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ORIGINAL ARTICLE

Improvement of dyspeptic symptoms after *Helicobacter pylori* eradication therapy in Japanese patients

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Abstract

Background and Aim: *Helicobacter pylori* eradication therapy effectively improves the abdominal symptoms and bowel habits of patients. Patients in whom dyspepsia is under control by 6 to 12 months after successful *H. pylori* eradication are defined as having *H. pylori*-associated dyspepsia, and patients with dyspepsia that is refractory to successful eradication are defined as having functional dyspepsia. Here, we aimed to investigate the association between *H. pylori* eradication and improvement of dyspepsia in the short and long term after eradication therapy.
Methods: Dyspeptic symptoms before treatment and at 2 and 12 months after eradication were evaluated using the Gastrointestinal Symptom Rating Scale (GSRS) in 282 *H. pylori*-positive Japanese patients who underwent eradication therapy.
Results: Of the Japanese *H. pylori*-positive patients, 48.2% (136/282) had upper abdominal symptoms. Eradication improved dyspepsia in 34.5% (47/136) of the patients at 2 months post eradication, which continued to be under control up to 12 months. A significant decrease at 2 and 12 months after eradication, compared with before eradication, was observed in total GSRS (from 25.7 ± 10.4 [before eradication, $n = 249$] to 23.3 ± 7.2 [after 2 months, $n = 249$] and 24.8 ± 7.8 [after 12 months, $n = 81$]; $P = 0.014$ and 0.321, respectively), gastric pain score (from 4.1 ± 1.9 to 3.7 ± 1.3 and 3.7 ± 1.2; $P = 0.025$ and 0.047), and constipation score (from 5.9 ± 3.1 to 5.2 ± 2.3 and 5.9 ± 3.0; $P < 0.021$ and 0.862).
Conclusion: *H. pylori*-positive dyspepsia patients should be recommended to undergo *H. pylori* eradication to alleviate dyspepsia-associated symptoms.

Introduction

Recently, international guidelines have strongly recommended the eradication of *Helicobacter pylori* from *H. pylori*-positive patients irrespective of whether they have dyspeptic symptoms.[1,2] As a result of increased opportunities to undergo eradication therapy and improvements in sanitation, *H. pylori* infection rates and gastric cancer incidence rates around the world are gradually decreasing.[3–5]

Functional dyspepsia (FD) is defined by the Rome IV criteria as a group of functional gastrointestinal disorders, including irritable bowel syndrome (IBS).[6] FD is thought to occur in 10–30% of general population, and is gradually increasing in developed countries.[7] *H. pylori* is known to often cause abdominal symptoms associated with chronic mucosal inflammation and injury, whereas it is unclear whether such symptoms in patients infected with *H. pylori* are caused by the infection or FD. Therefore, whether *H. pylori*-associated dyspepsia should be categorized as FD has long been debated.[8,9] The Kyoto Global Consensus report concluded that gastritis in *H. pylori*-infected patients with dyspepsia should be categorized as *H. pylori*-associated dyspepsia, separate from FD, if dyspeptic symptoms can be eliminated or controlled by 6–12 months after eradication.[10] The recent guidelines for FD strongly recommend the eradication as the first-line treatment for *H. pylori*-positive individuals with dyspeptic symptoms.[10–12] Because infection rates and strains differ between East Asian and Western countries, improvement of dyspepsia after eradication and the rate of *H. pylori*-associated dyspepsia are considered to differ among different geographic populations. Therefore, it is important to investigate the prevalence and characteristics of *H. pylori*-associated dyspepsia in Japan, which has a high infection rate, where patients are often infected with highly virulent *H. pylori* strains.

Because FD decreases the quality of life of an individual, it is important to clarify whether the merits of eradication simply lie in its ability to prevent gastric cancer and peptic ulcers, or whether they also extend to the long-term improvement of abdominal symptoms. Accordingly, the aims were as follows: (i) to determine the prevalence of *H. pylori*-associated dyspepsia and FD in *H. pylori*-positive Japanese patients; (ii) to evaluate the association between the outcomes of eradication and improvement of dyspeptic symptoms; and (iii) to investigate the risk of dyspeptic symptoms that are refractory to eradication, which are considered to be FD.

Methods

Patients and Study Design. A total of 282 *H. pylori*-positive patients who underwent eradication therapy between August 2015 and January 2020 were enrolled. Inclusion criteria were *H. pylori*-positive patients in whom severity of gastritis was determined by esophagogastroduodenoscopy (EGD), and who were evaluated using the Gastrointestinal Symptom Rating Scale (GSRS),[13,14] and then underwent eradication of *H. pylori* infection. Because this study was conducted using a retrospective design, written informed consent was not obtained from each enrolled patient.

At enrolment, all patients were subjected to an evaluation of their *H. pylori*-associated disease by EGD. Also, they completed the GSRS questionnaire to assess their abdominal symptoms. The severity of their symptoms was also evaluated at 2 and 12 months after eradication therapy. As study 1 (short-term study; 2 months post eradication), the improvement of dyspepsia after eradication was compared between patients in whom eradication was successful and those in whom it was unsuccessful. In addition, as study 2 (long-term study; 12 months post eradication), the time course of dyspepsia improvement after eradication in successful patients alone was analyzed.

