

# Long-term Ultrasonographic Follow-up Study of Gastric Motility in Patients with Functional Dyspepsia

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**Summary** Although patients with functional dyspepsia complain of epigastric symptoms, the relation between these symptoms and gastric motility remains controversial. There are few reports on the clinical course of functional dyspepsia, including changes in gastric motility, observed over a considerably long period. We conducted a study to examine association between changes in symptoms and changes in ultrasonographically evaluated gastric motility over a long-term follow-up period in patients with functional dyspepsia. Forty patients (18 men, 22 women; mean age, 53.7 years) with functional dyspepsia were followed up by medical interview, physical examination, endoscopy, and ultrasonography for gastric motility. Follow-up ranged from 1.0 to 7.8 years (mean, 3.0 years). Ultrasonographic evaluation of gastric motility included gastric emptying rate and antral contractions. During the follow-up period, patients were treated with proton pump inhibitors, H<sub>2</sub>-blockers, or prokinetics. Symptoms improved in 21 patients (group A), but symptoms persisted or worsened in 19 patients (group B). There were no significant differences in clinical characteristics between the two groups. Gastric motility improved in group A but not in group B. In conclusion, improved gastric motility appears to correspond to and may explain improved symptoms in some patients with functional dyspepsia.

**Key Words:** functional dyspepsia, gastric motility, ultrasonography

## Introduction

Functional dyspepsia (FD) is a common condition often encountered in clinical practice. Its pathophysiology has been associated with many factors such as delayed gastric emptying, impaired gastric accommodation, visceral hyper-

sensitivity, *Helicobacter pylori* (*H. pylori*) infection, and psychological factors [1, 2]. However, the degree of involvement of each factor is controversial. Whereas gastric dysmotility has been reported in 30%–50% of FD patients [2–4], placebo response has also been described in 50% of FD patients, and studies suggesting that gastric dysmotility plays only a small role in FD have also been reported [5]. Some reports describe improvement of FD symptoms in patients with improved gastric motility [6], but the follow-up periods in these studies were short. Reported long-term follow-up studies are scarce.

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Among the various methods for evaluating gastric motility, abdominal ultrasonography (US) is simple, minimally invasive, and provides real-time data [7, 8]. We conducted a long-term follow-up study of patients with FD to examine association between changes in symptoms and changes in US-evaluated gastric motility.

**Materials and Methods**

*Subjects*

One hundred fourteen consecutive FD patients seeking medical consultation at our hospital during the period 1994 through 2003 were recruited for this study. FD was diagnosed on the basis of the American Gastroenterological Association criteria for patients recruited from 1994 through 1999 and on the basis of the Rome II criteria for those recruited beginning in 2000 [9, 10]. Peptic ulcer, reflux esophagitis, and malignant neoplasm were ruled out by upper gastrointestinal endoscopy in all patients. *H. pylori* infection status was determined by endoscopic biopsy or blood test for *H. pylori* antibodies. Patients with a history of abdominal surgery, diabetes, or a neurologic disorder and those taking drugs affecting gastrointestinal motility were excluded from the study. During their initial medical consultation, patients responded to a questionnaire evaluating gastrointestinal symptoms and underwent abdominal US evaluation of gastric motility.

*Questionnaire*

The questionnaire was filled out on the same day but prior to US evaluation. Symptoms (i.e., upper abdominal pain, bloating, nausea, early satiety, and heartburn) were scored for severity as follows: 0, none; 1, mild; 2, moderate; and 3, severe. Patients with heartburn were classified as having gastro-esophageal reflux disease and were excluded. Scores (excluding heartburn score) were added to yield a total symptom score (minimum of 0 and maximum of 12). On the basis of the predominant complaint, we divided patients into three subgroups: those with a main symptom of pain as having ulcer-like FD, those with bloating and early satiety as having dysmotility-type FD, and those with another main symptom as having non-specific FD. Smoking history and medication types were also recorded.

*Assessment of H. pylori infection*

*H. pylori* infection status was determined by evaluating Giemsa-stained biopsy specimens and serum IgG antibodies against *H. pylori* (E-plate, Eiken, Tokyo, Japan). Biopsy specimens were taken from the antrum and corpus during upper gastrointestinal endoscopy. Confirmation of the presence of *H. pylori* by either of these examinations was taken as positivity for *H. pylori* infection.

*US assessment of gastric motility*

We adopted the method of Fujimura and Kusunoki to assess gastric motility ultrasonographically [11, 12]. In brief, after an overnight fast, patients sat in a chair, leaned slightly backwards, and drank 400 ml consommé soup (54.8 kJ, 0.38 g protein, 0.25 g fat, 2.3 g sugar per serving; Ajinomoto Co, Tokyo, Japan). The cross-sectional area of the gastric antrum was measured ultrasonographically. The frequency of contractions of the antrum was also measured in real time. An ultrasound probe was positioned vertically to permit simultaneous visualization of the antrum, superior mesenteric artery, and abdominal aorta.

