Prevalence of Histological Reflux Oesophagitis in H. Pylon Positive Patients: Effect of density of H. Pylori and Activity of Inflammation

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Abstract

Objective: Recently there has been a great interest in the role of Helicobacter pylori in gastroesophageal reulux disease. Many studies do not show any significant difference in the overall prevalence of H. pylon in patients with endoscopic oesophagitis and controls. In this prospective study we assessed the influence of H. pylori densit and activity of inflammation in different parts of stomach on histological oesophagitis.

Methods: One Hundred and forty consecutive patients undergoing endoscopy for dyspepsia and heartburn were evaluated. Three biopsies were taken from antrum and two each from corpus, cardia and lower oesophagus. Urease test (CLO test) was performed. Density and activity of infection was assessed in a semi-quantitative way.

Results: One Hundred and Fourteen (81%) patients from the 140 endoscoped, were positive for H. pylon and had HI. pylon positive antral gastritis. Of these 114 cases,H. pylonj were detectable in 104(91%) of biopsies taken from corpus and 96 (84%) of biopsies from cardia. There was a strong correlation of density of H. p Ion (0-3) in antrum with body and of body with cardia by Spearmcin correlation tests (p=0.000). But H. pylori were more dense in antrum as compared to corpus and in corpus as compared to cardia (p=0.0000 and 0.0003 respectively by wilcoxon's rank test). Neutrophil activity and degree of mononuclear infiltrate were also greater in antrum as compared to corpus (p=0.000 and 0.059). The activity and degree of inflammation was not significantly different in corpus-cardia pair. Out of 114 11. pylori positive patients, 75 had histological oesophogitis (p=0.855). Alter excluding cases of hiatal hernia (HF!) and gapping lower oesophageal sphincter (LOS), number of H. pylori positive patients decreased to 73, out of these 50 had histological oesophagitis (p=O.lO3). In all H. pylon positive patients with histological oesophagitis, H. pylori density (1-3) in antrum correlated with seventy of oesophagitis (P=0.011). Neutrophil activity in antrum and corpus also correlated with the severity of histological oesophagitis (P=0.024 and 0.035 respectively). Correlation further improved after excluding cases of HH and gapping LOS (P=0.002 for H. pylori density and 0.026 and 0.004 for activity in antrum and corpus). No correlation could he found of density and activity of infection in cardia with histological oesophagitis.

Conclusion: Our H. pylori positive patients had more dense and severe infection in antrum. Those who had histological oesophagitis in addition showed a positive correlation of the density of H. pylon in antrum and neutrophil activity in antrum and corpus with the severity of histological oesophagitis (JPMA 51:36; 2001).

Introduction

Helicobacter pylon is considered to be a pathogenic factor in gastritis, peptic ulcer, gastric cancer and MALT lymphoma[1,2]. Recently much interest has been generated to ascertain any relationship of H. pylon with gastroesophageal reflux disease (GORD). H. pylon is known to increase gastrin release and acid output[3-5]. It may also reflexly affect lower oesophageal sphincter and delay gastric emptying[6-10].

All these factors are known to play significant role in the pathogenesis of GORD[11-15]. There are studies to show increased prevalence of reflux oesophagitis in the patients with duodenal ulcer[16-18]. Contrary to this, recent work From the West shows that eradication of H. pylon from stomach may end up in GORD[19,20] and decline in the prevalence of H. pylori has been accompanied by an increase in GORD associated complications e.g. Barretts adenocarcinoma of distal oesophagus.
In low socio-economic strata of Karachi, majority of patients undergoing endoscopy for dyspepsia are positive for H. pylon. Many patients of dyspepsia have an overlap of both ulcer like and reflux like symptoms[21]. Studies have shed light on the role of acid reflux as well as of H. pylon in causing dyspepsia[22,23]. How does H. pylon influence the reflux disease in our patients is difficult to ascertain due to low number of H. pylon negative patients. In order to address ütnther the conflicting H. pylon -GORI) interaction, we did a prospective study. Purpose of this study was to determine the effects of colonization of antrum, corpus and cardia by H. pylori on reflux oesophagitis considering the following aspects (1) presence or absence of H. pylori (2) density of H. pylon colonization (3) severity of neutrophil activity and (4) degree of chronic inflammation.

