Recent Advances in the Definition and Management of Functional Dyspepsia

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In 2016, the Rome criteria were updated as Rome IV, and only minor changes were introduced for functional dyspepsia (FD). The major symptoms of FD now include not only postprandial fullness, but also epigastric pain and burning, and early satiation at above the “bothersome” level. Investigations into the effect of meal ingestion on symptom generation have indicated that not only postprandial fullness and early satiety but also epigastric pain and burning sensation and nausea (not vomiting) may increase after meals. *Helicobacter pylori* infection is considered to be the cause of dyspepsia if successful eradication leads to sustained resolution of symptoms for more than 6 months, and such a condition has been termed *H. pylori*-associated dyspepsia. Prompt esophagogastroduodenoscopy and *H. pylori* “test and treat” may be beneficial, especially in regions with a high prevalence of gastric cancer, such as east Asia. In terms of treatment, acotiamide, tandospirone, and rikkunshito are newly listed in Rome IV as treatment options for FD. Clinical studies in the field of FD should be strictly based on the Rome IV criteria until the next Rome V is published in 2026. (DOI: 10.2302/kjm.2020-0006-OA; Keio J Med 70 (1) : 7–18, March 2021)

Keywords: dyspepsia, bloating, fullness, epigastric pain, epigastric burning

Introduction

There has been continuous progress in gastroenterology in Japan, especially regarding gastrointestinal (GI) tract imaging, with a focus on morphology using endoscopy and abdominal X-rays. In contrast, despite the absence of organic disease, there has been little interest in so-called “functional gastrointestinal disorders (FGIDs),” which cause indefinite abdominal symptoms. However, because of increasing public interest in patient quality of life (QOL), attention has been increasingly focused on FGIDs, i.e., disorders that are associated with the physical and psychological stresses that prevail in modern society. The Rome criteria were amended as the Rome IV criteria and launched at Digestive Disease Week in San Diego, California, USA, May 21–25, 2016.¹ These amended Rome IV

publications updated the Rome III criteria of 2006² with new chapters, references, diagnoses, and graphics, and included the work of more than 120 specialists, including myself and clinicians from all over the world. The Rome IV book series includes Functional Gastrointestinal Disorders (vols. 1 and 2), Multidimensional Clinical Profile for Functional Gastrointestinal Disorders, Diagnostic Algorithms for Common GI Symptoms, Functional Gastrointestinal Disorders for Primary Care and Non-GI Clinicians, Pediatric Functional Gastrointestinal Disorders, and Diagnostic Questionnaires and Tables for Investigators and Clinicians.¹

In the field of gastroduodenal diseases, even though most gastroenterologists strongly focus on organic diseases such as peptic ulcers, chronic gastritis, and cancer, we renewed the classification and criteria of functional

Table 1. Rome IV Chapter Committee members (Gastroduodenal Committee)

Chair	Nicholas J. Talley	MD, PhD, FRACP	University of Newcastle, New Lambton, NSW, Australia
Co-chair	Vincenzo Stanghellini	MD	University of Bologna, Bologna, Italy
	Francis K.L. Chan	MD, FRCP	The Chinese University of Hong Kong, Hong Kong, China
	William L. Hasler	MD	University of Michigan Health System, Ann Arbor, MI, USA
	Juan-R Malagelada	MD, PhD	Autonomous University of Barcelona, Barcelona, Spain
	Hidekazu Suzuki	MD, PhD	Keio University School of Medicine, Tokyo, Japan
	Jan Tack	MD, PhD	University Hospital KU Leuven, Leuven, Belgium

gastroduodenal disorders as Rome IV³(Table 1).

