Review Article

Pancreatic dysfunction and duodenal inflammatory responses coordinate with refractory epigastric pain including functional dyspepsia

“A narrative review”

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ABSTRACT

Functional dyspepsia (FD) in the past, has been found to be associated with patients with pancreatic enzyme abnormalities and chronic pancreatitis in a certain population of patients who suffered from this disease. Since 2009, when the idea of early chronic pancreatitis (ECP) first emerged, the utility of endoscopic ultrasonography (EUS) has gained our attention as it may play an important role in distinguishing ECP from dyspepsia patients. Although the symptoms of patients with pancreatic enzyme abnormalities and pancreatic dysfunction overlap with those of dyspepsia, there are no available data to explain the direct relationships and linkages between pancreatic dysfunction and dyspeptic symptoms. The disturbance of exocrine pancreatic enzyme function and the reduction of pancreatic endocrine levels, such as insulin, may be associated with dyspeptic symptoms through impaired gastric emptying and duodenal inflammation. Recently, some studies have focused on the role of duodenal pathophysiology in gastric motility, bicarbonate secretion, and digestion. Since the reduction of bicarbonate secretion by pancreatic dysfunction fails to neutralize gastric acid in the proximal part of the duodenum, impaired bicarbonate secretion by pancreatic dysfunction in turn fails to protect the duodenal mucosa against gastric acid influx, thereby inducing duodenal inflammation. In addition, it has been suggested that elevated trypsin levels might be partly associated in part with duodenal inflammatory responses through PAR2-related immunomodulatory cells. This article offers a review on how duodenal inflammation may play a role in the etiology of FD and demonstrates whether pancreatic dysfunction may be associated with FD through intestinal inflammation.
Introduction

According to the Rome IV criteria, FD is defined as the presence of one or more of the following symptoms: postprandial fullness, early satiation, epigastric pain, or epigastric burning, with no evidence of organic disease to explain these symptoms, the criteria being fulfilled for the last three months with symptom onset at least six months prior to diagnosis\(^1\). Thus, the diagnostic criteria for FD require that one rule out any other potential causes (Figure 1)\(^2\). The relationship between pancreatic dysfunction and dyspepsia has been studied in the past\(^1\). Previous studies have reported that a certain population of FD shows an overlap with pancreatic enzyme abnormalities and chronic pancreatitis\(^3\) -\(^6\). Since 2009, when the concept of early chronic pancreatitis (ECP) was first introduced in the clinical diagnostic criteria for chronic pancreatitis, the utility of endoscopic ultrasonography (EUS) has attracted our attention as it may play a pivotal role in distinguishing ECP from dyspepsia patients. ECP patients were diagnosed with imaging findings of two or more EUS findings among four findings listed in Figure 2 and clinical findings of two or more symptoms including repeated attacks of epigastric pain, abnormalities in blood/urine pancreatic enzymes, exocrine pancreatic dysfunction, a chronic alcohol intake (60g/day) or variants in pancreatitis-related genes, and past history of acute pancreatitis (Figure 2). According to the FD diagnostic criteria, there should be no evidence of structural disease on ultrasonography, upper endoscopy, or computed tomography, which is likely to explain any of the symptoms of FD. That being said, if the patients show any structural abnormalities on EUS, which can detect slight abnormalities not detected by these other tests, the patient can still be diagnosed with FD based on the current criteria, even in the presence of structural abnormalities of the pancreas on EUS. If the patients have less than two structural abnormalities among those listed for ECP criteria, they are not to be diagnosed with ECP; patients should have two or more structural abnormalities to meet the ECP criteria for diagnosis.
While the pathophysiology of FD is not been fully understood and is considered to be multifactorial, it has been suggested that local inflammation in the gastrointestinal tract, and in particular, duodenal inflammation, may play an important role in the pathophysiology of FD. In this article, we reviews how local inflammation in the gastrointestinal tract may play a role in the pathophysiology of FD and addresses whether pancreatic dysfunction may be associated with functional dyspepsia through intestinal inflammation.
Pancreatic dysfunction and functional dyspepsia

