

Patients with established gastro-esophageal reflux disease might benefit from *Helicobacter pylori* eradication

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Abstract

Background The aim of this study was to investigate the effect of *Helicobacter pylori* (*H. pylori*) eradication in selected *H. pylori*-positive patients with a primary diagnosis of gastro-esophageal reflux disease (GERD) by using the 3-h postprandial esophageal pH monitoring.

Methods We recruited patients with erosive esophagitis at endoscopy and *H. pylori* infection at histology, successfully cured following eradication therapy; the selected *H. pylori*-positive patients had weekly reflux symptoms for at least six months and endoscopically established Grade A or B esophagitis. Twenty-nine eligible patients were initially subjected to esophageal manometry and ambulatory 3-h postprandial esophageal pH monitoring. All patients received *H. pylori* triple eradication therapy accompanied by successful *H. pylori* eradication. After successful eradication of *H. pylori* (confirmed by ¹³C urea breath test), a second manometry and 3-h postprandial esophageal pH monitoring were introduced to assess the results of eradication therapy, after a 3-month post-treatment period.

Results All 29 selected *H. pylori*-positive patients became negative due to successful *H. pylori* eradication, evaluated by ¹³C urea breath test after a 4-week post-treatment period. Post-eradication, 62.1% patients showed similar manometric pattern at baseline; 17.2% showed improvement; 17.2% normalization; and 3.4% deterioration of the manometric patterns. The DeMeester symptom scoring in the 3-h postprandial ambulatory esophageal pH monitoring was improved after eradication of *H. pylori* (median 47.47 vs. 22.00, Wilcoxon's signed rank; P=0.016). On comparing the pH monitoring studies for each patient at baseline and post-eradication period, 82.8% patients showed improvement and 17.2% deterioration of the DeMeester score.

Conclusion By using 3-h postprandial esophageal pH monitoring, this study showed, for the first time, that *H. pylori* eradication may positively influence GERD symptoms. Large-scale controlled relative studies are warranted to confirm these findings.

Keywords *Helicobacter pylori*, gastro-esophageal reflux disease, esophageal pH monitoring, DeMeester symptom scoring

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Introduction

Helicobacter pylori (*H. pylori*) infection is a well-known etiologic factor for many gastrointestinal diseases, such as

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Conflict of Interest: None

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chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. The gastric inflammation due to *H. pylori* may be antral-predominant gastritis, closely associated with duodenal ulceration, whereas corpus-predominant gastritis is associated with an increased risk of gastric cancer, though *H. pylori* atrophic gastritis affects both antral or corpus mucosa (multifocal atrophic gastritis). Eradication of *H. pylori* infection is recommended to prevent and/or treat these diseases. In addition, there are many important issues to be elucidated regarding the role of *H. pylori* in very severe pathologies such as esophageal cancer and other more benign disorders, common in the developed world, such as gastro-esophageal reflux disease (GERD), which carry a significant impact on health economics, and

patient morbidity. In this respect, symptoms like heartburn, acid regurgitation, and dysphagia are usually sufficient to confirm the diagnosis of GERD and initiate treatment. The most common test used to confirm excessive GERD is ambulatory 24-h esophageal pH monitoring; although this test cannot be regarded as a definitive gold standard for GERD diagnosis, it is indicated in several clinical situations defined by national or expert groups. The main limitation of the 24-h pH monitoring is its low tolerability [1]; patients report that pH testing frequently induces unpleasant side effects lasting for most of the day. Thus, a shorter monitoring period may be more tolerable [2].

To our knowledge, there are no data regarding the evaluation of the effect of *H. pylori* eradication in GERD patients, by using the 3-h postprandial esophageal pH monitoring. Therefore, the aim of this study was to evaluate the effect of *H. pylori* eradication in a Greek cohort with *H. pylori*-positive GERD, by using the 3-h postprandial esophageal pH monitoring, as a more flexible test for evaluating this disease.