Functional Gastroduodenal Disorders

In Rome IV, functional gastroduodenal disorders were again classified into four categories, in line with Rome III: (1) functional dyspepsia (FD), composed of postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS); (2) belching disorders, composed of excessive gastric and supragastric belching; (3) chronic nausea and vomiting disorders, composed of chronic nausea vomiting syndrome and cyclic vomiting syndrome (CVS); and (4) the newly listed cannabinoid hyperemesis syndrome (CHS) and rumination syndrome. There were some changes to each component, especially for belching disorders and chronic nausea and vomiting disorders.

Functional Dyspepsia

FD is a condition of impaired digestive function defined as the presence of dyspeptic symptoms such as PDS (mainly composed of early satiation or postprandial fullness) and EPS (mainly composed of epigastric pain or burning) in the absence of an organic disease.⁴ In the Rome IV section on FD,³ minor changes were introduced compared with Rome III.⁴ Among the major symptoms of FD, not only postprandial fullness but also epigastric pain and/or burning and early satiation are described as “bothersome” or “troublesome” symptoms. In line with Rome III, FD again includes two syndromes: PDS and EPS. PDS involves meal-induced dyspeptic symptoms, whereas EPS does not exclusively occur postprandially. However, these two syndromes can frequently overlap.⁵ Results of clinical research on the effect of meal ingestion on symptom generation has indicated that in patients with dyspepsia, not only postprandial fullness and early satiation but also epigastric pain or burning sensation and nausea (not vomiting) may increase after meals. Carbone et al.⁶ from the Translational Research Center for Gastrointestinal Disorders at the University of Leuven reported that by considering the relationship between epigastric pain and nausea in relation to meal ingestion, symptoms of PDS and EPS frequently coexist in patients with FD, and that postprandial symptoms substantially contribute

to the overlap diseases described in the previous Rome III definition. Carbone et al. also demonstrated that a more rigorous linking of symptoms to the time since the last meal for PDS may effectively separate PDS from EPS.⁶ Accordingly, the definition of PDS was slightly revised in Rome IV by including that, in addition to postprandial fullness and early satiation that are known to occur postprandially, other symptoms such as epigastric pain and burning in addition to bloating, belching, and nausea could also be triggered by ingesting a meal (Fig. 1).³ Furthermore, bloating, belching, and nausea can be present in both syndromes as possible adjunctive symptomatic features, although vomiting is extraordinary and should prompt a search for other diagnoses such as chronic nausea and vomiting syndrome or gastroparesis. Finally, the Rome IV criteria include not only PDS and EPS, but also the category of PDS and EPS overlap syndrome.

According to a population-based, cross-sectional survey,⁷ the prevalence of dyspepsia was 15%, but the overlap of FD subgroups was significantly less common than expected. In our web survey of 2012,⁵ the prevalence of FD was 7.0%, comprising PDS alone (4.7%), EPS alone (0.8%), and EPS-PDS overlap (1.5%), which suggests a lesser prevalence for the overlap syndrome in such a population-based survey. We also reported the results of other web surveys⁸ in which the prevalence of FD was 8.0%, including PDS alone (4.8%), EPS alone (0.8%), and EPS-PDS overlap (2.3%). In contrast, a house-to-house survey in a rural Indian community⁹ showed that the prevalence of FGIDs was 21.7% and that of dyspepsia was 14.7%. Among those with dyspepsia, 9% had EPS alone, 27% had PDS, and 64% had EPS-PDS overlap, suggesting a much higher rate of EPS-PDS overlap compared with that found in studies of other countries. Although a lower prevalence of EPS-PDS overlap was shown in a survey of a general Web population that could access the internet in Japan, a higher prevalence was shown in the population-based study in an Indian rural community. In a hospital-based population, the overlap of PDS and EPS is more frequently found than in the general population.¹⁰

The symptoms of FD not only significantly impair the patient's QOL but also contribute to the loss of work productivity. Brook et al. performed a retrospective analysis of payroll data and adjudicated health insurance medi-

Fig. 1. The revised categorization of postprandial distress syndrome and epigastric pain syndrome in Rome IV by including the concept of meal-related and meal-unrelated symptoms.

