Functional Dyspepsia: Pathogenesis, Diagnosis, and Treatment

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Functional dyspepsia (FD) is a functional gastroduodenal disorder presenting with dyspeptic symptoms such as postprandial fullness, early satiety, epigastric burning, or epigastric pain in the absence of organic disease. The factors supposed to be related with symptom generation are delayed gastric emptying, impaired accommodation of the proximal stomach, abnormal gastric acid secretions, visceral hypersensitivity, and psychological factors. If \textit{H. pylori} is positive, eradication treatment is recommended. The evidence-based clinical practice guideline for FD recently developed by The Japanese Society of Gastroenterology (JSGE) proposed a two-step pharmacological treatment. The first-line treatment includes prokinetic agents or acid suppression therapy. If initial treatment fails, anxiolytics, antidepressants, or traditional Japanese herbal medicine can be employed.

**Keywords**: functional dyspepsia, Rome III, postprandial distress syndrome, epigastric pain syndrome, \textit{H. pylori}

**Introduction**

Functional dyspepsia (FD) is a functional gastroduodenal disorder presenting with dyspeptic symptoms such as postprandial fullness, early satiety, epigastric burning, or epigastric pain in the absence of organic disease, resulting from gastroduodenal lesions. When FD patients present postprandial fullness and/or early satiety, they are sub-classified as postprandial distress syndrome (PDS). When they present epigastric burning and/or epigastric pain postprandial fullness and/or early satiety they are sub-classified as epigastric pain syndrome (EPS). The Domestic/International Gastroenterology Surveillance Study (DIGEST) reported the worldwide prevalence of upper gastrointestinal (GI) symptoms. A mean of 46.4% of subjects experiencing at least one GI symptom, while 28.1% experiencing upper GI symptoms. As stated above, upper GI symptoms are common in the world. FD is one of the most common GI disorders encountered in clinical practice. This article summarizes the pathogenesis, diagnosis, and treatment strategy for FD.
Pathogenesis
The pathophysiological factors supposed to contribute symptom generation in FD are delayed gastric emptying, impaired accommodation of the proximal stomach, abnormal gastric acid secretion, visceral hypersensitivity, and psychological factors. Postprandial gastric motility has two phases. After food ingestion, the first phase occurs when an accommodation reflex occurs in the proximal stomach and in the subsequent phase, distal gastric emptying occurs. Impaired accommodation and delayed gastric emptying are often linked to early satiation and postprandial fullness, namely PDS symptoms. By gastric barostat, impaired gastric accommodation to a meal was found in 40% of FD patients. In impaired gastric accommodation, role of nitric oxide is suggested. The pathophysiological role of delayed gastric emptying in FD is still unclear. Previously, delayed gastric emptying was evidenced in 59% of dyspeptic patients. However, the other group reported that its prevalence in the dyspeptic symptoms was 23%. Even in gastroparesis, which is characterized by delayed gastric emptying, the relationship between symptom improvement and accelerated gastric emptying is questioned. We should carefully discuss about pathophysiological role of gastric emptying in FD. Visceral hypersensitivity is involved in functional disorders throughout the gastrointestinal system, including non-erosive gastroesophageal reflux disease, irritable bowel syndrome, and FD. When a balloon was distended in the proximal stomach of FD patients and healthy controls by gastric barostat, the threshold at which pain was perceived was significantly lower in the FD patients than in the controls. Hypersensitivity to gastric distention has been reported in 30% to 35% of patients with FD. FD patients also seem to have hypersensitivity in the stomach and duodenum to gastric acid, bile acid, and some nutrients such as fat. Spontaneous duodenal acid exposure was found to be increased in a subset of FD patients with prominent nausea, and this was associated with more severe dyspeptic symptoms. A recent large-scale epidemiological study found that anxiety scores were higher in persons with FD symptoms than in persons without such symptoms. Anxiety disorders and depression are often regarded as comorbidities of FD. Talley et al. reported that a lower body mass index and a more consistent predominant symptom pattern were independent predictors of a decreased placebo response. In the trial, placebo response rates in FD patients were reported as 30% to 40%. No association was seen with age, gender, type of clinical center, baseline symptom score, baseline or change in gastric emptying, or baseline quality of life. Some FD patients may respond to hypnotherapy. Geeraerts et al. reported an association of a history of abuse and gastric sensorimotor function in FD. In the report, particularly sexual abuse, rather than physical abuse, influenced gastric sensitivity and motor function. Therefore, involvement of psychological factors in FD is suggested. The risk of irritable bowel syndrome increases after Salmonella infection. A similar phenomenon is observed in FD, called post-infectious FD (PI-FD). Compared with controls, persons who had experienced acute Salmonella gastroenteritis were about 5 times more likely to experience dyspepsia. Duodenal focal aggregation of T cells was found in PI-FD patients. Recently, Vanheel et al. reported increased duodenal permeability and low-grade inflammation in FD patients as demonstrated by increased infiltration of mucosal mast cells and eosinophils. Thus, the restoration of intestinal barrier integrity may be a potential therapeutic means of treating FD patients. Recently published meta-analysis suggests that H. pylori eradication has a small but statistically significant benefit in the treatment of FD. Helicobacter pylori-positive dyspeptic patients will need to be treated to achieve symptom relief. Several randomized controlled trials involving populations in the West observed H. pylori eradication had a small but statistically significant advantage over a placebo. On the other hand, a double-blind, randomized, placebo-controlled trial in Singapore showed a significant effect that 24% of patients receiving H. pylori eradication treatment achieved symptom resolution compared with only 7% receiving a placebo. In addition, a randomized study in India reported that H. pylori eradication treatment was superior to treatment with sucralfate in producing symptom relief (81% vs 33%, p = 0.0003). Success-
ful *H. pylori* eradication improved the quality of life (QOL) in patients with FD, in particular *H. pylori*-positive patients with ulcer-like FD or dysmotility-like FD in Japan.\(^{15}\) We previously reported that the muscle-specific miRNAs miR-1 and miR-133 were significantly down-regulated in the stomachs of *H. pylori*-infected mice. Gastric emptying was significantly accelerated, and the muscular layers of the stomachs were significantly thickened in *H. pylori*-infected mice. These findings provide insight into the molecular pathogenesis of gastric motility disorders, including functional dyspepsia.\(^{19}\) This also might be a reason *H. pylori*-associated dyspepsia is considered an organic disease and should be dealt as a different disease entity from FD.\(^{20,21,22}\) In 2014, specialists from all over the world gathered in Kyoto to discuss this issue. Finally, The Kyoto Consensus, which designated *H. pylori*-associated dyspepsia as a different disease entity from FD, was made.\(^{23,24}\) When *H. pylori* eradication therapy was effective for dyspeptic symptoms, patients can be considered as *H. pylori*-associated dyspepsia. The evaluation should be performed after 6–12 months of observation.

