Helicobacter Pylori Infection Is Protective Against Development Of Complications Of Gastro Esophageal Reflux Disease (GERD): A Study Done In Central Gujarat.

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Citation

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Abstract

Summary: The intend of the study was to investigate the prevalence and association of H. pylori and its virulent strain (cytotoxin-associated geneA: CagA) in patients with gastro esophageal reflux disease and to compare it with that in a control group and also to investigate its correlation with various clinical, endoscopic and demographic parameters. Between January 2007 and December 2009 a prospective study was performed on 202 patients (M: F=275:187) who underwent esophagogastro duodenoscopy. Patient's demographics, clinical indication for esophagogastro duodenoscopy and prevalence of reflux esophagitis in H.pylori positive and H.pylori negative group were reviewed. Endoscopic examination was performed to assess the severity of esophagitis by Los angeles grading system, and presence of Hiatus hernia. Biopsies were processed for Rapid urease test, Gram staining, and culture and serum sample was tested for the presence of IgG Antibody against Cytotoxin–associated GeneA, antigenic determinants. Risk factors which may affect the severity of Gastro esophageal reflux disease (age, gender, smoking, alcohol, tobacco, Hiatus hernia, and H. pylori status) were evaluated. Age and sex matched non- reflux healthy volunteers were recruited as control for comparison. The overall prevalence of H.pylori infection in gastro esophageal reflux patients was 44 % (89/202). Among those with Grade A&B esophagitis, there was no statistically significant differences in H. pylori infected and non-infected patients respectively 97.7% Vs 92.9% (P= 0.967). The seroprevalence of Cytotoxin–associated GeneA positive strain in Grade A&B, Grade C&D, and control subjects was (98/192) 51%, (4/10) 40%, (70/100) 70% respectively, P<0.01. There was a gradual fall seen in the prevalence of H. pylori according to the different grade of esophagitis and logistic regression analysis shows that absence of H. pylori is associated with Gastro esophageal reflux disease. On univariate analysis, we observed that hiatal hernia (P=0.00) was significantly related to the presence of reflux esophagitis whereas gender (P value= 0.66), smoking (p value= 0.77), Tobacco (P value= 0.67) and alcohol (P value =0.5) were not significantly associated to Gastro esophageal reflux disease. In conclusion H.pylori infection plays no role in the pathogenesis of Gastro esophageal reflux disease, instead it protects from the complications of Gastro esophageal reflux disease and Seroprevalence of Cytotoxin–associated GeneA positive H. pylori contributes in lowering the prevalence of Gastro esophageal reflux disease.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic, relapsing acid-peptic disorder characterized by recurrent troublesome reflux symptoms; esophageal injury, such as reflux esophagitis; a variety of extra esophageal complications, reduced salivary production, and altered esophageal mucosal resistance.[1, 2]

In Asia, GERD has been considered as an emerging digestive disease.[3]

A variety of abnormality contribute to the development of GERD including transient lower esophageal sphincter relaxation, low esophageal sphincter pressure, presence of hiatus hernia and diminished esophageal clearance of reflux gastric content.[4]

H. pylori infection clearly plays a role in the pathogenesis of peptic ulcer diseases and is a risk factor for gastric carcinoma.[4, 5] The relationship between H. pylori and GERD has been a subject of great dispute in recent years.[5]

Last few decades has witnessed a gradual decrease in the prevalence of H. pylori infection in the west and a dramatic

rise in the incidence of adenocarcinoma of esophagus and cardia.[6, 7, 8]

Whether H. pylori still play a protective role in these GERD patients is unknown.[9] Recently, numerous investigations have been performed to elucidate the role of H. pylori infection in GERD pathogenesis.[9]

However there are no evidence based explanation of this phenomena and further investigations are needed.

In the light of this background information, we conducted study of 202 GERD patients in order to determine the prevalence of H. pylori (HP) infection. We evaluated the contribution of HP infection on the severity of GERD and compared it with that in a control group, parameters such as demographics, clinical characteristics, and endoscopic findings were also assessed in HP infected and HP non-infected subjects.

MATERIALS AND METHODS

SELECTION OF PATIENTS

Two hundred two patients out of total 462 dyspeptic patients (age 15-90 yrs) with a chief complaint of heartburn and primary diagnosis of GERD referred to the DEEP Surgical Hospital and endoscopy clinic, Anand, between January 2007 and December 2009, were prospectively enrolled in this study and their data were recorded.

