Endoscopy-Guided Evaluation of Duodenal Mucosal Permeability in Functional Dyspepsia

Hideaki Ishigami, MD, PhD1, Tomoaki Matsumura, MD, PhD1, Shingo Kasamatsu, MD, PhD1, Shinsaku Hamanaka, MD, PhD1, Takashi Taida, MD, PhD1, Kenichiro Okimoto, MD, PhD1, Keiko Saito, MD, PhD1, Shoko Minemura, MD, PhD1, Daisuke Maruoka, MD, PhD1, Tomoo Nakagawa, MD, PhD1, Tatsuro Katsuno, MD, PhD1, Mai Fujie, CE2 and Makoto Arai, MD, PhD1

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 ± 3.7 Ω cm², 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.

Clinical and Translational Gastroenterology (2017) 8, e83; doi:10.1038/ctg.2017.12; published online 6 April 2017

Subject Category: Functional GI Disorders

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 gastro-duodenal 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,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

1Department of Gastroenterology and Nephrology, Graduate School of Medicine, Chiba University, Chiba-City, Japan and 2Clinical Engineering Center, Chiba University Hospital, Chiba-City, Japan

Correspondence: Makoto Arai, MD, PhD, Department of Gastroenterology and Nephrology, Graduate School of Medicine, Chiba University, Inohana 1-8-1, Chiba-City 260-8670, Japan. E-mail: araim-cib@umin.ac.jp

Received 26 September 2016; accepted 21 February 2017
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 cm². 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 O₂/CO₂ (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 cm². 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 cm², 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 χ²-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/m². 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 cm².

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 cm², 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

| Gender, female:male | 6:17 |
|---------------------|------|
| Age (years), mean ± s.d. (range) | 70.6 ± 10.7 (36–84) |
| BMI (kg/m²), 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 | 18 |
| 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.
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).

**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 ± 150.0; EPS, 434.4 ± 129.5; $P = 0.5$, unpaired $t$-test) and the presence of concomitant IBS syndrome (positive, 431.7 ± 107.6; negative, 470.5 ± 155.1; $P = 0.6$, 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.

**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       |
| Age (years), mean ± s.d.| 61.4 ± 14.7  | 58.2 ± 14.4       | 0.5       |
| BMI (kg/m²), mean ± s.d.| 22.4 ± 3.2   | 22.8 ± 3.9        | 0.7       |
| Hypertension, $n$       | 4            | 4                 | 1.0       |
| Hyperlipidemia, $n$     | 5            | 2                 | 0.7       |
| Endoscopic findings of  | 2            | 3                 | 1.0       |
| RE, $n$                 | 8            | 0                 | 0.001     |
| IBS, $n$                | 8            | 0                 |           |
| Medication              |              |                   |           |
| Acid-suppressive        | 20           | 0                 | <0.0001   |
| therapy, $n$            |              |                   |           |
| PPIs, $n$               | 17           | 0                 | <0.0001   |
| Acotiamide, $n$         | 8            | 0                 | 0.001     |
| Prokinetic agent, $n$   | 3            | 0                 | 0.1       |
| Probiotics, $n$         | 4            | 0                 | 0.04      |
| History of *H. pylori*  | 12           | 8                 | 0.2       |
| eradication, $n$        |              |                   |           |
| Atrophy, closed: open   | 13.8         | 17.6              | 0.5       |
| GSRS, median (range)    |              |                   |           |
| Total                   | 2.5 (1.1–3.6)| 1.2 (1.0–2.2)     | <0.0001   |
| Abdominal pain          | 2.3 (1.0–6.0)| 1.0 (1.0–2.3)     | <0.0001   |
| Acid reflux             | 2.5 (1.0–3.5)| 1.0 (1.0–2.5)     | <0.0001   |
| Diarrhea                | 2.3 (1.0–5.0)| 1.0 (1.0–3.0)     | 0.0004    |
| Constipation            | 2.3 (1.0–5.3)| 1.0 (1.0–3.0)     | 0.03      |

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.

