—Review—

Pancreatic Dysfunction and Duodenal Inflammatory Responses Coordinate with Refractory Epigastric Pain Including Functional Dyspepsia: A Narrative Review

Seiji Futagami and Mako Wakabayashi

Department of Gastroenterology, Nippon Medical School, Tokyo, Japan

Some patients with functional dyspepsia (FD) have abnormalities in pancreatic enzymes and chronic pancreatitis. Since 2009, when the idea of early chronic pancreatitis (ECP) first emerged, the utility of endoscopic ultrasonography gained attention, as it can help identify early chronic pancreatitis in patients with dyspepsia. Although the symptoms associated with pancreatic enzyme abnormalities and pancreatic dysfunction overlap with those of dyspepsia, no available data explain the direct relationships and linkages between pancreatic dysfunction and dyspeptic symptoms. Disturbance of exocrine pancreatic enzyme function and reduction in pancreatic endocrine levels, such as insulin, may be associated with dyspeptic symptoms through impaired gastric emptying and duodenal inflammation. Some recent studies have examined the role of duodenal pathophysiology in gastric motility, bicarbonate secretion, and digestion. Because reduced bicarbonate secretion, which is caused by pancreatic dysfunction, leads to a failure to neutralize gastric acid in the proximal duodenum, impaired bicarbonate secretion in turn fails to protect the duodenal mucosa against gastric acid influx, thereby inducing duodenal inflammation. In addition, elevated trypsin levels might be associated in part with duodenal inflammatory responses through PAR2-related immunomodulatory cells. This review describes how duodenal inflammation might affect the pathogenesis of FD and examines whether pancreatic dysfunction is associated with FD through intestinal inflammation. (J Nippon Med Sch 2022; 89: 255–262)

Key words: functional dyspepsia, pancreatic enzyme abnormalities, endosonography

Introduction

The Rome IV criteria define functional dyspepsia (FD) as the presence of one or more of the following symptoms—postprandial fullness, early satiation, epigastric pain, or epigastric burning—in a person with no evidence of organic disease that explains these symptoms. These symptoms must have been present for the preceding 3 months, with symptom onset at least 6 months before diagnosis[1]. Thus, the diagnostic criteria for FD require exclusion of all other potential causes (**Fig. 1**)[2]. The relationship between pancreatic dysfunction and dyspepsia has been studied[1]. Previous studies have reported that FD overlaps with pancreatic enzyme abnormalities and chronic pancreatitis in some patients[3–6]. Since 2009, when the concept of early chronic pancreatitis (ECP) was introduced to the clinical diagnostic criteria for chronic pancreatitis, the utility of endoscopic ultrasonography (EUS) has attracted attention, as it may play a pivotal role in distinguishing ECP from dyspepsia. ECP is diagnosed when imaging shows two or more of the four EUS findings shown in **Figure 2**. In addition, two or more relevant clinical symptoms or laboratory findings must be present (including repeated attacks of epigastric pain, abnormalities in blood/urine pancreatic enzymes, exocrine pancreatic dysfunction, chronic alcohol intake [≥60 g/day] or variants in pancreatitis-related genes, and past history of acute pancreatitis; **Fig. 2**). According to the FD diagnostic criteria, there should be no evidence of structural disease on ultrasonography, upper endoscopy, or computed tomography, as these could explain symptoms

Correspondence to Seiji Futagami, MD, PhD, Department of Gastroenterology, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8602, Japan
E-mail: seiji-f@nms.ac.jp
https://doi.org/10.1272/jnms.JNMS.2022_89-311
Journal Website (https://www.nms.ac.jp/sh/jnms/)