Patients and methods

Patients

Due to protocol, by introducing mainly the 3-h postprandial esophageal pH monitoring, we enrolled patients who had erosive esophagitis at endoscopy and *H. pylori* infection at histology, successfully cured following eradication therapy. Specifically, the selected *H. pylori*-positive patients had weekly reflux symptoms for at least six months. The twenty-nine selected *H. pylori*-positive patients who were eligible underwent esophageal manometry and ambulatory 3-h postprandial esophageal pH monitoring at baseline and 3-months post-*H. pylori* eradication regimen; successful eradication of *H. pylori* was observed in all 29 selected *H. pylori*-positive patients, confirmed by ¹³C urea breath test (UBT) at 4-week post-treatment period. All participants provided informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local ethics committee.

Exclusion criteria for the GERD patients were: any past history of gastric or esophageal surgery; suspected or confirmed malignant disease; previous *H. pylori* eradication regimens; anticoagulant treatment; esophageal ring stricture or esophagitis secondary to systemic diseases (e.g. scleroderma or ingested irritants); primary esophageal motility disorders; pregnancy or lactation; and age <18 years old. Patients with endoscopic evidence of active gastrointestinal bleeding and those with Zollinger-Ellison's syndrome were also excluded from the study. All patients had stopped acid suppression therapy (4 days beforehand for those taking antacids and 20 days beforehand for those using H₂-receptor antagonists or proton pump inhibitors) and underwent a 4-week washout period during which any medications known to affect gastrointestinal motility, like tricyclic antidepressants, were tapered. None of the patients

was receiving oral medication that could cause or deteriorate GERD symptoms [3].

Endoscopy

All 29 selected patients were seen at 9 a.m. after a 12-h fast. Intravenous sedation was given, and standard upper gastrointestinal endoscopy, using the Fujinon EPX-201 endoscopy system (Fujinon Optical Tokyo, Japan), was performed to identify evidence of macroscopic abnormalities. The degree of reflux esophagitis was graded from A (least severe) to D (most severe) according to the Los Angeles classification system. Two biopsy specimens were obtained from the antral region within 2 cm of the pyloric ring from each patient. One biopsy specimen was used for rapid urease slide testing of *H. pylori* infection (CLOtest) and the other biopsy specimen was placed in 10% formalin and submitted for histological examination to look for *H. pylori* organisms on Giemsa staining; the diagnosis of *H. pylori* infection was confirmed by histology.

Manometry and 3-h postprandial pH-monitoring study

All 29 patients were reviewed for baseline manometry and 3-h postprandial pH monitoring within 3 days. After an overnight fast esophageal manometry was performed using a 4-channel, silicone rubber, low compliance, pneumohydraulic-perfused manometric assembly without a sleeve sensor (Manometric pump-model PIP-4-8SS Mui Scientific). The manometric assembly was passed transnasally and the position of the lower esophageal sphincter (LES) was determined using the station pull-through technique at 0.5 cm intervals. Manometric examination of the LES also served as a guide for the correct placement of the pH-sensitive probe. After removal of the manometric catheter, a monocrystalline antimony pH catheter was passed transnasally and the electrode was positioned 5 cm above the proximal margin of the LES. The electrode was calibrated in buffers of pH 7 and pH 4 before each study (pHmetry UPS 2020, MMS- Medical Measurement Systems BV). The 3-h postprandial ambulatory esophageal pH monitoring study was then carried out. Patients were encouraged to avoid coffee, alcohol, fruit juices, and antacids. They were also encouraged to take their meal at the same time during the 3-h period. They were however instructed to proceed with their normal daily routine. The same meals were used during the second pH recording to minimize day-to-day pH variation. Data acquisition was performed using a portable solid-state data logger. The pH data were analyzed by a standard software programme. The start of a reflux episode was defined by an esophageal pH below the threshold of 4.0 and its end by an esophageal pH above 4.0. Parameters of esophageal acid exposure, including the DeMeester score, were then calculated for the 3-h postprandial period by standard software programme. All analyses were performed by a single investigator (J.M.). Abnormal GERD, or a positive test, was defined as pH<4 in the distal esophagus

