Gastroesophageal Reflux Disease in Time Covering Eradication for All Patients Infected with *Helicobacter pylori* in Japan

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Key Words

Gastroesophageal reflux disease · Non-erosive reflux disease · *Helicobacter pylori* · Reflux esophagitis · Hiatal hernia · Gastric mucosal atrophy

Abstract

Background: The prevalence of gastroesophageal reflux disease (GERD) has increased in Japan since the end of the 20th century due to changes in environmental factors, such as a decreased infection rate of *Helicobacter pylori* and increased ability of acid secretion in the Japanese population. In 2013, the Japanese health insurance system started to cover eradication treatment for all patients infected with *H. pylori* to prevent gastric cancer, suggesting we may soon be able to completely eradicate this infection in Japan. Re-clarification of the clinical characteristics of GERD in Japan is therefore required in time covering the eradication for all patients infected with *H. pylori*. **Summary:** In Japan, more than half of GERD patients exhibit non-erosive reflux disease, and a majority of erosive esophagitis (RE) cases have mild severity of GERD (Los Angeles classification of grades A and B). The prevalence of RE in *H. pylori*-positive patients is relatively low

(4.1%) compared to the general Japanese population (7.6–10.6%). In multivariate analysis to evaluate a risk of RE development, a risk in *H. pylori*-positive patients is elevated in those with mild gastric mucosal atrophy (C-I and C-II according to the Kimura–Takemoto classification, OR 12.14, 95% CI 1.28–115.26, $p = 0.03$) or with hiatal hernia (OR 5.24, 95% CI 1.80–15.22, $p < 0.01$). Here, we provide a comprehensive review of GERD in Japan, including associations between GERD and *H. pylori* infection, low-dose-aspirin-induced GERD, and pharmacological treatment for GERD. **Key Messages:** The recent decrease in the rate of *H. pylori* infection and increase in the proportion of elderly persons might have increased the prevalence of GERD in Japan.

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Introduction

Gastroesophageal reflux disease (GERD), including erosive esophagitis (RE) and non-erosive reflux disease (NERD), is estimated to affect approximately 20–30% of the population worldwide. In Japan, a recent study noted that acid reflux-related symptoms were reported at least

on a monthly basis in 6.6–9.8% of the population, with an increasing incidence of endoscopic GERD [1]. In general, GERD has a multifactorial pathogenesis that includes the reflux of gastric or bile acid into the esophagus, hiatal hernia, dysfunction of esophageal sphincter and esophageal motility, impairment of esophageal epithelial resistance, and hypersensitivity [2, 3]. Of these factors, prolonged and frequent esophageal reflux of gastric acid with low pH (i.e. pH <4) is a critical risk factor for esophageal mucosal injury [3]. Recent changes in environmental factors have increased the basal and stimulated gastric acid secretion in the Japanese population according to the time course from the 1970s to 1990s, irrespective of the age of subjects [3]. These high levels of gastric acid secretion combined with an aging population might be increasing susceptibility to GERD in Japan.

In 2013, the Japanese health insurance system pledged to cover treatment to eradicate *Helicobacter pylori* in patients with *H. pylori*-associated gastritis as confirmed by endoscopy. In Japan, the first-line eradication regimen consists of twice-daily dosing (b.i.d.) with amoxicillin, clarithromycin, and a proton pump inhibitor (PPI) or potassium-competitive acid blocker for 1 week. Given that *H. pylori* infection decreases the ability of gastric acid secretion in relation to advanced gastric mucosal atrophy and enhanced gastric mucosal inflammation [4, 5], the bacterium might be associated with the development of GERD. In addition, a gradual but significant decrease in the severity of gastric mucosal atrophy at all sites and intestinal metaplasia in the lesser curvature of the corpus is observed following *H. pylori* eradication [6]. These findings suggest the restoration of appropriate gastric acid secretion following eradication therapy [6]. With recent changes in healthcare law making eradication for all patients infected with *H. pylori* in Japan, the population might be at increased risk of developing GERD.

