Persistent Acid and Bile Reflux in Asymptomatic Patients With Barrett Esophagus Receiving Proton Pump Inhibitor Therapy

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Hypothesis: Symptom control does not reflect elimination of abnormal acid reflux or abnormal bile reflux in patients with long-segment Barrett esophagus receiving proton pump inhibitors (PPIs).

Design: Prospective survey.

Setting: University hospital.

Patients: Thirty-two patients with long-segment Barrett esophagus who were asymptomatic with PPIs.

Main Outcome Measures: Twenty-four–hour ambulatory pH and bile reflux monitoring while continuing PPIs.

Results: Abnormal acid reflux (pH < 4 for 11.9% [interquartile range, 6.8%-19.6%) of 24 hours] persisted in 15 patients (47%) who could not be distinguished from those with normal acid reflux (pH < 4 for <4.5% of 24 hours) by any endoscopic, manometric, or therapeutic characteristic. Abnormal bile reflux (absorbance > 0.14 for 8.7% [interquartile range, 3.9%-8.7%] of 24 hours) was detected in 11 (48%) of 23 patients, such that both normal bile reflux (absorbance > 0.14 for <1.8% of 24 hours) and normal acid reflux were observed in only 8 patients (35%). There was no association between abnormal acid reflux and abnormal bile reflux.

Conclusions: Despite symptom control with PPIs, both acid reflux and bile reflux were controlled in only one third of patients. Posttherapeutic monitoring of acid and bile reflux is recommended in future clinical trials of PPI treatment vs laparoscopic antireflux surgery.

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Barrett esophagus is associated with chronic gastroesophageal reflux disease (GERD) and predisposes to esophageal adenocarcinoma. There is a resurgence of interest in examining the role of antireflux therapy for patients with Barrett esophagus. The recently published Swedish data for patients with GERD conclude that the risk of developing esophageal adenocarcinoma remains increased after antireflux surgery. This study adds to the body of conflicting evidence for the role of proton pump inhibitor (PPI) therapy or antireflux surgery to predictably halt the progression of Barrett esophagus to dysplasia and carcinoma.

Acid suppression with PPIs is highly effective in controlling GERD symptoms, healing erosive esophagitis, and preventing strictures in patients with Barrett esophagus. Currently, the National Institute for Clinical Excellence in the United Kingdom and the American College of Gastroenterology both recommend symptom control and endoscopic healing of esophagitis as end points for titrating the dose of PPIs for Barrett esophagus. Despite symptom control with PPIs, abnormal acid reflux has been reported to persist in 38% of patients with Barrett esophagus. Cellular proliferation is significantly reduced and cellular differentiation is increased compared with the pretherapy measurements in biopsy specimens from patients with normalized acid reflux; however, this is not found in those with persisting abnormal acid reflux. Furthermore, there is serious concern that such incomplete elimination of acid reflux might actually facilitate the noxious potential of bile salts in the duodenogastroesophageal refluxate. Proton pump inhibitors decrease but do not completely eliminate bile reflux in patients with GERD.

Critical examination of the reflux status of patients with Barrett esophagus treated with PPIs, according to the current guidelines, is a necessary prelude to the design of any future clinical trial that compares such treatment with laparoscopic antireflux surgery. Consequently, we aimed, first, to examine the persistence of abnormal acid reflux in a cohort of patients with long-segment Barrett esophagus (LSBE) who were asymptomatic while receiving PPIs. Second, the prevalence of abnormal bile reflux...
flux in such asymptomatic patients and its association with persistent abnormal acid reflux were determined.

METHODS

PATIENTS

Consecutive patients with Barrett esophagus who were attending the outpatient clinic of an upper gastrointestinal surgical unit at a university hospital were prospectively identified from September 1999 to January 2001. Patients were included in this study if they had a circumferential segment of esophagus lined with specialized intestinal epithelium for 3 cm or longer (LSBE), did not have dysplasia, and were asymptomatic with PPI therapy. In general, the policy was to initially administer a high dose of PPIs to heal any concomitant esophagitis, to control symptoms, and to subsequently taper the treatment to the lowest dose that maintained symptom control. At the time of study recruitment, all patients had been taking PPIs for varying durations. Patients were excluded if they continued to experience symptoms of GERD while receiving PPIs, had previously undergone a fundoplication operation or any other esophageal, gastric, or biliary operations, were allergic to PPIs, had an uncontrolled clinically significant comorbidity, had alcohol or drug dependency, or were unable to provide informed consent or complete esophageal function tests.

