

The Prevalence of Erosive Esophagitis Is Not Significantly Increased in a Healthy Korean Population - Could It Be Explained?: A Multi-center Prospective Study

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Background/Aims

Researches on the potential risk factors for the development of erosive esophagitis have been conducted extensively, however, the results are conflicting. The aim of this multicenter study was to identify the prevalence rate and risk factors of erosive esophagitis and their interactions with residency status.

Methods

A total of 4,023 eligible subjects at 8 tertiary health care centers were evaluated using questionnaires, laboratory tests and endoscopy. Univariate and multivariate analyses were conducted to identify independent risk factors for erosive esophagitis.

Results

The prevalence rate of reflux esophagitis was 8.8%. Los Angeles grade A was common type of erosive esophagitis. Residence in a large urban areas was negatively associated with the development of erosive esophagitis (OR, 0.60; 95% CI, 0.40-0.90). The high body mass index ($\geq 25 \text{ kg/m}^2$) was more frequent in residents of small and medium-sized cities than those in big cities (38.8% and 26.9%, respectively; $P < 0.001$). Seronegativity of *Helicobacter pylori* was associated with increased erosive esophagitis (OR, 1.91; 95% CI, 1.48-2.46). Triglyceride $\geq 150 \text{ mg/dL}$ (OR, 1.65; 95% CI, 1.08-2.07), fasting glucose level $\geq 126 \text{ mg/dL}$ (OR, 1.73; 95% CI, 1.06-2.81), and hiatal hernia (OR, 3.11; 95% CI, 1.87-5.16) were also associated with erosive esophagitis.

Conclusions

The prevalence rate of erosive esophagitis and its risk factors in this study were similar to the result of 8.0% of nationwide study in 2006. Residency and obesity are more important independent risk factors than *H. pylori* infection status for development of erosive esophagitis in Korea. These results suggest that the prevalence rate of erosive esophagitis in Korea might not increase as in the Western countries.

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Key Words

Esophagitis; *Helicobacter pylori*; Risk factors

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Introduction

Endoscopy-diagnosed erosive esophagitis has been increasing in Asia over 2 decades, with a reported prevalence of 3.3 to 8.5% in Korea, China and Japan except Taiwan (ranging from 17.3 to 18.3%) which is similar to other Western developed countries.¹⁻⁶ The reasons for the high prevalence rate of erosive esophagitis are not clearly demonstrated, however, it could be related with western diet, increased obesity and aging of population.⁶ The prevalence rate of erosive esophagitis was 8%, in prospective nationwide multicentre studies of 25,536 health check-up Koreans.⁷ This prevalence rate was lower than that in Western countries.⁸ Association between high *Helicobacter pylori* infectivity and relatively low obesity rate has long been expected to maintain low prevalence of erosive esophagitis in Koreans.

The potential risk factors of erosive esophagitis are hiatal hernia, gender, hyperlipidemia, diabetes, alcohol, smoking, as well as *H. pylori* infection and obesity. Among them, *H. pylori* infection and obesity status are important on the prevalence of reflux esophagitis and have been studied throughout Asia.^{9,10} *H. pylori* seropositivity has been known to protect against gastroesophageal reflux in Asia, especially in the Far East.¹¹⁻¹³ Furthermore, patients with *H. pylori* infection have less severe gastroesophageal reflux disease,^{14,15} however, *H. pylori* infection does not always influence gastroesophageal reflux disease, and the effect of eradication of *H. pylori* on reflux esophagitis is controversial.¹⁶⁻²⁰ Given the regional differences in seroprevalence of *H. pylori* in Korea,²¹ multicenter, prospective studies on the risk factors of reflux esophagitis seem to be important.

Recently there was an increase in obese patients as defined by those with body mass index (BMI) greater than 25 kg/m² in Koreans which are lower than that in the Western countries.²² Korea Centers for Disease Control and Prevention studied urban and rural patients with obesity and reported significant differences, namely, 30.3% and 36.5%, respectively.²³ Thus, we need to know the change of seroprevalence of *H. pylori* and obesity influencing erosive esophagitis as well as other risk factors compared with previous Korean data. And also, by our data obtained from 8 health promotion centers, risk factor analysis of erosive esophagitis according to dwelling places is useful in elucidation of environmental factors.