cal and prescription claims collected over a 4-year period from more than 300,000 employees and reported that employees with FD incur greater costs at all places of service and have lower levels of productivity than employees without FD.¹¹ Lacy et al. carried out a large questionnaire survey by mail among patients who met the Rome III criteria for FD and demonstrated that FD patients incurred significant direct and indirect costs and that work productivity was impaired by dyspeptic symptoms.¹² Furthermore, Bytzer et al. carried out a study of primary care patients with uninvestigated dyspepsia and found that work productivity loss grew with increasing severity of dyspeptic symptoms. Following 2 weeks of treatment, the mean improvement in work productivity was significantly higher in terms of both absenteeism (1 h versus 0.1 h, $P < 0.05$) and presenteeism (5.3 h versus 4.3 h, $P < 0.05$) in patients treated with esomeprazole versus a placebo.¹³ Furthermore, a survey in the USA of participants who met the Rome III criteria for FD, irritable bowel syndrome with constipation and/or chronic idiopathic constipation, and/or reported gastro-esophageal reflux diseases showed that FGID overlap was associated with greater symptom burden and increased physician consultations.¹⁴ We also previously evaluated whether there is

a direct association between the presence of FD and the severity of impaired sleep quality and the economic loss resulting from decreased work.¹⁵ In our study, although the association between impaired sleep quality and FD was indirect, concomitant impaired sleep quality could worsen economic losses such as reduced work productivity.¹⁵

A Novel and Clear Definition of *Helicobacter pylori*-associated Dyspepsia

Although the literature shows that the impact of *Helicobacter pylori* eradication in patients with *H. pylori*-infected gastritis is modest, a meta-analysis indicated a small but significant efficacy of this therapy for the relief of dyspeptic symptoms.¹⁶ In addition, antibiotic treatment of only 7–14 days was considered to be cost-effective.¹⁷

According to a systematic review and meta-analysis of clinical trials, *H. pylori* eradication therapy in chronic gastritis patients with dyspepsia is effective in approximately 30%, with a number needed to treat (NNT) of 15 and a slight but statistically significant effect.¹⁸ However, this is not a treatment of FD; rather, it is a “treatment of *H. pylori*-associated dyspepsia (HpD).” If dyspeptic

Fig. 2. The novel definition of *Helicobacter pylori*-associated dyspepsia adopted at the Kyoto Global Consensus meeting for *H. pylori* infection.

symptom remission continues for 6 months or more after *H. pylori* eradication, the symptoms of dyspepsia are deemed to be due to *H. pylori* infection and the condition is diagnosed as HpD,^{19,20} as defined internationally by the Kyoto Global Consensus meeting with the participation of internationally acclaimed delegates from the USA, Europe, and Asia^{21,22} (Fig. 2). As described in the clinical management flow-chart of FD in Rome IV,³ before a diagnosis of FD is made, alarm feature evaluation, esophagogastroduodenoscopy, and *H. pylori* “test and treat” should be performed.³ Especially in Asia, where the prevalence of gastric cancer is higher than in other regions,²³ prompt endoscopy²⁴ and *H. pylori* testing and treatment would be beneficial.²⁵ Nonetheless, eradication of *H. pylori* in dyspepsia patients is the most effective approach in terms of medical economics, as has been reported in young Asian patients with uncomplicated dyspepsia.²⁶ Therefore, endoscopy should not be applied to all individuals, but should be limited to older patients who have a high risk for gastric malignancy.

