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【 ORIGINAL ARTICLE 】

Association between Functional Dyspepsia and Gastric Depressive Erosions in Japanese Subjects

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Abstract:

Objective The association between functional dyspepsia (FD) and endoscopic findings has not been fully elucidated. *Helicobacter pylori* infection is considered a key factor in the pathophysiology of FD. The Kyoto Classification of Gastritis (KCG) was proposed in 2014 to evaluate endoscopic findings based on the *H. pylori* status. We investigated the endoscopic findings associated with FD according to the KCG.

Methods This cross-sectional study included subjects who underwent esophagogastroduodenoscopy during a medical health check-up. We compared the endoscopic findings between subjects with FD and healthy controls (HCs) according to the KCG.

Results A total of 456 subjects were analyzed. Among them, the detection rate of FD was 5.5% (25/456 persons). In a univariate analysis of the endoscopic findings, a significantly lower proportion of subjects with FD had gastric red streak in comparison to HCs (0% vs. 18.6%, respectively; p=0.0124). Subjects with FD were more likely to have gastric depressive erosion (20.0% vs. 7.9%; p=0.0522). A higher proportion of the erosion-positive subjects had FD in comparison to erosion-negative subjects (12.8% vs. 4.8%). There were no significant differences in the other endoscopic findings, including gastric atrophy, intestinal metaplasia, enlarged fold, nodularity, and diffuse redness. A multivariate analysis revealed that gastric depressive erosion was significantly and independently associated with FD (odds ratio, 2.92; 95% confidence interval, 1.03-8.26; p=0.0436). In contrast, gastric red streak was not associated with FD (p=0.989).

Conclusion Gastric depressive erosions may be associated with dyspepsia.

Key words: dyspepsia, gastritis, *Helicobacter pylori*, stomach, upper gastrointestinal tract

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Introduction

The pathophysiology of functional dyspepsia (FD) is multifactorial; the factors involved include abnormal gastrointestinal (GI) motility (1, 2), visceral hypersensitivity (3), psychosocial factors (4, 5), and disorders of the autonomic nervous system (6) and central nervous system (7). FD was previously considered a non-organic disorder that was diagnosed by excluding organic diseases of the upper GI tract such as peptic ulcer and cancer on esophagogastroduodenoscopy (EGD) (8). However, *Helicobacter pylori* (*H. pylori*) infection is partly involved in the pathophysiology in a subset of patients with FD. In a guideline established by the American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) in 2017, *H. pylori* eradication therapy is strongly recommended for *H. pylori*-positive FD patients (9). This guideline was based on

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a meta-analysis that assessed 22 randomized controlled trials comparing eradication therapy to placebo antibiotics in 4,896 *H. pylori*-positive FD patients. The results revealed that *H. pylori* eradication had a statistically significant impact on dyspeptic symptoms: the relative risk for remaining dyspepsia was 0.91, while the number needed to treat was 12.5. In the Japanese guidelines for FD, which were established by the Japanese Society of Gastroenterology in 2015, early eradication therapy was also strongly recommended, and patients who become symptom-free 6-12 months after eradication were considered cases of "*H. pylori*-associated FD (10)."

The Kyoto Classification of Gastritis (KCG) was proposed at the 85th Congress of the Japan Gastroenterological Endoscopy Society in 2014 for the purpose of standardizing endoscopic findings based on the assessment of *H. pylori* status (11). This classification divides patients into three groups: active gastritis (current *H. pylori* infection), inactive gastritis (previous *H. pylori* infection), and non-gastritis *(H. pylori*-negative status). Furthermore, the endoscopic findings used in this classification are standardized as follows: atrophy, intestinal metaplasia, enlarged fold, nodularity, diffuse redness, depressive erosion, raised erosion, hematin, patchy redness, spotty redness, map-like redness, red streak, foveolar hyperplastic polyp, xanthoma, mucosal swelling, sticky mucus, fundic gland polyp, regular arrangement of collecting venules, and multiple white and flat elevated lesions. Although some reports investigated the association between gastric cancer and the KCG, no studies investigated the association between FD and the KCG (12, 13).

