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Endoscopy-Guided Evaluation of Duodenal Mucosal Permeability in Functional Dyspepsia

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OBJECTIVES: The pathophysiology of functional dyspepsia (FD) is not fully understood. Impaired duodenal mucosal integrity characterized by increased mucosal permeability and/or low-grade inflammation was reported as potentially important etiologies. We aimed to determine the utility of a recently developed simple catheterization method to measure mucosal admittance (MA), the inverse of mucosal impedance, for evaluation of duodenal mucosal permeability in patients with FD.

METHODS: We conducted two prospective studies. In the first study, duodenal MA of 23 subjects was determined by catheterization during upper endoscopy, and transepithelial electrical resistance (TEER) of duodenal biopsy samples in Ussing chambers was measured to assess the correlation between MA and TEER. In the second study, duodenal MA of 21 patients with FD fulfilling the Rome III criteria was compared with that of 23 healthy subjects.

RESULTS: The mean MA and TEER values were 367.5 ± 134.7 and $24.5 \pm 3.7\ \Omega\ cm^2$, respectively. There was a significant negative correlation between MA and TEER ($r = -0.67$, $P = 0.0004$, Pearson's correlation coefficient). The mean MA in patients with FD was significantly higher than that in healthy subjects (455.7 ± 137.3 vs. 352.1 ± 66.9, $P = 0.002$, unpaired *t*-test). No procedure-related complications were present.

CONCLUSIONS: We demonstrated the presence of increased duodenal mucosal permeability in patients with FD by MA measurement using a simple catheterization method during upper endoscopy.

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INTRODUCTION

Functional dyspepsia (FD) is one of the most common functional gastrointestinal disorders (FGIDs), affecting up to 10–20% of the general population.[1,2] FD is currently defined by the Rome IV criteria as the presence of one or more symptoms (bothersome postprandial fullness, early satiation, epigastric pain, epigastric burning) thought to originate in the gastroduodenal region, and no evidence of structural disease that is likely to explain the symptoms on routine examinations including upper endoscopy.[3] The pathophysiology of FD, although not well understood, is considered to be complex and multifactorial. A number of potentially important mechanisms and etiologies were proposed, including impaired gastric accommodation,[4] gastric or duodenal hypersensitivity to distention, acid and other intraluminal stimuli,[5–8] low-grade duodenal inflammation,[9–13] neuronal and structural changes in the submucosal ganglia in the duodenum,[14] acute gastrointestinal infection,[15] and psychosocial factors.[1,16] A recent study demonstrated increased duodenal mucosal permeability with low-grade inflammation in patients with FD,[17] suggesting that impaired duodenal mucosal barrier function might be contributing to the pathophysiology of FD. However, the measurement of mucosal permeability is not easily achievable in clinical practice as established methods remain complicated.

A minimally invasive method using a simple catheter that can be easily traversed through the working channel of an endoscope was recently developed as a tool to measure admittance, the inverse of impedance. On the basis of a previously reported finding of increased duodenal mucosal permeability in FD,[17] we hypothesized that duodenal mucosal admittance (MA) was higher in patients with FD and predicted that the easy and real-time evaluation of mucosal permeability during endoscopy would aid in determining FD pathophysiology in patients. However, the reliability of this catheter in human gut mucosa compared with established methods is unknown.

In this study, we determined the correlation between MA and transepithelial electrical resistance (TEER) in duodenal mucosa and evaluated whether duodenal MA was higher in patients with FD than in healthy subjects.

METHODS

Study protocol. We conducted two prospective studies to investigate our aims. In the first study, we evaluated the correlation between MA and TEER in normal-appearing duodenal mucosa. In the second study, we compared duodenal MA between patients with FD and healthy subjects. All protocols in both studies were approved by the ethical

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committee of Chiba University Hospital, and written informed consent was obtained from all subjects before enrollment. These studies were registered at the University Hospital Medical Information Network (UMIN000021113 and UMIN000021397).