In this way, HpD has been clearly defined, but the underlying pathophysiological mechanisms of HpD remain to be elucidated. According to the study by Kawamura et al.,²⁷ 12 months after *H. pylori* eradication, dyspepsia symptoms were alleviated in 34 patients (75.6%) and these were diagnosed as having had HpD. The mean pepsinogen (PG) I value in the HpD group was significantly lower than that in the non-HpD group, whereas the PG II

values in the HpD group tended to be lower than those in the non-HpD group. On multivariate logistic regression analysis,²⁷ the PG II level was found to be a significant predictive factor for dyspeptic symptom relief in the HpD group, suggesting that the response of host gastric mucosa to *H. pylori* is a possible pathogenic factor for HpD. It is well known that the production of mucosal inflammation-related reactive oxygen species (ROS) is characteristic during innate immune responses to *H. pylori*, and that *H. pylori* uses various enzymes to counteract ROS, thereby facilitating the establishment of persistent infection. Because ROS-enhancing *H. pylori* strains might evoke dyspeptic symptoms, Matsuzaki et al. investigated the effects of polymorphisms of antioxidant proteins produced by *H. pylori*, such as neutrophil-activating protein A (NapA),²⁸ They demonstrated that *H. pylori* producing NapA with serine at amino acid 70 (Ser 70-NapA) was isolated from dyspeptic patients more frequently than *H. pylori* producing NapA with threonine at the same position (age-adjusted odds ratio, 2.88; 95% confidence interval, 1.19–6.94; $P = 0.019$),²⁸ suggesting that Ser 70-NapA-producing *H. pylori* might be a possible pathogenic strain causing HpD.

Pathophysiology

Because of the heterogenous and multifactorial nature of FD, the underlying pathophysiology of the disease remains to be clarified. Three major pathogenic mecha-

Pathogenesis of Functional Dyspepsia (FD)

Fig. 3. The possible etiological/pathological factors of functional dyspepsia.

nisms are generally envisioned, namely those related to gastrointestinal motility impairment, visceral hypersensitivity, and psychosocial stress; however, it is not clear to what extent each of these is attributable. Recently, food factors and the gut microbiota along with low-grade inflammation and infection are also considered to be important pathological factors in addition to the three classic major factors (**Fig. 3**), but again, the contribution of each factor is not clear.

Among these, delay or acceleration of gut motility and hypersensitivity in a portion of the gastroduodenum are assumed to be major underlying mechanisms in FD. Especially in PDS, impaired gastric accommodation can lead to distal redistribution of the meal in the stomach, resulting in antral overload. PDS-related symptoms are thought to relate to gastroduodenal motility, including gastric accommodation and emptying.^{29,30} Partial inhibition or acceleration of gastric accommodation could worsen or improve dyspepsia.³¹ Delayed gastric empty-

ing could also be implicated in conjunction with nausea, vomiting, and postprandial fullness. However, the association between delayed gastric emptying and symptoms such as fullness or bloating are not always consistent.³² The correlation between accelerated gastric emptying and symptomatic improvement is also heterogeneous.³³ In contrast, EPS-related symptoms such as epigastric pain or burning were thought to be caused by hypersensitivity of the gastroduodenum.^{34,35} However, hypersensitivity to gastric mechanical distention is also associated with postprandial fullness, bloating, and belching and is not representative of EPS symptoms.^{34,36}

Recently the role of the duodenum has been gaining attention because this short portion of the small intestine is important for the symptomatic manifestation of FD. Impaired duodenal mucosal integrity and duodenal low-grade inflammation are associated with altered neuronal signaling and systemic immune activation, and these alterations may ultimately lead to the development