The study was approved by the Local Ethical Committee of Pramukh Swami Medical College, Karamsad, Gujarat. Dully filled Consent form was obtained by all the patients participating in the study.

Inclusion criteria: All the patients with the symptoms of heartburn and acid reflux as their chief complaint, which improved on acid suppressive therapy or with persistent vomiting and abdominal pain, were enrolled.

Exclusion criteria were the following: 1) Previous therapy to eradicate HP. 2) Patients taking aspirin or non-steroidal anti inflammatory drugs (NSAIDS) in the past 4 weeks 3) Previous surgical procedure on digestive tract. 4) Patients were on proton pump inhibitors (PPI) 5) other severe accompanying diseases.

METHODS

Demographics details of the GERD patients were recorded, including, Age, gender, smoking, alcohol, tobacco, presence of hiatus hernia. All recruited patients underwent EGD to assess the severity of reflux esophagitis and presence of hiatus hernia and to exclude coexisting peptic ulcers.

Esophagitis was graded by endoscopy according to the Los angeles Classification System for the endoscopic assessment of reflux esophagitis [10]: Grade A: One or more mucosal breaks no longer than 5 mm, non of which extends between the tops of the mucosal folds. Grade B: One or more mucosal breaks more than 5 mm long, none of which extends between the tops of two mucosal folds. Grade C: Mucosal breaks that extend between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference Grade D: Mucosal breaks which involve at least 75% of the esophageal circumference

H. pylori status was determined by performing various invasive and non invasive tests. Three fragments of biopsies/lesion were taken from each patient for RUT (1 fragment), Gram staining (1 fragment), Histopathology (1 fragment) by Warthin starry, Giemsa and H&E.

After endoscopy 5 ml of blood was collected from each patient and serum sample was processed for detection of H. pylori IgG antibodies against the CagA antigenic determinant of H. pylori by indirect solid phase enzyme immunoassay test kit (Immunocomb II, Orgenics, Israel).

Definition of “gold standard”:

Subjects were classified as having current infection with H.pylori if RUT was positive within 4 hrs, or if H.pylori were detected by any histopathological staining, or if H.pylori was cultured from the biopsy specimen, or if serology is positive along with any positive invasive tests(RUT, Histopathology, culture, gram staining). If only serology was positive than it is considered to be past infection.[11, 12]

Slides for histopathology were stained by H&E, Giemsa and Warthin Starry, histological assessment was performed by an expert pathologist (Dr. Jignesh Brahmbhatt) independently and in a blind manner.

Control study was done on 100 healthy asymptomatic non reflux individuals randomly selected from the same geographical area, without evidence of acid-related diseases or upper digestive tract symptoms.; serum sample of each was tested for the presence of H. pylori IgG antibody against CagA, Antigenic determinants of H. pylori by indirect solid phase enzyme immunoassay test kit (Immunocomb II,

Orgenics, Israel).

STATISTICAL ANALYSIS

Risk factors that may affect the severity of GERD were evaluated using bivariate logistic regression analysis. P values were calculated by Pearson chi square test using SPSS-15 software. P value < 0.05 is considered statistically significant

RESULTS

A total of 462 consecutive dyspeptic patients were included in this study, out of 462 patients, 202 were endoscopically diagnosed as GERD patients. Out of 202 patients, 118 were males and 84 were females with the mean age of 43± 16yrs (range 15-90yrs).

Out of 202 patients, 120 patients (59.4%) had a chief complain of abdominal pain with heart burn, 52 (25.7%) had the symptoms of persistent vomiting, 19 patients (9.4%) had Haemetemesis, 3 patients (1.4%) had Melena and 8 patients (3.9%) had Dysphagia.

Prevalence rate of GERD was found to be high 44%, may be due to low socioeconomic and educational level of these people. Yet it is comparatively low than the other gastro duodenal diseases (Table 1).

The patients were defined as HP positive according to our gold standard definition. On the basis of results all the patients were grouped as either HP positive or HP negative. We have already shown previously the assays sensitivity and specificity for a current, active infection (compare to RUT, and gram staining) has been 98.8% & 92.9% respectively. [13]

Out of 202 GERD patients, HP infection were diagnosed in 89(44%) patients, 52 males (58%) and in 37 females (42%), while 113(56%) patients with 66 males (58%) and 47 females (42%) were HP negative.