Ghrelin, a growth hormone-releasing peptide has been reported to play a role in the control of food intake and in energy homeostasis, and to stimulate gastric acid secretion and gastrointestinal motility.\(^{25,26}\) Akamizu et al. reported that repeated administration of ghrelin (3 µg/kg for 30 min twice a day for 2 weeks) has stimulatory effects on appetite in patients with FD.\(^{27}\) Arai et al. reported that rikkunshito, a traditional Japanese medicine, improved upper gastrointestinal symptoms in patients with FD accompanied by an increase in the levels of acylated ghrelin.\(^{28}\) Taken together, the role of ghrelin in FD symptom generation was suggested.

### Diagnosis

In 1994, the Rome criteria were developed in an attempt to meet the clinical need to systematically describe functional gastrointestinal disorders. The recent Rome III criteria, developed in 2006 are commonly employed. According to the Rome III criteria,\(^{1}\) FD is defined as the presence of early satiation, postprandial fullness, epigastric pain, or epigastric burning in the absence of an organic, systemic, or metabolic disease that could explain the symptoms (Table 1). These symptoms must have been present continuously for the past 3 months with initial symptom onset at least 6 months prior to diagnosis.

**Table 1. Rome III Diagnostic Criteria for Functional Dyspepsia**

<table>
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<th>Diagnostic Criteria for FD</th>
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<td>1. One or more of the following must be present:</td>
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<td>a. Bothersome postprandial fullness</td>
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<td>b. Early satiation</td>
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<tr>
<td>c. Epigastric pain</td>
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<td>d. Epigastric burning</td>
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- No evidence of structural disease (including on upper endoscopy) that is likely to explain the symptoms. These symptoms must have been present continuously for the past 3 months with initial symptom onset at least 6 months prior to diagnosis.

**Subclassification**

**Postprandial Distress Syndrome**

Diagnostic Criteria: Must include one or both of the following:

1. Bothersome postprandial fullness, occurring after ordinary-sized meals at least several times per week.
2. Early satiation that prevents completing a regular meal at least several times per week.

(Upper abdominal bloating, postprandial nausea, or excessive belching can be present. Epigastric pain syndrome may also be present.)

**Epigastric Pain Syndrome**

Diagnostic Criteria: Must include all of the following:

1. Pain or burning localized to the epigastrium of at least moderate severity at least once per week.
2. The pain is intermittent.
3. Not generalized or localized to other abdominal or chest regions.
4. Not relieved by defecation or passage of flatus.
5. Not fulfilling criteria for gallbladder or sphincter of Oddi disorders.

(The pain may be of a burning quality but without a retrosternal component. The pain is commonly induced or relieved by ingestion of a meal, but may occur while fasting. Postprandial distress syndrome may also be present.)
present continuously for the past 3 months with initial symptom onset at least 6 months prior to diagnosis. The Rome III criteria also proposed subclassification of FD as PDS or EPS. However, a cohort of FD patients who overlap PDS and EPS is reported. Recently, the Rome III criteria was revised as Rome IV. In Rome IV, not only postprandial fullness, but also epigastric pain, epigastric burning and early satiation should be ‘bothersome’ symptoms.

