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

Shuhei Agawa,[1] Seiji Futagami,[1,]* Hiroshi Yamawaki,[1] Katya Gudis,[1] Kazutoshi Higuchi,[1] Keiko Kaneko,[1] Mayu Habiro,[1] Yasuhiro Kodaka,[1] Nobue Ueki,[1] Yoshiyuki Watanabe,[2] Norio Motoda,[3] Ryuji Ohashi,[3] and Katsuhiko Iwakiri[1]

[1]Division of Gastroenterology and [3]Division of Pathology, Department of Internal Medicine, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8602, Japan
[2]Division of Gastroenterology, St. Marianna University School of Medicine, 2-16-1 Sugao, Kawasaki, Kanagawa 216-8511, Japan

We have reported that refractory functional dyspepsia patients with pancreatic enzyme abnormalities (FD-P). We tried to analyze 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-p-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.[1,2] 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] 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.
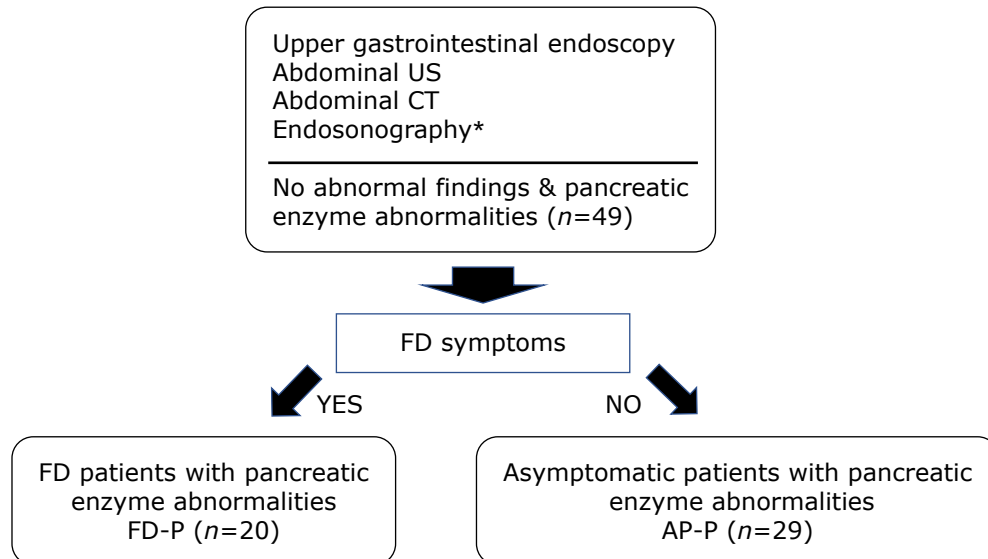
The pancreas plays a major role in digestion via exocrine pancreatic function. When gastric acid and food flow into the duodenum, the pancreas secretes pancreatic juice containing bicarbonate ions and digestive enzymes, thereby promoting digestion and the absorption of ingested food. Accordingly, exocrine pancreatic insufficiency due to organic disorders fails to alkalinize gastric acid and activate pancreatic 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 pancreas 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.[3–5,10]

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

---

*To whom correspondence should be addressed.
E-mail: seiji-f@nms.ac.jp

doi: 10.3164/jcbn.21-67
©2022 JCBN

J. Clin. Biochem. Nutr. | **March 2022** | vol. 70 | no. 2 | **175–181**

Fig. 1. Flowchart of this study. FD-P, functional dyspepsia with pancreatic enzyme abnormalities; AP-P, asymptomatic patients with pancreatic enzyme abnormalities. *The score of endosonography is less than 2.

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.[2] 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, stranding, cysts, dilated side branches and hyperechoic main pancreatic duct (MPD) margin.[11] 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, 130–400 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>) 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.[2] 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.[7] Clinical symptoms were evaluated with the Gastrointestinal Symptom Rating Scale (GSRS).[12] 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.[13] 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.

