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Effect of *H. pylori* infection on gastrin, ghrelin, motilin, and gastroesophageal reflux

ESOPHAGUS/STOMACH

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Original Article

ABSTRACT

Background/Aims: To evaluate the occurrence of gastroesophageal reflux and possible mechanisms in *Helicobacter pylori* infection.

Materials and Methods: Symptoms of *H. pylori*-infected children, their total gastroesophageal reflux episodes, acid exposure percentage, gastrin, ghrelin, and motilin levels were evaluated before and after *H. pylori* eradication.

Results: Forty-two *H. pylori*-infected children were eligible for this study. Acid exposure % and total reflux episodes before and after *H. pylori* eradication were 10.2%±14.8% vs. 7.71%±5.0% and 94.7%±102.1% vs. 64.6%±55.0%, respectively (p=0.28, p=0.082). There was an insignificant change in the serum gastrin (93.4±153.8 pmol/L vs. 1.28±149.4 pmol/L, p=0.67), ghrelin (7.69±197.5 pg/mL vs. 8.36±299.5 pg/mL, p=0.274), and motilin (75.1±81.2 pg/mL vs. 97.2±80.5 pg/mL, p=0.206) levels after eradication. Gastrin and ghrelin levels were negatively correlated after *H. pylori* eradication (r=–0.38, p=0.031). There was no association between gastroesophageal reflux episodes and gastrin, ghrelin, and motilin levels (r=0.25 and p=0.11; r= 0.24 and p=0.13; r=-0.23 and p=0.14, respectively)

Conclusion: *H. pylori* infection is neither protective nor harmful in the gastroesophageal reflux. Neither ghrelin nor motilin levels was associated with gastroesophageal reflux. None of gastrin, ghrelin, and motilin levels was affected by *H. pylori* infection. There is an inverse association between gastrin and ghrelin levels after *H. pylori* eradication.

Keywords: Gastroesophageal reflux, *H. pylori*, motilin, ghrelin, child

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a multifactorial, acid-peptic disorder that results from the reflux of gastric content into the esophagus. The main proposed mechanism in its development is the increased intermittent relaxation of the lower esophageal sphincter (LES). However, various host-related and environmental factors interfering with an intact competent esophagogastric junction and normal esophageal acid clearance may also contribute to GERD development.

The possible role of *H. pylori* infection in GERD has recently become a topic of major interest. Some studies have suggested a protective role of *H. pylori* and exacerbation of GERD after eradication (1), although other authors did not confirm this. These controversial results used to be explained with the anatomic location of *H. pylori* infection and the consequent hypo or hyper acidity. Within the context of these hypotheses, gastrin, which is the main regulatory hormone in acid secretion, gains importance (2,3).

H. pylori infection may lead to changes on various motility-regulating gastric hormones such as ghrelin and motilin (4-6). Motilin, an endogenous prokinetic hormone, is secreted by gastrointestinal endocrine cells. Besides initiating gastric contraction that distally propagates in the gastrointestinal tract, motilin increases LES pressure acting both via the enteric nervous system and directly on the LES muscle (7). To the best of our knowledge, only a few studies evaluated the effect of *H. pylori* infection on motilin secretion.

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Another peptide that is influenced by *H. pylori* infection is ghrelin. It is an appetite-increasing peptide that is structurally related to motilin and is produced by the enteroendocrine cells of gastric mucosa (5). It stimulates gastric acid secretion, gastrointestinal motility, gastric emptying via the vagus nerve, and histamine release (8). The effect of *H. pylori* infection on ghrelin concentration has been evaluated in a few studies (5). Nwokolo et al. (5) demonstrated that ghrelin increases after *H. pylori* eradication.

In this study, our primary aim was to evaluate the possible causal relationship between *H. pylori* infection and GERD occurrence in children. Gastrin level was measured to define the relationship between the *H. pylori* infection region and GERD occurrence. Because GERD is primarily a motility-related disorder, the secondary aim of our study was to evaluate the effect of *H. pylori* infection on prokinetic hormones, such as ghrelin and motilin, that may account for the occurrence of GERD in children.

