State of anxiety may be associated with exocrine pancreatic insufficiency in functional dyspepsia patients with pancreatic enzyme abnormalities

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We have reported that refractory functional dyspepsia patients with pancreatic enzyme abnormalities (FD-P) present with the prevalence of exocrine pancreatic insufficiency (EPI) in FD-P patients to clarify whether the pathophysiology of FD patients including clinical symptoms and quality of life were associated with EPI. We enrolled forty-nine patients presenting with typical symptoms of FD-P patients (n = 20) and asymptomatic patients with pancreatic enzyme abnormalities (AP-P) (n = 29). Five pancreatic enzymes (p-amylase, lipase, elastase-1, trypsin, and PLA2) were measured and STAI-state/trait and SF-8 were evaluated. Pancreatic exocrine function was analyzed using N-benzoyl-L-tyrosyl-L-aminobenzoic acid (BT-PABA). There were no significant differences in patient background between FD-P and AP-P patients. BT-PABA test scores for FD-P patients (61.67 ± 5.55) were significantly (p = 0.01) lower than in AP-P patients (95.38 ± 2.36). Physical component scale (PCS) in FD-P patients was significantly (p = 0.002) lower than that in AP-P patients. STAI-state was relatively (p = 0.054) associated with BT-PABA test in FD-P and AP-P patients by multiple logistic regression analysis. The prevalence of EPI in FD-P patients was significantly higher than that in AP-P patients and was relatively associated with state of anxiety. Further studies will be needed to clarify how EPI or pancreatic enzyme abnormalities are associated with the pathophysiology of FD-P patients.

Key Words: functional dyspepsia, exocrine pancreatic insufficiency, pancreatic enzyme abnormalities, state of anxiety

The major symptoms of functional dyspepsia (FD) consist of bothersome postprandial fullness, early satiety, epigastralgia and epigastric burning.¹² The symptom pattern and underlying pathology of FD are heterogeneous. Previous studies and our data demonstrated that refractory FD patients involves FD patients concomitant with pancreatic enzyme abnormalities and patients with FD symptoms could exhibit pancreatic enzyme abnormalities accompanying with abdominal fullness, epigastric pain and early satiety.³⁻⁵ Ashizawa et al.⁶⁻⁸ have also reported that anti-acid therapy-resistant FD involves FD patients with concomitant with chronic pancreatitis. Therefore, it may be useful for the treatment of refractory FD patients to determine the pathophysiology including exocrine pancreatic insufficiency (EPI) in FD patients with pancreatic enzyme abnormalities. Thus, it is critical to determine whether pancreatic enzyme abnormalities or EPI associate with functional dyspepsia. The pancreas plays a major role in digestion via exocrine pancreatic function. When gastric acid and food flow into the duodenum, the pancreas secretes pancreatic juice containing bicarbonate ions and digestive enzymes, thereby promoting digestion and the absorption of ingested food. Accordingly, exocrine pancreatic insufficiency due to organic disorders fails to alkalize gastric acid and activate digestive enzymes. Fujikawa et al.⁷ have reported impaired exocrine pancreatic function in FD patients. In the present study, we aim to clarify whether pancreatic dysfunction without obvious chronic pancreatitis or pancreatic stones can affect FD symptoms, or conversely, whether FD symptoms modify exocrine pancreatic function. Fujikawa et al.⁷ have also reported that most of FD patients exhibit EPI. They speculated that exocrine pancreatic function is dually controlled by the autonomic nervous system and gastrointestinal hormones. Since both disturbance of vagal activity and sympathetic hyperactivity are observed in FD, reduced vasovagal reaction and mental problems based on impaired vasovagal reaction in FD patients may be associated with pancreatic secretion. Certain FD patients were concomitant with pancreatic dysfunction and pancreatic enzyme abnormalities.⁴⁻⁵,⁸,⁹ In addition, previous studies and our data have reported that endosonography can reveal abnormalities in pancreas in patients with persistent dyspepsia.⁴⁻⁵,¹⁰

Therefore, in this study, we compared clinical characteristics and exocrine pancreatic function in FD patients with pancreatic enzyme abnormalities with those in asymptomatic patients with pancreatic enzyme abnormalities. We analyzed the prevalence of exocrine pancreatic insufficiency in FD patients with pancreatic enzyme abnormalities to clarify whether the pathophysiology of FD patients including clinical symptoms and quality of life were associated with exocrine pancreatic insufficiency.

