Original Article

Association between dyspeptic symptoms and endoscopic findings based on the Kyoto classification of gastritis in Japanese male

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The Kyoto gastritis classification is used to categorize the endoscopic characteristics of *Helicobacter pylori* infection-associated gastritis. We aimed to clarify the association among endoscopic findings and abdominal dyspeptic symptoms in Japanese male. We administered a questionnaire to 418 subjects who underwent endoscopy as part of a health check-up from August 2003 to April 2004 to investigate the association among endoscopic findings of the Kyoto classification and the presence of dyspeptic symptoms. Logistic regression analyses were performed to evaluate risk based on dyspeptic symptoms. Among 418 health check-up subjects, 21.3% (89/418) reported dyspeptic symptoms in the questionnaire. The incidence of fundic gland polyp among patients with dyspeptic symptoms was 12.4% (11/89), which was significantly higher than that among non-symptomatic subjects (4.3%, 14/329, $p = 0.004$). Logistic regression analyses showed that fundic gland polyp was a risk factor for dyspeptic symptoms [odds ratio (OR): 3.413, 95% confidence interval (CI): 1.430–8.142], while short-segment Barrett's esophagus and male sex were protective factors (OR: 0.569, 95% CI: 0.349–0.928 and OR: 0.333, 95% CI: 0.117–0.948, respectively). In conclusion, Endoscopic findings of fundic gland polyp may be associated with dyspeptic symptoms, which in turn may be a useful marker of gastric condition.

***Key Words*: abdominal symptom, gastritis, Kyoto classification, *Helicobacter pylori*, questionnaires**

In 1994, the World Health Organization's International Agency for Research on Cancer categorized *Helicobacter pylori* (*H. pylori*) as a group I carcinogenic factor of gastric cancer.[1,2] Over the following 30 years, much basic and clinical research focused on clarifying the association between *H. pylori* and gastric cancer. This has led to a global decline in the incidence of gastric cancer over the past half-century, especially in Western countries, due to a decrease in the *H. pylori* infection rate and increase in eradication therapy.[3] It is important to evaluate the relative impact of environmental, genetic and bacterial factors, and endoscopic findings on gastric cancer risk.[4,5] Pathological reporting systems, including the Houston-updated Sydney system and the operative link on gastritis assessment system, and endoscopic reporting systems, such as the Kyoto gastritis classification, are increasingly being used to identify patients at high risk for gastric cancer.[5–8] The Kyoto classification, which grades endoscopically-visible risk factors, first divides patients into three groups (*H. pylori*-negative, -positive, and previously infected) and, second, categorizes gastric cancer risk based on the scores for five features of gastritis (atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness).[5] Intestinal metaplasia and atrophy features of the Kyoto classification have been proven to be clinically useful for identifying patients at elevated risk for gastric cancer, irrespective of *H. pylori* infection.[5,9,10] It is reported that Kyoto classification of gastritis is useful for diagnosis of *H. pylori* infection in subjects with a high-negative titer of anti-*H. pylori* antibody.[11]

Functional dyspepsia (FD) is defined as "pain or upper abdominal discomfort, chronic or recurrent of at least 12 weeks duration, not necessarily consecutive, within the preceding 12 months" in the Rome IV criteria. Around 10% of the general population in the USA (12%), Canada (8%) and UK (8%) fulfill the Rome IV criteria.[12] In Japan, the prevalence of patients with dyspeptic symptoms is increasing. While the pathogenesis of FD is multifactorial (i.e., abnormal gastrointestinal motility, visceral hypersensitivity, psychosocial factors, and disorders of the autonomic and central nervous system),[13,14] the condition of the gastric mucosa in relation to *H. pylori* is considered a key factor. Guidelines established by the American College of Gastroenterology therefore strongly recommend *H. pylori* eradication for *H. pylori*-positive FD patients.[15] Similarly, the Japanese guidelines for FD recommend *H. pylori* eradication for *H. pylori*-positive dyspepsia patients, and those who are symptom-free 6–12 months after eradication are considered "*H. pylori*-associated FD" cases.[16] However, the association between dyspeptic symptoms and endoscopic severity of gastritis and endoscopic findings in Japan, where the *H. pylori* infection rate is higher than in Western populations, has not been fully elucidated.[17,18]

Because some endoscopic findings may be related to functional gastrointestinal abnormalities and/or dyspeptic symptoms,[17,18] identifying the characteristic findings may help clarify the pathophysiology of an individual's dyspeptic symptoms and the development of endoscopic findings. Thus, we retrospectively investigated how endoscopic findings and severity of gastritis are related to *H. pylori* in patients with and without dyspeptic symptoms.