MATERIALS AND METHODS

This prospective cohort study was conducted with children who presented with abdominal pain and dyspeptic symptoms to the Eskişehir Osmangazi University, Department of Pediatric Gastroenterology and Hepatology. Patients with chronic gastrointestinal disease and neurological sequela, celiac disease, cirrhosis, eosinophilic esophagitis, cerebral palsy, and those who received any prokinetics (metoclopropamid, domperidon, erythromycin, and rifaxamin), antibiotics, antacids, and acid blockers 1 month prior to recruitment were excluded from the study. Children who underwent upper gastrointestinal system endoscopy (Olympus XQ260N, Tokyo, Japan) and those with documented *H. pylori* infection (n=42) were prospectively recruited for measurements of gastrin, ghrelin, and motilin levels and 24-h ambulatory multichannel intraluminal impedance pH monitorization (MII-pH) before and after *H. pylori* eradication (as soon as eradication was demonstrated, in the same week). *H. pylori* infection was diagnosed with a positive urease test and/or histology. Esophagitis, if detected at endoscopy, was graded according to the Savary–Miller classification (9). At least six biopsies, three each from antrum and corpus, were obtained during endoscopy. Two of these biopsies were sent for histological examination and the remaining two (one from antrum and one from corpus) were used for the urease test. Biopsies were assessed according to the updated Sydney system (10). For *H. pylori* eradication, patients received a first-line regimen of triple therapy comprising lansoprozole (1–1.4 mg/kg/day), amoxicillin (30 mg/kg/day), and clarithromycin (15 mg/kg/day) for a two-week period. Those who did not achieve *H. pylori* eradication underwent a second-line regimen comprising lansoprozole (1–1.4 mg/kg for 14 days), metronidazole (30 mg/kg for 7 days), doxycycline (2 mg/ kg/day for 7 days), and bismuth subcitrate (8 mg/kg/day for 7 days). Patients in whom the first- and second-line therapy had failed to eradicate *H. pylori* infection were administered a third-line rescue treatment comprising lansoprozole (1–1.4 mg/kg/day), levofloxacin (10 mg/kg/day twice daily), and metronidazole (30 mg/kg/day three times a day). Eradication was examined via C14 urea breath test, 6 weeks after the termination of the eradication protocol (11).

Impedance pH monitorization was performed with an ambulatory MII-pH system (Ohmega, MMS, USA) using a pH tip™ disposable catheter (Unisensor AG, Switzerland). Storbel's formula [(0.252xbody length/height cm)+5] was used to estimate the appropriate probe location. Catheter was transnasally inserted, advanced until the pH dropped below 4, and then pulled back to the estimated length. The accuracy of the catheter level was checked with a chest X-ray. If required, adjustment was done so that the first electrode was positioned two vertebras above the diaphragm at the level of the vertebral column. Impedance values were recorded at six points. Acid exposure time % and total reflux episodes were compared before and after *H. pylori* eradication. Esophageal acid exposure time % of >4 was accepted as significant gastroesophageal reflux.

Serum gastrin (n=41), motilin (n=42) measurements were performed with commercially available ELISA kits (Diasource Immunoassay S.A., Belgium for gastrin and Cusabio Biotech Ca., Ltd., Hubie, China for motilin) after overnight fasting. Similarly, ghrelin (n=42) level was measured in the morning after overnight fasting before meal but with the RIA kit (Millipolar, Missouri, USA). The study was approved by the institutional ethics committee, and all parents provided written and verbal informed consent for each of these procedures.

Statistical analysis was performed with the software of SPSS 16.0 for windows (IMB corp., NY, USA). Normality for quantitative variables was checked with the Kolmogorov–Smirnov test. None of the nominal variables were normally distributed. Data were presented as the arithmetic mean±standard deviation. Mean of the normally distributed variables were compared with the Student's t-test and 95% confidence dense intervals were provided. Mean of non-normally distributed variables were evaluated with Wilcoxon sign test. For categorical variables, frequencies and percentages were determined, and variables were compared with the McNemar test. For correlation analysis, Spearman correlation tests (for ghrelin, motilin, and gastrin) was used. P value <0.05 was considered statistically significant.