Materials and Methods

Patients. This study enrolled 49 consecutive patients presenting with functional dyspepsia with pancreatic enzyme abnormalities (FD-P) (n = 20) and asymptomatic patients with...
pancreatic enzyme abnormalities (AP-P) \((n=29)\) after upper gastrointestinal endoscopy, abdominal ultrasonography and abdominal computed tomography from April 2013 to March 2020 (Fig. 1). We determined FD patients based on no abnormal imaging about upper gastrointestinal endoscopy, abdominal US, abdominal CT (Fig. 1). If there are FD symptoms accompanying with any pancreatic enzyme abnormalities in EUS score zero or one, FD-P patients were diagnosed. AP-P patients were defined by asymptomatic patients with pancreatic enzyme abnormalities (Fig. 1). FD patients were diagnosed according to the Rome III criteria. Exclusion criteria included severe heart disease, renal or pulmonary failure, liver cirrhosis, severe systemic illness, and history of malignant disease. We measured amylase, lipase, trypsin, PLA2, and elastase-1 levels in the sera of FD-P and AP-P patients. Written informed consent was obtained from all subjects prior to undergoing upper gastrointestinal endoscopy and abdominal ultrasonography for evaluation of dyspeptic symptoms. The study protocol was approved by the Ethics Review Committee (556-2-21) of Nippon Medical School Hospital.

**Endosonographic assessment.** An Olympus EUS-UCT 260 convex scanning endosonography (Olympus America, Melville, NY) at 7.5 MHz was used to perform EUS under conscious sedation in 20 FD patients with pancreatic enzyme abnormalities and 29 asymptomatic patients with pancreatic enzyme abnormalities (Fig. 1). Endosonographic parenchymal or ductal abnormalities were recorded. These abnormalities were defined as follows: lobularity with honeycombing, lobularity without honeycombing, hyperechoic foci without shadowing, stranding, cysts, dilated side branches and hyperechoic main pancreatic duct (MPD) margin. EUS score (from 0 to 7) is estimated by the sum of above EUS findings. When opinions differed among expert endoscopists, a final judgment was arrived at by consensus following a discussion of each individual case. Diagnoses of FD-P patients were made with imaging findings of zero or one EUS features with FD symptoms (Fig. 1).

**Definition of pancreatic enzyme abnormalities.** All serum trypsin, PLA2, lipase, p-amylase, elastase-1 values were measured using same automated chemistry analyzer (AU 5822 analyzer; Beckman Coulter, Brea, CA). The validated reference range of pancreatic enzymes at our hospital are 100–550 for trypsin, 150–400 for PLA2, 11–53 for lipase, 18–53 for p-amylase and 0–300 for elastase-1, respectively. Pancreatic enzyme abnormalities was determined by both of no abnormal imaging (upper gastrointestinal endoscopy, abdominal US, abdominal CT and endosonography, score \(2^\ast\)) and any pancreatic enzyme abnormalities including p-amylase, lipase, trypsin, PLA2, and elastase-1 (Fig. 1).

**Clinical symptoms.** Clinical symptoms of FD patients were evaluated according to the Rome III criteria. Clinical symptoms must have involved at least one of the following: early satiation, bothersome postprandial fullness, epigastric pain and epigastric burning. Diagnosis for postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS) was fulfilled with symptoms occurring for the last three months and the onset of symptoms occurring at least six months prior to diagnosis. In this study, FD symptoms including epigastric pain, epigastric burning, postprandial fullness and early satiety, and satisfaction with treatment, were assessed based on Rome III classification and evaluated as follows: 0, none; 1, very mild; 2, mild; 3, moderate; 4, severe; 5, very severe. Clinical symptoms were evaluated with the Gastrointestinal Symptom Rating Scale (GSRS). The GSRS is composed of 15 items that generate 5 components including gastroesophageal reflux, abdominal pain, indigestion, diarrhea, and constipation. Each item was rated according to severity on a scale of 1 (no discomfort at all) to 7 (very severe discomfort). We used the mean score of the GSRS and the 15 GI symptoms of the GSRS for the evaluation of dyspeptic symptoms.

**Clinical symptoms for dietary fat intake.** Patients reported their own clinical symptoms following the consumption of each of thirteen different types of foods (fried shrimp, processed cheese, croissants, meat balls, tomatoes, oranges, asparagus, hamburger, milk, apples, chicken nuggets, yogurt, and sweet potatoes) that included high-fat meals for a period of one month. In this study, high-fat meals were defined as those containing more than 16 g of fat per 100 g of food, such as fried shrimp (20.3 g fat/100 g), processed cheese (26 g fat/100 g), croissants (26.8 g fat/100 g) and meatballs (16.4 g fat/100 g) based on a previous study. Patients consuming high-fat meals evaluated their own clinical symptom scores as follows: 0, no complaints; 1, presence of any clinical symptoms including gastroesophageal reflux, abdominal pain, dyspepsia, diarrhea, and constipation.

