Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8669-16
Intern Med 56: 2979-2983, 2017
http://internmed.jp

【 ORIGINAL ARTICLE 】

Risk Factors for *Helicobacter pylori* Infection and Endoscopic Reflux Esophagitis in Healthy Young Japanese Volunteers

Yuichiro Tanaka[1], Yasuhisa Sakata[1], Megumi Hara[2], Hiroharu Kawakubo[1], Nanae Tsuruoka[1], Koji Yamamoto[1], Yoichiro Itoh[1], Hidenori Hidaka[1], Ryo Shimoda[1], Ryuichi Iwakiri[1] and Kazuma Fujimoto[1]

Abstract:

Objective The aim of this study was to determine the prevalence and risk factors of reflux esophagitis and *Helicobacter pylori (H.pylori)* infection and their interrelationship in healthy young Japanese volunteers.

Methods Between 2010 and 2016, 550 fifth-year medical students at Saga Medical School, aged 22 to 30 years, underwent upper gastrointestinal endoscopy and completed a questionnaire (frequency scale for symptoms of gastroesophageal reflux disease). *H. pylori* infection was determined by detecting urinary immunoglobulin G antibodies.

Results *H. pylori* antibodies were detected in 45 of the 550 subjects (8.2%). Endoscopic reflux esophagitis was detected in 38 out of 550 (6.9%): grade A in 37 subjects (97.3%) and grade B in 1. Most subjects with reflux esophagitis were *H. pylori*-negative (35/37). Nodular gastritis was observed in 33.3% (15/45) of *H. pylori*-positive subjects. The risk factors for *H. pylori* infection were drinking well water in childhood, nodular gastritis, and duodenal ulcer scars. The risk factors for endoscopic reflux esophagitis were male gender and obesity (body mass index ≥25).

Conclusion This study describes the risk factors for *H. pylori* infection and reflux esophagitis in healthy young Japanese subjects. The prevalence of reflux esophagitis was relatively high, and the infection rate of *H. pylori* was low compared with the aged Japanese population.

Key words: endoscopy, dyspepsia, gastroesophageal reflux, nodular gastritis, F scale

(Intern Med 56: 2979-2983, 2017)
(DOI: 10.2169/internalmedicine.8669-16)

Introduction

A recent study in Japan indicated that the *Helicobacter pylori* (*H. pylori*) infection rate increased with age by around 1% per year, whereas the population-wide infection rate decreased in a time-dependent manner (1). Several diseases, such as peptic ulcers, mucosa-associated lymphoid tissue lymphoma, gastric cancers and chronic gastritis, are induced by *H. pylori* infection (2, 3). Chronic gastritis, including nodular gastritis, has been recognized in relatively young adults (4, 5), but the prevalence of nodular gastritis in young Japanese adults is still unclear.

Several studies in Japan have shown that the eradication of *H. pylori* induced endoscopic reflux esophagitis, suggesting that *H. pylori* infection prevented endoscopic reflux esophagitis by decreasing gastric acid secretion (6-10). Several studies in Western countries also suggested that the eradication of *H. pylori* induced reflux esophagitis (11, 12). However, the precise relationship between *H. pylori* infection and endoscopic reflux esophagitis is not clear, and a direct relationship between *H. pylori* infection and reflux

[1]Departments of Internal Medicine and Gastrointestinal Endoscopy, Saga Medical School, Japan and [2]Preventive Medicine, Saga Medical School, Japan
Received: December 7, 2016; Accepted: March 31, 2017; Advance Publication by J-STAGE: September 25, 2017
Correspondence to Dr. Kazuma Fujimoto, fujimotk@cc.saga-u.ac.jp

Table 1. Characteristics of Healthy Young Adult Volunteers Who Underwent Upper Gastrointestinal Endoscopy in Japan (n=550).

