Helicobacter pylori infection in diabetes mellitus patients with peptic ulcer disease

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Abstract

Background and objectives: *Helicobacter pylori* infection is suspected to be associated with extra-gastrointestinal disorders such as diabetes mellitus (DM). It is still a subject of investigation whether *H. pylori* has a pathogenic role on DM or diabetic patients have an increased susceptibility to *H. pylori* infection. The aim of the present study was to find out the rate of *H. pylori* infection in individuals with and without DM.

Materials and methods: The study was conducted on 72 diabetic and 19 non-diabetic adult individuals with dyspeptic symptoms attending the BIRDEM General Hospital for diagnostic endoscopy. All cases were tested for *H. pylori* stool antigen by rapid immunochromatographic test (ICT), urease production in biopsy samples by rapid urease test (RUT), and serum anti-*H. pylori* IgA and anti-CagA IgG antibodies by enzyme-linked immunosorbent assay (ELISA). Any case that had peptic ulcer/erosion and was positive for *H. pylori* stool antigen or rapid urease test (RUT) was defined as *H. pylori* positive case.

Results: There was no significant (p=0.095) difference in *H. pylori* infection between diabetics and non-diabetics (68.1% vs 47.4%). Presence of ulcer and erosion were not significantly different among diabetics and non-diabetics. Anti-*H. pylori* IgA positivity rate in *H. pylori* positive diabetic and non-diabetic cases were 65.3% and 55.6% (p=0.575) respectively while anti-CagA IgG rate in those cases were 46.9% and 66.7% (p=0.276) respectively.

Conclusion: The present study did not reveal any significant difference in *H. pylori* infection between individuals with and without DM having peptic ulcer/erosion.

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Introduction

Helicobacter pylori, a gram-negative bacterium, is associated with chronic gastritis, gastric and duodenal ulcers, and in rare occasion gastric cancer and lymphoma [1]. *H. pylori* infection is more frequent in developing countries and an estimated 4.4 billion individuals are reported infected with *H. pylori* worldwide [2]. Besides gastroduodenal involvement, *H. pylori* is suspected to be associated with extra-gastrointestinal disorders such as diabetes mellitus (DM), cardiovascular diseases, and glaucoma [3]. Today, DM is a major public health concern worldwide. In 2015, it was estimated that there were 415 million people with DM aged 20-79 years, 5 million deaths attributable to DM and the total global health expenditure due

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to DM was estimated at 673 billion dollars [2]. If a causal relationship between *H. pylori* and DM becomes clear, it will lead to new preventive and therapeutic strategies for DM and the impact will be significant because of the large number of patients of both diseases [2].

Many studies have addressed the relationship between *H. pylori* infection and DM. However, the findings are conflicting. Several case-control studies have revealed higher prevalence of *H. pylori* infection in patients with DM [4]. Moreover, a meta-analysis carried out by Zhou et al. suggested a trend toward more frequent *H. pylori* infection in DM patients [5]. However, Tamura et al. found a significantly higher DM prevalence among individuals with *H. pylori* infection than those without [6]. Some studies reported no significant difference in the prevalence of *H. pylori* infection between diabetics and non-diabetics [7,8].

It is still debated whether *H. pylori* has a pathogenic role on DM or whether diabetic patients have an increased susceptibility to *H. pylori* infection [9]. No previous study has yet examined the *H. pylori* infection patients with DM in Bangladesh. Therefore, the aim of the study was to examine the rate of *H. pylori* infection in dyspeptic individuals with and without DM.