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**Fig. 1.** Flowchart of this study. FD-P, functional dyspepsia with pancreatic enzyme abnormalities; AP-P, asymptomatic patients with pancreatic enzyme abnormalities. \(^\ast\)The score of endosonography is less than 2.
**N-benzoyl-L-tyrosyl-p-aminobenzoic acid test.** The N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) test was used to evaluate exocrine pancreatic function. In brief, urine was collected early in the morning after overnight fasting and used as control. The patient ingested 500 mg of BT-PABA (Eizai Co., Ltd., Tokyo, Japan) with 200 ml of water. The urinary PABA excretion rate was measured in urine samples collected during a 6-hour period to evaluate exocrine pancreatic function. Exocrine pancreatic insufficiency was diagnosed using a cut-off value of 70%.

**Health-related quality of life.** The Social Functioning-8 (SF-8) test was used to measure health-related quality of life according to the Manual of the SF-8 Japanese Version.\(^{(14)}\)

**State-Trait Anxiety Inventory.** We evaluated anxiety using the Japanese version of the State-Trait Anxiety Inventory (STAI) (Form X). The State-Trait Inventory was developed by Spielberger et al.\(^{(15)}\) to determine individuals’ separate state and trait anxiety levels and has been standardized for Japan. The STAI is a well-validated 40-item self-reported questionnaire to evaluate degree of anxiety. State of anxiety reflects a “transitory emotional state or condition of the human organism that is characterized by subjective, consciously perceived feelings of tension and apprehension, and heightened autonomic nervous system activity.” State of anxiety may fluctuate over time and can vary in intensity. In contrast, trait of anxiety denotes “relatively stable individual differences in anxiety proneness”.

**Sample size.** In our study, we determined the sample size using the PS (Power and Sample size calculations program) software program, a gift from Vanderbilt University. The SD of the BT-PABA test of the AP-P patients was approximately 11.07 (\(\sigma = 11.07\)). Using the above data, setting \(\alpha = 0.05\), \(\beta = 0.80\), and the estimated mean of the BT-PABA test with AP-P patients = 14, enrolled 20 FD-P patients and enrolled 29 AP-P patients were estimated to be sufficient to identify clinically relevant differences.

**Statistical analysis.** For statistical evaluation of group data, Students’ t test for paired data and analysis of variance (ANOVA) for multiple comparisons were followed by Scheffe’s F test. The Mann-Whitney U test was used for analysis of categorical data. Data analyses were performed using a standard software package (SPSS ver. 13.0, Chicago, IL). A \(p\) value of less than 0.05 was statistically significant.

**Results**

**Characteristics of FD-P and AP-P patients.** Since it may be useful for the treatment of refractory FD patients to determine the pathophysiology of FD patients with pancreatic enzyme abnormalities, we compared characteristics of FD patients and asymptomatic patients with pancreatic enzyme abnormalities. There were not significant differences in age, sex, BMI, alcohol intake, smoking, past history of acute pancreatitis, or HbA1c between FD-P patients and AP-P patients (Table 1).

**Comparison of pancreatic enzyme abnormalities between FD-P and AP-P patients.** There were no significant differences in the ratio of pancreatic enzymes abnormalities including p-amylase (range: 56–153, 88.7 ± 16.5 for FD-P patients; range: 62–107, 75.3 ± 4.46 for AP-P patients), lipase (range: 91–116, 108 ± 8.0 for FD-P patients, range: 65–153, 88.8 ± 22.1 for AP-P patients), elastase-1 (range: 397–505, 451 ± 54.0 for FD-P patients, range: 32–691, 499 ± 102 for AP-P patients), trypsin (range: 556–2,520, 881 ± 137 for FD-P patients, range: 584–854, 702 ± 18.6 for AP-P patients) and PLA2 (range: 447–907, 578.5 ± 76.0 for FD-P patients, range: 402–621, 491 ± 21.8 for AP-P patients) between FD-P patients and AP-P patients. However, the ratio of trypsin abnormalities in both FD-P patients and AP-P patients was higher than for all other pancreatic enzymes (Table 2).

