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The influence of co-morbid IBS and psychological distress on outcomes and quality of life following PPI therapy in patients with gastro-oesophageal reflux disease

B. NOJKOV*, J. H. RUBENSTEIN*, S. A. ADLIS†, M. J. SHAW†, R. SAAD*, J. RAI*, B. WEINMAN* & W. D. CHEY*

*Division of Gastroenterology, University of Michigan Medical School, Ann Arbor, MI, USA; †Health Research Center, Institute for Research and Education, Park Nicollet Clinic, Health System Minnesota, MN, USA

Correspondence to:
Prof. W. D. Chey, GI Physiology Laboratory, University of Michigan Health System, 3912 Taubman Center, SPC 0362, Ann Arbor, MI 48109-0362, USA.
E-mail: wchey@umich.edu

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SUMMARY

Background
A subset of patients with gastro-oesophageal reflux disease (GERD) does not achieve complete symptom resolution with proton pump inhibitor (PPI) therapy. The factors which affect response to PPI therapy in GERD patients remain unclear.

Aims
To determine the prevalence and impact of irritable bowel syndrome (IBS) and psychological distress (PD) on GERD symptoms and disease-specific quality of life (QoL) before and after PPI therapy and to assess the same outcomes before and after PPI therapy in non-erosive reflux disease (NERD) and erosive oesophagitis (EO) GERD patients.

Methods
Patients undergoing oesophago-gastroduodenoscopy (OGD) for heartburn were recruited. Participants completed validated surveys: Digestive Health Symptom Index, Reflux Disease Questionnaire, Quality of Life in Reflux and Dyspepsia and Brief Symptom Inventory (BSI). IBS was defined as >3 Manning criteria and PD as BSI score >63. At OGD, patients were classified as NERD or EO. Patients were treated with rabeprazole 20 mg/day for 8 weeks before completing follow-up surveys.

Results
Of 132 GERD patients enrolled, 101 completed the study. The prevalence rates of IBS and PD were 36% and 41%, respectively. IBS independently predicted worse QoL before and after PPI therapy. PD independently predicted worse GERD symptoms and QoL before and after PPI therapy. There were no differences in symptoms or QoL between NERD and EO patients before or after PPI therapy.

Conclusions
IBS and PD impacted GERD symptoms and QoL before and after PPI therapy. Symptoms and QoL before and after PPI therapy were similar in NERD and EO patients.

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INTRODUCTION

Symptoms of gastro-oesophageal reflux disease (GERD) including heartburn and regurgitation are common, affecting approximately 20% of the general population on a weekly basis.[1, 2] A variety of medications are currently available to treat GERD. Proton pump inhibitors (PPIs) have proven more effective than histamine receptor antagonists and placebo both for the healing of erosive oesophagitis (EO) and for improvement of symptoms.[3, 4] Although a majority of treated patients experience symptom improvement or resolution, a significant subset report persistent symptoms despite PPI therapy. The predictors of response to PPI therapy have been only partially characterized. Practical issues can confound the effectiveness of PPI therapy. For example, medical noncompliance is an important issue for some patients. The manner in which a patient is instructed to take PPI therapy can also influence treatment efficacy.[5] Further, patients with typical GERD symptoms including heartburn and regurgitation are more likely to respond to PPI therapy than those with extraoesophageal symptoms such as asthma, hoarseness or cough.[6, 7]

When patients fail to improve with PPI therapy, detailed diagnostic testing with ambulatory oesophageal pH monitoring and/or impedence testing to exclude persistent acid or non-acid reflux have been recommended.[8] Despite such invasive testing, more than half of patients will have no identifiable relationship between acid or non-acid reflux episodes and GERD symptoms.[9, 10] In aggregate, these observations underscore the importance of understanding the factors which influence response of patients with GERD symptoms to PPI therapy.

