Risk Factors for Esophagitis in Extreme Acid Hypersecretors With and Without Zollinger–Ellison Syndrome

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Background & Aims: Whereas severe duodenal ulcer is the hallmark of acid hypersecretion in Zollinger–Ellison syndrome (ZE) and similar states, the esophagus also is at high risk. We quantified the incidence of esophagitis and various risk factors that might contribute to it. *Methods:* Sixty-eight acid hypersecretors (basal acid output >15 mmol/h), 50 patients with ZE, and 18 patients without ZE with normal gastrin levels were studied by gastric analysis, serum gastrin levels, and endoscopy. In 44 of 68 patients, esophageal manometry was performed after the esophagus had healed. *Results:* Erosive esophagitis, grade 2 or worse, was found in 65%; an additional 15% had heartburn only, for a total reflux disease incidence of 80%. ZE accounted for 95% of severe esophagitis. Patients with and without esophagitis had the same high overnight fasting gastric residual volume and acidity, as well as basal and peak acid and pepsin outputs. However, patients with esophagitis had a lower median lower esophageal sphincter pressure (LESP) of 15.5 vs. 23 mm Hg in those without symptoms; the critical discriminator threshold was 16 mm Hg. Multivariate analysis further identified frequent vomiting and obesity as positive predictors of esophagitis, whereas *Helicobacter pylori* was a strong negative predictor (odds ratio, 0.16), possibly related to an elevated LESP in patients infected with *H. pylori*. *Conclusions:* Erosive esophagitis is very common in acid hypersecretors. Identified risk factors that could promote abnormal esophageal exposure to the high acid and pepsin levels in our population of hypersecretors were vomiting, LESP < 16 mm Hg, and obesity, whereas *H. pylori* appeared to protect the esophagus not by reduced acid, but through an elevated LESP.

Since the first descriptions 50 years ago,[1,2] Zollinger–Ellison syndrome (ZE) has been characterized by extreme acid hypersecretion with aggressive and often complicated duodenal ulceration and rapidly recurring peptic ulcer after gastric surgery. The early literature reported a low prevalence of esophageal disease. For example, in 1964, Ellison and Wilson[3] reported that an ulcer was located in the esophagus in only 2 of 166 patients with ZE with peptic ulcers, but they made no mention of esophagitis. One esophageal ulcer and 4 patients with esophagitis were reported in 67 patients with ZE from the Mayo Clinic[4,5]; in a report from Denmark,[6] 3 of 34 patients with ZE had an esophageal stricture, but again, no mention was made of esophagitis. At the same time, it was reported that lower esophageal sphincter (LES) pressure (LESP) was physiologically controlled by gastrin[7,8] and linearly related to serum gastrin concentration in patients with ZE,[9] offering an explanation for the apparent resistance of the esophagus to injury in ZE.

In time, both function and pathological characteristics were found to be very different. Esophagitis later was reported to be present in 5 of 15 patients with ZE, but in 2 of the 5 patients, esophagitis was preceded by prolonged nasogastric intubation.[10] Miller et al.[11] reported a 42% prevalence of esophagitis; almost half of these were grade 1, in 122 patients with ZE, whereas an additional 19% had heartburn only. That report did not include manometry or describe other possible contributing factors, such as *Helicobacter pylori*, hiatal hernia, or gastric secretion before treatment. In a later study from the same group,[12] in 92 patients with ZE that included 37 patients from the previous report, esophagitis also was present in 42%, and almost half were grade 1. LESP was normal (>10 mm Hg) in 90% of patients and not related to serum gastrin levels. Other studies had already shown that LESP was neither gastrin dependent[10,12–14] nor significantly different in patients with ZE and controls.[12]

The apparently low prevalence of esophagitis in patients with ZE in 1960–1980 can be explained readily because it represents underdiagnosis in the years before the introduction and wide use of flexible fiberoptic esophagoscopy.[15] Even until the late 1970s and early 1980s, fiberoptic flexible upper gastrointestinal (GI) endoscopy of the esophagus was neither widely nor always

Abbreviations used in this paper: BAO, basal acid output; BMI, body mass index; BPO, basal pepsin output; DU, duodenal ulcer; GI, gastrointestinal; LESP, lower esophageal sphincter pressure; PAO, peak acid output; PPI, proton pump inhibitor; PPO, peak pepsin output; ZE, Zollinger–Ellison syndrome.

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competently practiced, and esophagitis was largely overlooked. The esophagus is now examined with each upper GI endoscopy, leading to the routine recognition, classification, and improved understanding of esophagitis and its complications. At the same time, medical treatment became available for effective control of acid secretion in patients with ZE and other acid peptic disorders,[16–20] first with histamine$_2$ receptor antagonists after 1978,[16,17] and 10 years later, with the more potent proton pump inhibitor (PPI) omeprazole.

We report a very high prevalence of esophageal reflux disease associated with extreme acid hypersecretion in patients, most with and some without ZE syndrome. We examined a variety of possible risk factors that might contribute to esophagitis, including demographics, various clinical features, gastric acid and pepsin secretion, and *H. pylori* infection, as well as esophageal manometry.

