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Helicobacter pylori and Pancreatic Disease

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Introduction

Since the first description of *H. pylori* infection of the gastric mucosa by Warren and Marshall [1], the bacterium has progressively gained importance and, nowadays, it is recognized as the main pathogenetic factor in chronic gastritis, ulcer disease and gastric neoplasms. In recent years, there is increasing evidence of an association of *H. pylori* gastric infection with various extragastric diseases. *H. pylori* infection induces changes in the physiology of the upper gastrointestinal tract. Its effects on exocrine pancreatic physiology, as well as on the onset and clinical course of exocrine pancreatic diseases, have been poorly investigated up to now. However, they are possible since the bacterium induces changes in the gastrointestinal physiology and because the exocrine pancreas interacts strictly with the stomach and the duodenum.

Effect of *H. pylori* on Pancreatic Physiology

The possible mechanisms by which *H. pylori* infection may influence pancreatic physiology have been the object of several studies. The damaging activity of *H. pylori* on the gastric mucosa and at the systemic level has been attributed to the excessive release of aggressive factors such as ammonia and lypopolysaccharides, as well as to the activation of leukocytes and the release of proinflammatory cytokines. Each of these factors could theoretically modify pancreatic physiology and influence the clinical course of diseases of the exocrine pancreas.

Jaworek *et al.* [2] studied the influence of NH_4OH given intraduodenally on the plasma levels of gastrin and exocrine pancreatic secretion in conscious dogs having chronic pancreatic fistulas. The effect of NH_4OH was, moreover, assessed on the secretory activity of in vitro isolated acini obtained from rat pancreases. The authors found that intraduodenal infusion of NH_4OH determines a significant increase in the pancreatic protein output and in the plasma gastrin levels which were related to NH_4OH duodenal concentrations. Conversely, NH_4OH administered during intravenous infusion of secretin and cholecystokinin or after pancreatic stimulation by ordinary feeding reduced the HCO_3^- and protein outputs as compared to controls but had no effect on postprandial plasma gastrin. Similarly, in isolated pancreatic acini, increasing concentrations of NH_4OH determined a concentration-dependent stimulation of amylase release while, when various concentrations of NH_4OH were added to a submaximal concentration of cerulein, stimulated enzyme secretion was significantly reduced. The same effects were obtained by simple alkalisation of the incubation medium by NaOH up to a pH 8.5. The authors concluded that while NH_4OH stimulates basal pancreatic secretion, probably by means of an increased release of gastrin, the inhibitory effect of NH_4OH on stimulated secretion is likely to be mediated, at least in part, by its

direct action on the pancreatic acini, possibly due to their alkalisation.

Hori *et al.* [3] have investigated the effect of the vacuolating toxin of *H. pylori* on the enzyme secretion of isolated rat pancreatic acini. They observed that pre-incubation of a suspension of pancreatic acini with the vacuolating toxin was followed by a significant reduction in CCK8/carbachol-induced amylase secretion from the acini. Moreover, the vacuolating toxin inhibited amylase secretion in a dose dependent-manner.

These two studies [2, 3] investigated the effect of isolated bacterium components, ammonia and vacuolating toxin on the pancreas, in models which only partially resemble the human physiology. With regard to human physiology, it is known that *H. pylori* inhibits the synthesis and release of somatostatin by gastric D-cells [4, 5, 6]. This inhibition is accompanied by a reduction in the antral density of D-cells which returns to normal after eradication [6]. As a consequence of the *H. pylori*-induced inhibition of the synthesis and release of somatostatin, the density of G-cells and the synthesis and release of gastrin increase significantly. The result of all these hormonal changes is a marked increase of gastric acid secretion without any change in the parietal cell sensitivity to gastrin [7, 8, 9, 10].