of dyspeptic symptoms. Supposed luminal candidates inducing duodenal barrier defects include acid, bile, the gut microbiota, and food factors (antigens); however, no causal association with symptoms has been consistently demonstrated. The recognition of duodenal pathophysiology in FD will hopefully lead to the discovery of new biomarkers and therapeutic targets.³⁷ Increased sensitivity to exogenous and endogenous acid in the duodenum and decreased duodenal acid clearance have been associated with nausea.^{38,39} Exogenous duodenal acid application decreases the threshold for discomfort to gastric balloon distention and blocks gastric accommodation in response to food intake.⁴⁰ In addition, the transient receptor potential vanilloid type-1 (TRPV1) selectively activates capsaicin, a pungent ingredient contained in chili and kimchi (a Korean food), and induces calcitonin gene-related peptide and substance P release, which may enhance visceral hypersensitivity and trigger abdominal pain and nausea.⁴¹ According to our previous Korea–Japan bilateral exchange collaborative research project, upper gastrointestinal symptoms were more common in subjects with a higher consumption of spicy foods that contain capsaicin (such as kimchi), regardless of their TRPV1 genotypes and *H. pylori* infection status, suggesting that capsaicin-rich foods may induce gastric fullness.⁴² Moreover, stress-induced increases in gastrointestinal permeability have been demonstrated in both animal models of FD⁴³ and healthy volunteers⁴⁴ undergoing a stressful experience. Recently, duodenal eosinophilia was reportedly related to anxiety.⁴⁵

The small intestinal microbiome also potentially contributes to FD pathogenesis. Although relative bacterial abundance in the small intestine is difficult to interpret, increased duodenal mucosal bacterial load was found to be correlated with food-related symptoms in response to a nutrient challenge and was inversely correlated with QOL.⁴⁶ Small intestinal inflammation leads to changes in the gut microbiota and alters the composition of bile acid.⁴⁷ Primary bile acid reduction may influence the diversity of the small intestinal microbiota resulting in proinflammatory bacterial overgrowth and low-grade mucosal inflammation, which can cause epithelial barrier dysfunction.⁴⁷ Beeckmans et al.⁴⁸ reported that fasting total bile acid concentrations in FD patients were reduced with a shift in the ratio of primary to secondary bile acids.

Gut–Brain Interaction

Immune disturbance and gut microbial dysbiosis evoke epithelial barrier dysfunction, impacting gut–brain communications via the hypothalamic–pituitary–adrenal axis. Rodino-Janeiro et al. demonstrated the role of stress and corticotropin-releasing factor in the regulation of gastrointestinal permeability.⁴⁹ Moreover, Zheng et al. showed that eosinophils express corticotropin-releasing hormone (CRH) in the jejunum in response to psychological stress

and that substance P and its receptors mediate the effect of stress via the CRH expression of eosinophils. These findings suggest that the eosinophil-derived CRH activation of mast cells induces jejunum epithelial barrier damage.⁵⁰ Structural and functional connectivity in areas of the brain such as the internal and external capsules and the pregenual anterior cingulate cortex, responsible for processing visceral afferent information, are disturbed in FD⁵¹ and enhanced in EPS, as revealed by magnetic resonance imaging in FD patients.⁵² Microbial alterations can modify levels of serotonin, dopamine, acetylcholine, and gamma aminobutyric acid, either by synthesis or consumption of these substances, leading to alterations in emotional state and behavior.⁵³ Bile acids function as gut hormones capable of influencing metabolic processes via receptors such as the farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5). Moreover, bile acids and their receptors have been detected not only in the GI tract but also in the brain, suggesting a possible gut–brain interaction.⁵⁴

Relationship between Early Chronic Pancreatitis and FD

Chronic pancreatitis is characterized by chronic progressive inflammation, fibrosis, and scarring in the pancreas with damage to pancreatic exocrine, endocrine, and ductal cells. Chronic pancreatitis has clinical features such as abdominal pain, exocrine and endocrine insufficiency, pancreatic cancer, and other complications. A role for chronic pancreatitis as a cause of dyspepsia has been reported.⁵⁵ In a case–control study, it was found that 27% of the study participants with FD had pancreatic juice abnormalities consistent with chronic pancreatitis.⁵⁶ Consequently, dyspeptic symptoms could be an indication of chronic pancreatitis. The recent guidelines for chronic pancreatitis included the criteria for early chronic pancreatitis (ECP).⁵⁷ ECP has clinical findings such as recurrent upper abdominal pain, abnormal pancreatic enzyme levels in serum or urine, abnormal pancreatic exocrine function, and a history of continuous heavy consumption of alcohol as well as characteristic findings on endoscopic ultrasonography (EUS) or endoscopic retrograde cholangiopancreatography. Recently Wakabayashi et al. reported that nearly half of patients with proton pump inhibitor (PPI)-resistant FD had abnormalities in their pancreatic enzymes.⁵⁸ Interestingly, half of these FD patients had pancreatic enzyme abnormalities compatible with a diagnosis of ECP, suggesting that PPI-resistant FD cannot be differentiated from ECP on the basis of clinical symptoms alone: endosonography must be used to identify the unique EUS characteristics of these diseases. Interestingly, Yamawaki et al. reported that EUS scores tended to be low in patients with refractory FD.⁵⁹ There is a possibility that ECP may be present among FD patients with pancreatic enzyme abnormalities. Furthermore, even if

