HELICOBACTER PYLORI INFECTION IN PATHOGENESIS OF GASTROESOPHAGEAL REFLUX DISEASE

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Gastroesophageal reflux disease (GERD) refers to the very common and constantly increasing conditions where reflux of gastric contents into the esophagus leads to development of characteristic symptoms. The esophagus, LES and stomach can be envisioned as a single functional unit controlled by neuro-hormonal factors. The abnormalities that contribute to GERD can start in any component of this unit, resulting particularly from disturbances in their control system. It is extremely important to identify factors and mechanisms leading to functional failure of this system so that causative therapy can be effectively applied. The key-role has been attributed to parasympathetic dysfunction, which may adversely affect motor activity of this area by increasing transient LES relaxation number and impairing LES pressure, esophageal acid clearance and motility of the proximal stomach. Recently, numerous investigations have been performed to elucidate the role of Helicobacter pylori (Hp) infection in GERD pathogenesis with the most concern given to its potency to increase gastric acid secretion. However, it appeared that this infection leads to much more complex changes in gastric mucosa including modification of afferent neural signals and specific gastric hormones release. Plasma ghrelin level is low in subjects infected and increases significantly after eradication. Since ghrelin, beside potency to increase gastric secretion has strong prokinetic action on LES functional unit, this phenomenon together with impaired vagal control may contribute to the Hp infection or eradication - related GERD development. Thus, ghrelin and vagal activity could be the missing links that partially explains relationship between GERD and Hp infection.

Key words: GERD, Helicobacter pylori, gastric secretion, motility, ghrelin.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a clinical condition that results from the reflux of gastric contents into the esophagus. The pathophysiology of
GERD is multifactorial with the disease ultimately related to the balance between factors tending to damage (or sensitize) the esophageal mucosa and those tending to preserve it (a competent esophagogastric junction (EGJ) and normal esophageal acid clearance (esophageal and gastric motility-dependent). GERD can be caused by malfunction of esophageal, lower esophageal sphincter (LES) and the stomach defense mechanisms. Most common factor in etiology of GERD is disturbed LES functions. The LES is defined as a zone of elevated intraluminal pressure at the EGJ junction. Motor LES and the proximal stomach dysfunction, acting as whole unit, results in increased number and duration of reflux episodes. Dysfunction of the LES occurs via one of several mechanisms including the most common vagal-dependent increased number of transient LES relaxations (tLESR), or - as the second mechanism - permanent decrease in LES pressure with lost high pressure zone (HPZ) causing that each increase of intraabdominal pressure overcomes LES resulting in reflux episode. transient LES relaxation is concerned as the main mechanism of reflux in patients with non-erosive reflux disease (NERD), whereas a hypotensive LES becomes relevant in patients with reflux esophagitis (RE). Delayed gastric emptying may also contribute to GERD. The postulated mechanism is such increase in intragastric pressure, which defeats the LES and leads to reflux.

Esophageal defense mechanism can be split into esophageal motility (responsible for acid clearance) and mucosal resistance. Alterations in primary and secondary esophageal peristalsis contribute to the increased acid exposure by delaying clearance. Adequate esophageal motility limits the exposure time, which is an extremely important factor in preventing mucosal injury. In the review by Kahrilas et al. abnormal peristalsis was identified in 25% of patients with mild esophagitis and in 48% of patients with most severe form of disease (1).

The presence of a hiatal hernia increases the number of reflux episodes by mechanically weakening EGJ and impairs esophageal clearance. Buttar et al. proposed that a hiatal hernia may contribute to reflux via variety of mechanisms like proximal migration of LES, impaired ability of the crura to function as an external sphincter, and trapped gastric contents in the hernial sac (2).