for more than 4% of the total recording time and DeMeester score >14.72 [4]. The DeMeester score, used as the basis for correlation between the subjects, was calculated for the 3-h postprandial period by a standard software program. The DeMeester score is a complex index that takes into account the percentage of total time with pH<4, pH<4 in upright position, pH<4 in supine position, the number of reflux episodes with intra-esophageal pH<4, the number of reflux episodes with intra-esophageal pH<4 with duration over 5 min and the reflux episode with the greatest duration in min.

H. pylori eradication regimen

All 29 *H. pylori* infected patients received the 10-day regimen including use of rabeprazole 20 mg, amoxicillin 1 g, and clarithromycin 500 mg b.i.d. for 10 days, followed by rabeprazole 20 mg q.d. for another 30 days. Subsequently, the ¹³C UBT was used to confirm *H. pylori* eradication at 4-week post-treatment period, thereby avoiding false negative UBT results if rabeprazole was not suspended 4 weeks before performing the test. Manometry and 3-h postprandial pH-monitoring studies were also repeated at a 3-month post-treatment period (~20 days post-UBT period) to define any changes in these parameters, following *H. pylori* eradication.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows package (version 11.0, SPSS, Chicago, IL, USA). Data were presented as means \pm SD, means with 95% CI or median values with 5th and 95th percentiles when appropriate. Wilcoxon's rank test was used to detect differences between baseline and 3-month *H. pylori* post-eradication period. For categorical variables, differences in frequencies were studied using the Fisher's exact test. Significance was set at $P < 0.05$.

Results

All 29 selected patients had endoscopically established Grade A or B esophagitis according to the Los Angeles classification system. Moreover, according to protocol, all 29 patients received successful *H. pylori* eradication therapy, as confirmed by UBT at 4-week post-treatment period.

Post-eradication, 18 out of 29 *H. pylori* positive patients (62.1%) showed the same manometric pattern as baseline; 5 patients (17.2%) showed improvement (propagation of esophageal peristalsis, pressure of LES); 5 patients (17.2%) normalization; and 1 patient (3.4%) deterioration of the manometric patterns (Table 1).

The overall DeMeester score in the 3-h postprandial ambulatory esophageal pH monitoring improved after eradication of *H. pylori* (median 47.47 vs. 22.00, Wilcoxon's signed rank; $P = 0.016$) (Fig. 1). Specifically, on comparing

Table 1 Post-eradication manometric pattern in *Helicobacter pylori*-positive patients with gastro-esophageal reflux disease (GERD)

Manometric pattern	GERD patients n=29	%
Normalization	5	17.2
Improvement	5	17.2
Stable	18	62.1
Deterioration	1	3.4

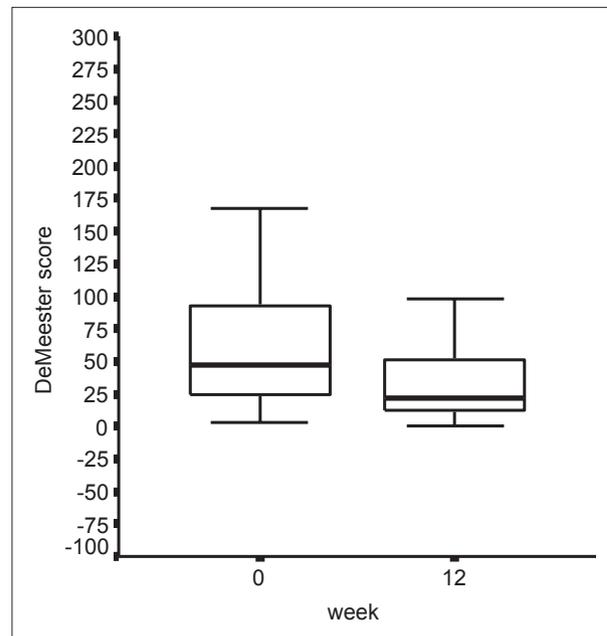


Figure 1 DeMeester score at baseline and 4-week post-eradication period in 29 *Helicobacter pylori*-infected patients with gastro-esophageal reflux disease. Bold horizontal lines express median values, boxes represent interquartile range