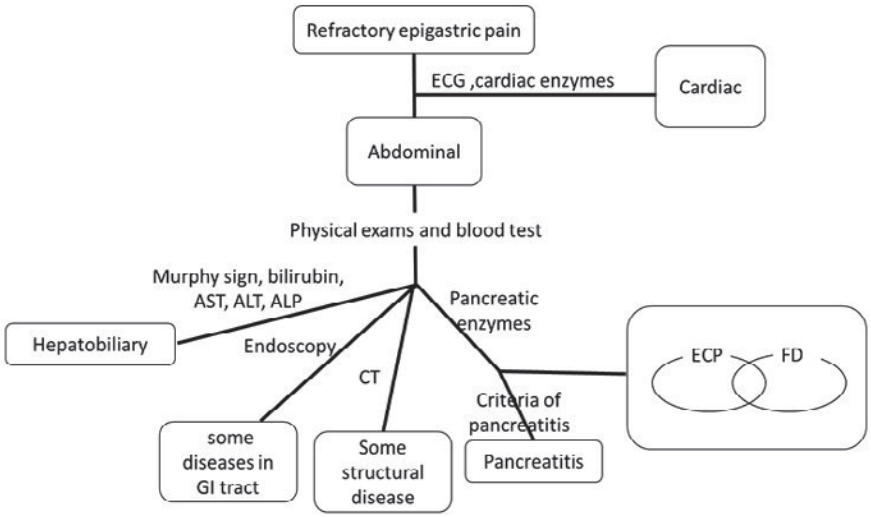

Fig. 1 Flowchart for diagnosis of refractory epigastric pain, including functional dyspepsia and early chronic pancreatitis
We exclude structural diseases, such as hepatobiliary diseases, GI tract diseases and chronic pancreatitis, through physical examination, blood testing, endoscopy, and CT scanning. After exclusion of structural diseases, functional dyspepsia and early chronic pancreatitis can be diagnosed.
ECG: electrocardiography; AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; CT: computed tomography; FD: functional dyspepsia

Diagnosis of early chronic pancreatitis

Clinical findings

1. Recurrent episodes of epigastric pain or back pain
2. Abnormalities in blood/urine pancreatic enzymes
3. Exocrine pancreatic dysfunction
4. Chronic alcohol intake (≥60 g/day) or variants in pancreatitis-related genes
5. Past history of acute pancreatitis

Imaging findings

a. EUS findings (more than 2 score including 1 or 2 items)
   1. Hyperechoic foci or strands
   2. Lobularity
   3. Hyperechoic MPD margin
   4. Dilated side branches

b. MRCP or ERCP images (irregular dilatation in more than three side branches)

Fig. 2 Diagnosis of early chronic pancreatitis

of FD. However, if patients exhibit any structural abnormalities on EUS, which can detect slight abnormalities not detectable by other tests, FD can still be diagnosed on the basis of the current criteria, even when structural abnormalities of the pancreas are detected by EUS. If patients have fewer than two structural abnormalities among those listed in the ECP criteria, ECP should not be diagnosed; patients must have two or more structural abnormalities to satisfy the ECP criteria for diagnosis.

Although the pathophysiology of FD is not fully un-

derstood and is considered multifactorial, local inflammation in the gastrointestinal tract, particularly duodenal inflammation, may be important in the pathophysiology of FD[7]. In this article, we review how local inflammation in the gastrointestinal tract may play a role in the pathophysiology of FD and examine whether pancreatic dysfunction is associated with functional dyspepsia through intestinal inflammation.

Pancreatic Dysfunction and Functional Dyspepsia

Pancreatic dysfunction can be classified as exocrine dysfunction, endocrine dysfunction, and decreased bicarbonate secretion. In ECP patients, pancreatic enzyme abnormalities due to exocrine dysfunction lead to elevation of pancreatic enzyme levels. Elevation of trypsin was found to be the most sensitive marker for ECP and FD patients, as we previously reported[8].