Therefore, we conducted this prospective multi-center study to investigate the interval change of prevalence of erosive esophagitis in healthy subjects and to find risk factors related to erosive esophagitis according to dwelling places.

Materials and Methods

Study Sample

A prospective study was carried out from January 2011 through December 2011 at 8 healthcare centers throughout Korea. Individuals with a history of gastrointestinal surgery or systemic diseases requiring chronic medication except hypertension and diabetes mellitus were excluded. This study was reviewed and approved by the Institutional review boards of the participating hospitals, and all participating subjects provided their written, informed consent. Residency status was divided into 2 types, according to big cities (Gyeonggi and Busan) and small and medium cities (Jeolla, Chungcheong, Gangwon and Jeju).

Questionnaire

Before endoscopy, clinical interviews based on a structured questionnaire were conducted, under the supervision of a well-trained interviewer, to assess personal and clinical data of all subjects. The questionnaire included questions about demographic data, presence of upper gastrointestinal symptoms, comorbidities, history of *H. pylori* eradication, drug history including NSAIDs and antibiotics, alcohol consumption, smoking history, consumption of dairy products, and family history of gastric cancer.²¹ BMI, cholesterol, triglyceride (TG), glucose level and *H. pylori* infection status were recorded.

Endoscopic Findings

Endoscopic reflux esophagitis was diagnosed if definite erosions were present. Minimal change esophagitis was excluded because of weak interobserver agreement.²⁴ The severity of esophagitis was graded from A through D, according to the Los Angeles (LA) classification.²⁵ The presence of hiatal hernia was endoscopically diagnosed if the distance from the esophago-gastric junction to the diaphragmatic impingement was more than 1 cm. The esophagogastric junction is defined as the proximal margin of the gastric mucosal fold. Edematous longitudinal fold of gastric mucosa taking a polypoid form was diagnosed as sentinel polyp. Benign peptic esophageal stricture was measured endoscopically and radiologically. Barrett's esophagus was suspected when endoscopic findings in the distal esophagus appeared to suggest gastric metaplasia, for example, salmon-pink colored columnar esophagus or presence of tongue-like projections.

Helicobacter pylori Serology Examination

Blood samples were collected from all participants before

endoscopy. The samples were immediately centrifuged and stored at -70°C . Assessment of *H. pylori* infection was based on enzyme-linked immunosorbent assay (ELISA) for anti-*H. pylori*

IgG using a Genedia kit (Genedia *H. pylori* ELISA; Green Cross Medical Science Corp, Eumsung, Korea) and duplicate determinations according to the manufacturer's guidelines. The

Table 1. Baseline Characteristics Between Subjects With Reflux Esophagitis and Those Without Reflux Esophagitis

Variable	Reflux esophagitis		Total (N = 4,023)	P-value
	Absent (n = 3,669)	Present (n = 354)		
Gender (n [%])				< 0.000
Male	2,087 (56.9)	271 (76.6)	2,358 (58.6)	
Female	1,582 (33.1)	83 (23.4)	1,665 (41.4)	
Age (n [%], yr)				0.741
≤ 39	789 (21.5)	76 (21.5)	865 (21.5)	
40-59	2,261 (61.6)	225 (63.5)	2,486 (61.8)	
≥ 60	619 (16.9)	53 (15.0)	672 (16.7)	
<i>H. pylori</i> IgG (n [%])				< 0.000
Positive	2,249 (61.3)	158 (44.6)	2,407 (59.8)	
Negative	1,420 (38.7)	196 (55.4)	1,616 (40.2)	
Hital hernia (n [%])				< 0.000
Yes	74 (2.0)	32 (9.0)	106 (2.6)	
No	3,595 (98.0)	322 (91.0)	3,917 (97.4)	
Barrett's esophagus (n [%])				0.037
Yes	24 (0.7)	6 (1.7)	30 (0.75)	
No	3,613 (99.3)	348 (98.3)	3,961 (99.25)	
BMI (n [%], 25 kg/m ²)				0.003
< 23	1,432 (39.5)	87 (24.7)	1,519 (38.2)	
$\geq 23, < 25$	944 (26.1)	90 (25.6)	1,034 (26.0)	
≥ 25	1,246 (34.4)	175 (49.7)	1,421 (35.8)	
Cholesterol (n [%], mg/dL)				0.820
< 200	1,695 (58.5)	173 (59.4)	1,868 (58.6)	
$\geq 200, < 240$	886 (30.6)	93 (32.0)	979 (30.7)	
≥ 240	317 (10.9)	25 (8.6)	342 (10.7)	
Triglyceride (mg/dL)				< 0.000
< 150	2,196	171	2,367 (74.2)	
≥ 150	700	121	821 (25.8)	
Glucose (mg/dL)				0.007
< 126	2,770 (95.9)	268 (92.1)	3,038 (95.5)	
≥ 126	119 (4.1)	23 (7.9)	142 (4.5)	
History of <i>H. pylori</i> eradication (n [%])				0.019
Yes	458 (12.6)	60 (17.0)	518 (13.0)	
No	3,186 (87.4)	293 (83.0)	3,479 (87.0)	
Alcohol consumption (n [%])				< 0.000
Yes	1,618 (45.0)	224 (64.4)	1,842 (46.85)	
No	1,975 (55.0)	124 (35.6)	2,099 (53.15)	
Smoking habit (n [%])				0.000
Yes	2,426 (67.3)	270 (77.4)	2,696 (68.2)	
No	1,180 (32.7)	79 (22.6)	1,259 (31.8)	
Urban dwelling (n [%])				0.043
Big city	936 (25.9)	71 (20.4)	1,007 (25.4)	
Small and medium sized cities	2,673 (74.1)	277 (79.6)	2,950 (74.6)	

