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NEUROGASTROENTEROLOGY AND MOTILITY DISORDERS OF THE GASTROINTESTINAL TRACT (S RAO, SECTION EDITOR)

New Approaches to Diagnosis and Treatment of Functional Dyspepsia

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Abstract

Purpose of Review The purpose of this article is to review the recent literature and discuss the new approaches to the diagnosis and treatment of functional dyspepsia (FD).

Recent Findings According to the recent American College of Gastroenterology (ACG) and Canadian Association of Gastroenterology (CAG) guideline for dyspepsia, *Helicobacter pylori* (*H. pylori*) eradication is recommended as a first treatment option, and proton pump inhibitors (PPIs), tricyclic antidepressants, and prokinetics are listed as second-line therapy. On the other hand, in the Japanese guideline for FD, PPIs and prokinetics are recommended as the first-line treatment. In Japan, acotiamide, a recently launched prokinetic, showed significant efficacy in several clinical trials performed either in Japan or Europe. Regarding non-pharmacological treatment, recent topics include acupuncture, electrical stimulation, gastric peroral endoscopic myotomy, and meal and lifestyle modification. These treatments have provided significant efficacy, which provides some insights into the main pathophysiology of this disease.

Summary Although FD is common among functional gastrointestinal disorders, it is not easy to relieve the dyspeptic symptoms of FD patients. Combinations of pharmacological and non-pharmacological treatment options are expected.

Keywords Functional dyspepsia (FD) · Diagnosis · Treatment · Proton pump inhibitor (PPI) · Acotiamide · Tricyclic antidepressant (TCA)

Introduction

Functional dyspepsia (FD), one of the major functional gastrointestinal disorders, refers to epigastric symptoms that occur without apparent organic disease, based on the premise that gastric dysfunction may be the cause [1••, 2]. FD is a common condition that affects up to 20% of the population [3] and is known to significantly impair patients' quality of life (QOL). Therefore, FD patients should be appropriately diagnosed and managed. However, the management of FD is challenging. Pharmacological treatment is often used in the clinical setting, yet its effectiveness has been reported to be very low. In this article, the recent literature is reviewed, and the new approaches to diagnosis and treatment of FD are discussed.

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Diagnosis of FD

Diagnostic Criteria of FD

FD is diagnosed based on symptoms and defined by the Rome criteria, where typical symptoms of FD are described as bothersome postprandial distention, early satiety, epigastric pain, and epigastric burning.

The Rome criteria for FD were revised in 2016 (Rome IV), and the updated guideline of the American College of Gastroenterology (ACG) and Canadian Association of Gastroenterology (CAG) was published in 2017 [1••, 4••]. In Rome IV, FD is classified as postprandial distress syndrome (PDS) or epigastric pain syndrome (EPS), based on the presence or absence of an association with meals, as well as symptom persistence for 3 of the prior 6 months; these descriptors

are similar to those in the Rome III criteria. "Bothersome" symptoms are highlighted in the revised Rome IV criteria more than in the Rome III criteria [5]. As there was an overlap of PDS and EPS in Rome III, in Rome IV, epigastric pain and burning after meal ingestion were included among PDS symptoms to increase specificity and reduce overlap between these categories. In the ACG/CAG guideline, FD is defined by symptoms of dyspepsia (predominantly epigastric pain) that last at least 1 month and are potentially associated with any other upper gastrointestinal symptom, such as epigastric fullness [4••].

In Japan, *Helicobacter pylori* gastritis has been covered by medical insurance since 2013; all regimens for eradication of *H. pylori* infection are covered by national health insurance. The clinical practice guidelines for FD in Japanese and English versions were issued by the Japanese Society of Gastroenterology in 2014 and 2015, respectively [2] (Fig. 1). These guidelines are based on the grading of recommendations assessment, development, and evaluation (GRADE) system, and FD is defined as "a condition chronically presenting symptoms centered in the upper abdomen, such as epigastric pain or discomfort, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms". In this definition, the symptoms and duration of the disease are not specified, unlike in the Rome IV criteria. These statements are written to be widely distributed and inform primary care physicians of this condition. In fact, it is up to each physician to determine whether the patients' symptoms are those of FD or not. In another statement in the Japanese guidelines, it is also stated that "FD is not identical to chronic gastritis" [6]. In Japan, FD is a diagnosis recognized by the insurance plan, and the medical fee for this condition is covered by medical insurance. Further recognition of this condition is needed to provide appropriate management for dyspepsia patients without organic causes.