Okada et al[9] reported elevated serum lipase levels in patients with idiopathic chronic dyspepsia. Interestingly, half of the enrolled patients with PPI-refractory FD had pancreatic enzyme abnormalities in our previous study[8]. In addition, Hashimoto et al[10] reported that 76.2% of FD patients had abnormal trypsin levels. Furthermore, Sahai et al[3] reported that dyspepsia might be an atypical presentation of pancreatic disease as diagnosed by endoscopic ultrasonography (EUS)[8]. Although the symptoms of patients with pancreatic enzyme abnormalities and pancreatic dysfunction overlap those of patients presenting with dyspepsia symptoms, no available data can explain the relationship between pancreatic dysfunction and dyspeptic symptoms. Fujikawa et al[11] found that more than 70% of FD patients with symptoms of postprandial distress syndrome had pancreatic exocrine dysfunction.

In addition, patients with severe aggravated pancreatic dysfunction, such as in diabetes, were reported to have gastroparesis[12,13]. Findings from these and other studies[11,13] suggest that dysfunction of exocrine pancreatic enzymes and diminished levels of pancreatic endocrine enzymes, such as insulin, may be associated with dyspeptic symptoms through impaired gastric emptying and duodenal inflammation. Gastric dysmotility and pancreatic secretion are controlled by multiple neurohormonal mechanisms, including GLP-1, CCK, and extrinsic parasympathetic pathways[12]. Therefore, delayed gastric motility is associated with a temporal mismatch between blood glucose and insulin secretion, which jeopardizes regulation of postprandial glycemia. Thus, gastric dysmotility might be linked with pancreatic dysfunction. Future studies should attempt to to clarify the effects of pancreatic dysfunction on the pathogenesis of FD.

Duodenal Inflammation Has Pivotal Roles in FD

Several studies of the interaction between FD and duodenal inflammation[7,14] have revealed a variety of inflammatory cells in the duodenal mucosa, including eosinophils, macrophages, and mast cells[15]. Although the brain-gut axis was reported to mediate activation of mast cells in the GI tract by stimulating production of corticotropin-releasing hormone (CRH), which has been linked to mucosal permeability via activation of migrated inflammatory cells[16], no study has evaluated prolongation of inflammatory cells in the intestine. Yuan et al reported that anxiety and depression are associated with increased mast cell counts and degranulation of duodenal mast cells in FD[17]. Migration of macrophage infiltration in the lamina propria and mesenchymal muscularis in urocortin 2-treated rat models[18] suggests that continuous CRF stimulation under stressful conditions aggravates mucosal inflammation during infection. In our study, we speculated that the microbiota, as well as LPS stimulation, has important roles in patients with FD or IBS. Infectious gastroenteritis is thought to be a risk factor for FD and IBS. Indeed, post-infectious functional gastrointestinal diseases is a separate category[19,20]. The gut microbiota can also indirectly influence FD symptoms through the brain-gut axis[21] and has an important role in host physiology, homeostasis, CNS function, and host behavior[22], thus inducing gut inflammation. Gut hormones secreted from duodenal mucosa, including GLP-1, GIP, and PYY, were important in gastric motility and nutrient absorption[23–25]. To clarify differences in duodenal inflammatory responses between functional dyspepsia with pancreatic enzyme abnormalities (FD-P) and ECP, we compared various phenotypes of duodenal inflammatory cells, such as GLP-1-positive cells and degranulated eosinophils, between FD-P patients and ECP patients[8,26]. Pancreatic enzyme excretion is also affected by environmental factors in the mucosa of the duodenum, and pancreatic dysfunction may, in turn, affect duodenal inflammatory responses (**Fig. 3**). However, no study has investigated the relationship between duodenal inflammatory responses and pancreatic dysfunction in patients with FD.