Methods

Patient selection

Patients of dyspepsia and heartburn undergoing upper gastrointestinal endoscopy were considered for the study after obtaining informed consent to the study protocol. Background data was collected on age, sex, social class, symptoms and medication. Only patients with upper gastrointestinal symptoms for at least one month were included. Exclusions were recent intake of proton pump inhibitors (PPIs) or non-stetoidal anti-inflammatory drugs (NSAIDs) within last two weeks or antibiotics in the last four weeks. Patients found to have varices or malignancy on endoscopy were also excluded from analysis. Our patients belonged to the low socioeconomic class.

Endoscopy

Endoscopy was performed with Olympus videoscope (GIF130) or fibro-optic scope (GIF2T20, GIFXQ20). Biopsy specimens were obtained with standard biopsy forceps (Olympus FB-24U). Biopsies were taken: three from antrum and two each from the body of stomach, cardia and distal oesophagus. Biopsies form body of stomach were obtained from greater curvature and one each from anterior and posterior wall. Gastric cardia biopsies were obtained with the endoscopy in the retroflexed position about 5mm from squamocolumner junction. In the case of hiatal hernia biopsies were obtained form hernia sac from the proximal edge' of gastric folds below 'Z' line. Oesophageal biopsies were taken about 3cm above the squamocolumner junction. Endoscopic grading of oesophagitis was performed by using the criteria of Hetzel et al 24 Grande I, erythema or hyperaemia of oesophageal mucosa with no macroscopic erosions; grade 2, superficial ulceration or erosions involving <10% of the last 5cm of oesophageal squamous mucosal surface; grade 3, superficial ulceration or erosions involving 10-50% of the last 5cm of oesophageal squamous mucosal surface; and grade 4, deep ulcers anywhere in the oesophagus or confluent erosions involving >50% of the last 5cm of oesophageal squamous mucosal surface.

Histology

An antral biopsy was used for urease test while rest of the biopsy specimens were stained with haematoxylin and eosin and Giemsa stains. Two experienced pathologists blind to the endoscopic findings assessed the specimens. Oesophageal specimens were evaluated for the presence or absence of histological oesophagitis using a four point visual analogue scale (0-3 scale) (Table 1). Grading of gastric specimens was done based on Sydney System modified by Dixon et al25. Following features were assessed (1) presence or absence of H. pylon (2) density of H. pylon colonization (3) severity of neutrophil activity and (4) degree of colonic inflammation (Table 1).

Table 1. Semiquantitative Evalution of Oesophageal And Gastric Biopsies.

A. Oesophagitis

0 = Normal papillae and basal layers; no polymorphonuclear cells (PNCs).

1 = Increase in papillae length and basal layer thickness, no PNCs.

2 = Increase in papillae length and basal layer thickness with PNCs+1.

3 = Marked increase in papillae length and basal layer thickness and numerous PNCs

B. H. pylori density

0 = No organism identified.

1 = Rare organisms present.

2 = Organisms present in many but not all high dry fields (40x).

3 = Plentiful bacteria in all fields.

C. Neutrophil activity

0 = No extravascualr neutrophils.

1 = Scattered lamina propria extravascular neutrophils.

2 = Neutrophils infiltrating a minority of gastric pits.

3 = Neutrophils infiltrating majority of gastric pits/infiltrate within foveolar lumen

D. Chronic inflammation.

0 = Occasional lymphocytes and plasma cells (up to 5).

1 = Mild increase in mononuclear cells (MNCs) (6-10/HPF).