Same author described the importance of esophageal mucosal resistance as a protective mechanism and classified it further into pre-epithelial and post-epithelial lines of defenses (3). Common finding is esophageal hypersensitivity to acid, contributing significantly to the typical clinical manifestation of the disease. However, it must be emphasized that GERD mostly refers to the reflux of gastric or duodenal contents into esophagus, leading to mucosal damage (RE) or symptoms of heartburn (NERD). Therefore, increased concentration of noxious compounds in the reflux content may contribute to the development of histological and endoscopic lesions. GERD, together with peptic ulcer disease and gastritis are traditionally classified as the acid-related diseases. Since it is undisputable fact that chronic H.p infection affects gastric acid production, the question may be raised if this condition contributes to GERD development.
Epidemiology

Surprisingly, from epidemiologic studies it appeared that an increasing recognition of gastro-oesophageal reflux in developed countries has been paralleled by the falling prevalence of Hp infection (4). These epidemiological data do not support a role of Hp in the pathogenesis of reflux disease, but suggest a negative association with the increasing incidence of oesophageal diseases. This observation led several investigators to estimate the prevalence of Hp in patients with GERD. In 1997 there was a prospective study published, confirming that the prevalence of Hp infection in patients with GERD is significantly lower than in the control group (5). That was supported by similar results obtained by other investigators. A meta-analysis summarizing the results of 14 case-control studies and 10 clinical trials found that Hp-negative status was associated with a significantly increased risk of GERD (pooled OR 1.34, 95 percent CI 1.15 to 1.55) (6). These interactions between Hp and GERD stem also from epidemiologic data showing an increase in the prevalence of GERD and adenocarcinoma of the esophagus in Western societies where the prevalence of Hp infection decreased.

Another area of investigation was related to relationship between severity of GERD and presence of infection. Several reports suggested that Hp-positive patients were less likely to have endoscopic and/or histological changes, and, when present, the severity of oesophagitis was decreased compared to those who were Hp-negative (7). All data cited above have led some authors to propose a ‘protective’ role of Hp infection against the development of oesophageal diseases. However, some other studies did not find any correlation between Hp status and the severity of esophagitis or histological parameters in either NERD groups (8). Moreover, there were even some reports about marked cardia inflammation associated with Hp infection and increasing severity of esophagitis positively correlating with the density of the bacteria’s in the gastric antrum and infection activity (9).

Hp infection and gastric acid secretion

The primary mechanism by which Hp influences the pathogenesis of GERD is modification of gastric acid secretion by interruption of feedback inhibition of gastrin release due to luminal acid increase. Gastrin levels in Hp infected patients are higher and these levels do not exhibit normal feedback relationship. Hypergastrinemia may by primary phenomenon arising due to Hp-related inhibition of somatostatin production in antral D-cells in patients with antral-predominant gastritis. This may be also an event secondary to decreased acid secretion in patients with long-standing chronic, atrophic corpus-predominant gastritis. Gutierrez et al. assessed the effect of Hp eradication on BAO and MAO in dyspeptic patients before and after eradication (10). Gastric acid secretion was less than normal in infected patients with corpus gastritis and came back to normal
range after treatment. Similar data have been reported recently by Haruma et al., who studied intragastric pH before and 1 year after the eradication in patients with severe atrophy of gastric corpus (11). 24 h pH improved after therapy and percentage of time >4 decreased from 65 to 28% suggesting that gastric secretory function have been restored. Feldman et al. studied in asymptomatic patients both esophageal acid exposure and gastric emptying before and after Hp eradication (12). BAO increased in patients with successful eradication, but not in those with persistent infection. However, basal and meal stimulated gastric secretion did not change after eradication. Pathological reflux developed in 30% eradicated patients and only 20% of patients who had persistent infection.

Obviously not only mechanisms leading to hypergastrinemia, but also acid secretion in Hp infected patients depends on the pattern of gastritis. Antrum predominant Hp gastritis increases gastric secretion, corpus – predominant Hp gastritis is associated with reduced gastric acid secretion and both return to normal after eradication. It is worthy to notice that corpus-dominant gastritis with lower acid output and secondary hypergastrinemia, which lead to increased LES pressure, is the condition where the GERD symptoms are most unlikely (13). On the other hand antral-predominant gastritis with increased gastric acid output may result in duodenal ulcer in patients with competent GEJ and adequate gastric emptying or GERD symptoms, even with RE, in patients in whom these mechanisms are impaired. Overall these results indicate differences in pathogenesis within group of patients with Hp induced gastritis.