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 patients then 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 h 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 29AP-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 pancreatic exocrine 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 (61.67 ± 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

	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

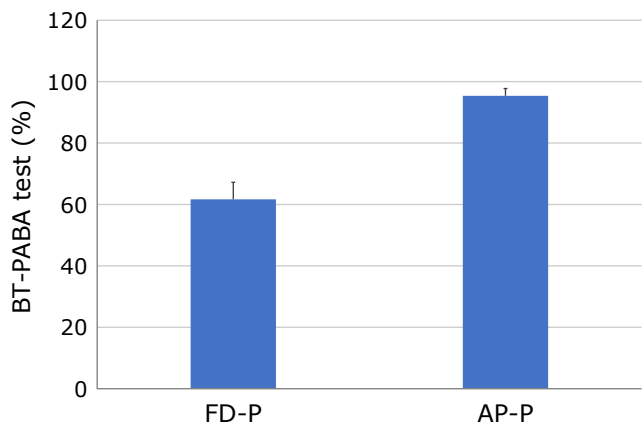| Pancreatic enzyme	FD-P (n = 20) (%)	AP-P (n = 29) (%)	p value
Lipase	10	13.8	0.663
Trypsin	75	82.8	0.302
PLA2	35	41.4	0.752
Elastase-1	15	13.8	0.668
p-Amy	30	37.9	0.972

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 ± 9.00, 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


Fig. 2. Comparison of pancreatic exocrine dysfunction between FD-P and AP-P patients. BT-PABA test (%) in FD-P patients (61.67 ± 5.55) was significantly ($p = 0.01$) lower than that (95.38 ± 2.36) in AP-P patients (Fig. 4). * vs AP-P patients, $p = 0.01$.

Table 3. Comparison of SF-8 and STAI scores between FD-P patients and AP-P patients

Factors		FD-P ($n = 20$)	AP-P ($n = 29$)	p value
SF-8	PCS	44.6 ± 2.40*	53.6 ± 1.31	0.002
	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-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, $p = 0.0024$.
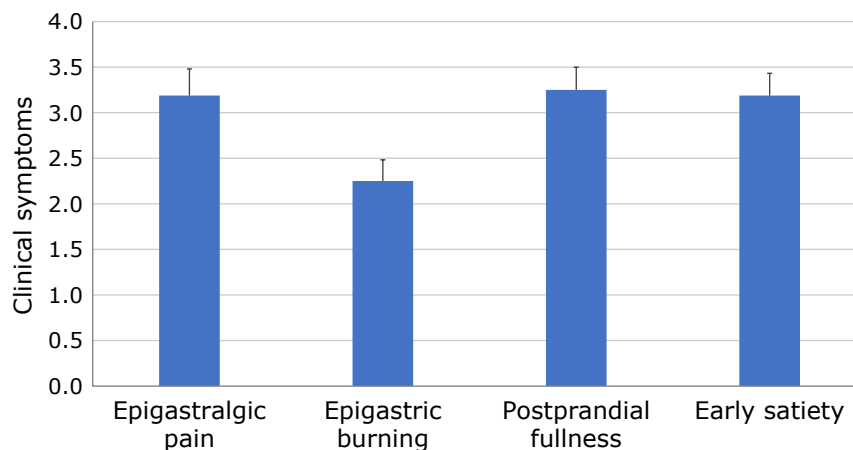
Fig. 3. Clinical symptoms in FD-P patients. FD-P patients exhibit epigastric pain (3.19 ± 0.29), epigastric burning (2.25 ± 0.23), postprandial fullness (3.25 ± 0.25) and early satiety (3.19 ± 0.25). FD-P, functional dyspepsia with pancreatic enzyme abnormalities.
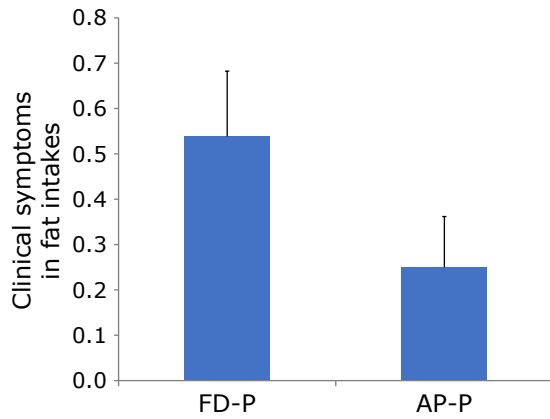
Fig. 4. Clinical complaints after fat intakes. Aggravation of clinical symptoms due to fat intakes in patients with FD-P were higher than that in patients with AP-P, albeit not statistically significant.

