

Analysis of the Relationship between *Helicobacter pylori* Infection and Diabetic Gastroparesis

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Abstract

Background: Whether *Helicobacter pylori* infection is associated with diabetic gastroparesis (DGP) is unclear. This study aimed to investigate the potential correlation between *H. pylori* infection and DGP.

Methods: In this study, 163 patients with type 2 diabetes mellitus and 175 nondiabetic patients who were treated in our department were divided into DGP, simple diabetes, non-DGP (NDG), and normal groups based on their conditions. The *H. pylori* infection rate in each group was calculated. *H. pylori* eradication therapy was performed for patients with *H. pylori* infection in each group. The eradication rates were compared between the groups, and the improvements in gastroparesis-associated symptoms were compared before and after treatment in patients with DGP.

Results: The *H. pylori* infection rate was 74.6% in the DGP group, which was significantly higher than that in the simple diabetes (51.1%, $P < 0.01$), NDG (57.7%, $P < 0.05$), and normal groups (48.0%, $P < 0.01$). With increased disease course, the incidence of DGP and the *H. pylori* infection rate gradually increased ($P < 0.05$). In the DGP group, the incidences of upper abdominal pain and distention, early satiety, and anorexia were 75.5%, 66.0%, and 67.9%, respectively, before eradication treatment; and 43.4%, 35.8%, and 39.6%, respectively, after eradication treatment, and the difference was statistically significant ($P < 0.01$). In patients with DGP with successful *H. pylori* eradication, the number of barium strips discharged after eradication was 5.9 ± 1.0 , which was significantly larger than that before treatment (4.1 ± 0.7 , $P < 0.01$). In addition, the number of barium strips discharged was significantly larger in patients with DGP with successful *H. pylori* eradication than those with failed *H. pylori* eradication ($P < 0.01$).

Conclusions: DGP development might be associated with *H. pylori* infection. *H. pylori* eradication can effectively improve dyspepsia-associated symptoms and delayed gastric emptying in patients with DGP.

Key words: Diabetic Gastroparesis; *Helicobacter pylori*; Infection

INTRODUCTION

Diabetic gastroparesis (DGP) is a common chronic complication of diabetes characterized by decreased gastric motility, delayed gastric emptying, and gastric rhythm disorders, with upper abdominal pain, early satiety, nausea, vomiting, and anorexia as its main clinical manifestations. Since Kassander^[1] originally named this condition in 1958, many studies have subsequently investigated DGP. While the pathogenetic mechanism underlying DGP remains unclear, most studies suggest that DGP is associated with neuropathy, hyperglycemia, changes in gastrointestinal hormones, and microvascular and gastrointestinal smooth muscle lesions. The *Helicobacter pylori* infection rate is higher in patients with diabetes than in healthy individuals; however, whether there is any correlation between *H. pylori* infection and DGP requires further investigations. In this prospective

cohort study, we explored the relationship between *H. pylori* infection in patients with type 2 diabetes mellitus (T2DM) and DGP and the effect of *H. pylori* eradication therapy on DGP.

METHODS

Ethical approval

The Research Ethics Committee of Queen Mary School of Nanchang University approved this study.

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Informed consent was obtained from all the enrolled subjects.

Participants

A total of 163 inpatients and outpatients with T2DM, including 91 males and 72 females aged 25–77 years (mean age: 51.4 ± 12.3 years), at our center were enrolled from January 2010 to December 2016. In addition, 175 age-, gender-, and economic condition-matched nondiabetic patients, including 98 males and 77 females aged 23–72 years (mean age: 50.3 ± 11.3 years), were also included. All subjects received blood glucose tests, endoscopies, ^{13}C -urea breath tests, and esophageal barium emptying tests. Subjects with the following conditions were excluded from the final analysis: (a) erosive gastritis, peptic ulcer, or gastric cancer confirmed by endoscopy and mucosal biopsy; (b) severe hepatobiliary/pancreatic disease; (c) a previous history of abdominal surgery; (d) use of proton pump inhibitor, H_2 receptor antagonist, bismuth, drugs affecting gastrointestinal motility, and/or antibiotic therapy within 1 month before presentation; (e) diabetic ketoacidosis; (f) end-stage diabetic nephropathy; (g) allergic to treatment drugs; and (h) pregnant women or breastfeeding mothers.

