

## Effect of *Helicobacter pylori* Eradication on the Development of Reflux Esophagitis and Gastroesophageal Reflux Symptoms: A Nationwide Multi-Center Prospective Study

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**Background/Aims:** A two-year, prospective, nationwide multicenter study was undertaken to evaluate the effect of *Helicobacter pylori* eradication on the development of reflux esophagitis (RE) and gastroesophageal reflux disease (GERD) symptoms in the Korean population. **Methods:** In total, 1,489 subjects without RE were enrolled at the outpatient clinics of 12 tertiary hospitals nationwide, and 452 subjects underwent follow-up (F/U) for 2 years to evaluate the development of RE and GERD symptoms. **Results:** RE was found in 33 subjects (7.3% of 452 subjects) and 14 subjects (7.3% of 192 subjects) during the first and second year of F/U, respectively. *H. pylori* status was not associated with the development of RE. RE was found in six (9.0%) of 67 *H. pylori*-negative patients, in 26 (11.2%) of 233 eradicated subjects and in eight (7.0%) of 114 noneradicated subjects ( $p=0.532$ ). Multivariate analysis showed that age  $\geq 60$  years (odds ratio [OR], 7.11; 95% confidence interval [CI], 1.92 to 26.41), alcohol consumption (OR, 4.43; 95% CI, 1.03 to 19.19) and F/U cholesterol levels  $\geq 200$  mg/dL (OR, 5.03; 95% CI, 1.32 to 19.17) were significant risk factors for the development of RE. There was no significant difference in the development of GERD symptoms or weight according to *H. pylori* status during the 2-year F/U. **Conclusions:** Eradication of *H. pylori* did not affect the development of reflux esophagitis or GERD

symptoms among patients in outpatient gastroenterology clinics in South Korea. (*Gut Liver* 2011;5:437-446)

**Key Words:** *Helicobacter pylori*; Eradication; Reflux esophagitis; Symptoms

### INTRODUCTION

*Helicobacter pylori* (*H. pylori*) infection plays a major role in the pathogenesis of peptic ulcer disease, chronic gastritis, gastric mucosa-associated lymphoid tissue lymphoma (MALToma), and the development of gastric cancer. However, its role in reflux esophagitis (RE) or gastroesophageal reflux disease (GERD) is not fully understood. In addition, the effect of *H. pylori* eradication on RE or GERD is unclear. Several reports have shown an association of *H. pylori* eradication with the development of RE<sup>1-5</sup> or GERD symptoms.<sup>6,7</sup> However, contradictory results have been reported<sup>8-11</sup> and sometimes a beneficial effect of *H. pylori* eradication on GERD has been observed.<sup>12-16</sup> This issue regarding the effect of *H. pylori* eradication on the development of RE is important because RE often requires chronic treatment with a proton pump inhibitor (PPI) due to frequent relapse of symptoms.<sup>17</sup> The Maastricht III Consensus Report already extended the recommendations of *H. pylori* eradication to patients with

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dyspepsia, along with those who chronically use PPI or non-steroid anti-inflammatory drugs (NSAID).<sup>18</sup> In South Korea, the eradication of *H. pylori* has been rapidly increasing<sup>19,20</sup> as well as the prevalence of RE<sup>21</sup> or Barrett's esophagus.<sup>22</sup> Therefore, if RE development increases after eradication of *H. pylori*, then the eradication of *H. pylori* should proceed with greater caution in South Korea.

Based on this background, a nationwide multicenter prospective study was undertaken to evaluate the effect of *H. pylori* eradication on the development of RE and GERD symptoms in South Koreans. In addition, factors affecting RE development were evaluated.

## MATERIALS AND METHODS

### 1. Subjects

This study was designed by the Scientific Committee of the Korean College of *Helicobacter* and Upper Gastrointestinal Research. A workshop was held on June 25, 2005 to approve the study design and to standardize the description of RE and gastroesophageal reflux symptoms in the questionnaire. Feedback from experts in this field and practical field tests were conducted to validate the reflux symptom questionnaire over 3 months.<sup>23</sup> Patients with gastritis, duodenal ulcers (DU) in the active or healing stages, and benign gastric ulcer (BGU) were enrolled in July 2006 for 1 year at the Gastroenterology Department of 12 tertiary hospitals nationwide. Most of the participants had gastroduodenal discomfort and underwent endoscopy to evaluate whether the symptoms were related to specific diseases such as gastric cancer, DU, BGU, or RE. Subjects with a previous history of gastric surgery, *H. pylori* eradication treatment, or systemic diseases requiring chronic medication were excluded. In addition, subjects current taking or with a history of taking H<sub>2</sub> blocker or PPI within at least 1 month were excluded from this study. Subjects with upper gastrointestinal endoscopy results showing evidence of RE, gastric cancer, dysplasia, MALToma, or esophageal cancer were excluded from this study. Additionally subjects with endoscopic findings of BGU scars or DU scars were also excluded from enrollment to avoid confusion in the analysis. The Institutional Review Board of the 12 participating hospitals approved this study, and written informed consent was obtained from all participants.

