

Clinical Study

Influence of *Helicobacter pylori* Infection on the Small Intestinal Mucosa

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Background/Aims. To investigate the role of *Helicobacter pylori* infection in the development of enteritis (small intestinal mucosal injury). **Methodology.** Between April 2007 and January 2013, 99 patients undergoing capsule endoscopy (CE) were tested for anti-*H. pylori* immunoglobulin G antibody (*Hp*-IgG) using an enzyme-linked immunosorbent assay (ELISA). None of the patients had been treated for *H. pylori* infection or diagnosed as having Crohn's disease or any other clinically apparent small intestinal disorders prior to the CE. **Results.** The overall *Hp*-IgG-positive rate was 26.3%. The incidence of enteritis, as diagnosed by CE, tended to be lower in the *Hp*-IgG-positive patients (23.1%) than in the *Hp*-IgG-negative patients (38.4%) ($P = 0.140$). When patients receiving aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), well-known causes of enteritis, were excluded, the incidence of enteritis in the *Hp*-IgG-positive patients (11.7%) was significantly lower than that in the *Hp*-IgG-negative patients (43.7%) ($P = 0.005$). A binomial logistic regression analysis revealed a significant negative relationship between *Hp*-IgG positivity and the presence of enteritis in patients receiving neither aspirin nor NSAIDs ($P = 0.017$). **Conclusions.** Our data indicated that *H. pylori* positivity was inversely associated with the prevalence of enteritis.

1. Introduction

Helicobacter pylori is a Gram-negative spiral-shaped micro-aerophilic bacterium that is known to colonize the gastric mucosa in humans [1]. Although *H. pylori* infection has been reported to be associated with an increased risk of gastric ulcer, duodenal ulcer, and atrophic gastritis [2, 3], little information is available on the possible association of *H. pylori* infection with enteritis (small intestinal mucosal injury).

The aim of the present study was to assess the incidence of enteritis by capsule endoscopy (CE) in anti-*H. pylori* immunoglobulin G antibody (*Hp*-IgG)-positive and *Hp*-IgG-negative patients.

2. Methodology

2.1. Patients. Between April 2007 and January 2013, *Hp*-IgG antibody was prospectively measured in 99 patients (70 men, 29 women; mean age, 63.4 ± 16.8 years; age range, 22–86 years) with obscure gastrointestinal bleeding (OGIB) at the Department of Gastroenterology, Dokkyo Medical

University. Prior to July 2012, OGIB was the only indication for CE that was covered by the national health insurance system of Japan.

Patients diagnosed as having Crohn's disease, small bowel tumor, suspected ileus or gastrointestinal stricture, or radiation enterocolitis or having a history of intra-abdominal surgery or pacemaker implantation were excluded from this study. In all patients, the CE, the upper and lower endoscopy, was performed within 60 days of the last bleeding episode. The characteristics of the 99 patients are summarized in Table 1.

This study was conducted with the approval of the ethics committee of Dokkyo Medical University, and written informed consent was obtained from all the patients.

2.2. Capsule Endoscopy. CE for identifying small intestinal lesions was performed using an M2A/PillCamTM SB or SB2 (Given Imaging Ltd., Yokneam, Israel). After the patients had fasted for 8 hours, they received 4 mL (40 mg) of simethicone just before swallowing the capsule endoscope. The patients were allowed to drink water from 2 hours and eat from 4

TABLE 1: Patient characteristics ($n = 99$).

	<i>Hp</i> (+)	<i>Hp</i> (-)	<i>P</i> value
Sex (male/female)	18 : 9	52 : 21	
Age (years)	68.0 ± 12.0	61.7 ± 18.0	0.103
Time from last bleeding episode until CE (days)	12.6 ± 13.4	12.3 ± 16.3	0.938
Past and present illness			
History of gastroduodenal ulcer	23.10%	10.90%	0.13
Gastritis	84.60%	72.60%	0.224
Neurological disorder (cerebral infarction, etc.)	26.90%	13.70%	0.127
Heart disease (valvular disease, etc.)	23.10%	42.50%	0.081
Liver disease (chronic hepatitis, etc.)	3.80%	15.10%	0.135
Diabetes mellitus	15.40%	26.00%	0.274

CE: capsule endoscopy.

hours after swallowing the capsule. The recorder was removed after 8 hours, and images were analyzed using the RAPID (Reporting and Processing of Images and Data, 2–6.5; Given Imaging Ltd.) software.

