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Original Article

Helicobacter pylori eradication and histopathological esophagitis in dyspeptic patients

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ABSTRACT

Background: The association of *Helicobacter pylori* with peptic ulcer disease, atrophic gastritis, gastric adenocarcinoma, MALT (mucosa associated lymphoid tissue) lymphoma is well recognized.

Aim: This study was conducted to see whether there was any relation between *H pylori* eradication and reflux esophagitis in Iran.

Methods: Eligible dyspeptic patients referred to Gastroenterology clinic in Baqiyatollah hospital were endoscopied and evaluated for endoscopic and pathologic esophagitis and the *H. pylori* infection status was determined by rapid urease test. *H. pylori* infection was treated by an anti *H. pylori* drug regimen and successfully eradicated patients according to negative C^{14} urea breath test were followed and re-endoscopy was performed 6-9 months after the end of treatment.

Results: From175 eligible patients,54% were *H. pylori* positive, 68 of them (72%) had successful H.P. eradication and 64 patients completed the follow-up. The rate of histopathologic inflammatory esophagitis was higher in second endoscopy, compared with that of first endoscopy, i.e., before *H. pylori* eradication (75% vs 40.6%) ($p<0.05$). Progression of pathological esophagitis was seen in 56.3% of patients between the two endoscopic evaluations in spite of no change in clinical and endoscopic findings. There were no significant differences in dietary and smoking habits and body weights on re-endoscopy session compared with that of the first endoscopy visit ($p>0.05$).

Conclusion: This study suggests that *H.pylori* eradication in dyspeptic patients may lead to increased frequency of histopathological esophagitis Hence, In patients presenting with symptoms of dyspepsia , a cautious approach should be exercised if *H.pylori* eradication is being contemplated.

KEYWORDS: Helicobacter pylori, eradication, esophagitis, dyspepsia

Introduction

The association of *H. pylori* with peptic ulcer disease, atrophic gastritis, gastric adenocarcinoma, MALT lymphoma is well recognized,[1] but its relationship with functional dyspepsia and GERD is unclear.[2,3] A "test and treat" approach based on non-invasive screening of adult patients less than 45 years (the age cut-off may vary locally) presenting to primary care clinic with persistent dyspepsia has been suggested after exclusion of those with alarm symptoms.[4]

Assuming a high prevalence of functional dyspepsia and *H.pylori* in general population, many patients would need to be treated by this approach, while their long-term outcome is unknown. In 1997 the hypothesis of relationship between *H.pylori* and GERD was suggested, although no correlation was noted between *H.pylori* and severity of esophagitis.[5-7] Recently many new epidemiologic studies have been conducted in this regard.[8,9] Along with decrease of *H. pylori* colonization

in the stomach in western countries, the prevalence of peptic ulcer disease and distal gastric cancer has also decreased.[10] On the other hand, the prevalence of GERD, Barrett's esophagus and esophageal adenocarcinoma (EAC) have increased in recent years, so that EAC have become more common than SCC (squamous cell carcinoma) in western countries.[8,11-13]

GERD is the main risk factor for Barrett's esophagus, which is the only known precursor lesion of EAC. Thus, the essential question that needs to be answered is the protective effect of *H.pylori* colonization in stomach on GERD and its complications. Up to now there are some debates about the protective function of *H.pylori* on GERD. Association is higher in Asian studies than among North American and European ones. Some meta-analyses show significant association between absence of *H.pylori* infection and GERD symptoms, and a positive association between anti *H.pylori* therapy and occurrence of both de novo and rebound/exacerbated GERD. The significance of these associations appears to have been inflated by the effect of single trials and by geographical variations.[14] Considering controversies regarding *H.pylori* association with GERD in different studies in different countries,[15-20] this study was performed to clarify the association between HP infection and GERD in Iran.

Methods

All eligible dyspeptic patients referred to gastro-intestinal endoscopy ward of Baqiyatollah referral hospital and who agreed for follow up upto 1 year were enrolled in the study. Patients with systemic disease, present or past history of malignancy, history of gastric outlet obstruction, recent antibiotic usage, NSAID usage and gastric surgery were excluded from the study. The study protocol was approved by research ethics committee of Baqiyatollah University of Medical Sciences. Informed consent was obtained from the patients before enrollment.

All the participants underwent upper gastrointestinal endoscopy with Olympus GIF 200 after local anesthesia of the pharynx by 10% lidocaine spray. Endoscopy was done by one of the two gastroenterologists and the appearance of the esophagus was recorded according to the Los Angeles criteria. *H.pylori* status was evaluated with rapid urease test (RUT) kit made by Chemenzyme Company (Tehran, Iran) which has been approved by the Reference laboratory of the Health and Education ministry of Iran.

