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Original Research Article

An Observational Study to Evaluate Endoscopic, 24-H Gastric and Esophageal Acid Profile among Patients with Gerd in Relation to H. Pylori, as the Latter Might Alter Gastric Acid Secretion

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Abstract

Aim: The aim of the present study was to evaluate the endoscopic, 24-h gastric and esophageal acid profile among patients with GERD in relation to H. pylori, as the latter might alter gastric acid secretion.

Methods: In this observational study, patients with heartburn of more than two months duration, referred to the Department of Gastroenterology for two years .One hundred patients were included.

Results: One hundred patients (mean age 42.6 (12.8) years; 73 [73%] men) fulfilled the criteria for diagnosis of GERD, had Carlsson-Dent score ≥6.0, had erosive esophagitis (EE); responded to omeprazole, had significant reflux on 24-h pH metry. Of 100 patients with GERD, 45 (45%) had H. pylori infection. Patients with and without H. pylori infection were comparable in respect to age, gender and Carlsson- Dent score. The average gastric pH, % time gastric pH <4, <3, <2 were comparable among the two groups; percentage of time gastric pH <1.5 was higher in patients without H. pylori infection. Patients with GERD with and without H. pylori infection had comparable esophageal pH metry findings. Patients older than 40 years without H. pylori infection had lower average esophageal pH and longer reflux time in minutes than those with H. pylori infection. Patients with higher LA had more esophageal acid exposure than those with ENRD and LA-A both the gastric acid profile was comparable among them. Gastric acid profile (% time gastric pH <1.5) showed a trend from pangastritis < normal gastric mucosa < antral gastritis. Patients with antral gastritis had more acidic stomach than those with pangastritis.

Conclusion: In conclusion, our study showed that presence of H. pylori in patients with GERD was associated with less acidic stomach and milder esophagitis. Patients without H. pylori infection and higher age especially males are at a higher risk of developing EE.

Keywords: Erosive esophagitis, Esophageal acid exposure, Gastric acid profile, Los Angeles classification, Multivariate analysis, Pepsinogen-I/II ratio

Introduction

Helicobacter pylori (HP) has been demonstrated the causative factor of various gastrointestinal diseases; nevertheless, the relationship between HP infection and gastroesophageal reflux disease (GERD) is still debated. [1] To date, different studies have examined the relation- ship between atrophic gastritis due to HP infection and reflux oesophagitis with conflicting results. Recent trials suggest that HP infection may be an important causative factor of atrophic gastritis. [2] HP infection has been associated to inflammation of gastric mucosa that increases cellular apoptosis and epithelium proliferation. The excessive apoptosis, leads to the atrophy of epithelial cells and glands and could contribute to carcinogenesis. Some authors have found an increase of reflux oesophagitis after HP eradication. On the contrary, other authors suggested a correlation between HP infection and presence and severity of reflux esophagitis. [3]

It was suggested that HP could contribute to GERD through different mechanisms: cardias inflammation causing sphincter weakness; increased acid secretion due to antral gastritis; delayed gastric emptying and citotoxin production causing esophageal epithelium injury. Conversely, other authors believe that HP infection may even protect against GERD and HP eradication may lead to an accelerated development of GERD in ulcer disease patients. [1,2,4-6] Further, previous studies have shown an increased effect of proton pump inhibitors on intragastric pH in HP-infected patients suffering from GERD with rapid heartburn relief and lack of relapse. [7]

The role of Helicobacter pylori (H. pylori) infection in the pathogenesis of gastro-oesophageal reflux disease (GERD) is still controversial. [8] Controlled epidemiological studies found neither an increased

prevalence of H. pylori infection nor a correlation of the infection with the endoscopic grade of oesophagitis. [9,10] Gastrin is also the most potent endogenous stimulant of gastric acid secretion. [11] A low serum gastrin level is indicative of high gastric acid secretion; whereas, high gastrin levels (like in chronic H. pylori infection and gastric atrophy) is associated with decreased gastric acid secretion. [12] Twenty-four hour pH metry has been widely used in the diagnosis of GERD. However, as H. pylori is known to alter gastric acid secretion, it would be worth evaluating 24- h gastric acid profile (in circadian rhythm) in patients with GERD in relation to H. pylori infection. The limited data available on this issue are contradictory and evaluated the basal and maximal acid output and not 24-h gastric acid profile. [13,14]

The aim of the present study was to evaluate the endoscopic, 24-h gastric and esophageal acid profile among patients with GERD in relation to H. pylori, as the latter might alter gastric acid secretion.