Grouping

The subjects were divided into four groups: (1) DGP group: 71 patients with T2DM who met the diagnostic criteria for gastroparesis, their fasting plasma glucose 7.8–14.6 mmol/L, average fasting plasma glucose 11.2 ± 3.2 mmol/L; (2) simple diabetes group: 92 patients with T2DM who did not meet the diagnostic criteria for gastroparesis, their fasting plasma glucose 7.5–14.4 mmol/L, average fasting plasma glucose 10.1 ± 2.9 mmol/L; (3) non-DGP (NDG) group: 52 nondiabetic patients who met the diagnostic criteria for gastroparesis; and (4) normal group: 123 nondiabetic patients who did not meet the diagnostic criteria for gastroparesis.

The *H. pylori* infection rate in each group was calculated. Patients with T2DM were subgrouped according to the disease course (<10 years, 10–20 years, and >20 years), and the incidence of DGP and *H. pylori* infection rate in each subgroup were analyzed. *H. pylori* eradication with standard quadruple therapy was performed for patients with confirmed *H. pylori* infection. The eradication rates were compared among these groups, and the improvements in gastroparesis symptoms were compared before and after eradication therapy in patients with DGP.

Diagnostic criteria for type 2 diabetes mellitus

The diagnostic criteria for T2DM proposed by the World Health Organization Diabetes Experts Committee in 1999 were applied in this study: (1) random plasma glucose ≥ 11.1 mmol/L (2000 mg/L) in the presence of diabetes symptoms; (2) fasting plasma glucose ≥ 7.0 mmol/L (1260 mg/L); (3) 2-h plasma glucose ≥ 11.1 mmol/L (2000 mg/L) following a 75-g oral glucose load. If one of the three items applied, a second test was performed to confirm the result. A diagnosis of T2DM was only confirmed after type 1 diabetes was excluded by

consulting with the department of endocrinology when glutamic acid decarboxylase antibody testing was negative.

Diagnostic criteria for gastroparesis

Gastroparesis was diagnosed if all the following conditions were present: (1) upper abdominal pain, early satiety, nausea, vomiting, anorexia, and other symptoms of indigestion; (2) no mechanical obstruction, peptic ulcer, erosive gastritis, esophagitis, tumor, or other organic diseases, as confirmed by endoscopy or upper gastrointestinal barium meal X-ray; and (3) barium strip emptying test in the upper gastrointestinal tract revealed delayed gastric emptying.

Barium strip emptying test in the upper gastrointestinal tract

Subjects were fasted for at least 8 h before the test. A standard meal (400 ml of water, 80 g of cooked pasta, 1 tea egg, and 20 g of peanuts) was served in the morning. All subjects finished eating within 15 min. A capsule with 10 small barium strips (Xi'an Janssen, Shaanxi, China) was swallowed, followed by immediate X-ray to confirm that the barium strips had entered the stomach. Six hours after the meal, an abdominal plain X-ray was performed in supine position. The number of residual barium strips in the stomach was recorded, and the patients with residual barium strips in the stomach were diagnosed with delayed stomach emptying.

Detection and diagnosis of *Helicobacter pylori* infection

H. pylori infection was detected by trained staff members using the ^{13}C -urea breath test kit (Boran Pharmaceutical, Beijing, China). Before the test, subjects were fasted for more than 2 h. Subjects were asked to maintain normal expiration before a straw was inserted into the bottom of a sample tube into which air was slowly exhaled for 4–5 s. After the straw was removed, the tube cover was immediately tightened. The sample was regarded as the exhaled air at 0 min. The subjects were then orally administered one vial of ^{13}C -urea granules with 80–100 ml of cold drinking water and asked to sit still. After 30 min, air samples were collected using the same method. The sample tubes containing the exhaled samples at 0 and 30 min were analyzed on the corresponding instruments. *H. pylori* was considered positive when the detected value was $\geq 4.0 \pm 0.4$.