Assessment of* H. pylori *infection and eradication therapy. *H. pylori* infection was diagnosed in all patients using the rapid urease test (Helicocheck; Institute of Immunology, Co., Ltd., Tochigi, Japan), the ^{13}C-urea breath test (Otsuka Pharmaceutical Co., Ltd., using a cut-off of 2.5‰), and a culture test. Patients were diagnosed as currently being infected if at least one of the three tests was positive.

Patients underwent eradication with vonoprazan (20 mg) twice daily (bid), and a combination of two antibiotics, namely clarithromycin (200 mg bid) and amoxicillin (750 mg bid) as the first-line treatment, metronidazole (250 mg bid) and amoxicillin (750 mg bid) as the second-line treatment, and sitafloxacin (100 mg bid) and amoxicillin (500 mg) four times daily (qid) as

Table 1 Baseline characteristics of the patients

	Total ($n = 282$)	Successful eradication ($n = 249$)	Unsuccessful eradication ($n = 33$)	*P*-value
Age (years, mean ± SD)	62.8 ± 12.4	62.6 ± 12.4	62.8 ± 12.9	0.929
Sex, male	146 (52.0%)	126 (50.8%)	20 (60.9%)	0.290
BMI (mean ± SD)	22.6 ± 3.6	22.6 ± 3.5	22.9 ± 4.3	0.655
Smoking history	109 (38.7%)	99 (39.8%)	10 (30.3%)	0.295
Alcohol consumption	149 (52.8%)	133 (53.4%)	16 (48.5%)	0.594
Kimura–Takemoto classification, C1/C2/C3/O1/O2/O3	3/19/20/85/79/66	3/18/18/74/72/58	0/1/2/11/7/8	0.872
Kyoto classification of gastritis, total score	4.5 ± 1.3	4.7 ± 1.3	4.9 ± 1.1	0.105
Atrophy score, 0/1/2	3/40/231	3/27/204	0/3/27	0.611
Intestinal metaplasia score, 0/1/2	102/116/56	94/100/50	8/16/6	0.373
Number of eradications, 1/2/3/4/5	199/46/33/3/1	172/43/30/3/1	27/3/3/0/0	0.625
Presence of epigastric symptoms before eradication	136 (48.2%)	114 (45.8%)	22 (66.7%)	0.024

Presence of epigastric symptoms is defined as a score >3 for one or more of the seven questions, including epigastric pain, hunger pain, nausea, borborygmus, satiety, eructation, and increased flatus.
BMI, body mass index.

the third-, fourth-, and fifth-line treatments, all for 7 days. At 6–8 weeks post treatment, outcome was evaluated using the ^{13}C-urea breath test.

Endoscopy and evaluation of gastritis severity. All *H. pylori*-positive patients underwent EGD for the evaluation of gastritis severity, including atrophy and intestinal metaplasia, which were scored using the Kimura–Takemoto gastric atrophy 6-grade classification[15] and the Kyoto classification.[16,17]

Questionnaires. Patients were administered the GSRS questionnaire before treatment and at 2 and 12 months after treatment. The severity of the patients' symptoms, including abdominal pain score, reflux score, diarrhea score, constipation score, and postprandial complaints score, were evaluated based on the GSRS questionnaire. Patients were considered to have dyspepsia if they scored 3 points or more in at least one question of pain or indigestion, irrespective of the eradication status.

Most of the subjects in this study were patients being treated at the outpatient service of an expert gastroenterologist (MS), who is a *H. pylori* infection specialist certified by the Japanese Society for *Helicobacter* Research. This expert gastroenterologist routinely performs *H. pylori* eradications, and evaluates patients using the GSRS questionnaire at every visit. GSRS questionnaires were directly administered by the doctor who examined the patient (MS).

Table 2 Gastrointestinal Symptom Rating Scale (GSRS) of the patients at 2 months post *Helicobacter pylori* eradication therapy

	Before eradication ($n = 282$)	After eradication ($n = 282$)	*P*-value
Total GSRS (mean ± SD)	25.8 ± 9.9	23.7 ± 7.6	<0.001
Reflux score	2.9 ± 1.6	2.7 ± 1.3	0.016
Gastric pain score	4.4 ± 2.2	3.9 ± 1.6	<0.001
Indigestion score	6.3 ± 2.7	6.1 ± 2.4	0.258
Diarrhea score	5.0 ± 3.0	4.6 ± 2.5	0.027
Constipation score	5.7 ± 3.2	5.1 ± 2.6	<0.001

Data analysis. Patient data, including age and body mass index (BMI), and scores of the Kyoto classification and the questionnaires are shown as the mean ± SD. The eradication rate was evaluated by intention-to-treat (ITT) analysis, and was calculated with 95% confidence intervals (CIs). Statistically significant differences in category data were determined by the χ^2 test. The *t*-test was used to compare GSRS and gastritis scores between patients with successful and unsuccessful eradication. Repeated-measures analysis of variance followed by the Scheffé multiple comparison test was used to compare GSRS scores before and after treatment. A *P*-value <0.05 was considered to indicate a statistically significant difference between the two groups, and all *P*-values were two-sided. Calculations were conducted using STATA version 17 software (StataCorp, College Station, TX, USA). Patients enrolled in this study overlapped with those of previous studies investigating the association between eradication and gastrointestinal diseases.[18–20]

Results

Characteristics of patients who underwent H. pylori eradication therapy. We analyzed a total of 282 patients. Eradication was successful in 249 patients (ITT analysis, 88.3%; 95% CI: 83.9–91.8%), and unsuccessful in 33 patients (Table 1). There were no significant differences between patients in the successful and unsuccessful eradication groups with regard to baseline characteristics.