Based on the above, re-clarification of the clinical characteristics of GERD in the time of eradication for all Japanese with *H. pylori* is required. Here, we review the association between GERD and *H. pylori* infection, low-dose-aspirin (LDA)-induced GERD, and pharmacological treatment for GERD in time covering the eradication for all patients infected with *H. pylori* in Japan.

GERD in Japan

The incidence of GERD, including RE and NERD, is increasing in Japan [1]. A meta-analysis was conducted of 30 studies that investigated the prevalence of RE in

Japanese outpatients and 12 that investigated subjects who underwent regular health check-ups in hospitals in Japan [1]. Results showed that, although the prevalence of RE ranged from 1.4 to 52.1%, the prevalence of RE in outpatients for treatment of disease or with complaints (10.6%) was higher than in subjects who underwent health check-ups (7.6%) [1]. Of 5,022 Japanese GERD subjects, NERD was identified in 2,944 (58.6%) and RE in 2,078 (41.4%) [1].

According to the Los Angeles classification, the reported prevalence of each grade of RE for 9,782 cases was as follows: grade A, 5,338 (54.6%); grade B, 3,169 (32.4%); and grade C/D, 1,275 (13.0%) [1], suggesting that a majority of RE patients (87.0%) have mild RE (grades A and B). Although the prevalence of symptomatic GERD ranges from 6.6 to 37.6%, the mean prevalence of GERD is 11.5% (3,216/27,870) when GERD is defined as the presence of heartburn at least twice per week [1]. In Japan, a major characteristic of GERD patients is that more than half have NERD and that the majority of RE cases are relatively mild in severity, which is in sharp contrast to findings of high prevalence of severe GERD in Europe and North America.

Association between GERD and *H. pylori* Infection in Japan

Several risk factors for RE have been identified, with the following considered to increase risk of RE: hiatal hernia [7], higher body mass index or obesity, old age, mild gastric atrophy [7] (such as closed-type atrophic gastritis according to the Kimura–Takemoto classification) [8], and absence of *H. pylori* infection.

H. pylori infection induces a decrease in gastric acid secretion in conjunction with the progression of gastric atrophy and enhanced gastric mucosal inflammation. Activated neutrophil and mononuclear cells infiltrate the gastric mucosa infected with *H. pylori* and secrete inflammatory cytokines as an immune response, such as IL-1 β and TNF- α , which are potent inhibitors of gastric acid secretion [4, 5]. Indeed, IL-1 β exerts 100-fold more potent inhibition than PPIs and 6,000-fold more potent inhibition than histamine-2 receptor antagonists on a molar basis [9]. This increased production of inflammatory cytokines in response to *H. pylori* infection then suppresses gastric acid secretion and exacerbates gastric mucosal inflammation [10]. In addition, gastric mucosal atrophy progresses with long-term *H. pylori* infection, suggesting a further decrease in gastric acid secretion.

These previous findings have clarified that *H. pylori* infection is inversely associated with the development of GERD.

The time covering the eradication for all patients infected with *H. pylori* is approaching in Japan. In the general population, the infection rate of *H. pylori* was recently reported as 74.9% in asymptomatic subjects born before 1950 and 20.7% in those born after 1950 [11]. However, given the relationship between *H. pylori* infection and GERD, this decreased infection rate is necessarily associated with increased prevalence of GERD, particularly in relatively young subjects.