New Motility Tests for the Diagnosis of FD

In the pathophysiology of FD, gastric motility disorders and visceral hypersensitivity are important factors that are directly associated with symptom deterioration [7–10]. According to previous reports, adaptive relaxation disorders and delayed gastric emptying are particularly associated with upper gastrointestinal symptoms. Barostat testing is generally regarded as the gold standard for measurement of gastric adaptive relaxation, but it has been used only for research purposes at a limited number of institutions because of its invasiveness as a test. A new measurement of the adaptive relaxation response

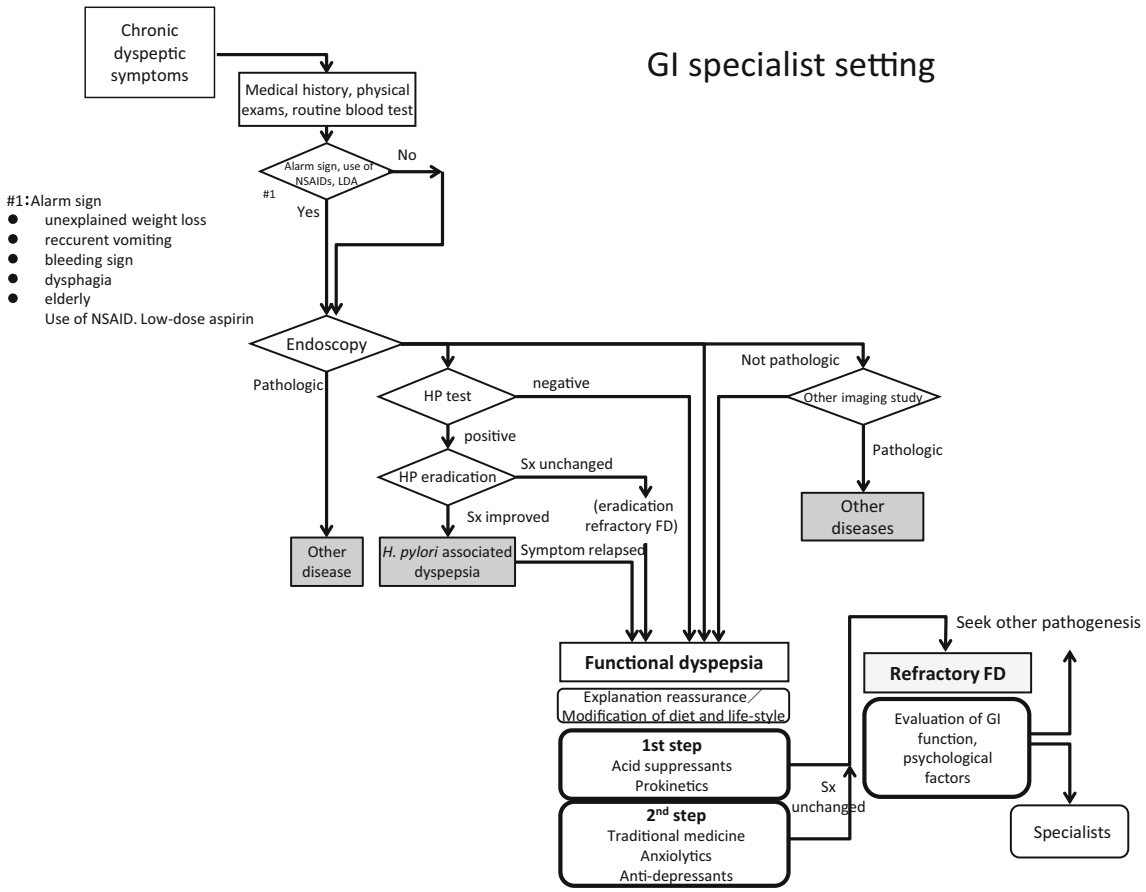

Fig. 1 Algorithm for diagnosis and treatment of FD in Japan (ref. 2). FD, functional dyspepsia

of the stomach using high-resolution manometry has attracted attention as a new noninvasive technique that can even be used in children [11•, 12]. Regarding the evaluation of gastric emptying, the 13-C urea breath test (UBT) is currently often used. There is overlap in the dyspeptic symptoms of idiopathic gastroparesis and FD, but only a minority of FD patients have delayed gastric emptying, suggesting that UBT is of particular value in distinguishing between idiopathic gastroparesis and functional dyspepsia. However, these tests are only regarded as auxiliary methods for making the diagnosis.

