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Review

What Is the Difference Between *Helicobacter pylori*-Associated Dyspepsia and Functional Dyspepsia?

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Advances in basic and clinical research have revealed that *Helicobacter pylori* (*H. pylori*) infection plays an important role in the development of gastroduodenal dysmotility and hypersensitivity, as also in dyspepsia symptoms. In addition, recent studies have proposed an inflammation-immunological model for the pathogenesis of functional dyspepsia. Since *H. pylori* is the major microbe that provokes a gastroduodenal inflammatory response, it should not be overlooked when considering the pathophysiology of dyspepsia symptoms. In fact, population-based studies have demonstrated that *H. pylori* is detected more frequently in dyspepsia patients. However, although many clinical studies tried to reveal the association of *H. pylori* infection with gastric motility dysfunction or hypersensitivity, the results have been conflicting. On the other hand, many etiological features were revealed for the development of *H. pylori*-associated dyspepsia, such as abnormal ghrelin or leptic secretion, altered expression of muscle-specific microRNAs, and duodenal inflammatory cell infiltration. In addition, therapeutic strategy for *H. pylori*-associated dyspepsia would be different from *H. pylori*-negative functional dyspepsia. This review focuses the issue of whether *H. pylori*-associated dyspepsia should be considered as a different disease entity from functional dyspepsia.
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Key Words
Duodenum; Ghrelin; *Helicobacter pylori*; MicroRNAs

Introduction

Functional dyspepsia (FD) is a syndrome characterized by chronic and recurrent gastroduodenal symptoms in the absence of any organic or metabolic disease that is likely to explain the symptoms.[1,2] FD is considered to be important to public health, because it is remarkably common, can be disabling, and can pose a major social and economic burden.[3] Since FD is a highly heterogeneous disorder, numerous pathophysiological mechanisms, such as gastroduodenal motor dysfunction, visceral hypersensitivity, central nervous system dysfunction, *Helicobacter pylori* (*H. pylori*) infection and psychosocial factors have been suggested to play a role in the development of FD.

Although numerous epidemiological trials have suggested a higher prevalence of *H. pylori* infection in FD patients, the results have been conflicting.[4] Results of a meta-analysis showed that the prevalence of *H. pylori* infection was greater in patients with dys-

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pepsia than in controls, with an odds ratio of 2.3 (95% CI, 1.9-2.7).[5] Although this result seems to support the role of *H. pylori* infection in the pathogenesis of dyspepsia, it appears that some of the studies that were included in the analysis were biased by the selection of controls not properly matched for age, socioeconomic status and ethnic background.[4]

However, recent studies have revealed a subset of patients who developed FD after an episode of gastrointestinal infection. These studies, proposing the concept of post-infectious FD, suggest that an inflammation-immunological circuit also plays an important role in the development of FD.[6] It is generally well-recognized that the major cause of gastroduodenal inflammation is *H. pylori* infection.[7] Since *H. pylori* induces activation of a complex and fascinating cytokine and chemokine network in the gastric mucosa,[8] it is of little surprise that *H. pylori* infection has been implicated in the pathogenesis of dyspepsia.

For this reason, one of the major research interest is the difference between *H. pylori*-associated dyspepsia and other functional dyspepsia.[9] In this review article, FD in patients with a present or even past history of *H. pylori* infection is defined as a different disease entity (*H. pylori*-associated dyspepsia [HpD]) from FD, especially by focusing on the etiological insight of HpD, and then discusses the therapeutic strategy of HpD.