To date, the association between FD and endoscopic findings has not been fully elucidated. Although Tahara et al. reported that linear redness in the antrum and duodenal ulcer scarring were positively associated with dyspepsia, their patients were not diagnosed with FD using the Rome criteria of functional gastrointestinal disorders (14). Chen et al. also reported that FD patients with gastric reddish streaks exhibited increased somatization and more stressful life events (15). In contrast, there were no significant differences in the endoscopic findings of patients with dyspepsia and asymptomatic patients in a Korean study (16). Thus, to clarify the pathophysiology of FD, we investigated the endoscopic findings associated with FD according to the KCG.

Materials and Methods

Study design and participants

This was a cross-sectional study. Between March 2015 and February 2016, a total of 695 consecutive subjects underwent medical health check-up including EGD and blood tests to detect anti-*H. pylori* immunoglobulin G antibodies in our clinic, MedCity21. The size of the sample depended on the period in which we could provide questionnaires to diagnose FD at this institute. The exclusion criteria were as follows: lack of data; history of abdominal surgery; detection of organic disease such as ulcer, acute gastric mucosal lesion, and neoplastic lesion on endoscopy; comorbidities; unknown result of *H. pylori* eradication; unknown history of *H. pylori* eradication; and false-negative for anti-*H. pylori* antibodies. We excluded subjects who took medications that may affect abdominal symptoms such as histamine H_2 receptor antagonists, proton-pump inhibitors (PPIs), mucoprotective drugs, prokinetics, nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and immunosuppressive drugs.

The study protocol was in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Osaka City University Graduate School of Medicine (March 2016, protocol number 3385). We disclosed the information about this study on our home page, and the subjects had the opportunity to opt out. This study was registered with the university hospital medical information network (UMIN) clinical trial registry (UMIN000022733) as an observational study. The following information was obtained from the medical records: age, sex, body mass index (BMI), present alcohol drinking, and present cigarette smoking.

The diagnosis of FD

FD was diagnosed according to the Rome III criteria. We assessed four dyspepsia symptoms that corresponded to the Rome III criteria: postprandial fullness, early satiation, epigastric pain, and epigastric burning (8). We used our original questionnaire to evaluate the frequency of dyspepsia symptoms according to the well-validated questionnaire in Japanese (17). Symptoms were assessed by a seven-point Likert scale: 0, none; 1, <1 day per month; 2, 1 day per month; 3, 2-3 days per month; 4, 1 day per week; 5, >1 day per week; and 6, every day. We also evaluated the dyspepsia and gastroesophageal reflux symptoms using the modified Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (FSSG), which is a validated questionnaire in Japan (18). This questionnaire includes an assessment of the dyspepsia score (range, 0-20) and gastroesophageal reflux score (range, 0-28). Subjects without FD were included as healthy controls (HCs). None of the HCs met the Rome III criteria for FD.

Endoscopic examination

EGD was performed by several expert endoscopists and the endoscopic findings for each patient were immediately addressed after the examination. The findings were retrospectively confirmed by one expert endoscopist to reduce interobserver variance. The findings were independently scored and evaluated according to the KCG and Kimura-Takemoto classification (11-13, 19). The Kimura-Takemoto classification classifies gastric atrophy into seven grades: Closed (C)-0, C-I, C-II, C-III, and Open (O)-I, O-II, and O-III. C-I, C-II, and C-III indicate closed-type atrophic patterns with a margin between the non-atrophic fundic mucosa and the atrophic mucosa in the lesser curvature of the stomach. O-I, O-II, and O-III indicate open-type atrophic patterns whose margins do not cross the lesser curvature. According

to the KCG, atrophy was classified into three grades: None = C-0 and C-I; Mild = C-II and C-III; and Severe = O-I, O-II, and O-III. Intestinal metaplasia of the stomach was scored into three grades: None, Within the antrum, and Up to the corpus. According to the KCG, diffuse redness of the stomach was also classified into three grades: None, Mild, and Severe. The following findings of the stomach based on the KCG were assessed as positive or negative: enlarged fold, nodularity, depressive erosion, raised erosion, hematin, patchy redness, spotty redness, map-like redness, red streak, foveolar hyperplastic polyp, xanthoma, mucosal swelling, sticky mucus, fundic gland polyp, regular arrangement of collecting venules, and multiple white and flat elevated lesions. Duodenal redness and erosion were also assessed as positive or negative. We assessed both the duodenal bulb and descending part. When endoscopic findings such as redness and erosion were observed at duodenal bulb and/or descending part, the case was considered positive.