Methods

Sixty-eight patients with basal acid hypersecretion were recruited and gave written consent for inclusion in this institutional review board–approved study using lansoprazole.[21] Acid hypersecretion is defined as basal acid output (BAO) > 15 mmol/h in patients without previous antrectomy or >5 mmol/h after antrectomy.[18,21–23] These included 2 causes. ZE (n = 50) was diagnosed by fasting and secretin-stimulated serum gastrin levels and/or histological identification of a gastrinoma.[21,22] Idiopathic acid hypersecretion[23,24] also was diagnosed in a subset (n = 18) of patients with duodenal ulcer (DU) who had not undergone surgery who had high rates of acid and pepsin secretion in the ZE range, but normal gastrin levels and no evidence of gastrinoma in long-term follow-up. Such hypersecretion is found predominantly in males with DU, with a prevalence of 10%–15%.[23,24]

Gastric analysis was performed using a fluoroscopically placed 14 F nasogastric tube, measuring overnight fasting residual volume followed by continuous aspiration in 10-minute sequential periods for 1 hour (basal period). Pentagastrin, 6 μg/kg, then was injected subcutaneously, and secretion was collected for another hour in 10-minute samples. In each sample, pH, acid by titration, and pepsin by hemoglobin digestion were measured, and output was calculated from the product of concentration and volume.[21,24,25] Peak outputs represent the sum of the highest 3 consecutive 10-minute periods after pentagastrin administration. Before gastric analysis, PPI treatment was suspended for at least 7 days and replaced by a high-dose histamine$_2$ receptor antagonist, which, in turn, was withheld for 36 hours.

All patients were interviewed, examined, and endoscoped by 1 physician (B.I.H.) at each visit throughout the study. Esophagitis was diagnosed at endoscopy only if, at least, erosions were present (≥grade 2) according to criteria listed in Table 1. Because of uncertainties inherent in minimal macroscopic evidence, we did not include grade 1 as a working diagnosis.

Table 1. Grading Scale for Classification of Esophagitis

Esophagitis Grading Scale	
Grade	Description
0	Normal-appearing mucosa by endoscopy
1	Mucosal edema, hyperemia, and/or friability of mucosa
2	One or more erosion(s)/ulceration(s) involving <10% of the distal 5 cm of the esophagus
3	Erosions/ulcerations involving 10%–50% of the distal 5 cm of the esophagus or an ulcer measuring 3–5 mm in diameter
4	Multiple erosions/ulcerations involving >50% of the distal 5 cm of the esophagus or a single large ulcer >5 mm in diameter

Hiatal hernia was diagnosed endoscopically, using both forward and retroflexed views. Barrett's metaplasia (≥3 cm) was documented photographically and confirmed by multiple biopsies showing columnar intestinal type epithelium. Evidence for so-called short-segment Barrett's was not systematically sought.

Esophageal manometry was performed after the original lesions had healed and patients were administered individually optimized doses of lansoprazole. Manometry was not part of the original protocol and was systematically undertaken only after the study was under way. Therefore, only 44 of the 68 hypersecretor patients (32 patients with ZE, 12 patients without ZE) were available for manometric study. Each study was performed after an overnight fast of at least 12 hours and at least 12 hours after the last dose in those administered twice-daily doses of lansoprazole and 24 hours after the last dose in those administered single daily doses. Compared with 24 patients who did not undergo manometric studies, the 44 patients studied were not different in age, age at onset of symptoms, duration of symptoms of ulcer or reflux, sex, race, smoking, family history of ulcer, prior treatment, ulcer or esophagitis prevalence, complications, basal or stimulated acid or pepsin output, fasting gastrin level, body mass index (BMI), or *H. pylori* (data not shown). All 68 patients were combined in the analysis with respect to the presence or absence of esophagitis.

A pressure profile of the LES was obtained by passing a solid-state omnidirectional probe (model no. P33-B4222-C05; Konigsberg Instruments Inc, Pasadena, CA) through the nose until all pressure ports were in the stomach. This established a gastric baseline pressure that served as a zero reference point for LESP. Gastric placement was confirmed by increased pressure excursions during inspiration and decreased pressure excursions during expiration. Using a strip chart recorder with a paper speed of 2.5 cm/s, an LESP station pull-through was then obtained by withdrawing the probe by 0.5-cm increments until both transducers entered the body of the esophagus. LESP was measured as the difference in millimeters of mercury from the end-expiratory resting basal gastric pressure to end-expiratory LESP in the immediate area of the respiratory inversion point during quiet respiration. We chose to measure

LESP from end-expiration to end-expiration because this respiratory reference point has been shown to most accurately measure intrinsic LESP from the smooth muscle sphincter.[26,27] LESP values from both transducers were averaged and served as the recorded value for that patient. (Other measurements included percentage of peristaltic and simultaneous contractions, percentage of nonconducted swallows, amplitude and duration 3 and 8 cm above the LES, and velocity [in centimeters per second]. There were no differences between those with and without esophagitis in these measurements.)

All tracings were interpreted blindly.

H. pylori

H. pylori was diagnosed by biopsy of the body and antrum, as well as by immunoglobulin G antibody tests,[22] and in all cases found, was present in both body and antrum; all patients had pangastritis. Only 5 of 18 patients without ZE with DU (28%) were *H. pylori* positive at entry, whereas 6 others had been successfully treated for *H. pylori* within 1 year before entry, but without clinical benefit because despite successful eradication, acid hypersecretion persisted and DUs recurred. Similar values for patients with ZE were 20 patients (40%) positive at entry and 5 patients pretreated. Including those treated before this study, the prevalence of *H. pylori* was similar: 61% in patients without ZE and 50% in patients with ZE. For purposes of analyzing risk factors, all patients who had been infected with *H. pylori*, even before starting the study, were considered positive with respect to esophageal disease before entry into the study because esophagitis predated the *H. pylori* treatment in each case.

