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ORIGINAL ARTICLE—ALIMENTARY TRACT

Evaluation of *Helicobacter pylori* status and endoscopic findings among new outpatients with dyspepsia in Japan

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Abstract
Purpose The 2005 ACG guidelines for the management of dyspepsia recommend eradication and proton pump inhibitors for patients who are *H. pylori*-positive and-negative, respectively. To establish Japanese guidelines for dyspepsia, we evaluated *H. pylori* status and endoscopic findings among outpatients with dyspepsia.
Methods The status of *H. pylori* in dyspeptic patients was determined by measuring urinary levels of anti-*H. pylori* antibody (RAPIRAN®). We then compared the endoscopic findings between *H. pylori*-positive and -negative patients.
Results The prevalence of *H. pylori* among 258 dyspeptic patients was 47.8%, and increased with age (11.1% at age 10–19 years; >50% at age >50 years). The prevalence of *H. pylori* in each age-group tended to be lower among male than female dyspeptic patients. Endoscopy ($n = 138$) showed that *H. pylori*-negative patients rarely had peptic ulcers or gastric cancer, and 84.7% had no endoscopic findings, which was significantly higher when compared to *H. pylori*-positive patients (67.3%) ($p = 0.029$).
Conclusions Over half of the dyspeptic Japanese patients examined were negative for *H. pylori*. Patients who are *H. pylori*-positive should undergo endoscopy to rule out gastric malignancy, peptic ulcers and other diseases.

Keywords *H. pylori* · Dyspepsia · Japan

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Introduction

Since *Helicobacter pylori* (*H. pylori*) was discovered by Warren and Marshall in 1982 [1], it has been found to be related to various gastroduodenal diseases, including peptic ulcer [2], gastric cancer [3] and mucosa-associated lymphoid tissue (MALT) lymphoma [4]. Eradication of *H. pylori* inhibits the recurrence of peptic ulcer [5], ameliorates MALT lymphoma [6] and lowers the risk of gastric cancer [7]. About 50% of people worldwide including Japan are thought to be infected with this bacillus [8], and prevalence increases with age in Japan, particularly in those over 40 years [9].

Although some reports have shown that *H. pylori*-positive patients tend to have dyspepsia [10, 11], the relationship between *H. pylori* infection and dyspepsia is controversial. The prevalence of *H. pylori* in Japan has been decreasing with steady improvements in sanitary conditions. Moreover, some reports have shown using endoscopy that *H. pylori*-negative patients do not have structural abnormalities [10]. The 2005 American College of Gastroenterology (ACG) guidelines for the management of dyspepsia [12] recommend tests for *H. pylori* infection among dyspeptic patients without alarm features as well as among *H. pylori*-positive patients, and proton pump inhibitors for *H. pylori*-negative patients.

It is important to recognize the prevalence of *H. pylori* in dyspeptic patients from the standpoint of eradication cost in Japan where prevalence of *H. pylori* is high [9]. And endoscopic findings are important for the indications that early endoscopy can provide. Japanese guidelines for dyspepsia can only be established after the prevalence of *H. pylori* infection and endoscopic findings in dyspeptic patients have been clarified. The present study evaluates *H. pylori* status and

endoscopic findings among outpatients with dyspepsia at a Japanese hospital.

Materials and methods

Subjects

We performed a prospective study of 4,331 new outpatients (1,914 men and 2,417 women; average age, 53.4; 53.1 and 53.7 years for men and women, respectively) at the Department of General Medicine in Oita University Hospital between 2002 and 2006.

Each patient completed a questionnaire regarding their reasons for attending the hospital, containing questions such as "What is wrong with you today?" Then a general physician obtained a detailed medical history. Patients whose chief complaint was dyspepsia were assigned to the dyspeptic group. Dyspepsia was regarded as "pain or discomfort centered in the upper abdomen". Symptoms associated with or described as discomfort were upper abdominal fullness, early satiety, bloating, belching, or nausea. Patients with heartburn or diarrhea were not considered dyspeptic. Patients with a history of *H. pylori* eradication were excluded from the study. The major chief complaints among the new outpatients were dyspepsia ($n = 258$), headache ($n = 243$), fever ($n = 217$), cough ($n = 200$), chest pain ($n = 178$), back pain ($n = 160$). Use of non-steroidal anti-inflammatory drugs (NSAIDs) and anti-ulcer agents as well as smoking status were also recorded.