Of the 282 patients, 136 patients had epigastric symptoms at baseline, including 62 with epigastric pain syndrome and 118 with postprandial distress syndrome (including 44 with both). Gastroesophageal reflux disease (GERD) is defined as having heartburn or acid regurgitation; IBS with constipation (IBS-C) as having constipation, hard stools, and a feeling of incomplete evacuation; and IBS with diarrhea (IBS-D) as having diarrhea, feeling the urgent need for defecation, and loose stools, using the GSRS questionnaire. The numbers of patients with GERD, IBS-C, IBS-D, and IBS-M were 49, 58, 35, and 20, respectively. FD and GERD overlapped in 37 patients, and FD and IBS overlapped in 51 patients.

Table 3 Gastrointestinal Symptom Rating Scale (GSRS) at 2 months post *Helicobacter pylori* eradication therapy between eradication-successful patients and eradication-unsuccessful patients

	Eradication outcome	Before eradication	After eradication	*P*-value
Total GSRS	Successful ($n = 249$)	25.5 ± 10.0	23.6 ± 7.7	<0.001
	Unsuccessful ($n = 33$)	27.6 ± 8.9	24.5 ± 6.7	0.033
Reflux score	Successful ($n = 249$)	2.9 ± 1.6	2.7 ± 1.3	0.011
	Unsuccessful ($n = 33$)	2.8 ± 1.4	2.8 ± 1.3	0.914
Gastric pain score	Successful ($n = 249$)	4.4 ± 2.2	3.8 ± 1.5	<0.001
	Unsuccessful ($n = 33$)	4.8 ± 2.4	4.3 ± 2.2	0.280
Indigestion score	Successful ($n = 249$)	6.2 ± 2.8	6.1 ± 2.5	0.444
	Unsuccessful ($n = 33$)	6.6 ± 1.9	6.1 ± 1.8	0.149
Diarrhea score	Successful ($n = 249$)	4.9 ± 3.1	4.6 ± 2.5	0.058
	Unsuccessful ($n = 33$)	5.3 ± 2.6	4.6 ± 2.6	0.238
Constipation score	Successful ($n = 249$)	5.7 ± 3.1	5.1 ± 2.6	<0.001
	Unsuccessful ($n = 33$)	6.3 ± 3.9	5.3 ± 2.6	0.150

Epigastric symptoms at the time of eradication were significantly higher in the eradication-unsuccessful group than in the successful group (66.7% *vs* 45.8%, $P = 0.024$) (Table 1).

Changes in GSRS scores at 2 months post H. pylori eradication therapy. In all patients, a significant decrease from baseline to 2 months post eradication was observed in total GSRS, reflux score, gastric pain score, diarrhea score, and constipation score (Table 2).

In the eradication-successful group, a significant improvement from baseline to 2 months post eradication was also observed in total GSRS (from 25.5 ± 10.0 to 23.6 ± 7.7, $P < 0.001$), reflux score (from 2.9 ± 1.6 to 2.7 ± 1.3, $P = 0.011$), gastric pain score (from 4.4 ± 2.2 to 3.8 ± 1.5, $P < 0.001$), and constipation score (from 5.7 ± 3.1 to 5.1 ± 2.6, $P < 0.001$) (Table 3). In the eradication-unsuccessful group, however, there were no significant differences between before and after eradication.