Patients with symptoms suggestive of GERD often report multiple symptoms referable to the gastrointestinal (GI) tract. For example, a recent study reported that a significant proportion of patients with GERD symptoms also experienced symptoms compatible with the diagnosis of the irritable bowel syndrome (IBS) and functional dyspepsia.[11] Co-morbid psychological distress (PD) is reportedly more common in patients with GERD symptoms.[12–16] A recent work suggests that major life stressors are associated with more severe and frequent GERD symptoms.[17] Whether co-morbid IBS or PD influences the response to PPI therapy in patients with GERD symptoms has not been prospectively studied.

Traditionally, patients with GERD have been classified as suffering from either EO or non-erosive reflux disease (NERD) by upper endoscopy. There is some evidence to suggest that patients with EO are more likely to respond to PPI therapy than those with NERD.[18] As EO is almost uniformly acid-related while NERD probably represents a heterogeneous group of abnormalities, this suggestion is mechanistically attractive. Unfortunately, there are few published studies which have directly compared the efficacy of PPI therapy on heartburn relief in EO and NERD patients from the same population.[19, 20] Further, a number of practical issues limit a clinician's ability to distinguish between patients with EO and patients with NERD in clinical practice.[21] For example, a vast majority of patients with GERD symptoms never undergo upper endoscopy. For the minority of affected patients who undergo upper endoscopy, the procedure is typically performed after initiation of PPI therapy, which would be expected to confound the endoscopist's ability to detect EO.

The aims of this study were to identify prospectively the percentage of GERD patients with co-morbid IBS and PD and to determine the impact of these co-morbidities on response of reflux symptoms to PPI therapy. We further assessed baseline symptom severity and quality of life (QoL) before and after PPI therapy in patients stratified by the presence or absence of EO.

MATERIALS AND METHODS

Patient population

Consecutive patients undergoing oesophago-gastroduodenoscopy (OGD) for the purpose of evaluating typical GERD symptoms including heartburn and/or regurgitation at the Medical Procedures Unit of the University of Michigan Health System were considered for enrolment in this study. To be eligible, patients had to be greater than 18 years of age and able to understand and provide written informed consent. They had to report heartburn and/or regurgitation as their primary complaint. They also had to experience these symptoms more than twice per week for at least 2 months. Heartburn was defined as a burning sensation beginning in the upper abdomen or lower chest and rising towards the neck. We defined regurgitation as an effortless return of gastric contents into the pharynx without nausea, retching or abdominal contractions.

Patients who had taken a PPI for any reason within 2 weeks of their upper endoscopy were excluded from this study. Patients using histamine-2 receptor antagonists were eligible for enrolment. Also, patients were not eligible if they were currently taking nonsteroidal anti-inflammatory drugs or antidepressant medications. Other exclusion criteria included: a recent history of exertional chest pain, decompensated heart failure, renal disease, pulmonary disease, melena or hematochezia, a known Zencker's diverticulum, GI malignancy, significant liver disease (evidence of coagulopathy, encephalopathy, ascites or varices), known bleeding disorder or active peptic ulcer disease (PUD) at OGD.

Protocol

Eligible patients who agreed to participate were asked to complete a series of validated survey instruments to assess:

1. reflux symptoms (Reflux Disease Questionnaire, RDQ includes total GERD score; heartburn, regurgitation and dyspepsia scales);[22]
2. gastrointestinal symptoms (Digestive Health Status Instrument, DHSI includes GERD/ulcer, IBS-diarrhoea predominant, IBS-constipation predominant, dysmotility and pain experience scales);[23, 24]
3. reflux and dyspepsia associated quality of life (Quality of Life in Reflux and Dyspepsia, QoLRAD includes total QoLRAD score; emotional distress, sleep disturbances, food/drink problems, physical/social functioning and vitality scales);[25]
4. psychological distress [Brief Symptom Inventory, BSI included nine primary scales from which a Global Severity Index (GSI) was calculated].[26]

Upon completion of the surveys, OGD was performed at which time, the presence or absence of EO was recorded. Patients were informed of any findings at endoscopy. All patients were then treated with open label rabeprazole 20 mg/day (Esai Co., Ltd, Tokyo, Japan) for 8 weeks. Upon completion of rabeprazole therapy, enrolees were seen by an investigator and asked to repeat three of the survey instruments (RDQ, DHSI and QoLRAD). During this visit, compliance with PPI therapy was assessed by interview and pill count. Figure 1 provides a flow diagram for the study.