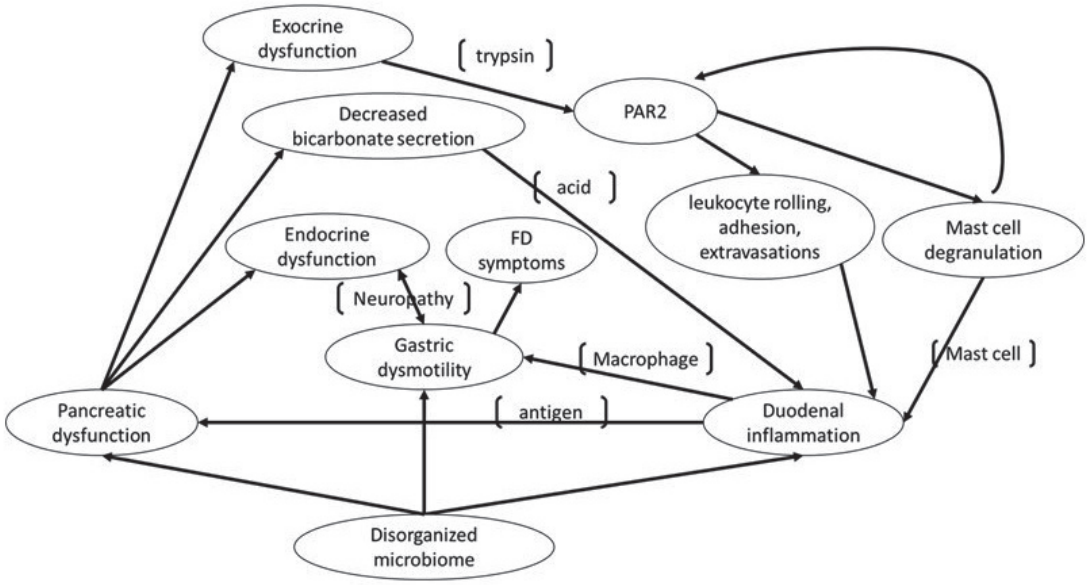

Fig. 3 Overview of roles of duodenal inflammatory responses through pancreatic dysfunction in the pathophysiology of dyspepsia

Association between Pancreatic Dysfunction and the Duodenum

(1) Decreased Pancreatic Bicarbonate Secretion in the Duodenum

Because reduced bicarbonate secretion due to pancreatic dysfunction fails to neutralize gastric acid in the proximal duodenum[27], impaired bicarbonate secretion by pancreatic dysfunction cannot protect duodenal mucosa from gastric acid influx, which induces duodenal mucosal inflammation (**Fig. 3**). Notably, duodenal inflammation[28] may further induce pancreatic dysfunction through the presence of leaky intestinal mucosa, which leads to an increase in antigenic load from the intestinal lumen, activation of the immune system, and, ultimately, destruction of pancreatic β cells (**Fig. 3**). Indeed, the intestinal mucosa of patients with type 1 diabetes mellitus exhibited elevated macrophage infiltration, where pancreatic dysfunction leads to destruction of β cells[28].

(2) Pancreatic Exocrine Dysfunction

Pancreatic acinar cells have the highest rate of protein turnover among human tissues, with synthesis and secretion of high volumes of digestive enzymes, and exhibit a rich network of ER[29]. In acute pancreatitis, stimulation caused by genetic alterations, alcohol, autoimmunity, and infections triggers inappropriate activation of trypsin[30]. Some of these processes may overlap with the constellation of factors associated with the pathogenesis of ECP and FD. This suggests that trypsin has a critical role as a first-line factor in the activation cascade of pancreatic enzymes (**Fig. 4**). Therefore, we hypothesized that in ECP and FD-P some processes trigger trypsin activation, which could lead to sustained pancreatic duct inflammation and sustained inflammation, thereby inducing pancreatic acinar cell death through activation of trypsinogen, infiltration of inflammatory cells, and upregulation of ER stress[31]. We reported that FD-P patients exhibited exocrine pancreatic dysfunction[32] as was the case in a previous study[33]. Because there were no available data on exocrine pancreatic dysfunction in ECP patients, studies of ECP patients are needed. We found that treatment with camostat mesilate improved epigastric pain in ECP patients[34], and Ishikura et al reported that camostat mesilate reduced pancreatic pain by inhibiting neuronal activation in rodents[35]. Their study suggests that camostat mesilate improves pancreatic pain by inhibiting neuronal activation. In addition, our previous 1-year follow-up study indicated that treatment including camostat mesilate improved EUS findings[26]. Further studies will be needed to clarify why camostat mesilate can improve EUS findings in ECP patients.