We categorized the patients into groups according to age as young (age $\leq$39 years); middle-aged (age 40–69 years) and elderly (age $\geq$70 years).

All subjects provided written, informed consent and the Ethics Committee of Oita University the approved study.

Evaluation of *H. pylori* status

We evaluated *H. pylori* status using a rapid urine test (RAPIRUN® *H. pylori* antibody, Otsuka Pharmaceutical Co., Tokyo, Japan). The reported sensitivity, specificity, positive and negative predictive values of the kit are 95.3, 96.7, 95.3 and 96.7%, respectively [13]. Antibodies in urine from each patient were immediately measured after collection, using the kit according the manufacturer's instructions. The same skilled technician analyzed all urine samples using the kits and interpreted the results after 15–30 min.

Analysis of upper gastrointestinal endoscopic findings

We examined the endoscopic findings of 138 among 258 dyspeptic patients. A skilled gastroenterologist who was blinded to the *H. pylori* status of the patients but not to their questionnaire answers performed all endoscopic procedures and diagnosed the findings. Two endoscopists who were unaware of the *H. pylori* status of each patient independently conducted a retrospective endoscopic diagnosis. Details of gastric cancer, peptic ulcer or reflux esophagitis were recorded. Grade M reflux esophagitis was not regarded as reflux esophagitis. Esophageal hiatal hernia or endoscopic gastritis (atrophic gastritis, erythematous gastritis and erosive gastritis) was also recorded, but not regarded as significant endoscopic findings. When two or more endoscopic findings were found in the same subject, all findings were recorded.

Statistics

We performed all statistical analyses using the SPSS statistical package for Windows. Data were statistically analyzed using Student's t test and the Chi-squared test. p values of <0.05 were considered significant.

Results

Analysis on the links between *H. pylori* and dyspepsia

The prevalence of *H. pylori* in 258 dyspeptic patients (107 males and 151 females) was 44.5% (115/258) and this increased with age (Fig. 1): 11.1% (2/18) at 10–19 years, 20.8% (10/48) at 20–29 years, 38.8% (14/36) at 40–49 years, and over 50% at age 50–79. Infection of *H. pylori* was less prevalent among those aged >80 than that at 70–79 years of age. Patients were divided according to age into young, middle-aged and elderly groups. The prevalence of *H. pylori* in each group tended to be lower among dyspeptic male than female patients (12.9 vs. 22.7% at young group and 45.0 vs. 58.4% at middle-aged group, and 68.0 vs. 90.0% at elderly group; $p = 0.700$, 0.150 and 0.070, respectively) (Table 1). Twenty-four in 258 (9.3%) dyspeptic patients used NSAIDs. NSAIDs use in males and females was equal (8.4% [9/107] vs. 9.9% [15/151]; $p = 0.67$). There was also no difference of NSAIDs use between *H. pylori*-positive and -negative patients (11.3% [13/115] vs. 7.6% [11/143]; $p = 0.32$).

Endoscopic findings and relationship to *H. pylori* positivity

Endoscopic findings based on *H. pylori* status were evaluated in 138 patients who underwent endoscopy (Table 2). Overall, 18.1% (25/138) of these patients had peptic ulcers, 6.5% (9/138) had reflux esophagitis and 2.1% (3/138) had gastric cancer, which was also identified in 3.2% (3/138) of