As shown in table 1, out of total 462 consecutive dyspeptic patients included in this study, 220were HP positive and 242 were HP negative, out of 220 HP positive 89 had GERD (40%) and out of 242 HP negative 113 had GERD (47%). This shows the low prevalence of GERD in HP infected than in HP non infected patients.

Further more we found no statistical difference regarding the severity of symptoms complain by the patients between HP positive and HP negative group (Table 2).

High prevalence of GERD was seen in age -group 31-40 yrs (29%) than in 41-50 yrs (22%), followed by 51-60 yrs (15%), 61-70 yrs (11%) and least was found in the older age group 71-80(4%).

Table 3 shows that smoking (p value= 0.77), drinking (P value =0.5), tobacco (P value= 0.67) intake was documented in 17(8.4%), 13(6.4%), and 34(16.8%) patients respectively and were not statistically associated with GERD (p value > 0.05, 2 test).

Out of 202 GERD patients, only 64 (32%) patients showed habits of either smoking, drinking or chewing tobacco. Out of these 64 patients, 25 were HP positive (40%), and 38 were HP negative (60%). One hundred and thirty eight (69%) GERD patients did not show any habits. Out of these 139 patients, 64 were HP positive (46%), 75 were HP negative (54%).

Sliding Hiatus hernia was found in only 14 cases out of 462 patients (3%), and all the 14 patients had GERD (P value 0.000, 2 test). Out of 14, 5 were HP positive (36%) and 9 were HP negative (64%), (P value=0.401 2 test).Shows no association between HP status and hernia.

Logistic regression coefficient shows that patients having hiatus hernia have approximately 22 times risk of getting GERD (Table 4). Chi square analysis shows that presence of hernia does not affect the severity of GERD, (P value 0.5).

Reflux oesophagitis was evidenced by endoscopy in 202 patients (44%), according to the Los-angeles classification, out of 202 patients, 183 were graded A (84 HP positive and 99 HP negative); 13 patients were graded (B&C), 4 HP positive and 9 HP negative, finally 6 patients were graded D (1 HP+ positive, 5 HP negative). All the patients with grade D esophagitis had an esophageal ulcer but none of them had Barrett epithelium.

Eighty nine GERD patients were confirmed to have HP infection, of these 84(94.3%) had mild (Grade A) esophagitis whereas 4 had Grade B&C esophagitis (4.4%) and only 1 had esophageal ulcer (1%). Amongst those with esophagitis, H. pylori non-infected had more Grade A&B esophagitis than infected patients respectively (55% Vs 46%). This shows the high prevalence of milder GERD in HP non infected patients.

One hundred age and sex matched non-reflux; healthy volunteers were studied as a control. Prevalence of H.pylori infection in patients with severe esophagitis (20%) was

significantly lower than mild esophagitis (45 %, Pvalue< 0.05 2 test) (Table 5).

Figure 1

Table 1: Prevalence of in various Gastro intestinal disorders:

Diseases	*Total no. of patients, n= 462*	*HP positive 220*	*HP negative 242*	*% prevalence*
GERD	202	89	113	44%
Gastritis	210	100	110	48%
Duodenitis	27	14	13	52%
Duodenal ulcer	09	8	1	89%
Gastric ulcer	07	6	1	86%
Esophageal varices	07	3	4	43%
Total	462	220	242	48%

Figure 2

Table 2: Clinical parameters of 202 GERD patients:

Symptoms	*Total, n=202*	*HP positive 89/202*	*HP negative 113/202*	*P value*
Heartburn with persistent abdominal pain	120	52(58%)	68(60%)	NS
Persistent Vomiting	52	24(27%)	28(25%)	NS
Haemetemesis	19	8(9%)	11(10%)	NS
Melena	3	2(2%)	1(0.8%)	NS
Dysphagia	8	3(3%)	5(4%)	NS

Figure 3

Table 3: Evaluation of various risk factors of GERD

Variable	*GERD , n=202*	*Total no (%)*	*P value*
	Gender (M:F= 275:187)		
Male	positive	118 (42.90%)	0.668
	negative	157 (57.09%)	
Female	positive	84 (44.91%)	
	negative	103 (55.08%)	
	Smoking, n=37/462		
negative, n=425	positive	185(43.5%)	0.776
	negative	240(56.5%)	
positive, n=37	positive	17(46%)	
	negative	20(54%)	
	Alcohol, n=24/462		
negative , n=438	positive	189(43%)	0.505
	negative	249(57%)	
positive, n=24	positive	13(54%)	
	negative	11(46%)	
	Tobacco, n=74/462		
negative No, n=388	positive	168(43%)	0.674
	negative	220(57%)	
positive, n =74	positive	34(46%)	
	negative	40(54%)	
	Hiatus hernia, n=14/462		
negative No, n=448	positive	188(42%)	0.000
	negative	260(58%)	
positive, n=14	positive	14(100%)	
	negative	0(0%)	
	***H. pylori* infection, n=220/462**		
negative No, n=242	positive	113(47%)	0.17
	negative	129(53%)	
positive, n=220	positive	89(40%)	
	negative	131(60%)	