Diagnosis of the H. pylori status

We used an anti-*H. pylori* antibody for the serological diagnosis of *H. pylori* infection (E plate Eiken *H. pylori* antibody®; Eiken Chemical, Nogi, Japan). The cutoff anti-*H. pylori* antibody value was 10 U/mL. According to the KCG, *H. pylori* status was divided into three conditions: active gastritis (current *H. pylori* infection), was diagnosed based on antibody values of ≥10 U/mL and endoscopic findings compatible with current *H. pylori* infection; inactive gastritis (previous *H. pylori* infection) was diagnosed when subjects had a history of *H. pylori* eradication, antibody values <10 U/mL, endoscopic findings compatible with past *H. pylori* infection, and no endoscopic findings of active gastritis; non-gastritis (*H. pylori*-negative status) was diagnosed when subjects had antibody values of <10 U/mL, no history of eradication therapy, and no endoscopic findings compatible with *H. pylori* infection. We cases in which the endoscopic findings were compatible with current *H. pylori* infection, but whose antibody values were <10 U/mL were considered to be false-negatives.

Outcome measurement

We compared the differences in the clinical characteristics and endoscopic findings, including depressive erosion between the subjects with FD and HCs. The endpoint of this study was to investigate the endoscopic findings associated with FD.

Statistical analyses

Data are expressed as the median and interquartile range for continuous variables and as numbers for categorical variables. For categorical variables, comparisons were performed using Fisher's exact test or the chi-squared test; continuous variables were compared using the Mann-Whitney U test. P values of <0.05 were considered statistically significant. A multivariate analysis was performed using logistic regression. We included two variables with lower p values in the univariate analyses in the logistic regression model. The association with FD was estimated by calculating the odds ratio (OR) and 95% confidence interval (CI). The OR represents the relative odds of the presence of FD given exposure to a variable. Spearman's rank correlation coefficients were calculated for correlation analyses. All statistical analyses were performed using EZR (version 1.34; Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for the R software program (version 3.3.2; The R Foundation for Statistical Computing, Vienna, Austria) (20).

Results

Detection of FD

A flow chart of the study participants is shown in Fig. 1. Of the 695 subjects, 239 subjects were excluded according to the following criteria: lack of data (n=26), history of abdominal surgery (n=90), organic disease detected on endoscopy [n=11 (gastric cancer, n=2; gastric ulcer, n=4; acute gastric mucosal lesion, n=2; duodenal adenoma, n=1; and duodenal cancer, n=2)], comorbidities [n=27 (hyperthyroidism, n=3; hypothyroidism, n=8; thyroid cancer, n=5; prostate cancer, n=1; myocardial infarction, n=2; nephrosclerosis, n=1; Crohn's disease, n=1; ulcerative colitis, n=1; manic depressive illness, n=4; and menopausal disorder, n=1)], current medication [n=34 (proton-pump inhibitor, n=14, histamine H_2 receptor antagonist, n=5; mucoprotective drugs, n=1; anti-anxiety drugs, n=4; corticosteroids, n=1; immunosuppressive drugs, n=1; NSAIDs, n=5; and low-dose aspirin, n=3)], unknown result of *H. pylori* eradication (n=22), unknown history of *H. pylori* eradication (n=3), and false-negative for anti-*H. pylori* antibodies (n=26). The remaining 456 subjects were analyzed in this study. We identified 25 subjects with FD; the remaining 431 subjects were considered to be HCs. The detection rate of FD was 5.5% (25/456).

