Observational Study

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# Epigastric symptoms of gallbladder dyskinesia mistaken for functional dyspepsia

## Retrospective observational study

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**Abstract**

Functional dyspepsia (FD) is a constellation of epigastric symptoms originating in the gastroduodenal region without organic and metabolic cause. However, similar confounding symptoms can also appear in patients with gallbladder (GB) dyskinesia. Therefore, symptoms of GB dyskinesia may be mistaken for FD. We aimed to identify GB dyskinesia as a cause of FD symptoms compatible with the Rome IV criteria and the need for an evaluation of GB function in patients with FD symptoms.

We investigated information of patients with FD symptoms who underwent a quantitative $^{99}Tc^{m}$-diisoproyl iminodiacetic acid cholescintigraphy (DISIDA scan) through electronic medical records, and GB dyskinesia was judged to be the cause of the FD symptoms if the symptoms disappeared as GB function normalized on the follow-up DISIA scan in patient with decreased GB function on the initial DISIDA scan.

A total of 275 patients underwent a DISIDA scan. Eighteen patients of them had FD symptoms compatible with the Rome IV criteria. Three were lost after undergoing a DISIDA scan. Eight had normal GB function, and the other 7 had decreased GB function on the initial DISIDA scan. In 4 of the 7 patients with GB dyskinesia, FD symptoms disappeared as GB function normalized. As a result, GB dyskinesia was the cause of the symptoms in 4 of 18 patients with FD symptoms compatible with the Rome IV criteria.

It is necessary to evaluate GB function in patients with refractory FD symptoms because the symptoms can be caused by GB dyskinesia.

**Abbreviations:** DISIDA scan = quantitative 99Tcm-diisoproyl iminodiacetic acid cholescintigraphy, EPS = epigastric pain syndrome, FD = functional dyspepsia, GB = gallbladder, GBEF = gallbladder ejection fraction, PDS = postprandial distress syndrome, PPI = proton pump inhibitor, RFD = refractory functional dyspepsia.

**Keywords:** functional dyspepsia, gallbladder dyskinesia, refractory functional dyspepsia

## 1. Introduction

There has never been a study that demonstrates gallbladder (GB) dyskinesia can be the cause of epigastric symptoms compatible with the Rome IV criteria for functional dyspepsia (FD)—standard diagnostic criteria for FD. FD, as defined by the criteria, is characterized by 1 or more of the following symptoms originating in the gastroduodenal region: postprandial fullness, early satiation, epigastric pain, and epigastric burning without evidence of structural or other disease that is likely to explain the symptoms. Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present.[1,2] On the other hand, similar confounding symptoms, such as postprandial pain in the epigastrium, bloating, dyspepsia, and nausea, can also appear in GB dyskinesia (decreased GB function).[3,4] Therefore, symptoms of GB dyskinesia can be mistaken for those of FD, so it may be necessary to evaluate GB function, particularly in patients with refractory functional dyspepsia (RFD) defined as FD with continuous symptoms for at least 6 months that is unresponsive to at least 2 kinds of medications, including acid suppressors, proton pump inhibitors (PPIs), prokinetics, and *Helicobacter pylori* eradication therapy.[5] In fact, we, the authors, occasionally have performed a quantitative $^{99}Tc^{m}$-diisoproyl iminodiacetic acid cholescintigraphy (DISIDA scan) in patients who had epigastric symptoms compatible with the Rome IV criteria (the standard criteria for diagnosing FD) but who did not respond to medical treatment. Some of them had decreased GB function and their symptoms disappeared after normalization of GB function. Therefore, we aimed to investigate whether GB dyskinesia is the actual cause of epigastric symptoms compatible with the Rome IV criteria for FD and whether evaluating GB function is necessary to exclude GB dyskinesia as a cause of epigastric symptoms before diagnosing FD.

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## 2. Subjects and methods

### 2.1. Study design

This is a retrospective, observational study.

### 2.2. Ethics

This study was approved by the institutional review board/ethics committee of Kangnam Sacred Heart Hospital, Hallym University College of Medicine. We were exempted from obtaining consent by the committee as this was retrospective study. However, written consent was obtaining from every patient before any diagnostic examination (e.g., upper gastrointestinal endoscopy, abdominal ultrasonography, abdominal computed tomography, and magnetic resonance imaging, etc.).

