Clinical Classification of Subgroups According to the Rome III Criteria Cannot be Used to Distinguish the Associated Respective Pathophysiology in Japanese Patients with Functional Dyspepsia

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Abstract

Objective Patients who meet the Rome III criteria for functional dyspepsia (FD) are generally classified into the following two subgroups, those with postprandial distress syndrome (PDS) and those with epigastric pain syndrome (EPS), in order to treat the dyspeptic symptoms caused by the respective pathophysiological conditions. However, whether simple classification of FD can accurately distinguish the pathophysiological differences between PDS and EPS remains to be clarified because the pathophysiology of FD is characterized and complicated by various factors.

Methods After classifying FD patients who were not receiving medication at the initial visit, we assessed and compared the following pathophysiological factors between the PDS and EPS groups: (1) the gastric reservoir and emptying functions using a radioisotope method (n=75), (2) the autonomic nervous system (ANS) function using electrocardiography (n=45), (3) gastric mucosal atrophy and intestinal metaplasia using histological examinations (n=47), (4) endoscopic findings of the stomach, such as superficial changes, abnormal gastroesophageal flap valves (n=67) and (5) Helicobacter pylori infection (n=48).

Results The FD patients exhibited higher rates of an impaired reservoir function (49.3%), gastric emptying disorders (54.7%) and relative hyperactivity of the sympathetic nervous system (31.9%) than the control subjects. However, endoscopic and histological changes of the stomach were similar in both the FD patients and control subjects. In addition, no differences were observed in the above-mentioned factors between the PDS and EPS groups.

Conclusion The simple classification of FD patients into two subgroups according to the Rome III criteria following diagnosis does not indicate any differences in the pathophysiology related to the respective dyspeptic symptoms of FD patients.

Key words: gastric motility, autonomic nervous system, H. pylori, postprandial distress syndrome, epigastric pain syndrome

Introduction

Recently, the prevalence of functional gastrointestinal disorders (FGIDs) has increased; however, no appropriate treatment regimens to cure FGIDs have so far been established. According to the Rome III criteria published in 2006 (1), the diagnosis of FGIDs is based on the following condi-
tions: the presence of bothersome symptoms originating from the digestive tract without organic diseases that continue to remain even after the administration of various treatments and thus decrease the quality of life (2). Functional dyspepsia (FD), classified as FGIDs, is defined as a disease of dyspeptic symptoms originating from the gastro-duodenal region without any organic, systemic or metabolic diseases that may be responsible for the symptoms. According to the Rome III criteria, the representative symptoms include bothersome postprandial fullness, early satiation, epigastric pain and epigastric burning (3). In accordance with these criteria, patients are generally classified into two distinct diagnostic subgroups based on symptoms before undergoing treatment, as follows: those with postprandial distress syndrome (PDS) and those with epigastric pain syndrome (EPS). In brief, PDS is a condition in which the patient experiences bothersome postprandial fullness and/or early satiation, so-called meal-related symptoms, while EPS is a condition in which the patient experiences other meal-unrelated symptoms (3). Therefore, patients in either subgroup may be easily differentiated according to their respective symptoms. Furthermore, similar to the pathophysiology of FGIDs, the pathophysiology of FD is related to symptoms characterized by multifunctional disorders of the upper GI tract, such as disorders of GI motility (4), abnormal acid secretion (5), visceral hypersensitivity (6), *Helicobacter pylori* (*H. pylori*) infection (7, 8), potent psychological factors (9, 10) and an imbalance of the autonomic nervous system (ANS) (11). The above dysfunctions indicate that each pathophysiological factor is directly associated with the four symptoms of FD; thus, distinct differences may exist in pathophysiology between the two subgroups. Although following a therapeutic approach for FD in line with the pathophysiology of each subgroup is appropriate, it is very difficult to investigate the pathophysiological factors of each FD patient at clinical institutions, including primary care hospitals. Therefore, it would be beneficial for most primary care clinicians, including gastroenterologists, to devise a simple classification of FD into subgroups according to representative symptoms that leads to an appropriate therapeutic approach according to the pathophysiology of FD. However, it remains to be clarified whether there are any distinct differences in several pathophysiological factors between PDS and EPS patients simply classified according to the Rome III criteria on the initial visit to medical institutions.

In this study, we investigated whether there are any differences in the pathophysiology between Japanese FD patients classified into the PDS and EPS subgroups according to the Rome III criteria.