* *P* value < 0.05 is considered significant, chi-square test

Figure 4

Table 4: Logistic regression of GERD in terms of five variables:

Variables	*coefficient*	*P- value*	*Odd ratio*	*95% C.I .for odd ratio*	
				lower	**upper**
Tobacco	**0.009**	**0.97**	**1.01**	**0.55**	**1.85**
Alcohol	**0.358**	**0.45**	**1.43**	**0.56**	**3.65**
Smoking	**0.269**	**0.47**	**1.31**	**0.63**	**2.71**
Hiatus hernia	**21.565**	**0.00**	**0**	**0**	-
***H. pylori* infection**	**- 0.238**	**0.22**	**0.79**	**0.54**	**1.15**

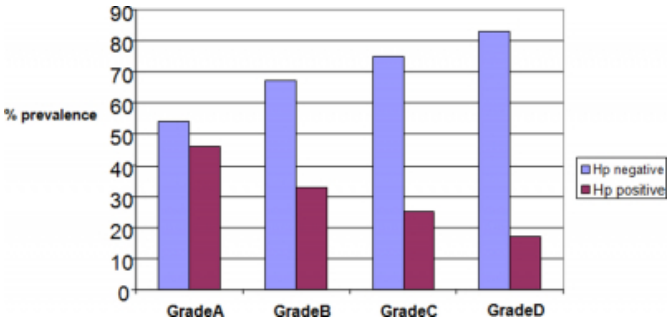
Figure 5

Table 5: Prevalence of infection and CagA positivity in patients with different degrees of GERD and Control patients:

	Grade A&B	*Grade C&D*	*Control volunteers*
No. of patients	192	10	100
Prevalence of HP infection	87(45%)	2(20%)	
Prevalence of CagA positive strain (%)	51%	40%	70%

Figure 6

Figure 1: Spectrum of GERD in Positive and Negative Patients



DISCUSSION

GERD is a common condition affecting nearly 30% of the population. [14, 15] The relationship between H. pylori and GERD is not well established, and in the medical literature is possible to find a variety of reports. While some authors find a close relationship between both conditions others do not report any relationship between them and finally other groups of authors maintain that this organism has a protective effect against GERD. [15]

Different studies have evaluated the prevalence of HP infection in the patients with GERD. [15] Absence of control group is the major short coming in several studies [16]

It was suggested that HP could contribute to GERD through different mechanisms: cardia inflammation causing lower esophageal sphincter weakness; increased acid secretion due to antral gastritis; delayed gastric emptying and cytotoxin production causing esophageal epithelium injury. [17]

Several protective mechanism have been postulated to explain the protective effect of H. pylori against GERD is by decreasing the potency of the gastric refluxate in patients with corpus predominant gastritis; improvement of gastro esophageal junction due to proximal gastritis and finally production of ammonium by gastric colonization of HP that could be a potential stopgap system.[17]

At epidemiological level a decrease in the incidence of gastro duodenal ulcer diseases in western countries has been observed in last few decades, probably due to reduction in H. pylori Infection , on the other hand incidence and prevalence of GERD,and adenocarcinoma of the esophagus have notably increased throughout the same period.[16] This opposite epidemic tendency suggests that it may act as an etiological factor of peptic ulcer disease and at the same time, as a protective agent against GERD and its complications. [16]

Rajendra et al [18] reported H. pylori infection may protect complicated reflux disease via induction of corpus atrophy. Shahabi S. et al [19] proposed a neuro- immunological mechanism for the protective effect of H. pylori on GERD.

Our study shows 44% overall prevalence of HP infection in GERD patients, this percentage confirms the result of other epidemiological studies which shows prevalence of 40% in most of the cases [20].

Young age group 31-40 yrs showed highest prevalence amongst the all, the plausible explanation for this may be due to their dependency on abusive habits.