Body Weight

In examining the role of obesity,[28] defined by BMI (BMI = kg/m^2 [weight/height]), we had to take into consideration that patients with severe esophagitis may have lost weight as a consequence, and by the time they presented for the study, may have had a lower BMI than when the reflux began. Because the earlier conditions were more relevant to the onset of esophagitis, we elected to use historic BMI data for various analyses relating to the influence of obesity.

Although 5 patients had gained from 10 to 50 lbs after the onset of symptoms, 26 patients had lost ≥20 lbs before entry (Table 2), including 18 of 44 patients with esophagitis. However, mean overall loss of BMI was the same in those with and without esophagitis (−1.7 vs. −1.8 units; Table 3).

Statistics

The appropriate univariate test, *t* test (paired and unpaired comparisons), Fisher exact, or Wilcoxon signed-rank test, and stepwise multivariate logistic regression were performed using SAS software (SAS Institute Inc, Cary, NC) to examine the relationship between esophagitis before treatment (dependent variable) and patient demographics and various measurements listed in Table 3 (independent variables). Means are expressed as ± SEM, and $P < 0.05$ is considered significant.

Table 2. Comparison of Pre-Entry History in Patients With Acid Hypersecretion With and Without ZE

	Non-ZE DU	ZE
No. of patients	18	50
Sex (M/F)	16:2	30:20[a]
Race (black/white)	1:17	20:30[b]
Age (*yr*)	44.1 ± 3.4	54.7 ± 1.8[b]
Gastrin (*pg/mL*)	75.9 ± 12.3	735.5 ± 119.5[c]
Erosive esophagitis	9 (50%)	35 (70%)
Grade 2	8	16
Grade 3 or 4	1	19[a]
Complications		
Barrett's	3	3
Stricture	0	10
Esophageal ulcer	0	6
Ulcer		
Duodenal[d]	17	39
Jejunal[d]	0	8
Bleed	12 (6)[e]	27 (17)
Perforation	2 (1)	7 (6)
Esophagitis + duodenal or jejunal ulcer	8	32
Symptoms		
Heartburn		
With esophagitis	6 (33%)	26 (52%)
No esophagitis	6 (33%)	4 (8%)[a]
Vomiting	5 (28%)	26 (52%)
Pain	17 (94%)	48 (96%)
Diarrhea	6 (33%)	25 (50%)
Weight loss (*lb*)		
20–40	1 (6%)	14 (28%)
>40	2 (11%)	9 (18%)
H. pylori		
Eradicated before entry	6	5
Positive at entry	5	20
LESP (*mm Hg*)	20.4 ± 1.4	18.8 ± 1.8
Gastric secretion		
BAO (*mmol/h*)	20.9 ± 1.4	28.2 ± 2.9[a]
PAO (*mmol/h*)	60.4 ± 3.5	49.5 ± 4.0[a]
BPO (PU, *1000/h*)	521.7 ± 81.4	413.1 ± 46.1
PPO (PU, *1000/h*)	1020.4 ± 132.1	759.7 ± 79.7

ZE, Zollinger–Ellison; DU, duodenal ulcer; LESP, lower esophageal sphincter pressure; BAO, basal acid output; PAO, peak acid output; BPO, basal pepsin output; PPO, peak pepsin output; PU, peptic units.
[a]$P < 0.05$ compared with patients without ZE.
[b]$P < 0.01$ compared with patients without ZE.
[c]$P < 0.001$ compared with patients without ZE.
[d]Postantrectomy; B-II.
[e]More than 1 episode.

Results

The 68 patients comprised 2 groups: 50 patients with ZE, 41 of whom had no prior gastric resection (intact ZE), and 9 patients who had prior antrectomy. There were 18 patients without ZE, all without antrectomy (Table 2). Patients without ZE were younger ($P < 0.01$) and predominantly white (white/black, 17:1) and male (men/women, 16:2; $P < 0.04$). Serum gastrin level was normal and 10-fold lower than the mean level in patients with ZE (Table 2).

Table 3. Characteristics of Patients With and Without Esophagitis Before Lansoprazole Treatment

	Esophagitis	
	Yes	No
No. of patients	44	24
ZE/non-ZE	35:9	15:9
Age (*yr*)	52.8 ± 2.1	50.3 ± 2.8
Length of history (*yr*)	12.8 ± 1.3	10.5 ± 2.3
Sex (M/F)	32:12	14:10
Race (black/white)	15:29	6:18
H. pylori (positive/negative)	18:26[a]	18:6
LESP (n = 44) (*mm Hg*)	17.8 ± 2.0[b]	21.5 ± 1.6
LESP (*median*)	15.5	20.0
LESP (*≤16/>16 mm Hg*)	16:11[a]	2:15
Hiatal hernia (positive/negative)	26:18	11:13
BMI (before symptoms) (kg/m^2)	28.0 ± 0.7	25.8 ± 1.3
BMI (at entry) (kg/m^2)	26.3 ± 0.8	24.0 ± 1.0
Smoking (yes/no)	21:23	12:12
Vomit (yes/no)	23:21	7:17
Gastric secretion		
Fasting residue:		
Volume (*mL*)	166 ± 25	159 ± 20
pH (*median*)	1.4	1.3
$[H^+]$ (*mEq/L*)	79.1 ± 6.1	81.1 ± 6.7
BAO (*mmol/h*)	28.3 ± 3.0	22.6 ± 2.5
PAO (*mmol/h*)	54.3 ± 4.4	50.2 ± 4.0
BPO (PU, *1000/h*)	443 ± 59	447 ± 53
PPO (PU, *1000/h*)	799 ± 86	887 ± 118

BMI, body mass index; ZE, Zollinger–Ellison; LESP, lower esophageal sphincter pressure; BAO, basal acid output; PAO, peak acid output; BPO, basal pepsin output; PPO, peak pepsin output.
[a]$P < 0.01$ compared with no esophagitis.
[b]$P < 0.05$ compared with no esophagitis.