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**Materials and Methods**

**Subjects**

All subjects were diagnosed with FD according to the Rome III criteria at Osaka City University hospital. We classified FD patients who were not receiving any medication into two subgroups according to the Rome III criteria and assessed the following factors: (1) the gastric reservoir function and emptying using radioisotope methods (n=75, men n=38, PDS:EPS=51:24, mean age=54.6), (2) the ANS function using electrocardiography (n=45, men n=23, PDS:EPS=24:21, mean age=54.2), (3) mucosal atrophy and intestinal metaplasia using pathological examinations of gastric biopsy samples (n=47, men n=29, PDS:EPS=31:16, mean age=56.2), (4) superficial changes and abnormal gastrosophageal flap valves based on the endoscopic findings of the stomach (n=67, men n=36, PDS:EPS=45:22, mean age=55.2) and (5) *H. pylori* infection (n=48, men n=28, PDS:EPS=33:15 mean age=55.5). Our study was conducted according to ethical guidelines for clinical studies, considering the patients’ human rights and privacy after obtaining written informed consent from all patients. The protocol of this study was approved by the Institutional Review Board of the Osaka City University Ethics Committee.

**Assessment of gastric emptying and the reservoir function**

Radionuclide examinations were performed using a previously described method (4, 12). In brief, the test meal consisted of a 200 g pancake (51.6 g carbohydrate, 8.1 g protein, 5.7 g fat and 291 kcal) containing 37 MBq of Tc-99m diethylamineminepentaacetic acid. The test meal was ingested with 100 mL of water within two minutes. After eating the test meal, all subjects were placed in the standing position, and a gamma camera (VERTEX-PLUS; ADAC Corp., CA, USA) recorded radioactivity in the upper abdomen. Anterior images of the abdomen were obtained immediately after intake of the test meal and at 10, 20, 30, 60, 90 and 120 minutes after intake. The ratio of radioactivity in the proximal portion of the stomach to that in the entire stomach was calculated after setting the region of interest. The half-time of gastric emptying, the time at which 50% of the peak radioactivity emptied from the stomach, of the entire and proximal stomach was calculated using a computer analysis software program (PEGASYS; ADAC Cor., CA, USA). We strictly defined cases with a delay in gastric emptying by using a cutoff value over the mean value + SD of the control data, according to our previous reports. In brief, the mean time required for gastric half-emptying of the entire stomach was 73±15 minutes in the healthy controls (12). The patients whose half-emptying time was higher than 88 minutes or lower than 58 minutes were defined as patients with a gastric motility disorder. Furthermore, according to the ratio of radioactivity in the proximal portion of the stomach to that in the entire stomach immediately after intake of the test meal (0 minute), we allocated the patients into either the impaired (<0.5) or normal/good reservoir function groups (>0.5).

**Assessment of the autonomic nervous system (ANS)**

Heart rate (HR) data obtained during a 24-hour monitor-
Assessment of the ANS function using electrocardiography

During the 24-hour monitoring period, the level of the HF component (parasympathetic activity) was lower in 73.5% of the FD patients; however, the index of LF/HF (sympathetic activity) was higher in 32.4% of the FD patients than in the control subjects. These results indicated an imbalance of the ANS system (relative ANS hyperactivity) in the FD patients. However, no differences were observed in the ANS function between the two subgroups (Table 2).

Pathological and endoscopic findings and H. pylori infection in the patients with FD

The pathological examinations showed the prevalence of mucosal atrophy and intestinal metaplasia to be 74.5% and 31.9%, respectively (Table 3). Endoscopic examinations of the stomach revealed superficial changes in 43.3% of the FD patients and abnormal gastroesophageal flap valves (grade III or IV) in 35.8% of the FD patients (Table 4). The incidence of H. pylori infection was 56.3% in the FD patients (Table 5). Similar to the results mentioned above, no differences were observed in any of the above described factors between the PDS and EPS subgroups (Tables 3-5).

Discussion

The results of the present study suggest that simple classification of FD into two subgroups (PDS and EPS) after diagnosis according to the Rome III criteria is not sufficient to determine the characteristic pathophysiology related to respective dyspeptic symptoms of FD patients, although various factors, such as gastric motility disorders and an imbalance of the ANS system, are associated with the pathophysiology of FD.