Age (years)	22.5 ± 1.8
Gender (men:women)	315:235
Body mass index (kg/m^2)	21.0 ± 3.1
Endoscopic esophagitis (Los Angeles classification)	
Grade 0	512 (93.0%)
Grade A	37 (6.7%)
Grade B	1 (0.2%)
Grade C	0
Grade D	0
Hiatus herniation	173 (31.5%)
Barrett's esophagus	
Short segment	58 (10.5%)
Long segment	0
Duodenal ulcers scar	7 (1.3%)
Nodular gastritis	16 (2.9%)
Helicobacter pylori infection	45 (8.2%)

esophagitis in young adults has not been clearly demonstrated.

The infection route of *H. pylori* in Japan is still unknown, but several studies have suggested that transmission between family members is an important route (5, 13). The drinking of well water might also be a major infection route in developing countries (6, 14).

Several studies in Japan have indicated risk factors for endoscopic reflux esophagitis (gender, obesity, hiatus herniation, smoking, alcohol consumption), but few studies have focused on risk factors for young adults (15). The aim of the present study was to determine i) the prevalence of reflux esophagitis and *H. pylori* infection in healthy young Japanese adults and ii) the risk factors for *H. pylori* infection and endoscopic reflux esophagitis.

Materials and Methods

The present study included 550 fifth-year medical students (men/women: 315/235) in Saga Medical School who provided their informed consent to participate between 2010 and 2016. The mean age of the students was 22.5±1.8 (range, 22-30) years old. All of the participants received upper gastrointestinal endoscopy performed by experienced endoscopists on the Japanese Board of Gastrointestinal Endoscopy. *H. pylori* infection was determined by the urinary antibody-coated bacteria test via the immunochromatography method (RAPIRUN®; Otsuka Pharmaceutical, Tokyo, Japan) (16).

Just before an endoscopic examination, the subjects completed the frequency scale for symptoms of gastroesophageal reflux disease (FSSG) questionnaire regarding upper gastrointestinal symptoms (17, 18). In addition, any history of drinking well water in childhood was determined through interviews.

Endoscopic esophagitis was diagnosed as grade A, B, C or D using the Los Angeles Classification (19). The FSSG questionnaire comprises 12 questions (regarding 7 acid reflux symptoms and 5 dysmotility symptoms). Each symptom was assigned a score (never=0; occasionally [30%] =1; sometimes [50%] =2; often [70%] =3; and always [100%] = 4). A positive symptom was defined as a symptom for which the subject evaluated the frequency with a score of ≥2 (sometimes, often or always). The seven questions regarding reflux symptoms were as follows: "Do you get heartburn?", "Do you sometimes subconsciously rub your chest with your hand?", "Do you get heartburn after meals?", "Do you have an unusual (e.g. burning) sensation in your throat?", "Do some things get stuck when you swallow?", "Do you feel a bitter liquid (acid) coming up into your throat?" and "Do you get heartburn if you bend over?" The five questions regarding acid-related dyspepsia were: "Does your stomach get bloated?", "Does your stomach ever feel heavy after meals?", "Do you feel sick after meals?", "Do you feel full while eating meals?" and "Do you burp a lot?"

This study was approved by the ethics committee of Saga Medical School. A statistical evaluation was carried out using χ^2 tests, Student's t-tests and multiple logistic regression analyses with the odds ratios and 95% confidence intervals determined using the SPSS software program (version 22; SPSS, Tokyo, Japan). Statistical significance was established at a p value of <0.05.

Results

Table 1 shows the characteristics of the 550 subjects (315 men, 235 women) in the present study. The mean age of the subjects was 22.5±1.8 years, and the mean body mass index (BMI) was 21.0±3.1 kg/m^2. Among the 550 subjects, 38 (6.9%) had endoscopic esophagitis (grade A: 37, grade B: 1), and 173 (31.5%) had hiatus herniation. The frequency of short-segmented Barrett's esophagus was relatively high (10.5%, n=58), whereas no subjects had long-segmented Barrett's esophagus. The frequency of positive *H. pylori* infection was 8.2% (45/550). No subjects received eradication therapy for *H. pylori* infection, and none had taken gastric acid secretion inhibitors. A duodenal ulcer scar was detected in 7 subjects (1.3%), including 3 *H. pylori*-positive subjects. Nodular gastritis was detected in 16 subjects (7 men, 9 women) (2.9%), including 15 *H. pylori*-positive subjects, by gastrointestinal endoscopy.