2 = Diffuse increase in MNCs (11-20/HPF).

3 = Diffuse dense increase in MNCs (>20/HPF).

Patient was considered H. pylon positive if histological examination of anyone of the multiple gastric biopsy specimens revealed H. pylori or the rapid urease test was positive.

Statistics

Calculations were performed using SPSS package. Significance was considered at 5% probability level.

Effects of presence or absence of H. pylori on presence or absence of oesophagitis were tested with chi square with Yate's correction. Spearman correlation coefficients were calculated for histological parameters of different biopsy sites in order to assess the correlation of gastritis with the severity of histological oesophagitis. Wilcoxon matched-pair signed-ranks test was used for comparison of paired samples to show differences in H. pylori gastritis in antrurn, corpus and cardia.

Results

During the study period, 140 consecutive patients who met the selection criteria were evaluated. Their demographic characteristics are given in Table 2.

Table 2. Demographic Characterstics of the study patients.

Total number of patients	140
Sex	
Male	85
Female	55
Age	
Mean ± S.D (yr.)	35.5 ±13.5
Median (range)	32(15-85)
Endoscopic findings: n (%)	
Hiatal hernia	31 (22)
Gapping lower oesophageal	25 (18)
Sphincter	
Clinical oesophagitis	49 (35)
Antral erythema (alone)	18(13)
Pangastric erythema	50 (36)
Duodenal disease	17 (12)
Histological oesophagitis*	91 (65%)
Positive H. pylori**	
Antrum	114 (81)
Corpus	104 (74)
Cardia	96 (69)

*p value for Spearman correlation for severity of clinical and histological oesophagitis = 0.009

**p values for Spearman correlation for H. pylori presence and density in different sites (antrum-corpus, corpus-cardia, antrum-cardia = 0.000 for each pair)

One Hundred and fourteen cases were positive for H. pylon. H. pylori positive antral gastritis was present in all 114 patients. Bacteria were detectable in 1 04 (91%) of corpus biopsies and 96 (84%) of biopsies taken from cardia. Though there was a strong correlation of density of H. pylori (0-3) in antrum with body and of body with cardia by Spearman correlation test, Wilcoxon's signed rank test

for paired samples showed significant differences in the density as we proceeded to the cardia (antrum > body. p=0.0000, body> cardia, p=0.0003). Neutrophil activity in antrum was greater than corpus (p=0000). A trend of decrease in the degree of mononuclear infiltrate was also noticed here (antrum> corpus. p=O.O592). The activity and degree of inflammation was not significantly different in corpus - cardia pair (p= 0.863 and 0.664 respectively).

H. pylon were present in 114 patients. Out of these 75 had histological oesophagitis. No apparent effects of presence of H. pylori in the stomach on presence or absence of histological oesophagitis could be found by using chi square with Yate's correction (p=O.855). As hiatal hernia and gapping lower oesophageal sphincter also contribute to the reflux oesophagitis, the analysis was done again after excluding above cases. Total H. pylon positive cases were 73, out of these 50 had evidence of histological oesophagitis (p=0.103). In 11. pylori positive cases with histological oesophagitis, the influence of gastritis of different parts of stomach on severity of histological oesophagitis was evaluated using Spearnian correlation test. In these cases, H. pylon density in the antruin and activity of' inflammation in antrum and corpus correlate with the severity of oesophagitis with significant p values (Table 3).

Table 3. H. Pylori positive patients with positive histological esophagitis: correlation of severity of esophagitis with different parmeters.

	All H. pylori positive cases (n=75)		H. pylori positive without hiatal hernia or gapping LOS (n=50)	
	Correlation coefficient	P value	Correlation coefficient	P value
H. pylori density				
Antrum	0.293	0.011*	0.429	0.002*
Corpus	0.114	0.330	0.217	0.130
Cardia	-0.001	0.994	0.073	0.616
Neutrophil activity				
Antrum	0.26	0.024*	0.315	0.026*
Corpus	0.244	0.035*	0.405	0.004*
Cardia	-0.035	0.961	0.062	0.668
Degree of mono-nuclear infiltration				
Antrum	-0.071	0.545	-0.204	0.156
Corpus	-0.117	0.319	-0.139	0.335
Cardia	-0.057	0.627	-0.144	0.317

*Statistically significant values.

