Original Article

Correlation Between Endoscopic and Histological Findings of Dyspeptic Patients and their Association with Helicobacter Pylori Infection

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Abstract
There is a high prevalence of H. pylori infection in Bangladeshi population that causes site specific diseases which includes gastritis, gastric ulcer, duodenal ulcer and gastric carcinoma. The Cross sectional study was carried out in the Department of Microbiology and immunology, Bangabandhu Medical University (BSMMU), during the period of September, 2018 to July, 2019. Dyspeptic patients, who underwent endoscopic examination at the Department of Gastroenterology of Dhaka medical College and Hospital, who fulfilled the inclusion criteria were enrolled as study population. Collected gastric and duodenal biopsy specimens from 142 patients were categorized as H. pylori positive cases (34.5%) and H. pylori negative cases (35.2%) based on the case definition used in the study by RUT, Histology and ureC gene PCR. All of the laboratory works were performed at Department of Microbiology and Immunology except Histology which was performed at the Department of Pathology of BSMMU. Endoscopic findings significantly co-related with histological findings (p = 0.001). Highest rate of H. pylori infection was found in 76% of duodenal ulcer cases and lowest in Adenocarcinoma group being 9% of total study population. H. pylori infection was positively associated with duodenal ulcer cases (p=0.014) and negatively with adeno carcinoma cases (p=0.002) in a statistically significant manner.

Key words: H. pylori, Gastroduodenal disease, Dyspepsia

Introduction
There is a high prevalence (67%) of H. pylori infection in Bangladeshi population.1 Commonest symptom of H. pylori infection, dyspepsia is considered as one of the most common causes of patient’s referrals to Gastroenterology Centers.2 Dyspepsia is generally defined as chronic or frequently recurring epigastric pain or discomfort originating in gastro duodenal region and may be accompanied with other gastrointestinal symptoms such as nausea, belching, vomiting, postprandial fullness and early satiety.3 In Asia 8%-30% people suffer from dyspepsia.4 Prevalence of H. pylori infection in dyspeptic patient in India was 32.9% among the adult population.5 Overcrowding, bad sanitation and unhealthy practice favor high prevalence of H. pylori in Bangladesh.6,7 The best specimens for isolation of H. pylori are biopsy samples obtained during endoscopy.8 The association of H. pylori with gastritis, duodenal ulcer and gastric cancer has been reported by investigators from different countries all over the world including ours.9,10,11,12,13

Materials and Methods
The Cross sectional study was carried out in the Department of Microbiology and immunology, Bangabandhu Medical University (BSMMU), during the period of September, 2018 to July, 2019.

Patient selection and Sample Collection
Dyspeptic patients, who underwent endoscopic examination at the Department of Gastroenterology of Dhaka Medical College and Hospital, aged from 18 to onward presenting with symptoms of dyspepsia for more than one month were included in the study.14 Patients who received H. pylori eradication treatment in the previous 2 months15, elderly individuals (65 years), had severe medical or surgical illnesses or used proton pump inhibitors, nonsteroidal anti-inflammatory drugs, colloidal bismuth compounds, or antibiotics within 4 weeks of enrollment

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were excluded from the study. Collected gastric and duodenal biopsy specimens from 142 patients were categorized as *H. pylori* positive cases (34.5%) an *H. pylori* negative cases (35.2%). According to case definition used in this study, patients were considered as *H. pylori* positive when positive results were obtained in at least two of the three tested methods Rapid urease test (RUT), histology for *H. pylori* and PCR for *ureC* gene and considered as negative when the results of all diagnostic tests were negative. Patients positive by only one test were considered as indeterminate or doubtful case. Gastroduodenal diseases were diagnosed by endoscopic and histopathological examination and established in accordance with the Sydney System Classification.

**Laboratory Procedures**

All of the laboratory works were performed at Department of Microbiology and Immunology except Histology which was performed at the department of Pathology of BSMMU.

Total four to five pieces of gastric tissue specimens were taken from gastric antrum, body and margins of the lesion. One specimen collected from the antrum was immediately placed into a screw capped bottle containing rapid urease test media to detect the presence of *H. pylori*. Two specimens were collected from the antrum and body, preserved in 1.5 ml micro centrifuge tube containing 1 ml phosphate buffer solution for detection of *H. pylori* *ureC* gene and stored at -20°C until DNA extraction from the samples was performed. One to two specimens, each collected from margins of erosion, ulcer or growth were collected in a screw capped plastic pot containing 10% buffered formalin and was sent to the Department of Pathology, BSMMU for histological examination.

**Histological Examination**

Tissue sections were prepared and stained with Hematoxylin and Eosin (H&E) for the diagnosis of gastroduodenal diseases and modified Giemsa stain for *H. pylori* detection. The biopsy specimens were analyzed by a pathologist without knowledge of the clinical and endoscopic finding of the patients.