Table 2 shows the risk factors for *H. pylori* infection in these subjects evaluated by a multivariate analysis. Gender and body weight were not markedly different between the *H. pylori*-positive and *H. pylori*-negative subjects. The smoking rate in both the positive and negative groups was very low, and the difference was not significant. The frequency of alcohol consumption tended to be higher in the positive subjects than in the negative ones, but not significantly so. The rates of hiatus herniation and Barrett's esophagus were not markedly different between the two positivity groups. The frequency of drinking well water in

Table 2. Risk Factors For *Helicobacter Pylori* infection as Evaluated by a Multivariate Analysis.

Factors	*H. pylori* (+) n=45 (8.1%)	*H. pylori* (−) n=505 (91.8%)	Odds ratio	95% CI	p value
Gender (men:women)	28:17	287:218	0.81	0.42-1.55	0.52
BMI (>25)	4 (8.9%)	23 (4.6%)	2.91	0.88-9.64	0.08
Smoking	1 (2.2%)	44 (8.7%)	0.43	0.54-3.33	0.42
Alcohol	42 (93.3%)	438 (79.6%)	2.58	0.75-8.94	0.14
Herniation	12 (26.7%)	161 (31.9%)	0.69	0.34-1.43	0.32
Barrett's esophagus	3 (6.7%)	55 (10.9%)	0.62	0.18-2.15	0.45
Drinking well water	21 (46.7%)	82 (16.2%)	4.96	2.59-9.50	<0.01

The age is presented as the mean ± standard deviation. *H. pylori*: *Helicobacter pylori*, BMI: body mass index (kg/m^2), DU: duodenal ulcer, 95% CI: confidence interval

Table 3. Risk Factors for Endoscopic Reflux Esophagitis as Evaluated by a Multivariate Analysis.

Factors	Esophagitis (+) n=38 (6.9%)	Esophagitis (−) n=512 (93.1%)	Odds ratio	95% CI	p value
Gender (men:women)	34:4	281:231	0.14	0.05 - 0.43	<0.01
BMI (>25)	6 (15.8%)	21 (4.1%)	5.23	1.76 - 15.52	<0.01
Smoking	1 (2.6%)	25 (4.9%)	0.37	0.05 - 3.02	0.36
Alcohol consumption	33 (89.5%)	447 (86.9%)	1.39	0.48 - 4.05	0.54
Herniation	17 (44.7%)	156 (30.3%)	1.35	0.66 - 2.75	0.41
Barrett's esophagus	5 (13.2%)	53 (10.2%)	1.39	0.49 - 4.00	0.54
H. pylori	3 (7.9%)	42 (8.2%)	0.66	0.15 - 2.90	0.58

The age is presented as the mean ± standard deviation. BMI: body mass index (kg/m^2), 95% CI: confidence interval, DU: duodenal ulcer, *H. pylori*: *Helicobacter pylori*

childhood was significantly higher in the *H. pylori*-positive subjects than in the *H. pylori*-negative subjects (46.7% vs. 16.2%).

Table 3 shows the risk factors for endoscopic reflux esophagitis as evaluated by a multivariate analysis. Reflux esophagitis was more frequently seen in men than in women. Specifically, 34 out of 315 men (10.8%) but only 4 out of 235 women (1.7%) suffered from reflux esophagitis. High BMI was a risk factor for endoscopic reflux esophagitis. Other factors, including smoking, alcohol consumption, hiatus herniation, Barrett's esophagus and *H. pylori* infection, were not risk factors for reflux esophagitis.

The results of the FSSG questionnaire for endoscopic reflux esophagitis symptoms are shown in Table 4. The FSSG scores were not markedly different between the reflux and non-reflux groups. The rate of positive symptoms was not markedly different for any question. These results suggest that a symptomatic diagnosis with the FSSG questionnaire might not be effective for detecting reflux esophagitis in young adults.