Study definitions

At OGD, the presence and severity of EO were determined using the Los Angeles classification.[27] All participants were evaluated for the presence of co-morbid IBS and psychological distress. Co-morbid IBS was defined as more than 3 Manning criteria on the DHSI.[28] The construct of the survey also allowed us to assess diarrhoea and constipation related symptoms in patients with IBS. Generalized psychological distress was defined as a GSI score higher than 63 on the BSI or a score of ≥63 on two of the primary scales.[26]

Power calculation

We performed power calculations for the treatment response to PPI therapy amongst patients with and without IBS and for patients with and without EO.

To compare symptom resolution with PPI in GERD patients with and without IBS, we had to make several assumptions based largely on expert opinion. We assumed that 60% of GERD patients without IBS would experience symptom resolution with PPI

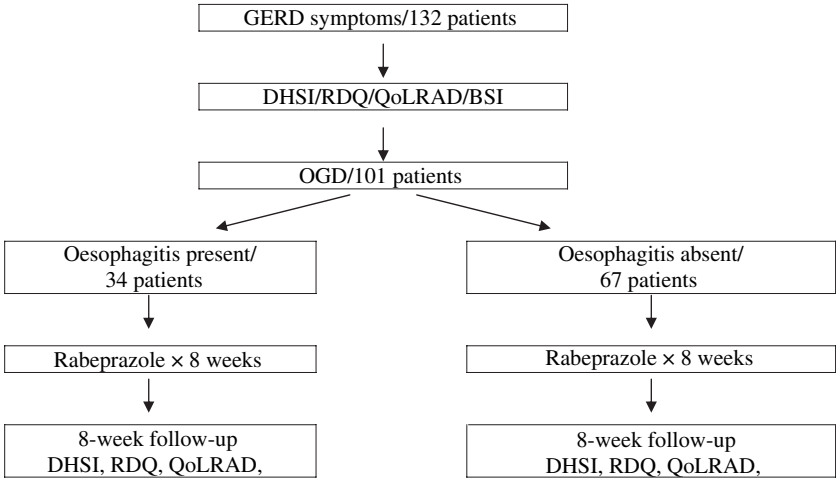

Figure 1. Study protocol.

therapy while 30% of GERD patients with IBS would achieve this outcome following PPI therapy. We also assumed that 40% of GERD patients would qualify for the diagnosis of IBS.[29] Given these assumptions, a sample size of 90 patients would provide 81% power and 120 patients would provide 91% power to detect significant differences between groups.

For the comparison of symptom resolution with PPI therapy in GERD patients with and without EO, we assumed that 57% of patients with EO vs. 37% of patients with NERD would achieve symptom resolution with PPI therapy[18] and that one-third of patients with GERD symptoms would have EO (based upon unpublished data from our endoscopic database). Given these assumptions, a sample size of 216 patients would provide us with 80% power, while a sample size of 291 would provide 90% power to detect significant differences between groups.

Statistical analysis

Responses to questionnaires before and after PPI therapy or based on the presence or absence of IBS, PD or EO were compared using ANOVA. A *P*-value of less than 0.05 defined a statistically significant difference between conditions.

Multivariable linear regression was performed on reflux symptoms from the RDQ, DHSI and QoLRAD for the presence of IBS as an independent factor, controlling for age, gender and the presence of psychological distress. A similar analysis was performed for the presence of psychological distress as an independent factor, controlling for age, gender and the presence of IBS.