Biomarkers of FD

No biomarker of FD has been identified. Although differences in ghrelin, cholecystokinin, serotonin, leptin, gastrin, calcium, and various genetic polymorphisms have been reported, no definite diagnostic indicator has been used in the diagnosis of FD. Nuclear magnetic resonance (NMR)-based analytical approaches to metabolomics have been used to identify changes in levels of glutamine, alanine, proline, high-density lipoprotein, β-glucose, α-glucose, low-density lipoprotein, and very low-density lipoprotein in patients with FD [13].

Treatment of FD

Generally, treatment of FD should be based on the etiology of the condition. However, as is well known, FD is a multifactorial and complex disease, and treatment based on its pathogenesis is difficult. Therefore, the current strategy for pharmacological treatments is empirical. In many guidelines or treatment recommendations, *Helicobacter pylori* (*H. pylori*) eradication is used as the treatment for infection-positive patients. Among many drugs besides *H. pylori* eradication treatment, acid inhibitory drugs, such as proton pump inhibitors (PPIs), are considered as the first treatment option, following the use of psychotropic agents and prokinetics. In the recently published ACG/CAG guideline, *H. pylori* eradication is also recommended as a first-line treatment option, and PPIs, tricyclic antidepressants (TCAs), and prokinetics are listed as second-line therapy (Figs. 2 and 3). Among the prokinetic agents, acotiamide, which has shown significant efficacy in several clinical trials performed either in Japan or Europe, has been introduced in Japan.

Recent non-pharmacological treatments include acupuncture, electrical stimulation, gastric peroral endoscopic myotomy (G-POEM), and meal and lifestyle modification. These treatments have provided significant efficacy, and they provide insight into the main pathophysiology of this disease. However, more evidence is necessary to establish them as treatments for FD (Fig. 3).

H. pylori Eradication Therapy

Eradication of *H. pylori* has been reported as both effective and ineffective for dyspepsia. However, based on the meta-analyses, *H. pylori* infection is thought to be associated with the onset of dyspepsia [14, 15]. *H. pylori* is considered to be a trigger of dyspepsia, but not in all cases of FD. In addition, eradication therapy is at least likely to reduce the risk of peptic ulcer or gastric cancer. The Kyoto global consensus meeting concluded the following: the disappearance or improvement of dyspepsia at 6–12 months after eradication of *H. pylori* defines *H. pylori*-associated dyspepsia and should be regarded as different from FD [16]. This consensus is also in the Rome IV criteria [1••]. Given the above, it is thought that eradication therapy should be performed because it is clearly effective for symptoms, although it is not significantly effective for FD.

