

Postprandial Symptoms Felt at the Lower Part of the Epigastrium and a Possible Association of Pancreatic Exocrine Dysfunction with the Pathogenesis of Functional Dyspepsia

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Abstract

Objective In symptom-dependent diseases such as functional dyspepsia (FD), matching the pattern of epigastric symptoms, including severity, kind, and perception site, between patients and physicians is critical. Additionally, a comprehensive examination of the stomach, duodenum, and pancreas is important for evaluating the origin of such symptoms.

Methods FD-specific symptoms (epigastric pain, epigastric burning, early satiety, and postprandial fullness) and other symptoms (regurgitation, nausea, belching, and abdominal bloating) as well as the perception site of the above symptoms were investigated in healthy subjects using a new questionnaire with an illustration of the human body. A total of 114 patients with treatment-resistant dyspeptic symptoms were evaluated for their pancreatic exocrine function using N-benzoyl-L-tyrosyl-p-aminobenzoic acid.

Results A total of 323 subjects (men:women, 216:107; mean age, 52.1 years old) were initially enrolled. Most of the subjects felt the FD-specific symptoms at the epigastrium, while about 20% felt them at other abdominal sites. About 30% of expressed as epigastric symptoms were FD-nonspecific symptoms. At the epigastrium, epigastric pain and epigastric burning were mainly felt at the upper part, and postprandial fullness and early satiety were felt at the lower part. The prevalence of patients with pancreatic exocrine dysfunction was 71% in the postprandial fullness group, 68% in the epigastric pain group, and 82% in the diarrhea group.

Conclusion We observed mismatch in the perception site and expression between the epigastric symptoms of healthy subjects and FD-specific symptoms. Postprandial symptoms were often felt at the lower part of the epigastrium, and pancreatic exocrine dysfunction may be involved in the FD symptoms, especially for treatment-resistant dyspepsia patients.

Key words: functional dyspepsia, upper gastrointestinal symptoms, pictogram, pancreatic exocrine secretion

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Introduction

Functional dyspepsia (FD) is a chronic disease that is frequently encountered in everyday clinical practice and is characterized by four epigastric symptoms: epigastric pain,

epigastric burning, early satiety, and postprandial fullness (1). Various brain-gut-derived factors are involved in the pathology of FD: anxiety and depression, low-grade mucosal inflammation, gastric acid secretion, and autonomic nervous system abnormalities. These factors cause gastrointestinal motility dysfunction and visceral hypersensitivity,

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which result in upper abdominal symptoms (2). Therefore, acid suppressants, prokinetics, antidepressants, anti-anxiety drugs, and herbal medicines are often used as the standard treatment of FD. However, these treatments are effective in only about 40-50% of FD patients, and some patients are treatment-resistant (3, 4).

Under the Rome IV diagnostic criteria for FD, the above epigastric symptoms occur at the epigastrium, defined as the region between the umbilicus and lower end of the sternum and marked by the midclavicular lines. The Rome IV criteria for an FD diagnosis indicate that both postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS) are food-related symptoms. In addition to four FD-specific symptoms, abdominal bloating, nausea, and belching are also recognized as symptoms of FD. Therefore, symptoms that can occur at sites other than the epigastrium may be perceived as epigastric symptoms. Additionally, numerous clinical studies have indicated that FD shows a high incidence of other concomitant functional gastrointestinal disorders (FGIDs), such as gastroesophageal reflux disease (GERD) and irritable bowel syndrome (IBS) (5). As such, some patients may develop resistance to treatment due to a mismatch in understanding between the patient and the physician regarding the details of the upper abdominal symptoms, the body site at which the symptoms are experienced, and the proper clinical diagnosis.

The pancreas sits adjacent to the stomach and duodenum in the epigastrium. The pancreas has endocrine-exocrine functions that are involved in metabolism, digestion, and absorption and plays important roles in lipid metabolism. Pancreatic damage due to chronic pancreatitis or pancreatic cancer is well known to be capable of causing various symptoms, such as indigestion, abdominal pain, abdominal bloating, and diarrhea (6). In patients with FD, eating a high-fat meal strongly induces nausea, abdominal pain, and abdominal bloating, and both fasting and postprandial cholecystikinin (CCK) levels are high (7). We have also shown that the indigestion score of the Gastrointestinal Symptom Rating Scale was high in patients with FD (8). Therefore, the upper abdominal symptoms at the epigastrium may result from functional disorders of the adjacent pancreas as well as the stomach and duodenum.