RESULTS

A total of 67 *H. pylori*-infected patients were recruited between December 2008 and December 2010. Twenty-one of them refused the second 24-h ambulatory MII-pH monitorization. *H. pylori* eradication could not be achieved in three patients, and one patient who was formerly diagnosed as *H. pylori* infected with urease test was *H. pylori* negative in histopathology and refused further eradication protocol. Therefore, 42 *H. pylori*-infected patients with a mean age of 14.1±2.91 (8–18) years were eligible. Demographic data, endoscopic, and histopathologi-

cal findings are outlined in Table 1. Thirty-eight of the patients were diagnosed with both pathology and urease test. The remaining four were diagnosed with only urease test. Mean *H. pylori* eradication time was 5.52±3.15 months (2–14 month). Their symptoms at diagnosis and after eradication are given in Table 2. None of them had atrophy or intestinal metaplasia.

At diagnosis, 27 (64.2 %) patients had GERD. Although the number of patient with GERD increased after *H. pylori* eradication (p=0.44), there was no difference in pre-/post-eradication acid exposure % and total reflux episodes (Table 2 and 3). Anatomic localization of *H. pylori* infection could be defined in 38 patients. *H. pylori* infection was corpoantral in 31 (73.8%), antrum limited in six (14.3%,) and corpus limited in one (2.4%) patient. Twenty-one of the 31 corpoantral-infected patients (67.7%) and three of the six antrum-infected patient (50%) had gastroesophageal reflux at diagnosis (p=0.35). In terms of gastroesophageal reflux occurrence, there was no difference between antrum-limited and corpus-limited *H. pylori* infection (p=0.38). However, the patient number was insufficient for achieving an exact statement.

Out of the 21 patients, 17 (80.9%) who were corpoantrally infected and had GERD at diagnosis continued to have GERD after *H. pylori* eradication. Although their mean reflux episode and acid exposure % decreased from 88.3±98.3 to 64.8±59.8 and from 16.0±19.1 to 10.8±4.78, respectively, these changes were statistically insignificant (95% CI: −15.6–62.6, p=0.22, 95% CI: −5.10–15.5, p=0.30, respectively). Similarly, three out of the six antrum-infected patients with pre-eradication GERD continued to have GERD after eradication. Their mean acid exposure % and reflux episode tended to increase; however, this increment was statistically insignificant [4.25±3.36 to 4.43±2.84, (95% CI: −3.23–2.86, p=0.88) and 73.5±51.3 to 78.8±46.3 (95% CI-34.50–23.83, p=0.66), respectively]. One patient in whom the infection was limited to corpus developed GERD after eradication; his acid exposure % and reflux episodes increased from 3.8% to 5.1% and from 19 to 25, respectively.

Regarding the effect of *H. pylori* infection on serum gastrin, ghrelin, and motilin levels, after eradication we observed a decrease in gastrin level and an increase in both the ghrelin and motilin levels. However, none of these changes were statistically significant (Table 3).

There was no correlation between the gastroesophageal reflux episodes and gastrin, ghrelin, and motilin levels (r=0.25 and p=0.11; r=0.24 and p=0.13; r=−0.23 and p=0.14, respectively).

Concerning gastrin and ghrelin association, we detected a negative correlation after *H. pylori* eradication (r=−0.38, p=0.031).

Table 1. Demographic, endoscopic, and histopathological findings

	Number (%)
Gender (F/M)	24 (57.1)/18 (42.9)
Endoscopic finding	38 (90.5)
Antral Nodularity	26 (61.9)
Antral Hyperemia	24 (57.1)
Corpal Hyperemia	15 (35.7)
Corpal Nodularity	9 (21.4)
Intragastric bile	6 (14.3)
Duodenal Hyperemia	4 (9.5)
Duodenal Ulcer	2 (4.8)
Duodenal exudate	2 (4.8)
Esophageal erosion (grade 1)	1 (2.4)
Histopathology	
Activated Chronic Gastritis	37 (88.1)
Esophagitis	6 (14.3)
Duodenitis	5 (11.9)
Chronic Gastritis	3 (7.1)
Acute Gastritis	2 (4.8)