### 2.3. Subjects

All patients aged ≥18 years and who received DISIDA scan in Kangnam Sacred Heart Hospital Hallym University College of Medicine between March 2012 and May 2016 were included. Exclusion criteria were patients with impaired mobility; an organic lesion causing epigastric discomfort or pain; history of major cerebral, cardiac or other vascular diseases (cardiac arrhythmia, uncontrolled hypertension, acute myocardial infarction within 3 months, and congestive heart failure); autonomic nervous system injury (spinal injury, etc.); renal insufficiency; electrolyte imbalance and history of gastrointestinal surgery (except appendectomy and hemorrhoidectomy).

### 2.4. Data collection

The patient list was obtained from the database of a picture archiving and communication system (INFINITT PACS; INFINITT Healthcare Co, Ltd, Seoul, Korea).

The patients' information obtained from the electronic medical records included age, sex, weight, height, medical or surgical history, character and site of symptoms, time of symptom initiation, symptom duration, timeline of symptom improvement, prescribed drugs, administration duration of the drugs, *H pylori* infection and eradication data, laboratory test results including hemoglobin A1c and thyroid function tests, and results of special studies including upper gastrointestinal endoscopy, abdominal ultrasonography, abdominal computed tomography, magnetic resonance imaging, endoscopic ultrasonography, and DISIDA scans.

### 2.5. Steps finding patients whose symptoms were compatible with the Rome IV criteria for a diagnosis of FD

First, patients < 18 years were excluded from subjects for analysis. Patients of incomplete information from poor medical records were also excluded. Then, patients corresponding to following cases were excluded step by step; patients with organic lesion that could be the cause of the symptoms; abnormal laboratory test results (serum levels of aspertate transaminase/alanine transaminase, bilirubin, gamma-glutamyl transferase, amylase, or lipase); acute or episodic symptoms; and symptoms that did not meet the Rome IV criteria for diagnosing FD (insufficient symptom duration or frequency).

### 2.6. GB scintigraphy—GB ejection fraction

The GB ejection fraction (GBEF) was measured with the DISIDA scan. The DISIDA scan was performed after the patients had fasted overnight. Each subject was given 8 mCi $^{99}Tc^{m}$-diisoproyl iminodiacetic acid intravenously under a large-field-of-view gamma camera. Serial hepatobiliary analogue images were obtained 5, 10, 20, 30, 45, and 60 minutes after the injection or until the GB was adequately filled. Immediately after the completion of the filling phase, the patients drank 200 mL milk containing about 13 g fat (130 kcal). Analogue images were recorded 30 minutes after ingestion of the milk. The GBEF was derived by calculating the counts within the GB before and 30 minutes after ingestion of the milk. Background regions over the liver were also generated and subtracted from the GB counts to derive the net GB count. A normal GBEF was > 40%, in accordance with previous studies of healthy volunteers.[6,7]

### 2.7. Conditions for judging GB dyskinesia to be the cause of the epigastric symptoms

We judged GB dyskinesia to be the cause of the epigastric symptoms if both the following conditions were met. The initial DISIDA scan performed when patient's symptom continued even after proper treatment for FD (compatible with RFD) demonstrated GB dyskinesia, and the follow-up DISIDA scan demonstrated GB function to be normalized and the patient's symptoms disappeared (Fig. 1).

## 3. Results

In total, 275 patients received DISIDA scans from March 2012 to May 2016. Seven patients were excluded because they were less than 18 years old. Four patients were excluded from the analysis because of poor medical records. Another 192 patients were excluded because they had an organic cause for the symptoms or abnormal laboratory test results. The organic causes included gallstones, sludge in the GB, GB polyps, GB adenomyomatosis, malignancy of the GB or bile duct, cholecystitis or cholangitis, pancreatitis, peptic ulcer disease, and reflux esophagitis. Fifty-three patients were excluded because their symptoms were acute or episodic, in the right upper quadrant or other abdominal locations, or they had symptoms inappropriate for FD. Another one patient was excluded due to insufficient symptom duration (<2 months) for the Rome IV criteria, although other conditions met the criteria (Fig. 2).