In patients with antral-predominant gastritis and duodenal ulcer, Hp eradication may result in complete recovery or GERD symptoms development. This latter phenomenon occurs in patients who already might have reflux esophagitis or non-erosive reflux disease, but which symptoms were masked by or accounted for duodenal ulcer. The dominance of symptoms due to antral gastritis probably depends on mechanical factors, leading to duodenal ulcer in patients with rapid gastric emptying and competent EGJ and contrary – to RE in patients with delayed emptying and incompetent EGJ. The same hypothetical factors are responsible for the diversity among patients who had Hp eradication - some of them may present with improvement of symptoms and in other healing of ulcer may unmask GERD that were formerly present but not dominant, resulting in the new diagnosis of RE or NERD. As it was stated previously, low vagal activity may play a pivotal role in reflux development in those settings (14).

In patients with corpus-predominant gastritis, acid secretion, plasma ghrelin levels and probably vagal activity dramatically decreases as a result of Hp infection. Eradication increases acid secretion and, in subset of patients who are predisposed to GERD, results in symptoms worsening or functional dyspepsia (FD). Thus, increase in intragastric acidity could contribute to GERD in subgroup of patients after Hp cure and may reflect recovery of parietal and neurocrine cells after resolution of inflammation and atrophy. Partially this recovery of gastric acid secretion may be related to restored plasma ghrelin level. In others, who are
at low risk for the GERD development the Hp eradication is followed by healing of gastritis and clinical improvement (Fig. 1).

*Hp infection and gastric neuroendocrine secretion*

Inflammatory and immune response induced by Hp affects various cell types in gastric mucosa that are important for gastric secretion, such as D, G, chief and

![Diagram](image-url)
parietal cells. Hp *gastritis* causes a reduction a mucosal somatostatin levels and hypergastrinemia (15). Gastric levels of leptin are higher in infected patients although serum levels of leptin may not be altered (16). Recently much attention was pointed toward the interaction between Hp infection and gastric ghrelin release.

Ghrelin is a 28-amino acid peptide identified as an endogenous ligand for growth hormone secretagogue receptor (17). Ghrelin influences appetite, energy balance, gastric motility and acid secretion. It is primarily produced by Gr neuroendocrine cells in the oxyntic gland area of the stomach, which is main source of circulating ghrelin. Ghrelin levels display a diurnal rhythm in humans in phase with plasma leptin levels, reaching peak at night during fasting and falling in the morning, however, unlike motilin, changes in plasma ghrelin in synchrony with phase III MMC has not been reported. Plasma ghrelin (“empty stomach hormone”) increases nearly twofolds before a meal and drops within one hour postprandially (18).

Animal studies revealed that ghrelin has distinct effects on gastrointestinal motility. It was shown to accelerate gastric emptying, enhance small bowel transit and overcome postoperative ileus. Ghrelin may exert these effects via specific ghrelin receptors located on myenteric, vagal and central neurons (19). It seems that ghrelin modify body functions mostly via vagal nerves. That hypothesis arises from the observation that ghrelin effects can be blocked by vagotomy and vagal deafferentations with capsaicin (20).

There was only one human study on ghrelin administered intravenously effects conducted to date. Tack *et al.* studied influence of ghrelin on interdigestive gastrointestinal motility in healthy volunteers (21). They observed induction of premature phase III of MMC (mostly of gastric origin) and prolonged increase in gastric proximal tone (60 min) after administration of ghrelin. Parallel pancreatic polypeptide plasma levels increased, but motilin, somatostatin and glucagon levels remained unaltered. However, these observations concern rather pharmacological ghrelin effects, as its high doses were used in the study. Direct effects of ghrelin on LES pressure in humans have not been studied yet but similarity with motilin in action on proximal stomach suggest that ghrelin may prevent reflux by increasing LES pressure.

Isomoto *et al.* studied ghrelin plasma concentration in patients with various upper gastrointestinal diseases (22). Ghrelin levels differed significantly among the different disease groups with lowest concentrations in patients with chronic *gastritis*, followed by gastric ulcer group. Ghrelin concentrations in patients with reflux *esophagitis* and duodenal ulcer were comparable to control group. Plasma ghrelin levels were significantly lower in Hp-positive than Hp-negative patients, but the significant difference among disease groups were still observed in infected and uninfected populations. Circulating ghrelin levels in Hp-positive patients were significantly lower in these with chronic *gastritis* than those with duodenal ulcer or reflux *esophagitis*. The scores correlated positively with plasma
pepsinogen I and I/II ratios and inversely with the extent of gastritis, suggesting that inflammatory and atrophic events of the gastric mucosa caused by Hp infection contribute to the diversity among these conditions. It is worth to mention that there was no correlation between circulating levels of ghrelin and gastrin. In another study the same authors have shown that there is also no correlation between plasma ghrelin and somatostatin levels irrespectively of Hp status (23). So one may conclude that decrease in ghrelin release is related to the somatostatin-gastrin-acid axis modulation driven by Hp infection.