Helicobacter pylori eradication regimen and efficacy

A standard quadruple therapy (esomeprazole magnesium 20 mg, amoxicillin 1000 mg, clarithromycin 500 mg, and bismuth potassium citrate 220 mg; *bid po* for 2 weeks) served as the eradication regimen in patients with the ^{13}C -urea breath test and confirmed as *H. pylori* infection. Efficacy was assessed after ruling out the impact of gastrointestinal prokinetic drugs. A second ^{13}C -urea breath test was performed 4 weeks after the end of treatment, and a negative result indicated that the eradication therapy was successful. In addition, specific gastrointestinal symptoms before and after treatment were recorded.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS Inc., Chicago, Illinois, USA). Measurement

data with normal distribution are presented as mean \pm standard deviation (SD), and intergroup comparisons were performed using *t*-test. Count data are presented as rate or incidence and were compared using Chi-square test. A value of $P < 0.05$ was considered significantly different.

RESULTS

Helicobacter pylori infection in each group

The *H. pylori* infection rate was 74.6% in the DGP group, which was significantly higher than that in the simple diabetes (51.1%, $\chi^2 = 9.382$, $P < 0.01$), NDG (57.7%, $\chi^2 = 4.814$, $P < 0.05$), and normal groups (48.0%, $\chi^2 = 13.132$, $P < 0.01$). There were no significant differences between the simple diabetes, NDG, and normal groups ($\chi^2 = 0.292$, 0.205, and 0.890, all $P > 0.05$; [Table 1]).

Incidences of diabetic gastroparesis and *Helicobacter pylori* infection in patients with type 2 diabetes mellitus with different disease courses

With longer disease courses, the incidence of DGP and the *H. pylori* infection rate gradually increased. The DGP incidences were 34.8% and 54.1% in the <10-year and 10–20-year groups, respectively, and were significantly different ($\chi^2 = 4.710$, $P < 0.05$). The rates of *H. pylori* infection were 62.5% and 84.4% in the <10-year and 10–20-year groups, which were also significantly different ($\chi^2 = 3.925$, $P < 0.05$; [Table 2]).

Response to *Helicobacter pylori* eradication regimen and influence of eradication therapy on gastroparesis-associated symptoms

The *H. pylori* eradication regimen was performed in 53 patients with DGP, 47 with simple diabetes, 30 with

NDG, and 59 normal subjects. The *H. pylori* eradication rate was 50.9% in patients with DGP, which was significantly lower than that in the simple diabetes ($\chi^2 = 4.794$, $P < 0.05$), NDG ($\chi^2 = 8.069$, $P < 0.01$) and normal groups ($\chi^2 = 16.640$, $P < 0.01$; [Table 3]).

In the DGP group, the incidences of upper abdominal pain and distention, early satiety, nausea, vomiting, and anorexia were 75.5%, 66.0%, 64.2%, 35.8%, and 67.9%, respectively, before eradication therapy and 43.4%, 35.8%, 52.8%, 22.6%, and 39.6% after eradication treatment. The differences were statistically significant for upper abdominal pain and distention, early satiety, and anorexia ($\chi^2 = 11.308$, 9.664, and 8.539, all $P < 0.01$), whereas the incidences of nausea and vomiting were not significantly different ($\chi^2 = 1.399$, 2.234, all $P > 0.05$). In the NDG group, the incidences of abdominal pain and distention, early satiety, nausea, vomiting, and anorexia were 73.3%, 60.0%, 63.3%, 30.0%, and 66.7%, respectively, before eradication therapy and 66.7%, 53.3%, 56.7%, 23.3%, and 50.0% after eradication treatment. The differences were not statistically significant ($\chi^2 = 0.271$, 0.278, 0.082, and 1.174, all $P > 0.05$; [Table 4]).