M: male, F: female

Table 2. Symptoms and gastroesophageal reflux at diagnosis and after eradication

	Pre-eradication n (%)	Post-eradication n (%)	p
Abdominal pain	16 (38.1)	7	0.049
Vomiting	10 (23.8)	0	0.002
Nausea	15 (35.7)	3 (7.1)	0.016
Epigastric pain	16 (61.9)	7 (16.7)	0.013
Heartburn	10 (23.8)	6 (14.3)	0.26
Regurgitation	15 (35.7)	6 (14.3)	0.049
Retrosternal pain	7 (16.7)	2 (4.8)	0.12
Halitosis	12 (28.6)	3 (7.1)	0.022
Chest Pain	3 (7.1)	1 (2.4)	0.31
Dyspepsia	3 (7.1)	0	0.083
Belching	5 (11.9)	3 (7.1)	0.48
Oral Aphts	3 (7.1)	0	0.083
Gastroesophageal reflux	27 (64.2)	30 (71.4)	0.44

N: number

DISCUSSION

Although the prevalence of *H. pylori* infection is not different between patients with GERD and healthy subjects, a significant proportion of patients with GERD also have *H. pylori* infection (12,13). Here we demonstrated that over half of the *H. pylori*-infected patients also had GERD. In contrast to studies demonstrating an inverse relation between *H. pylori* infection and GERD development, we could not demonstrate an increase in GERD after *H. pylori* infection eradication (13-15). Neither

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Table 3. Levels of hormones and impedance-pH measurements at diagnosis and after eradication

	Pre-eradication	Post-eradication	p (95% confidence interval)
Motilin (pg/mL)	75.1±81.3	97.2±80.5	0.17
Ghrelin (pg/mL)	7.69±197.5	8.36±299.5	0.65
Gastrin (pmol/L)	93.4±153.8	1.28±149.4	0.36 (-111.7-42.2)
Acid exposure %	10.2±14.8	7.71±5.01	0.28 (-2.16-7.2)
Total reflux episodes	94.7±102.1	64.6±55.0	0.082 (-3.96-64.2)

the amount of reflux episode nor the acid exposure time % changed after eradication. Those patients who had GERD in the infected state continued to have GERD in non-infected state. In such patients with dyspepsia, symptom analysis should be preciously performed at diagnosis. Usually *H. pylori* symptoms and reflux symptoms are nested. Most of the symptoms, such as abdominal pain, vomiting, epigastric pain, nausea, and halitosis, that can also be attributed to *H. pylori* infection improved after eradication (Table 2). Except regurgitation symptoms that are most likely associated to gastroesophageal reflux, such as retrosternal pain, belching, and heartburn, did not demonstrate any improvement or worsening.

Most of the studies evaluating the association of GERD and *H. pylori* infection have been conducted with adult patients. In these studies, the proposed primary mechanism by which *H. pylori* influences the pathogenesis of GERD depends on the modification of gastrin and gastric acid secretion. Gastrin is released by antral G cells, and it is often increased in *H. pylori*-infected adults (16,17). Depending on the anatomical region and the consequence of infection, the serum level of gastrin and its effect may vary. According to the current proposed mechanism, the protective effect is mediated by *H. pylori*-induced corpus-limited gastritis, which results in hypoacidity as a consequence of parietal cell destruction. This resulting hypoacidity leads to increased gastrin release that ends up with rebound hyperacidity and GERD development after eradication. On the contrary, in antrum-limited *H. pylori* infection, because of the destruction of somatostatin-secreting cells, an unopposed hypergastrinemia occurs during infection. Consequently, acid secretion increases from the intact corpal parietal cells, resulting in increased occurrence of GERD in the *H. pylori*-infected state. However, if the nature of gastritis is atrophic, then the opposite occurs. Gastrin level decreases because of the antral G cell atrophy, and the resulting hypoacidity provides protects from GERD development (2,3). In our study, we observed neither a change in the gastrin level nor in GERD occurrence between *H. pylori*-infected and non-infected state. In contrast to these hypotheses, we could not demonstrate any relationship between gastrin and GERD, which was comparable with a few studies in the literature (18-24). One of the reasons for this difference can be the predominant corpoantral infection in our patients. It appears that the hypoacidic state of corpus gastritis was opposed by the hyperacidic antral gastritis. Another reason can be the nature of the infection that *H. pylori* causes in children. Atrophic gastritis, which may be encounter to the hypogastrinemia and hypoacidity in adults, is rare in children (25). In a study, atrophic gastritis was detected only in 6% of the children. Gastric atrophy has been reported to exert an 80% decrease in GERD symptoms, and a decrease in gastrin level has been proposed as a predictor of atrophic gastritis. None of our patients had atrophic gastritis, and gastrin level did not change between pre- and post-eradication state. May be because of this, most of our patients had GERD even though they were infected with *H. pylori*, and we could not observe any change in GERD occurrence after eradication.