ENDOSCOPY AND HISTOLOGIC ANALYSIS

Esophagogastroduodenoscopy was performed to assess the length of LSBE and the presence of hiatus hernia, esophagitis, strictures, or ulcers, and 4-quadrant biopsy specimens were obtained at 2-cm intervals. The identification of specialized intestinal epithelium that contained Alcian blue–stained goblet cells by a gastrointestinal pathologist (C.S.V.) was essential for the diagnosis of Barrett esophagus.

ESOPHAGEAL MOTILITY

The pattern of motility throughout the esophagus and its sphincters was assessed using the standard station pull-through technique. An 8-channel, fluid-perfused polyvinyl catheter with a sensor configuration of 4 channels orientated radially around the probe tip, and the remaining 4 channels at 5-cm intervals proximally, were used to study esophageal body motility. Lower esophageal sphincter profiling was performed separately using a catheter with all 8 channels radially orientated around the probe tip, and the remaining 4 channels at 5-cm intervals. The identification of specialized intestinal epithelium for 3 cm or longer (LSBE) did not have dysplasia, and were asymptomatic with PPI therapy. In general, the policy was to initially administer a high dose of PPIs to heal any concomitant esophagitis, to control symptoms, and to subsequently taper the treatment to the lowest dose that maintained symptom control. At the time of study recruitment, all patients had been taking PPIs for varying durations. Patients were excluded if they continued to experience symptoms of GERD while receiving PPIs, had previously undergone a fundoplication operation or any other esophageal, gastric, or biliary operations, were allergic to PPIs, had an uncontrolled clinically significant comorbidity, had alcohol or drug dependency, or were unable to provide informed consent or complete esophageal function tests.

AMBULATORY INTRAESOPHAGEAL pH MONITORING

Twenty-four–hour ambulatory intraesophageal pH monitoring was conducted using a portable digital recorder at a sampling frequency of 0.6 Hz, connected to a mono-crystal antimony pH microelectrode. The pH electrode was passed transnasally and positioned 3 cm above the proximal margin of the manometrically identified lower esophageal high-pressure zone. All patients continued their PPI therapy and were confirmed to be symptom free throughout the monitoring. Recorded data were analyzed for frequency and duration of pH falling below a critical threshold of 4, and persistent abnormal acid reflux was defined as a distal esophageal pH of less than 4 for longer than 4.5% of the total monitoring period. During upright and supine positions, an esophageal pH of less than 4 for more than 4.5% and 3.5% of the respective monitoring periods was considered abnormal. Recorded data were also analyzed using the methods of Johnson and DeMeester, with a composite score of greater than 14.7 considered as abnormal.

BILIRUBIN SPECTROMETRY

Bile reflux was assessed during 24 hours using an ambulatory bilirubin spectrophotometer (Bilitec 2000; Synectics Medical AB, Roden, the Netherlands). The fiberoptic probe was positioned as described for the pH probe. For the first 10 patients, bile reflux monitoring was conducted after stopping PPI therapy for 2 weeks and was subsequently repeated 2 weeks after patients had recommenced their original PPI therapy. For the remaining patients, bile reflux studies were conducted while continuing PPIs. To avoid erroneous detection of bile reflux, dietary intake during the monitoring period was restricted to milk, water, or a liquid nutrient, with an absorption peak that was safely distant from that of bilirubin. Standard bile reflux monitoring software was used for data analysis. Abnormal bile reflux was identified if the esophagus was exposed to absorbance greater than 0.14 for longer than 1.8% of the total monitoring period. Abnormal bile reflux in the upright position was defined as absorbance greater than 0.14 for longer than 2.2% of the upright monitoring period, and in the supine position as absorbance greater than 0.14 for longer than 1.6% of the supine monitoring period.

STATISTICAL ANALYSES

The biostatistics software package SPSS 9.0 (SPSS Inc, Chicago, Ill) was used. All data were nonparametric, and summary statistics are expressed as median (interquartile range). The Mann-Whitney U test or chi-square test was used to compare variables between the groups with persistent abnormal acid reflux and normal acid reflux. The Wilcoxon matched pairs test was used to compare acid reflux before and after therapeutic modification. P<.05 was considered statistically significant.