Disorganized Microbiomes

The gut microbiota has a major role in human physiology because of its effects on metabolism, modulation of the mucosal immune system, facilitation of digestion, and modulation of intestinal architecture. Alterations in the gut microbiota are present in pancreatic disease and may have a role in the pathogenesis of several pancreatic diseases, including pancreatitis and pancreatic cancer[36]. Gut dysbiosis may contribute to the pathogenesis of pancreatic diseases[36]. Future studies should attempt to clarify

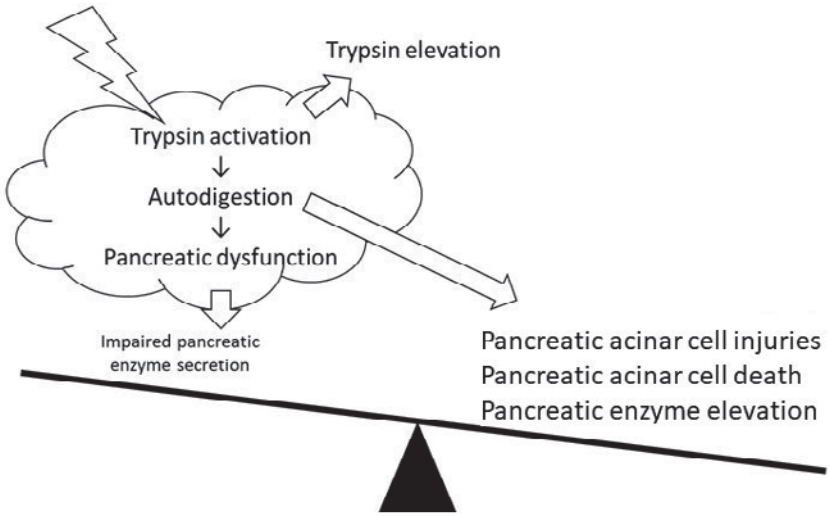

Fig. 4 Relationship between impaired pancreatic enzyme secretion and pancreatic enzyme levels

whether the microbiome in patients with ECP and FD-P affects progression of chronic inflammation in the pancreas. Small intestinal bacterial overgrowth (SIBO) has been observed in patients with chronic pancreatitis and is thought to be more likely to arise in patients with chronic pancreatitis, because of reduced pancreatic synthesis of antimicrobial peptides, impaired motility, and abnormal chyme formation in the lumen of small intestine. SIBO also exacerbates pancreatic exocrine insufficiency[36]. In addition, bacteria identified in human pancreatic cancers are representative of the major genera of gut bacteria, such as *Proteobacteria*[36]. However, evidence for a causal relationship between gut dysbiosis and pancreatic diseases is limited.

Trypsin-PAR2 Pathway

Trypsin works as an agonist on PAR-2 (protease activated receptor-2; strongly expressed in the small intestine, colon, liver, and pancreas) and induces leukocyte rolling, adhesion, extravasation, and release of mediators from mast cells, which, together with tryptase, also works on PAR-2 as agonists (**Fig. 3**)[37]. Infiltration of these leukocytes and mast cells in the small intestine may lead to inflammation of the duodenum. Tryptase is released from degranulated mast cells in association with PAR2 receptors on eosinophils, another type of inflammatory cell, and causes epithelial breakdown, immune activation, visceral hypersensitivity, and activation of additional eosinophils[38]. The mutual interaction between duodenal inflammation and pancreatic dysfunction further suggests that they synergistically worsen each other's effects.