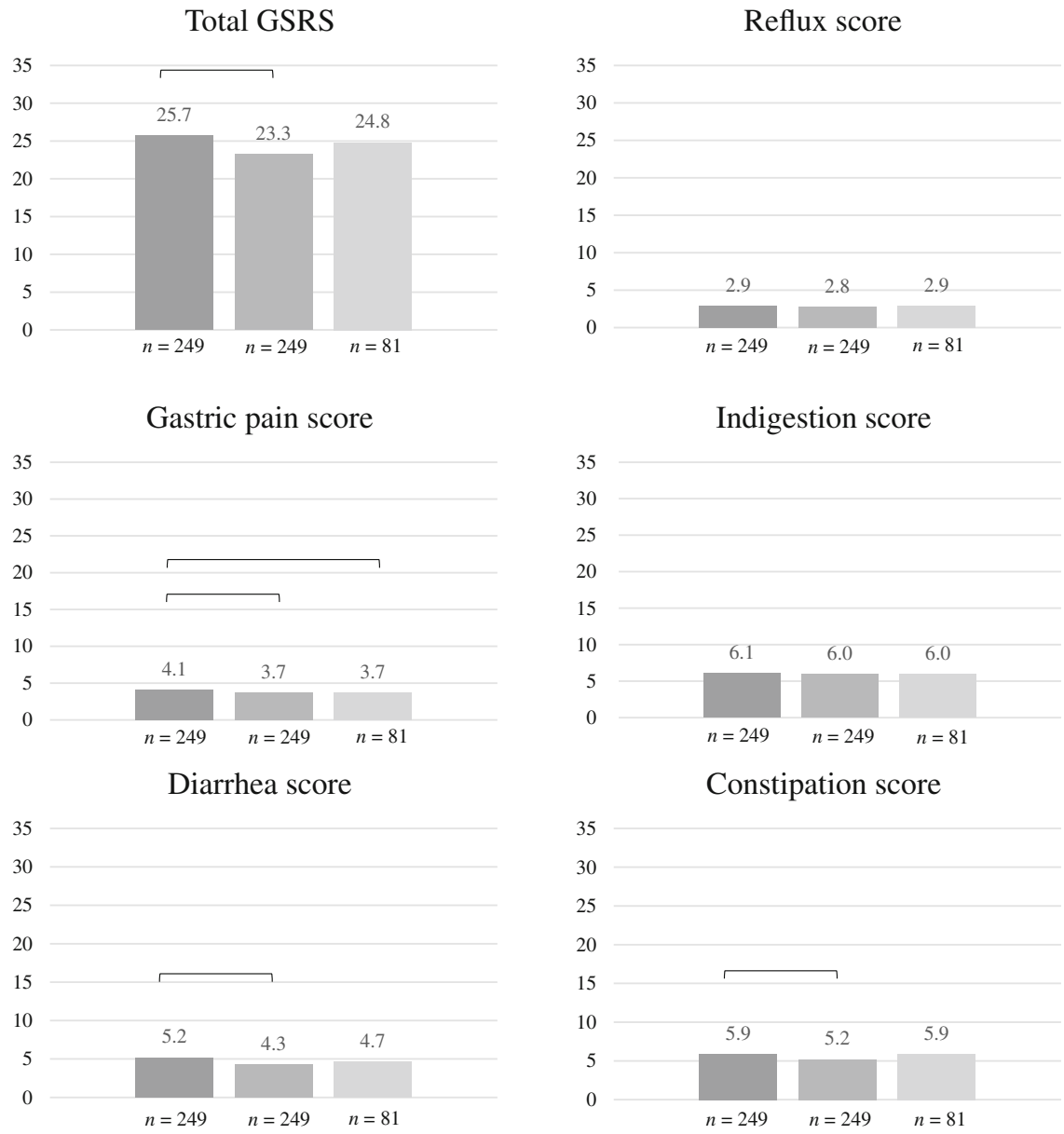

Figure 1 Changes in Gastrointestinal Symptom Rating Scale (GSRS) scores up to 12 months after *Helicobacter pylori* eradication in the successful-eradication group. Patients in the successful-eradication group for whom GSRS scores were calculated after 12 months demonstrated a significant decrease in gastric pain score between before eradication and 12 months post eradication. On the other hand, despite a significant decrease from before eradication to 2 months after eradication, there were no significant differences in total GSRS score and constipation score at 12 months compared with before eradication. (■), Before eradication; (■), 2 months after eradication; (■), 12 months after eradication.

Table 4 Gastrointestinal Symptom Rating Scale (GSRS) scores before and after *Helicobacter pylori* eradication between patients with and without epigastric symptoms at baseline

$n = 282$	Epigastric symptoms	Before eradication	After eradication†	*P*-value
Total GSRS	+ ($n = 136$)	31.3 ± 10.8*	26.2 ± 7.6*	<0.001
	− ($n = 146$)	20.6 ± 4.8	21.4 ± 6.8	0.142
Reflux score	+ ($n = 136$)	3.4 ± 1.9*	3.0 ± 1.5*	0.002
	− ($n = 146$)	2.5 ± 1.0	2.5 ± 1.0	0.828
Gastric pain score	+ ($n = 136$)	5.5 ± 2.7*	4.1 ± 1.7	<0.001
	− ($n = 146$)	3.4 ± 0.8	3.6 ± 1.4	0.107
Indigestion score	+ ($n = 136$)	8.1 ± 2.9*	7.1 ± 2.6*	<0.001
	− ($n = 146$)	4.6 ± 0.9	5.2 ± 1.9	<0.001
Diarrhea score	+ ($n = 136$)	5.9 ± 3.5*	4.9 ± 2.4*	0.002
	− ($n = 146$)	4.1 ± 2.1	4.2 ± 2.5	0.594
Constipation score	+ ($n = 136$)	6.8 ± 3.6*	5.7 ± 2.7	<0.001
	− ($n = 146$)	4.8 ± 2.4	4.7 ± 2.5	0.523

†Among 136 patients who had epigastric symptoms at baseline, 114 patients were successfully eradicated and 22 patients failed. Among 146 patients who had no symptoms at baseline, 135 patients ware successfully eradicated, and 11 patients failed.
*P <0.05 *versus* patients without epigastric symptoms (score >3 for one or more of the seven questions, including epigastric pain, hunger pain, nausea, borborygmus, satiety, eructation, and increased flatus) at baseline.

Long-term changes in GSRS scores in the eradication-successful group. Of 282 patients in whom the infection was successfully eradicated, 80 patients (28%) responded to the GSRS questionnaire at 12 months after the eradication. When we evaluated the changes of symptoms in these 80 patients, gastric pain score was significantly decreased up to 12 months compared with baseline (Fig. 1). However, although the short-term survey at 2 months showed significant improvements, there was no significant difference in total GSRS score, diarrhea score, and constipation score between before eradication and 12 months after eradication (Fig. 1).

Changes in GSRS scores by* H. pylori *eradication in patients with epigastric symptoms at baseline. Of the 282 patients, 136 patients (48.2%) had epigastric symptoms (score >3 for one or more of the seven questions) at baseline. Among them, 47 patients (34.5%) experienced improvements of their symptoms 2 months after eradication. When we compared changes in GSRS scores at 2 months between patients with symptoms at baseline and those without, patients with epigastric symptoms at baseline showed a significant improvement from baseline to 2 months post eradication in total GSRS score, reflux score, gastric pain score, indigestion score, diarrhea score, and constipation score (Table 4). On the other hand, in patients without symptoms at baseline, there was no significant difference in any of the scores between before and 2 months post eradication, except for an improvement in the indigestion score.