Clinical characteristics of the study participants

The clinical characteristics of the study participants are shown in Table 1. The univariate analysis revealed that FD patients had a significantly higher frequency of postprandial fullness, early satiation, and epigastric pain/burning [4.0 (2.0) vs. 0.0 (2.0), p<0.001; 0.0 (3.0) vs. 0.0 (0.0), p<0.001; 4.0 (3.0) vs. 0.0 (0.0), p<0.001, respectively]. Moreover, subjects with FD had significantly higher dyspepsia and gastroesophageal reflux scores [6.0 (5.0) vs. 2.0 (4.0), p<0.001; 4.0 (3.0) vs. 1.0 (3.0), p<0.001, respectively]. These results showed FD patients had more severe symptoms than the HCs. There were no significant differences in the age, sex, BMI, current cigarette smoking, or current alcohol drinking status of the FD patients and HCs. The *H. pylori* infection status of the FD patients and HCs did not differ to a statistically significant extent.

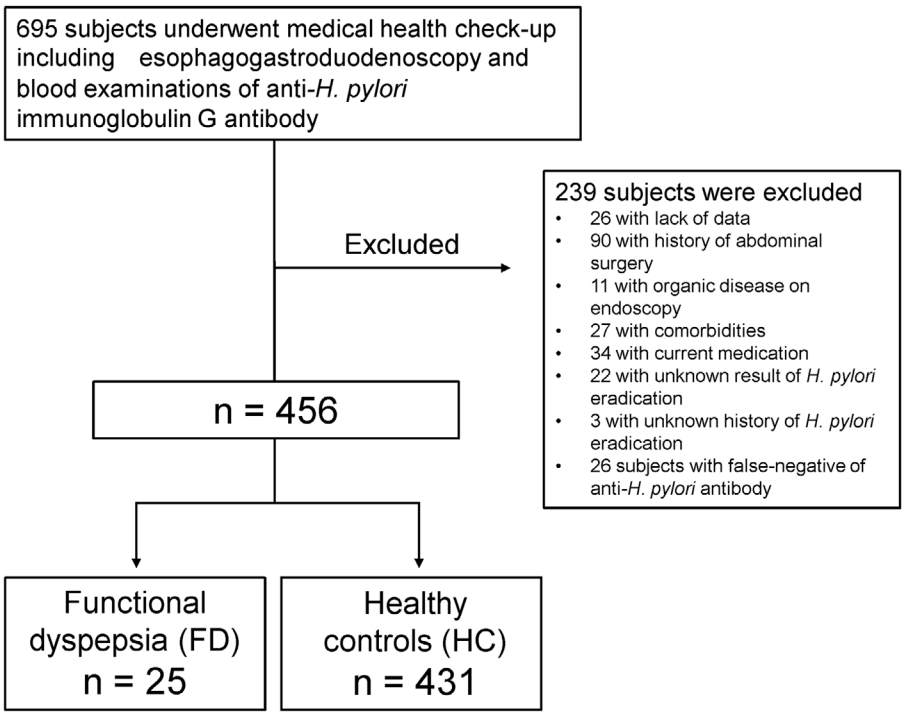

Figure 1. **A flowchart of the study participants. *H. pylori*: *Helicobacter pylori***

Table 1. **Clinical Characteristics of the Study Population.**

Variable	HC (n=431)	FD (n=25)	p value
Age, years	50.0 (18.0)	47.0 (16.0)	0.279
Male	226 (52.4%)	11 (44.0%)	0.539
BMI, kg/m^2	22.4 (3.90)	21.6 (5.80)	0.380
Current cigarette smoking	72 (16.7%)	1 (4.0%)	0.160
Current alcohol drinking	229 (53.1%)	14 (56.0%)	0.942
Frequency of postprandial fullness	0.0 (2.0)	4.0 (2.0)	<0.001
Frequency of early satiation	0.0 (0.0)	0.0 (3.0)	<0.001
Frequency of epigastric pain and burning	0.0 (0.0)	4.0 (3.0)	<0.001
Dyspeptic score on modified FSSG	2.0 (4.0)	6.0 (5.0)	<0.001
Gastroesophageal reflux score on modified FSSG	1.0 (3.0)	4.0 (3.0)	<0.001
Status of *Helicobacter pylori* infection			0.212
Active-gastritis	64 (14.8%)	5 (20.0%)	
Inactive-gastritis	72 (16.7%)	7 (28.0%)	
Non-gastritis	295 (68.5%)	13 (52.0%)	

Data are expressed as median (IQR) for continuous variables and as numbers (percentage) for categorical variables.