Materials and Methods

Patients and study protocol. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki,[19] The protocol of this study was reviewed and approved by the Institu-

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Table 1. Definition of *H. pylori* infection status

H. pylori IgG	Atrophy	Diffuse redness	*H. pylori* infection	Past *H. pylori*	*H. pylori* negative
≥10			○		
≥3, <10	+	+	○		
	+	−		○	
	−	−			○
<3	+	−		○	
	−	−			○

tional Review Board of Tokyo Medical University. This study enrolled subjects who underwent endoscopy as part of a health check-up or secondary check-up for gastric cancer after a barium X-ray examination from August 2003 to April 2004 at Fuyo Clinic, Tokyo. Inclusion criteria were subjects who underwent endoscopy at Fuyo Clinic and completed a score sheet on dyspeptic symptoms. Exclusion criteria were a history of esophageal and gastric surgery, lack of data on subject's background and lack of clear endoscopic images to evaluate endoscopic findings. Because this study was a retrospective observational study and written informed consent was not obtained from each patient, a document declaring an opt-out policy, through which any patient could refuse to be included in this study, was uploaded on the websites of Fuyo Clinic and Tokyo Medical University Hospital.

In this study, *H. pylori* infection was diagnosed using an anti-*H. pylori* IgG test and endoscopic findings of atrophy and diffuse redness (Table 1). The presence or absence of abdominal symptoms, such as heartburn, abdominal pain, nausea, distention, epigastric discomfort, and epigastralgia, were determined using a questionnaire. Patients with dyspepsia were defined as those with abdominal symptoms of heartburn, distention, nausea, epigastric discomfort, epigastralgia or abdominal pain. All patients underwent gastroduodenal endoscopy to determine endoscopic findings and severity of gastritis.

Endoscopy and severity of gastritis. Gastroduodenal endoscopy was performed and the severity of gastritis was scored according to the Kyoto gastritis classification and the Kimura-Takemoto classification.[20,21] In the Kyoto classification, the total score includes five parameters of gastritis, namely, atrophy (Kimura-Takemoto classification CI = Kyoto A0, CII–CIII = Kyoto A1, and OI–OIII = Kyoto A2), intestinal metaplasia (None: IM0, within antrum: IM1 and up to corpus: IM2), hypertrophy of gastric folds (negative: H0, positive: H1), nodularity (negative: N0, positive: N1), and diffuse redness (negative: DR0, mild: DR1, severe: DR2).[5–8] The presence of gastroesophageal reflux disease (GERD) was assessed according to the Los Angeles classification.[22]

Data analysis. Age, body mass index (BMI) and Kyoto classification scores are presented as mean ± SD. Statistically significant differences in category among any groups were determined using the χ^2 test. Statistically significant differences in endoscopic score between two groups (dyspepsia-positive vs -negative) were determined using the Mann-Whitney *U* test, and those among three groups (*H. pylori*-positive, -negative, and eradicated) were determined using the Mann-Whitney *U* test after significant differences were observed in the Kruskal-Wallis test. Statistically significant differences in mean age and BMI values between two groups (dyspepsia-positive vs negative) were determined using Student's *t* test, and those among three groups (*H. pylori*-positive, -negative, and eradicated) were determined using one-way ANOVA followed by the Scheffé multiple comparisons test. Univariate and multivariate logistic regression analyses were used to test the associations of candidate variables with development of dyspeptic symptoms. Multicollinearity among the variables was tested using the variance inflation factor. Factors with a p value <0.2 in the univariate analysis were further examined using multivariate analysis for their association with the risk of developing abdominal symptoms. $P<0.05$ was considered statistically significant and all p values were two-sided. Analyses were conducted using SPSS ver. 27 (IBM Inc.; Armonk, NY).