RESULTS

CLINICAL AND ENDOSCOPIC CHARACTERISTICS

There were 32 white patients comprising 28 men and 4 women aged 62 years (53-69 years). All patients were free of GERD symptoms and had been taking omeprazole (n=18; 20 mg [20-40 mg]), lansoprazole (n=12; 30 mg [30-60 mg]), or rabeprazole (n=2; 20 mg) for 30 months (12-48 months). Prior to commencing PPIs, patients recalled experiencing heartburn (90%), regurgitation (67%), dysphagia (20%), and respiratory symptoms (26%) for 8 years (5-13 years). On endoscopy, the length of LSBE was 6 cm (4-10 cm), and hiatus hernia (n=16) and esophagitis (n=2) were noted. No esophageal strictures or ulcers were identified. No differences in endoscopic or manometric characteristics between patients with persistent abnormal acid reflux and those with acid reflux within the physiologic range were detected (Table).

AMBULATORY INTRAESOPHAGEAL pH MONITORING

Persistent abnormal acid reflux (pH <4 for >4.5% of total monitoring period) was noted in 15 patients (47%).

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While in the supine position, abnormal acid reflux (pH < 4 for > 3.5% of supine period) was present in 14 of these 15 patients as well as in 2 additional patients who had cumulative acid exposure within the normal range for the entire monitoring period. While in the upright period, 6 of the 15 patients demonstrated abnormal acid reflux (pH < 4 for > 8.4% of upright monitoring period) (Figure 1). Composite Johnson-DeMeester scores were abnormal (43.6 [26.9-71.8]) for each of these 15 patients and for no others.

**MANAGEMENT OF PATIENTS WITH PERSISTENT ABNORMAL ACID REFLUX**

Two of the 15 patients with abnormal acid reflux declined therapeutic modification. For the remaining 13 patients, the original dose of PPI was doubled and administered in a split manner in the morning and at bedtime, as recommended for patients with bipositional reflux.19 Additionally, 300 mg of ranitidine at bedtime was administered to 12 patients who had supine acid reflux, as recommended for patients with persistent supine reflux.19 Repeated ambulatory pH monitoring was precluded by cardiac disease in 1 patient, declined by another, and 1 patient failed to follow-up. Normalization of acid reflux (pH < 4 for > 4.5% of total monitoring period) was confirmed in 7 of the remaining 10 patients. Abnormal acid reflux persisted in 3 patients (Figure 2); further therapeutic modification and pH monitoring were not conducted.

**BILIRUBIN SPECTROMETRY**

**Effect of PPI Therapy on Bile Reflux**

After discontinuation of PPIs, abnormal bile reflux was noted in 8 of 10 patients, with absorbance greater than 0.14 for 11.8% (4.5%-33.3%) of the 24-hour monitoring period. Following recommencement of PPI treatment, abnormal bile reflux was still present in 5 patients, but the duration was significantly reduced to 3.9% (2.3%-6.1%) (P = .04).

**Association Between Acid and Bile Reflux**

Twenty-three of the 32 patients consented to bile reflux monitoring while they were symptom-free with PPI therapy. Abnormal bile reflux (absorbance > 0.14 for 8.7% [3.9%-14.8%] of the total monitoring period) was noted in 11 (48%) of 23 patients (Figure 3). During the supine monitoring period, 9 of these 11 patients had abnormal bile reflux (15.8% [3.8%-26.7%] of the supine monitoring period). In the upright monitoring period, 10 of the 11 patients had abnormal bile reflux (6.2% [5.3%-8.7%] of the upright period). Eight patients had abnormal bile reflux during both the upright and the supine positions, 2 patients had abnormal reflux in only the supine position, and 1 patient had normal reflux in only the supine position. Five (45%) of 11 patients with abnormal bile reflux also had persistent abnormal acid reflux. There was no correlation between the magnitude of acid and bile reflux for the total monitoring period (P = .9), the supine monitoring period (P = .8), or the upright monitoring period (P = .6). Both acid reflux and bile reflux were controlled within normal limits in 8 (35%) of 23 patients.

**COMMENT**

Increased esophageal acid exposure is prevalent in almost 100% of patients with Barrett esophagus who do not receive antireflux therapy.1 In the present study, abnormal acid reflux persisted in 47% of patients with LSBE who were asymptomatic with PPI therapy. Such failure...
of PPIs to ensure normalization of acid reflux has been reported variably for 17%,20 40%,21 and 80%22 of patients with Barrett esophagus. Even when PPIs are administered at high doses, acid reflux persists in 16% of patients with Barrett esophagus who are taking 40 mg of omeprazole twice daily23 and in 38% of patients taking 60 mg of lansoprazole once daily.24 Furthermore, it has been argued that “normal” acid exposure while taking PPIs should be defined as that observed in healthy controls receiving PPIs (pH < 4 for <0.9% of monitoring period) and not that in controls who are not receiving acid suppression therapy; application of this definition would increase the proportion of patients identified as having persistent abnormal acid reflux.25