Influence of *Helicobacter pylori* Infection on Dyspepsia Symptoms and the Gastric Functions

A lot of clinical evidences have been published to investigate whether *H. pylori* infection is involved in gastric motility disorders and visceral hypersensitivity. However, all of these studies were small-scale studies, and the results were conflicting. Few studies have shown the association between gastric visceral hypersensitivity and *H. pylori* infection. Thumshirn et al[10] compared gastric motor and sensory functions in 17 patients with FD and 16 asymptomatic controls, and reported that *H. pylori* infection did not appear to influence gastric accommodation, but was associated with hypersensitivity in FD patients. On the other hand, some researchers were able to show the association between gastric motility dysfunction and *H. pylori* infection. Mearin et al[11] investigated the symptomatic pattern in 27 *H. pylori*-positive and 23 *H. pylori*- negative patients with FD, and showed that FD patients with *H. pylori* infection presented no distinctive symptoms in comparison with their *H. pylori*-negative counterparts, and that *H. pylori* infection was associated with diminished postprandial antral motility, but did not increase the perception of gastric distension. Tucci et al[12] evaluated the *H. pylori* infection status, histological features of the gastric mucosa, and the gastric motor and secretory functions in 45 consecutive patients with FD. *H. pylori* infection was found in 60% of FD patients, as compared with 33% of the 15 healthy controls. No difference was detected in the basal or stimulated gastric acid secretion between the FD patients and healthy controls. Gastric emptying was significantly delayed in FD patients as compared with that in healthy controls after adjustments for age and sex. Delayed gastric emptying was associated with a low frequency of *H. pylori* infection, female gender and young age. Epigastric pain or burning and postprandial fullness were more severe in patients with *H. pylori* infection and in those with delayed gastric emptying, respectively. Saslow et al[13] compared 8 *H. pylori*- positive and 8 *H. pylori*-negative asymptomatic subjects, and showed that *H. pylori* infection reduced accommodation, but had no effect on the overall sensation or motor functions of the stomach. However, some studies showed that *H. pylori* infection did not affect gastric motility or hypersensitivity. Leontiadis et al[14] evaluated 23 FD patients and 17 controls, and showed that although gastric emptying was delayed in FD patients, the gastric emptying rate was not associated with the *H. pylori* infection status, and was also not affected by eradication of the infection. Chang et al[15] compared 22 *H. pylori*- negative patients and 38 *H. pylori*- positive patients with FD, and showed that the *H. pylori* infection status appeared to have no influence on the incidence of delayed gastric emptying of digestible and indigestible solids.

Although the results of several clinical studies suggest that *H. pylori* infection may play a role in the development of FD, the precise pathogenesis of HpD could not be elucidated. Since gastric dysmotility and visceral hypersensitivity are induced by a number of confounding factors, such as diet, smoking and psychosocial stress, the association of *H. pylori* infection with gastric sensation or motor dysfunction might be difficult to be revealed only by clinical studies. A large-scale clinical study controlled for all of these factors would be difficult to design. Thus, novel biological markers for HpD other than gastric dysmotility and hypersensitivity must be identified. On next section, therefore, the possible pathophysiology of HpD will be reviewed.

Pathophysiological Link Between *Helicobacter pylori* Infection and Dyspepsia

Traditionally, gastric acid hypersecretion induced by *H. pylori*

infection of the gastric antral mucosa has been considered to play a role in the development of dyspepsia. About 10%-15% of patients with *H. pylori* infection show antral-predominant gastritis, which results in gastric acid hypersecretion.[16] In these patients, *H. pylori* induced a decrease in somatostatin secretion in the antral gland area, leading to an increase in the release of gastrin and subsequently to a rise in acid secretion.[17] This mechanism is also considered to underlie the development of duodenal ulcer. These phenomena are reversible, since normal feedback control of gastrin secretion is restored after *H. pylori* eradication.[17,18]

However, a few studies investigating the association between the severity of histological gastritis and that of dyspepsia symptoms yielded different results. Turkkan et al[19] reported that dyspepsia symptom scores were higher in patients with mild or moderate chronic inflammation of the corpus and antrum than in those with severe chronic inflammation, although the difference did not reach statistical significance. In studies conducted by Joshi et al[20] and Pereira-Lima et al,[21] no relationship was found between the severity of histological gastritis and the severity of the dyspeptic symptoms. Czinn et al[22] found a relationship between epigastric pain and the severity of inflammation. Similarly, van der Schaar et al[23] also found an indirect relationship between the severity of symptoms and the severity of inflammation of the corpus. From these results, we could not reach any definitive conclusion about the association of severity of gastritis or amount of gastric acid secretion with severity of the dyspepsia symptoms.