Measurement of MA. MA was measured using a tissue conductance meter (TCM AS-TC100, Asahi Biomed, Tokyo, Japan), which was 1.9 mm in diameter and had an electrode sensor at the tip, during upper endoscopy. Reference electrodes were placed on the flexor sides of bilateral forearms. After gentle irrigation of duodenal mucosa, the conductance meter was traversed through the working channel of the endoscope, and the tip was connected with the anal side of papillae and the area between the folds of the second part of the duodenum for 2–3 s. Alternating currents of 320 Hz and 30.7 kHz were then loaded at a constant voltage of 12.5 mV. MA was measured five times in each subject, and average MA values were used for analysis.

Measurement of TEER. TEER was measured by Ussing chambers (Physiologic Instruments, San Diego, CA, USA). Briefly, in all subjects, after the conclusion of MA measurements, four biopsy samples were taken with biopsy forceps (SwingJaw; outside diameter, 2.45 mm; Olympus, Tokyo, Japan) from areas in close proximity to the area of MA measurements. Immediately after the biopsy, samples were mounted on Ussing chambers adapted for this study, with an exposed tissue area of 0.005 cm^2. Mucosal and serosal compartments were filled with 3 ml Hanks' balanced salt solution. Solutions were maintained at 37 °C, and samples were continuously oxygenated with O_2/CO_2 (95/5%). Measurements were performed in open-circuit conditions, and TEER was calculated from the induced voltage (5, 10, or 15 mV) and current (μA) in each experiment and recorded once in each sample within 10 min after biopsy. The results were presented as Ω cm^2. Average TEER of four biopsy samples from each subject was used for analysis.

Study design

Correlation between MA and TEER. A total of 23 subjects participated in the first study evaluating the correlation between MA and TEER. All subjects were over 20 years of age and were without implanted pacemakers, cardioverter defibrillators, or intracranial electrical devices such as deep-brain stimulators as electrical current was necessary to measure MA.

Measurement of MA in patients with FD. A total of 21 subjects meeting the Rome III criteria for FD and 23 healthy subjects were enrolled in the FD and control groups, respectively. All subjects fulfilled the inclusion criteria of the first study and were either negative for *Helicobacter pylori* (*H. pylori*) or underwent *H. pylori* eradication more than 12 months ago. Exclusion criteria were severe heart, renal, or pulmonary failure, liver cirrhosis, severe systemic illness, diabetes mellitus, inflammatory bowel disease, history of gastroduodenal surgery, duodenal ulcer, and recent acute gastroenteritis. Subjects who took non-steroidal inflammatory drugs (NSAIDs), corticosteroids, other immunosuppressive drugs, or anticoagulants were also excluded. Patients with concomitant symptoms of irritable bowel syndrome (IBS) were not excluded. Abdominal symptoms were assessed using the Gastrointestinal Symptom Rating Scale (GSRS).[18]

Sample size. The mean TEER values in patients with FD and healthy volunteers were previously reported as 18.1 and 21.1 Ω cm^2, respectively.[17] These values were applied to the regression line representing the correlation between MA and TEER in the first study and were used to determine that the predicted MA values in patients with FD and healthy subjects were 524.0 and 450.7, respectively. Thus, the difference in MA values between the groups was determined as ∼73. In a pilot study in 10 healthy subjects, the standard deviation (s.d.) of MA was determined as ∼65. Thus, the sample size with a power of 90% and a significance level of 5% was calculated as 18 subjects. Considering a drop rate, a total of 20 subjects were aimed for enrollment in each group.

Statistical analysis. All statistical analyses were performed using JMP 12.0.1 (SAS Institute, Cary, NC, USA). Continuous variables were compared using the unpaired *t*-test, and frequency distributions were compared using the χ^2-test or Fisher's exact test. Pearson's correlation coefficient was used to determine the correlation between MA and TEER or MA and the items in GSRS. *P* values of <0.05 were considered statistically significant.

RESULTS

Correlation between MA and TEER. The characteristics of subjects in the first study are shown in Table 1. Six subjects were female, the mean age was 70.6 ± 10.7 years, and the mean body mass index (BMI) was 23.1 ± 4.1 kg/m^2.

In this study, MA was measured five times in each subject, and the mean s.e. was 39.1. In contrast, TEER was measured in four biopsy samples obtained from each subject, and the mean s.e. was 0.44 Ω cm^2.

