Effects of \textit{Helicobacter pylori} Eradication on Proximal Gastric Motor Functions in \textit{Helicobacter pylori} Associated Functional Dyspepsia Patients

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ABSTRACT

\textbf{Background:} Impaired gastric accommodation has been reported in functional dyspepsia. Effects of \textit{H. pylori} eradication on proximal gastric functions in patients with functional dyspepsia have not been well explored.

\textbf{Aim:} To prospectively study the effects of \textit{H. pylori} eradication on proximal gastric motor functions, especially gastric accommodation, in patients with \textit{H. pylori} associated functional dyspepsia.

\textbf{Patients and Methods:} Ten functional dyspepsia patients (5 male, 5 female, age 37 ± 2.2 years, mean ± SEM) with \textit{H. pylori} infection underwent a barostat study before and 3 months after \textit{H. pylori} eradication. Barostat study was performed using an electronic barostat and a silicone manometric catheter incorporated with a 1,200 ml polyethylene bag. Compliance and perception of the proximal stomach were studied by 2-24 mmHg slow ramp distensions. Gastric perception such as nausea, fullness, and pain symptoms were scored during slow ramp distensions using a seven-point Likert scale (0-6). Gastric accommodation was evaluated by continuous distention of the proximal stomach at 2 mmHg above the minimal distending pressure for 90 min with a 200 ml liquid caloric meal (Ensure\textsuperscript{®}, 212 kCl, 14.1% protein, 22% fat, 63.9% carbohydrate) given at the 30th min. Gastric accommodation was expressed as the percentage of the increase of proximal gastric volume induced by the meal compared to the mean volume during the basal period.

\textbf{Results:} After \textit{H. pylori} eradication, the proximal stomach volume after meal increased 229 ± 48 ml (97 ± 23%) significant greater than before eradication (141 ± 52 ml or 41 ± 18 %) (p <0.05). There were no significant differences of the gastric compliance, and gastric perception (first sensation and threshold of discomfort), evaluated before and after \textit{H. pylori} eradication (p >0.05). There were significant improvements in global dyspeptic symptoms after \textit{H. pylori} eradication.

\textbf{Conclusions:} \textit{H. pylori} eradication improves gastric accommodation and global dyspeptic symptoms in functional dyspepsia patients without significant changes of gastric compliance and gastric perception in response to mechanical distension. This finding suggests that \textit{H. pylori} infection may be associated with the impaired gastric accommodation found in functional dyspepsia patients.

\textbf{Key words:} functional dyspepsia, \textit{Helicobacter pylori}, gastric accommodation

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**INTRODUCTION**

Dyspepsia is among the most common GI disorders characterized by pain or discomfort centered in the upper abdomen. It is prevalent in more than one fourth of the general population and is a frequent reason for medical consultation. It accounts for 5% of office visits and 40-70% of gastrointestinal complaints in general medical practice. The costs for the evaluation and treatment of dyspepsia are enormous. Over a half to two-thirds of patients with dyspepsia demonstrate no focal or structural cause at endoscopy and are labeled as having functional dyspepsia. However, the pathophysiologic processes underlying the functional dyspeptic symptoms are poorly understood. Previous studies have shown that many factors may be responsible for functional dyspeptic symptoms, including visceral hypersensitivity, *H. pylori* infection, and gastric motor dysfunction. In term of gastric motor dysfunction, up to a half of functional dyspepsia patients have scintigraphy confirmed delayed solid gastric emptying. Antral hypomotility and impaired gastric accommodation have also been reported in patients with functional dyspepsia.

*H. pylori* infection is common in functional dyspepsia. Although the benefit of *H. pylori* eradication in patients with functional dyspepsia is controversial, a recent study has shown that *H. pylori* infection is associated with an increased risk of dyspepsia. The mechanisms that responsible for dyspeptic symptoms in patients with *H. pylori* infection are still inconclusive. Tack et al. reported the association between impaired gastric accommodation and symptom of early satiety in functional dyspepsia.