**Comparison of BT-PABA test scores between FD-P and AP-P patients.** To compare exocrine pancreatic dysfunction in FD-P patients with that in AP-P patients, we evaluated BT-PABA test scores (%) in both groups. BT-PABA test scores in FD-P patients (21.8 ± 5.55) were significantly (\(p = 0.01\)) lower than that (95.38 ± 2.36) in AP-P patients (Fig. 2).

### Table 1. Characteristics of FD-P patients and AP-P patients

| Characteristic          | FD-P (n = 20) | AP-P (n = 29) | \(p\) value |
|-------------------------|---------------|---------------|-------------|
| Age (years)             | 58.4 ± 3.57   | 61.6 ± 2.32   | 0.44        |
| Sex (F/M)               | 7/13          | 18/11         | 0.06        |
| BMI                     | 21.1 ± 0.74   | 21.5 ± 0.64   | 0.71        |
| Smoking                 | 24 ± 13.5     | 99.3 ± 57.5   | 0.28        |
| Alcohol                 | 9.76 ± 6.15   | 7.45 ± 2.56   | 0.70        |
| Past history of acute pancreatitis | 1/20 | 1/29 | 0.66 |
| HbA1c                   | 5.80 ± 0.119  | 5.841 ± 0.197 | 0.873       |

FD-P, functional dyspepsia with pancreatic enzyme abnormalities; AP-P, asymptomatic patients with pancreatic enzyme abnormalities.

### Table 2. Comparison of pancreatic enzyme abnormalities between FD-P patients and AP-P patients

| Pancreatic enzyme | FD-P (n = 20) (%) | AP-P (n = 29) (%) | \(p\) value |
|-------------------|-------------------|-------------------|-------------|
| Lipase            | 10                | 13.8              | 0.663       |
| Trypsin           | 75                | 82.8              | 0.302       |
| PLA2              | 35                | 41.4              | 0.752       |
| Elastase-1        | 15                | 13.8              | 0.668       |
| p-Amy             | 30                | 37.9              | 0.972       |

FD-P, functional dyspepsia with pancreatic enzyme abnormalities; AP-P, asymptomatic patients with pancreatic enzyme abnormalities.
Comparison of SF-8 and STAI scores between FD-P and AP-P patients. Physical component scale (PCS) (44.60 ± 2.40) were significantly (p = 0.02) lower in FD-P patients than that (53.56 ± 1.31) in AP-P patients (Table 3). In contrast, there was no statistically significantly difference in mental component scale (MCS) between FD-P patients (45.17 ± 1.84) and AP-P patients (47.43 ± 2.02) (Table 3). There were no significant differences in STAI-state (36.33 ± 8.51, 56.92 ± 7.91) and STA-trait (45.67 ± 0.00, 54.46 ± 8.44) scores between FD-P patients and AP-P patients (Table 3).

Clinical symptoms and clinical complaints associated with fat intakes in FD-P patients. FD-P patients exhibit epigastric pain (3.19 ± 0.29), epigastric burning (2.25 ± 0.23), postprandial fullness (3.25 ± 0.25) and early satiety (3.19 ± 0.25) associated with the consumption of fatty meals (Fig. 3). Aggravation of clinical symptoms with fat intakes in patients with FD-P was worse (p = 0.342) than in patients with AP-P, albeit not statistically significant (Fig. 4).

Multiple logistic regression analysis of BT-PABA test in FD-P patients and AP-P patients. To evaluate which factors are related to BT-PABA test as a marker of exocrine pancreatic insufficiency, we investigated several factors including age, sex, BMI, smoking, alcohol, trypsin level, EUS score, STAI-trait, STAI-state, PCS, and MCS for BT-PABA test in FD-P patients and AP-P patients by multiple logistic regression analysis. Interestingly, STAI-state was relatively (p = 0.054) associated with BT-PABA test in FD-P patients and AP-P patients for multiple logistic regression analysis (Table 4). In contrast, age, sex, BMI, smoking, alcohol, trypsin, EUS score and STAI-trait, PCS, and MCS were not significantly linked to BT-PABA test in FD-P patients.