In this study, we performed a two-part investigation taking into account the above background. In Study 1, subjects who underwent health examinations were investigated to determine what kind of upper abdominal symptoms they felt and where they felt those symptoms using a new questionnaire with an illustration of the human body. Notably, we divided the epigastrium into upper and lower parts. In Study 2, patients with chronic dyspepsia who showed resistance to standard treatments had their pancreatic exocrine function evaluated using the N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) test.

Materials and Methods

Subjects & patients

For Study 1, the subjects were 323 employees (216 men, mean age: 53 years old; 107 women, mean age: 50 years old) who underwent their annual periodic company general health examination between April and October of 2013. They were asked to describe any upper abdominal symptoms using a newly created questionnaire including an illustration of the human body (Naniwa scale, Fig. 1).

For Study 2, 114 outpatients (41 men, mean age: 59 years old; 73 women, mean age: 54 years old) with treatment-resistant dyspeptic symptoms at our hospital between 2007 and 2013 were included. They had no organic disease of the esophagoduodenal tract based on prior and present examinations of computed tomography (CT) and esophagoduodenoscopy. Treatment-resistant dyspeptic symptoms were defined as having dyspepsia that did not improve and was resistant to the initial treatments recommended in the Japanese Society of Gastroenterology's 2014 Functional Gastrointestinal Disorder Guidelines (i.e. acid suppressants, prokinetics) and also resistant to secondary treatments (e.g. antidepressants, anti-anxiety drugs, herbal medicines) (9). They were classified into three groups based on their dominant symptom: a postprandial fullness group, an epigastric pain group, and these symptoms accompanied with diarrhea group. In the previous report, the epigastric symptoms occurred within 30 minutes after a meal in FD patients (10). Therefore, we distinguished meal-related epigastric symptoms from meal-unrelated symptoms according to the above criteria by an interview.

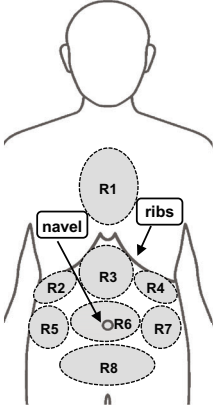
Evaluation of upper abdominal symptoms: Naniwa scale

Eight symptoms that had been experienced in the previous week were established: four FD-specific symptoms (epigastric pain, epigastric burning, early satiety, and postprandial fullness) and four other upper abdominal symptoms (regurgitation, nausea, belching, and abdominal bloating). To evaluate each symptom and its site based on the patient's awareness and severity, we created a new self-completed questionnaire, named as the Naniwa scale, which includes an illustration clearly depicting the abdominal regions and detailed descriptions of the symptoms (Fig. 1). The illustration depicted eight abdominal regions as follows: the sternum (No. 1), right hypochondrium (No. 2), left hypochondrium (No. 4), right flank (No. 5), left flank (No. 7), lower abdomen (No. 8); in addition, the epigastric region based on the Rome IV criteria was divided into two parts: the upper part (No. 3) and the lower part (No. 6). The severity of the symptoms was graded using a 7-point Likert scale as follows: 1, none; 2, aware of symptoms, but can easily ignore them; 3, mild symptoms that are easily tolerated; 4, moderate symptoms but not influencing the daily activities; 5,

A self-writing part of the new questionnaire (Naniwa Scale)