Proximal gastric accommodation in response to a meal is a complex process that involves both intra and extragastric reflexes. The extragastric reflexes originate from both the esophagus and the small intestine. Swallowing or distention of the esophagus and balloon distension or nutrient infusion in the duodenum induce reflex relaxation of the proximal stomach, which is mediated via the vagal pathway. Gastric distension induces reflex relaxation of the proximal stomach, a process known as adaptive relaxation that is most likely responsible for the accommodation of the stomach after ingestion of food and liquids. This adaptive relaxation reflex enables the stomach to increase its volume markedly without a corresponding increase in pressure, and is mainly mediated via an intrinsic gastrogastric reflex, independently of an external innervation and resistant to ganglionic blockage. Nitric oxide (NO) has been reported as a key mediator of proximal gastric relaxation. It serves as a non-adrenergic, non-cholinergic (NANC) neurotransmitter in nerves that supply gastrointestinal muscles. Recent studies indicate that n-NOS, n-NOS gene expression, and the changes of smooth muscle relaxation in response to L-NAME, an inhibitor of NO synthesis of the smooth muscle of the stomach, were decreased in *H. pylori* infection in animals. This finding indicates that impaired gastric accommodation in patients with *H. pylori* associated functional dyspepsia may be caused by the lack of NO secondary to n-NOS depletion after *H. pylori* infection.

This prospective study aimed at evaluating the changes of proximal gastric function especially gastric accommodation in response to *H. pylori* eradication in patients with *H. pylori* associated functional dyspepsia.

**MATERIALS AND METHODS**

**Study subjects**

Ten patients (5 male, 5 female, age 37 ± 2.2 years) with functional dyspepsia as defined by the ROME II criteria were included from the outpatient GI Clinic, King Chulalongkorn Memorial Hospital, Bangkok. All patients had a negative esophagogastrroduodenoscopy one month prior to the study. *H. pylori* infection was determined by the rapid urease test routinely done during endoscopy.

Exclusion criteria were: 1) subjects with underlying medical condition(s) including hypertension, cardiac, liver, renal, and pulmonary diseases, which would make participation in the study unsafe or impractical, 2) history or previous gastrointestinal surgery, 3) patients with history of allergic or adverse reactions to amoxicillin, clarithromycin, and omeprazole, 4) patients who were taking the medications which may affect gastrointestinal motility whether 7 days prior to entry of the study. Such medication include macrolide antibiotics, metoclopramide, domperidone, sildenafil, calcium channel blocker, beta blocker, anticholinergic, and opioid analgesics, 5) pregnant women, 6) ages less than 18 years or greater than 75 years, 7) inability to understand or to provide written informed consent, 8) presence of esophagitis, gastric atrophy, erosive or ulcer gastroduodenal lesions on endoscopy.
The study was approved by the Ethics Committee of the King Chulalongkorn Memorial Hospital. All patients gave written, informed consent to participate in the study.

**Study design**

Each patient underwent two barostat studies at before and 3 months after *H. pylori* eradication by taking amoxicillin 1,000 mg, clarithromycin 500 mg, and omeprazole 20 mg, orally twice a day for one week.

Urea breath test was employed to determine *H. pylori* eradication at week-4 after the treatment.

For each barostat study, the patient reported at the Gastrointestinal Motility Research Unit, King Chulalongkorn Memorial Hospital, at 8.00 am after an overnight fast. The patient was asked to score the severity of the following eight symptoms: epigastric pain, epigastric burning, early satiety, bloating, nausea, vomiting, bleching, and postprandial fullness, using a four-point Likert scale (0, no problem; 1, mild problem, can be ignored when you do not think about it; 2, moderate problem, cannot be ignored but does not influence daily activities; 3, severe problem, influences your concentration on daily activities).

**Gastric barostat study**

Each subject swallowed a deflated 1,200 ml polyethylene bag, tightly wrapped on the distal end of a silicone manometric catheter using manometric guidance, the polyethylene bag was placed at the proximal stomach 5 cm distal to the lower border of esophageal sphincter. The balloon was unfolded by inflation with 240 ml of air. The catheter was connected to an electronic barostat (Distender series II, G&J Electronics INC.) and fixed to the cheek. The subject was positioned at 60-degree inclination in the supine position. The study was performed in a quiet, private room.

After a 15-minute adaptation period, isobaric distentions were performed in stepwise increments of 2 mmHg, starting from 2 mmHg, each lasting for 1 minute, while the corresponding intragastric volume was recorded on a personal computer using protocol plus deluxe software (G & J Electronics INC.). The subjects was instructed to score this perception of the upper abdominal sensations at the end of every distention step. The end point of each sequence of distentions was established at an intrabag pressure of 24 mmHg, the threshold of pain (gastric perception score = 5), or the maximum volume of the balloon (1,200 ml). The minimal distending pressure (MDP) was defined as the first distention pressure, for which an intrabag volume of ≥30 cc and a continuous respiratory fluctuation in intrabag pressure were observed.