Duodenal Inflammation May Alter Gastric Motility

Because disturbance of gastric accommodation is a hallmark of FD, we used the ^{13}C-acetate breath test to measure AUC_5 and AUC_{15} values as the early phase of gastric emptying. Our data show that AUC_5 and AUC_{15} values in patients with ECP were significantly higher than those in FD-P patients[8]. This early phase of gastric emptying may be regulated by various incretins, such as GLP-1, GIP, and PYY-producing cells, in the upper small intestine, including those in the duodenum. In particular, GLP-1 and ghrelin coordinate to regulate early gastric emptying[39]. Previous studies reported that duodenal inflammation may modify early gastric emptying through various incretin-producing cells during duodenal inflammation in patients with FD. Indeed, among the population of inflammatory cells, macrophages modulate colonic peristaltic activity after stimulation by intestinal epithelial cell-secreted mediators in a CRH-dependent manner[40]. Impairment of the mucosal barrier is induced by duodenal inflammatory cell infiltration and increased mucosal permeability, which have a negative synergistic effect with each other.

Previous studies found a relationship between gastric dysmotility and pancreatic dysfunction[11]. However, further studies are needed to clarify whether pancreatic dysfunction is associated with gastric dysmotility through inflammatory responses in the duodenum.

Some Cases of FD with Pancreatic Abnormalities Progress to Early Chronic Pancreatitis

In Japan, to hinder the initial phase of chronic pancreatitis from progressing to chronic pancreatitis, new strate-

Table 1 Comparison of ECP and RFD[8, 10, 41]

			ECP	RFD
Cause			Alcohol, genetic, obstructive, idiopathic	Unknown (duodenal inflammation from multiple causes?)
Age			Late 50s	Late 50s
Sex			Male (in alcoholic ECP) Female predominance in non-alcoholic ECP	Female predominance
Symptoms	GSRS	Reflux	+	+
		Abdominal pain	+	+~++
		Dyspepsia	+	+
		Diarrhea	+	+
		Constipation	+	+
	FD symptoms	Early Satiety	+	++
		Postprandial abdominal fullness	++	++
		Epigastric pain	+	+
	Psychological symptoms	Anxiety	+	+
		Depressive mood	+	+
		Sleep disturbances	+	+
Abnormality of pancreatic enzyme		Amylase	+	−
		Lipase	+	−
		Elastase	−	−
		Trypsin	+	+ (in some patients)
		PLA-2	−	−
Gastric dysmotility	Overall		+	+
	Early phase (accommodation failure)		++	+~++
Duodenal inflammation			+	+
Microbiome			+	+
EUS findings			Total score of 2 is the most common	Most patients have positive result

ECP: early chronic pancreatitis; RFD: refractory functional dyspepsia; GSRS: Gastrointestinal Symptoms Rating Scale; EUS: endoscopic ultrasonography

gies for managing early chronic pancreatitis have been proposed[41]. The Japan Pancreatic Association (JPA) proposes that four clinical criteria, including epigastric pain and the presence of more than two EUS features, are needed for a diagnosis of early chronic pancreatitis (ECP)[41]. We previously compared the clinical characteristics of patients with FD and those with ECP but found no significant difference in GSRS score between these groups (**Table 1**). Interestingly, even though epigastric pain is a critical symptom in the diagnosis of ECP, our previous findings suggest that postprandial abdominal fullness and epigastric pain are as frequent in ECP as in FD (**Table 1**). In our previous study, nearly half (48%) of FD patients with pancreatic enzyme abnormalities had an EUS score of 1[8], which indicates that some FD patients who exhibit pancreatic organic abnormalities nevertheless fail to meet the criteria for ECP. We compared EUS findings in FD-P patients (n=54), ECP patients (n=26), and asymptomatic patients with pancreatic enzyme abnormalities (AP-P) (n=28). Lobularity (1/54: FD-P, 3/26: ECP and 0/28: AP-P), hyperechoic foci or strands (15/54: FD-P, 13/26: ECP and 4/28: AP-P), a hyperechoic MPD margin (6/54: FD-P, 14/26: ECP and 3/28: AP-P), and dilated side branches (0/54: FD-P, 3/26: ECP and 0/28: AP-P). However, there are no available data on the precise mechanisms of EUS findings in these diseases. Future studies should attempt to clarify differences in the mechanisms for EUS findings among these diseases.