Enteritis was defined as small intestinal mucosal injury, namely, the presence of ulceration, erosions, or erythema in the mucosa of the small intestine, as detected by CE.

2.3. *Helicobacter pylori* Infection Status. The *H. pylori* infection status was examined by enzyme-linked immunosorbent assay (ELISA) to detect *Hp*-IgG. The reported *Hp*-IgG-positive rate among patients with *H. pylori* infection is in the range of 92.0% and 97.1% [4, 5].

2.4. Statistical Analysis. Differences in the patient characteristics were tested for statistical significance by the student's paired *t*-test or Welch's *t*-test. A binomial logistic regression analysis was conducted to analyze the relationship between enteritis as the dependent variable and a history of gastroduodenal ulcer, gastrointestinal cancer, neurological disorder, heart disease, liver disease, serum C-reactive protein (CRP), *Hp*-IgG positivity, and aspirin/nonsteroidal anti-inflammatory drugs (NSAIDs) used as independent variables. The partial regression coefficient, odds ratios (OR), and 95% confidence intervals (CI) were calculated, and *P* values ≤ 0.05 were considered to indicate statistical significance. The statistical analyses were performed using the IBM SPSS 19.0 software for windows (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Relationship between *H. pylori* Infection and Enteritis. Of the 99 patients undergoing CE for OGIB, 26 were found to be *Hp*-IgG-positive (26.3%).

The incidence of enteritis among the 26 *Hp*-IgG-positive patients (6/26; 23.1%) tended to be lower than that in the remaining 73 *Hp*-IgG-negative patients (28/73; 38.4%) (*P* = 0.140; Figure 1).

3.2. Incidence of Enteritis among Patients Not Receiving Aspirin/NSAIDs. Because aspirin/NSAID use is well known to be associated with enteritis, the incidence of enteritis was

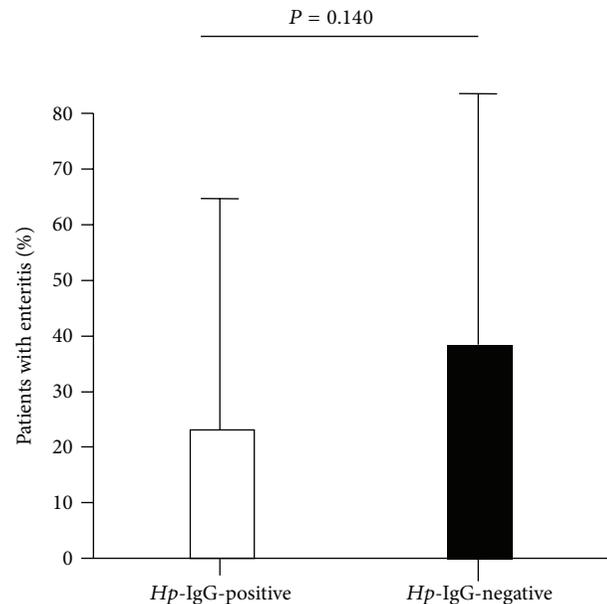


FIGURE 1: Incidence of enteritis in *Hp*-IgG-positive and *Hp*-IgG-negative patients.

determined in 65 of the 99 patients who were not receiving aspirin/NSAIDs. Analysis revealed that among the patients not receiving aspirin/NSAIDs, the incidence of enteritis in the 17 *Hp*-IgG-positive patients (2/17; 11.8%) was significantly lower than that in the 48 *Hp*-IgG-negative patients (21/48; 43.7%) (*P* = 0.005; Figure 2).