Pancreatic dysfunction can be divided into three categories: exocrine dysfunction, endocrine dysfunction and decreased bicarbonate secretion. First, pancreatic enzyme abnormalities due to exocrine dysfunction seen in ECP patients leads to an elevation of pancreatic enzyme levels. The elevation of trypsin has been shown to be the most sensitive marker for both ECP and FD patients, as shown in one of our previous studies. Okada et al. revealed relatively high serum lipase levels in patients with idiopathic chronic dyspepsia. Interestingly, half of the enrolled patients with PPI-refractory FD exhibited pancreatic enzyme abnormalities in our previous study. In addition, Hashimoto et al. also showed that 76.2% of FD patients were positive for abnormalities in trypsin levels. Furthermore, Sahai et al. have also reported that dyspepsia might be an atypical presentation of pancreatic disease as diagnosed by endoscopic ultrasonography (EUS). Although the symptomatology of patients with pancreatic enzyme abnormalities and pancreatic dysfunction overlap with those presenting with dyspepsia symptoms, there were no available data to explain a precise relationship between pancreatic dysfunction and dyspeptic symptoms. Fujikawa et al. have shown that over 70% of FD patients with symptoms of postprandial distress syndrome exhibited pancreatic exocrine dysfunction.

In addition, patients with severe aggravated pancreatic dysfunction such as diabetes mellitus, have been reported to exhibit gastroparesis. Considering these studies and those of others, dysfunction of exocrine pancreatic enzymes and reduction in pancreatic endocrine levels 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...
parasympathic pathways. Therefore, delayed gastric motility is associated with a time mismatch between blood glucose and insulin secretion jeopardizing the regulation of postprandial glycemia, and in turn, gastric dysmotility may be linked with pancreatic dysfunction. Further studies are warranted to clarify the impact of pancreatic dysfunction on the etiology of FD.

**Duodenal inflammation plays pivotal roles in FD patients**

Several studies have focused on the interaction between FD patients and duodenal inflammation and it has also been shown that a variety of inflammatory cells such as eosinophils, macrophages, and mast cells in the duodenal mucosa. Although the brain-gut-axis can be reported to mediate the activation of mast cells in the GI tract by stimulating the production of corticotropin-releasing hormone (CRH), which has been linked to mucosal permeability via the activation of migrated inflammatory cells, there are no data available on prolonging of inflammatory cells in the intestine. In addition, Yuan et al reported that anxiety and depression are associated with increased mast cell counts and degranulation of duodenal mast cells in FD. Considering the migration of macrophage infiltrations in the lamina propria and mesenchymal muscularis in urocortin 2-treated rat models, continuous CRF stimulation under stressful conditions may aggravate mucosal inflammation in the course of infection. In our study, we speculated that microbiota as well as LPS stimulation, play important roles in patients suffering from FD or IBS. Infectious gastroenteritis is thought to be a risk factor for the development of FD and IBS. Indeed, there is a separate category of post-infectious functional gastrointestinal diseases. Gut microbiota can also indirectly influence FD symptoms through the brain-gut axis and can play an important role in the host’s physiology, homeostasis, CNS function and the host’s behavior, subsequently
inducing gut inflammation. Gut hormones secreted from the duodenal mucosa, including GLP-1, GIP, and PYY have been shown to play critical roles in gastric motility and the absorption of nutrients. To clarify the differences in duodenal inflammatory responses between functional dyspepsia with pancreatic enzyme abnormalities (FD-P) patients and ECP patients, we compared various phenotypes of duodenal inflammatory cells such as GLP-1-positive cells and degranulated eosinophils between FD-P patients and ECP patients. Pancreatic enzyme excretion is also affected by environmental factors in the mucosa of the duodenum and in turn, pancreatic dysfunction may affect duodenal inflammatory responses (Figure 3). However, there are no available data on the relationship between duodenal inflammatory responses and pancreatic dysfunction in patients with FD.

