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The Effects of Advanced Diagnostic Methods and Disease Phenotypes on the Response to PPI in Patients with Gastroesophageal Reflux Disease

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ABSTRACT

Aims: The purpose of this study was to evaluate proton pump inhibitor (PPI) response rates for gastroesophageal reflux disease (GERD) phenotypes and functional heartburn (FH) according to the different diagnostic techniques.

Methods: This was a retrospective, noninterventional, single-center study, presenting real-life data. Among 1,233 patients, 510 patients agreed to respond and were evaluated via a validated questionnaire consisting of 28 questions. Patients were classified into: Group I (n=54) if the diagnosis was based only on history, Group II (n=151) if diagnosis was documented on history and upper gastrointestinal endoscopy (UGE), and Group III (n=305) if diagnosis was based on history, UGE, high-resolution manometry and intraesophageal 24-h ambulatory pH-impedance monitoring. Patients were classified into 5 phenotypes (according to the final diagnosis): erosive esophagitis (EE) (n=117), non-erosive reflux disease (NERD) (n=94), FH (n=58), reflux hypersensitivity (RH) (n=16) and Barrett esophagus (BE) (n=20). A response rate under 50% was accepted as being nonresponsive with double doses after 8 weeks of treatment. A very good response was defined as being over 80% improvement of typical symptoms.

Results: The response rates for heartburn and regurgitation of all the patients were 85.3% and 82.2%, respectively. The heartburn and regurgitation response rates of Group I patients were 79.6% and 70.4%; 91.4% and 85.4% for Group II; whereas 83.3% and 82.6% for Group III. The heartburn and regurgitation response rates of BE were 90% and 90%, for EE 88% and 87.2%, for NERD 85.2% and 85.1%, for RH 68.8% and 62.5% and for FH 72.4% and 74.1%. Response rates for both heartburn and regurgination were 40% in BE, 41.4% in EE, 18.8% in NERD, 24.1% in RH and 15.5% in FH.

Conclusions: We demonstrated higher PPI response rates than Western populations in all the GERD patients. More than 1/3 of the patients exhibited very good response rates for both heartburn and regurgitation. The response rates of patients who were diagnosed via all the diagnostic modalities are lower than those who were diagnosed via only history and UGE.

Key words: Barrett's esophagus – erosive esophagitis – nonerosive reflux disease – reflux hypersensitivity – functional heartburn – proton pump inhibitors.

Abbreviations: BE: Barrett esophagus; EE: erosive esophagitis; FH: functional heartburn; GERD: gastroesophageal reflux disease; HRM: high-resolution manometry; MII: multichannel intraluminal impedance; NERD: non-erosive reflux disease; PPI: proton pumb inhibitors; RH: reflux hypersensitivity; UGE: upper gastrointestinal endoscopy.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is characterized by the reflux of gastric contents into the esophagus, which causes troublesome symptoms (regurgitation, heartburn, cough and hoarseness, among other symptoms) and/or complications [1]. The cumulative prevalence of GERD in Western countries was calculated to be 16.1%, whereas the same prevalence was 23% in Turkey [2]. Within the typical range of symptoms, it has been reported that regurgitation is more common than heartburn in Turkey, which is similar to that of non-Western countries [3]. The most common treatment of GERD is via the use of proton pump inhibitors (PPIs). PPIs have been shown to have an inhibitory effect on gastric acid secretion, thus resulting in high rates of

esophageal mucosal healing and the rapid control of GERD-related symptoms [4]. However, the PPI response varies from no response to a very good response. It has been reported that a complete or partial response is observed in 56-79.5% of patients for typical GERD symptoms with a standard dose of PPI in Western countries [5, 6]. Response rates to PPIs are 64% for non-erosive reflux disease (NERD) and 76% for erosive esophagitis (EE) and these rates are assumed to be higher for heartburn than for regurgitation [7, 8]. Failure to achieve a satisfactory symptomatic response (less than 50% improvement) with a single or double dose of PPIs after an 8-week treatment period is traditionally considered to be refractory GERD [9]. However, it should be questioned as to whether the 50% cutoff response is satisfactory. A higher rate may be much more appreciated according to the patient's perspective.