	symptoms past one week recently	degree	region
1	Have you ever been bothered by pain in the area of your stomach? Stomach pain means any kind of pain felt in the solar plexus (immediately below the lower end of the bone in the middle of the chest).	1 2 3 4 5 6 7	① ② ③ ④ ⑤ ⑥ ⑦ ⑧
2	Have you ever been bothered by a burning sensation in the area of your stomach? Burning sensation means a hot, searing feeling in the stomach area (solar plexus).	1 2 3 4 5 6 7	① ② ③ ④ ⑤ ⑥ ⑦ ⑧
3	Have you ever been bothered by a problem of gastric acid reflux? Gastric acid reflux means a feeling that a sour or bitter fluid comes up in your throat from your stomach.	1 2 3 4 5 6 7	① ② ③ ④ ⑤ ⑥ ⑦ ⑧
4	Have you ever been bothered by your stomach becoming full immediately (early satiety)? Stomach becomes full immediately (early satiety) means that you become full immediately after starting to eat, and you cannot eat all of your food.	1 2 3 4 5 6 7	① ② ③ ④ ⑤ ⑥ ⑦ ⑧
5	Have you ever been bothered by nausea?	1 2 3 4 5 6 7	① ② ③ ④ ⑤ ⑥ ⑦ ⑧
6	Have you ever been bothered by belching?	1 2 3 4 5 6 7	① ② ③ ④ ⑤ ⑥ ⑦ ⑧
7	Have you ever been bothered by a heavy stomach feeling? A heavy stomach feeling is when, for several hours after a meal, your stomach feels heavy, or it feels like the food is remaining in your stomach.	1 2 3 4 5 6 7	① ② ③ ④ ⑤ ⑥ ⑦ ⑧
8	Have you ever been bothered by having a bloated feeling around your stomach? A bloated feeling around the stomach means that, unrelated to a meal, it feels like the stomach is filled with gas and is distended.	1 2 3 4 5 6 7	① ② ③ ④ ⑤ ⑥ ⑦ ⑧

↓



Please select number of abdominal region that you mainly feel symptoms

Figure 1. The Naniwa scale. The Naniwa scale is a self-completed questionnaire including an illustration of the human body that enables confirmation of the frequency, region, and degree of eight upper abdominal symptoms.

moderate-to-severe symptoms that occasionally limit the daily activities; 6, severe symptoms that often limit the daily activities; and 7, very severe symptoms often requiring rest.

N-benzoyl-*L*-tyrosyl-*p*-aminobenzoic acid (BT-PABA) test

The BT-PABA test was used to evaluate the subjects' pancreatic exocrine function. The reasons for exclusion were renal dysfunction, liver cirrhosis, a history of acute pancreatitis based on history taking and/or laboratory findings, or suspicion of chronic pancreatitis. In brief, urine was collected early in the morning with the patient in a fasted state and used as the control. The patients then ingested 500 mg of BT-PABA (Eizai Co., Ltd., Tokyo, Japan) with 200 mL of water. The urinary PABA excretion rate over the following 6 hours was used to evaluate the pancreatic exocrine function. Pancreatic exocrine dysfunction was diagnosed using a cut-off value of 70%.

Statistical analyses

The data were expressed as the mean \pm standard deviation. The age, abdominal circumference, and body mass index were compared using the Mann-Whitney U test. Current smoking status, alcoholic habit, and sex were compared using the χ^2 test. The level of significance was set at $p < 0.05$. The statistical analyses were performed using the SPSS version 16.0J software package (SPSS, Chicago, USA).

Results

Study 1

Background characteristics of subjects

About 50% of both the men and women were aware of some kind of upper abdominal symptom. The common symptoms were epigastric pain (men, 47.2%; women, 53.6%), postprandial fullness (men, 52%; women, 60.7%), regurgitation (men, 45.5%; women, 28.6%), and abdominal bloating (men, 29.3%; women, 26.8%) (Table 1). The respective incidences of other FD-specific symptoms (epigastric burning and early satiety) were relatively low (Table 1).

Perception of the abdominal site of FD-specific symptoms

The FD-specific symptoms felt at the whole epigastrium (Nos. 3+6) showed the following rates: epigastric pain (men, 60.7%; women, 86.7%), epigastric burning (men, 76.9%; women, 85.7%), early satiety (men, 70%; women, 85.7%), and postprandial fullness (men, 86.9%; women, 86.2%) (Fig. 2). However, the above four FD-specific symptoms were also felt at other abdominal sites, especially in men. The most common site of these symptoms outside of the epigastrium was the sternum (No. 1), especially in women (Fig. 2).

Table 1. Demographic Characteristics and Upper Gastrointestinal Symptoms in the Healthy Subjects.