3.3. Incidence of Enteritis in *Hp*-IgG-Positive Patients Receiving Aspirin and/or NSAIDs with or without a Proton Pump Inhibitor. Because it has been reported that proton pump inhibitors (PPIs) can exacerbate NSAID-induced small intestinal mucosal injury by inducing dysbiosis [6] and also exert both a bactericidal and a bacteriostatic effect against *H. pylori* [7–9], we compared the incidence of enteritis between a patient group receiving a PPI and a patient group not receiving PPI therapy among 26 *Hp*-IgG-positive patients receiving aspirin/NSAIDs. The results revealed that the incidence of enteritis

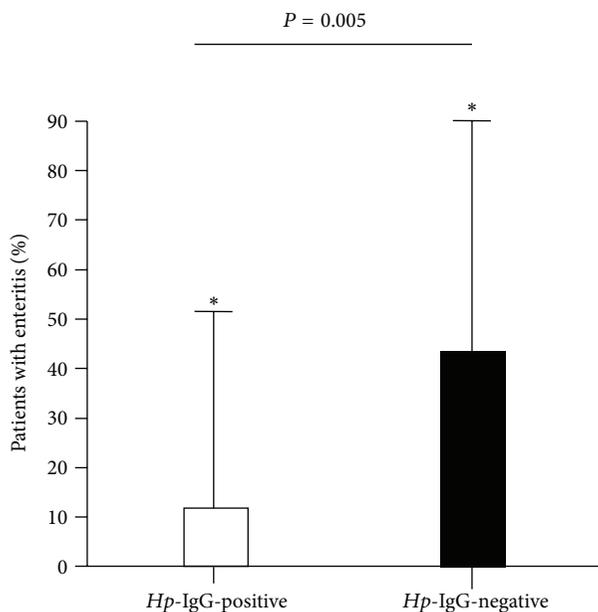


FIGURE 2: Incidence of enteritis in *Hp*-IgG-positive and *Hp*-IgG-negative patients receiving neither aspirin nor NSAIDs.

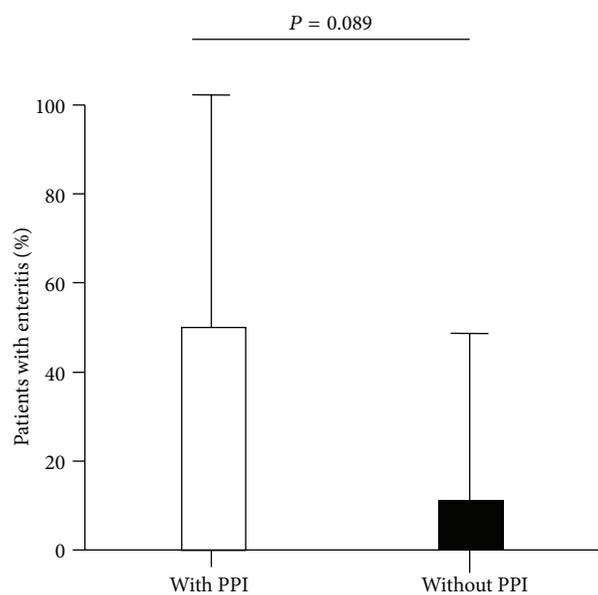


FIGURE 3: Incidence of enteritis in *Hp*-IgG-positive patients receiving aspirin/NSAIDs with or without a PPI.

tended to be higher in the patient group receiving PPI therapy (4/8; 50.0%) than in the patient group not receiving PPI therapy (2/18; 11.1%) ($P = 0.089$; Figure 3).

3.4. Incidence of Enteritis in *Hp*-IgG-Positive Patients Not on Aspirin/NSAIDs, Receiving or Not Receiving PPI Therapy. To determine the effect of only PPIs on the small intestinal mucosa, we compared the incidence of enteritis between a patient group receiving PPI therapy and a patient group not receiving PPI therapy among 17 *Hp*-IgG-positive patients not

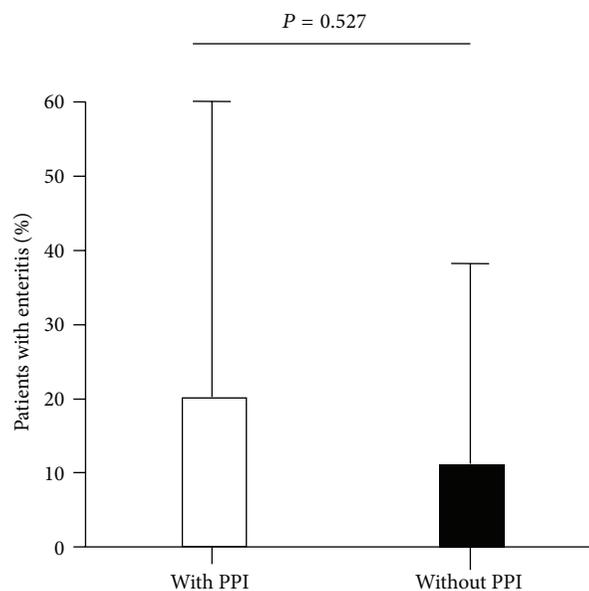


FIGURE 4: Incidence of enteritis in *Hp*-IgG-positive patients not on aspirin/NSAIDs, receiving or not receiving PPI therapy.