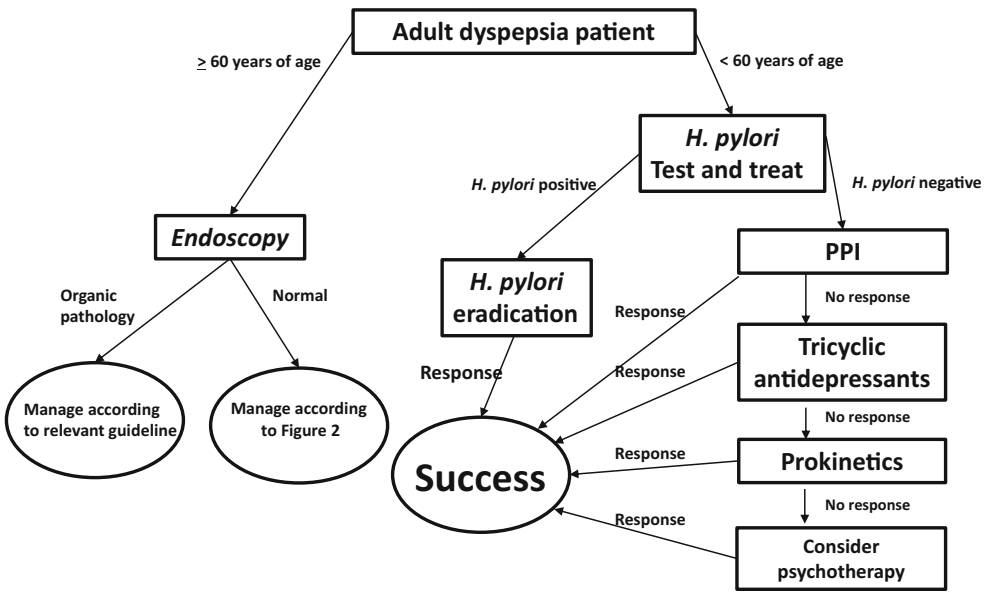

Fig. 2 Algorithm for the management of undiagnosed dyspepsia according to the ACG/CAG clinical guideline (ref. 4). ACG/CAG, American College of Gastroenterology and Canadian Association of Gastroenterology

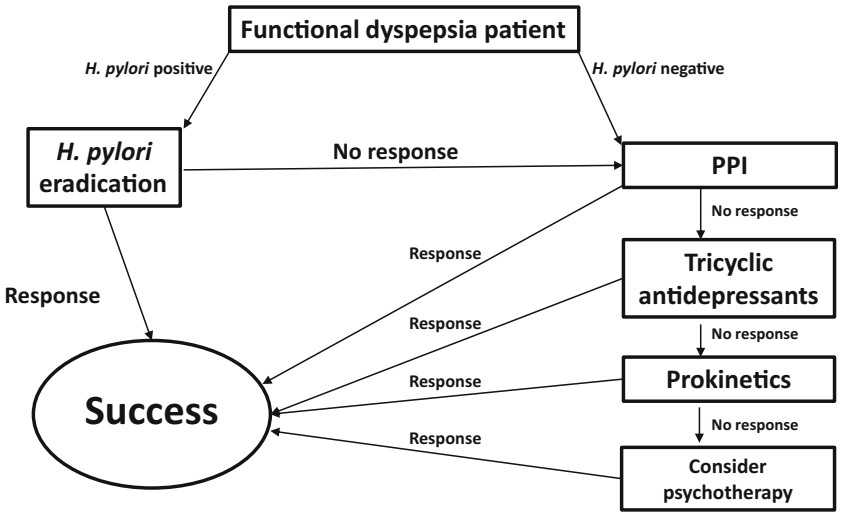

Fig. 3 Algorithm for the management of dyspepsia according to the ACG/CAG clinical guideline (ref. 4). ACG/CAG, American College of Gastroenterology and Canadian Association of Gastroenterology

The recent ACG/CAG guideline also recommends eradication of *H. pylori* as first-line treatment for patients with FD aged 60 years and older who are diagnosed as *H. pylori*-positive after organic diseases are ruled out by esophagogastroduodenoscopy [4••] (Fig. 1). In addition, for patients under the age of 60 years, noninvasive testing is recommended, and patients should be treated for *H. pylori* infection if positive.

Proton Pump Inhibitors

PPIs are considered first-line treatment for patients who are diagnosed with FD. Although many studies and meta-analyses have reported the effectiveness of PPIs, only around 14% of patients with dyspepsia show improvement [17•, 18]. Generally, there is no difference in acid-secretion function between FD and controls. However, it has been reported that postprandial acid exposure in the duodenum is greater in some patients with FD [19]. Patients with FD who have strong acid exposure in the duodenum may experience more severe symptoms than patients with FD who have normal acid exposure. It has been reported that motility and clearance in the duodenum are reduced by instillation of acid into the duodenum, and various upper abdominal symptoms may be more severe in patients with FD [20, 21]. Recent data suggest that low-grade inflammation is present in the duodenum of FD patients. The focus of research in the field has moved to gastric motility, low-grade inflammation, and mucosal permeability of the duodenum [22–24]. A recent study reported that PPIs suppress the duodenal eosinophilia of FD patients [25].