Because GERD is mainly a motility-related disorder, we also focused on esophageal motility-related hormones. Wu et al. (12) studied the effect of *H. pylori* infection on gastric motility in patients with non-erosive GERD. They could not demonstrate any significant difference in the esophageal sphincter pressure or esophageal peristaltic function between *H. pylori*-positive and -negative controls. However, they demonstrated that *H. pylori*-infected patients with reflux esophagitis have higher prevalence of esophageal motor abnormalities. Therefore, a concomitant esophageal motility abnormality appears likely rather than just the type or localization of gastritis. In this context, we studied the association of *H. pylori* infection and prokinetic hormones, ghrelin, and motilin. In the beginning, we hypothesized that *H. pylori* infection alters these prokinetic hormones; thus, infected patients will have impaired esophageal acid clearance and gastric emptying, contributing to GERD development. We realized that little is known regarding the effect of *H. pylori* infection on motilin secretion. To the best of our knowledge, only adult studies evaluated this association (6). Although we have found lower levels with infection, the difference between the infective and non-infective phase was insignificant. This finding was consistent with the study of Dominguez-Munoz et al. (6) that was conducted in adult patients. We could not determine any correlation between reflux episodes and motilin levels as well.

Animal studies revealed association between ghrelin and gastric emptying (2,26). With similar action as motilin, it has been proposed that the increase in ghrelin level can affect LES pressure and decrease GERD (27). Ghrelin was found to be decreased in both the plasma and gastric cell in *H. pylori* infection and to be increased after eradication (5,28-30). It has been reported that the decrease of ghrelin abolishes the control on LES and increases GERD development (27). However, we could not observe any significant increase in ghrelin level after eradication.

To date, two theories were proposed regarding the mechanism by which *H. pylori* infection leads to reduction in the plasma

ghrelin level. One is the direct effect of *H. pylori* infection on ghrelin secreting cells. If this was the case, we should have observed an increase in ghrelin level after eradication; however, this was not observed. The other possible proposed mechanism stated that hypergastrinemia that is observed in *H. pylori* infection leads to decrease in ghrelin release, and after eradication, decrease in gastrin level can result in increased ghrelin level and decreased GERD (5,31). Although there was no significant difference between infected and non-infected state in terms of ghrelin and gastrin levels solely, we observed a significant inverse relationship between gastrin and ghrelin levels after eradication. Despite this negative correlation, we could not demonstrate any decrease in GERD.

In conclusion, our findings suggest that *H. pylori* infection is unlikely to have a major effect on GERD occurrence and the relevant prokinetic hormones that affect the esophageal motor function. There is an inverse relationship between gastrin and ghrelin levels. The former decreases as the latter increases. However, even this does not have any effect on GERD occurrence.

This is the first study that evaluates the effect of *H. pylori* infection on motilin secretion in children. However, our study had certain limitations. First; it was an open-label, longitudinal study, and we did not have a control group. Although the time interval was long enough to avoid bias after eradication, this study still provided information regarding what happens in a previously *H. pylori*-infected child after eradication rather than the difference between an infected and non-infected child. However, these study types have certain advantages that cannot be ignored. Each subject acts as his/her own control. Despite this, additional motility and manometric studies would be helpful for further investigation that focused on the relation between *H. pylori* infection, gastroesophageal motility, and prokinetic hormone and gastroesophageal motility.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients' parents who participated in this study.

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