In patients with DGP with successful *H. pylori* eradication, the number of barium strips discharged after eradication was 5.9 ± 1.0 , which was significantly larger than that (4.1 ± 0.7) before treatment ($t = 7.991$, $P < 0.01$). In patients with DGP with failed *H. pylori* eradication, the number of barium strips discharged after eradication was 4.6 ± 0.7 , which was not significantly different from that (4.2 ± 0.9) before treatment ($t = 1.768$, $P > 0.05$). In addition, the number of barium strips discharged was significantly larger in patients with DGP with successful *H. pylori* eradication than in those in which *H. pylori* eradication had failed ($t = 6.304$, $P < 0.01$). In patients with DGP with successful *H. pylori* eradication, the number of barium strips discharged after eradication was 4.4 ± 1.0 , which was significantly larger than that (4.0 ± 0.8) before treatment ($t = 1.729$, $P > 0.05$). In patients with DGP with failed *H. pylori* eradication, the number of barium strips discharged after eradication was 4.2 ± 0.4 , which was not significantly different from that (4.6 ± 0.5) before treatment ($t = 1.265$, $P > 0.05$). In addition, the number of barium strips discharged was not significantly different between patients with NDG and successful *H. pylori* eradication and those with failed *H. pylori* eradication ($t = 0.211$, $P > 0.05$; [Table 5]).

Table 1: *H. pylori* infection rate in each group

Group	<i>n</i>	Number of <i>H. pylori</i> infection cases	<i>H. pylori</i> infection rate (%)
DGP group	71	53	74.6**‡
Simple diabetes group	92	47	51.1
NDG group	52	29	55.8
Normal group	123	59	48.0

* $\chi^2 = 9.382$, $P < 0.01$, compared with simple diabetes group; $\chi^2 = 4.814$, $P < 0.05$, compared with NDG group; $\chi^2 = 13.132$, $P < 0.01$, compared with normal group. DGP: Diabetic gastroparesis; NDG: Nondiabetic gastroparesis; *H. pylori*: *Helicobacter pylori*.

Table 2: Incidence of DGP and *H. pylori* infection rate in T2DM patients with different disease courses

Course of diabetes (years)	Number of diabetic patients	DGP group			
		<i>n</i>	Rate (%)	Number of <i>H. pylori</i> infection cases	<i>H. pylori</i> infection rate (%)
<10	92	32	34.8	20	62.5
10–20	61	32	54.1*	27	84.4*
>20	10	7	–	6	–
Total	163	71	43.6	53	74.6

* $\chi^2 = 4.710$, $P < 0.05$, $\chi^2 = 3.925$, $P < 0.05$, compared with the <10 years group. –: The number of cases was <20 cases, no rate was applied. DGP: Diabetic gastroparesis; *H. pylori*: *Helicobacter pylori*; T2DM: Type 2 diabetes mellitus.

Table 3: Response to *H. pylori* eradication regimen in each group, n

Group	Number of patients receiving <i>H. pylori</i> eradication regimen	Number of patients with successful <i>H. pylori</i> eradication	<i>H. pylori</i> eradication rate (%)
DGP group	53	27	50.9*†‡
Simple diabetes group	47	34	72.3
NDG group	29	24	82.8
Normal group	59	51	86.4

* $\chi^2 = 4.794$, $P < 0.05$, compared with simple diabetes group; † $\chi^2 = 8.069$, $P < 0.01$, compared with NDG group; ‡ $\chi^2 = 16.640$, $P < 0.01$, compared with normal group. DGP: Diabetic gastroparesis; NDG: Nondiabetic gastroparesis; *H. pylori*: *Helicobacter pylori*.