We investigated 395 *H. pylori*-positive dyspeptic patients, who provided written informed consent, from September 2011 to January 2015 at the University Hospital of Hamamatsu University School of Medicine. *H. pylori* infection was evaluated using an *H. pylori*-IgG, rapid urease test, polymerase chain reaction analysis for 23S rRNA gene, and a culture test (table 1). Endoscopic gastric mucosal atrophy was evaluated based on the Kimura-Takemoto classification [8]. The prevalence of GERD in the *H. pylori*-positive dyspeptic patients was 36.8% (145/395), with an NERD incidence rate of 32.7% (grade M: 12.2%, grade N: 20.5%) and RE rate of 4.1%; of note, this RE rate in our outpatients was lower than that noted in meta-analysis outpatients (10.6%) and subjects who underwent health check-ups (7.6%; fig. 1a) [1]. Among the GERD patients in our study, the proportion of RE is 11.1% (NERD: 88.9%), which is lower than that determined in the meta-analysis (41.1%; fig. 1b) [1]. The prevalence of each LA classification grade for RE was as follows: grade A (75.0%), grade B (18.8%), and grade C/D (6.2%; fig. 1c). In Japan, a majority of RE patients are of the mild type (grades A and B) in time covering the eradication for all patients infected with *H. pylori*. Endoscopic evaluation has shown that the prevalence of severe gastric mucosal atrophy patients is lower in patients with GERD than in those without (fig. 1d). In contrast, the prevalence of hiatal hernia is significantly higher in patients with GERD than in those without (fig. 1e). Of 395 *H. pylori*-positive dyspeptic patients, multivariate analysis found an increased risk of developing RE in *H. pylori*-positive patients with mild gastric mucosal atrophy (C-I and C-II according to the Kimura-Takemoto classification, OR 12.14, 95% CI 1.28–115.26, $p = 0.03$) or hiatal hernia (OR 5.24, 95% CI 1.80–15.22, $p < 0.01$; table 2).

In these years, although the incidence of GERD is increasing in Japan, the incidence of GERD in Japanese patients infected with *H. pylori* is not so high. In addition, the endoscopic severity of GERD in Japanese patients in-

Table 1. Characteristics of 395 *H. pylori*-positive dyspeptic Japanese patients enrolled in our study

Characteristic	Patients
Number of patients	395
Age, years, mean $\pm$ SE	57.9 $\pm$ 11.4
Sex, male:female, n	200:195
Height, cm	161.0 $\pm$ 8.5
Body weight, kg	58.6 $\pm$ 10.8
<i>H. pylori</i> infection (positive/negative)	395/0
Gastric mucosal atrophy (C-I and C-II/ C-III and O-I/O-II and O-III)	71/236/88
Hiatal hernia (+/-)	80/315
Barrett's esophagus (+/-)	140/255
PG I level	53.1 $\pm$ 32.3
PG I/PG II ratio	2.7 $\pm$ 1.7
Eradication history (naive/first/second time)	230/64/101

PG = Serum pepsinogen.

fectured with *H. pylori* is mild, such as NERD and grade A GERD. However, *H. pylori*-positive patients with mild gastric mucosal atrophy are likely to develop GERD, because of the high ability for acid secretion.

Association between GERD and *H. pylori* Eradication in Japan

Although *H. pylori* eradication therapy might actually improve RE and reflux-related symptoms for patients with extant GERD [12], the development of RE has been observed in 4.8–20.5% of formerly *H. pylori*-positive Japanese patients after eradication, with most cases found to be of mild severity (grade A or B GERD) [12, 13]. Further, following eradication, 4.6–10% of formerly *H. pylori*-positive patients experience recurrent GERD symptoms [12, 13]. Given that gastric mucosal atrophy gradually and significantly ameliorates and gastric acid secretion recovers following eradication [6], physicians should be prepared for the development of GERD after such therapy. However, most such cases of post-eradication, newly developed GERD are transient, and eradication therapy is rarely a clinical problem with long-term GERD treatment in Japan [14].

On the other hand, because *H. pylori*-positive patients with antral-dominant gastritis or mild gastric mucosal atrophy (C-I and C-II according to the Kimura-Takemoto classification) have a high ability for gastric acid secretion, acid secretion decreases in any of such patients after

Fig. 1. Prevalence of GERD in meta-analysis of 30 studies of Japanese outpatients and 12 studies of Japanese participants with health check-ups [1] versus that among *H. pylori*-positive dyspeptic patients in our university hospital (**a**). Proportion of NERD and RE in GERD patients in meta-analysis [1] and our present study (**b**). Endoscopic severity of esophageal mucosal injury in Japanese

patients with *H. pylori* infection and RE in meta-analysis [1] and our present study (**c**). Endoscopic severity of gastric mucosal atrophy in Japanese patients with *H. pylori* infection among non-GERD, NERD and RE patients (**d**). Prevalence of hiatal hernia in Japanese patients with *H. pylori* infection (**e**).