H. pylori, *Helicobacter pylori*; *H. pylori* IgG, serum *H. pylori* immunoglobulin G antibody; BMI, body mass index.

Genedia kit makes use of an *H. pylori* antigen obtained from Korean *H. pylori* strains and has a sensitivity and specificity in Korean adults of 97.8% and 92.0%, respectively. The cut-off optical density (OD 450 nm) of *H. pylori* IgG was 0.406.

Statistical Methods

Continuous variables were analyzed by Student's *t* test. Categorical variables were analyzed using chi-square (χ^2) test or Fisher's exact test. Univariate logistic regression and multivariate logistic regression analysis were used for the analysis of independent risk factors, which were expressed as the odds ratio (OR) and 95% confidence interval (CI). All *P*-values of less than 0.05 were considered statistically significant.

Results

Characteristics of Participants

Of the 4,086 patients, 4,023 were eligible for the study. Sixty-three patients were excluded because of incomplete filling of a questionnaire. Mean age was 48.7 ± 11.3 years, and 2,358 (58.6%) patients were men. The clinical and demographic data of the patients are summarized in Table 1, including sex, age, *H. pylori* IgG, hiatal hernia, Barrett's esophagus, BMI, lipid profile, glucose level, history of *H. pylori* eradication, alcohol consumption, smoking history and place of residence. *H. pylori* seropositivity was detected in 2,407 (59.8%) patients. Seroprevalence of *H. pylori* was increased with older age (40-49 years, 55.5%; 50-59 years, 60.20%; above 60 years, 62.6%). There was no gender difference of *H. pylori* infection status.

Prevalence and Grade of Erosive Esophagitis

The prevalence rate of reflux esophagitis in this study was 8.8%. The distribution of erosive esophagitis was LA-A (6.4%), LA-B (2.1%), LA-C (0.3%) and LA-D (0.1%). One mucosal break was more common than multiple. The degree of mucosal breaks (< 5, 5-10 and 10-20 mm) was particularly pronounced in 5 mm in all age groups (≤ 39 years, 73.3% vs. 26.7% vs. 0.0%; 40-59 years, 72.7% vs. 21.8% vs. 3.2%; ≥ 60 years, 70% vs. 26% vs. 2%). Absence of confluent erosions were most common in all age groups. The prevalence of erosive esophagitis was higher in men than in women, especially with LA-A, LA-B and LA-C. The prevalence rate of erosive esophagitis was similar in each aging group (≤ 39 years, 8.8%; 40-59 years, 9.1%; ≥ 60 years, 7.9%) (Table 2). The prevalence of seropositivity in residents of