Results

Patient characteristics in relation to *H. pylori* infection status. This study enrolled 418 subjects who underwent endoscopy as part of a health check-up from August 2003 to April 2004 at Fuyo Clinic, Tokyo. Of the 418 subjects, 34.7% (145/418) and 50.2% (210/418) were *H. pylori*-positive and -negative, respectively (Table 2).

When the patients were divided into three groups [*H. pylori*-negative ($n = 210$), -positive ($n = 145$), and previously infected ($n = 63$)], *H. pylori*-positive patients were older and had higher incidence of hypertension than those in the other groups (Table 2). Other characteristics, such as alcohol consumption, smoking status, disease incidence and drugs, were similar among the three groups. *H. pylori*-positive patients also had higher incidence of endoscopic findings of gastric ulcer, duodenal ulcer, duodenal ulcer scar, Kyoto gastritis classification score, xanthoma, hyperplastic polyp, mucosal swelling, sticky mucous, spotty redness, and multiple white and flat elevated lesions than those in the other groups (Table 3). In contrast, *H. pylori*-negative patients had higher incidence of short-segment Barrett's esophagus (SSBE), GERD, hiatal hernia, regular arrangement of collecting venules, hematin, red streak, and fundic gland polyp than those in the other groups (Table 3). There was no significant difference in the incidence of abdominal symptoms among the three groups (Table 4).

Patient characteristics in relation to dyspeptic symptoms. Patients with dyspepsia were defined as patients with symptoms such as heartburn, distention, nausea, epigastric discomfort, epigastralgia or abdominal pain. Of the 418 patients, 21.3% (89/418) reported symptoms in the questionnaire (Table 2). Patients with dyspeptic symptoms were more likely to be female ($p = 0.014$) and taking HMG-CoA reductase inhibitor ($p = 0.006$) or antianxiety drugs ($p = 0.001$). The other characteristics were similar between patients with and without dyspeptic symptoms (Table 2).

While most endoscopic findings were similar between patients with and without dyspepsia, the prevalence of SSBE and fundic gland polyp was significantly different ($p = 0.034$ and 0.004, respectively) (Table 3). The Kyoto classification score for enlarged folds was higher in patients with dyspepsia, while scores for atrophy, intestinal metaplasia, nodularity, and diffuse redness were similar between the two groups (Table 3).

Dyspepsia patients had higher incidence of a feeling of incomplete defecation and lower abdominal pain than patients without symptoms ($p = 0.004$ and $p<0.001$, respectively) (Table 4).

Risk factors for the incidence of dyspeptic symptoms. In univariate analysis, fundic gland polyp [odds ratio (OR): 3.173, 95% CI: 1.387–7.260, $p = 0.006$] was identified as a risk factor for dyspeptic symptoms, and sex (male) (OR: 0.317, 95% CI: 0.121–0.830, $p = 0.014$) and SSBE (OR: 0.602, 95% CI: 0.376–0.964, $p = 0.034$) as preventive factors (Table 5). Factors with a p value <0.2 in the univariate analysis (age, sex, SSBE, gastric ulcer scar, atrophy, fundic gland polyp, and sticky mucous) were subjected to multivariate analysis. Ultimately, fundic gland polyp was identified as a risk factor for dyspeptic symptoms (OR: 3.414, 95% CI: 1.430–8.142), and short-segment Barrett's esophagus and male sex as protective factors (OR: 0.569, 95%

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Table 2. Characteristics of patients enrolled in this study