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 (−1.28–0.441)	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.

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.[16] 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.[17] 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 that 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.[4] 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.[21] 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.[22] 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 need 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 chyme in the duodenum.[29] These neuro-

hormonal impairments including vagal pathway and GI hormones affect pancreatic secretion.[30] 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 enzyme abnormalities 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, KI, and NU: data collection; KG: editing, revising manuscript; SF: data collection, direction of experiment, writing the manuscript.

Acknowledgments

Conflict of Interest

No potential conflicts of interest were disclosed.

References

1 Tack J, Talley NJ, Camilleri M, et al. Functional gastroduodenal disorders. Gastroenterology 2006; 130: 1466–1479.

2 Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology 2006; 130: 1377–1390.

3 Sahai AV, Mishra G, Penman ID, et al. EUS to detect evidence of pancreatic disease in patients with persistent or nonspecific dyspepsia. Gastrointest Endosc 2000; 52: 153–159.

4 Wakabayashi M, Futagami S, Yamawaki H, et al. Comparison of clinical symptoms, gastric motility and fat intake in the early chronic pancreatitis patients with anti-acid therapy-resistant functional dyspepsia patients. PLoS One 2018; 13: e0205165.

5 Hashimoto S, Futagami S, Yamawaki H, et al. Epigastric pain syndrome accompanying pancreatic enzyme abnormalities was overlapped with early chronic pancreatitis using endosonography. J Clin Biochem Nutr 2017; 61: 140–145.

6 Ashizawa N, Hashimoto T, Miyake T, Shizuku T, Imaoka T, Kinoshita Y. Efficacy of camostat mesilate compared with famotidine for treatment of functional dyspepsia: is camostat mesilate effective? J Gastroenterol Hepatol 2006; 21: 767–771.

7 Fujikawa Y, Tominaga K, Tanaka F, et al. Postprandial symptoms felt at the lower part of the epigastrium and a possible association of pancreatic exocrine dysfunction with the pathogenesis of functional dyspepsia. Intern Med 2017; 56: 1629–1635.

8 Tominaga K, Fujikawa Y, Tsumoto C, et al. Disorder of autonomic nervous system and its vulnerability to external stimulation in functional dyspepsia. J Clin Biochem Nutr 2016; 58: 161–165.

9 Worning H. Exocrine pancreatic function in dyspepsia. Digestion 1987; 37 Suppl 1: 3–13.

10 Higuchi K, Futagami S, Yamawaki H, et al. Endosonographic features in patients with non-alcoholic early chronic pancreatitis improved with treatment at one year follow up. J Clin Biochem Nutr 2021; 68: 86–94.

11 Ito T, Ishiguro H, Ohara H, et al. Evidence-based clinical practice guidelines for chronic pancreatitis 2015. J Gastroenterol 2016; 51: 85–92.

12 Svedlund J, Sjödin I, Dotevall G. GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci 1988; 33: 129–134.

13 Engbers LH, van Poppel MN, Chin A Paw M, van Mechelen W. The effects of a controlled worksite environmental intervention on determinants of dietary behavior and self-reported fruit, vegetable and fat intake. BMC Public Health 2006; 6: 253.

14 Fukuhara S, Suzukamo Y. Manual of the SF-8 Japanese Version. Kyoto: Institute for Health Outcomes and Process Evaluation Research, 2004. (in Japanese)

15 Spielberger CD, Goursuch RL, Lushene RE. Manual for the State Trait anxiety inventory. Mountain View, CA: Consulting Psychological Press, 1983.

