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Review

Relationship between *Helicobacter pylori* infection and GERD

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Summary. Gastroesophageal reflux disease (GERD) is due to the chronic exposure of the esophageal mucosa to acid secretion from the stomach. *Helicobacter pylori* (H.p.) infection, is a risk factor for the development of peptic ulcer, atrophic gastritis and gastric cancer, and causes various effects on gastric function. The relationship between GERD and H.pylori infection is still subject of debate. *Background and aim:* In literature no clear causal relationship has been established between GERD and H. pylori infection, although some papers support the onset of esophagitis in patients in whom the infection has been cured. Aim of this work is to review the most recent literature data about the relationship between reflux disease and H. pylori infection. *Methods:* Articles reviewed were found through literature searches on PubMed, Google Scholar using keywords such as gastroesophageal reflux disease, *Helicobacter pylori*, acid-related disorders, GERD and esophagitis. (www.actabiomedica.it)

Key words: gastroesophageal reflux disease, *Helicobacter pylori*, acid-related disorders, GERD, esophagitis

Reflux disease and esophagitis, definition and pathophysiology

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal conditions in the general population (1), but an universally accepted definition is lacking since 2006 (2). According to Montreal classification, GERD is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications (3).

Probably a defective anti-reflux barrier and luminal clearance mechanisms are responsible for macroscopically detectable injury to the esophageal squamous epithelium (4), which concretizes in erosive esophagitis and Barrett's Esophagus. However, more than 70% of patients that experience heartburn do not have visible lesions at endoscopy (5) and they are termed as NERD (6) (Non Erosive Reflux Disease).

The pathophysiology of GERD is determined by a failure of the lower esophageal sphincter, that can be related to different factors such as hiatal hernia, obesity, pregnancy, drugs that act on the sphincter musculature, cigarette smoking. Other factors involved are a delay in gastric emptying, reduced oesophageal motility and an excessive stomach relaxation, but the variability of endoscopic findings depends on the different resistance and sensitivity of the individual patient's esophagus. The mucosa of GERD patients produces significantly larger amounts of various cytokines (4) that activate immune cell recruitment and migration, and are involved in the pathophysiology of the illness.

Helicobacter pylori

In 1983 two Australian researchers, B.J. Marshall and R. Warren published on Lancet a paper in

which they claimed the presence of "small curved and S shaped bacilli", later classified as *Helicobacter pylori* (7). Since that moment, *H. pylori* has been established as a major cause of chronic gastritis and peptic ulcer, being in fact involved in the pathogenesis of gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

H.pylori is a gram-negative microaerophilic bacterium, that generally colonizes the stomach in early life (8). It has the ability to reach the protective mucus layer at the surface of gastric mucosa and to survive the extreme acid content of the stomach thanks to its 4-6 flagella, and -by avoiding low pH areas using chemiotaxis- it first colonizes the antrum, where there are no acid-producers cells. Then it adheres to epithelial cells using the blood group antigen binding adhesin (BabA) that it binds to ABO/Leb (Leb) group antigens and fucosylated carbohydrates expressed by gastric epithelial cells (9). It produces a huge amount of urease, that metabolizes the urea present in the stomach in ammonia and carbon dioxide in order to produce a neutralized area where the bacteria can live (10). The virulence of the bacteria strains is linked to the presence of a pathogenicity island (cagPAI) locus of its genoma that encodes for the bacterial oncoprotein CagA (11), T4SS and to another factor encoded by a different locus, the vacuolating cytotoxin A (VacA). VacA causes massive vacuolation in epithelial cell lines forming pores in their membranes, determining the output of anions and urea (12).

H. pylori forges the stomach homeostasis inducing inflammation using proinflammatory cytokines and so influencing the activity of somatostatin-producing D cells, gastrin-producing G cells, and acid-producing parietal cells. *H. pylori* gastritis causes a reduction in somatostatin levels (13) and, since somatostatin negatively regulates gastrin, hypergastrinemia ensues (14, 15). Gastrin is a specific growth factor for *H. pylori* (16), so this potentially creates a positive-feedback loop. If not detected or cured, the bacterium or *H. pylori* continues its proliferation and inflammation of gastric mucosa causing the progressive loss of gastric glands. The atrophic changes markedly increase risk of gastric ulceration and non-cardia gastric adenocarcinoma (17, 18) but the lower acid production protects against duodenal ulceration, and probably against acid-induced complications of gastroesophageal reflux (19).