	Male (n=216)	Female (n=107)
Background		
Mean age (years)	53.3±9.3	49.8±9.0*
Mean BMI (kg/m ²)	24.4±3.2	20.9±3.3*
Waist circumference (cm)	87.3±9.7	77.7±7.2*
Current smoking (%)	37	2.8*
Alcoholic consumption (%)	79.2	49.5*
Upper gastrointestinal symptoms (%)		
epigastric pain	47.2	53.6
epigastric burning	22.0	14.3
regurgitation	45.5	28.6
early satiety	13.8	30.4
nausea	19.5	17.9
belching	17.9	17.9
postprandial fullness	52.0	60.7
abdominal bloating	29.3	26.8

BMI: Body mass index

Data are expressed as mean±SD or frequency (%)

*p<0.01 compared to male

Abdominal symptoms at the epigastrium

The abdominal symptoms felt at the epigastrium were epigastric pain, 26.9%; epigastric burning, 10.7%; early satiety 5.6%; postprandial fullness, 27.8%; and other symptoms, 29% (regurgitation, 6.8%; nausea, 4.7%; belching, 3.8%; abdominal bloating, 13.7%) (Fig. 3A). To examine the differences in the rates of FD-symptoms based on the portion of the epigastrium, we examined the incidence of EPS and PDS symptoms in the upper (No. 3) and lower parts (No. 6) of the epigastrium. In the upper part, the incidence of EPS and PDS symptoms was 58.5% and 41.5%, respectively (Fig. 3B). In contrast, in the lower part, the incidence of EPS and PDS symptoms was 29.0% and 71.0%, respectively (Fig. 3C).

Study 2

Background characteristic of patients with treatment-resistant dyspeptic symptoms

The 114 patients with treatment-resistant dyspeptic symptoms was classified into three groups according to the predominant complaints: postprandial fullness group (men:women, 21:21; mean age, 60.7 years old), epigastric pain group (men:women, 14:42; mean age, 51.4 years old), and diarrhea group (men:women, 6:10; mean age, 58.4 years old). The epigastric pain group included more women and was younger on the whole than the other groups (Table 2).

Pancreatic exocrine function in the treatment-resistant patients

The mean BT-PABA value was 65.4% in the postprandial fullness group, 62.9% in the epigastric pain group, and 60.5% in the diarrhea group. The percentage of patients with pancreatic exocrine dysfunction (PFD <70%) was 71.4% in the postprandial fullness group, 69.6% in the epi-

gastric pain group, and 81.3% in the diarrhea group (Table 2).

Discussion

The diagnosis and treatment of FGIDs are mainly based on the patient-reported outcomes. Therefore, the subjective impression (complaint from patients) should be matched to the information objectively received by physicians. However, in everyday clinical practice, it is difficult to differentiate between FD and non-erosive reflux disease merely by interviewing patients, and this difficulty may interfere with the assessment of treatments. Furthermore, the agreement between the physician and the patient in their assessment of the severity of symptoms is reportedly poor (11). Therefore, we first investigated how healthy workers recognize the kinds and sites of symptoms felt in the epigastrium using a newly created questionnaire including an illustration of the human body (Naniwa scale). The present results showed that epigastric pain and postprandial fullness were common epigastric symptoms, while the prevalence of other FD-specific symptoms was low. Conversely, some subjects recognized FD-nonspecific symptoms (regurgitation, nausea, belching, and abdominal bloating) as epigastric symptoms. While we do not know why some subjects mistook their symptoms, these results indicate that the understanding of symptom type can be quite vague in some subjects. It may be difficult for the Japanese general population to understand unfamiliar phrases like “epigastric burning” and “early satiety”. Therefore, subjects who feel these symptoms may select more familiar words, such as “epigastric pain” or “postprandial fullness”.

In some subjects, their perception of the site of FD-specific symptoms (epigastric pain, epigastric burning, early satiety, and postprandial fullness) did not completely match with the epigastrium. The most frequently mismatched body site was the sternum (No. 1). However, regurgitation (Naniwa scale, question #3) was almost always felt in the sternum (site #1 in the illustration) in the present study (data not shown). Although we did not know the reason of this difference between FD-specific symptoms and regurgitation felt at the sternum, such confusion may indicate the difficulty in differentiating viscerally referred symptoms in the general population.