	All patients (*n* = 418)	*H. pylori* infection (*n* = 145)	Past *H. pylori* infection (*n* = 63)	*H. pylori* negative (*n* = 210)	*p* value	Dyspepsia positive (*n* = 89)	Dyspepsia negative (*n* = 329)	*p* value
Age (years)	39.2 ± 8.3	42.6 ± 8.7	37.8 ± 7.9	37.2 ± 7.5	<0.001	38.0 ± 8.2	39.5 ± 8.4	0.145
Sex (male, *n*, %)	400 (95.7%)	139 (96.5%)	61 (96.8%)	200 (95.2%)	0.856	81 (91.0%)	319 (97.0%)	0.014
Body mass index (kg/m^2)	23.5 ± 3.6	23.9 ± 3.6	23.1 ± 3.1	23.3 ± 3.2	0.194	23.8 ± 3.3	23.4 ± 3.4	0.848
Smoking (*n*, %)	176 (46.0%)	66 (50.4%)	24 (41.4%)	86 (44.3%)	0.421	43 (48.9%)	133 (45.1%)	0.532
Alcohol consumption (*n*, %)	243 (63.4%)	87 (66.4%)	37 (63.8%)	119 (61.3%)	0.647	58 (65.9%)	185 (62.7%)	0.585
Helicobacter pylori infection (*n*, %)	144 (34.4%)	145 (100%)	0 (0%)	0 (0.0%)	<0.001	47 (52.8%)	149 (45.3%)	0.207
Disease								
Hypertension (*n*, %)	37 (8.9%)	20 (13.9%)	3 (5.0%)	14 (6.5%)	0.031	6 (6.7%)	31 (9.4%)	0.43
Hyperlipidemia (*n*, %)	5 (1.2%)	1 (0.7%)	2 (3.3%)	2 (0.9%)	0.286	2 (2.2%)	3 (0.9%)	0.304
Diabetes mellitus (*n*, %)	5 (1.2%)	2 (1.4%)	0 (0.0%)	3 (1.4%)	0.638	1 (1.1%)	4 (1.2%)	0.943
Heart diseases (*n*, %)	11 (2.6%)	5 (3.5%)	2 (3.3%)	4 (1.9%)	0.643	3 (3.4%)	8 (2.4%)	0.623
Cancer (*n*, %)	2 (0.5%)	1 (0.7%)	0 (0.0%)	1 (0.5%)	0.803	0 (0.0%)	2 (0.6%)	0.461
Drugs								
Antihypertensive drug (*n*, %)	3 (0.7%)	2 (1.4%)	1 (1.7%)	0 (0.0%)	0.215	1 (1.1%)	2 (0.6%)	0.609
3-hydroxy-3-methylglutaryl-CoA reductase inhibitor (*n*, %)	2 (0.5%)	0 (0.0%)	1 (1.7%)	1 (0.5%)	0.313	2 (2.2%)	0 (0.0%)	0.006
Hypoglycemic drug (*n*, %)	1 (0.2%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0.389	0 (0.0%)	1 (0.3%)	0.603
Antianxiety drugs (*n*, %)	3 (0.7%)	0 (0.0%)	0 (0.0%)	3 (1.4%)	0.224	3 (3.4%)	0 (0.0%)	0.001
Non-steroidal anti-inflammatory drugs (*n*, %)	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.9%)	0.37	0 (0.0%)	2 (0.6%)	0.461
Histamine receptor antagonist (*n*, %)	1 (0.2%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0.389	0 (0.0%)	1 (0.3%)	0.603
Nitrate (*n*, %)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0.609	0 (0.0%)	1 (0.3%)	0.603

CI: 0.349–0.928 and OR: 0.333, 95% CI: 0.117–0.948, respectively) (Table 5).

Discussion

The incidence of fundic gland polyp was higher among health check-up subjects with dyspeptic symptoms than those without, irrespective of endoscopic severity of gastritis and other endoscopic findings. In addition, fundic gland polyp was significantly associated with dyspeptic symptoms. Evidence suggests that fundic gland polyps are typically found in *H. pylori*-negative patients.[23] Given that the *H. pylori* infection rate is decreasing to 30% in Japan and the proportion of patients with dyspeptic symptoms is expected to increase, fundic gland polyps may be a useful indicator for identifying present and future patients with dyspeptic symptoms.