Materials and methods

Study population and case definition: The study was conducted on diabetic and non-diabetic adult individuals with dyspeptic symptoms attending the BIRDEM General Hospital for diagnostic endoscopy. Diabetes mellitus (DM) was defined as a condition of progressive pancreatic beta cell dysfunction having HbA1c level ≥6.5% or fasting plasma glucose (FPG) ≥7.0 mmol/l or two-hour plasma glucose ≥11.1 mmol/l during an OGTT or a random plasma glucose of ≥11.1 mmol/l in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis [10]. All participants were tested for peptic ulcer/erosion by endoscopy, *H. pylori* stool antigen, urease production in biopsy samples, and serum anti-*H. pylori* IgA and anti-CagA IgG and antibodies. Any case that had peptic ulcer/erosion and was positive for either *H. pylori* stool antigen or rapid urease test (RUT) was defined as *H. pylori* positive case. Participants taking any antibiotics, colloidal bismuth compounds, proton pump inhibitors (PPI) or H_2 blocker within the last four weeks were excluded. The study was approved by the Institutional Ethical Committee and written informed consent was obtained from all patients.

Sample collection: Twenty to thirty gram stool was collected from each individual for *H. pylori* stool antigen test. The test was carried out within 6 hours of collection of fecal sample. During endoscopy gastric biopsy specimen(s) was taken to detect *H. pylori* by rapid urease test (RUT). Blood (2.5 ml) sample was collected from each patient for the detection of anti-*H. pylori* IgA and anti-CagA IgG antibodies. Serum was separated and stored at -20^0C until tested.

H. pylori stool antigen assay: *H. pylori* stool antigen was detected by ICT test using ABON one step *H. pylori* antigen ICT test device (Inverness Medical Innovation Hong Kong Limited). After taking about 50 mg of stool from 3 different sites of collected stool, it was mixed with supplied extraction solution using vortex mixer. Then the tube was centrifuged for 5 minutes at 4000 rpm. Two drops of the supernatant was added to the sample well of the test kit.When a purple-pink line (test line) appeared in addition to the control line, the sample was considered positive.

Rapid urease test (RUT): The biopsy specimen was inoculated in the rapid urease test media and incubated for 4 hours at 37^0C. The sample was considered positive if the medium became pink in color.

Anti-H. pylori IgA and anti-CagA IgG detection by ELISA: Serum anti-*H. pylori* IgA and anti- CagA IgG antibodies were determined by ELISA using kit from DRG International Inc. USA. The test was performed and interpreted according to the manufacturer's instruction.

Results

A total of 72 diabetic and 19 non-diabetic adult individuals with dyspeptic symptoms were included in this study. The mean age of diabetics and non-diabetics was 56 ± 11.9 and 43 ± 15.4 years respectively (Table-1). Out of 72 diabetic cases,

Table-1: *Age of study population and distribution of gastroduodenal lesions among them*

Study population	Number	Mean Age ± SD (range) Years	Erosion case n (%)	Ulcer case n (%)
Diabetic	72	56 ± 11.9 (32-90)	61 (84.7)	11 (15.3)
Non-diabetic	19	43 ± 15.4 (24-78)	13 (68.4)	6 (31.6)
p value		0.0001*	0.11**	0.11**

*Note: *unpaired student's t test; **Z test (two-tailed).*

Table-2: *Rate of H. pylori infection in diabetics and non-diabetics*

Study population	Number	Number (%) of *H. pylori* positive cases by		
		Hp Stool Ag	RUT	Hp Stool Ag/RUT
Diabetic	72	49 (68.1)	34 (47.2)	49 (68.1)
Non-diabetic	19	9 (47.4)	5(26.3)	9 (47.4)
p value		0.095	0.101	0.095

Note: p value calculated by Chi square test; Hp – H. pylori, RUT – rapid urease test.

Table-3: *Anti-H. pylori IgA and anti-CagA IgG antibodies in H. pylori positive cases*

Study population	Number of *H. pylori* positive case	Positive for			
		Anti-Hp IgA		Anti-CagA IgG	
		n (%)	$\bar{x}$ ± SD OD	n (%)	$\bar{x}$ ± SD OD
Diabetic	49	32 (65.3)	1.81 ± 0.89	23 (46.9)	1.68 ± 1.0
Non-diabetic	9	5 (55.6)	1.95 ± 0.90	6 (66.7)	2.29 ± 0.99
p value		0.575	0.755	0.276	0.186

Note: p value calculated by Z test or by unpaired student's t test; Hp – H. pylori, RUT – rapid urease test; OD – optical density.