The reasons underlying refractory GERD generally involve many situations, including noncompliance with treatment, inadequate dosing, postprandial consumption, delayed gastric emptying, persistent acid reflux, nocturnal acid breakthrough, concomitant medications, fast metabolizers, nonacid reflux, duodenogastroesophageal reflux, psychiatric comorbidities, eosinophilic esophagitis and pill esophagitis [10]. Currently, the following four different phenotypes have been described in patients with GERD: EE, NERD, reflux hypersensitivity (RH) and functional heartburn (FH). Functional heartburn and reflux hypersensitivity exhibit lower response rates [11]. Moreover, there is a strong need to evaluate the PPI response rates for GERD phenotypes in different geographical areas, especially those areas exhibiting different profiles, such as diet, obesity and high Helicobacter pylori prevalences.

Thus, we aimed to evaluate the PPI response rates of different phenotypes of GERD and Barrett's esophagus (BE). Moreover, success rates with PPIs (according to the different diagnostic techniques) were also evaluated. Finally, we divided the response rates into two different cutoffs (50% and 80%), assuming that the latter cutoff reflected a much better and more satisfactory result from the perspective of the patient.

METHODS

This study was a retrospective, noninterventional, single-center study. A total of 1,233 patients were evaluated among the patients from the GERD database of the Ege University, Reflux Outpatient Clinic, with the patients taking continued PPIs. The inclusion criteria included ages >18-years-old, patients taking continued PPIs for at least 2 months and at least 22 days in a month, patients agreeing to respond to phone surveys and patients having predominantly typical esophageal symptoms for GERD (heartburn and regurgitation). The exclusion criteria included patients with known gastroduodenal ulcers, infectious or inflammatory conditions of the gastrointestinal tract, malabsorption syndromes, gastrointestinal obstruction, histories of gastrointestinal malignancy, progressive systemic sclerosis, severe cardiovascular, renal, hepatic, pulmonary or mental disorders, prior major gastrointestinal surgeries (including cholecystectomy) and pregnancy. Subjects were evaluated via a validated questionnaire consisting of 28 questions [11]. Questions included age, gender, height and weight, smoking, alcohol consumption, type of PPI, frequency of use, fasting state, time between PPI intake and meals, additional uses of drugs for reflux in addition to PPIs and additional medications for other diseases or symptoms (such as oral contraceptives, nonsteroidal anti-inflammatory drugs and medications for diabetes mellitus, heart disease, hypertension, hypothyroidism, hyperthyroidism, constipation and diarrhea). More questions were also asked about the frequency of heartburn/regurgitation within the last year while taking PPIs, whether heartburn/regurgitation persisted while taking PPIs, the effect of PPIs on heartburn/regurgitation as a percentage and the duration of reflux symptoms of patients on PPI treatment. The time between drug consumption and meals was evaluated if PPIs were taken at least less than 30 minutes before the meal.

Patients were initially classified according to GERD phenotypes, including EE, NERD, RH, BE and FH. The Los Angeles Classification was applied for the description of EE [12]. Barrett esophagus was accepted as the identification of endoscopically visible metaplastic columnar epithelium in the distal esophagus, which was histopathologically confirmed [13]. Histopathologically-confirmed BE was attributed to the presence of intestinal metaplasia [14]. The endoscopic appearance of BE was classified according to the Prague classification [15]. Moreover, NERD, FH and RH were defined according to previous publications [16, 17]. A response rate under 50% for either heartburn and/or regurgitation was accepted as being nonresponders with regular use of PPIs after 8 weeks of treatment. We also defined a very good response as being over 80% improvement of typical symptoms.

Patients were also classified into 3 groups (according to the applied diagnosis methodology). These groups were classified according to real-life practice. The first group was solely evaluated based on history. Gastroesophageal reflux disease was diagnosed once a week or as common heartburn and/or regurgitation if only a history was taken. The second group was evaluated via upper gastrointestinal endoscopy (UGE) in addition to history, and the third group was evaluated with history, UGE, high-resolution esophageal monometry (HRM) and intraesophageal 24-h ambulatory pH - multichannel intraluminal impedance (MII) monitoring. The first group reflects the primary health care; the second group reflects the management of patients admitted to hospital and the third group represents the management in the tertiary referral centers in Turkey.