Endoscopic findings and dyspeptic symptoms. The Kyoto Classification of Gastritis was proposed at the 85th Congress of the Japan Gastroenterological Endoscopy Society in 2014 as a tool for standardizing endoscopic findings. Although endoscopic findings and abdominal symptoms are useful indicators of a patient's ability to secrete gastric acid, *H. pylori* infection status and lifestyle (i.e., food, smoking, and medication), that *H. pylori* infection affects gastric condition and the development of gastric diseases means that it is important to clarify whether patients are infected with *H. pylori*.[24] However, the association of *H. pylori* infection with FD or dyspeptic symptoms; endoscopic findings such as endoscopic gastritis, peptic ulcer, gastric cancer, atrophy and erosion; and severity of gastritis has not been well investigated.[18,24–30] Jung *et al.*[26] reported that although about 40% of Korean patients with dyspeptic symptoms had endoscopic findings (i.e., peptic ulcer, reflux esophagitis, Barrett's esophagus, erosions, and gastric cancer), no particular finding was characteristic of patients with dyspeptic symptoms. However, Tahara *et al.*[18] reported that red streak in the antrum and duodenal ulcer scar in 87 Japanese patients with dyspeptic symptoms were independently associated with dyspepsia (OR: 3.90, 95% CI: 1.20–12.64 and OR: 3.41, 95% CI: 1.08–10.79, respectively). In addition, in univariate analysis of the risk factors of dyspepsia on endoscopic findings, Tanaka *et al.*[17] showed that a significantly lower proportion of FD patients had red streak compared to healthy non-symptomatic controls (0% vs 18.6%; $p = 0.0124$). Further, FD patients were more likely to have depressive erosion (20.0% vs 7.9%; $p = 0.0522$). However, these studies reported no significant differences in other endoscopic findings[18,25] or histological findings for inflammation and atrophy.[18] In this study, we found that although most endoscopic findings, severity of gastritis according to the Kyoto gastritis classification, and *H. pylori* infection status were not significantly correlated with dyspeptic symptoms, an endoscopic finding of fundic gland polyp may be associated with dyspeptic symptoms. The discrepancy between our findings and those of previous reports may be explained by the fact that the patients enrolled in this study were young and underwent endoscopy as part of a health check-up, and that not all patients with dyspeptic symptoms had FD.

Fundic gland polyp and dyspeptic symptoms. Fundic gland polyp is the most common type of gastric polyp detected using endoscopy. It is found in approximately 6% of patients who undergo endoscopy and represents 74% of all gastric polyps identified on histological evaluation.[30] A Chinese study showed that although the prevalence of endoscopic gastric polyps was similar between 2000 and 2010 [1.0% (68/6,784) vs 1.1% (183/17,337)], that of fundic gland polyps increased from 8.8% to 66.1%.[32] This change in the prevalence of gastric polyps over the past 10–20 years is most likely due to a decrease in the *H. pylori* infection rate.

Although the present study failed to show a significant association between dyspeptic symptoms and red streak in the antrum or depressive erosion, like fundic gland polyp, red streak and depressive erosion are characteristic of *H pylori* infection-negative patients. Gastric acid secretion is typically significantly different between *H pylori*-positive and -negative patients, with *H pylori*-positive patients showing decreased gastric acid secre-