Esophageal Disease

Forty-four (65%) of the 68 study patients had erosive esophagitis of grade 2 or worse, and 40 of the 44 patients also had a documented peptic ulcer then or previously in the duodenum or, in postantrectomy patients, originally in the duodenum and postoperatively in the jejunum (Table 2). Another 10 patients (15%) had frequent heartburn without observed esophagitis, whereas some of the patients with esophagitis did not report heartburn.

Pre-entry status is reported separately for the 18 control patients with non-ZE hypersecretion and the 50 patients with ZE (Table 2). Esophagitis was present in 9 patients without ZE (50%) compared with 35 patients with ZE (70%; P = not significant). Of 35 patients with ZE with esophagitis, 19 patients (54%) had grade 3 or 4 lesions compared with only 1 of 9 patients without ZE (11%) with esophagitis ($P < 0.02$). All 10 strictures and 6 esophageal ulcers and 95% of grade 3 or 4 lesions were found only in the ZE group, whereas 3 patients with ZE and 3 patients without ZE had Barrett's (Table 2). With the exception of degree of severity of esophagitis in patients with ZE, the prevalence of mucosal lesions, complications, and symptoms was statistically similar between the ZE and non-ZE subgroups (Table 2).

Ulcer

Among 68 patients, 64 patients (94%) had or previously had DU, for which 9 patients underwent a partial gastrectomy; despite that, all 9 patients had rapid relapse of peptic ulcer. Of 64 patients with ulcer, 39 patients (61%) had bled, 23 patients more than once, and 9 patients (13%) had experienced perforated ulcers, 7 patients more than once. Ulcer and ulcer complications were similar in the ZE and non-ZE groups: DU, 94%; bleeding, 54% vs. 67%; and perforation, 14% vs. 11% (Table 2).

Symptoms

Pain was almost universal in the population under study. Half the patients with ZE reported vomiting and diarrhea compared with 28% and 33% of patients without ZE, respectively (P = not significant). Patients with ZE also were more likely to have lost weight than those without ZE, although the difference was not statistically significant.

Gastric Secretion

Although all were hypersecretors, BAO was lower in patients without ZE, but their peak acid output was greater. Basal and peak pepsin outputs were numerically higher in patients without ZE, but these differences were not significant. Overall, gastric secretion with high acid and pepsin levels was balanced between the 2 hypersecretor classes.

The 2 groups were similar with respect to symptoms and manifestations of esophagitis or ulcer, acid and pepsin secretion, LESP, and *H. pylori* (Table 2) and were combined for additional analysis with respect to esophagitis.

Risk Factors for Esophagitis Before Treatment

Of 68 patients, 44 patients had esophagitis, and 24 patients did not (Table 3). The main differences found were: (1) the prevalence of *H. pylori* was lower in patients with esophagitis (41% vs. 75%; $P < 0.01$), and (2) LESP < 16 mm Hg was more common (59% vs. 12%; $P < 0.01$) in those with a history of esophagitis compared with those who never had esophagitis (Table 3).

Other than the exceptions cited, there were no differences between patients with and without a history of esophagitis (in a variety of measures [Table 3], including demographics, smoking history, volume or composition

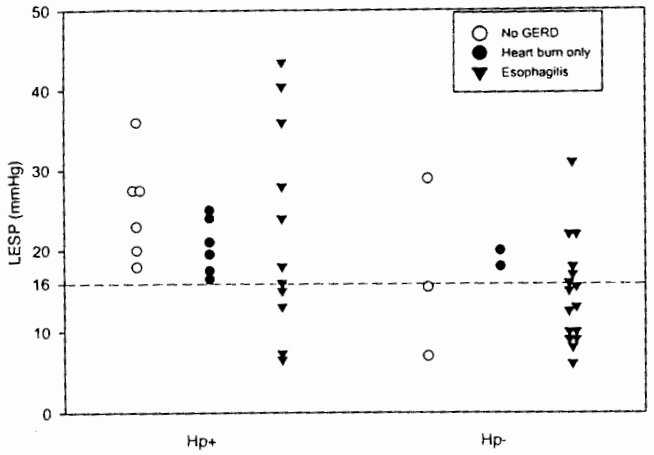

Figure 1. Lower esophageal sphincter pressure (LESP) distribution according to *H. pylori* (Hp) status (+ or −) in 3 groups: no reflux, heartburn only, and esophagitis (all grades). The critical LESP of 16 mm Hg is indicated by the dotted line.