Exocrine pancreatic secretion is inhibited by somatostatin [11, 12]. The paracrine effect of somatostatin in the gastric mucosa is unlikely to influence pancreatic secretion. However, the increased acid load in the duodenum could stimulate pancreatic secretion by means of the release of secretin [13]. Furthermore, gastrin exerts a weak CCK-like effect on pancreatic secretion [14]. In a recent study [15] performed on a group of 19 healthy subjects (11 *H. pylori* positive), Domínguez-Muñoz and Malfertheiner have found that both *H. pylori* positive and negative subjects had normal cyclical interdigestive pancreatic secretion and this was also normally coordinated with the gastrointestinal motility. *H. pylori* did not influence the coordination between hormone release and gastrointestinal motility, and the coordination between pancreatic secretion and gastrointestinal motility. Neither the interdigestive nor the postprandial release of PP and motilin were affected by the *H. pylori* infection while the post-prandial and interdigestive release of gastrin were higher in infected subjects. The interdigestive pancreatic secretion of amylase, lipase and chymotrypsin were significantly higher in *H. pylori* positive subjects than in *H. pylori* negative subjects while the postprandial pancreatic enzyme output tended to be higher in infected than in non-infected subjects. Hypergastrinemia with its CCK-like effects,or alternatively the increased acid load in the duodenum [13] through the stimulation of secretin secretion, could be involved in the interdigestive pancreatic hypersecretion found in the study while both factors would play a less important role physiologically in the postprandial stimulation of the pancreatic secretion. This study [15] clearly supports the concept that *H. pylori* infection in asymptomatic subjects is associated with changes not only in gastric physiology but also in the pancreatic function and that this link between the pancreas and *H. pylori* could theoretically have pathophysiological implications in pancreatic diseases.

H. pylori and Chronic Pancreatitis

Different hypotheses can be created in the interplay between *H. pylori* and the pancreas in patients with chronic pancreatitis (CP). The first is the possible role of *H. pylori* in the pathogenesis and evolution of CP, at least in the idiopathic forms; the second is the influence of *H. pylori* infection on the exocrine pancreatic secretion in patients with CP and pancreatic secretion impairment; and the third is whether CP is able to affect the gastrointestinal physiology in such a way as to influence the *H. pylori* colonization of the gastric mucosa and thereby the prevalence of *H. pylori* infection and peptic ulcer disease.

A speculative role of *H. pylori* in the pathogenesis of CP could be derived from the observation that some *Helicobacter* species lead to hepatic injury in some animal models

[16]. Recent data from Fox *et al.* [17] have also demonstrated the presence of other *Helicobacter* species in the bile and gallbladder tissue of individuals with chronic cholecystitis. About 10-30% of CP cases can be defined as idiopathic. Whether a bacterial infection may be the cause of at least a part of these CP cases remains a matter of debate. In a recent Italian study [18], the presence of *H. pylori* DNA sequences was assessed in the pancreatic juice of 40 patients with alcoholic CP and *H. pylori* infection using polymerase chain reaction with two primers homologous to a portion of the urease-C gene. While all gastric biopsies (used as positive controls) produced *H. pylori*-specific DNA products, no *H. pylori* urease-C gene sequences were detected in any of the pancreatic juices. The authors concluded that, in spite of the impaired antibacterial activity of pancreatic juice in patients with CP, *H. pylori* is not able to colonize the pancreas. This study, however, did not test sequences from other *Helicobacter* species and did not gain specific insight into the question as to whether *Helicobacter* could play a role in the pathogenesis of CP.

With regard to the second question, as to whether *H. pylori* infection may influence exocrine pancreatic function in patients with CP, in a series of 40 patients with CP, Manes *et al.* have recently demonstrated [19] that exocrine pancreatic function measured by means of a serum pancreolauryl test (PLT) is not different in the different morphological stages of disease (defined by ERCP changes) between infected and non-infected patients. This confirms the fact that the severity of the disease is the main factor in determining pancreatic function impairment in patients with CP.

The third question arises from the number of studies that have investigated the effect of CP on gastrointestinal physiology. Several authors have found an increased gastric acid secretion, both basal and after hormonal stimulation [20, 21], as well as an increased gastric acid level by means of 24 hour gastric pH-metry in patients with CP and exocrine pancreatic insufficiency [22, 23]. On the other hand, other authors have reported a reduced postprandial acid secretion with increased gastrinemia in patients with CP [24]. While all these studies lack endoscopic and histological data of the gastric mucosa, knowledge of the changes of the gastric mucosa are crucial for interpreting the contradictory findings reported on gastric acid secretion in CP. Changes in the gastric function described in CP could reflect the presence of *H. pylori* infection in the gastric mucosa rather than changes induced by the pancreatic disease. Manes *et al.* [19] have recently studied 40 patients with alcoholic CP as compared to 40 healthy subjects and 40 patients with alcoholic liver cirrhosis (without CP) with the aim of assessing the prevalence of *H. pylori* infection and the characteristics of the gastric mucosa. The alcoholic liver cirrhosis group was enrolled in order to evaluate a potential adjunctive toxic effect of alcohol on the gastric mucosa. The authors have found that the prevalence of *H. pylori* infection in patients with CP is similar to that of patients with alcoholic liver cirrhosis and healthy subjects (38% in CP, 30% in cirrhosis and 28% in asymptomatic subjects). They did not find any differences regarding activity, chronicity and distribution of *H. pylori* associated gastritis. Conversely, the frequency and the severity of *H. pylori* negative chronic gastritis in the antrum was significantly higher in patients with CP than in those with cirrhosis and in healthy subjects, the degree of mucosal abnormalities not being related to the severity of pancreatic insufficiency. In this study, moderate-severe *H. pylori* negative antral gastritis was significantly less frequent in patients with alcoholic liver cirrhosis than in those with CP and similar to that observed in non-alcoholic subjects. This observation leads to the hypothesis that factors other than alcohol, probably related to the CP *per se*, may be involved in the development of chronic antral gastritis in CP.