After a 15-minute adaptation period with the bag completely deflated, the pressure level was set at MDP +2 mmHg for at least 90 minutes. A 200 ml liquid meal (Ensure®, Abbott Laboratories, 212 kcal, 14.1% protein, 22% fat, and 63.9% carbohydrate) was administered at the 30th minute. The proximal gastric tone was monitored for at the 60th minute after the meal.

**Assessment of perception during gastric mechanical distensions**

Gastric perception was assessed in the fasting state during balloon distension using a symptom descriptive chart. The perceptions of three symptoms were recorded: 1) nausea, 2) fullness, and 3) abdominal discomfort. Symptoms were graded 0-6, 0 = none; 1 = first sensation of very low intensity; 2 = distinct sensation of distention but still without discomfort; 3 = mild discomfort; 4 = moderate discomfort; 5 = severe discomfort; 6 = worst ever, unable to tolerate. The subjects were asked to report their perceptions whenever the severity was changed. Threshold of discomfort was defined as the first level of pressure and the corresponding volume that provoked a score of ≥5. During the study, there was minimal interaction between the subject and the investigators to avoid bias.

**Data analysis**

Gastric accommodation was determined by subtracting the maximum intrabarostat bag volume during 1 hour postprandial period with the average volume of the 15-minute preprandial period. Gastric compliance was defined as the linear slope of a pressure-volume curve with values obtained during slow ramp inflation, where the pressure (mmHg) is represented on the X axis and the bag volume (ml) on the Y axis.

The gastric accommodation, gastric compliance and gastric perception threshold before and after *H. pylori* eradication were compared.

**Statistical analysis**

The sample size for the study was based on 80% power (at \( \alpha = 0.05 \)) that assessed the variances or post-prandial accommodation in a previous study (14). All data are presented as mean values ± SEM. Statistical
Table 1 Summarizes the clinical features of patients with functional dyspepsia.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male:female)</td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37 ± 2.2</td>
<td>26-47</td>
</tr>
<tr>
<td>Weight (kilograms)</td>
<td>61 ± 3.3</td>
<td>45-72</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162 ± 11.0</td>
<td>147-171</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23 ± 3.5</td>
<td>19.2-29.5</td>
</tr>
<tr>
<td>Duration of symptom (months)</td>
<td>23.5</td>
<td>6-72</td>
</tr>
</tbody>
</table>

Comparisons between the values before and after *H. pylori* eradication studies were performed by paired - t tests. A significant difference was defined as a *P* <0.05.

**RESULTS**

The patients’ characteristics were shown in table 1. All patients completed the studies after successful *H. pylori* eradication.

**Barostat study (gastric accommodation and compliance)**

The MDP was 8.2 ± 0.5 mmHg (range 6-10 mmHg). Before *H. pylori* eradication, the proximal stomach volume after meal increased by 141 ± 52 ml (41 ± 18% change) when compared to the values before meal. After *H. pylori* eradication, the proximal stomach volume after meal increased by 229 ± 48 ml (99 ± 23% change), which was significantly greater compared to those at the time prior to *H. pylori* eradication (*P* <0.05). (Figure 1)

Gastric compliance before *H. pylori* eradication were similar (100.7 ± 7.1 ml/mmHg vs 94.7 ± 8.0 ml/mmHg; *P* >0.05).

**Gastric perception**

There was no significant difference of the perception threshold before and after *H. pylori* eradica-
The threshold of the first gastric perception was $12.8 \pm 1.3$ mmHg and $10.6 \pm 0.7$ mmHg for before and after *H. pylori* eradication respectively ($p >0.05$), whereas the threshold of discomfort was $21.0 \pm 1.2$ mmHg and $20.4 \pm 1.4$ mmHg before and after *H. pylori* eradication respectively ($p >0.05$).