Table 2. Risk factors for GERD development in 395 *H. pylori*-positive dyspeptic Japanese patients in multivariate analysis

Factors	OR	95% CI	p value
Non-NERD/erosive gastritis	Reference		
Endoscopic atrophy: CIII–OI	4.54	0.54–38.28	0.16
Endoscopic atrophy: CI–CII	12.14	1.28–115.26	0.03
Hiatal hernia	5.24	1.80–15.22	<0.01
Barrett’s esophagus	1.49	0.51–4.38	0.46
Age	1.01	0.96–1.06	0.71
Sex, male	2.46	0.71–8.14	0.14

eradication therapy, suggesting that eradication therapy may prevent development of GERD in *H. pylori*-positive patients with antral-dominant gastritis or mild gastric mucosal atrophy.

Pharmacological Treatment for GERD

The main pharmacological treatment for GERD is inhibition of potent gastric acid secretion for 24 h, for which PPIs are considered effective. Curing RE requires that 24 hour intragastric pH not fall below 4.0 for longer than approximately 2–4 h [15]. In GERD management guidelines, an 8-week course of PPIs is recommended to treat RE symptoms [16]. At present, 4 types of PPIs (omeprazole, rabeprazole, lansoprazole, or esomeprazole) and potassium-competitive acid blockers (e.g. vonoprazan) are used to treat GERD in Japan.

In multicenter, randomized, double-blind study for Japanese RE patients, the healing rates for esomeprazole at 20 mg at week 8 was 87.3% (165/189), a value similar to the rate of omeprazole at 20 mg in a previous study (87.4%, 166/190) [17]. Estimated Kaplan–Meier recurrence-free rates for each maintenance therapy of GERD patients were as follows: esomeprazole 20 mg (92.0%), esomeprazole 10 mg (87.5%), and omeprazole 10 mg (82.7%) [17]. At a dose of 20 mg, a significant difference in cure rate was noted between esomeprazole and omeprazole ($p = 0.007$) [18].

The potassium-competitive acid blocker vonoprazan (TAK-438) was recently identified, exhibiting potent acid inhibition, low influence on CYP2C19, and rapid action for acid inhibition compared to other PPIs [19]. Studies in Japan and the United Kingdom have found respective mean 24-hour intragastric pH >4 holding time ratios of 100 and 93.2% and respective mean night-time pH >4 holding time ratios of 100 and 90.4% on day 7 of treat-

ment with vonoprazan 40 mg [20]. In a phase 3 randomized, double-blind, multicenter study, the healing rates of GERD with vonoprazan 20 mg were 90.7% at week 2, 96.6% at week 4, and 99.0% at week 8 [21]. Taken together, these previous findings suggest that vonoprazan, which has potent acid inhibition compared to other PPIs, may be useful in treating GERD.

Cure rates of GERD are influenced by a number of factors, such as genetic polymorphisms of CYP2C19, PPI dosage, presence of functional heartburn, status of *H. pylori* infection, and endoscopic severity of GERD [22]. In particular, risk factors for a poor response to PPIs include an RE grade C/D, being a CYP2C19 extensive metabolizer (EM), lacking *H. pylori* infection, and having severe spinal kyphotic deformity. Given their risk of being refractory to PPI therapy for GERD, CYP2C19 EMs require advanced treatments, such as increased PPI dosages and administration frequencies [22, 23].

Association between GERD and LDA in Time Covering Eradication for All Patients Infected with *H. pylori*

Aspirin is widely used as an antiplatelet drug to treat patients with cardio- or cerebrovascular diseases. However, a major drawback when administering aspirin, even at low doses, is the increased risk of gastrointestinal mucosal injury (2- to 5-fold) due to the inhibition of gastrointestinal mucosal COX-1 [24]. Interestingly, aspirin damages not only the gastric and enteric mucosa but also the esophageal mucosa. In logistic regression analysis accounting for age, gender, smoking and drinking habits, arthritis, and aspirin use, aspirin use was found to be the only factor contributing to the development of GERD.