It is interesting to note that while some populations of alcoholic ECP patients tend to be progressive[41], most non-alcoholic patients with ECP were found to have improved at 1 and 2 years of follow up[8,26]. Masamune et al have reported that four of 83 cases of ECP progressed to chronic pancreatitis[41]. However, the present FD-P patients and ECP patients were similar clinically[42], and some FD-P patients eventually developed ECP. Two of 33 cases of FD-P progressed to ECP. However, there are no available data that indicate which FD-P patients progress to ECP

or chronic pancreatitis.

Conclusion

In this review, we suggest that pancreatic dysfunction is associated with functional dyspepsia through duodenal inflammation. Future studies should examine the roles of immunomodulatory cells, such as eosinophils, macrophages and mast cells, in pancreatic dysfunction-related inflammatory responses in the duodenum.

Conflict of Interest: None.

References

1. Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal disorders. Gastroenterology. 2016;150:1380–92.
2. Fisher RS, Parkman HP. Management of nonulcer dyspepsia. N Engl J Med. 1998;339:1376–81.
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;52:153–9.
4. Andersen BN, Scheel J, Rune SJ, Worning H. Exocrine pancreatic function in patients with dyspepsia. Hepatogastroenterology. 1982;29:35–7.
5. Jayaveni S, Nithyanandham K, Rose C. In vitro secretion of zymogens by bovine pancreatic acini and ultrastructural analysis of exocytosis. Biochem Biophys Rep. 2016;5:237–45.
6. Whitcomb DC, Lowe ME. Human pancreatic digestive enzymes. Dig Dis Sci. 2007;52:1–17.
7. Walker MM, Talley NJ. The Role of duodenal inflammation in functional dyspepsia. J Clin Gastroenterol. 2017;51: 12–8.
8. Wakabayashi M, Futagami S, Yamawaki H, et al. Comparison of clinical symptoms, gastric motility and fat intake in the early chronic pancreatitis patients with antiacid therapy-resistant functional dyspepsia patients. PLoS One. 2018;13:e0205165.
9. Okada R, Okada A, Okada T, Okada T, Hamajima N. Elevated serum lipase levels in patients with dyspepsia of unknown cause in general practice. Med Princ Pract. 2009;18:130–6.
10. 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;61:140–5.
11. 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;56:1629–35.
12. 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;24:3821–33.
13. Camilleri M, Bharucha AE, Farrugia G. Epidemiology, mechanisms, and management of diabetic gastroparesis. Clin Gastroenterol Hepatol. 2011;9:5–12.
14. Vanheel H, Vicario M, Vanuytsel T, et al. Impaired duodenal mucosal integrity and low-grade inflammation in functional dyspepsia. Gut. 2014;63:262–71.
15. Jung HK, Talley NJ. Role of the duodenum in the pathogenesis of functional dyspepsia: A paradigm shift. J Neurogastroenterol Motil. 2018;24:345–54.
16. Miwa H, Oshima T, Tomita T, et al. Recent understanding of the pathophysiology of functional dyspepsia: role of the duodenum as the pathogenic center. J Gastroenterol. 2019;54:305–11.
17. 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;8:8010–4.
18. Yamawaki H, Futagami S, Sakasegawa N, et al. Acotiamide attenuates central urocortin 2-induced intestinal inflammatory responses, and urocortin 2 treatment reduces TNF-alpha productions in LPS-stimulated macrophage cell lines. Neurogastroenterol Motil. 2020;32:e13813.
19. Thabane M, Marshall JK. Post-infectious irritable bowel syndrome. World J Gastroenterol. 2009;15:3591–6.
20. Mearin F, Perelló A, Balboa A, et al. Pathogenic mechanisms of postinfectious functional gastrointestinal disorders: results 3 years after gastroenteritis. Scand J Gastroenterol. 2009;44:1173–85.
21. Ma Q, Xing C, Long W, Wang HY, Liu Q, Wang RF. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. J Neuroinflammation. 2019;16:53.
22. DePalma G, Collins SM, Bercik P. The microbiota-gut-brain axis in functional gastrointestinal disorders. Gut Microbes. 2014;5:419–29.
23. Halim MA, Degerblad M, Sundbom M, et al. Glucagon-like peptide-1 inhibits prandial gastrointestinal motility through myenteric neuronal mechanisms in humans. J Clin Endocrinol Metab. 2018;103:575–85.
24. Kirchner H, Tong J, Tschöp MH, Pfluger PT. Ghrelin and PYY in the regulation of energy balance and metabolism: lessons from mouse mutants. Am J Physiol Endocrinol Metab. 2010;298:E909–19.
25. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab. 2013; 17:819–37.
26. 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.
27. Schulze S, Pedersen NT, Jørgensen MJ, Møllmann KM, Rune SJ. Association between duodenal bulb ulceration and reduced exocrine pancreatic function. Gut. 1983;24: 781–3.
28. Pellegrini S, Sordi V, Bolla AM, et al. Duodenal mucosa of patients with type 1 diabetes shows distinctive inflammatory profile and microbiota. J Clin Endocrinol Metab. 2017;102:1468–77.
29. Case RM. Synthesis, intracellular transport and discharge of exportable proteins in the pancreatic acinar cell and other cells. Biol Rev Camb Philos Soc. 1978;53:211–354.
30. Ji B, Logsdon CD. Digesting new information about the role of trypsin in pancreatitis. Gastroenterology. 2011;141: 1972–5.
31. Saluja A, Dudeja V, Dawra R, Sah RP. Early intra-acinar events in pathogenesis of pancreatitis. Gastroenterology. 2019;156:1979–93.
32. Agawa S, Futagami S, Yamawaki H, et al. State of anxiety may be associated with exocrine pancreatic insufficiency in functional dyspepsia patients with pancreatic enzyme abnormalities. J Clin Biochem Nutr. 2022;70:175–81.