Finally, 18 patients had symptoms compatible with the Rome IV criteria for diagnosing FD and all corresponded to RFD (Table 1). Of these, 10 had epigastric pain syndrome (EPS, a subgroup of FD; epigastric pain, and/or epigastric burning), 3 had postprandial distress syndrome (PDS, the other subgroup of FD; postprandial fullness and/or early satiation), and the other 5 had both epigastric pain and postprandial fullness (overlap). Three of these patients did not revisit our hospital after undergoing the initial DISIDA scan (lost to follow-up); 2 of those had normal GB function and the other had GB dyskinesia. Of the remaining 15 patients whose symptoms met the FD criteria, 8 had normal GB function according to the initial DISIDA scan, so no follow-up DISIDA scan was performed. GB dyskinesia was demonstrated on the initial DISIDA scan in the other 7 patients. We prescribed 1 or 2 choleretic and litholytic drugs, such as ursodeoxycholic acid, Rowachol (terpene mixture), or a mixture of chenodeoxycholic acid and ursodeoxycholic acid for all 7 patients with GB dyskinesia. Mean duration from the initial DISIDA scan to the follow-up DISIDA scan was 5.6 months. The symptoms of 4 of these 7 patients disappeared after GB function normalized at the follow-up DISIDA scan. The

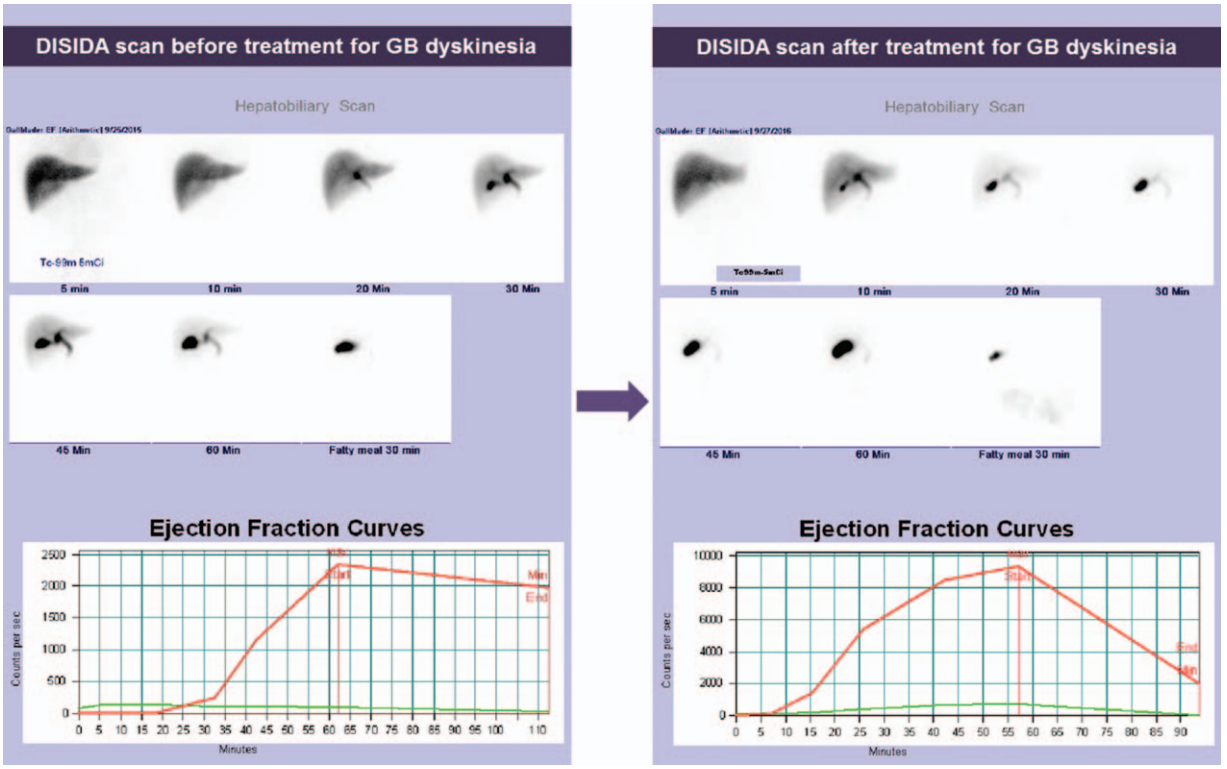


**Figure 1.** Decreased gallbladder (GB) function has been normalized with a treatment for GB dyskinesia. Ejection fraction of GB was 16% before the treatment and 78% after the treatment on $^{99}Tc^{m}$-diisoproyl iminodiacetic acid cholescintigraphy. DISIDA scan = $^{99}Tc^{m}$-diisoproyl iminodiacetic acid cholescintigraphy, EF = ejection fraction, GB = gallbladder, min = minutes.