the pH monitoring studies for each patient prior and after successful *H. pylori* eradication, 24 of 29 patients (82.8%) showed improvement; and 5 of 29 the patients (17.2%) showed deterioration of the DeMeester score. Moreover, 9 of the 24 (37.5%) patients with improved pH monitoring study, during the post-eradication period showed completely normal pHmetry (DeMeester score <14.72) post-treatment.

Discussion

To our knowledge, this is the first study aiming to evaluate the effect of *H. pylori* eradication in a cohort with GERD, by using 3-h postprandial esophageal pH monitoring; three months after successful eradication of *H. pylori* there was significant improvement in the severity of acid reflux, as judged by established criteria. Although analysis of esophageal and stomach acidity is the best method of studying the pathogenesis of GERD, it is difficult to perform 24-h pH monitoring in a

large number of patients, due to poor compliance. We therefore used the 3-h postprandial pH monitoring study as a sensitive and mainly more flexible method; the overall DeMeester score in the 3-h postprandial ambulatory esophageal pH monitoring was significantly improved with a concomitant improvement in pH monitoring after eradication of *H. pylori* in our patients.

To our knowledge, four relative studies exist in the literature comparing GERD before and after *H. pylori* eradication by using 24-h pH monitoring.

Verma *et al* [5], aimed to assess the prevalence of GERD before and after *H. pylori* eradication by using 24-h esophageal pH/manometry studies. Patients were followed up at 6 months and 1 year when they underwent a repeat 24-h pH/manometry; 20 patients were enrolled, though only 10 patients attended for a repeat 24-h pH/manometry study. *H. pylori* eradication: a) had no impact on percentage of time pH <4 and DeMeester Score; and b) induced no substantial changes in LES pressure and other esophageal manometry data. It is important to note that new onset GERD occurred very unusually one year after *H. pylori* eradication [5].

Tefera *et al* [6], expected that *H. pylori* eradication might increase GERD in reflux esophagitis patients, because increased prevalence of esophagitis has been reported following eradication of *H. pylori*. Twenty-five consecutive patients with *H. pylori* infection were enrolled; 24-h intra-esophageal pH recording was performed before and 12 weeks after eradication. *H. pylori* eradication, also confirmed by ¹³C UBT, induced no consistent change in gastro-esophageal acid reflux.

Manifold *et al* [7] studied 25 patients with *H. pylori* gastritis using 24-h esophageal and gastric pHmetry and gastric bilirubin monitoring before and after *H. pylori* eradication, also confirmed by ¹³C UBT. No differences were noticed in esophageal acid reflux, gastric alkaline exposure, or gastric bilirubin exposure before and after eradication. The authors concluded that *H. pylori* eradication induces no change in GERD or duodenogastric reflux.

Wu *et al* [8] also studied 25 patients with *H. pylori* erosive esophagitis using 24-h esophageal pHmetry. They concluded that *H. pylori* eradication increases esophageal acid exposure and might adversely affect the clinical course of disease in 21% of patients.

Differences in populations enrolled and methodologies might explain, at least partly, the discrepancies of our own and Verma's, Tefera's, Manifold's, and Wu's findings. Nevertheless, our and Verma's data indicate that *H. pylori* eradication might protect against GERD development [9].