Two biopsy samples were also obtained from about 2.5 cm above esophagogastric junction (EGJ) and oriented on a special filter paper and immersed in 10% formalin solution and sent to the histopathology department of the hospital, which were then processed and evaluated and reported by one pathologist who was blinded to the endoscopic and clinical findings of the patients. All biopsy specimens were obtained by the Jumbo biopsy forceps.

Histopathologic grading of esophagitis was done by a pathologist as non-inflammatory or inflammatory changes (acute or chronic), epithelial necrosis and epithelial repair(**Table 1**). Endoscopic classification of GERD was done according to "Los Angeles"' classification. [21] In addition to demographic, endoscopic and pathologic findings, other data regarding weight changes, food habits, appetite, bowel habits, smoking and ethanol or caffeine consumption were collected and recorded in questionnaires. In patients who were positive for *H. pylori* test, anti *H. pylori* drug regimens was administrated for two weeks. Eradication was done using the traditional quadruple treatment regimen for *H. pylori* including bismuth 240 mg BID, omeprazole 20 mg BID, amoxicillin 1gr, metronidazole 500 mg twice a day for two weeks.

Four to six weeks after the end of treatment, urea breath test (UBT) with C14 was performed in an outside radioisotope laboratory whose staffs were blind to the study design and the intervention administered to the patients. Patients had regular visits for follow up every 1-2 months . The follow up was done by two gastroenterologists. H2 blockers were administered to all the patients for 2 months after triple therapy and as needed thereafter. Six to nine months after successful eradication, re-endoscopy was performed in UBT negative patients (for long term result and detection of histopathological changes) by one of the same two gastroenterologists who was blinded to the first endoscopy report.

On re-endoscopy, biopsy specimens from about 2.5 cm above EGJ were obtained and after orientation of specimens on a special filter paper and immersion in 10% formalin solution sent to the same histopathology department to be examined by the same pathologist who was again blinded to the clinical and endoscopic status of the patients. The specimens were evaluated for histopathologic esophagitis. The patients were recommended not to take any prescription for at least 4 weeks before their re-endoscopy session. A questionnaire similar to the first one was also filled by a general practitioner who was working with the team. The frequencies of continuous variables were expressed as mean and standard deviation. Groups were

compared using unpaired Student t test and categorical variables were compared using chi square test. p values < 0.05 were considered significant. The data was analyzed by SPSS software version 11.0.

Table 1: Histopathological characteristics of esophagitis

1. Normal
2. Nonspecific
   a) Nuclear enlargement
   b) Spongiosis
   c) Acanthosis
3. Non inflammatory
   a) Basal cell hyperplasia
   b) Increased papillary height
4. Acute inflammatory changes
   a) Vascular congestion or stasis
   b) Mucosal edema
   c) Polymorphonuclear infiltration (neutrophils and eosinophils)
5. Chronic inflammatory changes
   a) Mononuclear leukocyte infiltration (macrophages)
   b) Increased macrophage activity
   c) Proliferation of fibroblasts
   d) Ingrowth of vascular endothelium
6. Epithelial Necrosis
   a) Erosion
   b) Ulceration
7. Epithelial repair
   a) Granulation tissue
   b) Fibrosis(stricture formation)
   c) Epithelial regenerationa
   d) Squamous replication
   e) Columnar metaplasia (Barrette esophagus)
   f) Dysplasia

Results

Of 175 consecutive eligible dyspeptic patients, 94 of them were positive for *H.pylori* infection (54%) and H.pylori was successfully eradicated by the 2 weeks anti *H.pylori* drug regimen in about 72% of these cases (68 cases). Mean time of follow-up was 7.6 months. Four patients didn't complete the study or refused to be re-endoscopied on follow-up. Thus 64 patients (44 male, 20 female) completed the study. The demographic characteristics of patients have been shown in **Table 2**.

Clinically, 52 patients (82%) had pyrosis or retrosternal burn. Endoscopically, according to Los-Angeles classification, there were normal distal esophageal mucosa, grade A and B esophagitis in 56.7%, 36.7% and 6.6% patients, respectively. Esophagitis grade C and D and Barrett's epithelium were not seen. Active duodenal ulcer was reported in 30% of patients. Histopathologically, inflammatory esophagitis was reported in (40.6% of the cases. The remaining cases had normal lower esophageal mucosa, non-specific inflammation and non-inflammatory changes (**Table 3**).