### 2. Upper gastrointestinal endoscopic examinations

All study subjects underwent upper gastrointestinal endoscopic examinations. The endoscopic findings of RE in the lower esophagus were classified according to the Los Angeles (LA) classification based on the longest length of the mucosal break, and confluence of erosions. A hiatal hernia was endoscopically defined as a distance from the esophagogastric junction to the diaphragmatic impingement of more than 1 cm. The esophagogastric junction was defined as the proximal margin of the

gastric mucosal fold.<sup>24</sup>

### 3. Questionnaire

Patients who agreed to participate in the study were interviewed in person by an assistant using the gastroesophageal reflux questionnaire, before the endoscopy. The questionnaire included questions about seven reflux symptoms including heartburn, acid regurgitation, chest pain, hoarseness, globus sensation, cough, and epigastric soreness. The questions were as follows: 1) Have you experienced heartburn? 2) Have you experienced acid regurgitation? 3) Have you experienced chest pain? 4) Have you experienced hoarseness? 5) Have you experienced a globus sensation in the throat? 6) Have you experienced a frequent cough? 7) Have you experienced epigastric soreness? If the patients replied yes to at least one of the seven questions about reflux symptoms, then they were further questioned about the reflux symptom periods. Body mass index (BMI) and the results of biochemical testing including glucose, cholesterol, triglyceride, and *H. pylori* tests were recorded by assistants.

### 4. *H. pylori* tests

Two biopsy specimens from the antrum and two from the body were fixed in formalin, and examined for the presence of *H. pylori* by modified Giemsa staining. One specimen from the lesser curvature of the antrum and one from the corpus were subjected to rapid urease testing (*Campylobacter*-like organism (CLO) test; Delta West, Bentley, Australia). *H. pylori* infection was diagnosed when at least one of these tests gave positive results.

### 5. Serum pepsinogen levels

Fasting serum was collected from all subjects at the beginning of the study. The samples were centrifuged immediately and stored at -70°C until used. Serum concentrations of pepsinogen (PG) I and II were measured using a latex-enhanced turbidimetric immunoassay (L-TIA) (HBi Co., Seoul, Korea, imported from Shima Laboratories, Tokyo, Japan), and PG I to PG II ratios (PG I/II) were calculated.<sup>25,26</sup>

### 6. Eradication treatments and follow-up study

When a subject with duodenal or gastric ulcers was found to be *H. pylori*-positive, the standard 7-day triple therapy (PPI b.i.d., 500 mg b.i.d. clarithromycin, and 1 g b.i.d. amoxicillin) was started for *H. pylori* eradication. Subjects with simple gastritis also received *H. pylori* eradication therapy when requested by the patient. To determine whether *H. pylori* had been eliminated, <sup>13</sup>C-urea breath testing was performed at least 4 weeks after completing the triple therapy. If *H. pylori* infection was found to present persistent after the first-line PPI-based triple therapy a 1- or 2-week course of bismuth-based quadruple therapy was started: 20 mg b.i.d. esomeprazole, and 300 mg q.i.d. tripotassium dicitrate bismuthate (DENOL®; Greencross, Seoul, Korea,

three tabs taken 30 minutes before meals and one tab taken 2 hours after dinner), 500 mg t.i.d. metronidazole, and 500 mg q.i.d. tetracycline.

Initially enrolled subjects underwent endoscopy and filled out a questionnaire every year for 2 years. The endoscopists were unaware of the questionnaire results. Patients with recurrence or occurrence of BGU were excluded from this study. Every participant was asked whether new GERD symptoms (heartburn, acid regurgitation, chest pain, hoarseness, globus sensation, cough, and epigastric soreness) had developed during follow-up period. In addition, patients answered questions about duration and frequency of their symptom (a. 1-2 times per year, b. 1-2 times per month, c. 1-2 times per week, d. 3-4 times per week, e. daily). In addition, they were asked whether they took PPI or H<sub>2</sub> blocker to relieve these GERD symptoms, and were also asked about the duration of PPI or H<sub>2</sub> blocker treatment. If the participants refused the follow-up endoscopy at the second year in after numerous requests, an interview was conducted to evaluate changes in weight, smoking habits, and alcohol consumption. In addition, the questionnaire regarding gastroesophageal reflux symptoms was re-administered. The main reason for refusal of endoscopy at the second year was that the patient disliked undergoing the procedure.