The correlation between MA and TEER is shown in Figure 1. The mean MA and TEER values in 23 subjects were 367.5 ± 134.7 and 24.5 ± 3.7 Ω cm^2, respectively. There was a significant negative correlation between MA and TEER ($r=-0.67$, $P=0.0004$, Pearson's correlation coefficient).

Table 1 Characteristics of subjects in the first study

	n **= 23**
Gender, female:male	6:17
Age (years), mean ± s.d. (range)	70.6 ± 10.7 (36–84)
BMI (kg/m^2), mean ± s.d.	23.1 ± 4.1
Diabetes mellitus, *n*	6
Use of low-dose aspirin, *n*	5
Use of NSAIDs, *n*	1
Status of H. pylori infection	
No *H. pylori* infection, *n*	1
History of *H. pylori* eradication, *n*	18
Current *H. pylori* infection, *n*	4

BMI, body mass index; *H. pylori*, *Helicobacter pylori*; NSAID, nonsteroidal anti-inflammatory drug.

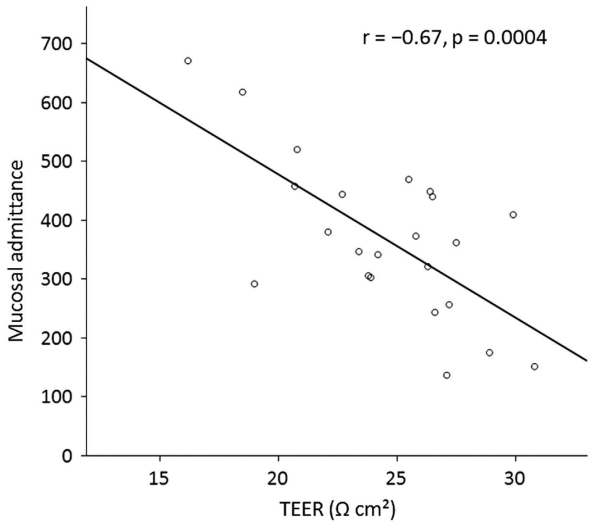

Figure 1 The correlation between mucosal admittance (MA) and transepithelial electrical resistance (TEER) measured in normal-appearing duodenal mucosa in 23 subjects. White dots represent the MA and TEER of each subject. There was a significant negative correlation between MA and TEER ($r = -0.67$, $P = 0.0004$, Pearson's correlation coefficient).

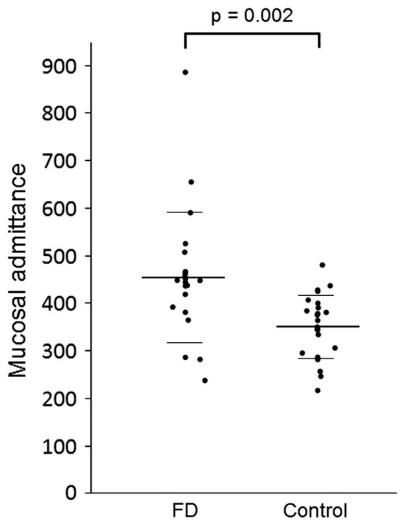

Figure 2 Comparison of mucosal admittance (MA), shown by black dots, among patients with functional dyspepsia (FD) and control subjects. The mean MA was significantly higher in the FD group than that in the control group (455.7 ± 137.3 vs. 352.1 ± 66.9, $P = 0.002$, unpaired *t*-test).

Table 2 Characteristics of patients with functional dyspepsia and control subjects in the second study