Table 2. Characteristics of Erosive Esophagitis According to Ages

	Age (yr)		
	≤ 39	40-59	$60 \leq$
LA classification			
Grade A	6.6	6.6	5.2
Grade B	2.2	2.1	2.2
Grade C	0.0	0.3	0.3
Grade D	0.0	0.0	0.1
Number of mucosal breaks			
Single	68	68	58
Multiple	32	32	42
Length of mucosal breaks			
< 5 mm	73.3	72.7	70.0
5-10 mm	26.7	21.8	26.0
10-20 mm	0.0	3.2	2.0
> 20 mm	0.0	2.3	2.0
Confluence of mucosal breaks			
None	100.0	96.5	95.0
< 75%	0.0	3.5	2.5
$\geq 75%$	0.0	0.0	2.5

LA classification, Los Angeles classification.
Data are present as percent.

big cities (Gyeonggi and Busan) and in small and medium cities (Jeolla, Chungcheong, Gangwon and Jeju) was 56.6% and 60.5%, respectively, while the prevalence rates of reflux esophagitis was 7.1% and 9.4%, respectively (Fig. 1). Endoscopically suspected Barrett esophagus was 0.8% (male, 0.9%; female, 0.5%). Stricture was not detected and sentinel polyp was very rare (0.1%).

Risk Factors for Reflux Esophagitis

Hiatal hernia was 2.6% and had no gender difference. Small size of hiatal hernia was more common (1 cm < size \leq 2 cm, 54.5%). Total frequency of BMI higher than 25 kg/m² was 35.8%. The frequency of obesity were significantly different between big, and small and medium-sized cities (26.9% and 38.8%, respectively; *P* < 0.001) (Fig. 2).

Univariate analysis identified significant differences regarding sex, *H. pylori* seronegativity, hiatal hernia, Barrett's esophagus, BMI ≥ 25 kg/m², TG ≥ 125 mg/dL, fasting glucose level ≥ 126 mg/dL, history of *H. pylori* eradication, alcohol consumption, smoking habit, residence in big cities and salty diet (Table 3). Multivariate analysis revealed that several factors were independently associated with an increased risk of reflux esophagitis: *H. pylori* seronegativity (OR, 1.91; 95% CI, 1.48-2.46),

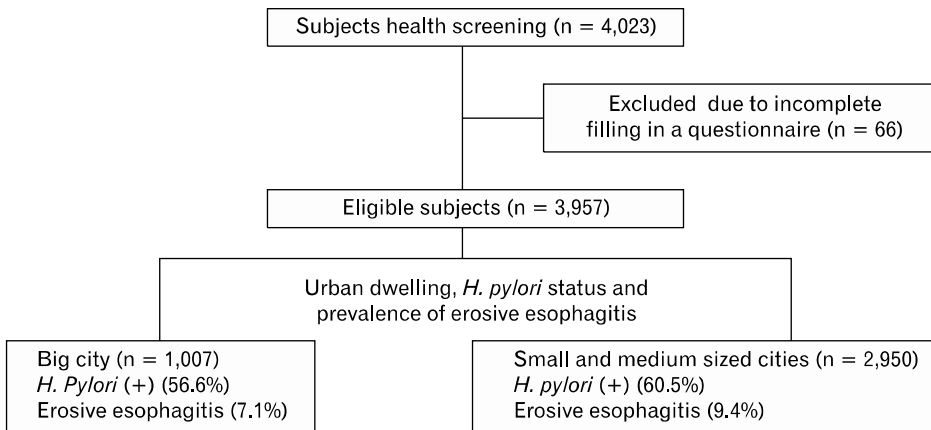


Figure 1. Prevalence of *Helicobacter pylori* seropositivity and erosive esophagitis in big city or small and medium-sized cities. The prevalence of seropositivity in residents of big cities was lower than that in small and medium-sized cities, while the prevalence rate of reflux esophagitis was higher in residents of small and medium-sized cities. *H. pylori*, *Helicobacter pylori*.