Upper gastrointestinal endoscopy and 24-h intraesophageal pH-MII monitoring indications included gastroesophageal reflux complaints that persisted or recurred despite appropriate treatment or before antireflux surgery. High-resolution esophageal monometry was performed to identify functional esophageal motility disorders and to evaluate defective peristaltism before the funduplication procedure for assisting in inserting an impedance-pH monitorization probe.

Statistical Analysis

Statistical analyses were performed via the Windows SPSS program (version 22.0, SPSS Inc., Chicago, IL). Kolmogorov–Smirnov and Shapiro–Wilk tests were used to analyze whether the data were normally distributed. For nonnormally

distributed data, median and min–max values were analyzed, whereas the mean and standard deviation values were used for normally distributed data. To compare the normally distributed data, a Student's t test was used, whereas the Mann–Whitney U test was used for the comparison of nonnormally distributed data. Chi-square or Fisher's exact tests were utilized to assess the categorical variables. A post hoc analysis was performed to identify the differences between the groups.

Ethical Approval

As stated in the 1964 Helsinki declaration and its subsequent amendments, all of the methods (including human subscribers) that were in our study were performed in compliance with the ethical standards of the national research committee. Written informed consent was obtained from all of the participants who were included in this study. After obtaining Ethics Committee Approval, the Clinical Trials Ethics Committee of Ege University, Faculty of Medicine, which is a tertiary level health care center, approved this study (with the decision number 21-2.1T/58) in February 2021.

RESULTS

There were 117 patients in the EE group, 94 patients in the NERD group, 58 patients in the FH group and 16 patients in the RH group. Table I shows the demographic features of patients according to the GERD phenotypes.

Table I. The demographical features of patients according to GERD phenotypes

Phenotypes	Age (mean±SD)	Gender (Female) %
Erosive esophagitis (n=117)	46±11	41.6
NERD (n=94)	46±12	61.3
Functional heartburn (n=58)	45±12	64.9
Reflux hypersensitivity (n=16)	45±11	75
Barrett's Esophagus (n=20)	43±11	30

NERD: non-erosive (gastroesophageal) reflux disese.

The PPI responses of typical symptoms according to GERD phenotypes showed that the highest response rates belonged to BE, followed by EE (90% and 88%, respectively), for heartburn. This was followed by NERD, with a response rate of 85.1%. The response rates were lowest with FH and RH, which were 72.4% and 68.8%, respectively (p=0.027). A similar pattern was observed for regurgitation. No difference was shown between heartburn and regurgitation for the PPI response. The PPI responses of heartburn and regurgitation according to disease phenotypes are shown in Fig. 1.

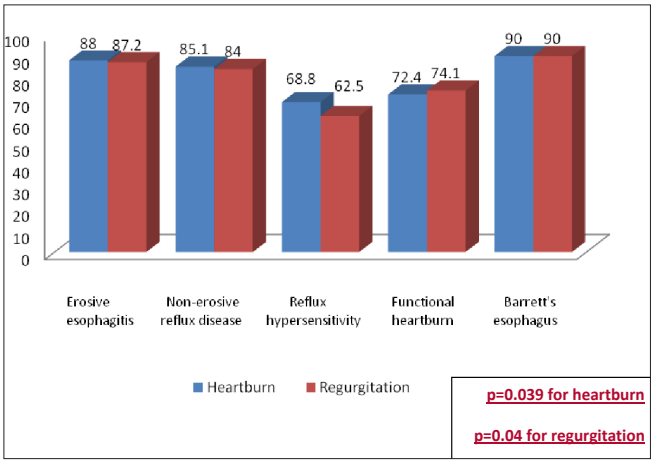

Fig. 1. PPI response rates according to GERD phenotypes.

The cumulative response rates for the traditional definitions (≥50%) for heartburn and regurgitation of all of the patients were 85.3% and 82.2%, respectively (p>0.05). Thirty-six percent of the patients had very good responses (≥80% response rate) for heartburn and 32.7% had very good responses for regurgitation. Response rates according to GERD phenotypes are summarized in Table II.