We also noted some differences in the perception of the site of FD-specific symptoms between men and women, a discrepancy which may be due to sexual differences, as sex-based differences in the regional activation site after pain stimulation have been reported (12). Thus, it is important to confirm details regarding the kind and sites of symptoms using a questionnaire with an illustration. In a previous study, the combined use of a questionnaire with pictograms that clearly explained epigastric symptoms was reported to improve the agreement between the physician's evaluation of symptoms and FD patients' complaints compared with using a questionnaire alone (13). While the above questionnaire is

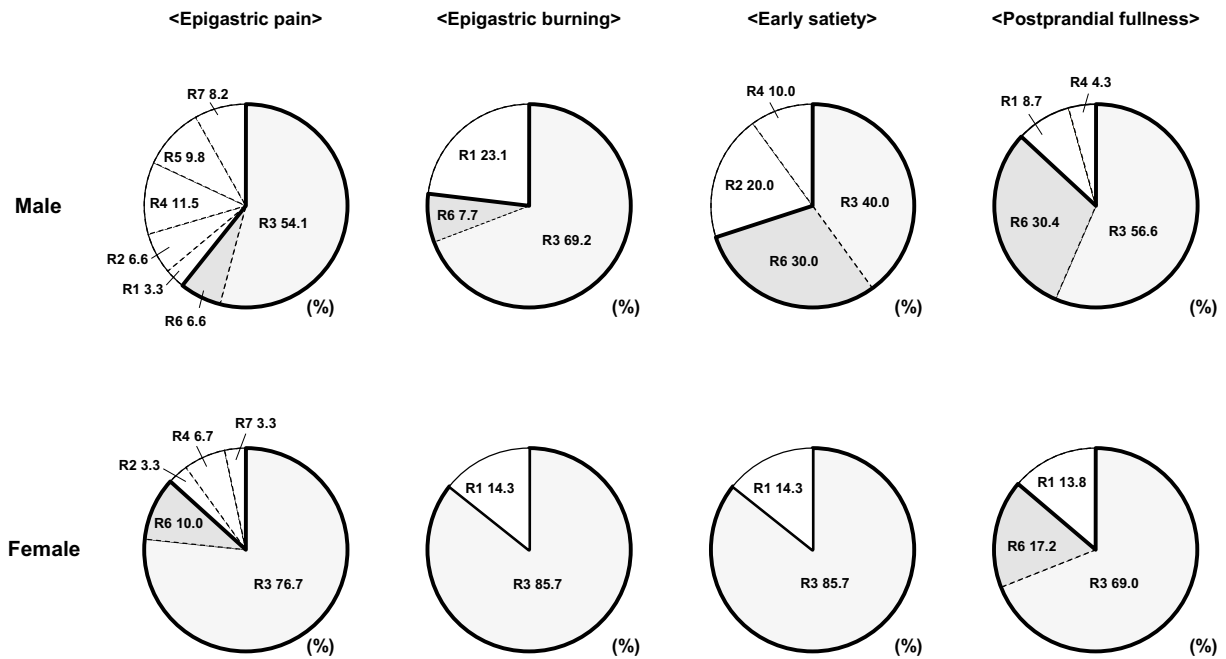


Figure 2. The perception of the abdominal site of FD-specific symptoms. The pie chart shows the rates of perception among healthy subjects of the abdominal site of FD-specific symptoms using the body illustration. Upper panel: men, lower panel: women