There are observations from animal models that ghrelin administration increases pancreatic polypeptide plasma levels, supported by suggestion that ghrelin stimulates PP release in humans also, which indicates that ghrelin may cause some vagal stimulation. Decreased ghrelin levels in Hp infected patients may reflect lack or diminished cholinergic control of proximal stomach and LES in favor of esophagitis development. This mechanism may be especially important in patients with antrum-predominant gastritis, who have the acid production preserved or even augmented.

Nwokolo et al. reported that plasma ghrelin increases significantly after Hp eradication in asymptomatic subjects, which correlates with intragastric acidity (24). This phenomenon probably reflects recovery of gastric mucosa and may be mediated by ghrelin either via a central pathway (with vagal nerves involvement) or locally given the close juxtaposition of parietal and ghrelin cells in the stomach. The net effect of eradication is gastric acid production increase, which may contribute to GERD de novo symptoms development in patients cured from Hp infection in whom chronic gastritis or gastric ulcer (low gastric acid secretion) were recognized previously. In this subset of patients Hp infection prevents GERD symptoms due to low acidity of reflux content before eradication (Fig.1).

Hp vs esophageal pH, motility and autonomic dysfunction

Tefera et al. performed studies on esophageal acid exposure before and 12 weeks after eradication (25). There was no significant change in reflux symptoms score and total time pH < 4 in eradicated vs infected patients. Similarly Manifold et al studying 25 patients with Hp gastritis before and after Hp eradication did not found differences in acid alkaline reflux or bilirubin exposure in both groups (26). Wu et al studied patients with RE and healthy controls (27). There was no difference in the severity of esophagitis or acid exposure between Hp-positive and Hp-negative groups. However, subjects infected had lower basal LES pressure and decreased amplitude of distal esophageal contractions than controls. Moreover, esophageal dysmotility and subsequent low acid clearance was more prevalent in Hp-positive patients. In another study Wu et al. studied esophageal acid exposure in patients with GERD before and after Hp eradication (28). He found no difference in the percentage of time the esophageal pH was < 4, but the percentage of time with esophageal pH was < 2 was significantly increased in
patients with successful Hp eradication. All this data strongly suggest that chronic Hp infection is associated with esophageal dysmotility. So the question arises why GERD seems to be more prevalent in post-eradication treatment. The most obvious mechanism is that the motility disturbances are counterbalanced by low acidity of reflux content.

From the epidemiological studies it is known that in some Hp-positive GERD patient’s eradication results in symptoms improvement, but in others it causes symptoms worsening or even de novo development when not occurring previously. As the studies cited above have shown strong effect of Hp eradication on distal esophageal motility and LES but little effect on distal esophageal acid exposure, the pathways responsible must involve more mechanisms than Hp-related EGJ dysfunction and acid production disturbances. These mechanisms may be associated with impaired control of autonomic nervous system. It was shown in the study performed by Lee et al. that in comparison with NERD subjects, autonomic tonus in patients with endoscopically confirmed esophagitis (even without symptoms) is lower (29). Moreover, study focusing on HRV-based analysis showed more precisely that especially parasympathetic activity impairment contributes to reflux development (14). In another study positive correlation between Hp infection and parameters reflecting vagal tone has been reported (30). This phenomenon may underlie one of the mechanisms by which Hp exerts preventive rather than pathogenic role in GERD development.

CONCLUSIONS

The analysis of currently available data suggests that the mechanisms related to Hp infection and following its eradication involve gastric acid and neuroendocrine secretion, esophageal and gastric motility changes and autonomic nervous system disturbances. The net effect of these sometimes contrary influences determines the occurrence, intensiveness and type of reflux-associated clinical manifestations.

REFERENCES


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