	FD ($n = 21$)	Control ($n = 23$)	*P* value
Gender, female:male	15:6	17:6	1.0[a]
Age (years), mean ± s.d.	61.4 ± 14.7	58. 2 ± 14.4	0.5[b]
BMI (kg/m^2), mean ± s.d.	22.4 ± 3.2	22.8 ± 3.9	0.7[b]
Hypertension, *n*	4	4	1.0[a]
Hyperlipidemia, *n*	5	2	0.7[a]
Endoscopic findings of RE, *n*	2	3	1.0[a]
IBS, *n*	8	0	0.001[a]
Medication			
Acid-suppressive therapy, *n*	20	0	< 0.0001[a]
PPIs, *n*	17	0	< 0.0001[a]
H2RAs, *n*	3	0	0.1[a]
Acotiamide, *n*	8	0	0.001[a]
Prokinetic agent, *n*	3	0	0.1[a]
Rikkunshito[c], *n*	4	0	0.04[a]
Probiotics, *n*	2	1	0.6[a]
History of *H. pylori* eradication, *n*	12	8	0.2[a]
Atrophy, closed:open	13:8	17:6	0.5[a]
GSRS, median (range)			
Total	2.5 (1.1–3.6)	1.2 (1.0–2.2)	< 0.0001[d]
Abdominal pain	2.3 (1.0–6.0)	1.0 (1.0–2.3)	< 0.0001[d]
Dyspepsia	2.5 (1.0–4.5)	1.3 (1.0–2.5)	< 0.0001[d]
Acid reflux	2.5 (1.0–3.5)	1.0 (1.0–2.5)	< 0.0001[d]
Diarrhea	2.3 (1.0–5.0)	1.0 (1.0–3.0)	0.0004[d]
Constipation	2.3 (1.0–5.3)	1.0 (1.0–3.0)	0.03[d]

BMI, body mass index; FD, functional dyspepsia; GSRS, gastrointestinal symptom rating scale; *H. pylori*, *Helicobacter pylori*; H2RA, histamine H2-receptor antagonist; IBS, irritable bowel syndrome; PPI, proton pump inhibitor; RE, reflux esophagitis.
[a]Fisher's exact test.
[b]Unpaired *t*-test.
[c]Traditional Japanese medicine.[32]
[d]Wilcoxon's rank-sum test.

Measurement of MA in patients with FD. The characteristics of patients with FD and control subjects are shown in Table 2. There were no significant differences in gender, age, BMI, hypertension, hyperlipidemia, endoscopic findings of reflux esophagitis, history of *H. pylori* eradication, and extent of atrophic gastritis between the groups. The number of subjects who were taking proton pump inhibitors (PPIs), acotiamide, and the traditional Japanese medicine Rikkunshito were statistically higher in the FD group than in the control group ($P < 0.0001$, $P = 0.001$, $P = 0.04$, respectively; Fisher's exact test). The GSRS scores in the FD group were statistically higher than those in the control group for all parameters. In the FD group, 11, 9, and 1 subject was diagnosed with postprandial distress syndrome (PDS), epigastric pain syndrome (EPS), and PDS plus EPS, respectively. In addition, eight subjects had concomitant symptoms of IBS. None of the subjects had post-infectious FD.

MA values of subjects in the FD and control groups are shown in Figure 2. The mean MA in the FD group was significantly higher than that in the control group (455.7 ± 137.3 vs. 352.1 ± 66.9, $P = 0.002$, unpaired *t*-test). The 5th and 95th percentiles of MA values were 241.4 and 862.1, respectively, in the FD group and were 221.9 and 471.2, respectively, in the control group. MA values of five patients with FD were above the 95th percentile of those in healthy subjects. In the FD group, there were no significant differences in MA values according to the FD subtype (PDS, 475.3 ± 150.0; EPS, 434.4 ± 129.5; $P = 0.5$, unpaired *t*-test) and the presence of concomitant IBS symptoms (positive, 431.7 ± 107.6; negative, 470.5 ± 155.1; $P = 0.5$, unpaired *t*-test). In addition, there were no significant correlations between MA and any of the items in the GSRS ($r = -0.29$–0.26, Pearson's correlation coefficient).

The relation between age or gender and MA. No significant difference was observed in the mean MA between 23 subjects