**Association between pancreatic dysfunction and the duodenum**

(1) *Decreased pancreatic bicarbonate secretion in the duodenum*

Since reduced bicarbonate secretion due to pancreatic dysfunction fails to neutralize gastric acid in the proximal part of the duodenum, impaired bicarbonate secretion by pancreatic dysfunction cannot protect the duodenal mucosa against gastric acid influx and it induces duodenal mucosal inflammation (Figure 3). Notably, it has been suggested that duodenal inflammation further induces pancreatic dysfunction via leaky intestinal mucosa, which leads to an increase in antigenic load from the intestinal lumen, activating the immune system and eventually results in the destruction of pancreatic β cells (Figure 3). Indeed, it has been reported that the intestinal mucosa of patients with type 1 diabetes mellitus shows elevated levels of macrophage infiltration, where pancreatic dysfunction leads to the destruction of beta cells.

(2) *Pancreatic exocrine dysfunction*
Pancreatic acinar cells have the highest rate of protein turnover among human tissues with synthesis and secretion of the high volumes of digestive enzymes and exhibit a rich network of ER\textsuperscript{29}. In acute pancreatitis, certain stimulations including genetic alterations, alcohol, autoimmunity, and infections, trigger the inappropriate activation of trypsin\textsuperscript{30}. Some of these stimulants may overlap with the constellation of factors associated with the etiology of ECP and FD. This suggests that trypsin plays a critical role as a first-line factor in the activation cascade of pancreatic enzymes (Figure 4). Therefore, we hypothesized that in ECP and FD-P, some stimulations trigger the activation of trypsin. This phenomenon may then lead to sustained pancreatic duct inflammation and sustained inflammations, which induce pancreatic acinar cell death through the activation of trypsinogen, the infiltration of inflammatory cells and the upregulation of ER stress.\textsuperscript{31} We have also reported that FD-P patients have also exhibited exocrine pancreatic dysfunction\textsuperscript{32} as well as previous study\textsuperscript{33}. Since there were no available data about the exocrine pancreatic dysfunction in ECP patients, further studies will be needed to clarify it in ECP patients. In our data, the treatment with camostat mesilate improved epigastric pain in ECP patients.\textsuperscript{34} Ishikura et al have reported that camostat mesilate reduce pancreatic pain through the inhibition of neuronal activation in rodents\textsuperscript{35}. Considering of Ishikura’s study, camostat mesilate may improve pancreatic pain through the inhibition of neuronal activation. In addition, we have reported the treatment including camostat mesilate improved EUS findings in one year-follow up study\textsuperscript{26}. Further studies will be needed to clarify why camostat mesilate can improve EUS findings in ECP patients.

\textbf{(3)Disorganized microbiomes}

The gut microbiota plays a major role in human physiology through its effects on metabolism, modulation of the mucosal immune system, facilitation of digestion, and
modulation of intestinal architecture. Gut microbiota alterations are also found in pancreatic disease and have been considered to play a role in the pathogenesis of several pancreatic diseases, including pancreatitis and pancreatic cancer. Gut dysbiosis is thought to contribute to the pathogenesis of pancreatic diseases. Further studies will be needed to clarify whether the microbiome in patients with ECP and FD-P affects the advances of chronic inflammation in the pancreas. Small intestinal bacterial overgrowth (SIBO) has been observed in patients with chronic pancreatitis. SIBO is thought to be more likely to arise in patients with chronic pancreatitis due to reduced pancreatic synthesis of antimicrobial peptides, impaired motility and abnormal chyme formation in the lumen of small intestine. Then, SIBO also exacerbates pancreatic exocrine insufficiency. In addition, the bacteria identified in human pancreatic cancers are representative of the major genera of gut bacteria such as *Proteobacteria*. However, there is still only limited evidence supporting a causal relationship between gut dysbiosis and pancreatic diseases.

**Trypsin-PAR2 pathway**

Trypsin works on PAR-2 (protease activated receptor-2; is strongly expressed in the small intestine, colon, liver and pancreas) as an agonist and induces leukocyte rolling, adhesion, extravasation, and release of mediators from mast cells, both of which together with tryptase also work on PAR-2 as agonists (Figure 3). 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 cells, and brings about epithelial breakdown, promotes immune activation, induces visceral hypersensitivity, and activates more eosinophils. The mutual interaction
between duodenal inflammation and pancreatic dysfunction further suggests the possibility that they synergistically worsen each other’s effects.