Ghrelin, which is produced and secreted by the A-like cells of the oxyntic glands of the stomach, has a well-established role in increasing appetite and food intake and in stimulating gastric emptying and acid secretion.[24-28] These functions are mediated, at least in part, via vagal nerve pathways.[29,30] In gastroduodenal mucosal injury, the levels of plasma ghrelin increased in response to the physiological demand for the purpose of gastroduodenal cytoprotection.[31,32] However, in the presence of *H. pylori*-induced severe gastric mucosal atrophy, the plasma ghrelin concentrations shifted to lower levels.[33-36] Taken together, *H. pylori* infection may induce gastric motor dysfunction and reduce appetite with suppressed ghrelin secretion. Therefore, this peptide may play a role in the onset of FD, especially HpD. In fact, alterations of the plasma ghrelin levels have been reported in FD patients, which frequently correlated with the FD symptom score.[37-39] Some studies showed that plasma ghrelin levels were significantly lower in patients with dysmotility-like FD.[28,37] Concerning the active ghrelin levels, they were also decreased in patients with postprandial fullness and/or early satiation,[40] whereas similar between dysmotility-like FD patients and healthy controls.[37] Moreover, recent study showed that repeated ghrelin administrations had stimulatory effects on food intake in FD patients.[41] However, the opposite results, such as enhanced ghrelin levels in FD patients, were also reported.[38,42] Leptin is also produced in the stomach, and activates vagal nerve ternimals, reduces appetite and increases mucin secretion.[43] Leptin may also play a role in the onset of FD, since patients with dysmotility-like dyspepsia have been reported to show higher serum concentrations of leptin.[44] On the other hand, serum leptin levels and expression of leptin mRNA in the gastric mucosa was enhanced in *H. pylori*-positive patients,[44,45] suggesting that *H. pylori* infection may reduce appatite with enhanced leptin secretion. The circulatory levels of ghrelin and leptin in HpD patients have not yet been investigated, warranting future research.

We recently investigated the role of microRNAs (miRNAs) in gastric motility disorders associated with *H. pylori* infection,[46] and the results provided a novel insight into the molecular pathogenesis of HpD. Histologic examination showed prominent thickening of the muscular layer of the gastric corpus in *H. pylori*-infected mice. In addition, gastric emptying was significantly accelerated in *H. pylori*-infected mice. The miRNA expression profile revealed that the muscle-specific miRNAs, *miR-1, miR-133a* and *miR-133b*, were downregulated in the stomach of *H. pylori*- infected mice. The expression levels of histone deacetylase 4 and serum response factor, which are target genes of *miR-1* and *miR-133* known to enhance muscular hyperproliferation, were increased. Taken together, chronic *H. pylori* infection downregulates the expressions of muscle-specific miRNAs and upregulates the expression of histone deacetylase 4 and serum response factor, which might cause hyperplasia of the muscular layer of the stomach and deregulation of gastric emptying in mice. Further human studies will be necessary to validate the association between aberrant expression of muscle-specific miRNAs in the muscular layer of the stomach and HpD.

Duodenum - A Crossroad Between *Helicobacter pylori* and Dyspepsia

Recent studies have emerged implicating abnormal motor and autonomic responses in the duodenum perhaps triggering functional responses, including pain and abnormal gastric emptying. Increased duodenal acid exposure has been reported in patients with dyspepsia symptoms. At the level of the duodenum, abnormalities may exist in the stimulus intensity, mucosal

mRNA expression, biosynthesis, release or inactivation of the mucosal mediators, or in the receptor expression on the afferent nerve endings.[47]