## 7. Statistical analysis

The patients were categorized according to age in 10-year intervals. New development of reflux esophagitis and GERD symptoms (heartburn, acid regurgitation, chest pain, hoarseness, globus sensation, cough, and epigastric soreness) follow-up period was analyzed according to *H. pylori* eradication. Chi-square tests were performed to assess the association between each covariate and development of RE. Covariates that showed significant association by the chi-square tests were considered for the multiple logistic regression analyses. Model fit was assessed by the Hosmer-Lemeshow goodness-of-fit test. The variables that were significant in the model or improved model fit were included in the final model. The final models showed an appropriate goodness of fit ( $p > 0.10$ ). All analyses were performed using SAS statistical software (SAS Institute, Cary, NC, USA). A  $p$ -value of less than 0.05 was considered statistically significant.

## RESULTS

### 1. Characteristics of participants

In total 1,489 subjects (855 males, 57.4%; 634 females, 42.6%) were included in the study. The mean age was 51.3 years and all participants were ethnically Korean. Follow-up endoscopy with the questionnaire was performed 1 year later and 452 subjects received an endoscopy 1 year after enrollment. The characteristics of 452 subjects are described in Table 1 including gender, age, BMI, endoscopic diagnosis, smoking habit, alcohol consumption, hiatal hernia, glucose, cholesterol, triglyceride, *H.*

*pylori* infection, and pepsinogen levels. There were no statistical differences in these variables between the 1,489 initially enrolled and 452 follow-up subjects. Four hundred fifty-two subjects had DU in the active or healing stage (68, 15.1%), BGU in the active or healing stage (115, 25.4%), or gastritis (269, 59.5%). There were 385 individuals (85.2%) with *H. pylori* infections and the remaining 67 subjects (14.8%) were not infected. When reflux symptoms of 452 subjects were analyzed at enrollment, epigastric soreness was the most frequent symptom, reported by 127 subjects (28.1%), followed by heartburn (27 subjects, 6.0%), chest pain (25 subjects, 5.5%), acid regurgitation and globus sensation (21 subjects, 4.6%), cough (7 subjects, 1.5%), and hoarseness (2 subjects, 0.4%).

**Table 1.** Baseline Characteristics of the Initially Enrolled Subjects and Patients Undergoing Follow-Up for 2 Years

Variable category	Initially enrolled subjects (n=1,489)	Followed-up subjects (n=452)
Gender		
Male	855 (57.4)	271 (60.0)
Female	634 (42.6)	181 (40.0)
Age, yr	51.3±12.4	53.8±11.1
16-29	60 (4.0)	5 (1.1)
30-39	206 (13.9)	46 (10.2)
40-49	402 (27.0)	106 (23.4)
50-59	420 (28.2)	142 (31.4)
60-69	301 (20.2)	121 (26.8)
≥70	100 (6.7)	32 (7.1)
Body mass index	23.8±3.2	23.9±3.1
Endoscopic diagnosis		
Duodenal ulcer (active or healing stage)	336 (22.6)	68 (15.1)
Benign gastric ulcer (active or healing stage)	333 (22.3)	115 (25.4)
Gastritis	820 (55.1)	269 (59.5)
Smoking (current:past)	387 (26.0):115 (7.7)	108 (23.9):51 (11.3)
Alcohol consumption (current:past)	624 (41.9):52 (3.5)	203 (44.9):21 (4.6)
Hiatal hernia	60 (4.0)	16 (3.5)
Glucose, mg/dL	103.1±30.2	102.5±31.4
Cholesterol, mg/dL	188.6±39.4	187.7±38.8
Triglyceride, mg/dL	136.6±50.5	139.1±48.9
<i>H. pylori</i> infection	1189 (79.9)	385 (85.2)
Pepsinogen level		
Pepsinogen I, ng/mL	65.5±23.1	69.0±22.1
Pepsinogen II, ng/mL	18.6±11.3	18.4±11.2
Pepsinogen I/II ratio	3.95±1.55	3.75±1.64

Data are presented as mean±SD or number (%).