symptoms of 1 of them disappeared despite persistent GB dyskinesia at the follow-up DISIDA scan. Symptoms and GB dyskinesia persisted at the follow-up DISIDA scan in another one patient. None of the patients had persistent symptoms despite normalization of GB dyskinesia at the follow-up DISIDA scan. The other one patient in whom the symptoms disappeared refused to undergo a follow-up DISIDA scan, so GB function when symptoms disappeared was unknown. Hence, FD symptoms were demonstrated to be caused by GB dyskinesia in 4 of 18 patients (Fig. 3).

## 4. Discussion

FD, as defined by the Rome IV criteria, is a medical condition that significantly impacts the daily activities of patients and is characterized by 1 or more of the following symptoms; postprandial fullness, early satiation, epigastric pain, and epigastric burning that remain unexplained after a routine clinical evaluation. Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present.[1,2] However, symptom definitions remain somewhat vague and are potentially difficult to interpret by patients, practicing physicians, and investigators alike.[1] GB dyskinesia is a relatively rare condition but the main clinical presentation, pain in the upper right abdominal quadrant and in the epigastrum, is not easily distinguishable from that occurring in highly prevalent conditions, such as gastroesophageal reflux disease, irritable bowel syndrome, and FD.[8] Symptoms such as nausea, bloating, postprandial epigastric pain, and upper abdominal fullness can appear in both patients with FD and GB dyskinesia.[3,4] In addition, a routine clinical investigation that includes upper endoscopy, medical imaging, and laboratory testing does not demonstrate abnormalities in patients with either FD or GB dyskinesia.[1,9] Therefore, it can be difficult and confusing to identify the cause of the symptoms. For example, in

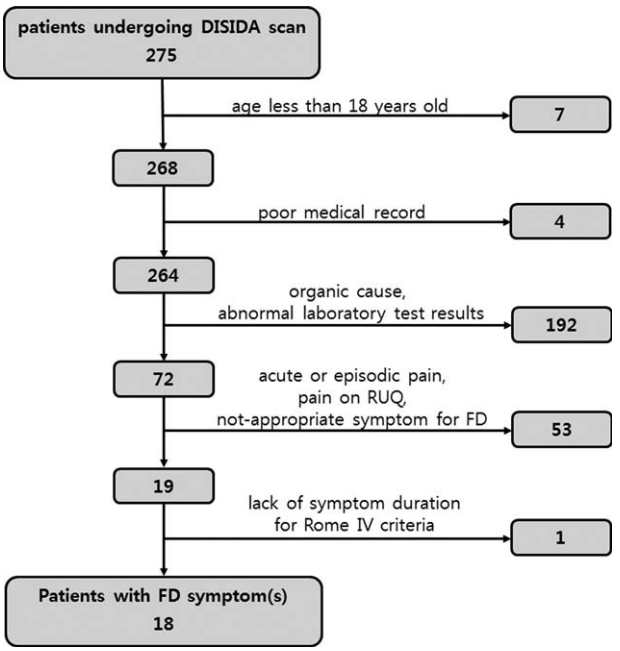


**Figure 2.** Steps finding patients whose symptoms were compatible with the Rome IV criteria for a diagnosis of functional dyspepsia in patients receiving cholescintigraphy. DISIDA scan = $^{99}Tc^{m}$-diisoproyl iminodiacetic acid cholescintigraphy, FD = functional dyspepsia, RUQ = right upper quadrant abdomen.