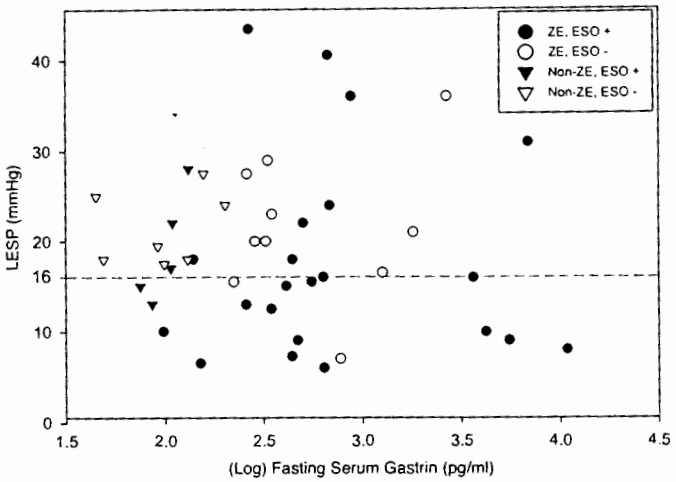

Figure 2. Relation of lower esophageal sphincter pressure (LESP) to (log) fasting serum gastrin level. Diagnosis (Zollinger–Ellison syndrome [ZE], non-ZE, and esophagitis [ESO]; present [+] and absent [−]). The correlation between LESP and gastrin was not significant ($r^2 = 0.00085$). The critical LESP of 16 mm Hg is indicated by the dotted line.

of overnight fasting gastric residue, and basal or stimulated acid or pepsin outputs, which, in turn, were several-fold greater than in healthy controls or patients with DU).[25]

Manometry

Mean LESP was significantly lower in those with a history of esophagitis (Table 3). Median LESP in patients with esophagitis was 15.5 mm Hg compared with 23 mm Hg in those without symptoms (Figure 1). Moreover, actual LESP was highly predictive of esophagitis. The best discriminating LESP value was based on the median value of 16 mm Hg and was validated by both univariate and multivariate analyses. By multivariate analysis for the outcome of reflux esophagitis at various levels of LESP from 14–20 mm Hg, 16 mm Hg gave the most significant discriminant value ($P = 0.0172$). By sequential univariate analysis, the same conclusion was reached regarding 16 mm Hg ($P = 0.002$). With LESP < 16 mm Hg, as determined previously, the relative risk for esophagitis was 10.9 (95% confidence interval, 2.07–57; $P < 0.01$), with 16 of 18 patients (89%) having esophagitis compared with only 11 of 26 patients (42%) with an LESP > 16 mm Hg ($P < 0.01$; Figure 2). None of the other manometric measurements (described in Methods) was different between those with and without esophagitis (data not shown).

LESP was not related to fasting serum gastrin measured on the same day as manometry ($r = 0.03$; Figure 2) or BAO measured before lansoprazole treatment ($r = 0.08$; Figure 3). There was no obvious combination of LESP and BAO that was more predictive of esophagitis at entry than LESP alone (Figure 3). None of 8 patients who had heartburn without esophagitis and only 2 of 9 patients without gastroesophageal reflux disease had an LESP < 16 mm Hg (Figure 1). Also shown in Figures 1 and 3, *H. pylori*–positive patients had a higher LESP and were more likely to be free of esophagitis.

Multivariate Analysis for Risk Factors

Predictor variables for the diagnosis of esophagitis that were significant at a 2-tail nominal $P < 0.25$ were entered into a stepwise multivariate logistic analysis comparing patients with and without esophagitis. As listed in Table 4, for the entire population,

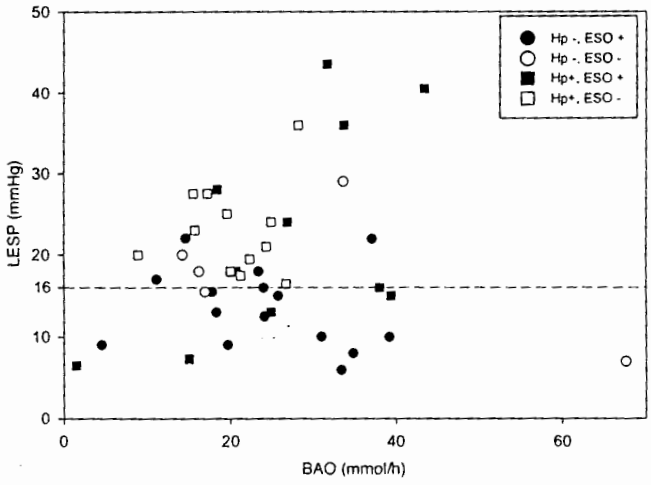

Figure 3. Lower esophageal sphincter pressure (LESP) related to basal acid output (BAO). Coordinates identified by *H. pylori* status (+ or −) and presence of esophagitis (ESO; + or −). Correlation between LESP and BAO was not significant ($r^2 = 0.007$). The critical LESP level of 16 mm Hg is indicated by the dotted line.

Table 4. All-Patients Multivariate Analysis for Risk Factors (independent variables) for the Outcome of Esophagitis (dependent variable)

Variable	Odds ratio	95% Wald confidence limits		P
Body mass index	1.23	1.07	1.41	0.004
H. pylori positive	0.16	0.04	0.61	0.007
Vomiting	5.22	1.23	22.13	0.025
Zollinger–Ellison	3.90	0.93	16.31	0.063
Hiatal hernia	3.32	0.89	12.47	0.075
Length of history	1.06	0.99	1.14	0.089

NOTE. Variables with $P > 0.25$: sex, race, smoking, age, basal acid output, and fasting residue gastric contents: volume and $[H^+]$. N = 68.