Table 3. Endoscopic characteristics of patients enrolled in this study

	All patients (*n* = 418)	*H. pylori* infection (*n* = 145)	Past *H. pylori* infection (*n* = 63)	*H. pylori* negative (*n* = 210)	*p* value	Dyspepsia positive (*n* = 89)	Dyspepsia negative (*n* = 329)	*p* value
Endoscopic disease								
Hiatal hernia (*n*, %)	268 (64.1%)	77 (53.1%)	41 (65.1%)	150 (71.4%)	0.002	56 (62.9%)	212 (64.4%)	0.791
Short-segment Barrett's esophagus (*n*, %)	234 (56.0%)	68 (46.9%)	36 (57.1%)	130 (61.9%)	0.019	41 (46.1%)	193 (58.7%)	0.034
Gastroesophageal reflux diseases (*n*, %)	82 (19.6%)	19 (13.1%)	15 (23.8%)	48 (22.9%)	0.05	19 (21.3%)	63 (19.1%)	0.643
Gastric ulcer (*n*, %)	21 (5.0%)	20 (13.8%)	1 (1.6%)	0 (0.0%)	<0.001	5 (5.6%)	16 (4.9%)	0.772
Gastric ulcer scar (*n*, %)	18 (4.3%)	4 (2.8%)	2 (3.2%)	12 (5.7%)	0.359	1 (1.1%)	17 (5.2%)	0.095
Duodenal ulcer (*n*, %)	9 (2.2%)	7 (4.8%)	0 (0.0%)	2 (1.0%)	0.021	3 (3.4%)	6 (1.8%)	0.372
Duodenal ulcer scar (*n*, %)	18 (4.3%)	18 (12.4%)	0 (0.0%)	0 (0.0%)	<0.001	4 (4.5%)	14 (4.3%)	0.921
Gastric cancer (*n*, %)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—	0 (0.0%)	0 (0.0%)	—
Endoscopic Kyoto classification								
Atrophy	0.4 ± 0.8	1.4 ± 0.6	1.0 ± 0.1	0.0 ± 0.0	<0.001	0.5 ± 0.7	0.4 ± 0.7	0.703
Intestinal metaplasia	0.5 ± 0.2	0.1 ± 0.4	0.0 ± 0.1	0.0 ± 0.0	<0.001	0.1 ± 0.3	0.0 ± 0.2	0.163
Enlarged folds	0.1 ± 0.4	0.4 ± 0.5	0.0 ± 0.2	0.0 ± 0.0	<0.001	0.2 ± 0.4	0.1 ± 0.3	0.007
Nodularity	0.0 ± 0.1	0.0 ± 0.2	0.0 ± 0.0	0.0 ± 0.0	0.008	0.1 ± 0.1	0.1 ± 0.1	0.242
Diffuse redness	0.3 ± 0.5	1.5 ± 0.7	0.0 ± 0.0	0.0 ± 0.0	<0.001	0.2 ± 0.5	0.3 ± 0.6	0.341
Total score	0.9 ± 1.5	3.4 ± 1.4	1.1 ± 0.3	0.0 ± 0.1	<0.001	1.0 ± 1.6	0.9 ± 1.4	0.531
Endoscopic finding								
Regular arrangement of collecting venules (*n*, %)	240 (57.4%)	11 (7.6%)	44 (69.8%)	185 (88.1%)	<0.001	48 (53.9%)	192 (58.4%)	0.454
Bile reflux (*n*, %)	5 (1.2%)	1 (0.7%)	2 (3.2%)	2 (1.0%)	0.286	1 (1.1%)	4 (1.2%)	0.954
Map-like redness (*n*, %)	1 (0.2%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0.059	0 (0.0%)	1 (0.3%)	0.603
Xanthoma (*n*, %)	8 (1.9%)	8 (5.5%)	0 (0.0%)	0 (0.0%)	<0.001	0 (0.0%)	8 (2.4%)	0.137
Hematin (*n*, %)	41 (9.8%)	5 (3.4%)	7 (11.1%)	29 (13.8%)	0.005	6 (6.7%)	35 (10.6%)	0.273
Red streak (*n*, %)	118 (28.2%)	6 (4.1%)	25 (39.7%)	87 (41.2%)	<0.001	28 (31.5%)	90 (27.4%)	0.445
Fundic gland polyp (*n*, %)	25 (6.0%)	1 (0.7%)	4 (6.3%)	20 (9.5%)	0.003	11 (12.4%)	14 (4.3%)	0.004
Hyperplastic polyp (*n*, %)	8 (1.9%)	8 (5.5%)	0 (0.0%)	0 (0.0%)	<0.001	1 (1.1%)	7 (2.1%)	0.54
Mucosal swelling (*n*, %)	27 (6.5%)	26 (17.9%)	1 (1.6%)	0 (0.0%)	<0.001	4 (4.5%)	23 (7.0%)	0.395
Patchy redness (*n*, %)	5 (1.2%)	4 (2.8%)	1 (1.6%)	0 (0.0%)	0.06	0 (0.0%)	5 (1.5%)	0.242
Sticky mucous (*n*, %)	33 (7.9%)	33 (22.8%)	0 (0.0%)	0 (0.0%)	<0.001	4 (4.5%)	29 (8.8%)	0.18
Antral erosion (*n*, %)	60 (14.4%)	22 (15.2%)	8 (12.7%)	30 (14.3%)	0.896	15 (16.9%)	45 (13.7%)	0.448
Raised erosion (*n*, %)	21 (5.0%)	11 (7.6%)	1 (1.6%)	9 (4.3%)	0.15	6 (6.7%)	15 (4.6%)	0.403
Spotty redness (*n*, %)	86 (20.6%)	57 (39.3%)	8 (12.7%)	21 (10.0%)	<0.001	17 (19.1%)	69 (21.0%)	0.698
Multiple white and flat elevated lesion (*n*, %)	37 (8.9%)	37 (25.5%)	0 (0.0%)	0 (0.0%)	<0.001	8 (9.0%)	29 (8.8%)	0.959