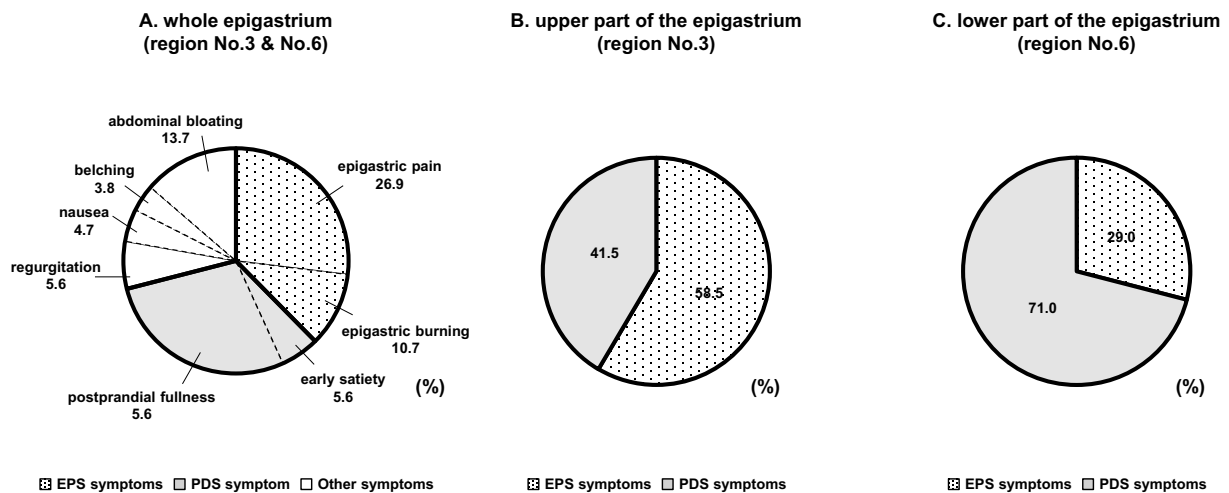


Figure 3. The abdominal symptoms at the epigastrium: whole (A), upper part (B), and lower part (C). The pie chart (A) shows the rate of upper abdominal symptoms felt at the whole epigastrium (Nos. 3+6) among healthy subjects. The pie charts show the rates of postprandial distress syndrome (PDS), including postprandial fullness and early satiety, and epigastric pain syndrome (EPS), including epigastric pain and epigastric burning, in the upper part (No. 3) (B) and lower part (No. 6) (C) of the epigastrium.

useful for distinguishing various upper abdominal symptoms, the Naniwa scale is useful for distinguishing the perception sites of those upper abdominal symptoms.

When the epigastrium was divided into upper and lower parts, many subjects reported experiencing EPS symptoms in the upper part of the epigastric region (No. 3), while many PDS symptoms were felt in the lower part (No. 6). These findings suggest that FD symptoms were caused by gastroduodenal functional disorders (acid secretion and gastroduodenal motility), especially EPS symptoms. However,

PDS-type FD is generally meal-related dyspepsia. Therefore, the digestive tract function known as “digestion” and the manifestation of symptoms may be important for determining the pathophysiology of PDS-type FD. Indeed, many studies have examined the gastroduodenal motility and symptoms relevant to the pathophysiology of PDS, although no close correlation between them has been observed (14). Therefore, we surmise that meal-related dyspepsia is not caused just by simple food retention and motility disorders; other physiological functions may also be involved.

Table 2. Demographic Characteristics and Pancreatic Exocrine Function in the Patients with Treatment-resistant Dyspeptic Symptoms.

	Postprandial fullness (n=42)	Epigastric pain (n=56)	Overlap (n=16)
Background			
Mean age (years)	60.7±13.4	51.4±16.9	58.4±13.8
sex (male)	50.0	25.0	37.5
Mean BMI (kg/m ²)	21.1±3.6	20.6±4.0	21.0±3.5
Serum amylase (IU/L)	100.3±65.6	90.7±28.4	82.9±31.4
Urinary amylase (IU/L)	409.8±384.8	339.4±244.8	290.9±120.9
Alcoholic consumption (%)	35.1	13.5	43.8
Current smoking (%)	24.3	15.4	37.5
<i>H. pylori</i> infection:negative/positive/unknown (%)	59.5/16.7/23.8	53.6/17.9/28.6	25.0/18.8/56.3
Pancreatic exocrine function			
BT-PABA (%)	65.4±10.5	62.9±16.2	60.5±10.4
Prevalence of pancreatic exocrine dysfunction (%)	71.4	69.6	81.3

BMI: Body mass index, N-benzoyl-L-tyrosyl-p-aminobenzoic acid: BT-PABA

Data are expressed as mean±SD or frequency (%)

The pancreas plays a major role in digestion via the pancreatic exocrine function. When gastric acid and food flow into the duodenum, the pancreas secretes pancreatic juice containing bicarbonate ions and digestive enzymes, thereby promoting the digestion and absorption of ingested food (15). Accordingly, pancreatic exocrine insufficiency due to organic/nonorganic disorders fails to alkalize gastric acid and activate pancreatic digestive enzymes. Such conditions cause poor digestion, especially of lipids. As a result, various abdominal symptoms such as abdominal pain, abdominal bloating, weight loss, and fatty stool may appear. However, whether or not the pancreatic exocrine function is reduced in patients with FD is unclear.