**2. *H. pylori* treatment results and weight change during the 2-year follow-up**

Among the 452 subjects who had received an endoscopy 1 year after enrollment, 192 (42.5%) another endoscopy in the second year of follow-up, and the remaining 260 subjects (57.5%) responded to a telephone interview. Initially, 67 subjects (14.8%) were diagnosed as *H. pylori*-negative. Among 385 *H. pylori*-positive cases, 233 cases (51.6%) were found to be eradicated, 114 subjects (25.2%) were not treated or the infec-

tion was not eradicated, and 38 (8.4%) did not receive follow-up *H. pylori* tests (Table 2). Participants were weighted prior to enrollment and 1 and 2 years after enrollment, there was no significant difference in weight based on the *H. pylori* status during follow-up.

**3. Development of reflux symptoms during the 2-year follow-up depending on *H. pylori* eradication**

Analysis based on development of reflux-related symptoms during the 2-year follow-up was performed according to *H. py-*

**Table 2.** Weight Changes Based on *H. pylori* Eradication in the 452 Follow-Up Subjects

Variable	No. (%)	Initial, kg	1 yr later, kg	2 yr later, kg
<i>H. pylori</i> -negative	67 (14.8)	63.0±12.1*	64.7±12.7	63.9±11.7
<i>H. pylori</i> -positive	385 (85.2)			
Eradicated after treatment	233 (51.6)	63.7±11.0	63.9±11.2	63.4±9.8
Untreated or persistent infection	114 (25.2)	63.1±11.1	64.8±11.0	64.8±11.3
No test after eradication	38 (8.4)	64.9±11.5	65.1±11.8	64.9±11.6

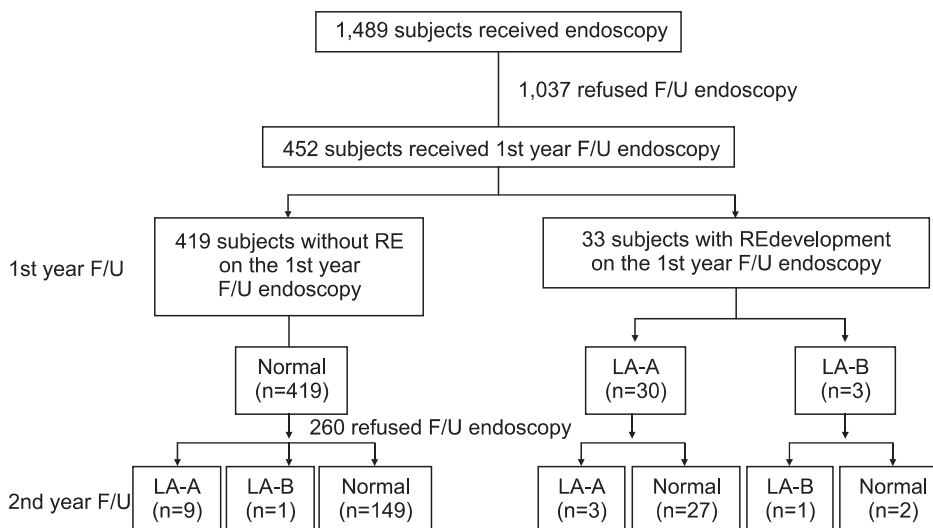
\*Mean±SD.

**Table 3.** The Development of Reflux Symptoms During the 2-Year Follow-Up Based on *H. pylori* Eradication

Symptom*	<i>H. pylori</i> -negative (n=67)	<i>H. pylori</i> -eradicated (n=233)	Persistent <i>H. pylori</i> infection (n=114)	p-value
Heartburn	2 (3.0)	8 (3.5)	6 (5.3)	0.537
Acid regurgitation	4 (6.0)	17 (7.4)	7 (6.2)	0.736
Chest pain	2 (3.0)	6 (2.7)	6 (5.7)	0.591
Hoarseness	0 (0)	1 (0.4)	0 (0)	0.195
Globus sensation	2 (3.0)	8 (3.5)	1 (0.9)	0.185
Cough	4 (6.0)	3 (1.3)	1 (0.9)	0.514
Epigastric soreness	7 (10.5)	3 (1.3)	1 (0.9)	0.901

Data are presented as number (%).

\*The occurrence of each symptom was counted individually.