BMI ($P < 0.01$), vomiting ($P < 0.03$), and, marginally, the diagnosis of ZE ($P = 0.06$) were predictors for the diagnosis of esophagitis before treatment, whereas *H. pylori* infection was a significant negative predictor (odds ratio, 0.16; 95% confidence interval, 0.04–0.061; $P < 0.01$). Demographics, the diagnosis of ZE, hiatal hernia and duration of symptoms, BAO, volume and acidity of fasting gastric contents, and smoking were not statistically significant predictor variables. As noted, LESP < 16 mm Hg conferred a 10.9-fold relative risk for esophagitis (Figures 1–3).

Possible risk factors associated with *H. pylori*. The significant apparent protective effect of *H. pylori* on esophagitis requires an examination for possible mechanisms whereby such an effect could be mediated. Only 50% of 36 *H. pylori*–positive patients had esophagitis compared with 81% of *H. pylori*–negative patients ($\chi^2 = 7.2$; $P < 0.01$). *H. pylori*–positive patients with and without esophagitis had a 50% higher LESP (22.8 vs. 15.2 mm Hg; $P < 0.01$) than corresponding patients in the *H. pylori*–negative group. However, within the respective positive and negative subgroups, those with and without esophagitis had the same LESP (Table 5), but within the *H. pylori* group, none of the patients with esophagitis had an LESP < 16 mm Hg. Moreover, within each group (Table 5), other putative risk factors (all measures of gastric acid and pepsin secretion, hiatal hernia, BMI, or vomiting) were not significantly different between those with and without esophagitis (Table 5). The majority of patients with no reflux symptoms or those with heartburn only were in the *H. pylori*–positive group, and all those patients had an LESP >16 mm Hg (Figure 1).

Risk Factors Associated With Obesity

Patients were divided into tertiles: BMI < 24 kg/m^2, BMI of 24–28; kg/m^2, and BMI >28 kg/m^2. The

Table 5. *H. pylori* Status and Esophagitis Before Treatment

	H. pylori Positive		*H. pylori* Negative	
	Esophagitis	No esophagitis	Esophagitis	No esophagitis
N[a]	18	18	26	6
Age (*yr*)	52.1 ± 3.7	48.4 ± 3.5	53.2 ± 2.6	55.9 ± 3.5
ZE/Non-ZE	14:4	11:7	21:5	4:2
Sex (M/F)	11:7	11:7	21:5	3:3
Race (black/white)	7:11	5:13	8:18	1:5
Gastrin				
ZE (*pg/mL*)	723 ± 167	446 ± 131	980 ± 266	564 ± 133
Non-ZE (*pg/mL*)	105.8 ± 53.2	75.6 ± 9.7	66.8 ± 8.9	40.0 ± 2.0
LESP[a] (*mm Hg*) (n = 44)	22.5 ± 3.9	23.0 ± 1.6	14.6 ± 1.6	17.9 ± 3.6
LESP (<16/>16 mmHg)	5:6	0:12[b]	11:5	2:3
Hiatal hernia (positive/negative)	10:8	9:9	16:10	2:4
Body Mass Index (BMI) (*kg/m^2*)	27.3 ± 1.5	24.3 ± 1.2	25.6 ± 0.9	23.1 ± 1.7
Smoking (yes/no)	9:9	10:8	12:14	2:4
Vomiting (yes/no)	9:9	6:12	14:12	1:5
Gastric Secretion				
Fasting Residue				
Volume (*mL*)	167 ± 30	141 ± 20	165 ± 37	215 ± 52
pH (median)	1.3	1.3	1.4	1.25
$[H^+]$ (*mmol/L*)	87.6 ± 7.8	75.3 ± 8.4	73.3 ± 8.8	97.6 ± 6.6[b]
BAO (*mmol/h*)	24.7 ± 3.0	20.9 ± 2.0	31.3 ± 4.8	29.0 ± 8.3
PAO (*mmol/h*)	54.1 ± 6.6	49.8 ± 3.9	54.4 ± 6.1	53.5 ± 12.5
BPO (PU, 1000/h)	361 ± 39	468 ± 67	487 ± 87	402 ± 94
PPO (PU, 1000/h)	717 ± 101	922 ± 152	852 ± 127	681 ± 157

[a]$P < 0.01$, *H. pylori*–positive patients compared with *H. pylori*–negative patients.
[b]$P < 0.05$, compared with esophagitis patients.

Table 6. Esophagitis and Identified Possible Intermediate Factors at Various Body Mass Index Levels

	BMI (kg/m^2)		
	<24	24–28.5	>28.5
N	23	23	22
Mean BMI (kg/m^2)	22.2 ± 0.3	26.2 ± 0.3	33.7 ± 0.8
Esophagitis[a] (yes/no)	10:13[b]	17:6	17:5
Hiatal hernia (positive/negative)	12:11	15:8	10:12
Vomiting (yes/no)	11:12	10:13	9:13
LESP (*mm Hg*)	18.6 ± 2.2	20.3 ± 2.4	18.8 ± 2.7
LESP (*<16/>16 mm Hg*)	6:8	5:10	7:8
BAO (*mmol/h*)	27.4 ± 4.5	22.6 ± 2.5	29.7 ± 4.1
H. pylori (positive/negative)	12:11	11:12	13:9

[a] $P < 0.01$, BMI < 24 kg/m^2 compared with BMI ≥ 24 kg/m^2.
[b] $P < 0.05$, BMI < 24 kg/m^2 compared with BMI ≥ 24–28.5 or >28.5 kg/m^2.
BMI, body mass index; LESP, lower esophageal sphincter pressure; BAO, basal acid output.

proportion of those with esophagitis was significantly lower in patients with a BMI < 24 kg/m^2. There were no differences in hiatal hernia, vomiting, LESP, or BAO. Thus, no intermediate or enabling mechanism for the effect of obesity on esophagitis could be identified from our data (Table 6).