Female patients were less responsive than male patients. Unresponsiveness to PPI for heartburn among females was 17.4%, whereas this rate was 11.2% among males (p=0.049). For regurgitation, unresponsiveness rates were 20.6% for females and 14.3% for males (p=0.069).

A statistically significant difference could not be achieved in nonresponsive patients for heartburn or regurgitation between single and double doses. However, it must be mentioned that only 11.8% of patients were taking double-dose PPIs for heartburn, and 13.5% of the patients were taking double-dose PPIs for regurgitation among nonresponsive patients. Among responsive patients, 8.1% of patients were using double doses for heartburn, and 7.5% of patients were using double doses for regurgitation.

Table II. Response rates according to GERD phenotypes

Phenotypes	Heartburn		Regurgitation	
	50-79% response % (n)	≥80% response % (n)	50-79% response % (n)	≥80% response % (n)
Erosive esophagitis (n=117)	48.7 (57)	39.3 (46)	51.3 (60)	35.8 (42)
NERD (n=94)	43.6 (41)	41.4 (39)	42.6 (40)	41.4 (39)
Functional heartburn (n=58)	48.3 (28)	24.1 (14)	58.6 (34)	15.5 (9)
Reflux hypersensitivity (n=16)	50 (8)	18.8 (3)	43.8 (7)	18.8 (3)
Barrett esophagus (n=20)	50 (10)	40 (8)	50 (10)	40 (8)

NERD: non-erosive gastroesophageal reflux disese. Data is presented as percent and number of 50-79% and ≥80% response rates and numbers among all patients.

Add-on therapy with PPIs, such as antacids, sodium alginate, H2 receptor antagonists and prokinetics, was evaluated. Eighty-four percent of patients were taking sodium alginate as an add-on therapy. Additional drug consumption rates were 18.5% for Group I, 38.4% in Group II, 24.9% in Group III and 28.2% for all of the patients (p=0.003). A total of 23.1% of patients with EE, 25.5% of patients with NERD, 25% of patients with RF and 27.6% of patients with FH were on combination therapy with PPIs (p=0.929). From a different viewpoint, 26.7% of nonresponsive patients and 28.5% of responsive patients were taking additional drugs for heartburn (p=0.744). Similarly, 29% of nonresponsive patients and 28.2% of responsive patients were using additional drugs for regurgitation (p=0.937). The rate of additional drug use was not significantly different between males and females; 29.6% of females and 26.5% of males were using additional drugs (p=0.432).

The PPI response of patients was also analyzed according to the different levels of diagnostic modalities. Fifty-four patients were diagnosed with GERD with only history (Group I), 151 patients were evaluated with history and UGE (group II) and 305 patients underwent UGE, HRM and 24 h intraesophageal MII-pH (off-PPI) (Group III). The mean age of Group I patients was 44±17 (SD) years, Group II patients was 47±14 years and Group III patients was 46±12 years. Sixty-seven percent of Group I patients were female, whereas the percentages of the female sex were 58.3% and 53.2% in Group II and Group III, respectively (p=0.11).

The heartburn response rate of Group I patients (history only) was 79.6%; the response rates were 91.4% for group II (history+EGD) and 83.3% for group III (history+EGD+ 24 h pH-MII) (p= 0.033). The response rates for regurgitation of Group I patients was 70.4%; responses rates were 85.4% for Group II and 82.6% for Group III (p=0.044). Fig. 2 shows the PPI response rates according to the effect of advanced diagnostic modalities on the PPI response. The highest rate was found in group II, which was based on history + UGE (91.4% and 85.4%, respectively).

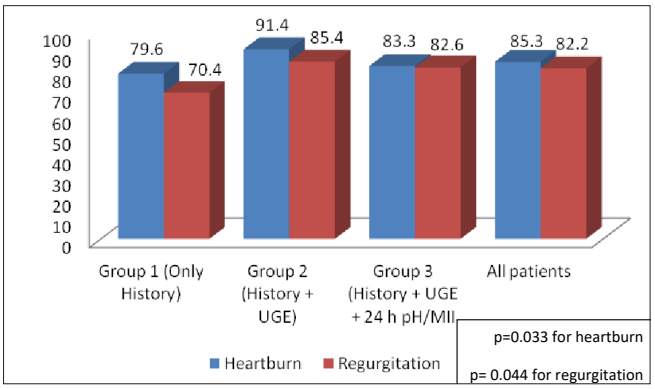

Fig. 2. PPI response rates according to diagnostic modalities.