Table 4. Abdominal symptoms of patients enrolled in this study

	All patients (*n* = 418)	*H. pylori* infection (*n* = 145)	Past *H. pylori* infection (*n* = 63)	*H. pylori* negative (*n* = 210)	*p* value	Dyspepsia positive (*n* = 89)	Dyspepsia negative (*n* = 329)	*p* value
Heart burn (*n*, %)	31 (7.4%)	13 (9.0%)	5 (7.9%)	13 (6.2%)	0.609	31 (34.8%)	0 (0.0%)	<0.001
Distention (*n*, %)	59 (14.1%)	23 (15.9%)	10 (15.9%)	26 (12.4%)	0.593	59 (66.3%)	0 (0.0%)	<0.001
Nausea (*n*, %)	11 (2.6%)	3 (2.1%)	2 (3.2%)	6 (2.9%)	0.864	11 (12.4%)	0 (0.0%)	<0.001
Epigastric discomfort, before meal (*n*, %)	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	0.37	2 (2.2%)	0 (0.0%)	0.006
Epigastralgia, usual (*n*, %)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0.609	1 (1.1%)	0 (0.0%)	0.054
Epigastralgia, after meal (*n*, %)	7 (1.7%)	2 (1.4%)	0 (0.0%)	5 (2.4%)	0.409	7 (7.9%)	0 (0.0%)	<0.001
Epigastralgia, before meal (*n*, %)	15 (3.6%)	7 (4.8%)	2 (3.2%)	6 (2.9%)	0.607	15 (16.9%)	0 (0.0%)	<0.001
Dysphagia (*n*, %)	10 (2.4%)	1 (0.7%)	1 (1.6%)	8 (3.8%)	0.151	10 (11.2%)	0 (0.0%)	<0.001
Abdominal pain (*n*, %)	25 (6.0%)	9 (6.2%)	2 (3.2%)	14 (6.7%)	0.585	25 (28.1%)	0 (0.0%)	<0.001
Appetite loss (*n*, %)	7 (1.7%)	1 (0.7%)	2 (3.2%)	4 (1.9%)	0.41	76 (6.7%)	1 (0.3%)	<0.001
Defecation disorder (*n*, %)	36 (8.6%)	13 (9.0%)	7 (11.1%)	16 (7.6%)	0.675	10 (11/2%)	26 (7.9%)	0.32
Feeling of incomplete defecation (*n*, %)	22 (5.3%)	9 (6.2%)	4 (6.3%)	9 (4.3%)	0.667	10 (11.2%)	12 (3.6%)	0.004
Lower abdominal pain (*n*, %)	7 (1.7%)	3 (2.1%)	1 (1.6%)	3 (1.4%)	0.897	6 (6.7%)	1 (0.3%)	<0.001

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Table 5. Univariate and multivariate analysis of the development of dyspepsia