Complicated Esophagitis

Fourteen patients had complicated esophagitis: 6 patients with discrete esophageal ulcers, 5 of those with strictures, and 2 patients with Barrett's; 5 other patients had stricture (total n = 10), 1 patient with Barrett's and another 3 patients (total n = 6) with Barrett's esophagus at least 3 cm in length without other complications. There were only a few significant differences between those with simple and complicated esophagitis, mainly that the esophageal ulcer/stricture group was confined to the ZE population (Table 2). Neither hiatal hernia nor *H. pylori* was different. Because 2 of the strictures were midesophageal, the role of pills in delaying healing or causing relapse could not be ruled out, either in the initial presentation or later. Patients with complications had the same gastric secretion and gastrin values as those with uncomplicated esophagitis (data not shown). Patients with uncomplicated esophagitis were more obese than those with no esophagitis (BMI, 27.7 ± 0.9 vs. 24.0 ± 1.0 kg/m^2; $P = 0.004$) or those with stricture (BMI, 21.1 ± 1.0 kg/m^2; $P < 0.001$), who had lost weight after onset of symptoms.

Barrett's esophagus. Six male patients, 3 patients without ZE and 3 patients with ZE, had long-segment >3-cm lesions at entry. Three of the 6 patients were *H. pylori* positive in the fundic mucosa of the stomach, but not the metaplastic mucosa. There were no differences between those with Barrett's and other groups without or with esophagitis in any of the multiple parameters examined (data not shown).

Discussion

Before adequate diagnostic procedures were generally or widely available, esophagitis was reported to rarely affect patients with ZE.[3–6] However, in the early 1980s, when flexible upper-GI endoscopy began to be more widely used and included the esophagus, it became apparent that esophagitis is a common lesion in patients with ZE.[11] The 70% prevalence of erosive esophagitis in our patients with ZE was greater than the 42% esophagitis rate reported by Miller et al.[11] and later by Strader et al.[12] We found not only a greater prevalence of esophageal disease, but also that patients with ZE had more severe esophagitis than previously reported.[3–6,10,11] For example, in the 2 large overlapping series describing esophagitis in patients with ZE,[11,12] only 24% of all patients with ZE had grade 2 or worse esophagitis. Conversely, in our study, 70% of patients with ZE had grade 2 or worse erosive esophagitis, and more than half of those had grade 3 or 4 esophagitis; furthermore, 40% of those, in turn, had complicated lesions (stricture, ulcer, or Barrett's). From our own laboratory, in 223 patients with conventional DU in whom the median BAO was 6.1 mmol/h, the prevalence of esophagitis was 12.5%.[25]

High acid and pepsin secretion per se would seem to be a sufficient explanation for the frequent esophagitis in the acid hypersecretor population. However, underlying acid or pepsin secretion was not significantly greater in patients with esophagitis, implying that it is not high secretion per se, but abnormal esophageal exposure that determines damage.[29,30] Similar findings and conclusions had been reached previously in studies of various groups of patients without hypersecretion and either uncomplicated esophagitis[25] or esophagitis complicated by strictures[31] or associated with Barrett's,[32] but who had the same or lower acid and pepsin secretion as appropriately matched controls. Hence, we sought to identify risk factors in the presence of acid and pepsin hypersecretion that might have contributed to the development of esophagitis in patients with very high rates of esophagitis before treatment.

Ideally, one also should have a direct measure of acid exposure, but because these patients had severe esophageal and ulcer disease and required other more critical studies and urgent treatment, the addition of 24-hour pH studies was not reasonable or feasible. Moreover, the

standard criteria of time/frequency of pH < 4 has never been validated for patients with marked hypersecretion in this range. It is likely that such studies would have confirmed excessive esophageal exposure given the highly acid gastric contents, with pH near 1, but the threshold of pH of 4.0 might then be meaningless.

Several factors that had not been examined by most others for patients with ZE in detail in relation to esophagitis were examined in this study. These include hiatal hernia and gastric acid and pepsin secretion, including the volume and composition of overnight residue, *H. pylori* status,[33] smoking, and the role of frequent vomiting. Risk factors for developing esophagitis identified by logistic regression were vomiting, absence of *H. pylori*, LESP < 16 mm Hg, and obesity. In a study of LESP in 92 patients with ZE[12] that included 37 patients previously reported,[11] 90% had an LESP > 10 mm Hg, but the relation of LESP to esophagitis was not examined.