RESULTS

In all, 132 enrolled patients completed the first set of surveys and received study medication between June 2002 and July 2006. It should be noted that there is an 'open access' policy at the University of Michigan, which allows primary care physicians to order OGD without prior consultation with a gastroenterologist. Approximately 40% of study participants were scheduled directly through their primary care provider. The remainder of the study population was referred from the Gastroenterology Clinics of the University of Michigan Health System. Of the 132 patients initially enrolled, 31 patients (23.5%) were excluded because of active PUD at OGD, being lost to follow-up or failure to complete the second set of surveys. These patients were labelled as protocol violations and excluded from the final analysis.

Prevalence of co-morbid IBS and PD

Using a threshold of greater than 3 Manning criteria, the prevalence of co-morbid IBS in the total population of GERD patients was 35.6%. There was no difference in the prevalence of IBS in patients with NERD or EO (35% and 36%, NS). The prevalence of psychological distress in the overall population of GERD patients was 40.6%. There was no significant difference in the prevalence of psychological distress in those with NERD vs. EO (41% vs. 37%, NS).

Impact of co-morbid IBS on GERD symptoms and QoL

Gastro-oesophageal reflux disease-related symptom burden (DHSI, RDQ) and disease-specific QoL (QoLRAD) were assessed in patients stratified by the presence or absence of co-morbid IBS. At baseline, GERD patients with co-morbid IBS had significantly greater GERD-related symptom burden on both the GERD + ulcer subscale of DHSI and total GERD score of RDQ than GERD patients without IBS ($P = 0.014$ and $P = 0.022$, respectively). On both of these survey instruments, higher scores suggest a greater symptom burden. Controlling for age, gender and psychological distress, IBS was associated with worse GERD/ulcer symptoms on the DHSI (+7.77, $P = 0.04$), and trended towards worse GERD symptoms on the RDQ (+3.75, $P = 0.06$). After PPI therapy, there were significant improvements in GERD symptoms in patients with and without co-morbid IBS ($P < 0.0001$), but there were no significant differences in the magnitudes of improvement in DHSI and RDQ scores among patients with co-morbid IBS compared to patients without IBS (−3.85, $P = 0.41$ and −0.80, $P = 0.73$, respectively, controlling for age, gender and psychological distress). The presence of IBS was not associated with the post-therapy DHSI and RDQ scores, after controlling for age, gender and psychological distress (−1.38, $P = 0.72$ and +1.44, $P = 0.48$, respectively) (Table 1).

Gastro-oesophageal reflux disease patients with co-morbid IBS had significantly worse disease-specific QoL by total QoLRAD score (−0.95, $P = 0.0001$) and for each subscale ($P < 0.003$ for each) compared with GERD patients without co-morbid IBS, controlling for

Table 1. Digestive Health Status Instrument (DHSI)-gastro-oesophageal reflux disease (GERD) + Ulcer and Reflux Disease Questionnaire (RDQ)-GERD scores in GERD patients with and without co-morbid irritable bowel syndrome (IBS) before and after proton pump inhibitor (PPI) therapy

Scale	IBS (s.d.)	No IBS (s.d.)	*P*-value (IBS vs. no IBS)
DHSI-GERD + ulcer			
Baseline	41.8 (19.4)	33.3 (19.1)	0.014
Follow-up	20.3 (21.0)	16.1 (16.4)	0.232
P-value for difference	0.0001	0.0001	
RDQ-GERD			
Baseline	17.1 (9.5)	13.0 (9.4)	0.022
Follow-up	8.5 (10.2)	6.2 (7.1)	0.213
P-value for difference	0.0001	0.0001	

age, gender and psychological distress. Following PPI therapy, patients with and without co-morbid IBS experienced significant improvements in disease-specific QoL as measured by total QoLRAD score ($P < 0.0001$) and all subscales ($P < 0.001$). The magnitude of improvement in QoLRAD score was greater in patients with co-morbid IBS than in those without IBS, controlling for age, gender and psychological distress (+0.53, $P < 0.025$). Post-treatment total QoLRAD and subscale scores were lower in patients with co-morbid IBS than in those without IBS, although these differences were not statistically significant (Table 2).