Prokinetic Agents (Acotiamide)

Although meta-analyses have reported the relatively high effectiveness of prokinetic agents, reports are inconsistent. It is likely that publication bias occurred. Moreover, previous studies used cisapride, which has been withdrawn due to cardiovascular side effects. Therefore, many specialists have questioned the efficacy of prokinetic agents. Acotiamide was released in 2013 in Japan, and it improves enterokinesis by acting directly on peripheral synaptic clefts to increase acetylcholine levels, while other prokinetic agents such as mosapride and trimebutine act on the nerve plexus in the gastrointestinal tract. Large-scale, double-blind, placebo-controlled trials have proven that acotiamide is effective for patients who are classified as having PDS-type FD [26, 27]. A recent study using gastric scintigraphy reported that acotiamide significantly improved gastric accommodation and emptying, thereby relieving abdominal fullness in patients with PDS-type FD [28] (Figs. 4 and 5). In addition, chronic administration of acotiamide appears to be safe and effective and improves patients' QOL [29••]. In recent reports, a PPI combined with acotiamide reduced upper abdominal postprandial distention and early satiety more significantly in patients with FD and heartburn. Therefore, greater therapeutic efficacy may result from proper treatment based on a correct understanding of patients' complaints [30].

Tricyclic Antidepressants

The ACG/CAG guideline recommended the use of TCAs for FD following a trial of PPIs, and TCAs should be used prior to prokinetic agents when PPIs are not effective (Fig. 2). The effects of psychoactive agents on FD were examined in 13 randomized controlled trials (RCTs), and their usefulness was reported, with a number needed to treat (NNT) of six [31•, 32, 33]. In addition, three trials reported the usefulness of TCAs [34]. RCTs showed no apparent advantage of selective serotonin reuptake inhibitors (SSRIs) for symptoms of

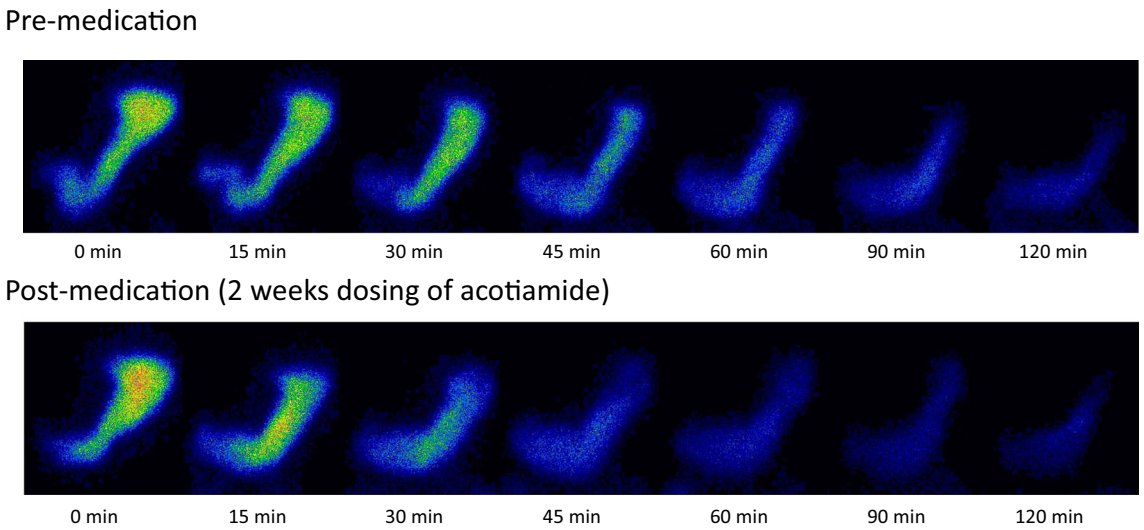

Fig. 4 Effect of acotiamide on gastric motility using gastric scintigraphy. Representative images of the gastric scintigraphy of Japanese FD patients of pre and post medication of acotiamide. The gastric radioactivity was apparently increased after 2 weeks of dosing of acotiamide, suggesting that gastric accommodation was clearly improved. This is a representative image of the patients who participated in our clinical study (ref. 28). FD, functional dyspepsia

FD. In the ACG/CAG guideline, TCA is recommended as second-line therapy following use of PPIs.