Similar conclusions arise from another study [25] which investigated the prevalence of *H. pylori* infection in patients with CP, with and

without duodenal ulcers, in comparison to a control group of individuals with a simple duodenal ulcer. In this study, 27% of the patients with CP had duodenal ulcer. The prevalence of IgG antibodies against *H. pylori* was 22% in patients with CP without ulcer and 60% in those having CP and ulcers. In comparison, 86% of the controls having simple duodenal ulcers were infected with *H. pylori*. This fact suggests that *H. pylori* contributes to, but is probably not the only cause of duodenal ulcers in patients with CP. In this case too, the changes in gastrointestinal physiology determined by CP are likely to play a significant role in the pathogenesis of duodenal ulcers in these patients.

H. pylori and Acute Pancreatitis

A possible role of *H. pylori* in the development and evolution of acute pancreatitis (AP) has not been extensively studied up to now. However, while *H. pylori* is unlikely to be a cause of AP, even in the so-called idiopathic forms, it is not possible to exclude the fact that the bacterium could somewhat influence the evolution of the disease. Increased stimulation of the gland by hypergastrinemia or duodenal acidification, as well as the early translocation of *H. pylori* or of its toxins through the gastric and duodenal mucosa into the pancreas, are potential mechanisms by which the bacterium could influence the evolution of AP. Warzecha *et al.* [26] have studied the effect of *H. pylori* infection of the gastric mucosa on the clinical course of the disease in a model of ischaemia/reperfusion-induced acute pancreatitis in rats. In this study, *H. pylori* infection resulted in a significant reduction of pancreatic blood flow and aggravation of pancreatic damage and ischaemia, after reperfusion of the pancreas. Plasma amylase and lipase, as well as IL-1beta and IL-10 were significantly higher in infected rats. The authors interpreted their data as evidence of an injurious effect of *H. pylori* infection of the stomach in the course of acute pancreatitis. This is probably related to the release of lipopolysaccharides by bacteria which leads to the activation of leukocytes and the augmentation of pancreatic and systemic inflammation [26].

H. pylori and Pancreatic Cancer

No studies are available on this topic. Since pancreatic cancer is more frequent in the lower social classes, a casual association with *H. pylori* infection is possible although it has never been demonstrated. However, on the basis of current knowledge, it is not possible to exclude a pathogenetic association between *H. pylori* and pancreatic cancer. Local gastric *H. pylori* inflammation causes the chronic release of bacterial and host-dependent cytotoxic substances and pro-inflammatory mediators leading to systemic effects of infection. A model of *Helicobacter*-induced hepatic carcinogenesis in mice associated with persistent *Helicobacter hepaticus* infection has recently been developed [16]. The hypothetical existence of a *Helicobacter* species capable of chronically infecting the pancreatic tissue deserves further study.

Conclusions

H. pylori infection is the most widely diffuse infection in the world. Gastric infection with *H. pylori* is the cause of gastric pathologies, but is also able to determine systemic effects and diseases. In recent years, there is increasing evidence that *H. pylori* infection can also affect the pancreas. From a practical clinical standpoint, data are still too scarce to affirm the fact that the infection is capable of influencing the course of pancreatic pathologies in a clinically evident way, so that it is probably premature to routinely test and eraticate *H. pylori* infection in pancreatic patients. With further study, our understanding of the relationship between the pancreas and *H. pylori* will improve, undoubtedly clarifying the real position of *H. pylori* infection in pancreatology.

Keywords Carcinogens; Fluids and Secretions; Gastric Acid; Gastric Juice; Gastric Mucosa; Gram-Negative Bacteria; *Helicobacter*; *Helicobacter pylori*; Hydrogen-Ion Concentration; Organisms Category; Pancreatic Diseases; Pancreatic Function Tests; Pancreatic Insufficiency; Pancreatic Neoplasms; Pancreatitis; Pancreatitis, Alcoholic; Risk Factors

Abbreviations AP: acute pancreatitis; CP chronic pancreatitis; PLT: pancreolauryl test

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