receiving aspirin/NSAIDs. The results revealed enteritis in 1 of 5 (20.0%) patients receiving PPI therapy, as compared to 1 of 12 (8.3%) patients not receiving PPI therapy ($P = 0.526$; Figure 4).

3.5. Incidence of Enteritis in *Hp*-IgG-Negative Patients Receiving Aspirin/NSAIDs with or without PPI. To examine whether PPI therapy may have the same effect in *Hp*-IgG-negative patients as in *Hp*-IgG-positive patients, we compared the incidence of enteritis between a group receiving PPI therapy and a group not receiving PPI therapy among 25 *Hp*-IgG-negative patients receiving aspirin/NSAIDs. The results revealed enteritis in 3 of 8 (37.5%) patients receiving PPI therapy, as compared to 4 of 17 (23.5%) patients not receiving PPI therapy ($P = 0.489$; Figure 5).

3.6. Factors Associated with Enteritis. A binomial logistic regression analysis for patients not receiving aspirin/NSAIDs revealed that enteritis positively correlated with the male sex, advanced age, neurological disorder, elevated serum CRP, and history of gastroduodenal ulcer and negatively correlated with *Hp*-IgG-positivity, heart disease, liver disease, diabetes mellitus, and gastritis (Table 2). Only the negative relationship with *Hp*-IgG positivity was statistically significant at $P < 0.05$.

4. Discussion

H. pylori infection is known to be associated with many gastrointestinal disorders such as gastritis, gastric ulcer, gastroesophageal reflux disease (GERD), gastric cancer, and NSAID/aspirin-induced gastric injury [2, 3, 10, 11]. Although *H. pylori* presence has also been detected in the small intestine [12], there are few reports on how *H. pylori* may affect the small intestinal mucosa. Until now, only small intestinal bacterial

TABLE 2: Factors associated with enteritis (binomial logistic regression analysis).

Factor	Partial regression coefficient	Odds ratio	95% confidence interval	P value
Sex	0.316	1.371	0.309–6.078	0.678
Age	0.023	1.023	0.980–1.068	0.297
Presence of heart disease	–0.21	0.81	0.183–3.582	0.781
Presence of liver disease	–0.869	0.42	0.035–5.027	0.493
Presence of neurological disorder	2.137	8.477	0.692–103.820	0.094
Presence of diabetes mellitus	–0.485	0.616	0.109–3.468	0.582
CRP value	0.096	1.101	0.331–3.659	0.876
<i>Hp</i> -IgG-positive	–2.976	0.051	0.004–0.590	0.017*
Presence of gastritis	–0.071	0.931	0.220–3.945	0.923
History of gastroduodenal ulcer	0.222	1.248	0.201–7.762	0.812

Hp: *helicobacter pylori*; CRP: C-reactive protein; NSAIDs: nonsteroidal anti-inflammatory drugs. * A statistically significant negative correlation was shown between *Hp*-IgG-positive and enteritis in Table 2.

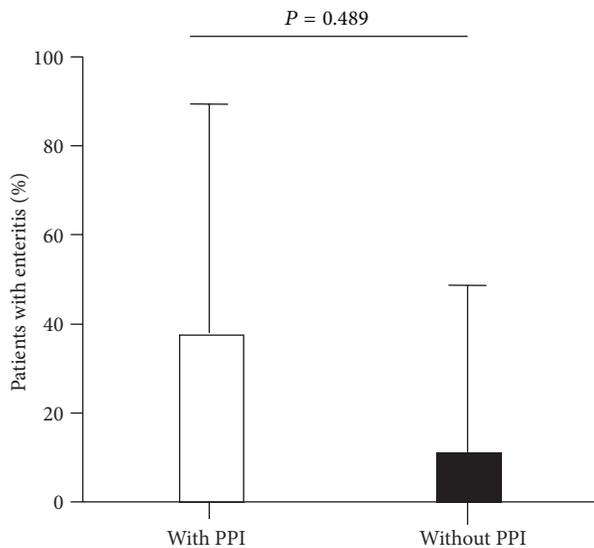


FIGURE 5: Incidence of enteritis in *Hp*-IgG-negative patients receiving aspirin/NSAIDs with or without a PPI.

overgrowth (SIBO) [13–16] and the phenotype of Crohn's disease [17] have been reported to be associated with *H. pylori* in the small intestine.