**Duodenal inflammation may alter gastric motility**

Since the disturbance of gastric accommodation is a hallmark of FD, we measured AUC₅ and AUC₁₅ values as the early phase of gastric emptying using the $^{13}$C-acetate breath test. Our data show that AUC₅ and AUC₁₅ values in patients with ECP were significantly higher than those in FD-P patients. 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. Especially, GLP-1 and ghrelin coordinate to regulate the early phase of gastric emptying. Previous studies have shown that duodenal inflammation may modify early gastric emptying through various incretin-producing cells during duodenal inflammation in patients with FD. Indeed, macrophages, among the population of inflammatory cells, modulate colonic peristaltic activity after stimulation by intestinal epithelial cell-secreted mediators, in a CRH-dependent manner. Impaired mucosal barrier is induced by duodenal inflammatory cell infiltration and increased mucosal permeability with a negative synergistic effect on each other.

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

**Certain FD patients with pancreatic abnormalities advance into early chronic pancreatitis**
In Japan, to hinder the initial phase of chronic pancreatitis from advancing into chronic pancreatitis, new strategies for addressing chronic pancreatitis in its early stages have been proposed. According to the Japan Pancreatic Association (JPA), four clinical criteria including epigastric pain and the presence of more than two EUS features, are needed for the diagnosis of early chronic pancreatitis (ECP). We have previously compared the clinical characteristics of patients with FD with those of patients with ECP. However, we did not find significant differences in GSRS scores between FD patients and ECP patients (Table 1). Interestingly, even though epigastric pain has been considered as one of the critical symptoms in the diagnosis of ECP, our previous study suggests that both postprandial abdominal fullness and epigastric pain are as frequently seen 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, which means that there are some FD patients who although, to a certain extent, exhibit pancreatic organic abnormalities, they nevertheless fail to meet the criteria of ECP. We compared EUS findings in FD-P patients (n=54) with those in ECP patients (n=26) and those in asymptomatic patients with pancreatic enzyme abnormalities (AP-P) (n=28). In our data, 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), 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 was no available data about the precise mechanisms of EUS findings occurred in these diseases. Further studies will be needed to clarify the differences in the mechanisms in EUS findings among these diseases.

It is interesting to note that while some populations of alcoholic ECP patients tend to be progressive, most non-alcoholic ECP patients are found to get better at 2 years of follow up or 1 year follow up. Masamune et al have reported that four cases of eighty-three ECP advanced into chronic pancreatitis. On the other hand, in our data, FD-P patients and ECP
patients were similar clinical populations\textsuperscript{42} and some FD-P patients are seen to eventually develop ECP. In our data, two cases of thirty-three FD-P patients advanced into ECP patients. However, there are no available data what kinds of FD-P patients advance into ECP or chronic pancreatitis.

**Conclusion**

In this review, we suggest that pancreatic dysfunction may be associated with functional dyspepsia through duodenal inflammation. Further studies are needed to clarify the roles of immunomodulatory cells such as eosinophils, macrophages and mast cells in pancreatic dysfunction-related inflammatory responses in the duodenum.
Figure legends

Figure 1. Flowchart of diagnosis of refractory epigastric pain including functional dyspepsia and early chronic pancreatitis

We have to exclude structural diseases such as hepatobiliary diseases, GI tract diseases and chronic pancreatitis through the physical examinations, blood tests, endoscopy and CT scanning. After exclusion of structural disease, we can diagnose functional dyspepsia and early chronic pancreatitis.

ECG: electrocardiography; AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; CT: computed tomography; US: Ultrasonography; FD: Functional dyspepsia

Figure 2. Diagnosis of early chronic pancreatitis

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

Figure 4. The relationship between impaired pancreatic enzyme secretion and pancreatic enzyme levels
References

1. Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal Disorders. Gastroenterology 2016; 150: 1380-1392.

2. Fisher RS, Parkman HP. Management of nonulcer dyspepsia. N Engl J Med 1998; 339: 1376-1381.

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. Andersen BN, Scheel J, Rune SJ, Worning H. Exocrine pancreatic function in patients with dyspepsia. Hepatogastroenterology 1982; 29: 35-37.

5. Jayaveni S, Nithyanandham K, Rose C. In vitro secretion of zymogens by bovine pancreatic acini and ultra-structural analysis of exocytosis. Biochem Biophys Rep 2016; 5: 237-245.