Furthermore, Talley et al[48] proposed that changes in the duodenal eosinophil count might be an underlying feature of FD. They also showed that eosinophils were significantly increased in both the bulb and second portion of the duodenum in FD, whereas increase of the mast cells in the second portion of the duodenum was noted in irritable bowel syndrome (IBS).[49,50] A link between eosinophils (and other inflammatory cells) and FD would have therapeutic implications. Eosinophils are critically dependent on the cytokine IL-5 for their maturation in the bone marrow, which also influences eosinophil migration and survival. Kindt et al[51] reported that stimulated lymphocyte expression of IL-5 and IL-13 was enhanced, whereas stimulated monocytic IL-12 and lymphocytic IL-10 expression were reduced in both FD and IBS. Based on these findings, anti-inflammatory agents, possibly including novel biologics such as anti-IL-5 humanized antibodies, could be explored as a possible therapeutic candidates for FD.

Active duodenitis has been reported to be more common in patients with *H. pylori* infection.[52] Genta et al[52] reported that *H. pylori* was detected in the gastric metaplastic epithelium of 67.6% of patients with active inflammation of the duodenum. On the other hand, *H. pylori* infection is well-known to cause eosinophil infiltration of the gastric mucosa.[53] Taken together, *H. pylori* might be one of the causes of duodenal eosinophilia, as well as of the onset of dyspepsia symptoms.

In addition, Gargala et al[54] reported that the number of intraepithelial lymphocytes in the duodenal mucosa was significantly greater in *H. pylori*-positive FD patients than in healthy controls, but not different between *H. pylori*-negative FD patients and healthy controls. The expressions of CD95/Fas and HLA-DR-expressing $CD3^+$ lymphocytes were lower in *H. pylori*-negative FD patients than in healthy controls. These findings suggest that the phenotypic characteristics of intraepithelial lymphocytes may be different between HpD and *H. pylori*-negative FD.

Treatment for *Helicobacter pylori*-Associated Dyspepsia

Although a number of clinical trials have assessed the efficacy of *H. pylori* eradication for the treatment of FD, the studies drew different conclusions. However, it is quite clear that *H. pylori* eradication treatment is effective in at least a subset of patients with FD.[7,55-58] According to a meta-analysis of randomized controlled trials to determine the effect of *H. pylori* eradication on dyspepsia symptoms, *H. pylori* eradication therapy appears to have a small but statistically significant effect in HpD.[59] Harvey et al[60] showed that *H. pylori* eradication gave cumulative long-term benefit, with a continued reduction in the development of dyspepsia severe enough to require a consultation with a general practitioner up to at least 7 years.

The efficacy for patients with HpD in Asia would be different from those in Western countries, since Asian population differs from the Western population in many respects, such as prevalent *H. pylori* strains, including cagA gene polymorphisms, levels of acid secretion in the stomach and the severity or pattern of gastritis.[58,61] In fact, Gwee et al[62] showed that the patients with FD in Asia would have a benefit from treatment for *H. pylori* infection with as much as a 13-fold increased chance of symptom resolution following its eradication in a double blind, randomized and placebo-controlled trial in Singapore-based Asian population.

There is no evidence of treatment for HpD patients after the successful eradication of *H. pylori*. At present, acid suppression is a frequently used first-line therapy for FD. A meta-analysis of randomized controlled trials of proton pump inhibitors (PPIs) for FD reported that this class of agents was superior to placebo.[63] However, much of this benefit may be explained by the presence of concomitant unrecognized gastroesophageal reflux disease (GERD). Xiao et al[64] showed that the prevalence of pathologic esophageal acid reflux without typical reflux symptoms (silent reflux) was 31.7% in FD patients. In addition, PPIs were effective in 83.1% of FD patients with silent reflux, and in 54.3% of those without silent reflux. On the other hand, inverse associations are observed between the presence of *H. pylori* infection and GERD, because of the reduction in gastric acid production by *H. pylori* colonization of the gastric mucosa.[65,66] This suggests that the efficacy of PPIs in HpD may be weaker than that in *H. pylori*-negative FD, which may show strong overlap with GERD.