Kampo Medicines

In the Japanese FD guidelines, some Kampo medicines are recommended for patients who do not respond to PPIs and prokinetic agents. Although the effectiveness of some Kampo medicines, such as hangekobokuto and rikkunshito, has been reported, no high-quality or well-organized reports have been published. A recent RCT using placebo and rikkunshito showed significant improvement of dyspeptic symptoms in patients with PDS-type FD [35•, 36] (Fig. 5). Recent advances in making placebo with similar smell and taste to rikkunshito could make the evidence along these lines more reliable; it is hoped that further high-quality evidence will become available (Fig. 6).

Acupuncture

Many articles have been published on the use of acupuncture for dyspepsia, mainly in China. However, the sample size was small in all articles, and few reports provided high-level evidence for an active or placebo effect. RCTs comparing acupuncture and sham treatment reported that acupuncture significantly improved dyspeptic symptoms. However, a meta-analysis comparing acupuncture and prokinetic agents found no significant differences in the improvement of dyspepsia [37, 38]. A recent RCT comparing percutaneous electrical and normal acupuncture found that the former was effective for dyspepsia in patients with refractory FD [39]; however, further detailed examination is required because of a faulty study design.

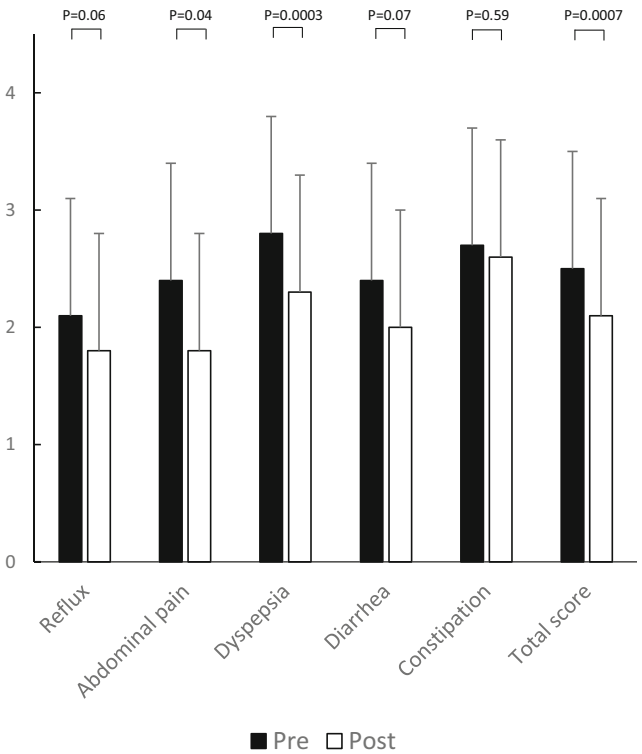

Fig. 5 Effect of acotiamide on GSRS in Japanese FD patients. The abdominal pain and dyspepsia score was significantly improved after study drug administration of acotiamide (abdominal pain: pre, 2.4 ± 1.3; post, 1.8 ± 0.6; $p = 0.04$, dyspepsia: pre: 2.8 ± 0.8, post: 2.3 ± 0.8, $p = 0.0003$). The total GSRS score was also significantly improved in the acotiamide group (pre, 2.5 ± 0.6; post, 2.1 ± 0.6, $p = 0.0007$) (ref. 28). GSRS, Gastrointestinal Symptom Rating Scale; FD, functional dyspepsia