**Fig. 1.** Development of reflux esophagitis, as determined by the Los Angeles (LA) grades at follow-up (F/U) endoscopic examinations after 1 or 2 years.

**Table 4.** Univariate Analysis of Reflux Esophagitis Development during the 2-Year Follow-Up

Variable	Non-reflux esophagitis (n=409)	Reflux esophagitis (n=43)	Total (n=452)	p-value
Gender				0.088
Male	240 (58.7)	31 (72.1)	271 (60.0)	
Female	169 (41.3)	12 (27.9)	181 (40.0)	
Age, yr				0.032
16-39	46 (11.3)	5 (11.6)	51 (11.3)	
40-59	232 (56.7)	16 (37.2)	248 (54.9)	
≥60	131 (32.0)	22 (51.2)	153 (33.8)	
<i>H. pylori</i> eradication state	(n=374)	(n=40)	(n=414)	0.532
<i>H. pylori</i> -negative	61 (16.3)	6 (15.0)	67 (16.2)	
Eradicated	207 (55.4)	26 (65.0)	233 (56.3)	
Noneradicated	106 (28.3)	8 (20.0)	114 (27.5)	
Smoking habit	(n=341)	(n=31)	(n=372)	0.054
Nonsmoking-nonsmoking	260 (76.2)	20 (64.5)	280 (75.3)	
Nonsmoking-smoking	21 (6.2)	2 (6.5)	23 (6.2)	
Smoking-nonsmoking	3 (0.9)	2 (6.5)	5 (1.3)	
Smoking-smoking	57 (16.7)	7 (22.6)	64 (17.2)	
Alcohol consumption	(n=340)	(n=30)	(n=370)	
Nonalcohol-nonalcohol	199 (58.5)	9 (30.0)	208 (56.2)	0.006
Nonalcohol-alcohol	37 (10.9)	3 (10.0)	40 (10.8)	
Alcohol-nonalcohol	4 (1.2)	0 (0)	4 (1.1)	
Alcohol-alcohol	100 (29.4)	18 (60.0)	118 (31.9)	
Initial finding of hiatal hernia				0.160
Yes	12 (3.5)	3 (7.0)	15 (3.3)	
No	397 (96.5)	40 (93.0)	437 (96.7)	
Disease				0.012
Duodenal ulcer	60 (14.7)	8 (18.6)	68 (15.0)	
Benign gastric ulcer	96 (23.5)	19 (44.2)	115 (25.5)	
Gastritis	253 (61.8)	16 (37.2)	269 (59.5)	
Pepsinogen				
Pepsinogen I, ng/mL	60.6±12.1	75.9±17.9	65.5±23.1	0.035
Pepsinogen II, ng/mL	18.5±11.7	18.2±12.0	18.6±11.3	0.893
Pepsinogen I/II ratio	3.68±1.11	4.41±1.28	3.95±1.55	0.043
Weight				
Initial weight, kg	62.9±0.54	67.1±1.98	64.2±1.11	0.094
Follow-up weight, kg	63.9±0.61	69.4±2.17	64.3±1.13	0.018
Cholesterol				
Initial, mg/dL	187.7±12.1	187.5±7.8	187.7±10.8	0.981
Follow-up, mg/dL	188.7±8.1	211.5±10.0	190.9±9.2	0.047
Triglyceride				
Initial, mg/dL	139.6±6.1	131.9±18.2	139.0±9.8	0.730
Follow-up, mg/dL	144.2±9.6	141.1±25.8	144.0±11.0	0.861

Data are presented as mean±SD or number (%).



lori infection (Table 3). New development of epigastric soreness was the most common symptom, especially in the *H. pylori*-negative group (10.5%) but there was no statistical significance associated with *H. pylori* infection. The percentage of participants with new development of other reflux symptoms such as heartburn, acid regurgitation, chest pain, hoarseness, globus sensation and cough were found to be 0% to 6.0%, there was no significant difference associated with *H. pylori* eradication (Table 3).

#### 4. Development of RE during the 2-year follow-up

RE was found in 33 subjects (7.3% of 452 subjects) and 14 subjects (7.3% of 192 subjects) at the first and second year of follow-up, respectively. Among the 33 patients who developed RE at the 1st follow-up 30 (90.9%) showed LA-A and 3 (9.1%) showed LA-B (Fig. 1). Among the 30 subjects with LA-A at the first follow-up, 27 did not have RE at the second year and three subjects were found to have persistent LA-A (Fig. 1). Among the three subjects with LA-B, only one had persistent LA-B at the second year follow-up. Ten subjects who did not have RE at the first year follow-up turned out to have LA-A (nine subjects) or LA-B (one subject) at the second year follow-up. Finally, RE was found in 14 subjects at the second year follow-up (Fig. 1). In summary, there were 33 RE patients at the first year follow-up, and cases of RE were found in 14 patients RE patients at the second year follow-up. Three patients continuously had LA-A and one patient persistently showed LA-B at the first and second year follow-up, respectively. In total, RE developed in 43 patients during the 2-year follow-up period.