Discussion

It may be useful for the treatment of refractory FD patients to determine the pathophysiology of FD patients with pancreatic enzyme abnormalities. In this study, we aimed to compare clinical characteristics and EPI in FD patients with pancreatic enzyme abnormalities with those in asymptomatic patients with

| Table 3. Comparison of SF-8 and STAI scores between FD-P patients and AP-P patients | FD-P (n = 20) | AP-P (n = 29) | p value |
|---|---|---|---|
| SF-8 PCS | 44.6 ± 2.40* | 53.6 ± 1.31 | 0.002 |
| SF-8 MCS | 45.2 ± 1.84 | 47.4 ± 2.02 | 0.418 |
| STAI STAI-state | 36.3 ± 8.51 | 56.9 ± 7.91 | 0.089 |
| STAI STAI-trait | 45.7 ± 8.90 | 54.5 ± 8.44 | 0.483 |

FD-P, functional dyspepsia with pancreatic enzyme abnormalities; AP-P, asymptomatic patients with pancreatic enzyme abnormalities; PCS, physical component score; MCS, mental component score; SF-8, Social Functioning-8; STAI, State-Trait Anxiety Inventory. * vs PCS in AP-P, p = 0.0024.
pancreatic enzyme abnormalities. The main findings of this study are 1) in the present study, the prevalence of EPI was significantly higher in FD-P than in AP-P patients, 2) PCS in FD-P patients was significantly lower than that in AP-P patients, 3) STAI-state was relatively associated with BT-PABA test in FD-P patients and AP-P patients by multiple logistic regression analysis.

In our previous data, 347 FD patients involved 47 (13.5%) FD patients with pancreatic enzyme abnormalities when we examined five pancreatic enzymes such as p-amylase, trypsin, elastase-1, lipase, and PLA2 in FD patients. In the present study, the prevalence of EPI in FD-P patients was significantly higher than that in AP-P patients. In addition, EPI has been associated with an increased risk of mortality in patients with chronic pancreatitis due to the increased risk of pancreatic cancer and concomitant infection events.(18) EPI in chronic pancreatitis is considered to be clinically significant when it reaches a 90% threshold in the reduction of pancreatic enzymes, therefore, mild or moderate EPI in FD-P patients may not be associated with FD symptoms such as abdominal distention, early satiety and abdominal fullness. In addition, age also contributes to hypoperfusion fibrosis and atrophy of the pancreas, which in turn results in moderate EPI in 10% and severe EPI in 5% of subjects aged >70 years evaluated by fecal elastase levels.(19) Although in our study, there were no significant differences in the mean age between the two groups, BT-PABA test showed significantly lower urinary PABA excretion rates in FD-P patients than in AP-P patients. Moreover, EPI can itself cause GI motility disorders or exacerbate underlying GI tract motility disorders.(18) We followed FD-P using endosonography in about 4 years. Eight patients of 53 FD-P patients aggravated with endosonographic features in 4 years. Interestingly, 2 FD-P patients progressed to early chronic pancreatitis. Considering that BT-PABA test scores in FD-P patients were significantly lower than that in asymptomatic patients with pancreatic enzyme abnormalities, it is a critical issue to estimate precisely whether certain FD-P patients may progress to chronic pancreatitis using endosonography.

Previous studies have reported a relationship between exocrine pancreatic insufficiency and gastric motility. Long et al.(19) have reported that gastric emptying of liquid fat meals was abnormally rapid in patients with pancreatic insufficiency. In our study, the early phase of gastric emptying was disturbed in FD-P patients.(14) Regan et al.(20) have reported that the rate of acid delivery into duodenum and duodenal acidity were reduced in postprandial hour in advanced exocrine pancreatic insufficiency. When gastric acid in the duodenum is not balanced out by alkaline pancreatic secretions, it may induce a prolonged secretin stimulus that interacts with the pancreatic ductal cells, increasing the rate of ductular cell activity and turnover.(21) Considering of the disturbance of gastric emptying and abnormal eating behavior in FD patients, impaired postprandial gastric emptying and duodenal acidity may contribute to pancreatic enzyme abnormalities through the upregulation of secretin or the disturbance of vagus nerve activity. In contrast, elevation in trypsin levels may be associated with duodenal microinflammation through the activation of PAR2, trypsin receptor, expression in the duodenum and trigger in FD symptoms. In addition, exocrine pancreatic insufficiency may be also associated with duodenal acidity through the diminished secretion of bicarbonate that may in turn contribute to FD symptoms. Taken together, the pathophysiologic factors involved in FD patients may be associated with pancreatic enzyme abnormalities, and in turn, pancreatic enzyme abnormalities and exocrine pancreatic insufficiency may also contribute to FD symptoms. Further studies will be needed to clarify these correlations between the pathophysiology of FD and exocrine pancreatic insufficiency.