**Category of study population on the basis of Histological findings**

The study population were diagnosed as chronic gastritis, chronic gastric ulcer, duodenal ulcer, intestinal metaplasia and gastric carcinoma by histological examination. For evaluation of results of the study, gastroduodenal diseases were categorized into three groups- a) Gastritis, b) Peptic ulcer diseases (chronic gastric ulcer and duodenal ulcer) and c) Gastric carcinoma and/or precancerous lesions (intestinal metaplasia and gastric adenocarcinoma group).

**DNA Extraction and *ureC* Gene PCR**

DNA from gastric tissues were extracted by using the QIAamp (QIAGEN) DNA Mini Kit according to the manufacturer’s instructions. For confirming the presence of *H. pylori* DNA in tissue, the *ureC* gene was identified by PCR using the following forward and reverse primer-A A G C T T T T A G G G G T G T T A G G - G T T T;AAGCT-TACTTTCTAACACTAACGC. The DNA were denatured at 94°C for 5 minutes, followed by 35 cycles at 93°C for 1 minute, 55°C for 30 seconds, and 72°C for 1 minute with a final extension at 72°C for 10 minutes. The PCR product was analyzed in 2% agarose gel with ethidiurn bromide which was prepared in 1xTAE (Tris Acetic acid EDTA- Ethylene diamine tetra acetic acid) buffer by electrophoresis for 30 minutes to detect specific band of 294 bp.

**Statistical Analysis**

The prevalence of *H. pylori* infection by PCR for *ureC* gene and rapid urease test, from gastric mucosal biopsy is 67% in Bangladeshi population. Acceptable error was 5%. The statistical analysis was performed using SPSS software package version-23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). The Chi-square test or Fisher’s exact test were used to compare between proportions. Values of p< 0.05 were considered statistically significant.

Figure-I: Agarose gel electrophoresis analysis showed amplified DNA product of *ureC* (294 bp). Lane P =positive results. Positive control (PC): *ureC* positive *H. pylori*, negative control (NC): amplified product of PCR without DNA.
Correlation between Endoscopic and Histological findings of dyspeptic...

Results

Table-I: Endoscopic findings of the study population in relation to age (n=142).

| Age group (in year) | Endoscopic findings |
|---------------------|---------------------|
|                     | Normal n (%) | Gastritis n (%) | Gastric ulcer n (%) | Ulcero-proliferative growth n (%) | Duodenal ulcer n (%) |
| 18-25 (15)           | 1(16.6)       | 7(9.4)          | 1(3.5)              | 1(7.1)                           | 5(25)                |
| 26-35 (21)           | 1(16.6)       | 13(17.5)        | 3(10.7)             | 0(0)                             | 4(20)                |
| 36-45 (32)           | 1(16.6)       | 18(24.3)        | 8(28.5)             | 1(7.1)                           | 4(20)                |
| 46-55 (34)           | 3(50)         | 16(21.6)        | 7(25)               | 4(28.5)                          | 4(20)                |
| 56-65 (27)           | 0(0)          | 14(18.9)        | 6(21.4)             | 4(28.5)                          | 3(15)                |
| 66-75 (10)           | 0(0)          | 4(4.4)          | 2(7.1)              | 4(28.5)                          | 0(0)                 |
| >75 (3)              | 0(0)          | 2(2.7)          | 1(3.5)              | 0(0)                             | 0(0)                 |
| Total (142)          | 6(100)        | 74(100)         | 28(100)             | 14(100)                          | 20(100)              |

Table I shows among 142 total cases, majority (74) were endoscopically reported as gastritis, followed by gastric ulcer (28), duodenal ulcer (20), ulcer-cicatricial growth (14) and normal cases (6). The study population ranged from 18 to more than 75 years of age, with mean age 46.2±15.9 years. Majority of gastritis (24.3%) and gastric ulcer (28.5%) patients were in age group 36-45 years of age. Most cases of ulcer-cicatricial growth were observed at a frequency of 4 (28.5%) in every decade starting from 46 years to 75 years. Most of the duodenal ulcer cases 5 (25%) were found between 18-55 years of age.

The relation between endoscopic and histological findings are shown in Table-II.

All endoscopically diagnosed normal cases (6) were diagnosed as gastritis of various grades. Among 74 endo-scopically reported gastritis cases 70 (94.5) had gastritis, 3 (4%) had intestinal metaplasia and 1 (1.3) specimen did not contain enough tissue for histological diagnosis in histology. Out of 28 endoscopically diagnosed gastric ulcer cases; 15 (53.5) were diagnosed as gastritis, 10 (35.7) as chronic gastric ulcer, 2 (7.1%) as intestinal metaplasia and 1 (3.5%) as adenocarcinoma in histology. All 20 of the duodenal ulcer cases in endoscopy were diagnosed as duodenal ulcer in histology. Out of 14 ulcer-cicatricial growth in endoscopy 12(85.7%) were diagnosed as adenocarcinoma and 2(14.2) as gastritis in histology. Endoscopic findings were significantly co-related with histological findings (p = 0.001).