Table 4: Influence of *H. pylori* eradication therapy on the symptoms of DGP, n (%)

Symptoms	Before <i>H. pylori</i> eradication		After <i>H. pylori</i> eradication	
	DGP patients (n = 53)	NDG patients (n = 29)	DGP patients (n = 53)	NDG patients (n = 29)
Upper abdominal pain	40 (75.5)	22 (73.3)	23 (43.4)*	20 (66.7)
Early satiety	35 (66.0)	18 (60.0)	19 (35.8)†	16 (53.3)
Nausea	34 (64.2)	19 (63.3)	28 (52.8)	17 (56.7)
Vomiting	19 (35.8)	9 (30.0)	12 (22.6)	8 (23.3)
Anorexia	36 (67.9)	20 (60.0)	21 (39.6)‡	15 (50.0)

* $\chi^2 = 11.308$, $P < 0.01$, † $\chi^2 = 9.664$, $P < 0.01$, ‡ $\chi^2 = 8.539$, $P < 0.01$, compared with the incidences before *H. pylori* eradication therapy. DGP: Diabetic gastroparesis; NDG: Nondiabetic gastroparesis; *H. pylori*: *Helicobacter pylori*.

Table 5: Improvement of gastric emptying in DGP patients with successful *H. pylori* eradication (amount of barium strips discharged)

Classification	DGP group (n = 53)		NDG group (n = 29)	
	Before eradication	After eradication	Before eradication	After eradication
With successful <i>H. pylori</i> eradication	4.1 ± 0.7	5.9 ± 1.0*†	4.0 ± 0.8	4.4 ± 1.0
Failed in <i>H. pylori</i> eradication	4.2 ± 0.9	4.6 ± 0.7	4.2 ± 0.4	4.6 ± 0.5

* $t = 7.991$, $P < 0.01$, compared with before eradication; † $t = 6.304$, $P < 0.01$, compared with patients who failed in *H. pylori* eradication. DGP: Diabetic gastroparesis; NDG: Nondiabetic gastroparesis; *H. pylori*: *Helicobacter pylori*.

DISCUSSION

Patients with diabetes often display dyspepsia symptoms, such as upper abdominal fullness, early satiety, nausea, vomiting, and anorexia. In some patients, while endoscopy or upper gastrointestinal imaging may not reveal organic gastrointestinal lesions, gastrointestinal motility testing can identify dynamic abnormalities, such as gastroparesis. While the pathogenesis of DGP remains unclear, it is believed that neuropathy, hyperglycemia, changes in serum gastrointestinal hormones, microvascular disease, and metabolic disorders contribute to this condition.^[2-6] In recent years, research has found that *H. pylori* infection is also common in patients with diabetes. *H. pylori* is a micro-aerobic bacterium that colonizes between the surface of the gastric mucosa and the mucous membrane. It is closely related to chronic gastritis, peptic ulcer, and gastric cancer. As a common parasitic bacterium in the stomach, its chronic transmission in patients with diabetes can cause or aggravate dyspeptic symptoms.

In our current study, the incidences of gastric papillitis and *H. pylori* infection were investigated in 163 patients with T2DM. We determined that the *H. pylori* infection rate was significantly higher in the DPG group than those in the simple diabetes, NDP, and normal groups. With increased

disease course, the incidence of DPG and *H. pylori* infection rate gradually increased. Furthermore, the *H. pylori* infection rate was significantly higher in patients with T2DM and DPG than in those without DPG, suggesting that patients with T2DM with *H. pylori* infection are more likely to develop the clinical manifestations of gastroparesis. The higher *H. pylori* infection rate in patients with diabetes may be explained by the following mechanisms:^[7-11] (1) diabetes-related deficiencies in cellular and humoral immunity can increase *H. pylori* susceptibility; (2) mechanical and potential changes in the stomach due to diabetic autonomic neuropathy may lower the gastric mucosa's ability to remove bacteria; and (3) in patients with diabetes, nonenzymatic mucin glycosylation can increase salivary mucin in the gastric mucosa and thus promote the binding of *H. pylori* with the gastric mucosa.