Discussion

The present study revealed that the *H. pylori* infection rate was less than 10% in young adults in Japan, which was consistent with previous results (1). This study also indicated that the risk factors for *H. pylori* infection in young adults were drinking well water in childhood, nodular gastritis and duodenal ulcer scars shown by upper gastrointestinal endoscopy. Previous studies in Japan have suggested that a major infection route is transmission between family members-i.e. to a child from siblings, parents or grandparents (13, 20, 21). The results of this study suggested that drinking well water in childhood might be another infection route for *H. pylori* in Japan, as observed in developing countries (14).

The prevalence of endoscopic esophagitis was not affected by *H. pylori* infection in young adults in the present study. Several previous studies in Japan showed that the prevalence of reflux esophagitis was lower in *H. pylori*-positive subjects than in *H. pylori*-negative subjects (6-10). The low infection rate in young adults as indicated in this study might be one of the reasons why *H. pylori* infection showed no influence on endoscopic esophagitis.

Previous studies have reported that nodular gastritis was diagnosed in relatively young women (4, 5). The present study demonstrated that the prevalence of nodular gastritis was 33% in *H. pylori* positive adults in their 20s in Japan, and the prevalence was not markedly different between men and women. Regarding atrophic gastritis, the present study

Table 4. A Comparison of the Upper Gastrointestinal Symptoms Evaluated by the FSSG Questionnaire between Endoscopic Esophagitis-positive and Endoscopic Esophagitis-negative Subject.

	Esophagitis (+) (n=38)	Esophagitis (−) (n=512)	Odds ratio	95% CI	p value
Heartburn	1 (2.5%)	17 (3.3%)	0.81	0.11 - 6.29	0.84
Stomach gets bloated	7 (17.9%)	79 (15.4%)	1.20	0.51 - 2.80	0.68
Stomach feels heavy after meals	8 (20.5%)	98 (19.2%)	1.09	0.48 - 2.43	0.54
Subconsciously rub your chest with your hand	3 (7.6%)	35 (6.8%)	1.13	0.33 - 3.86	0.84
Feel sick after meals	5 (12.8%)	50 (9.8%)	1.35	0.51 - 3.62	0.55
Heartburn after meals	5 (12.8%)	40 (7.8%)	1.72	0.64 - 4.66	0.275
Unusual sensation in your throat	2 (5.1%)	18 (3.5%)	1.48	0.33 - 6.61	0.61
Feel full while eating meals	2 (5.1%)	53 (10.4%)	0.47	0.11 - 1.99	0.29
Get stuck when you swallow	0 (0%)	14 (2.75%)	-	-	0.35
Bitter liquid coming up into your throat	6 (15.4%)	34 (6.67%)	2.55	0.10 - 6.50	0.054
Burp a lot	6 (15.4%)	65 (12.7%)	1.25	0.50 - 3.09	0.64
Heartburn if you bend over	2 (5.13%)	10 (2.0%)	2.70	0.57 - 12.8	0.19
Number of subjects with FSSG scores of more than 8	13 (33.3%)	114 (22.3%)	1.73	0.87 - 3.49	0.117

95% CI: confidence interval. A positive symptom was defined as one for which the subject evaluated the frequency with a score of ≥2.

did not evaluate the presence of atrophic gastritis with the upper gastrointestinal endoscopy.

The risk factors for endoscopic reflux esophagitis were male gender and obesity (BMI>25). Our previous study indicated that obesity was a risk factor for reflux esophagitis in men in their 30s and 40s (22, 23), and several studies in Japan have shown that obesity exacerbates endoscopic reflux esophagitis (24, 25). These data are compatible with the present results for endoscopic reflux esophagitis in adults in their 20s. Why the prevalence of reflux esophagitis was high in men in the present study was not clear, although obesity and alcohol drinking are more popular in men than in women in Japan. However, in the present study, endoscopic esophagitis was not affected by alcohol consumption, smoking or hiatus herniation. In addition, the smoking rate was very low in the present study (4.7%) compared with the Japanese average rate (19.3%), possibly due to that the subjects in the present study were medical students and therefore more conscientious of the effects of smoking. Alcohol consumption was evaluated based on the frequency of drinking, not by the quantity consumed. The rate of hiatus hernia was also low in the present study.