**Table 1**

**Details of patients with symptom of functional dyspepsia compatible with Rome IV diagnostic criteria.**

| Nu. | Age/sex | BMI | Symptom of functional dyspepsia | GB function (GB ejection fraction, %) | | From initial to follow-up DISIDA scan (mo) | Prescribed drug for GB dyskinesia | Relieved symptom as normalization of GB function |
|---|---|---|---|---|---|---|---|---|
| | | | | At initial DISIDA scan | At follow-up DISIDA scan | | | |
| 1 | 35/M | Unknowable | EP+PF | Normal (58) | — | — | — | — |
| 2 | 35/M | Unknowable | EP | Decreased (39) | Normal (60) | 7.4 | UDC | Relieved |
| 3 | 57/F | 21.6 | EP | Decreased (40) | Unknownable | — | UDC+Row | Relieved |
| 4 | 60/F | 16.1 | EP | Decreased (39) | Normal (86) | 4.6 | UDC+Row | Relieved |
| 5 | 28/F | 16.5 | EP | Normal (74) | — | — | — | — |
| 6 | 50/F | 19.9 | EP | Normal (80) | Lost follow-up | — | — | — |
| 7 | 60/F | 24.2 | EP | Abnormal (15) | Abnormal (30) | 6.1 | UDC+Row+U&C | Relieved |
| 8 | 22/F | Unknowable | PF | Abnormal (23) | Decreased (23) | 6.5 | UDC | None |
| 9 | 53/F | 21.3 | EP | Normal (79) | — | — | — | — |
| 10 | 25/F | Unknowable | EP | Normal (79) | — | — | — | — |
| 11 | 62/F | 38.3 | EP+PF | Abnormal (0) | Normal (60) | 14.0 | UDC+Row+U&C | Relieved |
| 12 | 50/F | Unknowable | PF | Normal (70) | — | — | — | — |
| 13 | 50/F | 20.7 | PF+ES | Abnormal (16) | Normal (71) | 6.2 | UDC+Row | Relieved |
| 14 | 51/M | 25.7 | EP | Abnormal (36) | Lost follow-up | — | UDC | — |
| 15 | 40/F | Unknowable | EP+PF | Normal (63) | — | — | — | — |
| 16 | 52/F | 19.4 | EP+PF | Normal (63) | Lost follow-up | — | — | — |
| 17 | 55/F | 26.9 | EP+PF | Normal (90) | — | — | — | — |
| 18 | 40/F | 21.5 | EP | Normal (82) | — | — | — | — |

"Unknowable" means case that related information, height and weight, could not be obtained because of poor medical records.

DISIDA scan = 99Tcm-diisoproyl iminodiacetic acid cholescintigraphy, EB = epigastric burning, EP = epigastric pain, ES = early satiation, GB = gallbladder, PF = postprandial fullness, Row = rowachol (terpene mixture), U&C = mixture of ursodeoxycholic acid and chemodeocycholic acid, UDC = ursodexocycholic acid.

a previous study, a conventional diagnostic workup that included upper gastrointestinal endoscopy and imaging was unable to detect the cause of dyspepsia in 47 patients with epigastric symptoms, but GB dyskinesia was found to be the cause of symptoms in 6 of the patients after hepatobiliary scintigraphy.[10]