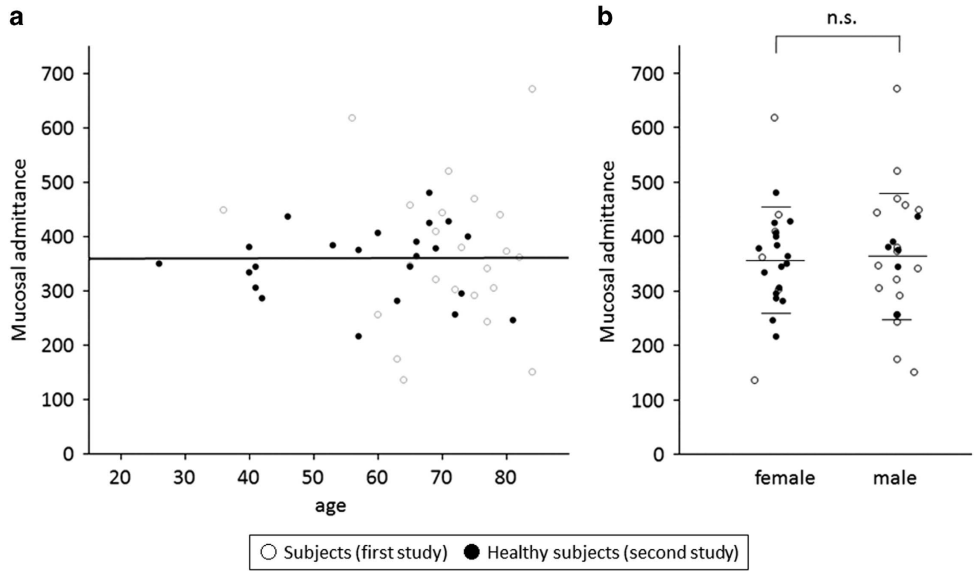

Figure 3 The correlation between mucosal admittance (MA) and (**a**) age or (**b**) gender. White dots represent 23 subjects in the first study, and black dots represent 23 healthy subjects in the second study. (**a**) There was no significant correlation between age and MA ($r = 0.003$, $P = 1.0$, Pearson's correlation coefficient). (**b**) There was no significant difference in the mean MA between females and males (355.7 ± 97.6 vs. 363.8 ± 114.7, $P = 0.8$, unpaired *t*-test).

Table 3 The relation between mucosal admittance and the use of medications

	Use		No use		*P* value
	Number	MA	Number	MA	
Subjects in the first part (n = 23)					
Low-dose aspirin/NSAIDs	6	359.3 (255.8–457.2)	17	361.2 (135.8–670.7)	0.9[a]
Patients with FD (n = 21)					
Acotiamide	8	405.8 (237.0–885.2)	13	447.2 (380.4–654.3)	0.4[a]
Rikkunshito	4	475.3 (418.1–589.8)	17	447.2 (237.0–885.2)	0.5[a]

FD, functional dyspepsia; MA, mucosal admittance; NSAID, nonsteroidal anti-inflammatory drug.
Values were median (range).
[a]Wilcoxon's rank-sum test.

in the first study and 23 healthy subjects in the second study (367.5 ± 134.7 vs. 352.1 ± 66.9, $P = 0.6$, unpaired *t*-test). Moreover, no correlation was observed between MA values and age when we analyzed all subjects excluding patients with FD ($r = 0.003$, $P = 1.0$, Pearson's correlation coefficient; Figure 3a). In addition, no significant difference was observed in the mean MA between females and males (355.7 ± 97.6 vs. 363.8 ± 114.7, $P = 0.8$, unpaired *t*-test; Figure 3b).

The relation between MA and the use of medications. The relation between MA and the use of medications is presented in **Table 3**. In the first study, no significant difference was observed in the mean MA between subjects taking and not taking low-dose aspirin/NSAIDs ($P = 0.9$, Wilcoxon's rank-sum test). In the FD group, no significant differences were observed in the mean MA between patients taking acotiamide and those taking Rikkunshito ($P = 0.4$ and 0.5, respectively, Wilcoxon's rank-sum test).

Safety of measurement of MA. No subject complained of procedure-related symptoms, such as abdominal pain, or any adverse symptoms after the procedure. In addition, no procedure-related complications, such as bleeding requiring hemostasis, perforation, or arrhythmia, were present.