33. 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;56:1629–35.
34. Yamawaki H, Futagami S, Kaneko K, et al. Camostat mesilate, pancrelipase, and rabeprazole combination therapy improves epigastric pain in early chronic pancreatitis and functional dyspepsia with pancreatic enzyme abnormalities. Digestion. 2019;99:283–92.
35. Ishikura H, Nishimura S, Matsunami M, et al. The proteinase inhibitor camostat mesilate suppresses pancreatic pain in rodents. Life Sci. 2007;80:1999–2004.
36. Akshintala VS, Talukdar R, Singh VK, Goggins M. Gut microbiome in pancreatic disease. Clin Gastroenterol Hepatol. 2019;17:290–5.
37. Patel M, Patel M, Shah G. Investigation of possible role of the PAR-2 receptor in intestinal inflammation. J Young Pharm. 2010;2:54–8.
38. 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.
39. Goyal RK, Guo Y, Mashimo H. Advances in the physiology of gastric emptying. Neurogastroenterol Motil. 2019; 31:e13546.
40. Baritaki S, deBree E, Chatzaki E, Pothoulakis C. Chronic stress, inflammation, and colon cancer: A CRH system-driven molecular crosstalk. J Clin Med. 2019;8:1669.
41. Masamune A, Nabeshima T, Kikuta K, et al. Prospective study of early chronic pancreatitis diagnosed based on the Japanese diagnostic criteria. J Gastroenterol. 2019;54: 928–35.
42. Futagami S, Yamawaki H, Agawa S, et al. Comparison of functional dyspepsia and early chronic pancreatitis. J Nippon Med Sch. 2020;87:2–6.

(Received, September 13, 2021)
(Accepted, November 22, 2021)
(J-STAGE Advance Publication, January 25, 2022)