Long-term changes in GSRS scores in patients with epigastric symptoms at baseline. Of the 136 patients with epigastric symptoms at baseline, 36 patients (26.5%) responded to the GSRS questionnaire at 12 months after eradication. In these patients, the total GSRS score and gastric pain score were significantly decreased up to 12 months compared with baseline (Fig. 2).

Discussion

H. pylori-associated gastritis often causes dyspepsia and abdominal pain. Therefore, eradication therapy is recommended for *H. pylori*-positive patients as a first-line treatment.[11] In this study, we found that 48.2% of Japanese *H. pylori*-positive patients had abdominal symptoms: 22.0% of patients experienced gastric pain of score 3 or greater, and 41.8% of patients experienced indigestion of score 3 or greater on the GSRS questionnaire. *H. pylori* eradication improved dyspepsia-associated symptoms in 34.5% of patients at 2 months post eradication, and was controlled through to 12 months in most patients with symptoms before treatment, and who responded to treatment at 2 months. This study showed that among *H. pylori*-positive dyspepsia patients, 34.5% were considered to have *H. pylori*-associated dyspepsia. Therefore, *H. pylori*-positive patients with dyspeptic symptoms should undergo eradication to alleviate dyspeptic symptoms, as stated in the Kyoto Global Consensus report and the Clinical Guidelines for Functional Dyspepsia in Korea and Japan.[10–12,21]

Association between* H. pylori *infection and dyspepsia. The Korean clinical guidelines state that eradication is a reasonable treatment for *H. pylori*-positive dyspepsia patients because eradication can provide the long-term relief of symptoms (recommendation: weak; quality of evidence: high).[21] The British guidelines also recommend that dyspepsia patients be offered noninvasive testing for *H. pylori* ("test and treat"), and if infected with *H. pylori*, given eradication treatment (recommendation: strong; quality of evidence: high), and that *H. pylori*-naïve patients and eradicated patients be offered empirical acid suppression therapy (strong and high).[12] Although the therapeutic efficacy of eradication in patients with functional dyspepsia or *H. pylori*-associated dyspepsia is sometimes difficult to evaluate due to the possibility of placebo effects,[22] it is generally estimated that approximately 5–10% of dyspepsia is attributable to *H. pylori* infection around the world.[23,24] In 17 randomized control trials,