#### 5. Analysis of risk factors for RE development

To evaluate the risk factors for RE during the 2-year follow-up period, univariate analysis was performed to examine gender, age, *H. pylori* eradication, smoking habit, alcohol consumption, initial finding of hiatal hernia, underlying disease, serum

pepsinogen, weight changes, and cholesterol and triglyceride levels (Table 4). Gender showed no correlation with RE development but there was an increase of RE incidence with age (14.4%  $\geq 60$  years vs 6.4% 40 to 59 years). *H. pylori* eradication was not associated with RE development of RE. That is, among 67 *H. pylori*-negative patients, RE development was found in 6 (9.0%), RE development was found in 26 (11.2%) out of 233 subjects in which *H. pylori* had been eradicated, and RE developed in 8 (7.0%) out of 133 patients with persistent *H. pylori* infections ( $p=0.532$ ). Smoking showed a marginal difference in RE development, but alcohol consumption had a statistically difference impact (Table 5). That is, the nonalcohol-non-alcohol group had 4.3% RE, the alcohol-non-alcohol group 0%, which was lower than the non-alcohol-alcohol group 7.5%, and the alcohol-alcohol group showed 15.2% ( $p=0.006$ ). The presence of an underlying disease was found to influence the development of RE. RE development was frequent observed in patients with BGU (16.5%), this was more common than in patients with DU (11.8%) or gastritis (5.9%) ( $p=0.012$ ). Serum pepsinogen level was also associated with development of RE. PG I levels were higher in the group that developed RE ( $75.9 \pm 17.9$  ng/mL) than in the group that did not develop RE ( $60.6 \pm 12.1$  ng/mL) ( $p=0.035$ ); however, there was no significant difference in the PG II levels between these 2 groups. Finally, the PG I/II ratio was higher in the RE group ( $4.41 \pm 1.28$ ) than in the group without RE ( $3.68 \pm 1.11$ ) ( $p=0.043$ ). Initial body weight was not significantly associated with the development of RE. However, body weight was increased in the RE group at follow-up, and this was significantly associated with RE development ( $p=0.028$ ). Similar to body weight, cholesterol levels also showed a significant association with the development of RE in the univariate analysis. Initial cholesterol levels were similar between the groups with and without RE. However, the follow-up cholesterol levels were higher in the RE group ( $211.5 \pm 10.0$ ) than in the group without RE ( $188.7 \pm 8.1$ ). In contrast, triglyceride levels showed no sig-

**Table 5.** Multivariate Analysis of Reflux Esophagitis Development during the 2-Year Follow-Up

Variable	Non-reflux esophagitis (n=409)	Reflux esophagitis (n=43)	OR	95% CI
Age, yr			7.11	1.92-26.41
16-39	46 (11.3)	5 (11.6)		
40-59	232 (56.7)	16 (37.2)		
$\geq 60$	131 (32.0)	22 (51.2)		
Alcohol consumption	(n=340)	(n=30)	4.43	1.03-19.19
Nonalcohol-non-alcohol	199 (58.5)	9 (30.0)		
Nonalcohol-alcohol	37 (10.9)	3 (10.0)		
Alcohol-non-alcohol	4 (1.2)	0 (0)		
Alcohol-alcohol	100 (29.4)	18 (60.0)		
F/U cholesterol $\geq 200$ mg/dL	188.7 $\pm$ 8.1	211.5 $\pm$ 10.0	5.03	1.32-19.17

Data are presented as mean $\pm$ SD or number (%).

OR, odds ratio; CI, confidence interval; F/U, follow-up.

nificant association with the development of RE.

Among the significant findings identified by the univariate analysis, the following were identified as significant risk factors for RE development by multivariate analysis: age  $\geq 60$  years vs below 60 years (odds ratio [OR], 7.11; 95% confidence interval [CI], 1.92 to 26.41), alcohol consumption at follow-up (OR, 4.43; 95% CI, 1.03 to 19.19), and elevated follow-up cholesterol levels (OR, 5.03; 95% CI, 1.32 to 19.17) (Table 5).