Table-II: Relation between Endoscopic findings and histological findings of study population

| Endoscopic findings | Histological Findings |
|---------------------|-----------------------|
|                      | Gastritis n (%) | Chronic gastritis n (%) | Duodenal ulcer n (%) | Intestinal metaplasia n (%) | Adenocarcinoma n (%) | Not enough tissue n (%) | P value |
| Normal (n=6)         | 1(100)            | 0(0)                    | 0(0)                 | 0(0)                         | 0(0)                   | 0(0)                  |         |
| Gastritis (n=74)     | 70(94.5)          | 0(0)                    | 3(4.0)               | 0(0)                         | 0(0)                   | 1(1.3)                |         |
| Gastric ulcer (n=28) | 15(53.5)          | 10(35.7)                | 0(0)                 | 2(7.1)                       | 1(3.5)                 | 0(0)                  |         |
| Ulcero-cicatricial growth (n=14) | 2(14.2) | 0(0)                    | 0(0)                 | 0(0)                         | 12(85.7)               | 0(0)                  | 0.001p  |
| Duodenal ulcer (n=20) | 5(25)             | 20(100)                 | 0(0)                 | 0(0)                         | 0(0)                   | 0(0)                  |         |
| Total (n=142)        | 93                 | 10                      | 20                   | 5                            | 13                     | 1                    |         |

s = significant

Table-III shows detection rate of H. pylori by three invasive diagnostic tests: (n=142)

| Name of the test           | Number of Positive (%) |
|---------------------------|------------------------|
| Rapid urease test          | 86 (60.6)              |
| Histological staining      | 35 (24.6)              |
| PCR for ureC gene          | 41 (28.9)              |

Kismat et al
Table-IV: Category of study population as per case definition (n=142):

| Study population             | Number of cases (%) |
|------------------------------|---------------------|
| H. pylori positive cases     | 49 (34.5%)          |
| H. pylori negative cases     | 50 (35.2)           |
| H. pylori indeterminate cases| 43 (30%)            |

Table IV shows. Out of 142 cases 49 (34.5%) were defined as H. pylori positive cases, 50 (35.2) were defined as H. pylori negative cases. 43 (30.2) cases were considered as doubtful or indeterminate cases as they yielded only one test positive.

Table-V: Distribution of gastro-duodenal diseases among H. pylori positive and negative cases

| Group                      | Gastro-duodenal disease | Case definition | H. pylori positive cases | H. pylori negative cases | p value |
|----------------------------|-------------------------|-----------------|--------------------------|--------------------------|---------|
| Gastritis group (59)       | Gastritis (n=59)        |                 | 30 (50.8)                | 29 (40.1)                | 0.743ns |
| PUD group (25)             | Chronic gastric ulcer (n=8) |                | 3 (37.5)                | 5 (62.5)                | 0.479ns |
|                            | Duodenal ulcer (n=17)   |                 | 13 (76.4)               | 4 (23.5)                | 0.914s  |
| Carcinoma & precancerous  | Adeno-carcinoma (n=12)  |                 | 1 (9.0)                 | 11 (91.6)               | 0.092s  |
| group (15)                 | Metaplasia (n=3)        |                 | 2 (66.6)                | 1 (33.3)                | 0.545ns |

s = significant
ns = not significant

In this study detection of H. pylori was done by three invasive diagnostic tests; rapid urease test, histological staining (Modified Giemsa) and PCR amplifying ureC gene. RUT was positive in 86 (60.6%) cases. In other studies of Bangladesh, where rapid urease could detect H. pylori in 54.05% and 53.3% cases. In our study H. pylori was detected in 35 (24.6%) cases by modified Giemsa staining. Similar to 25.71% and 34.4% from gastric biopsy specimens. In contrast with 73.6% H. pylori positive by histological staining. Sensitivity and reliability of histology increases with the number and localization of the collected biopsy specimens. It is ideal to obtain two biopsy specimens from the antrum and two from the corpus. Obtaining only one sample for histology might have decreased the positivity of histological examination in this study. ureC gene was detected by PCR in 41 (28.9%) cases in this present study. Similar finding 31% H. pylori positive cases in gastric biopsy by ureC gene PCR.