Our results indicated that the incidence of small intestinal mucosal injury tended to be lower in *Hp*-infected patients than in non-*Hp*-infected patients. Because aspirin or NSAIDs inhibit cyclooxygenase (COX) and prostaglandin (PG) production at inflamed sites and may increase the risk of mucosal damage in the small intestine [18, 19], the incidence of enteritis was determined in patients not receiving aspirin/NSAIDs; the results of this evaluation revealed that the rate of enteritis was significantly lower in the *Hp*-infected patients than in the *Hp*-noninfected patients. These findings suggest that *H. pylori* infection might protect the small intestinal mucosa against injury.

The possible reason for the low rate of enteritis in patients with *H. pylori* infection is that *H. pylori* can cause pangastritis and reduce gastric acid production [20–23], thereby raising

the pH of the small intestine and protecting against small intestinal mucosal injury.

Another reason is that *H. pylori* may play an important role in the intestinal mucosal barrier function and establish a stable relationship with the intestinal bacterial flora, thereby protecting the small intestinal mucosa against damage.

There has been no evidence to date indicating that *H. pylori* may protect against small intestinal mucosal injury. Castro-Rodriguez et al. reported that *H. pylori* infection was not associated with acute or persistent diarrheal disease [24].

Recently, it has been reported that PPIs can exacerbate NSAID-induced small intestinal mucosal injury by inducing dysbiosis [6]. The PPIs, omeprazole and lansoprazole, significantly exacerbated naproxen- and celecoxib-induced intestinal ulceration and bleeding. While omeprazole did not result in mucosal injury or inflammation, it produced marked shifts in the numbers and types of enteric bacteria, including a significant reduction in the jejunal *Actinobacteria* and *Bifidobacterium* spp. Restoration of small intestinal *Actinobacteria* numbers through administration of selected (*Bifidobacteria*-enriched) commensal bacteria during treatment with omeprazole and naproxen prevented intestinal ulceration and bleeding. In other words, the enteritis induced by PPI use appeared to result from destruction of the intestinal bacterial flora.

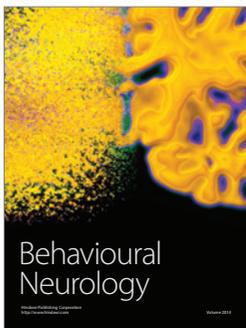
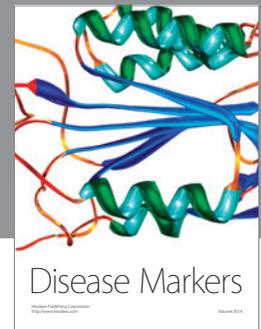
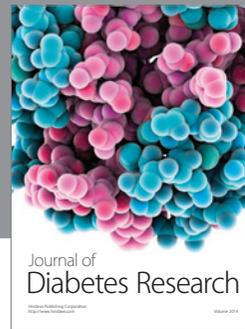
Our study indicated that among *Hp*-infected patients receiving aspirin/NSAIDs, the incidence of enteritis tended to be higher in the patient group receiving PPIs than in the patient group not receiving PPIs. The reason is that in addition to exacerbating NSAID-induced small intestinal mucosal injury, as mentioned above, PPIs also exert bacteriostatic activity against *H. pylori* [7–9, 25]. For similar reasons, there were no significant differences in the incidence of enteritis between the patients receiving PPIs and those not receiving PPIs or between the *Hp*-infected and *Hp*-uninfected patient groups.

In conclusion, *H. pylori* infection was found to be associated with a reduced incidence of enteritis. Our findings suggest that *H. pylori* might protect against small intestinal mucosal injury and play an important role in the intestinal

mucosal barrier function. Further studies are needed for a more precise elucidation of the influence of *H. pylori* on the small intestinal mucosa.

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