In the present study, the BT-PABA test was used to evaluate the pancreatic exocrine function in treatment-resistant dyspepsia patients. The present results indicated that the function was decreased in approximately 70% of patients. The patients had undergone at least an abdominal X-ray examination, abdominal ultrasonography, and abdominal CT examination. There was no evidence of calcification of the pancreas or pancreatic stones, so-called signs of classical chronic pancreatitis. Therefore, the pancreatic exocrine dysfunction was unlikely to be due to an organic disorder. Age-related morphological changes such as fibrosis in the pancreas have been reported (16). Recently, an interesting report described the pancreatic functional changes with aging (17). After excluding patients with pancreatic disease, it was shown that the frequency and distance of pancreatic juice discharge was negatively related to aging by cine-dynamic magnetic resonance cholangiopancreatography (MRCP). Furthermore, the BT-PABA test was positively correlated with the cine-dynamic MRCP findings (18). The rate of pancreatic exocrine dysfunction among healthy subjects over 60 years of age reportedly ranges from 10% to 20% based on fecal pancreatic elastase-1 levels (19, 20). However, the intractable FD patients in this study were not elderly. Accordingly, we believe that the rate of pancreatic exocrine dys-

function in the FD patients in the present study was relatively high (about 70%).

Like the stomach and duodenum, the pancreatic exocrine function is dually controlled by the autonomic nervous system and gastrointestinal hormones. Because a decreased vagal activity and sympathetic hyperactivity are often observed in FD (21), a decreased vasovagal reaction has the potential to cause not only delayed gastric emptying but also decreased pancreatic juice secretion. Increased amounts of undigested food might cause a compensatory increase in the secretion of gastrointestinal hormones such as CCK, which have an inhibitory effect on gastric emptying. Accordingly, pancreatic exocrine disorder may also occur as a manifestation of a mild decrease in the pancreatic function due to not only age-related changes but also functional gastrointestinal disease. These responses may therefore involve meal-related symptoms at the lower epigastrium, especially PDS. The Rome IV FD diagnostic criteria indicate that both PDS and EPS are food-related symptoms. The criteria further state that, in addition to four FD-specific symptoms, abdominal bloating, nausea, and belching may also be symptoms of FD. These points support the present findings that pancreatic exocrine dysfunction is also associated with the pathophysiology of meal-related FD. However, in the present study, we recruited FD patients resistant to the primary and secondary treatments recommended in the Japanese Society of Gastroenterology's 2014 Functional Gastrointestinal Disorder Guidelines. Thus, the recruited FD patients may have intractable types of FD. Therefore, we cannot confirm whether or not the rates of pancreatic exocrine dysfunction are high in overall FD patients. However, we believe that pancreatic exocrine dysfunction may be at least partially involved in the pathophysiology of such intractable FD patients. Further investigation will be needed.

Several limitations associated with the present study warrant mention. First, the study cohort included subjects who underwent company health examinations and FD patients.

Second, the Naniwa scale has not been validated. Therefore, after this pilot study, we would like to conduct a validation study in a larger population of FD patients to evaluate their symptoms. Third, conducting examinations twice is better for confirming the reproducibility of the BT-PABA test. Therefore, it will be necessary to examine the relationship between upper abdominal symptoms and the pancreatic exocrine function in patients with FD using the Naniwa scale and the BT-PABA test more than once and/or to conduct other pancreatic exocrine function tests such as the enzyme-linked immunosorbent assay (fecal elastase 1) and ¹³C-mixed triglycerides breath test.

In conclusion, we observed mismatch in the perception site and expression between the epigastric symptoms and FD-specific symptoms of healthy subjects. PDS-type symptoms are often felt at the lower part of the epigastrium, and pancreatic exocrine dysfunction may be involved in the pathogenesis of FD, especially for treatment-resistant dyspepsia patients. It is extremely important to clearly match symptoms, including their severity and perception site, preferably using a specific questionnaire including an illustration of the human body, between the patient and physician since FD and IBS are functional diseases that are diagnosed and managed based on the patient-reported outcomes.

Author's disclosure of potential Conflicts of Interest (COI).

Tetsuo Arakawa: Advisory role, Otsuka Pharmaceutical Co., Ltd. and Eisai Co., Ltd.; Research funding, Otsuka Pharmaceutical Co., Ltd. and Eisai Co., Ltd. Yasuhiro Fujiwara: Advisory role, Eisai Co., Ltd.; Research funding, Eisai Co., Ltd.

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