H. pylori infection causes or aggravates dyspeptic symptoms in patients with diabetes, which may be related to the following factors. First, diabetic microvascular disease causes demyelinating autonomic neuropathy, which decreases gastrointestinal motility, slows or stops the movement of food from the stomach to the small intestine, and stimulates the secretion of gastric juice. This favors the colonization and growth of *H. pylori* in the

gastric mucosa. Colonization of *H. pylori* in the antrum, through the release of interleukin, tumor necrosis factor, and other inflammatory factors, may further stimulate gastrin release.^[12] Second, during the pathogenesis of diabetes, some factors can cause a decrease in the number of capillaries and thickening of endothelial vascular basement membranes, leading to local tissue hypoxia. In addition, *H. pylori* infection directly and indirectly (e.g., by secreting toxins and activating the host immune response) causes structural damage of D cells in the gastric antral mucosa and reduces their number, leading to a significant reduction in the synthesis and release of somatostatin. As a result, gastrointestinal electromyographic findings and exercise status are altered, causing gastrointestinal symptoms. Studies have confirmed that *H. pylori*-associated high gastrin is not caused by increasing the number of G cells but may be due to the reduced number of D cells and their functional impairment, which may weaken the inhibitory effect of somatostatin.^[13,14] Third, abnormally elevated hormones (e.g., pancreatic polypeptide, glucagon, cholecystokinin, and gastrin) in the gastrointestinal tract can inhibit gastric emptying.^[15-17] Fourth, gastrointestinal motility can be affected by altering endogenous nitric oxide levels.^[18,19]

In our current study, an *H. pylori* eradication regimen was performed in 53 patients with DGP, 47 with simple diabetes, 30 with NDG, and 59 normal subjects. It was found that upper abdominal pain, early satiety, anorexia, and other symptoms of indigestion were remarkably improved in patients with DGP, in whom *H. pylori* was successfully eradicated. In addition, the number of barium strips discharged was significantly larger in patients with DGP with successful *H. pylori* eradication than that before treatment and in those with failed *H. pylori* eradication. Thus, the eradication of *H. pylori* can improve gastric emptying in patients with DGP and then improve the symptoms of dyspepsia, which further confirmed that *H. pylori* is associated with DGP. However, whether *H. pylori* infection is a cause or trigger factor of DGP still needs further study. The possible mechanisms involved in this process include decreased pancreatic polypeptide, glucagon, cholecystokinin, gastrin and gastrointestinal hormone levels, D cell damage reduction and improved somatostatin synthesis and release. Which specific mechanism is the major one needs further research.

Our study showed that the *H. pylori* infection rate in the NDG group was significantly lower than that in the DGP group but was not significantly different from the normal and simple diabetes groups. In addition, indigestion symptoms (e.g., epigastric pain, early satiety, nausea, vomiting, and anorexia) and the number of barium strips discharged were not significantly changed after *H. pylori* eradication therapy compared with preeradication therapy values. This suggested that NDG had no connection with *H. pylori* infection.

Furthermore, the eradication rate of *H. pylori* was 50.9% in patients with DGP, which was significantly lower than that in the simple diabetes, NDG, and normal groups. One

of the reasons for the low eradication rate of *H. pylori* in patients with DGP may be due to the frequent and substantial use of antibiotics in patients with diabetes for accompanied infections in other locations, which causes the development of drug-resistant *H. pylori* strains. In addition, diabetic microvascular changes can weaken the absorption of antibiotics, and thus, the plasma drug cannot reach the minimum inhibitory concentration, which ultimately can also lead to a decreased eradication rate.

In conclusion, DGP is associated with *H. pylori* infection. Eradication of *H. pylori* helps relieve dyspepsia symptoms and improve delayed gastric emptying in patients with DGP.

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Conflicts of interest

There are no conflicts of interest.

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