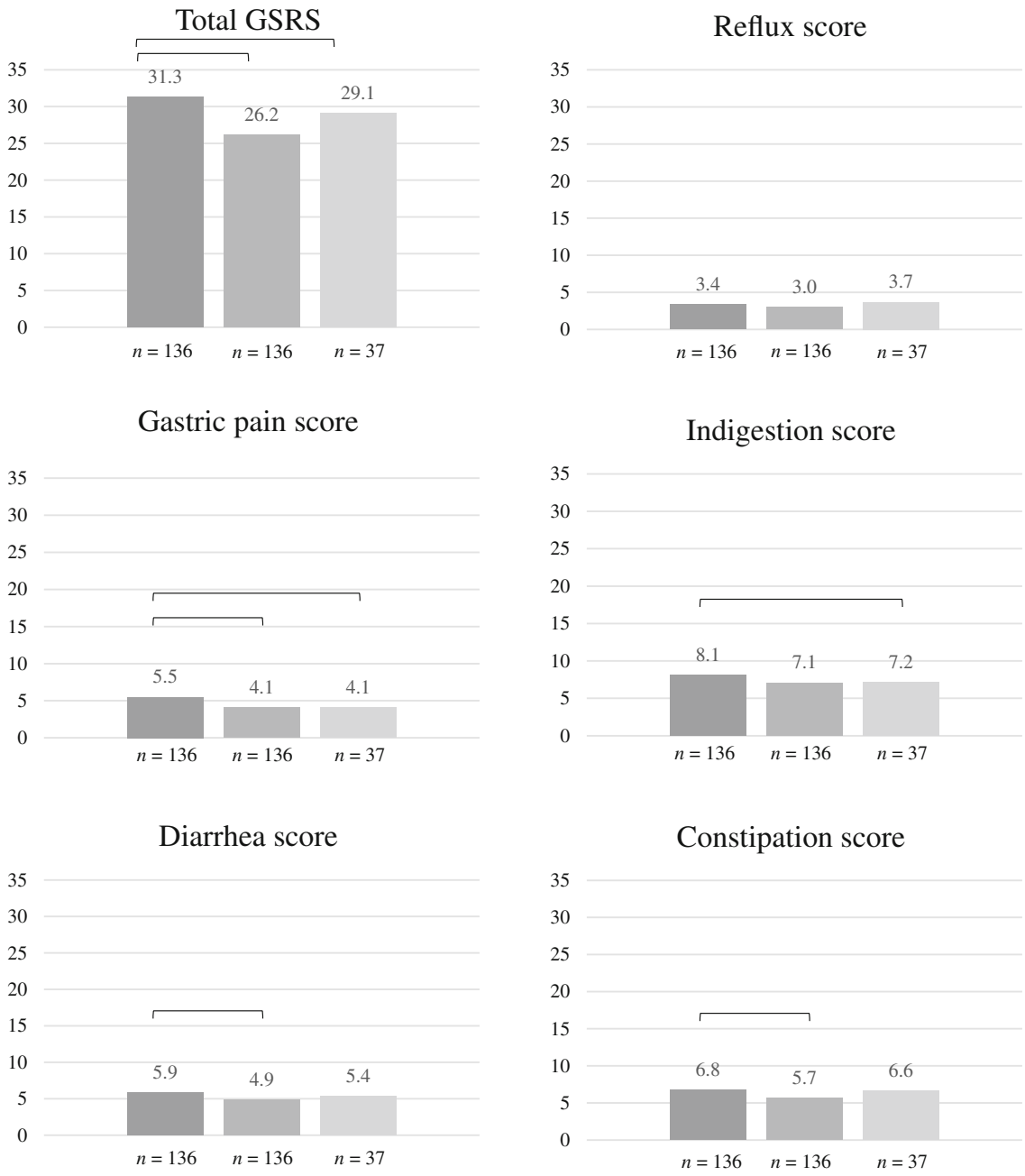

Figure 2 Changes in Gastrointestinal Symptom Rating Scale (GSRS) scores up to 12 months after successful *Helicobacter pylori* eradication in the patients with epigastric symptoms before eradication therapy. In patients who had epigastric symptoms at baseline ($n = 136$) and who responded to the GSRS questionnaire at 12 months after *H. pylori* eradication ($n = 37$), total GSRS score, gastric pain score, and indigestion score significantly decreased between before eradication and at 12 months post eradication. Other scores showed a significant improvement in the short term but there was no significant difference in scores 12 months after the eradication. Among the 136 patients who had epigastric symptoms at baseline, 114 patients ware successfully eradicated and 22 patients were unsuccessful. In 2 months after eradication, 114 patients with successful eradication and 22 with failed eradication were included. All 37 patients who answered the GSRS questionnaire at 12 months after *H. pylori* eradication were successfully eradicated of the infection. (■), Before eradication; (■), 2 months after eradication; (■), 12 months after eradication.

the relative risk of reduction of dyspepsia after eradication in *H. pylori*-positive dyspepsia patients was 10.0% (95% CI: 6.0–14.0%), and the number needed to treat to cure one patient with functional dyspepsia was 14.[24] Another meta-analysis of studies of non-Asian populations showed that eradication induced a statistically significant improvement of dyspeptic symptoms

(relative risk: 1.22).[21] Therefore, in Western countries in which infection rates are low, the contribution of *H. pylori* to dyspepsia symptoms may be significant but small. On the other hand, Tsuda *et al.*[25] reported that half of *H. pylori*-positive dyspeptic patients could be classified as having *H. pylori*-associated dyspepsia and that two-thirds of the patients could be classified as having *H. pylori*-associated dyspepsia or FD at the questionnaire evaluation 1 month after eradication. In the present study, 34.5% of *H. pylori*-positives with dyspeptic symptoms showed an improvement in their symptoms after eradication. The cost effectiveness of eradication, adverse effects, reinfection rates, and increase in resistant bacteria are expected to be higher in areas with a high prevalence of infection, including Asian countries, compared to areas with a low prevalence, such as Western countries. Therefore, the rate of improvement of dyspepsia after eradication and the prevalence of *H. pylori*-associated dyspepsia may differ among different geographic populations. Eradication is known to be more effective for *H. pylori*-associated dyspepsia patients in Asian countries, which have higher infection rates.[25,26]

Although the cause of this discrepancy in efficacy of eradication between Western and East-Asian countries is unclear, differences in infection rates and *H. pylori* strain types may be possible causes. In fact, virulence factors of *H. pylori* play important roles in the development of gastric mucosal injuries and inflammation associated with gastritis, peptic ulcers, atrophy, intestinal metaplasia, and malignancy.[27,28] More than 90–95% of strains isolated in East-Asian countries carry the *cag* pathogenicity island, which has a high virulency,[29,30] and 40% of strains isolated in Western countries are *cagA*-negative.[29,30] To confirm this hypothesis, further studies will be necessary to investigate whether the prevalence of *H. pylori*-associated dyspepsia between these regions is a result of the different strains with different virulence factors.

Association between* H. pylori *infection and gut microbiota. Alterations in gastrointestinal motility, visceral hypersensitivity, permeability, and low-level immune activation in the stomach and duodenum may play a role in FD via their association with the gut microbiota.[31,32] Shanahan *et al.*[31] reported that differences in the relative abundance of the phyla Firmicutes and Bacteroidota showed an inverse association between Streptococcus and Prevotella, which in addition to Fusobacterium could also be linked with FD symptom burden, and that the relative abundance of *Veillonella* spp. was also inversely associated with gastric emptying. On the other hand, in *H. pylori*-positive patients, irrespective of FD, the dominant bacterial phyla are Firmicutes, Bacteroidetes, and Actinobacteria, which account for 97.7% of the total gut bacteria,[33] suggesting that *H. pylori* is a major factor in gastric microbial dysbiosis. Therefore, although the profile of gastrointestinal microbiota is expected to differ between patients with *H. pylori*-negative FD and *H. pylori*-associated dyspepsia, it is unclear whether the gut microbiota in patients with FD are associated with those in patients with *H. pylori*-associated dyspepsia.