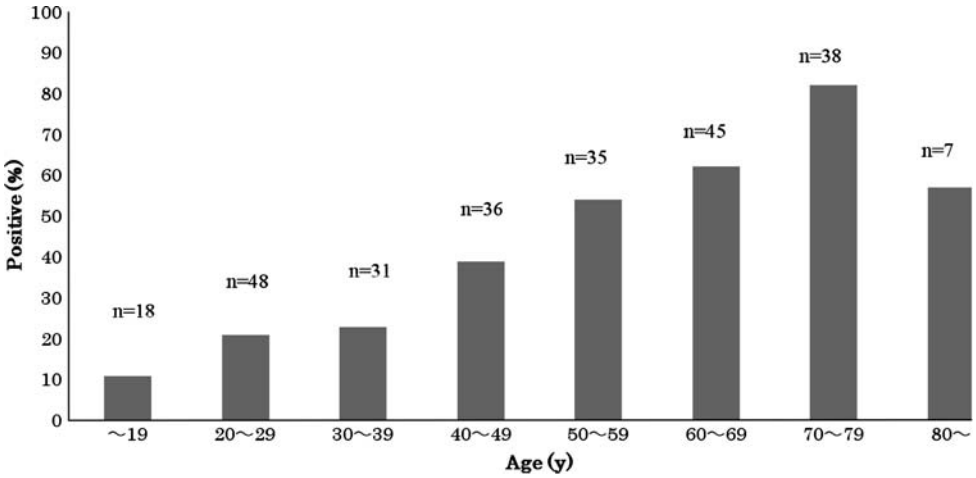

Fig. 1 Prevalence of *H. pylori* in 258 dyspeptic patients. Prevalence of *H. pylori* determined using rapid urine was 44.5% overall, and increased with age

Table 1 *H. pylori* prevalence in dyspeptic patients by age and gender

	Male	Female	*p* value
Young	12.9% (4/31)	22.7% (15/66)	0.700
Middle-aged	45.0% (23/51)	58.4% (38/65)	0.150
Elderly	68.0% (17/25)	90.0% (18/20)	0.070
All	41.1% (44/107)	47.0% (71/151)	0.340

Data are given as percentage (number) of patients

Table 2 Endoscopic findings for dyspeptic patients

	H. pylori positive	*H. pylori* negative	*p*
n	92	46	
Age	58.0 ± 15.1	49.8 ± 18.2	<0.01*
Male/female	32/92	12/34	ns
Smoker	23 (25.0%)	19 (41.3%)	0.049*
NSAIDs	7 (7.6%)	5 (5.4%)	ns
Anti-ulcer agent	10 (10.8%)	7 (7.6%)	ns
Endoscopic findings			
Gastric cancer	3/92 (3.2%)	0/46 (0%)	0.21
Peptic ulcer	23/92 (25.0%)	2/46 (4.3%)	0.0029*
Reflux esophagitis	4/92 (4.3%)	5/46 (10.8%)	0.14
No significant findings	62/92 (67.3%)	39/46 (84.7%)	0.029*

**H. pylori* positive patients vs. *H. pylori* negative patients

H. pylori-positive patients. There was no gastric cancer in *H. pylori*-negative patients. The prevalence of peptic ulcers was significantly higher among *H. pylori*-positive than -negative patients (25.0% [23/92] vs. 4.3% [2/46]; $p = 0.0029$). All *H. pylori*-negative patients were in the scar phase and half of the *H. pylori*-negative patients with peptic ulcers patients were taking NSAIDs. The prevalence of *H. pylori* in patients with peptic ulcers was 92.0% (23/25). The prevalence of reflux esophagitis tended to be lower in *H. pylori*-positive than -negative patients (4.3% [4/92] vs. 10.8% [5/46]; $p = 0.14$). Of the 46 *H. pylori*-negative and 92 *H. pylori*-positive patients, 39 (84.7%) and 62 (67.3%), respectively, were considered endoscopically normal (no significant findings; $p = 0.029$). Among these endoscopically normal *H. pylori*-positive and -negative patients, use of NSAIDs and anti-ulcer agents did not significantly differ, whereas more *H. pylori*-negative patients smoked ($p = 0.049$).