We previously reported that, in 80 patients taking LDA and the 80 age- and sex-matched non-LDA con-

Fig. 2. a Incidence of esophageal mucosal injury in LDA users and non-LDA controls. Of the recruited 91 patients taking LDA who underwent endoscopy for dyspeptic symptoms or who came for a health check-up at the University Hospital of Hamamatsu University School of Medicine, 80 patients were enrolled after obtaining written informed consent. In addition, of about 10,000 trails of endoscopy during the same period, 80 age- and sex-matched controls were randomly selected from among outpatients not taking LDA who underwent endoscopy for dyspeptic symptoms or for a health check-up. **b** Relationship between intragastric pH and percentage time with pH <4.0 in 15 *H. pylori*-negative healthy young Japanese volunteers with non-GERD-related symptoms. All patients with an intragastric pH >5 and <4.0 for <40% of the time developed esophageal mucosal injury on administration of aspirin [25].

controls who underwent gastroscopy for dyspeptic symptoms or for ulcer and cancer screening irrespective of symptoms, the incidence of esophageal mucosal injury in LDA user was 40.0%, which is significantly higher than that in non-LDA controls (21.3%; fig. 2a) [25], and that the severity of GERD differed significantly between LDA users and nonusers, and the prevalence of endoscopic color change to redness, but not a mucosal break (grade A according to the Los Angeles classification), in LDA users was higher (35.0%, 28/80) than in the controls (16.3%, 13/80) [25]. In addition, we reported that 7-day LDA administration in a prospective study induced GERD in approximately half of 15 *H. pylori*-negative healthy young volunteers with non-GERD-related symptoms (7 individuals [47%] developed endoscopic redness [$n = 5$] and erosion (grade A GERD according to the Los Angeles classification [$n = 2$]) [26]. These observations suggested that endoscopic characteristics of LDA-induced GERD may be of mild severity (e.g. grade M

NERD), not RE [25]. However, given the lack of information on the association of LDA with NERD, a further study is required to clarify whether or not this endoscopic characteristic is required.

While a study in mice found no evidence that acidified saline alone caused esophageal mucosal damage, the addition of aspirin did induce damage [27]. Further, esophageal mucosal damage was ameliorated when the mucosa was submerged in an aspirin-containing solution with a pH of at least 6, no lower [27]. Control of acid secretion is therefore important for preventing or reducing aspirin-induced esophageal damage.

Our prospective study in 2011 found that the occurrence and prevention of LDA-induced GERD were closely related to intragastric pH during treatment [26]. Preventing the development of LDA-induced GERD required obtaining a mean 24-hour pH >5.0 with pH <4.0 for <40% of the time (fig. 2b) [26]. These findings strongly suggest that aspirin-induced esophageal mucosal in-

jury can be prevented by combined administration with half-dose and standard dose of a PPI [28].

A recent double-blind comparative study of 452 patients receiving aspirin found that incidence rates of RE at 24 weeks were 2% in patients treated with rabeprazole at a dose of 5 mg and 0% in those treated at a dose of 10 mg, which is markedly lower than the rate in patients receiving teprenone at a dose of 50 mg t.i.d. (8.6%) [29]. Although LDA therapy is being used with increasing frequency to treat and prevent arterial thrombotic disease, administration with a PPI is required to prevent the development of drug-induced ulcers and GERD in subjects currently taking LDA for cardiovascular protection.

Conclusion

Here, we reviewed the association between GERD and *H. pylori* infection, LDA-induced GERD, and pharmacological treatment for GERD in time covering the eradication for all patients infected with *H. pylori* in Japan. *H. pylori* infection is associated with decreased development of GERD in Japan. In time covering eradication for all patients infected with *H. pylori* in Japan where all of Japanese *H. pylori* patients are eradicated by permission from Japanese government, the prevalence of *H. pylori*-

negative subjects with increased ability of gastric acid secretion is expected to increase. In addition, the proportion of an aging population increases in Japan. These observations suggest that in time covering eradication for all patients infected with *H. pylori* in Japan, the prevalence of GERD in Japanese is increasing, as observed in Western countries.

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Disclosure Statement

None of the authors has any conflict of interest related to this study.

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