Discussion

Infection with H. pylon is common and may coexist with another process e.g. GORD. H. pylon is not present in the squamous epitheliurn of distal oesophagus. Will the presence of El. pylon in the stomach and cardia influence GORD? Recently there has been a great interest in the role of H. pylon in reflux disease. Most of the studies do not show any significant difference in the overall prevalence of H. pylon in patients with GORD and control population[26-28]. Many of these studies define 'reflux group'

based on symptoms and compare it with a group of 'controls'; a heterogeneous group of patients undergoing endoscopy for reasons other than reflux.

In our study instead of reporting the prevalence of H. pylori in patients with GORD. we have assessed the prevalence of oesophagitis in patients with gastritis independent of any symptom-based group. We examined the potential influences of presence or absence of H. pylon infection, effect of its density, activity and degree of inflammation and distribution of 11. pylon in different parts of stomach on reflux oesophagitis. Instead of focusing on endoscopic oesophagitis, we have compared histological oesophagitis with histological changes in stomach to pick up niicroscopic influences of infection independent of conibunding variables of symptoms. We share the feelings of Wilkinson, et al, that endoscopy alone, without histology, has poor sensitivity and specificity for diagnosing diffuse mucosal diseases of oesophagus and stomach[29].

Factors involved in the pathogenesis of GORL) include lower oesophageal sphincter dysfunction w it h inappropriate LOS relaxations[30,31], disturbed or delayed gastric emptying[32,33], disturbed or delayed gastric accommodation response to swallowing[34], impaired oesophageal clearance of gastric contents[35] and hypersecretion of gastric acid[36].

High incidence of oesophagitis has been reported in patients with duodenal ulcer disease[16-18]. The reason is not clear though increase in basal acid output, hypergastrenemia and altered gastric emptying may be the contributing factors. In duodenal ulcer patients H. pylon causes increase in basal acid output and increase in meal stimulated gastrin release[37,38]. reduced accommodation (diastolic dysfunction) of stomach to a meal and delayed gastric emptying[6-10]. All these factors might be contributing.

Theoretically H. pylon could contribute to the development of' reflux disease even in patients without duodenal ulcer by increasing acid secretion with predominant ant ral gastritis and impairing gastric emptying. Other possible mechanisms could be production of cytotoxins harmful to oesophageal mucosa and by reflex impairment of function of lower oesophageal sphincter by inflammation of fundus[49] as studies have shown a neural mechanism controlling LOS with afferent limb of the reflex arc originating in fundus[40,41]. However recent epidemiological studies from the West have shown a decline in peptic ulcer and H. pylori paralleling with increasing incidence of GORD. Barrett's and adenocarcinoma of oesphagus.[42,43]. It has been suggested that H. pylon may have a potentially protective effect against GORD. The corpus inflammation induced by Cag A positive strains may lead to atrophic gastritis with loss of gastric acidity[44]. Ammonia generated by H. pylon may also be responsible for neutralizing the acid. So the eradication of H. pylon may reverse this effect, leading to an increase in the frequency of GORD.

Our study does not show any influence of presence or absence of H. pylon on presence or absence of oesophagitis; a conclusion shared by many other workers. Most of our patients were H. pylon positive and we do not have an adequate size comparison group of H. pylon negative patients. But an interesting correlation was seen in our H. pylon positive patients with histological oesophagitis. In these cases, density of H. pylon infection in antrum and neutrophil activity in antrum and corpus positively correlated with the severity of histological oesophagitis. Our relatively young patients had predominant antral gastritis, probably still having high acid output. Few other workers have shown a positive association of H. pylon with oesophagitis as well[45-46].