For the diagnosis of FD, excluding organic diseases is essential. Broad and diverse diseases, namely peptic ulcer, reflux esophagitis, abdominal cancer, biliary tract disease, pancreatitis, and coronary artery disease can present dyspepsia. For differential diagnosis, esophagogastroduodenoscopy (EGD) is the most important. In general practice, laboratory testing and imaging (abdominal ultrasound) are widely used in the evaluation of patients with dyspepsia. The Japanese Society of Gastroenterology (JSGE) recently developed an evidence-based clinical practice guideline for FD. The guideline states that when prompt access to EGD is not applicable, starting initial treatment (maximum four weeks) without EGD under the diagnosis as uninvestigated FD is stated as an option. However, such an initial treatment is limited within 4 weeks. It is reasonable to consider aggressive and prompt workup including EGD for patients with several alarm signs (e.g., unintended weight loss, progressive dysphagia, persistent vomiting, family history of cancer, evidence of GI bleeding).

As stated above, to consider possibility of *H. pylori*-associated dyspepsia, diagnostic tests for *H. pylori* infection are recommended. Nonsteroidal anti-inflammatory drugs or low dose aspirin can cause dyspepsia. If patients with dyspepsia are taking such medications, they should not be diagnosed as FD.

**Treatment**

According to the guideline by JSGE, once a patient is diagnosed with FD, the doctor should carefully explain the pathophysiology, reassure the patient of the benign nature of this condition, establish a good doctor-patient relationship, and then provide advice for daily living. *H. pylori* eradication is positioned separately from other treatment flows for FD with a high evidence level (strong recommendation). As pharmacological treatment, the guideline proposed two step treatment. If *H. pylori* eradication therapy was effective for dyspeptic symptoms, patients are considered to have *H. pylori*-associated dyspepsia. As pharmacological treatment, the guideline proposed a two step treatment. For the initial treatment, prokinetic agents or acid inhibitors, namely proton pump inhibitors (PPIs) or histamine H2 receptor antagonists (H2RA), are strongly recommended. As for the second-line treatment, anxiolytics, antidepressants, and Japanese herbal medicine should be considered (weak recommendations). If patients do not respond to these treatment regimens, they are classified as having refractory FD (Figure 1). These patients should be further examined for other organic disorders or referred to specialists using other approaches such as psychosomatic treatment.

We conducted a multicenter, randomized, placebo-controlled trial to investigate the effect of lansoprazole on FD. The scores for epigastric pain and epigastric burning were significantly improved in the lansoprazole group compared to the placebo group. A meta-analysis of placebo-controlled, randomized trials of PPIs in FD patients showed a significant benefit of 13% for PPIs over placebos. FD patients with epigastric pain (EPS group according to Rome III) rather than patients with meal-induced symptoms (PDS group according to Rome III) seemed to respond to PPIs. A
meta-analysis of placebo-controlled, randomized trials with H2RA in FD patients showed a significant benefit of 23% for H2 antagonists over placebo. Several types of prokinetic agents are used. Domperidone is a butyrophenone derivative that exerts antidopaminergic effects on peripheral dopamine-2 receptors. Trimebutine maleate is an opioid agonist that acts on the peripheral delta, mu, and kappa receptors. Mosapride is a 5-HT4 receptor agonist that also exhibits 5-HT3 receptor antagonist properties. A meta-analysis of placebo-controlled, randomized trials with prokinetic agents in FD patients showed a significant benefit of 33% for prokinetic agents over placebo. Recently, a new prokinetics, acotiamide which was specially designed for FD treatment was approved by Japanese health insurance and became available for FD treatment in Japan. Over 4 weeks, acotiamide significantly reduced symptom severity and eliminated meal-related symptoms in patients with FD. A meta-analysis of placebo-controlled, randomized trials with acotiamide in FD patients showed a significant benefit for acotiamide over placebo (pooled risk ratio 1.29). In a double-blind placebo-controlled study, amitriptyline significantly reduced total clinical symptom score and nausea in FD patients.

Eradication of *H. pylori* infection plays a limited, however significant role in the treatment of FD. Therefore, if *H. pylori* is positive, eradication treatment is recommended. Moreover, eradication treatment is strongly recommended because it prevents *H. pylori*-associated diseases such as gastric cancer. The committee of the Japanese Society for Helicobacter Research revised the guidelines for diagnosis and treatment of *H. pylori* infection in 2015. In 2013, *H. pylori* eradication therapy for gastritis was approved by national health insurance in Japan. Accumulation of data of *H. pylori* eradication on FD is expected. Antianxiety agents and herbal medicine have also been reported to be effective in FD. We conducted a multicenter, randomized, placebo-controlled, parallel-group trial to investigate the effect of rikkunshito, a traditional Japanese herbal medicine, on FD. In this study, epigastric pain was significantly improved in the rikkunshito group.

**Conclusion**

FD has great impact on QOL and also on socioeconomic costs. However, the mechanisms of FD are not fully understood. Further research is needed to provide better medical care for FD patients.

**References**