## DISCUSSION

Since *H. pylori* is a major cause of gastric cancer, eradication of *H. pylori* infections has become an important goal for the prevention of gastric cancer in high-risk groups. In South Korea, *H. pylori* eradication has rapidly increased from 13.9% in 2005<sup>19</sup> to 37.4% in 2007 among subjects presenting for a health check-up.<sup>20</sup> In addition, the prevalence of RE<sup>21</sup> or Barrett's esophagus is increasing<sup>22</sup> similar to other Asian countries. Furthermore, since the rates of on demand *H. pylori* treatment or relapse in RE patients are also high in South Korea,<sup>15</sup> it is very important to determine whether the risk of GERD or RE increases after *H. pylori* eradication. There have been several reports suggesting that GERD occurs after eradication of *H. pylori* in patients with or without peptic ulcers.<sup>8,9,27-30</sup> This development of GERD following the eradication of *H. pylori* might be related to an increase in refluxate acidity due to the disappearance of the neutralizing effect of bacterial ammonia production and corpus gastritis induced by persistent *H. pylori* infection.<sup>31,32</sup> In contrast, there have been some reports of the beneficial effect of *H. pylori* eradication for ameliorating symptoms of GERD.<sup>12-16</sup> The reason for these conflicting reports could originate from the underlying gastric mucosal status. For instance, a meta-analysis showed that the frequency of GERD is not increased after eradication of *H. pylori* among dyspeptic patients, but there was the risk of GERD development increased 2-fold after *H. pylori* eradication among patients with peptic ulcers.<sup>33</sup> Similarly, the univariate analysis of the present multicenter prospective study showed that the development of RE was more frequent after treating active or healing cases of BGU (16.5%) or DU (11.8%) than gastritis (5.9%) ( $p=0.012$ ) although this significance was not found in the multivariate analysis. In addition, PG I levels and PG I/II ratios, which have been used as indicators of acid secretion,<sup>34</sup> were found to be significantly higher in the group that developed RE compared to the nonRE group. This could support the hypothesis that acid secretion determines the development of RE.

A lack of association between RE or GERD symptoms and *H. pylori* eradication in the present study might reflect the lower prevalence of RE or GERD in South Korea compared to other Eastern as well as Western countries. The prevalence of RE has increased in Japan from 3% in the late 1970s to 10% to 15% in the late 1990s based on the results of upper-gastrointestinal

endoscopies,<sup>35</sup> and from 2.7% in the early 1990s to 13.4% in 2000 to 2001 in a Malaysian study.<sup>36</sup> In a South Korean study conducted in 1999, the prevalence of RE was 5.3% for patients with gastrointestinal symptoms,<sup>37</sup> and was 3.4% in a group of asymptomatic subjects presenting for a health check-up in 2001.<sup>38</sup> In 2006 RE prevalence increased to 7.9% among subjects presenting for a health check-up,<sup>21</sup> which is still lower than the levels reported in other Asian countries like Japan<sup>35,39</sup> and Malaysia.<sup>36</sup> Furthermore, the degree of RE found in the present study was relatively mild. That is, 39 out of 43 RE subjects (90.7%) had LA-A, while only four were found to have LA-B (9.3%). In addition, among 30 patients who participated in the follow-up during the second year 27 patients did not show definite mucosal breaks around z-line, suggesting that RE could be transient, which is consistent with the findings of a Japanese study.<sup>5</sup> Still, the precise reasons why the prevalence of RE or GERD is lower in South Korea than other Asian countries is not clear. This might be related to life style factors such as the consumption of certain kinds of food or a high prevalence of atrophic gastritis<sup>21</sup> due to the high infection rate of *H. pylori*.<sup>19</sup> Comparative studies on the prevalence of RE or GERD and its associated factors among South Korea and other Asian countries could help clarify this issue.