Discussion

Dyspepsia is a complaint commonly seen in clinical practice [14]. Some reports [10, 11] have observed that dyspeptic symptoms are more frequent among *H. pylori*-positive patients. Although changes in gastric acid secretion by *H. pylori* infection or functional abnormalities in gastric movement might contribute to dyspepsia, the relationship has not been fully elucidated [15–17]. Shimatani et al. [10] reported that dyspepsia symptoms are more frequent among *H. pylori*-positive patients in Japan. Our results contradict these findings and might be due to differences in subjects (they studied patients undergoing medical check-ups). However, Sasaki et al. [18] and Kawamura et al. [19] found no relationship between dyspepsia and *H. pylori* status. These studies were also conducted among persons attending medical check-ups. Few reports have described the prevalence of *H pylori* with dyspepsia in a hospital setting. In our study, over half of the dyspeptic Japanese patients examined were negative for *H. pylori*. Therefore, factors other than *H. pylori* might play a role in the development of dyspepsia in the hospital setting. The prevalence of *H. pylori* in patients with dyspepsia tended to be lower in males than in females. Reports indicate that obesity and smoking are more important than *H. pylori* infection for dyspepsia [20, 21]. It is possible that many dyspeptic male patients are obese or smoke. More male than female patients smoked in the present study (data

not shown), but we did not have sufficient information about obesity to draw any conclusions. These issues require further study.

The endoscopic findings of dyspeptic patients revealed peptic ulcers, reflux esophagitis and gastric cancer in 18.1, 6.5 and 2.1% of patients, respectively. An ACG technical review has shown that the incidences of these three conditions are 5–15, 5–15 and <2%, respectively [22]. Our results are consistent with these values.

Half of the *H. pylori*-negative patients with peptic ulcers used NSAIDs, which should be considered in a diagnosis of peptic ulcers in *H. pylori*-negative dyspeptic patients. Thomson et al. [23] evaluated endoscopic findings from dyspeptic patients, and found that peptic ulcers were more prevalent among patients using NSAIDs. Reflux esophagitis was also more frequent in *H. pylori*-negative patients [23]. Acid output might be higher among *H. pylori* negative patients [24]. No structural abnormalities on endoscopy were identified in 67.3 and 84.7% of *H. pylori*-positive and-negative patients and the difference was significant ($p = 0.029$). Shimatani et al. [10] examined young patients undergoing medical check-ups, and found no abnormalities on endoscopy in *H. pylori*-negative patients. Our results agree with their findings. However, the possibility of selection bias cannot be denied because the prevalence of *H. pylori* in patients who underwent endoscopy was higher than that among overall dyspeptic patients. Attending physicians might routinely order endoscopy for *H. pylori*-positive patients. Furthermore, we did not examine alarm features. The 2005 ACG guidelines for the management of dyspepsia [12] recommend endoscopy for dyspeptic patients with alarm features.

In conclusion, we investigated the prevalence of *H. pylori* and endoscopic findings in dyspeptic Japanese patients and found that over half of them were *H. pylori*-negative. Patients who are *H. pylori*-positive should undergo endoscopy to rule out gastric malignancy and peptic ulcer diseases.

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Conflict of interest statement None.