such patients do not meet the diagnostic criteria for ECP, FD patients with abnormal pancreatic enzymes may develop chronic pancreatitis in the future. Consequently, it is important to distinguish between these two diseases.

Therapeutic Management of FD

It is important to reassure patients that there is no structural cause for symptom generation, no explanatory pathophysiology, and no exact information on the natural history of FD. In addition, it should be confirmed that treatment will be primarily directed toward the predominant symptoms. Lifestyle modification, including food habits or exercise, may lead to symptom relief; however, there is a distinct lack of evidence based on the results of randomized controlled trials (RCTs), to support this. But, since there seems to be an association between FD and lower exercise levels, regular or daily exercise could be a therapeutic option for FD.

In terms of the therapeutic options for FD, PPIs are the traditional first-line therapy; however, potassium-competitive acid blockers, such as vonoprazan⁶⁰ and tegoprazan,⁶¹ are now being launched. Ongoing drug development is focusing on gastric motility with prokinetics (dopamine-2 antagonists and 5-HT₄ agonists) and fundus relaxant therapies (acotiamide and azapirones) and on sensitivity with peripherally acting neuromodulators (guanylate cyclase and cannabinoid agonists) and centrally acting neuromodulators. Drugs under development for gastroparesis may also be effective in FD therapy, especially for PDS. Emerging data are becoming available on probiotics and antibiotics and on phytotherapeutic herbal agents.^{62,63} Duodenal low-grade inflammation is a newly emerging target that may also respond to histamine and leukotriene receptor blockers in addition to PPIs.

Diet Therapy for FD

Among FD cases refractory to drug therapy, gluten-dependent FD as a clinical presentation of non-celiac gluten sensitivity (NCGS) should be included. Shahbazkhani et al.⁶⁴ reported a randomized, double-blind, placebo-controlled trial in which, of 77 patients with refractory FD, 50 (65%) did not respond to a gluten-free diet, while 27 (35%) showed gastrointestinal symptom improvement on a gluten-free diet. After blind gluten ingestion, symptoms recurred in 5 patients (6.4% of patients with refractory FD and 18% of gluten-free diet responders), suggesting the presence of NCGS. As shown by this study,⁶⁴ NCGS is highly prevalent among patients with refractory FD, and a diagnostic/therapeutic roadmap evaluating the effect of gluten-free diets in patients with FD should be included.

Anti-secretory Agents for the Treatment of FD

Once a diagnosis of FD has been determined, anti-secretory agents should be considered as the best treatment option. Impaired duodenal clearance of gastric acid and duodenal hypersensitivity to locally infused acid in cohorts with FD³⁸ suggest the treatment efficacy of acid suppression. A Cochrane meta-analysis reported a relative risk of symptoms remaining of 0.88 (95% CI, 0.02–0.94) with PPIs versus placebo in 18 RCTs.⁶⁵ Two of these RCTs showed a trend towards a benefit of PPIs in PDS, but no benefit in EPS.⁶⁵ In contrast, an RCT reported by ourselves, showed exclusive efficacy of PPI (lansoprazole 15 mg) for EPS but not for PDS.⁶⁶ However, the frequent overlap of PDS and EPS means that PPI usage is a justifiable option for FD therapy. Even when looking at the effectiveness against FD of PPI and H₂ receptor antagonists, we cannot exclude the effects of overlap of gastroesophageal reflux diseases.