Materials and Methods

In this observational study, patients with heartburn of more than two months duration, referred to the Department of Gastroenterology, PARAS, HMRI Hospital, Patna, Bihar, India for two years. One hundred patients were included. The patients were evaluated for the presence of GERD by fulfilling at least two of these criteria:

1) Carlsson-Dent score of >6 [15],

2) presence of endoscopic GERD,

3) significant reflux on 24-h pH metry (% time esophageal pH <4 for ≥5% of recorded time) [16],

4) histological assessment of esophagitis [17] and 5) response to omeprazole 20 mg/day. [18,19]

All patients were off acid suppressive drugs and prokinetics at least one month before inclusion, and none had received anti- H. pylori therapy in the past. Patients were allowed to take antacids if they had intolerable symptoms, till one week before pH metry. Informed consent was taken from each patient and Patients, who could not remain off PPI for one month, were excluded from the study.

Investigations

Esophagogastroduodenoscopy was performed using a forward-viewing endoscope (Olympus video endoscope). Esophagitis, if present, was graded using Los Angeles (LA) classification. [20] Patients without any erosion in esophagus were classified as endoscopy negative reflux disease (ENRD). Barrett's esophagus (BE) was diagnosed by the criteria as described previously. [21] Hiatus hernia was defined as a distance of >2 cm between squamocolumnar junction and the impression of the crural diaphragm. Six biopsies of 3–5 mm were obtained (three each from antrum and corpus) during the procedure. Of these, two biopsies each from antrum and corpus were used for histological examination and rest two were used for H. pylori detection.

H. pylori infection was diagnosed using rapid urease test (RUT), histology and anti-H. pylori IgG enzyme linked immunoabsorbent assay (ELISA), diagnostic criteria being any two of the three given tests positive. RUT was performed using an in-house RUT solution, the sensitivity and specificity of which have been validated previously. [22] Gastric biopsies were stained with hematoxylin and eosin, and Giemsa, to evaluate H. pylori. ELISA was done for IgG antibodies (H. pylori-IgG ELISA) using commercially available kit (Genesis Diagnostics, Cambridgeshire, UK). This has been validated previously in our population. [23]

Histological examination of gastric biopsies was performed. Two biopsies (3–5 mm) per site (antrum and corpus) were assessed by a single expert pathologist for the presence and grading of gastritis according to the updated Sydney system (1994). The pathologist was unaware about the endoscopic findings. When the scores between the two biopsies were different, the more severe scores were selected.

Twenty-four hour dual channel pH metry was performed in subset of patients who gave consent for this procedure. Eighty-three patients underwent 24-h dual channel pH metry after an overnight fast using a pH meter (Naik-II, RedTech, CA, USA) and antimony pH probes (the two sensors placed 15 cm apart) as per the protocol described previously [38]. Prior to pH metry, esophageal manometry was performed using an eight-channel (4 radial and 4 concentric ports) water perfusion system (RedTech, CA, USA) to localize and measure lower esophageal sphincter (LES) pressure and to study esophageal body motility. In three patients, in whom esophageal manometry could not be performed, the pH probe was placed 5 cm above the change in pH of the proximal sensor from acidic to alkaline. After 24-h, pH data was downloaded and analyzed for esophageal acid exposure and gastric acid profile using the Naik-II software from RedTech, CA, USA. [16,24]

Statistical analysis

Patients were categorized on the basis of presence and absence of H. pylori infection and on different grades of esophagitis (ENRD, LA-A, and LA grades B-D). Inter- group comparison between two or more than two continuous variables was performed by Mann-Whitney U or Kruskal Wallis tests, respectively. Variables found significant by latter analysis were subjected to post-hoc analysis by Mann-Whitney U test. Categorical variables were compared using Chi-squared test with Yates'

correction as applicable. P-values <0.05 were considered significant. Pearson correlation coefficient (CC) was calculated to assess the degree of association between the two variables. Categorical variables found significant in univariate analysis were subjected to multivariate analysis by binary logistic regression. Presence and grades of esophagitis were taken as dependent variable and forward LR method was chosen.