In this regard, *H. pylori* infection is frequent in Greek patients with GERD and even with non-endoscopic reflux disease and *H. pylori* eradication leads to better control of GERD symptoms and improves esophagitis [10]. Moreover, consistent associations with the Greek data were shown by others [11], also reporting improvement in reflux symptoms following *H. pylori* treatment. It is important to note that some other authors, usually prior supporters of the theory that *H. pylori* "protects" against GERD, relented their initial findings, claiming that *H. pylori* eradication does not cause or protect against GERD, and, moreover, recommending

H. pylori eradication in GERD [12]. Additionally, although epidemiologic studies do not suggest causality with *H. pylori*, however, such studies support our and others' findings; for instance, a large study (~21,000 cases) showed that the decrease in *H. pylori* infection parallels the decrease in peptic ulcer prevalence, and the increase in GERD and reappearance of GERD after *H. pylori* eradication is rare [8], also reported by Verma *et al* [5]. Much evidence further potentiates the concern that *H. pylori* is not "protective" against GERD [13].

The interplay between *H. pylori* and host factors plays an important role in the pathogenesis of GERD. Specifically, *H. pylori* may contribute to GERD pathogenesis by several mechanisms including the release of several mediators, cytokines and nitric oxide (NO) which may adversely affect the LES; cause direct damage of the esophageal mucosa by bacterial products; increase production of prostaglandins that sensitize afferent nerves and reduce LES pressure; and augment acidity (by gastrin release) that exacerbates GERD [10,14]. Specifically, there is the concept that gastric inflammation at the cardia may lower the threshold for transient relaxation of the LES by altering the sensitivity of vagal sensory receptors [15]. *H. pylori* gastritis is accompanied by release of the abovementioned NO, cytokines and prostaglandins that promote damage to the adjacent esophageal mucosa [16]. There is good evidence to indicate that the excessive production of prostaglandins in reflux esophagitis drives a vicious cycle of LES dysfunction, reflux, mucosal inflammation, aggravated LES dysfunction and further reflux. Moreover, the predominantly antral *H. pylori* gastritis is associated with an augmented gastrin release; increased acidity along with a higher volume of gastric juice may aggravate reflux disease. Finally, in a recent critical review [17] regarding the complicated data available on the topic of *H. pylori* association with GERD, the authors concluded that: Intra-esophageal pH recording data fail to confirm increased acid reflux following *H. pylori* eradication; esophageal manometric studies suggest that bacterial eradication reduce rather than favor acid reflux into the esophagus; clinical studies suggest that *H. pylori* eradication is not considerably associated with reflux symptoms or erosive esophagitis onset; and some data also suggest an advantage in curing the infection when esophagitis is already present.

The present series have certain limitations: 1) the sample size, though the biggest in the relevant literature, was rather small, given that even the introduction the 3-h postprandial esophageal pH monitoring is not always easily acceptable by the patients; 2) the missed patients with a persistent *H. pylori* infection may preclude assessing whether the observed pH-recording modifications are definitely due to the bacterial loss; and 3) only 1 biopsy specimen was used for histology. This is an inadequate sampling protocol for routine endoscopic practice; 5 biopsies (2 antrum, 1 angulus, 2 corpus) being advised by current guidelines for an accurate upper endoscopy. However, due to large number of patient recruitment to find our selected *H. pylori* positive GERD patients, we were obliged to take only 1 instead of 5 biopsies for many obvious reasons mainly including the time burden of histological evaluation.

In conclusion, this study shows that *H. pylori* eradication may positively influence GERD symptoms. However,

Summary Box**What is already known:**

- The most common test used to confirm gastroesophageal reflux disease (GERD) is ambulatory 24-h esophageal pH monitoring, though characterized by a low tolerability
- Intra-24-h esophageal pH recording data rather fail to confirm increased acid reflux following *Helicobacter pylori* (*H. pylori*) eradication

What the new findings are:

- By using the 3-h postprandial esophageal pH monitoring as a more flexible method, this study showed, for the first time, that *H. pylori* eradication may positively influence GERD symptoms

large-scale controlled relative studies are warranted to evaluate these findings in depth.

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