We determined the following two variables: gastric emptying rate (GER) and antral motility index (MI) (Table 1). The GER was estimated by measuring the change in the antral cross-sectional area between 1 min and 15 min after ingestion of the consommé soup (Fig. 1A, B). The MI was estimated by calculating the frequency of antral contractions and changes in cross-sectional area over 3 min. We defined baseline values as those obtained at the initial consultation. The US examiner was unaware of the responses to the questionnaire. The examinations were conducted with an SSA-270A, 380A, or 390A (Toshiba, Tokyo, Japan) ultrasound machine with a 3.5 MHz convex probe. As previously reported, the normal range for GER is 45.4%–78.6% and that for MI is 6.49–9.57 [13].

*Follow-up*

All patients were followed up until December 2003. We treated FD with drugs in the following order: prokinetics, anti-ulcer drug, *H. pylori* eradication, and antidepressants alone, and primarily used the most effective medicine. Symptoms reported on the questionnaire were then analyzed in relation to the US-based gastric motility findings obtained during the initial consultation. Patients for whom follow-up was less than 1 year were excluded from the analysis.

As a rule, gastric motility and abdominal symptoms were evaluated annually or when symptoms changed. We compared the baseline symptoms and baseline gastric

Table 1. US evaluation of gastric motility

Gastric emptying rate (GER)
GER = (A1–A15) / A1 (%)
Antral contractions
Motility index (MI) = amplitude × frequency
amplitude: {A (relaxed) – A (contracted)} / A (relaxed) × 100
frequency: No. of antral contractions / 3 min

US: ultrasonography

A1: antral cross-sectional relaxed area 1 min after ingestion

A15: antral cross-sectional relaxed area 15 min after ingestion

A (relaxed): antral cross-sectional relaxed area

A (contracted): antral cross-sectional contracted area

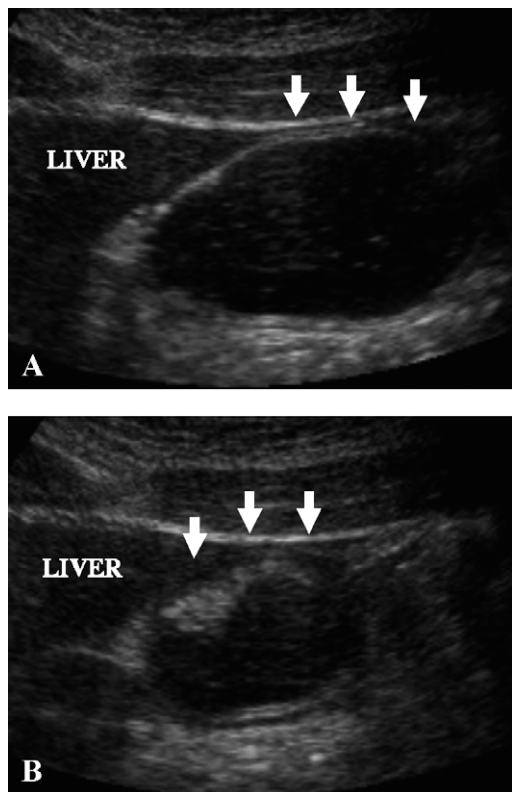


Fig. 1. Ultrasonographic assessment of gastric motility. Cross-sectional view of the gastric antrum (arrows) at 1 min (A) and 15 min (B) after ingestion of the consommé soup.

motility values with those at the final follow-up examination. We defined improvement of FD symptoms as improvement by more than two points in the symptom score or a symptom score of 0 at follow-up.

#### Statistical analysis

Values are shown as mean  $\pm$  SD. The Mann-Whitney U test was used to analyze differences in clinical characteristics between groups of patients, and the Wilcoxon signed-rank test was used to assess changes in gastric motility within groups. A  $p$  value of less than 0.05 was considered statistically significant. This study was performed under approval of the Ethics Committee of Hiroshima University.

## Results

#### Patient characteristics

Of the original 114 FD patients, 74 were excluded because of a short follow-up period (less than 1 year); thus, 40 patients (18 men, 22 women; mean age, 53.7 years; range, 16–82 years) completed the study. FD subtypes were as follows: ulcer-like type,  $n = 2$ ; dysmotility type,  $n = 15$ ; and non-specific type,  $n = 23$ . The mean follow-up period was 3.0 years (range, 1.0–7.8 years). Twelve patients were

treated with prokinetics, 20 with H<sub>2</sub>-blockers or proton pump inhibitors, and 8 with other drugs. Twenty-nine patients were examined for *H. pylori* infection, of which 14 were positive and 15 were negative. Eradication of *H. pylori* was achieved in 4 of the 14 *H. pylori*-positive patients. No organic disorder such as peptic ulcer or malignancy was detected endoscopically during the follow-up period.

