ranging from 1.65 (95%CI: 1.30-2.09)^[16] to 1.38 (95%CI: 1.22-1.77)^[23]. However, none of the meta-analyses reported a significant association between CagA-positive seropositivity and pancreatic cancer^[23,24].

Bearing all this data in mind, it could be concluded that the published scientific evidence (although somewhat inconsistent) supports a role for *H. pylori* in the development of pancreatic cancer. The exact mechanism involved in the influence of *H. pylori* on pancreatic carcinogenesis is still unclear and has yet to be explained fully. However, if *H. pylori* is found to increase the risk of developing pancreatic cancer, this could be another reason for targeting *H. pylori* for eradication, especially in individuals with a specific genetic burden, such as a family history of pancreatic cancer.

H. PYLORI AND PANCREATITIS

Although there have been some studies on animal models suggesting a possible role for *H. pylori* infection in acute pancreatitis^[25], no author has so far reported a significant association between *H. pylori* infection and acute pancreatitis in humans. Khan *et al.*^[13] undertook a study of 50 patients with acute alcoholic pancreatitis and 50 alcoholic controls but found no association between *H. pylori* infection and the occurrence of acute pancreatitis.

However, the relationship between *H. pylori* and chronic pancreatitis, and autoimmune chronic pancreatitis in particular, has been the subject of more research. In approximately 60% of cases autoimmune pancreatitis is associated with the presence of other autoimmune diseases such as Sjögren's syndrome, sclerosing extrahepatic cholangitis, primary biliary cirrhosis, autoimmune hepatitis, retroperitoneal fibrosis, salivary gland swelling, inflammatory bowel disease, Hashimoto's thyroiditis and gastric peptic ulceration^[26-28]. All of these diseases, including autoimmune pancreatitis itself, are characterized by similar pathohistological findings including fibrotic changes and/or lymphoplasmacytic inflammation. However, to

date, no study has isolated *H. pylori* DNA from samples of patients affected with autoimmune pancreatitis^[21].

It has been suggested previously that *H. pylori* infection exists as a possible common cause of these conditions acting *via* a mechanism involving the molecular mimicry of host structures^[29]. In 2005 Guarneri *et al.*^[14] reported significant homology between human CA type II and *H. pylori* α -CA, an enzyme fundamental for the survival of the bacterium in the gastric environment. As human CA type II is expressed in the pancreatic ductal epithelium, *H. pylori* could trigger autoimmune pancreatitis by mimicking the host's CA type II protein. Then, in 2009, Frulloni *et al.*^[15] identified *H. pylori* plasminogen-binding protein (PBP) antibodies in 95% of patients with autoimmune pancreatitis. However, PBP antibodies were not detected in patients with either alcohol-induced chronic pancreatitis or intraductal papillary mucinous neoplasm. *H. pylori* PBP was found to have substantial homology with ubiquitin-protein ligase E3 component n-recogin 2 (UBR2), an enzyme highly expressed in the acinar cells of the pancreas, and thus this could be another pathway through which *H. pylori* provokes molecular mimicry-induced autoimmune pancreatitis. The following year, our group (Löhr *et al.*^[30]) conducted a study on autoimmune pancreatitis samples using gene and protein expression profiling as well as immunoassays. Our research confirmed that acinar cells, in addition to ductal cells, are the target of immune-related inflammatory process-characterizing autoimmune pancreatitis, supporting a molecular mimicry mechanism between *H. pylori* PBP and human UBR2. All this data provides a solid theoretical basis for the hypothesis that gastric *H. pylori* infection can trigger autoimmune pancreatitis in genetically predisposed subjects. Moreover, in a series of patients with chronic pancreatitis, Dore *et al.*^[31] reported a reversal of elevated pancreatic enzymes after *H. pylori* eradication. However, although prevention and treatment strategies for autoimmune pancreatitis acknowledge *H. pylori* as the cause, or one of the causes, of this disease, future clinical studies that include a large number of cases will be needed in order to confirm these findings.

In conclusion, summarizing the data from available clinical studies supports a role for *H. pylori* in pancreatic carcinogenesis and autoimmune pancreatitis. Although the exact mechanisms are still unknown, molecular mimicry may play a role in the development of autoimmune pancreatitis, while pancreatic carcinoma may develop in response to *H. pylori* colonization of the antrum leading to an increase in secretin secretion and pancreatic bicarbonate output resulting in ductal epithelial cell proliferation. However, further research is needed to confirm these theoretical assumptions on the role of *H. pylori* in the development of pancreatic disease.

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