Results

Table 1: Gastric acid profile and esophageal acid exposure in patients with GERD in relation to H. pylori infection

Parameter		*H. pylori* positive (*n*=45)	*H. pylori* negative (*n*=55)	*p*-value
Age (mean [SD]) y		38.2 (12.4)	42.6 (12.8)	0.78
Male gender (*n* [%])		38	45	0.52
Carlsson-Dent score (median [range])		11.2 (1–17)	10.5 (1–17)	0.32
Endoscopy (*n* [%])	ENRD	20	15	0.02
	EE	22	38	0.008
	Unclassified	3	2	-
Los Angeles grade (n [%])	A	20	30	0.01
	B	25	25	0.35
	> LA-A	22 (37.2)	24 (37.5)	0.98
24-h pH parameters (median [range])		*n*=35	*n*=35	
Gastric	Average gastric pH	2.54 (1.84–3.88)	2.45 (1.85–3.38)	0.17
	% time gastric pH<1.5	0.98 (0–43.56)	3.62 (0–61.06)	0.01
Esophageal	Average esophageal pH	6.29 (4.37–7.47)	6.16 (2.92–7.63)	0.25
	% reflux time	3.35 (0–37.68)	3.96 (0–76.15)	0.99
	Time pH <4 (h)	0.80 (0–9.02)	0.81 (0–18.25)	0.67
	Longest reflux (min)	8.3 (0–114.2)	12.45 (0–178.8)	0.19
pH parameters in patients >40 years		(*n*=10)	(*n*=20)	*p*-value
Gastric	Average gastric pH	2.5 (1.84–3.2)	2.35 (1.91–3.13)	0.40
	% time gastric pH<1.5	0.35 (0–33.53)	4.42 (0–61.06)	0.02
Esophageal	Average esophageal pH	6.29 (5.76–7.01)	6.01 (5.47–6.64)	0.02
	% reflux time	3.22 (0.02–14)	6.33 (0.49–21.57)	0.28
	Time pH <4 (h)	0.77 (0.01–3.31)	1.16 (0.12–5.07)	0.42
	Longest reflux (min)	6.2 (0.3–20.6)	14 (1.7–72.7)	0.008

One hundred patients (mean age 42.6 (12.8) years; 73 [73%] men) fulfilled the criteria for diagnosis of GERD, had Carlsson-Dent score ≥6.0, had erosive esophagitis (EE); responded to omeprazole, had significant reflux on 24-h pH metry. Of 100 patients with GERD, 45 (45%) had H. pylori infection. Patients with and without H. pylori infection were comparable in respect to age, gender and Carlsson-Dent score. The average gastric pH, % time gastric pH <4, <3, <2 were comparable among the two groups; percentage of time gastric pH <1.5 was higher in patients without H. pylori infection. Patients with GERD with and without H. pylori infection had comparable esophageal pH metry findings. Patients older than 40 years without H. pylori infection had lower average esophageal pH and longer reflux time in minutes than those with H. pylori infection.

Table 2: Twenty-four-hour pH parameters in patients with different endoscopic grades of esophagitis

Parameter	ENRD	LA-A	Higher LA	*p*-value
Average gastric pH	2.5 (1.87–3.09)	2.38 (1.85–3.38)	2.49 (1.84–3.88)	.910
% time gastric pH <1.5	1.04 (0–46.39)	2.89 (0–38.67)	1.13 (0–61.06)	.884
Average esophageal pH	6.19 (3.35–7.47)	6.27 (2.92–7.63)	6.15 (4.37–7.26)	0.950
Time esophageal pH <4.0 in h	0.6 (0.03–15.68)	0.49 (0–18.25)	1.69 (0–9.02)	1 vs. 3=0.014
				2 vs. 3=0.003
% reflux time	2.56 (0.12–65)	2.82 (0–76.15)	7.17 (0–37.68)	1 vs. 3=0.017
				2 vs. 3=0.016
Longest reflux (min)	6.1 (0.7–91.4)	4.7 (0–178.8)	14.8 (0–114.2)	1 vs. 3=0.007
				2 vs. 3=0.012

Patients with higher LA had more esophageal acid exposure than those with ENRD and LA-A both the gastric acid profile was comparable among them.