Prokinetics

Although prokinetics have been shown to give a relative risk reduction of 33% compared with placebos and have an NNT of 6, most data are based on clinical trials with domperidone and cisapride.^{67,68} However, cisapride has now disappeared from the market. In such cases, publication bias is also a concern. Treatment with pure prokinetics such as erythromycin, which does not induce an anti-emetic effect, promotes non-physiological gastric emptying by inducing faster GI motility in the postprandial phase. However, it has been determined that the effect of erythromycin is weaker than that of other treatments that combine prokinetic action and anti-emetic effects. Acotiamide,^{69,70} licensed for use in FD in Japan and India, is a novel acetylcholinesterase inhibitor that relaxes the gastric fundus.⁶⁹ In Japan, acotiamide⁷¹ is the only drug officially approved by the national insurance system for the treatment of FD. However, itopride, a dopamine D₂ receptor antagonist that inhibits acetylcholinesterase, causes few adverse events and improves the feeling of relaxation and early satiety after meals. In addition, pyloric injection of botulinum toxin seems to be effective against gastroparesis and related dyspepsia symptoms.⁷²

Ghrelin agonists such as relamorelin,⁷³ and 5-HT₄ agonists such as prucalopride⁷⁴ and velusetrag,⁷⁵ alter gastroduodenal function in patients with gastroparesis, but without clear efficacy for FD. Ghrelin agonists worsen postprandial gastric fundal relaxation (accommodation),⁷⁶ suggesting little benefit in FD. Neuromodulators such as gabapentin have been shown to reduce upper gastrointestinal visceral sensation, which appeared to improve FD symptoms in one retrospective, open-label study.⁷⁷

Other Treatment Options for FD

In addition to anti-secretory agents, novel drugs such as tansospirone,⁷⁸ buspirone,⁷⁹ and the herbal products STW-5⁸⁰ and rikkunshito^{62,81,82} are newly listed in the Rome IV criteria. This is the first time that Japanese herbal medicines are listed in the Rome classification. In a crossover trial in 17 patients, buspirone reduced bloating and postprandial fullness.⁷⁹ Although we performed a double-blind, placebo-controlled, randomized controlled clinical trial for the efficacy and safety of rikkunshito on Rome III criteria-based FD and showed that global patient assessment tended to improve with rikkunshito,⁶² evidence-based clinical data are still lacking in terms of such complementary and alternative medicine. We also reported that a low baseline level of plasma des-acyl ghrelin was associated with an increased treatment efficacy of rikkunshito against FD.⁸² In that report, the absence of alcohol consumption was also clinically useful in predicting the response to rikkunshito.⁸² However, further scientific evidence on the use of these Japanese traditional herbal medicines⁸³ is necessary.

Psychotropic drugs such as antidepressants are often used as second-line treatments of FGIDs. A multicenter RCT in North America that compared a tricyclic antidepressant (TCA) with a recent selective serotonin reuptake inhibitor (SSRI) showed that the effect of the SSRI was not significantly different from that of the TCA, although it was less well tolerated, and low-dose amitriptyline, a TCA, was more effective than the placebo, whereas escitalopram, an SSRI, was not.⁸⁴

Locally delivered budesonide, targeting increased eosinophils,⁸⁵ is now under investigation for FD. Novel eosinophil-suppressing drugs are also under testing for FD. A monoclonal antibody against Siglec-8, an inhibitory receptor selectively expressed on both eosinophils and mast cells, appears promising in animal models⁸⁶ and is now undergoing clinical trials in eosinophilic gastrointestinal diseases.