H. pylori eradication affects gut microbiota in the long term,[34,35] and can lead to the restoration of gastric microbiota to a status similar to that in *H. pylori*-negatives.[36] In the present study, eradication improved abdominal symptoms during the subsequent 12 months in dyspepsia patients, which was similar to previous observations of improved bowel habits in patients after eradication.[18,19] This observation may suggest that changes of gastric microbiota may contribute to improvements of *H. pylori*-associated dyspepsia. However, it is unclear whether the improvement of dyspeptic symptoms in patients with *H. pylori*-associated dyspepsia is a result of "restoration from *H. pylori* virulency" or "recovery from dysbiosis."

Association between improvement of epigastric symptoms and constipation. Eradication treatment improved both upper abdominal symptoms and constipation in patients of the eradication-successful group. Of the 98 patients whose gastric pain score improved after eradication, surprisingly, about 60% also experienced improvements in constipation. The pathogenesis of functional gastrointestinal diseases is thought to involve multiple factors in a complex manner, and symptoms overlap and transitions may occur in these diseases. There are reports that in patients with FD, postprandial distress syndrome is often associated with IBS-C.[37] In patients with such functional gastrointestinal diseases, changes in the intestinal microbiota as a result of eradication may contribute to the symptomatic improvement of constipation.[18] Therefore, patients with such functional gastrointestinal diseases should be analyzed cross-sectionally.

Limitations. This study has several limitations. First, this was a single-center retrospective study with a small sample size. Second, because this study was a single-arm retrospective study, and not a placebo-controlled trial, it was difficult to accurately compare the effects of eradication on symptoms between the groups. Therefore, we would like to perform a prospective randomized trial to compare the effects of eradication on the symptoms of patients as a future study. Third, we did not analyze the gut microbiota. Fourth, because the long-term survey was a retrospective study, patients who enrolled in a short-term survey had the choice of undergoing endoscopy at a hospital 12 months after the eradication. Therefore, this study may have selection bias. Fifth, although food adjustments and medications, such as proton pump inhibiters, prokinetic drugs, or other anti-secretory agents, after eradication may affect the questionnaire scores, there was no data regarding these points. Sixth, because patients were given a choice regarding the hospital at which they wished to undergo endoscopy to evaluate their gastric condition 12 months after eradication, 202 patients chose to undergo endoscopy at a hospital or health check-up center. Therefore, we were not able to evaluate abdominal symptoms of all patients at 12 months post treatment.

In conclusion, we found that 34.5% of *H. pylori*-positive Japanese patients with abdominal symptoms experienced an improvement of symptoms at 2 months post eradication and that most patients continued to show improvement of dyspepsia in the long term. *H. pylori* eradication may more effectively improve the symptoms of *H. pylori*-associated dyspepsia in patients from Asian populations than from Western populations, owing to different *H. pylori* infection rates, *H. pylori* virulency, and gut microbiota. Thus, *H. pylori* eradication is an effective treatment for *H. pylori*-positive patients with dyspeptic symptoms.