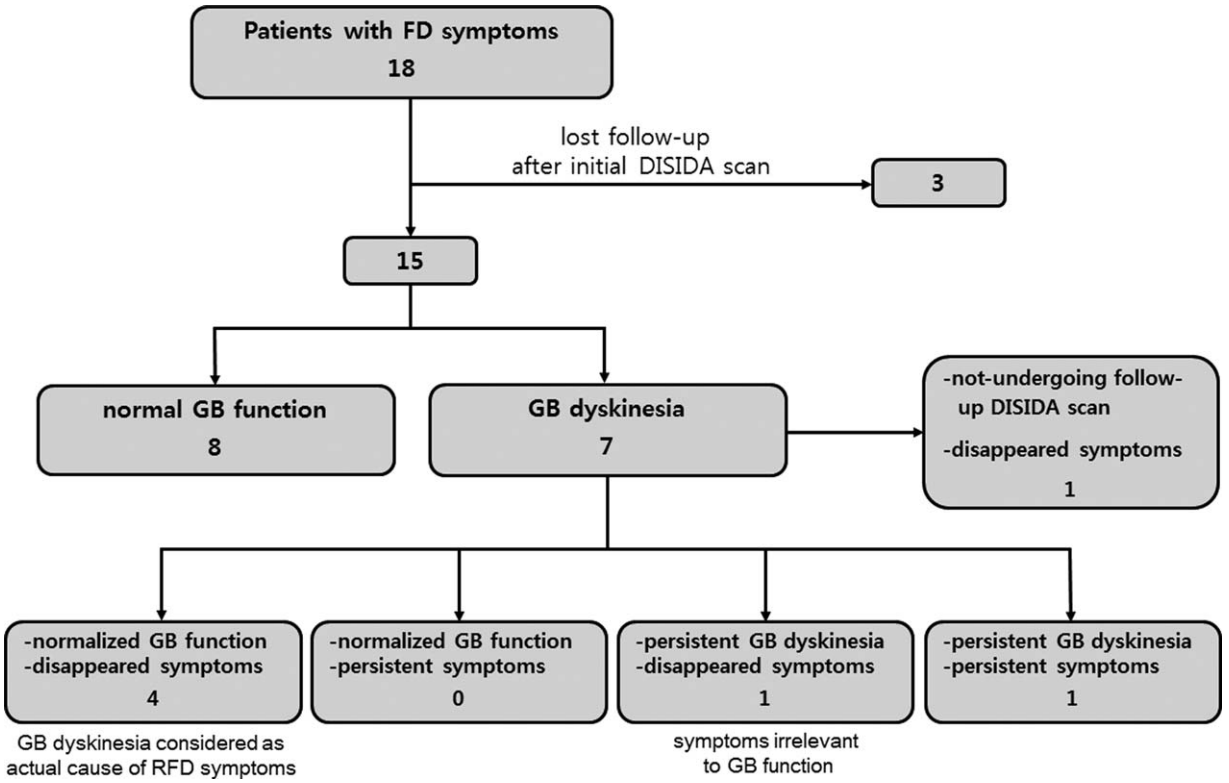


**Figure 3.** Illustration showing whether the symptoms of functional dyspepsia disappeared or not, as the gallbladder function was normalized in patients with symptoms compatible with the Rome IV criteria for diagnosing functional dyspepsia. DISIDA scan = $^{99}Tc^{m}$-diisoproyl iminodiacetic acid cholescintigraphy, FD = functional dyspepsia, GB = gallbladder.

RFD is FD with symptoms that last for at least 6 months and is unresponsive to at least 2 medical treatments such as acid suppressants, proton pump inhibitors, prokinetics, or *H pylori* eradication therapy[5]; it accounts for 24.4% (390/1600) of all FD diagnoses according to a previous study.[11] Indeed, GB dyskinesia might be the real cause of FD symptoms in some patients with RFD considering that similar confounding symptoms can appear in either FD or GB dyskinesia.

In the present study, GB dyskinesia was considered to be the cause of RFD symptoms in 4 of 18 patients (22.2%) with symptoms compatible with the Rome IV criteria for FD because 2 conditions suggested in the Method section (disappeared symptom as normalization of GB function) were met. All the 18 patients with FD symptoms had RFD possibly because we had performed a DISIDA scan only for patients with FD symptoms who did not respond to FD treatment. One patient with FD symptoms and decreased GB function at the initial DISIDA scan continued to have decreased GB function at the follow-up scan but the symptoms disappeared. In this case, the FD symptoms were considered to not be related to the decreased GB function. In fact, patients can be asymptomatic despite having a decreased GB function.[4] We considered GB dyskinesia to be a possible cause of the symptoms in another patient in whom symptoms and decreased GB function persisted at the follow-up DISIDA scan, although the symptoms were compatible with the Rome IV criteria for FD. We recommended cholecystectomy for this patient but it was refused.

We only treated the 7 patients with FD symptoms and GB dyskinesia at the initial DISIDA scan with choleretic and litholytic agents, as described above, and 4 of them eventually had normalized GB function. However, it was uncertain whether the effect was due to the drug treatment because their value has not been evaluated formally, although patients with GB dyskinesia may respond to medical treatments, such as ursodeoxycholic acid,[9] and sample size of this study was too small to conclude it.

This study had a few limitations. First, it was not randomized and the subjects were not enrolled consecutively. The sample size was too small for this study to have high validity. Therefore, the result that GB dyskinesia was the actual cause of the symptoms in 22.2% of patients with RFD is not highly reliable. Second, confounding conditions associated with reduced emptying of the GB, such as obesity, diabetes, and several drugs (e.g., calcium channel antagonists and oral contraceptives) could not be controlled appropriately because of poor medical records and the small sample size. Third, a *H pylori* infection can affect dyspepsia symptoms but *H pylori* infection status was not investigated.

Nonetheless, this study is still valuable as this is the first study that suggests GB dyskinesia can be the actual cause of epigastric symptoms even compatible with the Rome IV criteria in a not-neglected proportion of the patients with RFD.

In conclusion, it may be necessary to evaluate GB function in patients with RFD symptoms because the symptoms can be caused by GB dyskinesia. And, a randomized, well-controlled and larger study is necessary for confirmation.

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