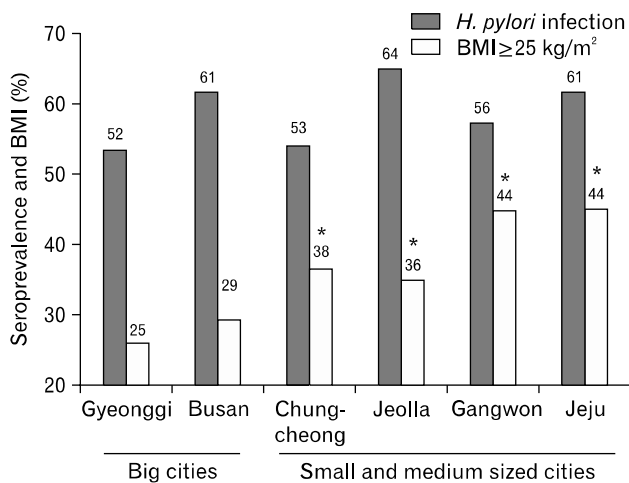


Figure 2. Comparison of seroprevalence of *Helicobacter pylori* infection and high body mass index (BMI) according to the geographic area. The high BMI level was more frequent in residents of small and medium-sized cities than those in big city (**P* < 0.001).

BMI ≥ 25 kg/m² (OR, 1.49; 95% CI, 1.08-2.06), TG ≥ 150 mg/dL (OR, 1.65; 95% CI, 1.08-1.06), fasting glucose level ≥ 126 mg/dL (OR, 1.72; 95% CI, 1.06-2.81) and hiatal hernia (OR, 3.10; 95% CI, 1.86-5.16). The OR of residents in a big city for the prevalence of reflux esophagitis was 0.59 (95% CI, 0.39-0.90) (Table 4).

Discussion

The prevalence of reflux esophagitis in Korea has increased since the 1990s. In 1999, the prevalence of reflux esophagitis in patients with gastrointestinal symptoms was 5.3%.²⁶ The prevalence of erosive esophagitis in patients undergoing regular health check-up was 8.0% in 2006.⁷ In this study, the prevalence of re-

Table 3. Univariate Analysis on the Risk for Reflux Esophagitis

Variable	OR	95% CI	<i>P</i> -value
Gender, male	2.46	1.91-3.18	< 0.000
<i>H. pylori</i> IgG negativity	1.93	1.55-2.41	< 0.000
Hiatal hernia	4.82	3.14-7.42	< 0.000
Barrett's esophagus	2.59	1.05-6.39	0.037
BMI ≥ 25 kg/m ²	1.58	1.16-2.14	0.003
TG ≥ 150 mg/dL	2.17	1.69-2.78	< 0.000
Glucose ≥ 126 mg/dL	1.88	1.18-2.98	0.007
History of <i>H. pylori</i> eradication	1.42	1.05-1.90	0.019
Alcohol consumption	2.19	1.74-2.75	< 0.000
Smoking habit	1.66	1.28-2.15	< 0.000
Big urban dwelling	0.76	0.58-0.99	0.043

H. pylori, *Helicobacter pylori*; BMI, body mass index; TG, triglyceride.

Table 4. Multivariate Analysis on the Risk for Reflux Esophagitis

Variable	OR	95% CI	<i>P</i> -value
<i>H. pylori</i> IgG negativity	1.91	1.48-2.46	< 0.000
Big urban dwelling	0.59	0.39-0.90	0.014
BMI ≥ 25 kg/m ²	1.49	1.08-2.06	0.014
TG ≥ 150 mg/dL	1.65	1.08-2.06	0.000
Glucose ≥ 126 mg/dL	1.72	1.06-2.81	0.028
Hiatal hernia	3.10	1.86-5.16	< 0.000

H. pylori, *Helicobacter pylori*; BMI, body mass index; TG, triglyceride.

flux esophagitis was 8.8%, which is similar to the previous study.

Seroprevalence of *H. pylori* were 59.5% and 59.8% in 2005 and 2011, respectively. The relationship between *H. pylori* and reflux esophagitis is not clear yet. In a recent large case-control study, *H. pylori* seropositivity was inversely associated with the risk of reflux esophagitis, and the prevalence of *H. pylori* infection was lower in reflux esophagitis cases than in controls (38.4% vs.

58.2%, $P < 0.001$).¹³ In our large sample, the prevalence of *H. pylori* infection was also lower in reflux esophagitis cases than in patients without reflux esophagitis (44.6% vs. 61.3%, $P < 0.0001$) and the OR of *H. pylori* seronegativity for the development of reflux esophagitis was 1.91 (95% CI, 1.48-2.46). *H. pylori* infection was inversely correlated with the risk of erosive esophagitis.