Similar to the rationale for selecting therapeutic approaches to treat various other diseases, the rationale for selecting treatment for FD is based on the underlying pathophysiology of FD. However, it is very difficult to determine the primary distinct pathophysiology present in each FD patient. In past decades, numerous papers have described analyses of the pathophysiology of FD: evaluation of gastric motility using radioisotope methods (4), ultrasound or 13C breath tests (17); evaluation of the gastric reservoir function using barostat methods (12) or radioisotope methods (4);
The ANS system than the control subjects, consistent with a decreased ANS function, gastric motility disorders and an imbalance of the nervous system may predict the pathophysiology and can indicate a more adequate therapeutic approach. However, treatment with these drugs is not always adequate to relieve bothersome symptoms in FD patients, and the overall efficacy rates are only approximately 50-70%. The reasons for such unfavorable results may include difficulty in precisely determining the primary distinct pathophysiology responsible for dyspeptic symptoms in each patient. Therefore, simple, easy, and noninvasive methods are required to determine the predominant pathophysiology present in each patient with FD.

Patients are diagnosed with FD according to the Rome III criteria, and FD patients are classified into each subgroup (PDS or EPS) or overlap solely on the basis of their symptoms. In fact, representative symptoms of FD, such as postprandial fullness and epigastric pain, are suspicious of dysfunctions of the gastric reservoir, motility disorders and excessive acid secretion. These results lead to the hypothesis that the simple classification of FD patients based on symptoms may predict the pathophysiology and can indicate a noninvasive and appropriate therapeutic approach. However, the presence of distinct differences in pathophysiological factors between PDS and EPS subgroups is required to prove this hypothesis. In the present study, the FD patients had a significantly higher prevalence of an impaired reservoir function, gastric motility disorders and an imbalance of the ANS system than the control subjects, consistent with previously reported findings (4, 11). Considering these findings, the diagnosis of FD and the methods selected in the present study are suitable for analyzing the pathophysiological factors associated with symptoms of FD. However, our results did not show any differences in pathophysiological factors between the two subgroups. In addition, although H. pylori infection has been reported to be related to the symptoms of FD (7, 8), no differences were observed in the rate of infection between the two subgroups. In other words, the simple classification of FD patients into subgroups according to the Rome III criteria does not reveal any differences in the pathophysiology. It has been reported that although homozygous TRPV1 315C influences the susceptibility of Japanese FD patients, no differences are observed in this parameter between PDS and EPS patients (18). This report may also support our present findings. Therefore, these phenomena can complicate the treatment of FD in addition to multifunctional disorders of the upper GI tract and the multiple symptoms of FD. Therefore, devising objective and simple methods for evaluating individual symptoms related to the pathophysiology of FD is required in the future.

There are some limitations associated with the present study, particularly the study design. Ideally, all assessments of pathophysiological factors should be examined in the same patients. However, under usual clinical conditions, it is very difficult to conduct all of these examinations in the same patients without administering additional treatment because the patients have already suffered from long-term symptoms before visiting the hospital. In addition, it takes a long time to complete these examinations in the hospital, and patients with FD cannot always receive all examinations for various reasons, including long working hours, exposure to radiation and so on. If a prospective mass study, not a retrospective study, were to be conducted, we could include five combined examinations before administering any therapeutic interventions. For these reasons, differences in the numbers of participants in each compared analysis are thought to be a limitation of the present study.

Furthermore, some controversial results compared to those reported in previous studies are presented in this study (19, 20). The aim of the present study was to evaluate whether the simple classification of FD patients into two subgroups (PDS and EPS) according to the patients’ respective complaints alone in the clinical field may accurately indicate the specific pathophysiology involved in each patient. If so, the simple classification of FD patients according to the Rome III criteria is more beneficial for selecting therapeutic interventions than special examinations, such as evaluations of gastric emptying or ANS analyses. However,
the results of the present study suggest that the simple classification of FD patients according to their dominant symptoms does not indicate the pathophysiology involved in the individual patient, although this study included a small number of examined patients. These controversial findings indicate that clinicians must conduct the required examinations in each patient in order to identify the dominant cause related to the patient’s symptoms. In addition, for the present controversial findings, we speculate that EPS and PDS patients may have a similar or common pathophysiology related to their respective dyspeptic symptoms. Moreover, differences in the populations of Western countries and Japan must also be considered. Further studies combining examinations of larger numbers of FD patients are required.

In conclusion, the simple classification of FD patients into two subgroups (PDS and EPS) according to the Rome III criteria does not suggest any differences in the pathophysiology and thus cannot indicate the appropriate or tailor-made treatment for individual patients with FD.

The authors state that they have no Conflict of Interest (COI).

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