Clinical symptoms were evaluated by the FSSG questionnaire (17, 26-29) before the endoscopic examination. Regarding the scores for the 12 evaluated symptoms, there were no marked differences between the normal subjects and those with endoscopic esophagitis. All of the subjects with reflux esophagitis in the present study had mild symptoms of grade A or B under the Los Angeles classification, which might be one of reasons why they did not complain of clinical symptoms.

H. pylori infection was only detected by the presence of urinary IgG antibodies with immunochromatography and not evaluated by other methods, such as the rapid urease test or the urea breath test. The sensitivity of the immunochromatography method is lower than with other methods, which might be one reason why there were several *H. pylori*-negative subjects among those with duodenal ulcer scars or nodular gastritis. This observation warrants further explanation.

In summary, the present study of healthy young adult volunteers who received upper gastrointestinal endoscopy revealed the following: i) the infection rate of *H. pylori* was 8.2%, ii) the prevalence of endoscopic reflux esophagitis was 6.9%, iii) *H. pylori* infection had no influence on the prevalence of endoscopic reflux esophagitis, iv) nodular gastritis accounted for 33.3% of *H. pylori* infection, v) the risk factors for *H. pylori* infection were drinking well water in childhood, nodular gastritis and duodenal ulcer scars and vi) the risk factors for endoscopic reflux esophagitis were male gender and obesity (BMI>25).

The authors state that they have no Conflict of Interest (COI).

References

1. Hirayama Y, Kawai T, Otani J, Kawakami K, Harada Y. Prevalence of *Helicobacter pylori* infection with healthy subject in Japan. J Gastroenterol Hepatol **29**: 16-19, 2014.
2. Furuta T, Delchier JC. *Helicobacter pylori* and non-malignant diseases. Helicobacter **14**: 29-35, 2009.
3. Matsuo T, Ito M, Tanata S, Yoshihara M, Chayama K. Low prevalence of *Helicobacter pylori*-negative gastric cancer among Japanese. Helicobacter **16**: 415-419, 2011.
4. Miyamoto M, Haruma K, Yoshihara M, et al. Nodular gastritis in adults is caused by *Helicobacter pylori* infection. Dig Dis Sci **48**: 968-975, 2003.
5. Shiotani A, Kamada T, Kumamoto M, et al. Nodular gastritis in Japanese young adults: endoscopic and histological observations. Gastroenterology **42**: 610-615, 2007.
6. Koike T, Ohara S, Sekine H, et al. *Helicobacter pylori* infection prevents erosive reflux esophagitis by decreasing gastric acid se-