DISCUSSION

Our study showed a significant negative correlation between MA and TEER in the duodenum. Moreover, this was the first study to demonstrate the presence of increased duodenal mucosal permeability in patients with FD during upper endoscopy. Increased mucosal permeability observed in this study was consistent with a previous report showing impaired duodenal mucosal barrier function in patients with FD. Specifically, Vanheel *et al.*[17] used an *ex vivo* approach to reveal reduced TEER and increased paracellular passage in patients with FD compared with healthy volunteers. In addition, they showed that the expression levels of several cell adhesion proteins were altered and that these changes were correlated with the extent of increased permeability and the severity of low-grade inflammation. They suggested that impaired duodenal mucosal integrity could facilitate the

passage of luminal antigens through the epithelium and lead to low-grade inflammation. Several studies also reported duodenal low-grade inflammation in patients with FD, as evidenced by increased number of eosinophils, mast cells, and macrophages in the duodenal mucosa compared with controls.[9–14] These earlier studies, together with our findings, provide support for impaired duodenal mucosal integrity as a pathophysiology underlying FD; however, the exact mechanisms are still not fully understood. The previous results on low-grade duodenal inflammation in post-infectious FD[15] and corticotropin-releasing hormone-increased intestinal permeability[19] suggest that several factors can change the mucosal permeability, which might promote the sensitivity for antigens and low-grade inflammation and lead to the development of FD symptoms. Interestingly, similar findings found in the intestine and cecum in patients with IBS, a common FGID, were considered as part of the disease pathophysiology.[20–23] Therefore, evaluating the gut permeability is critical for further understanding of FGIDs.

Our study only demonstrated increased mucosal permeability in the second part of duodenum, although the extent of increased mucosal permeability in FD and whether the particular part of duodenum is essential for FD are unknown. Therefore, clarifying whether such abnormalities are more globally present is also important for further understanding of the pathophysiology of FD.

In FD, concise and easy evaluation of focal mucosal permeability is needed. Ussing chamber, widely used as an established method to evaluate mucosal permeability, requires biopsy samples and is a moderately complicated procedure for clinical practice. The lactulose/mannitol test, another established approach with the advantage of assessing whole-gut permeability including the intestine, cannot evaluate focal changes in gut permeability. Importantly, our results demonstrated that MA measurement in duodenum via catheterization during upper endoscopy was comparable to the Ussing chamber method and showed that patients with FD had higher duodenal MA. Moreover, another important finding of this study was that the contribution of age and gender to duodenal MA were limited. Considering the chronic, fluctuating,[24] and multifactorial[4–17] characteristics of FD, this easy and real-time evaluation of duodenal mucosal permeability should be beneficial for further understanding of FD.

Although the evidence for the efficacy of this method is limited, two previous studies support its utility. One study revealed increased epithelial permeability of middle ear cholesteatoma compared with the post-auricular skin and external auditory canal skin using MA measurement with catheterization and concluded that the difference was at least partially dependent on the difference of tight junction protein expression.[25] Another study revealed that the electrical impedance of skin, which was calculated from the values measured by this method, was higher than those of the nasal turbinate and nasal polyps and that *claudin-1* mRNA levels paralleled electrical impedance values.[26] Although we did not evaluate the expression of tight junction proteins in this study, increased MA in patients with FD was likely caused by decreased expression of tight junction proteins, based on a previous study by Vanheel *et al.*[17]

The present study did not show significant correlations between MA and any of the items in the GSRS, which was consistent with a previous study, although the authors in the previous study emphasized the necessity of further investigation to confirm this outcome.[17] We predicted that increased duodenal mucosal permeability was related to the development or maintenance of FD symptoms to a certain degree, and a correlation between permeability and symptom severity remains possible based on previous reports demonstrating the correlation between intestinal permeability and IBS severity score in patients with IBS.[22,23,27] However, this potential outcome is challenging to demonstrate as symptom severity might be affected by multiple factors including subjective reporting. Further, the absence of well-established questionnaires similar to those used for IBS severity scoring system[28] hinders proper evaluation of FD severity.