$^d$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

| Use | Number | MA Number | MA | \( P \) value |
|-----|--------|-----------|----|-------------|
| Subjects in the first part (n = 23) | Low-dose aspirin/NSAIDs | 6 | 399.3 (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.
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 FD15 and corticotropin-releasing hormone-increased intestinal permeability19 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 multifactorial13–17 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.22–27 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 system11 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 control 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 was 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 Shingo Kasamatsu, Shinsaku Hamanaka, Takashi Taida, interpreted data, and assisted in writing the manuscript. Daisuke Maruoka assisted in conducting the experiment and Kenichiro Okimoto, Keiko Saito, Shoko Minemura, and Shingo Kasamatsu, Shinsaku Hamanaka, Takashi Taida, interpreted data, and assisted in writing the manuscript. Tomoo Nakagawa and Tatsuro Katsuno assisted in interpreting data 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 Highlights

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 interpretation 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 pathophysologies underlying FD.

1. Aro P, Talley NJ, Roininen J et al. Anxiety is associated with uninvestigated and functional dyspepsia (Rome III criteria) in a Swedish population-based study. Gastroenterology 2013; 144: 94–100.
2. Kaj M, Fujikawa Y, Shibata M et al. Prevalence of overlaps between GERD, FD and IBS and impact on health-related quality of life. J Gastroenterol Hepatol 2010; 25: 1151–1156.
3. Stanghellini V, Chan F, Hauser WL et al. Gastrointestinal disorders. Gastroenterology 2016; 150: 1380–1392.
4. Tack J, Pessevaux H, Coull B et al. Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology 1998; 115: 1346–1352.
5. Lemann M, Dederding JP, Florrie B et al. Abnormal perception of visceral pain in response to gastric dilation in chronic idiopathic dyspepsia. The irritable stomach syndrome. Dig Dis Sci 1991; 36: 1249–1254.
6. Oshima T, Okugawa T, Tomita T et al. Generation of dyspeptic symptoms by direct acid and water infusion into the stomachs of functional dyspepsia patients and healthy subjects. Aliment Pharmacol Ther 2012; 36: 1282–1292.
7. Samson M, Verhagen MA, van Berge Henegouwen GP et al. Abnormal clearance of exogenous acid and increased acid sensitivity of the proximal duodenum in dyspeptic patients. Gastroenterology 1999; 116: 515–520.
8. Hamm J, Fuhrer M, Papil L et al. Hypersensitivity for capsaicin in patients with functional dyspepsia. Neurogastroenterol Motil 2002; 14: 89–96.
9. Talley NJ, Walker MM, Aro P et al. Non- ulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. Clin Gastroenterol Hepatol 2007; 5: 1175–1183.
10. Walker MM, Talley NJ, Prabhakar M et al. Duodenal mastocytosis, eosinophilia and intraepithelial lymphocytosis as possible disease markers in the irritable bowel syndrome and functional dyspepsia. Aliment Pharmacol Ther 2009; 29: 765–773.
11. Walker MM, Salehian SS, Murray CE et al. Implications of eosinophilia in the normal duodenal biopsy—an association with allergy and functional dyspepsia. Aliment Pharmacol Ther 2010; 31: 1229–1236.
12. Kindt S, Tertychnyy A, de Hertogh G et al. Intestinal immune activation in presumed post-infectious functional dyspepsia. Neurogastroenterol Motil 2009; 21: 832–856.
13. Futagami S, Shindo T, Kawagoe T et al. Migration of eosinophils and CCR2/CCL8-mediated positive cells into the duodenal mucosa of patients with postinfectious functional dyspepsia. Am J Gastroenterol 2010; 105: 1835–1842.