DISCUSSION

Unresponsiveness to PPIs is a major problem in the management of GERD. We evaluated the PPI response rates of different phenotypes of GERD and divided them into different cutoff values. Success rates with PPIs with the different diagnostic techniques were also assessed.

The FH and RH phenotypes are known to have lower PPI response rates. In our study, among GERD phenotypes, the lowest response rates among phenotypes were observed in RH and FH (68.8% and 72.4%, respectively, which was not surprising), and the highest response rates were observed in BE (90%) and EE (88%) patients.

This rate is very similar to the study performed by Armstrong et al. [18], which found adequate heartburn control with a rate of 88% and complete remission with a rate of 40% in patients with EE by using 40 mg pantoprazole per day.

According to a review, the healing rates of patients with EE changed from 85-96% after 8 weeks of therapy, regardless of the brand of PPI and the severity of the disease. It is well known that a 10-15% discrepancy can occur between healing rates and symptom relief [19]. A meta-analysis demonstrated that four weeks of PPI therapy achieved complete relief of heartburn, with a pooled estimate in EE patients of 0.72, whereas this number was 0.73 in NERD patients [20]. Eight weeks of PPI therapy achieved relief in both the EE and NERD patients. Additionally, there was no difference between the two groups. In this study, among NERD subtypes, the highest response rates were observed in the actual NERD patients who were evaluated with both endoscopy and 24-h pH measurement. This meta-analysis is compatible with our findings [20].

Another study enrolled 203 NERD patients after 4 weeks of therapy and showed that 57% of patients had satisfactory symptom relief (no more than one episode of heartburn of moderate severity during the week) [21]. However, this study enrolled NERD patients according to endoscopic findings and GERD-related symptoms. Symptom relief was lower than that in our study, which could be explained by two main differences. First, the GERD-related symptoms that were involved in this study were regurgitation, heartburn, belching, bloating and early satiety. In our study, we only involved typical symptoms, such as heartburn and regurgitation response rate. It is difficult to assume that belching, bloating and early satiety are all GERD symptoms. The other reason is that we evaluated "true" NERD patients who were diagnosed by using both endoscopy and 24-h ambulatory pH-impedance monitoring. Therefore, it can be proposed that the previously reported low response rate in studies with patients who were classified as NERD is likely the result of the inclusion of patients with upper gastrointestinal symptoms that do not belong to GERD, as well as less responsive phenotypes [10].

Functional reflux disorders, including RH and FH, are known to have lower response rates to PPIs. In our study, it was found that the PPI response rate for heartburn was 68.8% in patients with RH and 72.4% in patients with FH; these rates for regurgitation were 62.5% and 74.1%, respectively. Due to the fact that RH was defined as the condition in which patients with normal esophageal acid exposure have reflux episodes (acidic, weakly acidic or alkaline) associated with heartburn, the PPI response is expected to be lower. In a recently published study, Ribolsi et al. [22] found that after a careful history and optimal PPI dosing, the real refractoriness to PPIs was 20% in NERD patients. In this study, the RH group comprised 42% of

PPI-refractory patients. This finding was also similar to our findings; the least treatable patients with PPI were RH patients. Another interesting study found that more than 41% of patients with RH could have 75% symptom (heartburn) relief with PPIs, which is compatible with our 18.8% of RH patients who showed very good responses [23]. Interestingly, the PPI response rates of our FH patients were higher than those in the literature. It is always a possibility that patients could not press the button in the appropriate time during the 24 h intraesophageal MII-pH.

When we assessed all of the patients for the traditional (≥50%) response rate to PPIs, we found that 85.3% and 82.2% of heartburn and regurgitation patients responded, respectively. These figures were higher than those in the majority of previous studies for both heartburn and regurgitation. Another difference from the literature is that the response rates to both typical symptoms were similar. We believe that the traditional PPI-response rate (≥50%) is not sufficient in daily practice from the patient's perspective and that a higher level of satisfaction is needed. For that reason, we increased the response rate to ≥80% and showed that the PPI response was 36% for heartburn and 32.6% for regurgitation. We suggest a similar approach for future studies for the satisfaction with PPIs for the good of the patient.