#### Change in symptoms

Symptoms of 21 of the 40 patients who were followed up improved. These 21 patients were referred to as group A. Sixteen patients had no change in symptoms, and symptoms of 3 patients worsened. These 19 patients were referred to as group B. Clinical characteristics are shown per group in Table 2. There was no significant difference between the two groups. During the initial medical consultation, the total symptom score in group A was  $4.89 \pm 1.52$ ; that in group B was  $4.47 \pm 2.76$ . Follow-up scores were  $1.95 \pm 1.72$  and  $4.58 \pm 2.69$  for group A and group B, respectively. In group A, the initial symptom score was significantly higher than the follow-up score ( $p < 0.01$ ), but in group B there was no significant difference between the initial symptom score and the follow-up score.

#### Change in gastric motility

Gastric motility was assessed by US in all 40 patients. Prevalence of abnormal GER at baseline was 50% (20/40) and that of MI was 32.5% (13/40). No correlation between gastric motility evaluated by US and symptom score of the 40 FD patients was noted (Fig. 2). In group A, however, follow-up GER and MI values were significantly higher than baseline values, whereas in group B, no significant difference was observed between baseline and follow-up values (Fig. 3).

## Discussion

In this study, with a mean follow-up period of 3 years, we observed significant improvement in US-evaluated gastric motility that corresponded with improvement of symptoms in patients with FD, indicating an association between gastric motility and FD symptoms. In addition, no relation was noted between the improvement in symptoms and age, sex, smoking status, or *H. pylori* infection status.

These results suggest that gastric dysmotility plays an important role in the pathophysiology of FD. Gastric dysmotility in FD patients has been documented by many previous studies [1–4, 14, 15], but in most of these studies, results were based on one observation, and if subsequent changes in gastric motility were reported, the follow-up periods were short. In one study that evaluated FD patients by means of gastric emptying scintigraphy, the authors reported that subsequent re-evaluation 1 year after *H. pylori*

Table 2. Clinical features of the two patient groups\*

	Group A (n = 21)	Group B (n = 19)
Mean age upon recruitment (years)	50.5 ± 17.8	53.1 ± 16.9
Sex ratio (M/F)	8/13	10/9
Mean follow-up period (years)	3.09 ± 1.92	2.84 ± 1.60
FD subtype		
ulcer-like type	1	1
dysmotility type	8	7
non-specific type	12	11
US findings (baseline)		
GER	44.1 ± 20.2	50.9 ± 20.8
MI	7.29 ± 2.12	7.46 ± 2.59
Medications (n)		
Prokinetic drugs	8	4
Anti-ulcer drugs	10	10
<i>Helicobacter pylori</i> infection (n)		
positive	8	6
negative	8	7
Smoking status (n)		
smoking	3	2
non-smoking	18	17

FD: functional dyspepsia, GER: gastric emptying rate, MI: motility index, US: ultrasonography

\*Differences were not significant

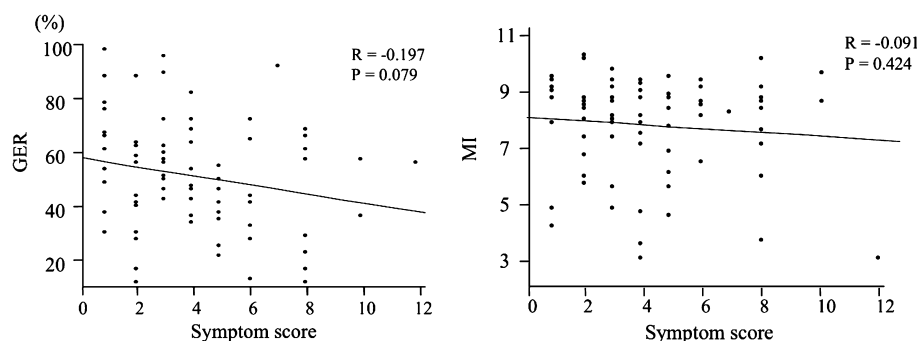


Fig. 2. Correlation between US-determined gastric motility and symptom score. No correlation was noted. US: ultrasonography, GER: gastric emptying rate, MI: motility index

eradication therapy showed no change in the GER [16]. To the contrary, our long-term follow-up study showed improvement in both symptoms and gastric motility. FD symptoms usually persist. Thus, to understand the pathophysiology of FD, it may be necessary to monitor patients for a substantially long period.