The present study did not evaluate whether MA measurement can differentiate FD from other similar presentation; however, we evaluated duodenal MA in 12 patients of our preliminary data who were referred for upper endoscopy for gastroesophageal reflux disease (GERD) symptoms (e.g., reflux, regurgitation, etc.) irrespective of whether they were taking PPIs and who had no endoscopic findings of reflux esophagitis. The mean duodenal MA was significantly lower in patients with GERD symptoms than in the FD group (360.1 ± 101.4 vs. 455.7 ± 137.3, $P = 0.02$, unpaired *t*-test), and no significant difference was observed in the mean MA between patients with GERD symptoms and the control group (360.1 ± 101.4 vs. 352.1 ± 66.9, $P = 0.8$, unpaired *t*-test; **Supplementary Figure 1** online). No significant differences were observed in gender, age, BMI, hypertension, hyperlipidemia, history of *H. pylori* eradication, and extent of atrophic gastritis between the groups, albeit the number of patients taking PPIs was significantly higher in the FD group and patients with GERD symptoms than in the control group ($P < 0.01$ and $P < 0.01$, respectively; **Supplementary Table 1**). These results suggest that MA measurement helps differentiate FD from other similar presentation, and the impact of PPIs on the duodenal mucosa is limited. Further refinements are expected to confirm whether MA measurement could be a potential biomarker for FD.

The major limitation of this study was the high frequency of FD-related medication use by patients with FD at the time of enrollment, albeit their limited therapeutic effects on gastrointestinal symptoms for subjects included in the study. The frequency of subjects who received acid suppressive therapy, particularly PPIs, was significantly higher in the FD group than in the control group. PPIs are one of the therapeutic options for FD that were found to provide symptomatic relief.[29,30] In contrast, a previous study reported that esomeprazole, a PPI, induced upper gastrointestinal tract transmucosal permeability.[31] Relevant to this study, Vanheel *et al.*[17] reported that the difference in TEER between patients with FD and healthy volunteers remained significant after correction for several potentially confounding factors including acid-suppressive therapy. In addition, Walker *et al.*[10] reported that the mean duodenal eosinophil count and prevalence of duodenal eosinophilia were significantly higher in patients with PDS than those without prominent upper gastrointestinal symptoms, which did not show a significant association with PPI use. These results, together

with our findings described in the discussion, suggested that the impact of PPIs on the duodenal mucosa was limited compared with the changes occurring because of FD. Moreover, no significant difference was observed in MA among subjects taking and not taking medications such as low-dose aspirin/NSAIDs, acotiamide, or Rikkunshito. The impact of FD-related medications and low-dose aspirin /NSAIDs on the duodenal mucosa was limited in this study, although the number of subjects were small. The therapeutic effects of FD-related medications on increased duodenal mucosal permeability should be investigated in a future study.

In conclusion, we demonstrated a significant negative correlation between MA and TEER in duodenum and found that duodenal mucosal permeability was increased in patients with FD using real-time measurement of MA by catheterization during upper endoscopy.

CONFLICT OF INTEREST

Guarantor of the article: Makoto Arai, MD, PhD.
Specific author contributions: Hideaki Ishigami designed the study, conducted the experiment, collected data, analyzed and interpreted data, and wrote the manuscript. Tomoaki Matsumura and Makoto Arai designed the study, analyzed and interpreted data, and assisted in writing the manuscript. Shingo Kasamatsu, Shinsaku Hamanaka, Takashi Taida, Kenichiro Okimoto, Keiko Saito, Shoko Minemura, and Daisuke Maruoka assisted in conducting the experiment and collecting data. Tomoo Nakagawa and Tatsuro Katsuno designed the study. Mai Fujie assisted in interpreting data and writing the manuscript. All authors have approved the final version of the manuscript.
Financial support: None.
Potential competing interests: None.

Study Hightlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The pathophysiology of functional dyspepsia (FD) is considered to be complex and multifactorial.
- ✓ Increased duodenal mucosal permeability and low-grade inflammation were observed in patients with FD.
- ✓ A standard method to evaluate duodenal mucosal permeability requires biopsy samples and *ex vivo* evaluation.

WHAT IS NEW HERE

- ✓ An endoscopy-guided, catheter-based conductance meter could evaluate duodenal mucosal permeability in real-time.
- ✓ Duodenal mucosal permeability determined with the new catheterization method correlated with that determined by the Ussing chamber method.
- ✓ Increased duodenal permeability in FD was demonstrated during upper endoscopy.

TRANSLATIONAL IMPACT

- ✓ The easy and real-time evaluation of mucosal permeability is beneficial for understanding one of the pathophysiologies underlying FD.

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