Impact of co-morbid PD on GERD symptoms and QoL

Before PPI treatment, co-morbid psychological distress was associated with a greater GERD symptom burden (GERD + ulcer subscale of DHSI +7.80, $P = 0.021$; GERD score of RDQ +3.1, $P = 0.077$, both controlling for age, gender and IBS). After 8 weeks of PPI therapy, there were statistically and clinically significant reductions in symptom burden as measured by DHSI compared with baseline in patients with and without psychological distress ($P = 0.0001$). There was no significant association between co-morbid psychological distress and the magnitude of change in the DHSI GERD/ulcer score ($P = 0.763$) or RDQ ($P = 0.216$), controlling for age, gender and IBS. Post-treatment GERD symptom burden remained significantly greater for patients with co-morbid psychological distress compared with those without psychological distress (GERD + ulcer subscale of DHSI +9.6, $P = 0.012$, GERD score of RDQ +4.90, $P = 0.007$, controlling for age, gender and IBS) (Table 3).

Patients with co-morbid psychological distress had significantly worse disease-specific QoL (QoLRAD −0.98, $P < 0.0001$) at baseline than those without psychological distress, controlling for age, gender and IBS. Post-treatment disease-specific QoL as measured by total QoLRAD (−0.74, $P = 0.006$) and all subscale scores ($P < 0.03$ for each) were significantly lower in patients with co-morbid psychological distress compared with those without psychological distress. However, there was no significant difference in the magnitude of change in QoLRAD scores following PPI therapy in patients with or without co-morbid psychological distress ($P = 0.278$) (Table 4).

Table 2. Quality of Life in Reflux and Dyspepsia (QoLRAD) scores in gastro-oesophageal reflux disease patients with and without co-morbid irritable bowel syndrome (IBS) before and after proton pump inhibitor therapy

QoLRAD-total score	IBS (s.d.)	No IBS (s.d.)	*P*-value (IBS vs. no IBS)
Baseline	3.35 (1.28)	4.26 (1.16)	0.0001
Follow-up	4.79 (1.42)	5.17 (1.08)	0.12
P-value	<0.0001	<0.0001	

Table 3. Digestive Health Status Instrument (DHSI)-gastro-oesophageal reflux disease (GERD) + Ulcer and Reflux Disease Questionnaire (RDQ)-GERD scores in GERD patients with and without co-morbid psychological distress (PD) (BSI > 63) before and after proton pump inhibitor therapy

Scale	PD (s.d.)	No PD (s.d.)	*P*-value (PD vs. no PD)
DHSI-GERD + ulcer			
Baseline	40.1 (19.4)	32.3 (18.7)	0.021
Follow-up	23.1 (22.9)	13.5 (11.8)	0.012
P-value for difference	0.0001	0.0001	
RDQ-GERD			
Baseline	16.1 (10.0)	13.0 (9.1)	0.077
Follow-up	9.8 (10.4)	4.9 (5.7)	0.007
P-value for difference	0.0001	0.0001	

Table 4. Quality of Life in Reflux and Dyspepsia (QoLRAD) scores in gastro-oesophageal reflux disease patients with and without co-morbid psychological distress (PD) before and after proton pump inhibitor therapy

QoLRAD-total score	PD (s.d.)	No PD (s.d.)	*P*-value (PD vs. no PD)
Baseline	3.35 (1.26)	4.33 (1.13)	<0.0001
Follow-up	4.61 (1.54)	5.35 (0.74)	0.006
P-value	<0.0001	<0.0001	

PD = BSI ≥ 63 or two primary scale scores ≥63.