Studies suggest that smoking reduces LES muscle function, increases acid secretion, impairs muscle reflexes in the throat, and damages protective mucus membranes. Smoking reduces salivation, which helps neutralize acid.[21, 22]

Alcohol has mixed effects on GERD. It relaxes the LES muscles and, in high amounts, may irritate the mucus membrane of the esophagus. Small amounts of alcohol, however, may actually protect the mucosal layer. A combination of heavy alcohol use and smoking increases the risk for esophageal cancer. [23]

Univariate statistical analysis showed a moderately strong, dose-dependent relationship between increased duration of daily tobacco smoking and risk of reflux symptoms (P <

.0001). [23] Multivariate analysis showed that individuals who had smoked daily for more than 20 years were 70% more likely to have symptoms of reflux compared with those who had smoked daily for less than a year [23]

We found no significant correlation or outcome between habits and development of GERD (Table 3). This conflicting report was may be as majority of our patients were not chronic smokers or alcoholics. This result may be contradictory to the other authors who had shown the influence of smoking on GERD [24]

The presence of a hiatal hernia increases the number of reflux episodes by mechanically weakening esophagogastric junction (EGJ) and impairs esophageal clearance [25].

Huang X et al [26] and Buttar et al [27] proposed that hiatal hernia contributes to reflux via variety of mechanisms like proximal migration of LES, impaired ability of the crura to function as an external sphinter, and trapped gastric content in the hernial sac.

In our study we found significant correlation of hiatus hernia with GERD (P value 0.00, 2 test), considered by some authors as a supporting element of GERD and significantly associated with the development of esophagitis [28], in our study out of 462 patients, only 14 patients had hiatus hernia and all had GradeA esophagitis. This finding shows that HP infection protects against the development of complications of GERD in subjects with hiatus hernia. Our finding is consistent with the Award and colleagues [28,] who found that HP infection and hiatus hernia in patients with GERD do not accelerate the disease.

To avoid inter-observer variation and bias in assessing the severity of esophagitis, our study was designed so that all cases were assessed by a single endoscopist who viewed video tape of the endoscopic examination without knowing the H. pylori status of the patients[29] .In this study 95% patients had Grade A& B esophagitis, only 5% had severe esophagitis, HP positive rate in grade A&B is 45% whereas HP negative rate in grade A&B is 55% .This finding shows that H. pylori non-infected had more Grade A&B esophagitis than infected patients, We also found that gradual fall is observed as the Grade of esophagitis increases, fluctuating the prevalence from 46% to 17% respectively (figure 1). These results parallels to several reports which suggest that HP positive patients are less likely to have endoscopic/ histological changes, and when present, the severity of esophagitis was decreased [30]

As a whole, out of 89 HP positive 82 patients had mildest form of GERD, correlates with the fact of protective mechanism of HP on complications of GERD.

CagA positive strains are considered to be more virulent and induce more severe corpus gastritis [30]. It has been postulated that not only the presence of H. pylori but also the virulence of each genotype would be important in the protection from GERD and its complications. Thus it is demonstrated that patients who are infected by CagA positive genotypes, which are more virulent, have a less probability of suffering GERD and its complications[30]. Recent studies reported that in H. pylori infected GERD patient's CagA negative strains are more commonly found among those with complications. [31, 32, 33]

We found positivity for anti CagA antibody in 51% of Grade A&B and 40% of Grade C&D patients. This difference in prevalence did not show statistically significant difference by chi- square test (2>0.05).

Our study correlate with the study of Vicari et al [32] who studied the relationship between CagA positive H. pylori and GERD complications; found predominance of CagA negative strains among severe and complicated GERD patients.

Chow et al. [33] also confirmed the inverse relationship between both. Milder esophagitis in H. pylori infected GERD patients (87/89) can be explained by the high prevalence of CagA positive strain. This finding also suggests that the high prevalence of cagA positive H. pylori contribute to lower the prevalence of GERD. Anti cag A status was found significantly high (P value < 0.05) in the general population of Anand (70%).

Our control study results correlates with the study of Haruma et al [34] 2000, Koike et al [35] 1999, Wu et al [36] 1999.

In Conclusion, Prevalence of H. pylori in GERD patients is lower than that in general population and its presence is associated with the milder form of GERD. Based on these findings it seems that role of H. pylori in the development of GERD is protective and high prevalence of CagA positive H. pylori may contribute to lower prevalence and protect against the complications of GERD.

However, this is an evolving area with ongoing research; still relationship between HP and GERD needs to be clarify,

and better designed, large scale prospective studies and trials are required.

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