Table 3: Distribution of antral and pangastritis among patients with GERD in relation to H. pylori infection and gastric acid profile

		Gastric mucosa	
H. pylori status	Normal mucosa (N)	Antral gastritis (A)	Pangastritis (P)
Present	4	16	14
Absent	11	9	1
Total	15	25	15
Gastric acid profile in relation to gastritis status			
% time gastric pH < 1.5	1.2 (0.0-46.4)	3.2 (0.0-43.5)	0.35 (0.0-33.5)
PG-I/PG-II ratio	15.4 (9.5-35.1)	13.6 (8.3-32.4)	11.4 (6.6-23.5)
Gastrin-17 levels	2.0 (0.01-21.0)	4.9 (0.06-51.0)	13.0 (1.1-53.0)
Gastric acid profile in relation to *Hp* and gastritis			
Parameter	*Hp*+ve, antral (A+)	*Hp*-ve, antral (A-)	*Hp*+ve, pangastritis (P+)
% time gastric pH < 1.5	1.9 (0-43.5)	11.3 (0.6-38.6)	0.3 (0-33.5)
PG-I/PG-II ratio	12.8 (8.3-19.0)	15.2 (10.8-32.4)	11.8 (6.6-23.5)
Gastrin-17 levels	8.1 (0.6-16.8)	2.5 (0.06-16.8)	10.25 (1.1-30.5)
Esophagitis in relation to *Hp* and gastritisParameter	*Hp*+ve, antral (A+)	*Hp*-ve, antral (A-)	*Hp*+ve, pangastritis (P+)
EE (%)	13/21 (61.9%)	10/12 (83.3%)	10/16 (62.5%)

Gastric acid profile (% time gastric pH <1.5) showed a trend from pangastritis < normal gastric mucosa < antral gastritis. Patients with antral gastritis had more acidic stomach than those with pangastritis. Gastric acid profile was comparable in patients with normal gastric mucosa than those with antral or pangastritis. Patients with pangastritis had lower PG-I/PG-II ratio than those with normal gastric mucosa. Patients with normal gastric mucosa had lower gastrin-17 levels than those with antral gastritis as well as pangastritis. Patients with H. pylori-positive gastritis had less acidic stomach, lower PG- I/PG-II ratio and higher gastrin-17 levels than those with gastritis who were H. pylori-negative.

Table 4: Results of univariate analysis and multivariate analysis for risk of GERD

Variable	*p*-value	OR (95% CI)
Univariate analysis Gastrin-17≤10 pg/L	0.002	11.77 (2.71–51.09)
Absence of *H. pylori*	0.02	2.76 (1.22–6.26)
Presence of hiatus hernia	0.0003	6.93 (2.58–18.57)
Male gender	0.028	2.52 (1.11–5.74)
Low LES pressure (<10 mmHg)	0.07	2.86 (1.00–8.17)
Age >40 years	0.01	2.86 (1.23–6.67)
Multivariate analysis Gastrin-17≤10 pg/L	0.018	5.07 (1.35–19.13)
Age >40 years	0.015	6.18 (1.47–29.96)
Presence of hiatus hernia	0.007	7.99 (1.92–33.17)
After removal of above three variables		
Absence of *H. pylori*	0.032	3.53 (1.10–11.24)

Parameters found significant on univariate analysis were entered into a multivariate model. Multivariate analysis showed that serum gastrin-17 ≤ 10 pg/L, presence of hiatus hernia and age >40 years were independently associated with higher risk of GERD. Patients having these parameters had 80.3% correct prediction for having EE. Removal of above three independent parameters from multivariate analysis showed an independent association of absence of H. pylori infection with presence of EE. Patients without H. pylori infection had 73.2% correct prediction for having EE.