H. pylori and Reflux Disease

Knowledge on *H. pylori* has recently experienced a shift: the Kyoto Consensus Conference on *H. pylori* concluded that the bacteria should be defined as an infectious disease even in asymptomatic patients and *H. pylori*-infected subjects should receive eradication therapy (20). The World Health Organization published an IARC monograph in which is stated that *H. pylori* eradication represents the best strategy to prevent gastric cancer (21) and this was recently approved from high risk gastric cancer incidence countries such as Japan. In 1997, Labenz et al. have suggested the hypothesis that *H. pylori* eradication can lead to reflux disease (22) and nowadays the relationship between gastroesophageal reflux disease and H.pylori infection is still subject of debate.

On the other hand, the Maastricht V/Florence Consensus report claims that H.pylori eradication has not a clinical importance in acid production changes (23).

Epidemiological views

Some papers in literature claim that the prevalence in H.pylori infection has declined in parallel with a decrease of peptic ulcer and an increase of reflux esophagitis (24) but to understand better current data reported on this topic it's important to distinguish between GERD symptoms, erosive esophagitis, Barrett's Esophagus and adenocarcinoma (25). Gastric acid secretion is a key factor in the development of reflux disease. Nevertheless, it's unquestioned the role of the bacteria in the development of gastric atrophy, that is the most important mechanism that protects the esophagus from the excessive exposure of acid (26), since the atrophy of the corpus may undermine parietal cells secretion (27). Supporting this, a case-control study from Korea -that is a nation with high prevalence of atrophic gastritis- showed the association between H.pylori seropositivity and a reduced risk

for erosive esophagitis (OR: 0.44; 95% CI: 0.39-0.49) (28). On the other hand, in Western World there is an opposite time trend in peptic ulcer disease and distal gastric cancer, that are decreasing, and reflux esophagitis, which is increasing (29). In particular, cag-A positive strains of bacteria have been associated with a lower incidence of GERD (27). An Iranian study of 2017 showed that there was no difference of *H. pylori* prevalence in GERD patients compared with controls, but the prevalence of the cagA gene of *H. pylori* and the co-existence of cagA and cagE were significantly higher in the control group (30). Bor et al. investigated on this essay in a study conducted in Turkey, where the population is characterized with both Eastern and Western countries lifestyles, coming to the conclusion that there is no relationship between the infection and GERD (31).

Eradication therapy "consequences"

Several studies have shown the inverse relationship between the occurrence of GERD and H.p. infection, in particular an increased severity of the disease is documented in patients with pre-existing symptoms (32-34). McColl et al. showed a markedly resolution of dyspepsia in patients in whom the eradication therapy was successful when compared with subjects with a persistent infection. However, this study didn't show a correlation between GERD occurrence and H.p. cure in ulcer patients (35). Yaghoobi et al. instead, found that there was two folds increased risk of GERD development with successful eradication among patients with peptic ulcer compared to untreated controls, but this was not found in dyspeptic patients (36).

Conclusions

Relying to several population studies, is noticeable an inverse relationship between H.pylori and GERD (19, 37), but considering the single patient this relationship is difficult to explain, since GERD is a disease determined by several concomitant factors.

For example, mentioning a problem of the new era such as obesity, it's well known from literature that an elevate BMI can affect the development of the disease (38), regardless the presence of *H. pylori* but the role of weight loss is unclear.

Another known risk factor, that is important to consider in the single patient, is smoking habit, that is another well known risk factor for the developing of GERD. Several mechanisms are responsible of the association between smoking and reflux symptoms, although they mostly normalize after 3 to 8 minutes finishing a cigarette (39). However, recently the HUNT study reported that smoking cessation improves GERD symptoms only in patients with a normal BMI (40). Moreover, recent studies suggest a link between pro-inflammatory genotypes and less severity of GERD (41, 42) as well as H.p. infection. In conclusion, studies combining all these factors (including H.p. infection, host factors, life style habits) are needed to better define their effect on the onset of GERD.

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