Although EPI has been thought to be partly important in the pathophysiology of dyspepsia, the precise relationship between the aggravation of EPI and FD symptoms were not determined. Kleveland et al.(23) have reported that short-term pancreatic enzyme replacement failed to improve symptoms in non-ulcer dyspepsia (NUD) patients. On the other hand, gastric myoelectricity has been shown to be impaired in chronic pancreatitis and improved with pancreatic enzyme replacement.(24) Further studies will be needed to clarify how pancreatic exocrine insufficiency associates with the pathophysiology of FD patients. However, current studies suggest that exocrine pancreatic insufficiency is regulated by several factors such as CCK, GLP-1, 5-HT, as well as the vagovagal pathway system.(25–27) To clarify whether the pathophysiology of FD-P patients including anxiety associated with vagovagal pathway modify pancreatic exocrine insufficiency, we performed multivariate analysis for exocrine pancreatic insufficiency. Age, sex, MCS, PCS, trypsin, and EUS scores were not significantly associated with exocrine pancreatic insufficiency in FD-P patients. Interestingly, STAI-state was relatively associated with exocrine pancreatic insufficiency in FD-P patients. STAI-state, a test for assessing anxiety, which have been reported to be associated with gastric emptying.(28) The disturbance of gastric emptying into the duodenum may be associated with the abnormalities of various GI hormones such as CCK and GLP-1 through the changes of the composition of the enzyme in the duodenum.(29) These neuro-

### Table 4. Multiple logistic regression analysis for BT-PABA test in FD-P Patients and AP-P patients

| Factors                | OR (95% CI) | p value |
|------------------------|------------|---------|
| Age (years)            | 0.419 (0.128–0.441) | 0.266   |
| Sex                    | 1.99 (24.30–28.28) | 0.853   |
| BMI                    | −0.740 (−3.253–1.772) | 0.483   |
| Smoking                | −0.082 (0.341–0.177) | 0.451   |
| Alcohol                | 0.703 (0.213–1.620) | 0.106   |
| Trypsin                | 12.76 (16.50–42.03) | 0.581   |
| EUS score              | −11.89 (−39.04–15.26) | 0.311   |
| STAI-state             | 0.500 (0.11–1.013) | 0.054   |
| STAI-trait             | −0.351 (−0.905–0.203) | 0.165   |
| PCS                    | 0.561 (0.828–1.949) | 0.347   |
| MCS                    | 0.622 (1.323–2.567) | 0.448   |

FD-P, functional dyspepsia with pancreatic enzyme abnormalities; PCS, physical component score; MCS, mental component score; SF-8, Social Functioning-8; STAI, State-Trait Anxiety Inventory; BT-PABA test, N-benzoyl-l-tyrosyl-p-aminobenzoic acid.
hormonal impairments including vagal pathway and GI hormones affect pancreatic secretion.\(^{(39)}\) Therefore, the impairment of gastric emptying into duodenum related with STAI-state may be associated with exocrine pancreatic insufficiency through neurohormonal disturbances.

In the present data, we show that the excretion of trypsin was highly impaired from among all other pancreatic enzymes. As described in Table 2, whereas in a previous study, we reported that trypsin levels in duodenum were similar tendency to serum trypsin levels (data not shown). Jimenez-Vargas et al.\(^{(31)}\) have reported that trypsin receptor, PAR2 expression in the colon of patients with IBS. In addition, duodenal inflammation accompanying with the accumulation of eosinophils and macrophages has been linked to FD.\(^{(32–35)}\) Considering of previous studies and our data, high levels of trypsin may affect duodenal inflammatory responses through PAR2 expression in the duodenal mucosa. Thus, duodenal inflammation and elevated levels of duodenal PAR2 expression driven by the up-regulation of trypsin levels may appear to trigger FD symptoms. We have also reported that the elevation of duodenal inflammatory responses including GLP-1 producing cells expression in FD-P patients and exocrine pancreatic insufficiency has been also reported to be affected by gut hormones such as GLP-1.\(^{(4,10,25–27)}\) Further studies will be needed to clarify how the exocrine pancreatic insufficiency may associate with the pathophysiology of FD patients including the disturbance of physical quality of life through duodenal inflammatory responses.

**Author Contributions**

SA: data collection, writing the manuscript; HY, KH, KK, YK, RO, YW, MH, KL, and NU: data collection; KG: editing, revising manuscript; SF: data collection, direction of experiment, writing the manuscript.

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**Conflict of Interest**

No potential conflicts of interest were disclosed.

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