NERD vs. EO

Of the 101 patients who successfully completed the protocol, 67 had no evidence of oesophagitis and 34 had EO found during OGD. Details regarding patients in the two groups are provided in Table 5. Patients enrolled in this study had a high baseline GERD-related symptom burden as assessed by the DHSI and RDQ. There was no significant difference in baseline GERD symptoms in patients with NERD or EO as measured by the GERD + ulcer subscale of DHSI or the overall GERD, heartburn or regurgitation subscales of RDQ. After 8 weeks of PPI therapy, GERD symptoms significantly improved from baseline in patients with NERD ($P < 0.0001$) and EO ($P < 0.0006$). In fact, post-treatment symptom scores were similar to those reported in persons with no GERD.[23, 24] No significant differences in GERD symptom scores on DHSI or RDQ were observed in patients with NERD or EO following PPI therapy (Table 6).

Table 5. Demographics of patients with gastro-oesophageal reflux disease symptoms

	NERD	EO	*P*-value
Number of patients	67	34	
Mean age	48.4	49.4	NS
Age range	18–77	23–73	
Percent female (# female)	64.2% (43)	32.5% (11)	<0.05
Percent with hiatal hernia	47.8% (32)	47% (16)	NS
Grade of oesophagitis (Los Angeles Classification)			
A		11	
B		15	
C		5	
D		3	

NERD, non-erosive reflux disease; EO, erosive oesophagitis.

Table 6. Digestive Health Status Instrument (DHSI)-gastro-oesophageal reflux disease (GERD) + Ulcers subscale, and Reflux Disease Questionnaire (RDQ) subscale scores in erosive oesophagitis (EO) and non-erosive reflux disease (NERD) patients before and after proton pump inhibitor therapy

Scale	EO (s.d.)	NERD (s.d.)	*P*-value EO vs. NERD
DHSI-GERD + Ulcer			
Baseline	40.2 (17.3)	38.7 (18.9)	0.6747
Follow-up	18.9 (22.1)	17.3 (16.9)	0.7028
P-value	<0.0001	<0.0001	
RDQ-GERD			
Baseline	17.1 (9.1)	15.9 (9.0)	0.5293
Follow-up	9.0 (11.1)	6.4 (7.2)	0.2512
P-value	<0.0006	<0.0001	
RDQ-heartburn			
Baseline	8.8 (6.1)	7.5 (5.6)	0.3178
Follow-up	4.6 (6.3)	2.7 (3.9)	0.1512
P-value	0.0027	<0.0001	
RDQ-regurgitation			
Baseline	8.4 (5.0)	8.4 (5.5)	0.9910
Follow-up	4.6 (5.2)	3.7 (4.1)	0.3806
P-value	0.002	<0.0001	

Regarding disease-specific QoL, no significant differences between NERD and EO patients were observed in total QoLRAD scores or any of its subscales (emotions, sleep, food, physical/social functioning, vitality) at baseline. Both patients with NERD and EO enjoyed significant increases in total QoLRAD scores and for all subscales after PPI therapy signifying statistically and clinically significant improvements in disease-specific QoL. No significant differences in QoLRAD scores between the two groups were observed following PPI therapy.

DISCUSSION

There is broad consensus that PPIs provide the most effective form of medical therapy for patients with symptoms suggestive of GERD.[4, 27, 30] PPI therapy is highly effective at healing EO. However, symptom resolution rates following PPI therapy in patients with GERD symptoms have typically been lower than rates of EO healing. Predictors of response to PPI therapy in GERD patients remain poorly elucidated.