It would be reasonable to propose that both a relatively lower LESP, as described here, and vomiting facilitated increased esophageal acid and pepsin exposure and contributed to the development and severity of esophagitis. However, we also have no information in our patients on the frequency of transient lower esophageal relaxation, an important mechanism implicated by others in reflux disease.[30] The LES, the control of which is complex,[29,30,34] is the principal gatekeeper in preventing excessive esophageal exposure to gastric contents and merits closer evaluation. One major component of LES competence, LESP, was studied here. LESP had been reported to be related to serum gastrin concentration,[7–9] but this was later refuted.[10,12–14] We confirm here that LESP is not related to serum gastrin secretion over a wide range of values or related to acid output. LESP was not greater in patients with ZE than in hypersecretors without ZE with normal gastrin secretion, with or without esophagitis, contrary to a previous report in a small series.[10]

However, LESP < 16 mm Hg (measured after healing to avoid possible confounding influence caused by active esophagitis[34]) was most clearly predictive of esophagitis before treatment, with an 11-fold greater risk for esophagitis. This threshold value of 16 mm Hg, which was the median value in our patients with esophagitis, is greater than that of 10 mm Hg generally considered to represent the lower limit of normal LESP.[25,34] The greater threshold may reflect an altered balance between LESP and gastric contents of high volume and acidity in hypersecretors required to prevent reflux. An effective LES is especially relevant during sleep, when both swallowing and transient LES relaxations do not occur[30] and when the LES thus is the only defense of the esophagus against reflux. This is even more important in the present hypersecretor patients in whom the average fasting gastric juice volume before treatment was 166 mL, with a mean acid concentration of 80 mmol/L and pH of 1.4. These values are considerably greater than those in 220 healthy controls in our laboratory, for whom average residual volume was 50 mL, median pH of 2.7,[25] or in 332 patients with DU with 70 mL of residual volume and median pH of 2.1,[25] all with a much lower prevalence of esophagitis. The development of esophagitis in two thirds of hypersecretors and its severity thus is not apparently a direct effect of acid hypersecretion per se, but most likely related to greater exposure to gastric contents with low pH fluid and high pepsin content caused by distal esophageal dysfunction and, in many patients, frequent vomiting.

Two significant risk factors that may not have had a direct effect in causing esophagitis were *H. pylori*, a negative risk factor, and obesity, a positive risk factor. We therefore examined possible intermediate mechanisms related to each of these. The role of *H. pylori* in esophagitis is still controversial.[23,35–37] *H. pylori* prevalence appeared to be no different in patients with conventional esophagitis compared with controls in a meta-analysis of >2000 patients.[37] Moreover, in a controlled study of *H. pylori* eradication in patients with esophagitis, patients who remained *H. pylori* positive relapsed earlier than those in whom *H. pylori* was eradicated.[35] However, in our study, we found a much greater prevalence of *H. pylori* in those without esophagitis. The apparent protective effect of *H. pylori* infection in esophagitis[33] was striking in this study, with a relative risk reduced by 84%. Esophagitis has been reported in a significant number of patients to follow eradication of *H. pylori* for DU.[36] In our patients, esophagitis preceded the eradication of *H. pylori* in all cases, and eradication during this[38] and other[35] studies did not promote new esophagitis or relapse. Although it has been suggested that *H. pylori* effects may be caused by lower acid output ascribed to pangastritis, the same was not true in these hypersecretors, in whom all infected patients had pangastritis but no atrophy and persistent hypersecretion.[22]

One possible mechanism for the observed protection might be the 50% greater LESP seen in the present *H. pylori*–infected patients (22.8 vs. 15.2 mm Hg; $P < 0.01$). This difference could still be caused by chance, and data lack the power to detect a moderate or weak association with other factors. The finding requires additional investigation. However, there was no difference

in LESPs between those with and without esophagitis among *H. pylori*–positive patients who had a 50% prevalence of esophagitis. The same was true in *H. pylori*–negative patients who, as a group, had lower LESP values and an 81% prevalence of esophagitis. The apparent protective effect against esophagitis, but not heartburn, was not associated with differences in any of the other putative risk factors (vomiting, gastric acid or pepsin secretion, hiatal hernia, or BMI) between those with and without esophagitis in either *H. pylori*–positive or *H. pylori*–negative subgroups. Other than the greater LESP, the mechanism(s) of the apparent protective effect of *H. pylori*[33] or why esophagitis was more likely in its absence remain unexplained. It is not clear whether our population[38] is atypical in this respect because 1 manometric study of patients with *H. pylori* infection and esophagitis showed a lower LESP and more dysmotility than in uninfected patients or controls.[39] This requires additional study. We found no dysmotility related to *H. pylori* in our patients.

Obesity has been implicated as one of the risk factors for esophagitis[28] and confirmed here by a >2-fold greater incidence of esophagitis in those with a BMI > 24 kg/m^2 and the lowest incidence of esophagitis in those with the lowest BMI. We could not uncover an obvious mechanism from our measurements for the added risk for developing esophagitis caused by obesity.

In conclusion, we show a very high prevalence of (severe) esophagitis in patients with acid and pepsin hypersecretion and identify 3 major positive predictors for the development of esophagitis; LESP < 16 mm Hg, vomiting, and obesity, all potential promoters of reflux, and 1 strongly negative predictor, infection with *H. pylori*, which was associated with a significantly elevated LESP, but no change in secretion status. These facts need to be studied in other populations with esophagitis, in which *H. pylori* effects are still controversial. Acid and pepsin secretion rates were no different in those with esophagitis, but because excessive acid and pepsin exposure is the immediate and critical cause of erosive esophagitis, the only effective treatment for esophagitis, as for peptic ulcer in patients with ZE and similar hypersecretors, is elimination of the large and highly acid reservoir of gastric juice by potent suppression of acid secretion, which can be done most reliably with PPIs.

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