BMI: body mass index, FD: functional dyspepsia, FSSG: Frequency Scale for the Symptoms of Gastro-esophageal Reflux Disease, HC: healthy controls, IQR: interquartile range

Endoscopic findings of the stomach and duodenum

The results of the univariate analysis are shown in Table 2. The analysis of the endoscopic findings revealed that a significantly lower proportion of FD patients had gastric red streak in comparison to HCs (0% vs. 18.6%; p=0.0124). FD patients were more likely to have gastric depressive erosion (20.0% vs. 7.9%; p=0.0522). Erosion-positive subjects had higher proportion of FD in comparison to erosion-negative subjects (12.8% vs. 4.8%). Representative endoscopic images of red streak and depressive erosion are shown in Fig. 2. The depressive erosions we observed in this study were 2-3 mm in width and there were 1-3 erosions. There were no significant differences in other endoscopic findings, including gastric atrophy, intestinal metaplasia, enlarged folds, nodularity, diffuse redness, raised erosion, hematin, patchy redness, spotty redness, map-like redness, foveolar hyperplastic polyp, xanthoma, mucosal swelling, sticky mucus, fundic gland polyp, regular arrangement of collecting venules, or multiple white and flat elevated lesions of the stomach. In addition, there were no significant differences in duodenal redness or erosion.

Table 2. Endoscopic Findings of the Stomach and Duodenum.

Variable	HC (n=431)	FD (n=25)	OR (95% CI)	p value
Stomach				
Atrophic gastritis				0.212
None	302 (67.0%)	14 (56.0%)	1 (Reference)	
Mild	78 (18.1%)	8 (32.0%)	2.21 (0.773-5.88)	
Severe	51 (14.9%)	3 (12.0%)	1.27 (0.226-4.77)	
Intestinal metaplasia				0.162
None	410 (95.1%)	22 (88.0%)	1 (Reference)	
Within antrum	14 (3.3%)	2 (8.0%)	2.65 (0.276-12.7)	
Up to corpus	7 (1.6%)	1 (4.0%)	2.65 (0.0565-22.2)	
Enlarged fold	11 (2.6%)	0 (0%)	0.00 (0.00-7.14)	1.000
Nodularity	2 (0.5%)	1 (4.0%)	8.83 (0.145-175)	0.156
Diffuse redness				0.570
None	361 (83.8%)	20 (80.0%)	1 (Reference)	
Mild	15 (3.5%)	1 (4.0%)	1.20 (0.0272-8.63)	
Severe	55 (12.7%)	4 (16.0%)	1.31 (0.314-4.12)	
Depressive erosion	34 (7.9%)	5 (20.0%)	2.91 (0.0803-8.68)	0.0522
Raised erosion	50 (11.6%)	4 (16.0%)	1.45 (0.348-4.55)	0.520
Hematin	45 (10.4%)	2 (8.0%)	0.746 (0.0826-3.19)	1.000
Patchy redness	8 (1.9%)	1 (4.0%)	2.20 (0.0477-17.6)	0.401
Spotty redness	30 (7.0%)	3 (12.0%)	1.82 (0.330-6.60)	0.413
Map-like redness	8 (1.9%)	0 (0%)	0.00 (0.00-10.5)	1.000
Red streak	80 (18.6%)	0 (0%)	0.146 (0.00-0.717)	0.0124
Foveolar-hyperplastic polyp	7 (1.6%)	1 (4.0%)	2.52 (0.0538-20.9)	0.365
Xanthoma	22 (5.1%)	0 (0%)	0.00 (0.00-3.21)	0.624
Mucosal swelling	13 (3.0%)	0 (0%)	0.00 (0.00-5.86)	1.000
Sticky mucus	21 (4.9%)	1 (4.0%)	0.814 (0.0189-5.52)	1.000
Fundic gland polyp	116 (26.9%)	5 (20.0%)	0.679 (0.195-1.92)	0.641
Regular arrangement of collecting venules	318 (73.8%)	16 (64.0%)	0.632 (0.255-1.67)	0.351
Multiple white and flat elevated lesions	5 (1.2%)	1 (4.0%)	3.53 (0.0721-33.4)	0.288
Duodenum				
Redness	34 (7.9%)	1 (4.0%)	0.487 (0.0115-3.18)	0.710
Erosion	9 (2.1%)	1 (4.0%)	1.95 (0.0428-15.1)	0.434

Data are expressed as numbers (percentage).