	Univariate analysis			Multivariate analysis		
Parameter	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Age	0.979	0.952–1.007	0.145			
Sex (male)	0.317	0.121–0.830	0.014	0.333	0.117–0.948	0.039
Body mass index >22 (kg/m^2)	0.898	0.527–1.528	0.691			
Smoking	1.164	0.723–1.875	0.532			
Alcohol consumption	1.15	0.697–1.895	0.585			
Helicobacter pylori infection	1.352	0.845–2.162	0.207			
Disease						
Hypertension	0.695	0.280–1.722	0.43			
Hyperlipidemia	2.498	0.411–15.185	0.304			
Diabetes mellitus	0.923	0.102–8.366	0.943			
Heart diseases	1.4	0.364–5.389	0.623			
Cancer	0.944	0.986–1.002	0.461			
Endoscopic disease						
Hiatal hernia	0.937	0.576–1.522	0.791			
Short-segment Barrett's esophagus	0.602	0.376–0.964	0.034	0.569	0.349–0.928	0.024
Gastroesophageal reflux diseases	1.146	0.644–2.040	0.643			
Gastric ulcer	1.161	0.415–2.270	0.773			
Gastric ulcer scar	0.209	0.027–1.589	0.13	0.119	0.014–1.036	0.054
Duodenal ulcer	1.238	0.245–6.239	0.796			
Duodenal ulcer scar	1.243	0.391–3.952	0.721			
Endoscopic Kyoto classification						
Atrophy	0.782	0.556–1.098	0.155	0.868	0.568–1.326	0.513
Intestinal metaplasia	0.616	0.192–1.975	0.415			
Enlarged folds	0.87	0.441–1.714	0.687			
Nodularity	0.4	0.066–2.433	0.32			
Diffuse redness	0.268	0.513–1.331	0.433			
Total scores	0.907	0.767–1.072	0.254			
Endoscopic finding						
Regular arrangement of collecting venules	0.835	0.522–1.338	0.454			
Bile reflux	0.923	0.102–8.366	0.943			
Map-like redness	—	—	—			
Xanthoma	0.976	0.959–1.992	0.537			
Hematin	0.607	0.247–1.493	0.273			
Red streak	1.264	0.763–2.094	0.362			
Fundic gland polyp	3.173	1.387–7.260	0.006	3.413	1.430–8.142	0.006
Hyperplastic polyp	0.523	0.063–4.305	0.54			
Mucosal swelling	0.626	0.211–1.860	0.395			
Patchy redness	0.985	0.972–0.998	0.242			
Sticky mucous	0.487	0.167–1.423	0.18	0.199	0.203–2.408	0.571
Antral erosion	1.279	0.676–2.421	0.448			
Raised erosion	1.513	0.570–4.021	0.403			
Spotty redness	0.89	0.492–1.607	0.698			
Multiple white and flat elevated lesion	1.022	0.450–2.320	0.959			

tion due to the progression of gastric atrophy and upregulation of activated pro-inflammatory cytokines.[33] Therefore, greater gastric acid secretion in *H pylori*-negative patients may increase the risk of dyspeptic symptoms. A meta-analysis of randomized controlled trials comparing any proton pump inhibitor (PPI) with placebo or prokinetics for the treatment of FD showed that PPIs were more effective than placebo (RR: 0.88, 95% CI: 0.82–0.94) and slightly more effective than prokinetics (RR: 0.89, 95% CI: 0.81–0.99) at relieving overall dyspeptic symptoms in FD patients.[34] This evidence suggests that PPIs are effective treatments for FD, in whom dyspeptic symptoms may be related to gastric acidity. However, it remains unclear whether fundic gland polyps are responsible for dyspeptic symptoms; thus, further study is required to clarify the direct association among gastric acidity, fundic gland polyps and dyspeptic symptoms.

Limitations. This study has a few limitations. First, this was a single-center retrospective study with a small sample size. Second, we did not have data on the severity of dyspeptic symptoms and did not use established questionnaires such as the F scale[35,36] and the gastrointestinal symptom rating scale.[36,37] Third, although *H. pylori* infection was diagnosed using an anti-*H pylori* IgG test and endoscopic findings of atrophy and diffuse

redness, *H. pylori* infection status (*H. pylori*-positive, -negative, and eradicated) is difficult to confirm with confidence. Fourth, because we did not have data on the duration of abdominal symptoms, we were unable to diagnose functional dyspepsia in patients with dyspeptic symptoms.

Conclusion

The presence of fundic gland polyps is a risk factor for dyspeptic symptoms in Japanese subjects who underwent endoscopy as part of a health check-up. Although details of the mechanism underlying the development of dyspepsia in patients with fundic gland polyps are unclear, that fundic gland polyp is a characteristic endoscopic finding in *H. pylori*-negative subjects suggests that it may be related to *H. pylori* infection or gastric acid secretion.

Author Contributions

Conceptualization, KT, MS, and TK; methodology, KT, MS, and TK; software, KT and MS; formal analysis, KT and MS; investigation, TO and TK; writing–original draft preparation, KT, MS, and TK; writing–review and editing, KT, MS, MH, NN, EI, RN, MF, TI, TO, TK; supervision, TO, TI, TK; project administration, TO and TK.

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Abbreviations

GERD	gastroesophageal reflux disease
H. pylori	*Helicobacter pylori*
OR	odds ratio
SSBE	short-segment Barrett's esophagus

Conflict of Interest

No potential conflicts of interest were disclosed.

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