Previous studies done in H. pylon positive patients have shown increased basal, meal stimulated and gastrin releasing peptide (GRP) stimulated gastrin concentrations[47-49] resulting in increased basal acid and GRP stimulated acid secretion[50,37]. Eradication of H. pylon results in normalization of acid response[48-50]. Eradication of H. pylon also restores the cholecystokinin (CCK) stimulated release of somatostatin from D cells[51]. It has been suggested that inflammatory mediators and cytokines, TNFa and IL 113 are responsible for the release of gastrin and attenuation of effect of CCK on D cells[52]. So

active inflammation and release of these cytokines mediators are responsible for increase in acid output. . A subgroup of patients does exhibit lowering of gastric acid secretion associated with corpus predominant gastritis with atrophic changes[53]. Our patients had pangastritis but the group with histological oesophagitis still had very active antral inflammation probably pouring out higher acid. Recent studies in which biopsies were taken from different sites have shown that even the patients of duodenal ulcer have pangastritis with H. pylon spreading up to the cardia[54,55,27]. So when the infection is present in antrum, it is present usually in the rest of stomach and activity of inflammation seems to be more important predictor of increased acid output than mere distribution.

Recent belief of negative association of H. pylon infection with GORD has been developed froni some reports that eradication of H. pylori may be followed by development of GORD[19,20,56]. In one study reflux oesophagitis occurred in 25.8% of patients with duodenal ulcer after successful eradication therapy compared to 12.9% patients who remained positive for H. pylon during the follow up period of 3 years[19]. Other studies do not favour it. In one short-term study of 244 patients with peptic ulcer disease, symptoms of GORD were present in 20% of patients. Symptoms remained the same in 83% of patients, improved in 11% and worsened in only 6% of individuals who underwent successful eradication therapy[57]. ln another study during a 6 month follow up of 242 patients with duodenal ulcer, new symptoms of heartburn developed in 20%, irrespective of their H. pylori status[58], may be that may patients of duodenal ulcer have co-existing GORD[59] and symptoms of reflux are masked by the initial diagnosis as these patients are on antacids and anti-secretary drugs. Withdrawal of these drugs and weight gain after cure of infection would account for recurrence of symptoms.

In a study done by Pieramico 0 et al[60], overall prevalence of H. pylori in patients presenting with GORD was 48.7%. Patients with oesophagitis had a statistically greater prevalence of infection (56.9%) compared with no oesophagitis. This was comparable with a prevalence of 54.2% in patients with non-ulcer dyspepsia.

In our study, though the density of H. pylon in cardia correlated with the density in the corpus and antrum by Spearman correlation, Wilcoxon's signed rank test for paired samples showed a significant reduction in the absolute density as we proceeded to the cardia (antrum body > cardia). Neutrophil activity and mononuclear infiltrates were greater in antrum as compared to corpus and there was no significant difference in corpus - cardia pair. Both antral and cardiac mucosae mainly consist of surface mucus cells with low acidity, one may expect a similar density of H. pylori colonization and inflammatory activity in both areas. Why the density of H. pylon in cardia is low is not clear. Similar results have been shown by Hackeisberger A et al[54]. H igher inflammatory activity in the antrurn as compared to rest of stomach indirectly reflects that our patients were producing more, thereby influencing the severity of GORD. No correlation of density of H. pylon colonization in cardia or inflammatory activity of cardia with severity of histological oesophagitis could be found. Rather activity of cardiac gastritis was correlated with that of the corpus.

If we admit that theoretically H. pylon could contribute to the development of pathophysiological abnormalities which would make GORD more likely, then it seems logical that dense and active H. pylon infection in the antrum would make the histological oesophagitis worse mainly through altered gastric acid production. Further work is needed based on pH studies and biopsies before and after H. pylon eradication.

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