The OR represents the relative odds of the occurrence of FD given the exposure to the variable.

CI: confidence interval, FD: functional dyspepsia, HC: healthy controls, OR: odds ratio

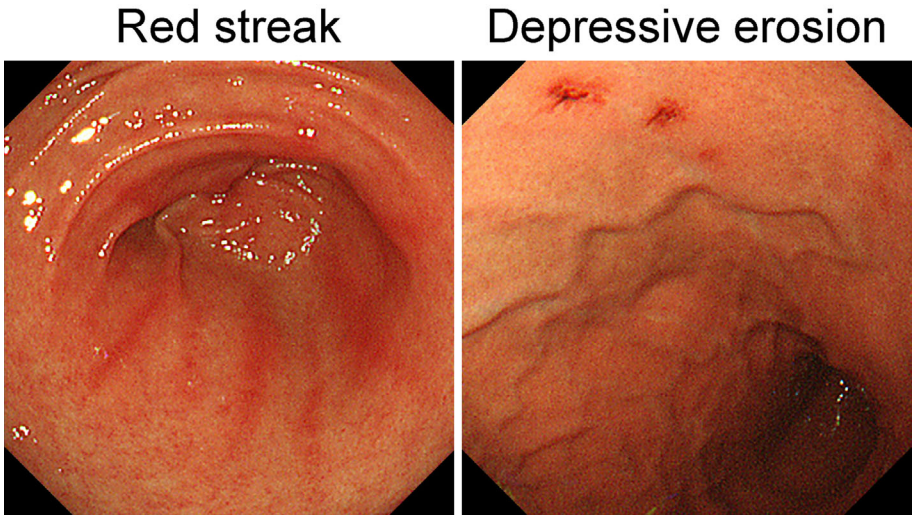

Figure 2. Representative endoscopic images of gastric red streak and depressive erosion.

Table 3. Crude and Multiple-adjusted Odds Ratios for Functional Dyspepsia.

Variable	Crude-OR		Multiple-adjusted OR	
	OR (95% CI)	p value	OR (95% CI)	p value
Depressive erosion	2.91 (0.0803-8.68)	0.0522	2.92 (1.03-8.26)	0.0436
Red streak	0.146 (0.00-0.717)	0.0124	<0.001	0.989

CI: confidence interval, OR: odds ratio

Independent endoscopic findings associated with FD

Gastric depressive erosion and gastric red streak were entered into the multivariate analysis as explanatory variables. The results are shown in Table 3. Gastric depressive erosion was positively associated with FD (OR, 2.92; 95% CI, 1.03-8.26; p=0.0436). In contrast, gastric red streak was not associated with FD (p=0.989). These results indicate that gastric depressive erosion was the only independent endoscopic finding associated with FD.

Correlation between gastric depressive erosion and dyspepsia symptoms

In the correlation analyses, gastric depressive erosion was not significantly correlated with the frequency of postprandial fullness, early satiation, and epigastric pain/burning (p=0.220; r=0.0576, p=0.475; r=-0.0335, and p=0.791; r=0.0125, respectively).