There are several possible explanations for the persistence of acid reflux and the absence of symptoms in patients with LSBE. First, specialized intestinal epithelium is less sensitive to noxious stimuli than squamous epithelium,26 and symptoms are inaccurate in estimating the severity of acid reflux in patients with LSBE.27 Second, some patients are refractory to PPIs because of decreased bioavailability, rapid metabolism by the cytochrome P450 system, or some intrinsic abnormality of the proton pump itself.28 Third, nocturnal gastric acid breakthrough (intragastric pH < 4 for >1 hour during the overnight period) is observed in 80% of patients with LSBE treated with PPI twice daily and is associated with abnormal nocturnal GER in half of such patients.29 Finally, defective esophageal motility, which is characteristic of LSBE,27 increases the risk of reflux persisting during PPI therapy.30

Asymptomatic patients with continuing abnormal acid reflux were indistinguishable from those with normal acid reflux parameters on the basis of clinical, endoscopic, and manometric characteristics. Persistent abnormal acid reflux was not more prevalent in older patients in this series, although age-related reduction in chemosensitivity to GER has been reported.31 Similarly, there was no association between the persistence of acid reflux and the length of the columnar-lined segment, although there is a positive correlation between length and severity of untreated GER.32 As expected with LSBE,27 all patients had a mechanically defective lower esophageal sphincter, but this was not significantly more deficient in those with continuing abnormal acid reflux.

With serial pH monitoring and repeated treatment modification, Srinivasan et al33 reported optimal acid control in all patients with Barrett esophagus. In the present study, acid reflux was confirmed to be normalized following modification of antireflux therapy in only 7 of 15 patients with persistent abnormal acid reflux. Abnormal acid reflux persisted in 3 patients despite 1 cycle of therapeutic modification. Treatment modification and/or reflux-status verification could not be conducted for the remaining 5 patients. Thus, reflux control (pH < 4 for <4.5% of 24h) with PPI therapy was successfully achieved in only 75% (24 of 32) of patients in the present study.33

Bile reflux is a prominent feature of LSBE. Without antireflux therapy, abnormal bile reflux is present in up to 80% of patients with LSBE,34 and median duration of esophageal exposure to bile varies from 13%34 to 38%35 of the monitoring period. Proton pump inhibitors significantly decrease the duration of bile reflux in GERD patients but do not predictably reduce bile reflux to within the normal range.9,10 In the present study, abnormal bile reflux persisted in 48% of patients who were taking PPIs and were free of GERD symptoms. It is possible that increasing the dose of PPI therapy may have further re-

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**Figure 2.** Before and after line plot for cumulative esophageal exposure to a pH of less than 4 during 24 hours following revision of therapy in 10 patients with persistent acid reflux. Only 2 patients had persistent acid reflux following revision of therapy.

**Figure 3.** Scatterplot of bile reflux monitoring results in 23 patients who were asymptomatic with proton pump inhibitor therapy. Abnormal bile reflux (absorbance, >0.14 for 8.7 interquartile range, 3.9%-14.8% of 24 hours) was detected in 11 patients (48%). Normal results are in the box.
duced bile reflux, but this was not tested. Such disparity between symptom control and bile reflux is not surprising because symptoms of GERD appear to be caused predominantly by acid rather than bile reflux.39 Furthermore, there was no association between persistence of abnormal acid reflux and abnormal bile reflux, such that both acid reflux and bile reflux were within normal limits for only one third of patients.

In conclusion, despite symptom control with PPI therapy, abnormal acid reflux persisted in 15 (47%) of 32 patients with Barrett esophagus. Abnormal bile reflux persisted in 11 (48%) of 23 patients who underwent bilirubin spectrophotometry. Either abnormal acid reflux or abnormal bile reflux was prevalent in 13 (65%) of these 23 patients. Recent data support the notion that continuing acid and bile reflux facilitates neoplastic progression of Barrett esophagus.33 Furthermore, current evidence suggests that normalization of the esophageal milieu with respect to both acid and bile is the desired therapeutic goal.38 Retrospective series of laparoscopic antireflux surgery performed in a specialist unit have reported excellent symptom control and functional outcome as well as high rates of normalization of acid reflux.39 The present data suggest that posttherapeutic measurement of acid reflux and bile reflux should be incorporated into any future clinical trial of PPI therapy vs laparoscopic antireflux surgery.

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