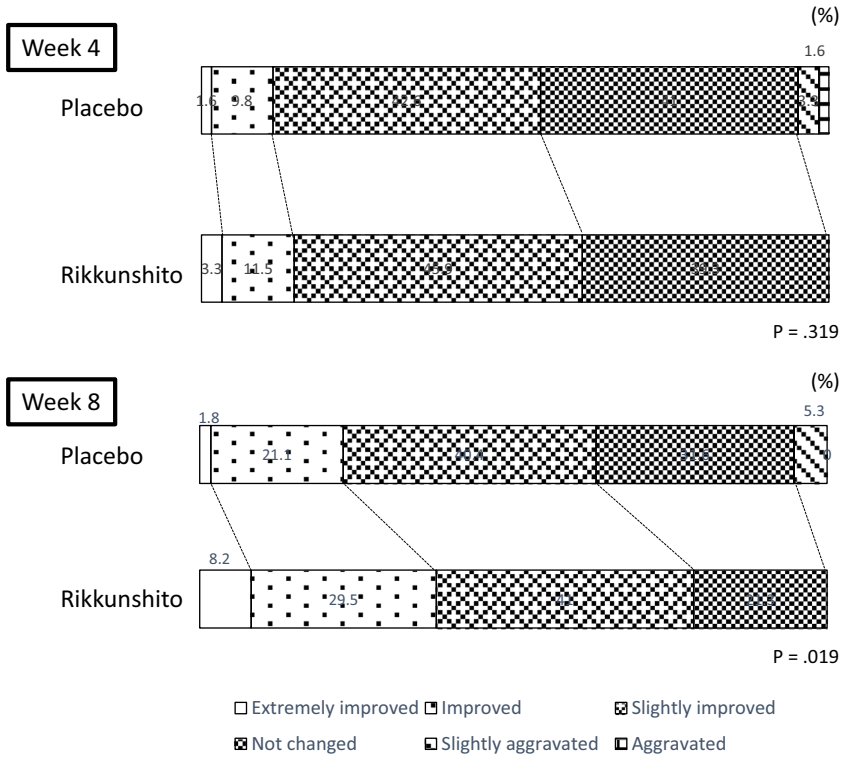

Fig. 6 Effect of rikkunshito on overtreatment efficacy after for 4- and 8-week treatment. The incidence of extremely improved and improved after 8-week treatment of rikkunshito was 8.2% and 29.5% that was significantly higher than those of placebo group (1.8% and 21%) ($p = 0.019$) (ref. 35)

Electrical Stimulation

Gastric electrical stimulation using a laparoscopically implanted device in the abdomen reportedly improves gastric emptying and dyspepsia in patients with gastroparesis [40, 41]. Continuous electrical stimulation may act directly on the gastric myenteric plexus and the vagus nerve (nausea and vomiting are induced by vagus stimulation). This may become a new therapy for refractory gastroparesis.

Gastric Peroral Endoscopic Myotomy

Peroral endoscopic myotomy (POEM) is a novel therapy for esophageal achalasia. G-POEM has reportedly been found to be useful for gastroparesis [42–44]. G-POEM improves gastric emptying by forming a tunnel in the mucosa, similar to that in POEM, and an incision through the muscular layers of the pyloric region enables passage through the pyloric ring. Gastric emptying was significantly improved, and clinical improvement was achieved in 70–80% of patients. G-POEM also improved symptoms of dyspepsia (e.g., nausea, early satiety, and distention) and QOL in the early period after surgery. Although the indications, safety, and efficacy of G-POEM remain controversial, this treatment may prove useful for intractable dyspepsia.

Meal and Lifestyle Modification

RCTs have reported that a high-fat FODMAP (fermentable oligosaccharide, disaccharide, monosaccharide, and polyols) diet and gluten-containing food contribute to the onset of dyspepsia. Wheat protein, milk protein, fruit juice, peppers, chilies, coffee, and alcohol affect sensation and motility in the gastrointestinal tract and induce dyspeptic symptoms [45]. However, some RCTs and meta-analyses showed that ingestion of peppermint, caraway seeds, and STW 5 herbal extracts is effective [46]. FD symptoms may be affected by individual lifestyles, and an improved lifestyle may relieve dyspeptic symptoms. Therefore, patients whose symptoms persist after treatment should attempt lifestyle modification.

Conclusion

This article provided an update of the diagnosis and treatment of FD based on current topics and knowledge. FD is now covered by national health insurance in Japan, and basic concepts of diagnosis and treatment of FD are being established. However, medical doctors and staff have not widely used this disease name, FD. It is expected that dyspeptic symptoms will be appropriately managed based on the concept for the diagnosis and treatment of FD.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the author.

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