Discussion

This is the first study to compare endoscopic findings using the KCG between subjects with FD and HC. We demonstrated that gastric depressive erosion was independently associated with FD. To our knowledge, this is the first report to show the importance of gastric depressive erosion in subjects who meet the Rome criteria for FD. Gastric erosion is defined as an endoscopically detectable mucosal break without penetration of the muscularis mucosae (21). In previous reports, gastric erosion was a common finding in asymptomatic volunteers and patients with non-ulcer dyspepsia and was often chronic or relapsing (22-24). Thus, it was unclear whether gastric erosion was responsible for the symptoms of dyspepsia. In the Rome criteria, it is not clearly shown whether gastric erosion is considered an organic abnormality or not that is responsible for symptoms. The gastric depressive erosions observed in this study were very mild. Nevertheless, interestingly, we found that gastric depressive erosion was associated with FD. Thus, gastric depressive erosion may be partly responsible for dyspepsia in patients who meet the criteria for FD. As a clinical management, a PPI test may be useful for dyspepsia patients with gastric erosion. When both the erosion and symptoms are cured by the administration of a PPI, they should not be considered FD patients and we should consider gastric erosion as an organic disease. On the other hand, when dyspepsia is not cured by PPI, they should be considered 'true' FD patients, even if they have gastric erosion.

The causes of gastric erosion are multifactorial and include psychological stress, physical stress, *H. pylori* infection, cigarette smoking, alcohol consumption, and NSAID use (21, 22). Our results showed no significant differences in the rates of *H. pylori* infection, current cigarette smoking, or current alcohol drinking. We excluded subjects who were taking NSAIDs. Thus, FD patients may have had more gastric erosions than HCs due to psychological stress or other non-specific stimuli. A previous study showed that psychological stress and anxiety were deeply involved in the pathophysiology of FD (25). In FD, delayed gastric emptying leads to the retention of the gastric contents, which may cause gastric erosion.

Visceral hypersensitivity and allodynia are involved in the pathophysiology of FD (26). A previous report showed that FD patients had hypersensitivity of the stomach due to gastric distension stimuli and hypersensitivity of the duodenum due to acid and lipid stimuli (27-29). In this context, FD patients may be more likely to feel stronger symptoms than HCs. Moreover, in FD patients the expression of transient receptor potential vanilloid 1 (TRPV1) mRNA in the gastric mucosa and polymorphisms of the TRPV1 gene are upregulated in comparison to HCs in Asian countries, including Japan (30-32). We hypothesize that the nerve terminals of intrinsic primary afferent neurons may be exposed to gastric acid due to gastric erosion. Thereafter, gastric acid may cause the perception of pain via TRPV1 activation in FD patients, while HCs with gastric erosion do not perceive pain.

In addition, the mechanism of visceral hypersensitivity partly involves the sensitization of the central nervous system. The central serotonergic and noradrenergic receptor systems are involved in the processing of the sensory activities of the GI tract. Some studies have suggested alterations in the central serotonergic, noradrenergic, and autonomic nervous system, which might partially explain the symptoms of FD (6, 7, 33). Accordingly, FD patients might experience symptoms such as epigastric pain due to gastric erosion, which did not cause symptoms in HCs.

The KCG is used to assess endoscopic findings based on the *H. pylori* status. From this point of view, we revealed that endoscopic findings, such as the degree of gastric atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness, were not associated with FD, which was consistent with some previous studies (34, 35). These results

may imply that it is difficult to distinguish between FD patients and HCs with endoscopic findings based on the *H. pylori* status alone. The FD guidelines showed evidence that the number needed to treat was 12.5 to reduce the symptoms of dyspepsia by *H. pylori* eradication (9). This result may also indicate that it is difficult to estimate the efficacy of eradication therapy prior treatment based on the endoscopic findings.

This study is associated with several limitations. First, because the FD patients in this study were subjects of a medical health check-up, the strength of dyspepsia symptoms might be weaker than in outpatients with FD in the hospital setting. Consequently, it is unclear whether the same results may be observed in the hospital setting. The subjects in this study might not be representative of true FD patients who require medical care because they had weak symptoms. Moreover, the exclusion of subjects with medications such as H2 receptor antagonists might have affected the results. Second, we could not observe which *H. pylori* status was associated with gastric depressive erosions in FD because the number of study participants was relatively small. Third, the *H. pylori* infection status was not examined using a urea breath test or stool antigen test, both of which have a high diagnostic yield. This limitation might have resulted in some misinformation regarding the background characteristics of the patients.

In conclusion, gastric depressive erosions may be associated with dyspepsia. We believe that this study can provide new insight into the clinical management of patients who meet the Rome criteria for FD.

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

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