**Table 2** Dyspeptic symptom score in study population before and after *H. pylori* eradication

<table>
<thead>
<tr>
<th>Symptom score</th>
<th>Before HP treatment</th>
<th>After HP treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric pain</td>
<td>1.8</td>
<td>0.8</td>
<td>0.004*</td>
</tr>
<tr>
<td>Epigastric burning</td>
<td>2.4</td>
<td>1.4</td>
<td>0.004*</td>
</tr>
<tr>
<td>Early satiety</td>
<td>1.6</td>
<td>0.6</td>
<td>0.03*</td>
</tr>
<tr>
<td>Bloating</td>
<td>1.7</td>
<td>1.1</td>
<td>0.19</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.9</td>
<td>0.1</td>
<td>0.04*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.5</td>
<td>0</td>
<td>0.10</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.1</td>
<td>1.2</td>
<td>0.78</td>
</tr>
<tr>
<td>Postprandial fullness</td>
<td>1.8</td>
<td>0.9</td>
<td>0.03*</td>
</tr>
<tr>
<td>Global symptom</td>
<td>11.8 ± 1.5</td>
<td>6.1 ± 1.1</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

*P <0.05, statistical significant

Dyspeptic symptom score before and after *H. pylori* eradication

There was a significant improvement of global dyspeptic symptom score after *H. pylori* eradication compared to before eradication ($11.8 \pm 1.5$ vs $6.1 \pm 1.1$, $p = 0.005$). When individual symptoms were considered: epigastric pain, epigastric burning, early satiety, nausea, and postprandial fullness were significantly improved ($p <0.05$), whereas bloating, vomiting, and bleeding did not improve ($p >0.05$). (Table 2)

**DISCUSSION**

This study was the first to evaluate gastric accommodation in functional dyspepsia patients before and after *H. pylori* eradication, using a standard barostat technique. It was found that at 3 month after *H. pylori* eradication, gastric accommodation was significantly improved compared to before eradication, without significant effects on proximal gastric compliance and gastric perception.

Impaired gastric accommodation was present in 40% of functional dyspepsia patients, and was found in both *H. pylori* positive and *H. pylori* negative functional dyspepsia. A previous study demonstrated that asymptomatic volunteers with *H. pylori* infection had impaired gastric accommodation compared to asymptomatic volunteers without *H. pylori* infection. However, there was no study exploring the effects of *H. pylori* eradication on gastric accommodation in functional dyspepsia patients.

In animal studies, *H. pylori* infection has been shown to down regulate n-NOS gene expression resulting in reduced gastric relaxation(18). Thus, it is possible that eradication of *H. pylori* may improve gastric accommodation in functional dyspepsia patients by improving n-NOS gene expression.

Several possible pathophysiologic mechanisms have been postulated in functional dyspepsia, but it is fair to say that the pathophysiology of functional dyspepsia is unclear. Some of the proposed mechanisms are delayed gastric emptying(8-11), visceral hypersensitivity(1-5), impaired accommodation(14,15), *H. pylori* infection(6,7), abnormal duodenoejunal motility(12,13), and central nervous system dysfunction. Impaired gastric accommodation was associated with symptoms of early satiety and weight loss(14). The mechanism underlying impaired postprandial relaxation of gastric fundus is unknown. Several possible pathways can be involved. Soon after the discovery of *H. pylori*, a causal relationship between *H. pylori* infection and duodenal or gastric ulcers was established. In functional dyspepsia, the role of *H. pylori* is less clear. Meta-analysis data showed that prevalence of *H. pylori* infection was greater in dyspepsia patients(20), but there was no evidence for a strong association between *H. pylori* infection and functional dyspepsia, due to weakness in study design and execution, and there was not enough evidence to rule out a modest association(21).

This study shows that after *H. pylori* eradication, the volume increases of proximal stomach relaxation induced by meals (gastric accommodation) were significantly increased compared to those at the time before eradication. It seems that *H. pylori* infection is associated with impaired gastric accommodation prevalent in functional dyspepsia patients. This finding indicates that the impaired gastric accommodation in patients with *H. pylori* is associated with functional dyspepsia. Whether the impaired gastric accommodation in functional dyspepsia with *H. pylori* infection is caused by the lack of NO secondary to n-NOS depletion warrants further study.

There was significant improvement of dyspeptic symptom score after *H. pylori* eradication, including...
epigastric pain, epigastric burning, early satiety, nausea, and postprandial fullness. Previous studies have provided equivocal evidence of \textit{H. pylori} eradication on symptom improvement. Moreover, some papers showed a difference in symptom improvement in studies in which the period of observation was less than 12 months compared with studies in which follow up was for more than 12 months\textsuperscript{(21)}. The limitation of our study in the evaluation of the effect of \textit{H. pylori} eradication on symptom improvement was a short periods of follow up (about 12 weeks). This cannot exclude the placebo effect, as dyspeptic symptoms in functional dyspepsia patients usually wax and wane. The small sample size also may be associated with type II error.

In conclusion our study demonstrated that \textit{H. pylori} infection is associated with impaired gastric accommodation as found in functional dyspepsia patients.

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