cretion. Gut **49**: 330-334, 2001.
7. Kawai T, Yamamoto K, Fukuzawa M, et al. *Helicobacter pylori* infection and reflux esophagitis in young and middle-aged Japanese subjects. J Gastroenterol Hepatol **25**: 80-85, 2010.
8. Iijima K, Koike T, Shimosegawa T. Reflux esophagitis triggered after *Helicobacter pylori* eradication: a noteworthy demerit of eradication therapy among the Japanese? Front Microbiol **9**: 566, 2015.
9. Sugimoto M, Uotani T, Ichikawa H, Andoh A, Furuta T. Gastroesophageal reflux disease in time covering eradication for all patients infected with *Helicobacter pylori* in Japan. Digestion **93**: 24-31, 2016.
10. Fujiwara Y, Arakawa T. Epidemiology and clinical characteristics of GERD in the Japanese population. J Gastroenterol **4**: 518-534, 2009.
11. Yachida S, Saito D, Kozu T, et al. Endoscopically demonstrable esophageal changes after *Helicobacter pylori* eradication in patients with gastric disease. J Gastroenterol Hepatol **16**: 1346-1352, 2001.
12. Labenz J. Current role of acid suppressants in *Helicobacter pylori* eradication therapy. Best Pract Res Clin Gastroenterol **15**: 413-431, 2001.
13. Okuda M, Tachikawa T, Maekawa K, Fukuda Y. Transmission route of *H.pylori*. Nihon Rinsho **71**: 1339-1345, 2013 (in Japanese, Abstract in English).
14. Rolle-Kampczyk UE, Fritz U, Lehmann I, Richter M, Herbarth O. Well water - one source of *Helicobacter pylori* colonization. Int J Hyg Environ Health **207**: 363-368, 2004.
15. Takashima T, Iwakiri R, Sakata Y, et al. Endoscopic reflux esophagitis and *Helicobacter pylori* infection in young healthy Japanese volunteers. Digestion **86**: 55-56, 2012.
16. Murakami K, Kamada T, Ishikawa H, et al. An evaluation of the performance of a novel stick-type kit for rapid detection of *Helicobacter pylori* antibodies in urine. Clin Lab **57**: 481-487, 2011.
17. Kusano M, Shimoyama Y, Sugimoto S, et al. Development and evaluation of FSSG: frequency scale for the symptoms of GERD. J Gastroenterol **39**: 888-891, 2004.
18. Komatsu-Tanaka M, Iwakiri R, Fujimoto K, et al. Clinical symptoms of FSSG in gastroesophageal reflux disease are critical for PPI treatment: Japanese multi-centers with 185 patients. Dig Endosc **24**: 407-411, 2012.
19. Armstrong D, Bennett JR, Blum AL, et al. The endoscopic assessment of esophagitis: a progress report on observer agreement. Gastroenterology **111**: 85-92, 1996.
20. Okuda M, Osaki T, Lin Y, et al. Low prevalence and incidence of *Helicobacter pylori* infection in children: a population-based study in Japan. Helicobacter **20**: 133-138, 2015.
21. Urita Y, Watanabe T, Kawagoe N, et al. Role of infected grandmothers in transmission of *Helicobacter pylori* to children in a Japanese rural town. J Paediatr Child Health **49**: 394-398, 2013.
22. Fujimoto K, Iwakiri R, Okamoto K, et al. Characteristics of gastroesophageal reflux disease in Japan: increased prevalence in elderly women. J Gastroenterol **38**: 3-6, 2003.
23. Furukawa N, Iwakiri R, Koyama T, et al. Proportion of reflux esophagitis in 6010 Japanese adults: prospective evaluation by endoscopy. J Gastroenterol **24**: 441-444, 1999.
24. Moki F, Kusano M, Mizuide M, et al. Association between reflux oesophagitis and features of the metabolic syndrome in Japan. Aliment Pharmacol Ther **26**: 1069-1075, 2007.
25. Iwakiri K, Kinoshita Y, Habu Y, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2015. J Gastroenterol **51**: 751-767, 2016.
26. Danjo A, Yamaguchi K, Fujimoto K, et al. Comparison of endoscopic findings with symptom assessment systems (FSSG and QUEST) for gastroesophageal reflux disease in Japanese centres. J Gastroenterol Hepatol **24**: 633-638, 2009.
27. Akutagawa K, Iwakiri R, Hara M, et al. Risk factors for low response to proton-pump inhibitor treatment in reflux esophagitis and non-erosive reflux disease evaluated by the frequency scale for the symptoms of gastroesophageal reflux disease. Esophagus **12**: 225-232, 2015.
28. Kawakubo H, Tanaka Y, Tsuruoka N, et al. Upper gastrointestinal symptoms are more frequent in female than male young healthy Japanese volunteers as evaluated by questionnaire. J Neurogastroenterol Motil **22**: 248-253, 2016.
29. Takeshita R, Sakata Y, Hara M, et al. Higher frequency of reflux symptoms and acid -related dyspepsia in women than men regardless of endoscopic esophagitis: analysis of 3,505 Japanese subjects undergoing medical health checkups. Digestion **93**: 266-271, 2016.