References

1. Marshall B, Warren J. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984;1(8390):1311–5.
2. NIH Consensus Conference. *Helicobacter pylori* in peptic ulcer disease. NIH Consensus Development Panel on *Helicobacter pylori* in peptic ulcer disease. JAMA. 1994;272(1):65–9.
3. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med. 2001;345(11):784–9.
4. Wotherspoon A, Ortiz-Hidalgo C, Falzon M, Isaacson P. *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. Lancet. 1991;338(8776):1175–6.
5. Graham D, Lew G, Klein P, Evans D, Evans DJ, Saeed Z, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. A randomized, controlled study. Ann Intern Med. 1992;116(9):705–8.
6. Wotherspoon A, Doglioni C, Diss T, Pan L, Moschini A, de Boni M, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. Lancet. 1993;342(8871):575–7.
7. Uemura N, Mukai T, Okamoto S, Yamaguchi S, Mashiba H, Taniyama K, et al. Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. Cancer Epidemiol Biomarkers Prev. 1997;6(8):639–42.
8. Mégraud F, Brassens-Rabbé M, Denis F, Belbouri A, Hoa D. Seroepidemiology of *Campylobacter pylori* infection in various populations. J Clin Microbiol. 1989;27(8):1870–3.
9. Asaka M, Kimura T, Kudo M, Takeda H, Mitani S, Miyazaki T, et al. Relationship of *Helicobacter pylori* to serum pepsinogens in an asymptomatic Japanese population. Gastroenterology. 1992;102(3):760–6.
10. Shimatani T, Inoue M, Iwamoto K, Hyogo H, Yokozaki M, Saeki T, et al. Prevalence of *Helicobacter pylori* infection, endoscopic gastric findings and dyspeptic symptoms among a young Japanese population born in the 1970s. J Gastroenterol Hepatol. 2005;20(9):1352–7.
11. Rosenstock S, Kay L, Rosenstock C, Andersen L, Bonnevie O, Jørgensen T. Relation between *Helicobacter pylori* infection and gastrointestinal symptoms and syndromes. Gut. 1997;41(2):169–76.
12. Talley N, Vakil N. Guidelines for the management of dyspepsia. Am J Gastroenterol. 2005;100(10):2324–37.
13. Graham D, Reddy S. Rapid detection of anti-*Helicobacter pylori* IgG in urine using immunochromatography. Aliment Pharmacol Ther. 2001;15(5):699–702.
14. Talley N, Zinsmeister A, Schleck C, Melton Lr. Dyspepsia and dyspepsia subgroups: a population-based study. Gastroenterology. 1992;102(4 Pt 1):1259–68.
15. Mearin F, de Ribot X, Balboa A, Salas A, Varas M, Cucala M, et al. Does *Helicobacter pylori* infection increase gastric sensitivity in functional dyspepsia? Gut. 1995;37(1):47–51.
16. Armstrong D. *Helicobacter pylori* infection and dyspepsia. Scand J Gastroenterol Suppl. 1996;215:38–47.
17. Pfaffenbach B, Adamek R, Bartholomäus C, Wegener M. Gastric dysrhythmias and delayed gastric emptying in patients with functional dyspepsia. Dig Dis Sci. 1997;42(10):2094–9.
18. Sasaki N. Endoscopic diagnosis of gastritis in relation to *Helicobacter pylori* infection and subjective symptoms. J Clin Gastroenterol. 1995;21:S135–9.
19. Kawamura A, Adachi K, Takashima T, Murao M, Katsube T, Yuki M, et al. Prevalence of functional dyspepsia and its relationship with *Helicobacter pylori* infection in a Japanese population. J Gastroenterol Hepatol. 2001;16(4):384–8.
20. Woodward M, Morrison C, McColl K. The prevalence of dyspepsia and use of antisecretory medication in North Glasgow: role of Helicobacter pylori versus lifestyle factors. Aliment Pharmacol Ther. 1999;13(11):1505–9.
21. Wildner-Christensen M, Hansen J, De Muckadell O. Risk factors for dyspepsia in a general population: non-steroidal anti-inflammatory drugs, cigarette smoking and unemployment are more

important than *Helicobacter pylori* infection. Scand J Gastroenterol. 2006;41(2):149–54.
22. Talley N, Vakil N, Moayyedi P. American gastroenterological association technical review on the evaluation of dyspepsia. Gastroenterology. 2005;129(5):1756–80.
23. Thomson A, Barkun A, Armstrong D, Chiba N, White R, Daniels S, et al. The prevalence of clinically significant endoscopic findings in primary care patients with uninvestigated dyspepsia: the Canadian adult dyspepsia empiric treatment: prompt endoscopy (CADET-PE) study. Aliment Pharmacol Ther. 2003;17(12):1481–91.
24. Delaney B, McColl K. Review article: *Helicobacter pylori* and gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2005;22(Suppl 1):32–40.