Considerable overlap of different GI symptoms has been reported in recent community-based studies.[11, 31] Other studies have reported a significant overlap between GERD and IBS with prevalence rates of IBS in

GERD patients ranging from 19% to 71%.[29, 32] We found the prevalence of IBS (>3 Manning criteria) to be 36% in our cohort of patients with GERD symptoms. Our study was not designed to compare the prevalence of IBS in patients with GERD and the general population. Acknowledging this point, our observed IBS prevalence of 36% in GERD patients appears to be greater than the IBS prevalence reported in a recent systematic review for the general population (range 4–20%, weighted mean based on seven studies including 37 501 persons = 12%).[29]

Psychiatric distress is relatively common in the general population and primary care setting. The National Survey on Drug Use and Health reported that the prevalence of 'serious mental illness' (defined as being diagnosed with a mental, behavioural or emotional disorder using DSM-IV criteria within the past 12 months) was 9.2% in the general US population in 2003.[33] In a study which used the PRIME-MD Patient Health Questionnaire, 825 (28%) of 3000 patients from eight geographically and economically diverse US primary care practices qualified for a psychiatric diagnosis.[34] Considerable overlap between GERD and psychological distress has also been reported.[14–16] Population-based studies have identified psychiatric disease as a risk factor for GERD symptoms.[14–16] A case–control study found that patients with psychiatric disease were 2.7 times more likely to report heartburn than nonpsychiatric controls.[15] These studies did not stratify patients based on the presence or absence of EO. A small study from Russia recently reported that patients with endoscopy negative disease were more likely to exhibit anxiety or hypochondria than patients with EO.[35] In this study, we confirmed the presence of considerable overlap between GERD and psychological distress. Forty-one per cent of our GERD patients had a BSI score of greater than 63 documenting the presence of significant co-morbid psychological distress. We did not identify significant differences in the prevalence of psychological distress between patients with EO vs. endoscopy negative disease.

Perhaps the most interesting findings in our study involved the impact of co-morbid IBS and psychological distress on GERD symptoms before and after PPI therapy. Patients with IBS had more severe GERD symptoms at baseline, but experienced a magnitude of improvement in GERD symptoms similar to patients without IBS after PPI therapy. Before PPI therapy, GERD patients with IBS also reported a significantly reduced disease-specific QoL (total QoLRAD and all subscale scores) compared with GERD patients without IBS. After PPI therapy, GERD patients with and without IBS enjoyed significant improvements in QoL. After PPI therapy, there was a trend towards worse disease-specific QoL as measured by total QoLRAD score in GERD patients with IBS when compared with GERD patients without IBS, but observed differences did not reach statistical significance ($P = 0.12$).

Co-morbid psychologic distress was independently associated with more severe GERD symptoms at baseline, and more residual symptoms after PPI therapy. Co-morbid psychological distress also predicted a worse disease-specific QoL (total QoLRAD and all subscale scores) in GERD patients both before and following PPI therapy.

To our knowledge, this is the first study to describe the important effects of co-morbid IBS and psychological distress on symptom burden and disease-specific QoL before and after PPI therapy in patients with GERD. Regression analyses demonstrate that co-morbid IBS and psychological distress exert independent effects on symptoms and/or QoL in GERD patients.

The pathophysiological basis of our findings remains to be determined. There is a previous work to suggest that patients with functional dyspepsia and IBS experience more severe symptoms and are more likely to be hypersensitive to gastric balloon distention than patients with functional dyspepsia but no IBS.[36] Based on such data, it is attractive to speculate that our findings may be explained by altered brain–gut interactions or visceral sensation, features commonly identified in patients with functional bowel disease.[37–39] Further studies to evaluate these possibilities are eagerly awaited.