6. Whitcomb DC, Lowe ME. Human pancreatic digestive enzymes. Dig Dis Sci 2007; 52: 1-17.

7. Walker MM, Talley NJ. The Role of Duod 2017; 51: 12-18.

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 anti-acid 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: 130-136.

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: 140-145.
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: 1629-1635.

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: 3821-3833.

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: 262-271.

15. Jung HK, Talley NJ. Role of the Duodenum in the Pathogenesis of Functional Dyspepsia: A Paradigm Shift. J Neurogastroenterol Motil 2018; 24: 345-354.

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: 305-311.

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: 8010-8014.

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: 3591-3596.
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: 1173-1185.

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: 419-429.

23. Halim MA, Degerblad M, Sundbom M, Karlbom U, Holst JJ, Webb DL, et al. Glucagon-Like Peptide-1 Inhibits Prandial Gastrointestinal Motility Through Myenteric Neuronal Mechanisms in Humans. J Clin Endocrinol Metab 2018; 103: 575-585.

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: E909-919.

25. Campbell JE, Drucker Dj. Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab 2013; 17: 819-837.

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: 781-783.

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: 1468-1477.
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: 1972-1975.

31. Saluja A, Dudeja V, Dawra R, Sah RP. Early Intra-Acinar Events in Pathogenesis of Pancreatitis. Gastroenterology 2019; 156: 1979-1993.

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, in press.

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: 1629-1635.

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: 283-292.

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: 290-295.

37. Patel M, Patel M, Shah G. Investigation of Possible Role of the PAR-2 Receptor in Intestinal Inflammation. J Young Pharm 2010; 2: 54-58.

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: 928-935.

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.
Fig. 1
Fig. 2

Diagnosis of early chronic pancreatitis

Clinical findings

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

Images

a. EUS findings (more than 2 score including 1 or 2 item)
   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. 3
Fig. 4

Trypsin activation
↓
Autodigestion
↓
Pancreatic dysfunction

Trypsin elevation

Impaired pancreatic enzyme secretion

Pancreatic acinar cell injuries
Pancreatic acinar cell death
Pancreatic enzyme elevation
Table 1 Comparison of ECP and RFD$^{8,10,41}$

|                | ECP                                      | RFD                                      |
|----------------|------------------------------------------|------------------------------------------|
| Etiology       | Alcohol, genetic, obstructive, idiopathic| Unknown (duodenal inflammation from multiple causes?) |
| Age            | Late 50s                                 | Late 50s                                 |
| Sex            | Male in alcoholic ECP                    | Female predominance                       |
|                | Female predominance in non-alcoholic ECP |                                          |
| Symptoms       | GSRS                                     |                                          |
|                | Reflex                                   |                                          |
|                | +                                        | +                                        |
|                | Abdominal pain                           |                                          |
|                | +                                        | + ~++                                    |
|                | Dyspepsia                                |                                          |
|                | +                                        | +                                        |
|                | Diarrhea                                 |                                          |
|                | +                                        | +                                        |
|                | Constipation                             |                                          |
|                | +                                        | +                                        |
| FD symptoms    | Early Satiety                            |                                          |
|                | +                                        | ++                                       |
| Psychological symptoms          | Anxiety       | + | + |
|--------------------------------|---------------|---|---|
|                                | Depressive mood | + | + |
| Psychological symptoms          | Sleep disturbances | + | + |
| Abnormality of pancreatic enzyme| Amylase       | + | - |
|                                | Lipase        | + | - |
|                                | Elastase      | - | - |
|                                | Trypsin       | + | + (in some patient) |
|                                | PLA-2         | - | - |
| Gastric dysmotility             | Overall       | + | + |
|                                | Early phase (Accommodation failure) | ++ | +~++ |
| Duodenal inflammation           |               | + | + |
| Microbiome                      |               | + | + |
| EUS findings                    | Total score of 2 | More than half of the patient |
| ECP: Early chronic pancreatitis; RFD: Refractory functional dyspepsia; GSRS: Gastrointestinal Symptoms Rating Scale; EUS: Endoscopic ultrasonography | is the most common finding |