84.7% and 15.3% had erosion and ulcer respectively while the rates were 68.4% and 31.6% among the non-diabetic individual. Table-2 shows the *H. pylori* infection among the individuals with and without DM. The rate of *H. pylori* infection in individuals with and without DM was 68.1% and 47.4% (p=0.095) respectively by stool antigen/RUT tests. The rate of *H. pylori* infection was not significantly (p>0.05) different in two groups either by stool antigen or by RUT tests separately. Table-3 shows that anti-*H. pylori* IgA positivity rate in *H. pylori* positive diabetic and non-diabetic cases were 65.3% and 55.6% (p=0.575) respectively while anti-CagA IgG rate in those cases were 46.9% and 66.7% (p=0.276) respectively. Mean OD values of anti-*H. pylori* IgA and anti-CagA IgG antibodies of *H. pylori* infected DM cases were not significantly different from that of non-diabetics.

Discussion

The role of *H. pylori* infection in type 2 DM (T2DM) is unclear and it is still debated whether *H. pylori* has a pathogenic role in the development of diabetes or whether diabetic patients have an increased susceptibility to *H. pylori* infection. Impairment of cellular and humoral immunity in diabetic patients could enhance an individual's susceptibility to acquire *H. pylori* infection and altered glucose metabolism might facilitate *H. pylori* colonization in the gastric mucosa. Also, diabetes induced reduction of gastrointestinal

motility and acid secretion may further promote bacterial colonization and infection rate in the gut [9]. *H. pylori* infection may also contribute to the development of diabetes as the infection is associated with chronic low-grade inflammation with up-regulation of cytokines such as C-reactive protein, tumor necrosis factor and interleukin 1*β*, which may influence pancreatic *β* cell secretion and thus function of insulin. In addition, *H. pylori* induced gastritis affects the secretion of gastric hormones, including leptin, ghrelin, gastrin, and somatostatin, which could affect insulin sensitivity and glucose homeostasis [11,12]. A prospective study showed that those who were sero-positive for *H. pylori* infection at the enrolment were 2.7 times more likely to develop T2DM compared to sero-negative individuals at any given time [13]. It was reported that T2DM patients with *H. pylori* infection required higher levels of serum insulin to reach the same degree of glycemic control compared to T2DM patients without *H. pylori* infection [14]. Another study reported that the level of HbA1c tended to improve after eradication of *H. pylori* infection [15]. Also, It was observed that the eradication rate of *H. pylori* infection in T2DM patients was lower [16].

In this study, we assessed the association of *H. pylori* infection with DM. To our knowledge, this is the only study in Bangladesh that addressed the association between *H. pylori* infection and DM. We did not find any significant difference in the rate of *H. pylori* infection between individuals with and without DM. Also, we did not find any significant difference in the incidence of ulcer and erosion between diabetics and non-diabetics. Previous studies that investigated the association between *H. pylori* infection and DM reported conflicting results. Some studies demonstrated significant positive association [17-21] while others reported no such association [22-27]. Prevalence of *H. pylori* infection in diabetics and non-diabetics were reported as 28.1% vs. 29.25% [25], 37.3% vs. 35.2% [26], and 50.8% vs. 56.4% [27] respectively.

We did not find any significant differences with regard to *H. pylori* infection by CagA positive strains as measured by anti-CagA IgG antibodies as well as in anti-*H. pylori* IgA and anti-CagA IgG antibody concentrations between diabetic and non-diabetic individuals. It seems that DM or *H. pylori* did not have greater adverse effects on the intestinal mucosal immune compartment of diabetic individuals.

Our study had some limitations. The study had small number of cases particularly in non-diabetic group, and we did not focus on the uniformity of duration of diabetes, glycemic status and anti-diabetic medications. Nevertheless, our study did not show any increased association of *H. pylori* infection in DM patients with peptic ulcer disease. However, diabetic patients with *H. pylori* infection may be monitored for the development of hitherto unknown systemic or local complications.

Competing interest

The authors declared no competing interests.

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