To deal with unresponsiveness to PPIs, different diagnostic procedures should be used. However, many centers or health care professionals do not have the necessary equipment. Therefore, many guidelines suggest starting with a basic approach, which is a PPI therapeutic trial for the the management of GERD [24]. If PPI therapeutic trials fail, UGE is generally the second choice. According to the results of UGE, either a new therapeutic approach can be arranged, such as add-on therapy or a double dose of PPI, or more advanced technologies can be applied, such as esophageal high-resolution manometry followed by a 24 h pH-MII study. There is a need for real-life data to evaluate the PPI-unresponsive rates for each stratification strategy and different cutoff values for the unresponsiveness.

We evaluated the different approaches for the evaluation of PPI unresponsiveness by starting from the basic approach, such as the PPI test according to the history of the patient followed by UGE and the endmost 24 h intraesophageal pH-MII measurement & esophageal high-resolution manometry. When patients were evaluated according to the diagnostic procedures, heartburn (79.6%) and regurgitation (70.4%) response rates were lowest in Group I patients who were evaluated only with their history. This group represents the PPI trial mainly for primary health care. According to a meta-analysis, the partial PPI response of patients who were only evaluated with history was 71% for heartburn after 4 weeks of PPI therapy and 49% after 8 weeks of PPI therapy [20]. Cochrane database reviews have stated that remission of heartburn was calculated to be 63%. When further diagnostic modalities were applied, significantly better response rates were achieved.

In our clinical practice, patients with GERD were checked to determine whether they were using their drugs adequately at every visit. This approach could help to reduce noncompliance with treatment.

Due to the fact that some of the patients exhibit unsatisfactory PPI response rates, additional drugs are needed during clinical follow-up. Therefore, we also analyzed additional drug use according to the phenotypes. Add-on therapy rates were highest in Group II, as expected, although EE patients were generally involved in that group.

The strengths of our study include the high number and adequate evaluation of 305 patients. To the best of our knowledge, this study is the first to investigate PPI response rates according to phenotypes and the first to describe and investigate different cutoff values for responses.

Our study had some limitations. The study design was retrospective, except for the fact that PPI responses were requested by experienced physicians. There were only 16 patients with RH, which may be the reason for the high response levels. Additionally, this study was based on patients' declarations. Therefore, we recorded the drugs regarding how patients declined, and we likely had limited information about patients' psychiatric problems and add-on drugs. It is well known that patients with RH and FH generally have additional psychiatric problems [25].

Our retrospective analysis could not provide comparative results for each stratification level because many patients were admitted to our reflux outpatient clinic following UGE. However, our GERD center is the largest in Turkey, with more than 8,800 patients in the database and many referrals. Almost all of the referral patients consulted without a 24-h pH-MII study and were naive for advanced diagnostics. We believe that our results may provide the response rates and related factors reflecting the daily clinical routines and needs and stratification according to the different diagnostic techniques.

CONCLUSIONS

We demonstrated higher PPI response rates than Western populations in all GERD patients. The response rate was not different regarding regurgitation compared to heartburn and was the highest in erosive esophagitis and lowest in reflux hypersensitivity and functional heartburn. Interestingly, response rates were similar between erosive esophagitis and nonerosive reflux disease. In our study, more than 1/3 of patients had a very good response rate (≥80% response) for both heartburn and regurgitation. It should be noted that these results were collected from a single/tertiary referral center with difficult-to-treat cases. Most likely due to this reason, the response rates of patients who were diagnosed by using all diagnostic modalities are lower than those who were diagnosed with only history and upper gastrointestinal endoscopy.

Conflicts of intetest: None to declare.

Authors' contributions: S.B. conceived the study analyzed and interpretated the data, drafted the manuscript, and critically revised it for important intellectual content. N.D. was responsible for literature search, ethical approval, acquisition of data, analysis and interpretation of data, drafting of the manuscript .

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