16 de la Iglesia-Garcia D, Vallejo-Senra N, Iglesias-Garcia J, López-López A, Nieto L, Domínguez-Muñoz JE. Increased risk of mortality associated with pancreatic exocrine insufficiency in patients with chronic pancreatitis. J Clin Gastroenterol 2018; 52: e63–e72.

17 Capurso G, Traini M, Piciucchi M, Signoretti M, Arcidiacono PG. Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. Clin Exp Gastroenterol 2019; 12: 129–139.

18 Fieker A, Philpott J, Armand M. Enzyme replacement therapy for pancreatic insufficiency: present and future. Clin Exp Gastroenterol 2011; 4: 55–73.

19 Long WB, Weiss JB. Rapid gastric emptying of fatty meals in pancreatic insufficiency. Gastroenterology 1974; 67: 920–925.

20 Regan PT, Malagelada JR, Dimagno EP, Go VL. Postprandial gastric function in pancreatic insufficiency. Gut 1979; 20: 249–254.

21 Stevens T, Conwell D, Zuccaro G, et al. Analysis of pancreatic elastase-1 concentrations in duodenal aspirates from healthy subjects and patients with chronic pancreatitis. Dig Dis Sci 2004; 49: 1405–1411.

22 Talamini G. Duodenal acidity may increase the risk of pancreatic cancer in the course of chronic pancreatitis: an etiopathogenetic hypothesis. JOP 2005; 6: 122–127.

23 Kleveland PM, Johannessen T, Kristensen P, et al. Effect of pancreatic enzymes in non-ulcer dyspepsia. A pilot study. Scand J Gastroenterol 1990; 25: 298–301.

24 Lu CL, Chen CY, Luo JC, et al. Impaired gastric myoelectricity in patients with chronic pancreatitis: role of maldigestion. World J Gastroenterol 2005; 11: 372–376.

25 Mussa BM, Sood S, Verberne AJ. Implication of neurohormonal-coupled mechanisms of gastric emptying and pancreatic secretory function in diabetic gastroparesis. World J Gastroenterol 2018; 24: 3821–3833.

26 Owyang C, Logsdon CD. New insights into neurohormonal regulation of pancreatic secretion. Gastroenterology 2004; 127: 957–969.

27 Konturek SJ, Pepera J, Zabielski K, et al. Brain-gut axis in pancreatic secretion and appetite control. J Physiol Pharmacol 2003; 54: 293–317.

28 Simpson KH, Stakes AF. Effect of anxiety on gastric emptying in preoperative patients. Br J Anaesth 1987; 59: 540–544.

29 Mussa BM, Sood S, Verberne AJ. Implication of neurohormonal-coupled mechanisms of gastric emptying and pancreatic secretory function in diabetic gastroparesis. World J Gastroenterol 2018; 24: 3821–3833.

30 Roze C. Central regulation of pancreatic secretion. In Tache Y, Wingate DL, eds. Brain-gut Interactions, FL: CRC Press, 1991; 187–198.

31 Jimenez-Vargas NN, Pattison LA, Zhao P, et al. Protease-activated receptor-2

in endosomes signals persistent pain of irritable bowel syndrome. *Proc Natl Acad Sci U S A* 2018; **115**: E7438–E7447.

32 Futagami S, Shindo T, Kawagoe T, *et al*. Migration of eosinophils and CCR2-/CD68-double positive cells into the duodenal mucosa of patients with postinfectious functional dyspepsia. *Am J Gastroenterol* 2010; **105**: 1835–1842.

33 Du L, Shen J, Kim JJ, Yu Y, Ma L, Dai N. Increased duodenal eosinophil degranulation in patients with functional dyspepsia: a prospective study. *Sci Rep* 2016; **6**: 34305.

34 Vanheel H, Vicario M, Vanuytsel T, *et al*. Impaired duodenal mucosal integrity and low-grade inflammation in functional dyspepsia. *Gut* 2014; **63**: 262–271.

35 Yuan HP, Li Z, Zhang Y, Li XP, Li FK, Li YQ. Anxiety and depression are associated with increased counts and degranulation of duodenal mast cells in functional dyspepsia. *Int J Clin Exp Med* 2015; **8**: 8010–8014.