On the other hand, a gastro-protective agent for chronic gastritis would be a therapeutic candidate for HpD. Rebamipide, a gastro-protective anti-ulcer drug, has been used for the improvement of dyspepsia symptoms in Japan, Korea, China and some other countries. Rebamipide is known to suppress gastric mucosal inflammation, which is thought to be related to its activity in the inhibition of superoxide anion production from neutrophils and scavenging hydroxyl radicals.[67,68] Rebamipide administration after *H. pylori* eradication could promote the restoration of atro

phic mucosa in Mongolian gerbils.[69] Chitapanarux et al[70] reported that rebamipide treatment improved symptom, endoscopic and histologic features of chronic gastritis in patients with dyspepsia symptoms refractory to PPIs. Talley et al[71] reported a double-blind, placebo-controlled and multicenter study of rebamipide for the treatment of FD patients with or without *H. pylori* infection. Although a significant improvement of individual symptoms at 8 weeks was not detected, the ratio of patients who requested usage of the study medication again was greater in the rebamipide groups compared with the placebo group in *H. pylori*-positive patients. During the planning of this study, it was originally projected that a sample size of 100 patients per treatment group would be sufficient to detect a difference in response rate of approximately 20% between the rebamipide treatment group and the placebo treatment group with 80% power at the 0.05 significance level. However, because of the slow patient recruitment and unexpected budget constraints, the trial had stopped prior to completion of enrollment. Based on the enrolled population of approximately 50 patients per arm in the *H. pylori*-negative study and 30 patients per arm in the *H. pylori*-positive study, the detectable differences would be 30% and 40%, respectively. The 30% superiority over the placebo would be non-realistic hurdle for any medication for FD. Miwa et al[72] also reported a double-blind, placebo-controlled and single-center study of rebamipide for the treatment of FD patients. Although the mean changes in overall symptoms after 4 weeks of treatment were not significantly different between the rebamipide and placebo treatment groups, the improvement in symptom score was significantly greater in the rebamipide group for bloating, belching and pain or discomfort that was relieved after a meal. Social restriction and pain intensity were also improved in the rebamipide group. The ratio of subjects with *H. pylori* infection were 54.1% in the rebamipide group and 42.4% in the placebo group. However, they did not perform subanalysis by *H. pylori* status as the number of subjects was rather small. As rebamipide has an anti-inflammatory effect, it might be effective for HpD, but not for FD patients without gastritis. However, there is not enough evidence for the efficacy of rebamipide for dyspepsia symptoms of HpD patients.

Therefore, the efficacy of all the existing medical treatment, including a gastro-protective agent, for FD should be re-evaluated for HpD and *H. pylori*-negative FD. Well-designed studies to investigate a suitable therapeutic strategy for HpD are needed.

Conclusions

Several mechanisms have been postulated for the development of HpD. Some of these mechanisms would be reversible, while others might not. Therefore, it would be reasonable that the *H. pylori* "test-and-treat" strategy is not effective in all HpD patients, but is effective in only a subset of HpD patients. *H. pylori* infection evokes significant inflammatory changes, not only in the gastric mucosa, but also in the gastric muscular layer as well as in the duodenum. However, most patients with *H. pylori* infection do not have any symptoms. We therefore need to conduct further investigation about the true relationship between dyspepsia symptoms and *H. pylori* infection to determine whether there might be identifiable risk factors for the onset of symptoms.

When the Rome III criteria were developed, the role of *H. pylori* infection in FD was controversial. Now, however, the pathophysiology underlying disturbances of gastroduodenal motor or sensory function and dyspepsia symptoms caused by *H. pylori* infection is gradually being elucidated. Therefore, when HpD is considered as an organic disease and as a different disease entity from FD, these conflicting results of previous studies might become more comprehensible. Further studies will be necessary to determine whether HpD should be separated from FD. In addition, the differences in the therapeutic strategies between HpD and *H. pylori*-negative FD are also necessary to be investigated in the future.

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