Follow-up endoscopy and lower esophageal mucosa biopsy, similar to the first endoscopy was performed in 64 UBT negative patients 6-9 months after the end of 2 weeks *anti-H.pylori* therapy and demographic and clinical characteristics of the patients were gathered again. Endoscopic appearance of lower esophageal mucosa did not change in 34 (53%) cases, but in 13 (20%) patients grade of esophagitis increased. Histopathologically, inflammatory lower esophagitis was reported in 48 cases (75%), while the remaining 16 (25%) had normal esophageal mucosa, non-inflammatory or non-specific esophagitis. Although no grading changes were noted in 21 patients (32.8%), increased grading of pathologic esophagitis was observed in 36 patients (56.3%) ($p<0.05$). Clinically, reflux symptoms did not change in 40 patients (62.5%), but increased in 2 patients (3.1%) and decreased in 22 cases (34.4%). There were no significant differences in dietary and smoking habits in re-endoscopy session compared with those of the first endoscopy visit ($p>0.05$). Forty three patients (74%) had no change in their weight despite of increased appetite in 23 cases (36%). No significant correlation was noted between increased grading of pathologic esophagitis and variables such as sex, age, dietary habit, hiatus hernia and duodenal ulcer.

Table 2: Demographic characteristics of patients who completed the study

Parameters	Male	Female	Total
n (%)	44 (68.8%)	20 (31.3%)	64
Age (Mean±SD)(yrs)	36.39±10.3	41.85±15.8	38.09±12.4
Weight (Mean±SD)(kg)	71.16±10.5	63±10	68.6±11
Height (Mean±SD)(cm)	171.67±7.9	159.67±7.4	168.33±9.4
BMI (body mass index) (Mean± SD) (kg/m2)	21.06±1.7	20.37±0.9	20.8±1.5

Table 3: Clinical, endoscopic and pathologic findings before and after eradication

Variables	Before eradication (%)	After eradication (%)	p-value
Reflux symptomse≥one time/day	22.6	10.9	NS
Normal esophagus (endoscopic)	56.7	64	NS
Grade A esophagitis (endoscopic)	36.7	25	NS
Grade B esophagitis (endoscopic)	6.6	9.4	NS
Grade C esophagitis (endoscopic)	—	1.6	NS
Inflammatory esophagitis(pathologic)	40.6	75	< 0.05*

**p<0.05 significant*

NS: non significant

Discussion

Six to nine months after successful eradication of *H.pylori*, clinical and enodoscopic findings of reflux esophagitis did not change, but the pathologic grading of reflux esophagitis increased; a difference that was not related to the patients age, sex, endoscopic view, change in body weight or dietary habits. Although increased reflux esophagitis have been shown in several studies, the mechanism of injury has not been clearly defined. Some proposed hypotheses are as follow: Inflammatory infiltration secondary to gastric *H.pylori* colonization can cause serious damage to parietal cells and decrease in acid secretion.[20,22,23] After successful *H.pylori* eradication, parietal cell acid secretion returns to normal and thus may facilitate gastro-esophageal acid reflux.[24-26]

Supporting evidences are provided by studies showing independent protective role of cag A+ *H.pylori* and 1L 1b and 1L RN allele polymorphism against GERD [27] and very low prevalence of GERD in some areas like China and Japan (<5%), where there is high prevalence of Cag+ *H.pylori* (80%).[13,28] However, this theory has not been accepted because almost all duodenal ulcer patients have antral gastritis and high acid secretion.

Another hypothesis is urease effect of *H.pylori* leading to ammonium production in stomach that can potentially neutralize acid load in esophago-gastric junction. This process should stop after *H.pylori* eradication.[29,30] Some studies provide evidences that *H.pylori* eradication cause decrease in gastric pH in omeprazole recipients. It seems that *H.pylori* aggravates inhibitory effect of omeprazole on acid secretion so that the presence of *H.pylori* can accelerate improvement of esophagitis.[31-33]

The issue of correlation between *H.pylori* colonization and gastric motility is another controversial theory. While many studies have shown no correlation between *H.pylori* and gastric motility,[34-36] other authors emphasize on the effect of gastrin on LES (lower esophageal spincter) pressure increase. It is postulated that a decrease in serum gastrin level after *H.pylori* eradication may decrease LES pressure and hence facilitate reflux esophagitis. Epidemiologically, some studies have shown significantly lower prevalence of *H.pylori* colonization in GERD patients in comparison with general population (23-31% vs 51-61%). [37,38] However, decreased prevalence of H.pylori in caucasian population of developed countries parallels the increased prevalence of EAC as a final complication of GERD.[39,40] The major limitation of our study was the absence of control group and short follow-up time.

In conclusion, this study suggests that *H.pylori* eradication in dyspeptic patients may lead to increased frequency of histopathological esophagitis Hence, in patients presenting with symptoms of dyspepsia , a cautious approach should be exercised if *H.pylori* eradication is being contemplated.

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