Another explanation for a lack of association between RE and *H. pylori* eradication in the present study could be related to the absence of definite weight gain after *H. pylori* eradication in Koreans. Previous studies showed that *H. pylori* infection is inversely related to obesity<sup>40,41</sup> and that increased body weight is often observed after *H. pylori* eradication.<sup>42</sup> Since ghrelin is mainly synthesized and secreted by the gastric mucosa, the inverse effect of *H. pylori* infection on body weight has been attributed to the difference in plasma ghrelin concentrations in patients with or without *H. pylori* infections.<sup>43</sup> However, in the present study there was no definite weight change observed according to *H. pylori* infection at the enrollment or *H. pylori* eradication after 2 years of follow-up. Since most of the previous studies were performed during short term follow-up (e.g., 12 weeks) after successful eradication,<sup>40</sup> it is possible that weight gain after *H. pylori* infection, which could be related to the increase of ghrelin, might be temporary. However, as the weight gain after successful *H. pylori* eradication was frequently observed in Japanese patients,<sup>42</sup> further study is necessary to confirm this finding in Koreans.

One of the characteristics of Korean patients with GERD is that they frequently complain of epigastric soreness or epigastric pain, which is usually classified as symptom of functional dyspepsia. This was similar to a Korean report showing that 18.8% patients that complained of functional dyspeptic symptoms were found to have RE and while 27.6% of patients with epigastric pain had RE.<sup>44</sup> This is the reason why epigastric soreness was included as one of the reflux symptoms in our study. When the occurrence of these symptoms were analyzed based

on *H. pylori* eradication during the 2-year follow-up, there was no association of new development of any GERD symptoms (heartburn, acid regurgitation, chest pain, hoarseness, globus sensation, cough, or epigastric soreness) with *H. pylori* eradication. This finding is rather different from the results of a Japanese study.<sup>14</sup>

In the present study, the incidence of RE per year regardless of *H. pylori* eradication was 7.3%, which is similar to the RE prevalence rate, 7.9% reported in 2006.<sup>21</sup> Since RE was transient in the present study, new development and the disappearance of RE might be somehow balanced among Koreans. In addition, the rate of newly developed GERD symptoms (heartburn, acid regurgitation, chest pain, hoarseness, globus sensation, cough, and epigastric soreness) during the 2-year follow-up was only 0% to 10.45%. This is similar to the finding that the prevalence of GERD according to symptom occurrence was found to be 5.1% among health check-up subjects in 2006,<sup>21</sup> and 3.5% in the rural and urban areas of Asan-si in South Korea, in a 2000 to 2001 survey (n=1,471).<sup>45</sup> So far, there has been no prospective multicenter study examining the incidence of RE or GERD symptoms, nor the relationship of *H. pylori* eradication with RE or GERD symptoms in South Korea. From this point of view, the multicenter, prospective study presented here is very meaningful as it has provided clues regarding the incidence of RE and GERD symptoms among South Koreans.

The significant risk factors for reflux esophagitis are known to include male gender, alcohol consumption, smoking, BMI  $\geq 25$ , abdominal obesity, and metabolic syndrome.<sup>21,46,47</sup> Similarly, the multivariate analysis of the present study showed that an age  $\geq 60$  (OR, 7.11; 95% CI, 1.92 to 26.41), alcohol consumption at follow-up (OR, 4.43; 95% CI, 1.03 to 19.2), and elevated cholesterol levels at follow-up (OR, 5.03; 95% CI, 1.32 to 19.2) were risk factors for the development of RE. Therefore, persons of advanced age ( $\geq 60$  years-old) with significant alcohol intake and cholesterol levels over 200 mg/dL should be watchful for the development of RE.

The present study had several limitations. First, there was a significant 1-year endoscopic follow-up loss after initial enrollment. Most of this follow-up loss may have occurred when the patients did not have any reflux or dyspeptic symptoms. Biennial endoscopy or barium gastrography has actually been recommended for gastric cancer screening starting at the age of 40 by the South Korean government since 2001. However, there was no statistical difference in gender, age, BMI, endoscopic diagnosis, smoking habits, alcohol use, occurrence of hiatal hernias, cholesterol levels, triglycerides, *H. pylori* infection, or pepsinogen levels between the 1,489 initially enrolled patients and 452 follow-up subjects. Second, the follow-up period was probably too short to detect the effect of *H. pylori* eradication on RE development. However, as pepsinogen I or PG I/II ratio reflecting the gastric acid secretion<sup>34</sup> has been already increased up to the level of *H. pylori*-negative group 1 year after *H. py-*

*lori* eradication in Koreans,<sup>21</sup> there might be little possibility of further occurrence of RE due to *H. pylori* eradication after long-term follow-up more than 2 years.

In conclusion, our study demonstrated that the eradication of *H. pylori* did not cause the development of RE or GERD symptoms over 2 years of follow-up. These results support the hypothesis that *H. pylori* eradication could be performed in South Korea without concerns about an increased risk of GERD or RE development.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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