We were also interested in investigating whether there was a difference in symptom severity or QoL in patients with EO vs. endoscopy negative disease. It has been suggested that PPI therapy may be less effective in patients with endoscopy negative disease than in those with EO.[18] This suggestion is intuitively attractive given the diversity of factors which can contribute to the development of GERD symptoms in patients with endoscopy negative disease. For example, recent work found a reduced likelihood of pathological acid reflux on ambulatory oesophageal pH monitoring in endoscopy negative patients compared to those with EO.[9] Further, there are some data to suggest that abnormal oesophageal acid exposure by pH monitoring correlates with response to PPI therapy in patients with GERD symptoms.[40] Unfortunately, there are virtually no controlled trials which have directly compared symptom

responses to PPI therapy in patients with endoscopy negative disease and EO. A recent systematic review[18] supports this suggestion but should be viewed as no more than hypothesis generating.

Our prospective nonrandomized, open label trial directly compared PPI efficacy in endoscopy negative and EO patients from the same population. Using responses to validated disease-specific survey instruments (RDQ, DHSI, QoLRAD), we found no difference in symptom response or improvements in QoL to PPI therapy between patients with endoscopy negative disease and EO. In fact, we found that both groups had a level of symptoms comparable to a non-GERD population after 8 weeks of PPI therapy.[23, 24]

A number of factors may explain why we found no difference in treatment response to PPI therapy between endoscopy negative and EO patients. First, our study is one of the first to compare directly the efficacy of PPI therapy in patients with endoscopy negative disease and EO from the same population. This eliminates problems attributable to differences in study populations, methodology, and outcome measures inherent to the aggregation of data from different studies, as is done in a systematic review.[18] Unlike most previous studies, we used validated survey instruments and evaluated changes in survey scores from baseline as opposed to assessing whether a patient did or did not have symptoms at the end of therapy. It is unclear how well responses on integrated symptom surveys correlate with a binomial symptom response outcome measure. We attempted to limit contamination of our study cohort with patients recently treated with PPI therapy, which could cause patients with EO to be misclassified as suffering from NERD. To be eligible for this protocol, patients could not have taken a PPI within 2 weeks of OGD. It could be argued that 2 weeks might not have been long enough to ensure that a subset of NERD patients were not in reality patients with healed EO. However, we would point out that more than 90% of study participants had either never taken a PPI or not taken a PPI within a month of their OGD. As such, we feel that the impact of previous PPI use on our results was negligible. Further, we did not exclude patients taking histamine-2 receptor antagonists from this study. It is possible that a small percentage of patients with EO could have been misclassified as endoscopy negative patients related to the use of these drugs. It is also likely that our study did not have sufficient power to detect a small difference in treatment response between patients with NERD and patients with EO. In fact, we fell short of the sample size necessary to show a 20% difference in PPI response between patients with EO vs. patients with NERD. Finally, it is possible that the open label design of our trial may have inflated treatment responses and obscured small differences in response rates between groups.

In summary, we found that co-morbid IBS and psychological distress but not the presence or absence of EO influenced symptom expression and disease-specific QoL before and after PPI therapy. It is tempting to suggest that co-morbid IBS or psychological distress reduced the likelihood of GERD symptoms to improve with PPI therapy. However, we do not feel that our results support this hypothesis as GERD patients with these co-morbidities enjoyed degrees of improvement in GERD symptom burden and disease-specific QoL similar to patients with no co-morbid IBS or psychological distress. The greater symptom burden and reduced disease-specific QoL at baseline in GERD patients with IBS or psychological distress tended to translate into more residual symptoms and lower QoLRAD scores following PPI therapy. These findings can be better understood by considering two persons, person 1 who has a full glass of water and person 2 who has a half glass of water. If both persons drink a half glass of water, person 1 will still be left with a half glass of water, while person 2 will be left with an empty glass. The same analogy can be applied to GERD patients with co-morbid IBS or psychological distress. While the quantitative degree of GERD symptom improvement with PPI therapy may be the same, the symptom experience before and after PPI therapy is often different. Thus, these findings may provide an explanation for a subset of patients currently deemed to be 'PPI failures' in clinical practice. Whether the impact of co-morbid IBS and psychological distress is specific for PPI therapy or more generalizable to other therapies and conditions is a question that deserves further study.

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