explained by differences in the exposure to environmental factors such as higher prevalence of smoking in men, Sex hormones affecting immunity and the inflammatory response to H. pylori differently in men and women. The study population ranged from 18 to more than 75 years of age, with mean age being 46.2±15.9 years. Most cases of ulcero-proliferative growth were observed after the age of 45 years. The finding reflects the fact that gastric cancer is rare before the age of 40, but its incidence steadily climbs thereafter. All endoscopically diagnosed normal cases (6) were diagnosed as gastritis of various grades. Among 74 endoscopically reported gastritis cases 70 (94.5%) had gastritis of various grades, 3 (4%) had intestinal metaplasia. Endoscopic gastritis has a good correlation with histologic gastritis however normal endoscopic appearance is a poor predictor of histologic gastritis. It is also in line with the findings that normal gastric mucosa could be correctly diagnosed endoscopically in about 80% of cases. Most 15 (53.5%) of the endoscopically diagnosed gastric ulcer cases; were diagnosed as gastritis, 10 (35.7%) as chronic gastric ulcer, 2 (7.1%) as intestinal metaplasia and 1 (3.5%) as adenocarcinoma in histology. Similar to another study where 50% of endoscopically diagnosed gastric ulcer cases were diagnosed as gastritis and adenocarcinoma of stomach in histopathology. Out of 14 ulcero-proliferative growth in endoscopy 12 (85.7%) were diagnosed as adenocarcinoma and 2 (14.2) as gastritis in histology. Similar correlations were found in another study of Bangladesh.

Discussion
Demographic data obtained in this study correlated with the findings of a previously conducted similar study in Dhaka, Bangladesh. Most of the study population, 91(64%) were male and only 51, (36%) were female, male female ratio being 1.7:1 in both studies. Male predominance of H. pylori infection in adult is a global and homogeneous phenomenon. This can be

Bangladesh J Med Microbiol 14 Volume 13: Number 2 July 2019
Kismat et al
According to case definition used in this study, out of 142 cases 49 (34.5%) cases were defined as H. pylori positive cases as they were H. pylori positive by at least two of the three tests and 50 (35.2%) were defined as H. pylori negative cases as they were H. pylori negative by all three tests. Rest of the 43 (30%) cases were positive only by rapid urease test. This is similar to the finding of Iranian (31%)\(^3\) and Bangladeshi (47%)\(^6\) study. Higher H. pylori prevalence rates were described to be 60.2\(^{30}\) to 76.7\(^{34}\) by both invasive and noninvasive methods in other studies. Prevalence of H. pylori infection varies between and within geographic regions depending on socioeconomic factors. Its prevalence also varies depending on the method used to detect infection because gastric biopsy-based tests may give false negative results due to sampling error and serological tests may provide false positive results as they cannot differentiate current infection from past exposure.\(^{35}\) In this study, only 1-2 gastric biopsy tissue was used in each test for determining H. pylori, while the organism is unevenly distributed throughout the gastric mucosa; this could also be a contributing factor to the lower prevalence of the present study. Moreover, the noncompliance of the participant with not using proton pump inhibitor four weeks prior to endoscopic examination might produce a false negative result with RUT, culture and histology. Unjudical use of antibiotics for other diseases may contribute to false negative results. Recently, several studies from Asian and Middle East countries reported declining trend in H. pylori infection with improvement of hygienic condition.\(^{36,37,38}\)

In the study, highest infection rate of H. pylori 76.4% was observed in duodenal ulcer cases and lowest being only one (9.1%) in adeno carcinoma cases. In contrast to the findings of 100% of duodenal ulcer and 60% gastritis patients having H. pylori infection\(^1\) in another study. In this study 66.6% of intestinal metaplasia had H. pylori infection. H. pylori acts as a promoter in the progression from normal to metaplastic epithelium, possibly by inducing a hyper proliferative state in the inflamed gastric mucosa.\(^{39}\) Regarding low prevalence of H. pylori in only one (9.0%) of carcinoma cases of our study, it is close to another study where 27.5% of H. pylori was found in adeno carcinoma cases.\(^{11}\) In gastric cancer patients, glandular atrophy and intestinal metaplasia, which are considered to be the precursor of gastric cancer, are frequently found in the biopsy specimen. Glandular atrophy and intestinal metaplasia prevent adequate evaluation of H. pylori status in patients with gastric cancer, as these are the environments in which H. pylori might disappear. Moreover, the distribution of atrophy and intestinal metaplasia is uneven, and that might also affect the sensitivity of the various biopsy sites.\(^{40}\)

**Conclusion**

Endoscopic examination can be used as a good method for diagnosis of gastric diseases in absence of histopathology as significant co-relation with histological findings was observed. However normal endoscopic appearance is a poor predictor of histologic gastritis. H. pylori infection maybe positively associated with duodenal ulcer cases and negatively with adeno carcinoma cases in a statistically significant manner. The sample size of the included studies were relatively small especially for individual disease analysis. The study was conducted in a single hospital in Dhaka, Bangladesh; therefore, the participants may not have been representative of the Bangladeshi population as a whole.

**Acknowledgments:** This study was funded by Bangladesh Medical Research Council.

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Kismat et al
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