14. Critto C, Beissias T, Desmet AS et al. Evidence for neuronal and structural changes in submucous ganglia of patients with functional dyspepsia. Am J Gastroenterol 2015; 110: 1205–1215.
15. Tack J, Demedts I, Dehondt G et al. Clinical and pathophysiological characteristics of post-infectious functional dyspepsia. Gastroenterology 2002; 122: 1738–1747.
16. Hu WH, Wong WM, Lam CL et al. Anxiety but not depression determines health care-seeking behavior in Chinese patients with dyspepsia and irritable bowel syndrome: a population-based study. Aliment Pharmacol Ther 2002; 16: 2081–2088.
17. Vanheel H, Viciano M, Vanuytsel T et al. Impaired duodenal mucosal integrity and low-grade inflammation in functional dyspepsia. Gut 2014; 63: 265–271.
18. Svedlund J, Sjodin I, Dotevall G. GSR—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci 1988; 33: 129–134.
19. Vanuytsel T, van Wamoo S, Vanheel H et al. Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. Gut 2014; 63: 1299–1309.
20. Zhou Q, Souba WW, Croce CM et al. MicroRNA-29a regulates intestinal membrane permeability in patients with irritable bowel syndrome. Gut 2010; 59: 775–784.
21. Martinez C, Viciano M, Ramos L et al. The jejunum of diarrhea-predominant irritable bowel syndrome shows molecular alterations in the tight junction signaling pathway that are associated with mucosal pathobiology and clinical manifestations. Am J Gastroenterol 2012; 107: 736–746.
22. Martinez C, Lobo B, Pigrau M et al. Diarrhoea-predominant irritable bowel syndrome: an organic disorder with structural abnormalities in the jejunal epithelial barrier. Gut 2013; 62: 1160–1168.
23. Vellis-Nebot M, Frin-Mathy G, Bizoueche H et al. Functional bowel symptoms in quiescent inflammatory bowel diseases: role of epithelial barrier disruption and low-grade inflammation. Gut 2014; 63: 744–752.
24. Olszewska LB, Guidjones H, Jonsdottir HH et al. Natural history of functional gastrointestinal disorders: comparison of two longitudinal population-based studies. Dig Liver Dis 2012; 44: 211–217.
25. Koizumi H, Suzuki H, Ohbuchi T et al. Increased permeability of the epithelium of middle ear cholesteatoma. Clin Otolaryngol 2015; 40: 106–114.
26. Suzuki H, Koizumi H, Ikezaki S et al. Electrical impedance and expression of tight junction components of the nasal turbinates and polyp. ORL J Otorhinolaryngol Relat Spec 2016; 78: 16–25.
27. Vellis-Nebot M, Dainese R, Amry R et al. Combination of allergic factors can worsen diarrheic irritable bowel syndrome: role of barrier defects and mast cells. Am J Gastroenterol 2012; 107: 75–81.
28. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997; 11: 395–402.
29. Veldhuyzen van Zanten SJ, Chiba N, Armstrong D et al. A randomized trial comparing omeprazole, ranitidine, cisapride, or placebo in Helicobacter pylori negative, primary care patients with dyspepsia: the CADET-HN Study. Am J Gastroenterol 2005; 100:1477–1488.

30. Iwakiri R, Tominaga K, Furuta K et al. Randomised clinical trial: rabeprazole improves symptoms in patients with functional dyspepsia in Japan. Aliment Pharmacol Ther 2013; 38:729–740.

31. Mullin JM, Valenzano MC, Whitby M et al. Esomeprazole induces upper gastrointestinal tract transmucosal permeability increase. Aliment Pharmacol Ther 2008; 28:1317–1325.

32. Arai M, Matsumura T, Tsuchiya N et al. Rikkunshito improves the symptoms in patients with functional dyspepsia, accompanied by an increase in the level of plasma ghrelin. Hepatogastroenterology 2012; 59:62–66.

Supplementary Information accompanies this paper on the Clinical and Translational Gastroenterology website (http://www.nature.com/ctg)