Acupuncture for FD

The evidence for acupuncture treatment for FD has been insufficient. Wang et al. at the Beijing University of Chinese Medicine recently performed a pilot randomized clinical trial to show the superiority of three sessions per week versus one session per week of acupuncture for symptomatic relief of FD, especially PDS.⁸⁷ They showed that, after 4 weeks, the complete elimination rate of core symptoms was 26.7% (95% CI 12.3%–45.9%) for three sessions/week (H) and 10.0% (95% CI 2.1%–26.5%) for one session/week (L) ($P=0.095$) and that there were significant differences between the H and L groups at weeks 8, 12, and 16 ($P=0.038$, 0.02, and 0.02). Although they have obtained data from high-quality clinical trials, this result is still preliminary; a multicenter RCT of acupuncture for PDS with a

larger sample is necessary to validate these results.

Functional Gastroduodenal Disorders other than FD

Belching disorders

In the Rome IV criteria, excessive supragastric and gastric belching are clearly distinguished, which was not the case in the previous Rome III criteria.^{4,88} Because belching does not always arise from swallowing air, the disease term “aerophagia” is not used to describe excessive belching conditions in Rome IV. Recent progress in both high-resolution manometry and high-resolution impedance monitoring systems has enabled the objective differentiation of supragastric belching from gastric belching. For supragastric belching, according to an open-label study, speech therapy (treatment for stuttering etc.) conducted by a well-informed speech therapist significantly relieved these symptoms.⁸⁹

Nausea and vomiting disorders

Although chronic nausea can be induced without association with vomiting, vomiting in the absence of nausea may prompt a suspicion of organic disease of the central nervous system. Nausea may be either meal related or meal unrelated, suggesting potential pathogenic heterogeneity. Minor changes to the criteria of cyclic vomiting syndrome (CVS) were included to formalize the observation that some patients report milder inter-episodic symptoms other than vomiting, and the absence of vomiting for at least a week between episodes was a distinguishing feature. After all, stereotypical episodes of CVS include sudden onset of vomiting and a short overall duration of less than a week. On the other hand, cannabinoid hyperemesis syndrome (CHS) is the completely distinct disease from CVS because it exhibits different epidemiology, such as marijuana smoking, and has a specific pathological bathing behavior such as prolonged hot baths or showers. CHS often occurs in males who use cannabis daily (3–5 times/day) over at least 2 years. However, in Japan, where marijuana smoking is legally prohibited and the prevalence of its use is low, CHS will likely be very rare.

Rumination syndrome

Continuous relapsing regurgitation of recently ingested food into the mouth is a representative symptom of rumination syndrome. In this syndrome, regurgitation is not preceded by retching. In the Rome IV revision, effortless regurgitation, which is usually not preceded by nausea, is emphasized as a major diagnostic point of rumination syndrome. All these points are newly inserted to Rome IV based only on clinical experience, not on scientific evidence.

Conclusion

With the Rome IV classification, development of new therapeutic drugs in the field of gastroduodenal disorders should be further enhanced. The Rome IV criteria are especially applicable for such scientific therapeutic developments as clinical trials. For the management of FD, the development of novel drugs and the repurposing of existing therapies are needed to target promising new mucosal disease targets.⁹⁰ Alternatively, modulation of the relevant gastric or small intestinal microbiomes may transform the management of FD. Our increased understanding of the pathophysiology, diagnosis, and treatment of FD is of major interest, and the emergence of disease-controlling therapies are eagerly anticipated.

Conflicts of Interest

The author received scholarship funds for research from Daiichi-Sankyo, Otsuka Pharmaceutical Co, Ltd, MSD Co., Mylan EPD, Tanabe, and Takeda Pharmaceutical Co. and received service honoraria from Astellas Pharm, AstraZeneca K.K., EA Pharma Co, Ltd, Mylan EPD, Otsuka Pharm, Takeda Pharm, and Tsumura Co.

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