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References

1 Malfertheiner P, Megraud F, O'Morain CA *et al*. Management of *Helicobacter pylori* infection–the Maastricht IV/Florence Consensus Report. *Gut*. 2012; **61**: 646–64.
2 Asaka M, Kato M, Takahashi S *et al*. Guidelines for the management of *Helicobacter pylori* infection in Japan: 2009 revised edition. *Helicobacter*. 2010; **15**: 1–20.
3 Tsuda M, Asaka M, Kato M *et al*. Effect on *Helicobacter pylori* eradication therapy against gastric cancer in Japan. *Helicobacter*. 2017; **22**: e12415.
4 Sugano K. Effect of *Helicobacter pylori* eradication on the incidence of gastric cancer: a systematic review and meta-analysis. *Gastric Cancer*. 2019; **22**: 435–45.
5 Sugimoto M, Murata M, Yamaoka Y. Chemoprevention of gastric cancer development after *Helicobacter pylori* eradication therapy in an East Asian population: meta-analysis. *World J. Gastroenterol.* 2020; **26**: 1820–40.
6 Stanghellini V, Chan FK, Hasler WL *et al*. Gastroduodenal disorders. *Gastroenterology*. 2016; **150**: 1380–92.
7 Mahadeva S, Goh KL. Epidemiology of functional dyspepsia: a global perspective. *World J. Gastroenterol.* 2006; **12**: 2661–6.
8 Suzuki H, Nishizawa T, Hibi T. Can *Helicobacter pylori*-associated dyspepsia be categorized as functional dyspepsia? *J. Gastroenterol. Hepatol.* 2011; **26**: 42–5.
9 Sugano K. Should we still subcategorize *Helicobacter pylori*-associated dyspepsia as functional disease? *J. Neurogastroenterol. Motil.* 2011; **17**: 366–71.
10 Sugano K, Tack J, Kuipers EJ *et al*. Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut*. 2015; **64**: 1353–67.
11 Miwa H, Nagahara A, Asakawa A *et al*. Evidence-based clinical practice guidelines for functional dyspepsia 2021. *J. Gastroenterol.* 2022; **57**: 47–61.
12 Black CJ, Paine PA, Agrawal A *et al*. British Society of Gastroenterology guidelines on the management of functional dyspepsia. *Gut*. 2022; **71**: 1697–723.
13 Svedlund J, Sjodin I, Dotevall G. GSRS–a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig. Dis. Sci.* 1988; **33**: 129–34.
14 Sugimoto M, Hasegawa T, Nishino M *et al*. Improvement of gastroesophageal reflux disease in Japanese patients with spinal kyphotic deformity who underwent surgical spinal correction. *Dig. Endosc.* 2016; **28**: 50–8.
15 Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy*. 1969; **1**: 87–97.
16 Sugimoto M, Ban H, Ichikawa H *et al*. Efficacy of the Kyoto Classification of gastritis in identifying patients at high risk for gastric cancer. *Intern. Med.* 2017; **56**: 579–86.
17 Tanaka F, Tominaga K, Fujikawa Y *et al*. Association between functional dyspepsia and gastric depressive erosions in Japanese subjects. *Intern. Med.* 2019; **58**: 321–8.
18 Murata M, Sugimoto M, Otsuka T *et al*. Successful *Helicobacter pylori* eradication therapy improves symptoms of chronic constipation. *Helicobacter*. 2018; **23**: e12543.
19 Murata M, Sugimoto M, Miyamoto S, Kawai T. Long-term improvement in constipation-related symptoms after *Helicobacter pylori* eradication therapy. *Helicobacter*. 2022; **27**: e12863.
20 Sugimoto M, Murata M, Iwata E, Nagata N, Itoi T, Kawai T. Risk of reflux-related symptoms and reflux esophagitis after *Helicobacter pylori* eradication treatment in the Japanese population. *J. Clin. Med.* 2021; **10**: 1434.
21 Oh JH, Kwon JG, Jung HK *et al*. Clinical practice guidelines for functional dyspepsia in Korea. *J. Neurogastroenterol. Motil.* 2020; **26**: 29–50.
22 Moayyedi P, Soo S, Deeks J *et al*. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *Cochrane Database Syst. Rev.* 2000: CD002096.
23 Moayyedi P, Forman D, Braunholtz D *et al*. The proportion of upper gastrointestinal symptoms in the community associated with *Helicobacter pylori*, lifestyle factors, and nonsteroidal anti-inflammatory drugs. Leeds HELP Study Group. *Am. J. Gastroenterol.* 2000; **95**: 1448–55.
24 Delaney B, Ford AC, Forman D, Moayyedi P, Qume M. Initial management strategies for dyspepsia. *Cochrane Database Syst. Rev.* 2005; **3**: CD001961.
25 Tsuda M, Kato M, Ono S *et al*. Changes of dyspeptic symptom after successful eradication in *Helicobacter pylori*-associated dyspepsia. *Digestion*. 2020; **101**: 165–73.
26 Jin X, Li YM. Systematic review and meta-analysis from Chinese literature: the association between *Helicobacter pylori* eradication and improvement of functional dyspepsia. *Helicobacter*. 2007; **12**: 541–6.
27 Broutet N, Tchamgoue S, Pereira E, Lamouliatte H, Salamon R, Megraud F. Risk factors for failure of *Helicobacter pylori* therapy–results of an individual data analysis of 2751 patients. *Aliment. Pharmacol. Ther.* 2003; **17**: 99–109.
28 van der Hulst RW, Weel JF, Verheul SB *et al*. Treatment of *Helicobacter pylori* infection with low or high dose omeprazole combined with amoxycillin and the effect of early retreatment. *Aliment. Pharmacol. Ther.* 1996; **10**: 165–71.
29 Yamaoka Y, El-Zimaity HM, Gutierrez O *et al*. Relationship between the cagA 3′ repeat region of *Helicobacter pylori*, gastric histology, and susceptibility to low pH. *Gastroenterology*. 1999; **117**: 342–9.
30 Yamaoka Y, Orito E, Mizokami M *et al*. *Helicobacter pylori* in North and South America before Columbus. *FEBS Lett.* 2002; **517**: 180–4.
31 Shanahan ER, Kang S, Staudacher H *et al*. Alterations to the duodenal microbiota are linked to gastric emptying and symptoms in functional dyspepsia. *Gut*. 2022; **72**: 929–38.
32 Zhou L, Zeng Y, Zhang H, Ma Y. The role of gastrointestinal microbiota in functional dyspepsia: a review. *Front. Physiol.* 2022; **13**: 910568.
33 Zhou Y, Ye Z, Wang Y *et al*. Long-term changes in the gut microbiota after triple therapy, sequential therapy, bismuth quadruple therapy and concomitant therapy for *Helicobacter pylori* eradication in Chinese children. *Helicobacter*. 2021; **26**: e12809.
34 Martín-Núñez GM, Cornejo-Pareja I, Roca-Rodríguez MDM *et al*. *H. pylori* eradication treatment causes alterations in the gut microbiota and blood lipid levels. *Front. Med. (Lausanne)*. 2020; **7**: 417.
35 Kakiuchi T, Yamamoto K, Imamura I *et al*. Gut microbiota changes related to *Helicobacter pylori* eradication with vonoprazan containing triple therapy among adolescents: a prospective multicenter study. *Sci. Rep.* 2021; **11**: 755.
36 Guo Y, Zhang Y, Gerhard M *et al*. Effect of *Helicobacter pylori* on gastrointestinal microbiota: a population-based study in Linqu, a high-risk area of gastric cancer. *Gut*. 2020; **69**: 1598–607.
37 Talley NJ, Dennis EH, Schettler-Duncan VA, Lacy BE, Olden KW, Crowell MD. Overlapping upper and lower gastrointestinal symptoms in irritable bowel syndrome patients with constipation or diarrhea. *Am. J. Gastroenterol.* 2003; **98**: 2454–9.