Discussion

Recent data suggest an overall increase in the prevalence and severity of gastroesophageal reflux disease (GERD) in the West. [25-27] Role of various host physiological, dietary and environmental factors have been extensively investigated in the pathogenesis of GERD [28-32]; however, the role of Helicobacter pylori (H. pylori) infection in pathogenesis of GERD is still controversial. H. pylori infection may either increase or decrease gastric acid secretion, thereby increasing or decreasing the severity of GERD. [33] Furthermore, the role of gastric acid in GERD severity is supported by the efficacy of acid suppressive drugs in its treatment.

One hundred patients (mean age 42.6 (12.8) years; 73 [73%] men) fulfilled the criteria for diagnosis of GERD, had Carlsson-Dent score ≥6.0, had erosive esophagitis (EE); responded to omeprazole, had significant reflux on 24-h pH metry. Of 100 patients with GERD, 45 (45%) had H. pylori infection. Patients with and without H. pylori infection were comparable in respect to age, gender and Carlsson-Dent score. The average gastric pH, % time gastric pH <4, <3, <2 were comparable among the two groups; percentage of time gastric pH <1.5 was higher in patients without H. pylori infection. Patients with GERD with and without H. pylori infection had comparable esophageal pH metry findings. Patients older than 40 years without H. pylori infection had lower average esophageal pH and longer reflux time in minutes than those with H. pylori infection. Patients with higher LA had more esophageal acid exposure than those with ENRD and LA-A both the gastric acid profile was comparable among them. Gastric acid profile (% time gastric pH <1.5) showed a trend from pangastritis < normal gastric mucosa < antral gastritis. Esophageal acid exposure was comparable among patients with GERD with and without H. pylori infection; this has also been shown in previous studies. [34] However, among patients >40 years old, absence of H. pylori infection was associated with higher esophageal acid exposure. A previous study on healthy volunteers showed that advancing age had no influence on gastric acid secretion in H. pylori-negative subjects. [35] Gastric acid secretion decreases with age in H. pylori-positive subjects because of the increasing prevalence of atrophic gastritis. [36] We found that gastric acid profile was similar in males and females, in contrast to the studies on healthy population. [37] Male patients had higher esophageal acid exposure and higher endoscopic grades of GERD than females, probably due to more exposure to dietary and environmental factors than women. [38]

Patients with antral gastritis had more acidic stomach than those with pangastritis. Gastric acid profile was comparable in patients with normal gastric mucosa than those with antral or pangastritis. Patients with pangastritis had lower PG-I/PG-II ratio than those with normal gastric mucosa. Patients with normal gastric mucosa had lower gastrin-17 levels than those with antral gastritis as well as pangastritis. Patients with H. pylori-positive gastritis had less acidic stomach, lower PG- I/PG-II ratio and higher gastrin-17 levels than those with gastritis who were H. pylori-negative. Parameters found significant on univariate analysis were entered into a multivariate model. Multivariate analysis showed that serum gastrin-17 ≤ 10 pg/L, presence of hiatus hernia and age >40 years were independently associated with higher risk of GERD. Patients having these parameters had 80.3% correct prediction for having EE. Removal of above three independent parameters from multivariate analysis showed an independent association of absence of H. pylori infection with presence of EE. Patients without H. pylori infection had 73.2% correct prediction for having EE. Gastrin-17 levels tended to be lower in patients without H. pylori infection indicating high acid output and therefore is associated with increased risk of GERD and BE. [39] We also found a correlation of serum PG-I levels and PG-I/PG-II ratio with gastric acidity among patients with GERD irrespective of presence or absence of H. pylori infection. In patients with H. pylori infection, higher PG-I and PG-II levels were associated with higher acidity of the stomach. The PG-I/ PG-II ratio did not correlate with gastric acidity; this might be related to the fact that our study population included patients with antral (high acid) and pangastritis (reduced acid) both among H. pylori infected group, thus balancing the effect of each other. Secondly, presence of H. pylori itself increases the gastric pH probably due to inflammation of the stomach and buffering of acid because of ammonia. [40,41] However, among patients without H. pylori infection, higher PG-I/PG-II ratio correlated with gastric acidity.

Conclusion

In conclusion, our study showed that presence of H. pylori in patients with GERD was associated with less acidic stomach and milder esophagitis. Patients without H. pylori infection and higher age especially males are at a higher risk of developing EE.

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