The association between *H. pylori* seropositivity and residence location is well known.²¹ According to geographic area in 2005, seroprevalence was 57.6% and 60.5% in big cities (Seoul and Gyeonggi, respectively), while higher than 60% in small and medium cities. The seroprevalence of *H. pylori* between 2005 and this study was not changed in big and small-medium cities. Differences in socioeconomic condition, sanitation and hygienic practices may explain this result. Taken together, the seroprevalence was slightly lower in big city residence than small and medium sized cities, suggesting that this difference could not explain the different prevalence rate of erosive esophagitis according to dwelling status.

Asides from *H. pylori* infection, obesity is another major risk factor for erosive esophagitis.^{27,28} However, recent studies on the association between BMI and erosive esophagitis have resulted in heterogeneous data.²⁹⁻³² There are no large-scale prospective studies involving healthy subjects with erosive esophagitis in the aspect of dwelling places. Relationship between obesity and erosive esophagitis is well known,²⁸ however, the gender effect is controversial.³³⁻³⁵ Our study showed that rate of obesity in big city dwelling was less frequent than that in small and medium cities after adjusting for potential confounding factors. According to KNHANES obesity data from 1998 to 2009 (1998, 2005 and 2007-2009), Korean with a BMI ≥ 25 kg/m² was found to be 25.9%, 34.8% and 35.8% in men, 27.5%, 28.3% and 26.1% in women, respectively.²² This result suggests that the prevalence of obesity was recently stagnated, and that there is a decreasing tendency in women. Our study shows that the prevalence rate of erosive esophagitis was lower in big city dwelling than in small and medium cities dwelling (7.1% and 9.4%, respectively) due to less frequent rate of obesity ($P < 0.001$) and these data were obtained after adjusting for confounding factors, including *H. pylori* infection, TG, glucose and hiatal hernia. This lower rate of BMI ≥ 25 kg/m² in big city residence may be explained by the fact that they may have a chance to receive a regular private health screening and engage in regular exercise maintaining a healthy weight.

Many other studies have found that hiatal hernia is associated with a high risk of reflux esophagitis.³⁶⁻³⁹ In our study, according to univariate analysis hiatal hernia (OR, 3.02; 95% CI, 1.87-5.16) was significantly associated with reflux esophagitis (all $P < 0.0001$).

Factors that are consistently reported to be associated with reflux esophagitis include advanced age, diabetes, hyperlipidemia, alcohol and smoking.^{19,40-45} In the present study, multivariate analysis identified high TG (OR, 1.65; 95% CI, 1.08-2.07) and elevated fasting glucose (OR, 1.73; 95% CI, 1.06-2.81) level as risk factors. Reports of the effects of smoking and alcohol consumption on the development of reflux esophagitis have been inconsistent.^{44,45} In our study, according to univariate analysis alcohol consumption (OR, 2.19; 95% CI 1.74-2.76) and smoking habit (OR, 1.66; 95% CI, 1.28-2.16) were significantly associated with reflux esophagitis (all $P < 0.0001$).

The present study has several potential limitations. First, 527 (13.1%) patients with *H. pylori* eradication were included. The reasons for eradication were peptic ulcers (24.9%), gastro-duodenitis (33.7%), patients' choice (35.9%) and family history of gastric cancer (2.6%). However, these subjects were equally distributed among cases and controls and there was no statistically significant difference between patients with and without reflux esophagitis, with respect to *H. pylori* eradication. Second, *H. pylori* infection status was evaluated only by serologic testing. Therefore, we did not assess the current or past infection status. Third, analysis of risk factors did not take into account the severity of reflux esophagitis.

In conclusion, the prevalence rate of erosive esophagitis and its risk factors in this study were similar to nationwide study in 2006. *H. pylori* seropositivity and residence in a large city were inversely related to the risk of reflux esophagitis in a large-sample, multicenter study of the Korean population. The degree and duration of obesity would be important risk factor for the development of erosive esophagitis in the future. Factors associated with metabolic syndrome including high TG and elevated fasting glucose level and hiatal hernia were also related to the risk of reflux esophagitis.

This study is meaningful in that as it has provided clues regarding the prevalence of erosive esophagitis and risk factors in healthy subjects. Further studies are necessary to determine the potential risk factors for the development of erosive esophagitis and we should pay attention to the changes in the prevalence of obesity in Koreans.

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