In this study, we found no correlation between gastric motility and symptom score, suggesting that symptom severity may not relate directly to gastric dysmotility among patients. Even though the gastric motility data may be the

same among patients, the sensation of symptoms experienced by the patients may be different. In the same patient, however, a change in gastric motility is associated with change in symptom score. Thus gastric motility does appear to affect symptom change in FD patients. Nevertheless, the role of gastric dysmotility in the progression of FD may be limited. Some of our group A patients showed no change in gastric motility, and some of our group B patients showed improved gastric motility. In addition, GER and MI rose in some of our group A patients, but baseline GER and MI

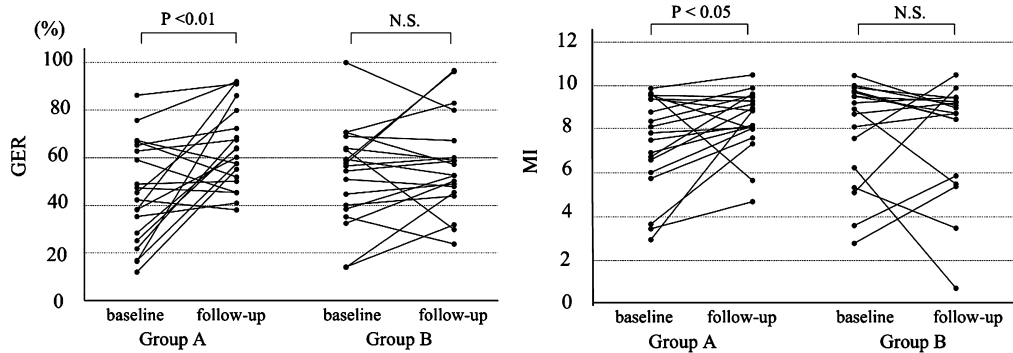


Fig. 3. Changes in US-determined gastric motility in patients with FD. In group A, follow-up GER and MI were significantly higher than baseline values, whereas in group B, no significant difference was observed between baseline and follow-up values. US: ultrasonography, FD: functional dyspepsia, GER: gastric emptying rate, MI: motility index, N.S.: not significant

were already high in those patients. This finding suggests that in the FD patients in whom there was no association between symptoms and gastric dysmotility, other factors could have been responsible for the pathogenesis of FD. We did not evaluate adaptive relaxation of the proximal stomach, which is the other motility factor associated with FD. Association between FD and gastric dysmotility might have increased if impaired gastric reservoir function had been evaluated.

Prevalence of FD subtype in Japanese people is different from that of Western people. Dysmotility-type dyspepsia is the most common subtype in Japan [17]. In the present study, non-specific-type dyspepsia was most frequent, and prevalence of dysmotility-type was higher than that of ulcer-like dyspepsia. Most of the non-specific type patients in our study complained of either abdominal pain or dysmotility symptoms such as early satiety or bloating, with dysmotility being the most common symptom in this study. Reports suggesting that FD subtypes have little association with the pathophysiology and treatment of the disease are numerous [1, 18, 19]. In the present study, there was no significant difference in the distribution of the subtypes between the two groups of patients. Moreover, there were even some patients with ulcer-like FD in whom both symptoms and gastric motility improved. These findings are consistent with previously reported findings that prokinetics improve not only abdominal fullness but also abdominal pain of FD patients [20].

Many previous studies have shown a generally good prognosis for FD, with improvement of symptoms in approximately 50% of patients [18, 21–22]. This is consistent with our results; however, it was difficult for us to predict outcomes in patients on the basis of ultrasonographic findings obtained during patients' initial consultation because there was no significant difference in baseline gastric motility between the two groups. Moreover, because patients were being treated with different medications, it

was impossible to say which drug contributed to improved gastric motility. There is no consensus on the issue of which drug is effective for FD [23–25]. Antidepressants and placebo as well as acid inhibitors and promotility drugs are reported to be effective, underscoring the notion that many factors influence the pathophysiology of FD [5, 25, 26].

Our study group was small, and there is a need to investigate the effects of various drugs on gastric motility in patients with FD. Thus, further research into this common disorder is warranted, and prospective randomized controlled study is needed.

Although many methods exist for evaluation of gastric motility, including evaluation of gastric accommodation with a barostat or of gastric emptying by means of an isotope or breath test, US offers a simple, less invasive, and real-time approach [27]. US is a good method for repeat evaluations. FD is characterized by delayed gastric emptying, decreased antral contraction, and impaired reservoir function of the proximal stomach [7, 8, 11, 12, 15]. We evaluated gastric motility using a liquid meal that patients did not usually take. However, delayed gastric emptying of liquid is common in FD patients and is improved by medication [4, 14]. The 54.8-kJ liquid meal we used in the present study provided less energy content than a usual daily meal. We have already shown that gastric emptying and MI produced by this liquid meal are significantly lower in patients with FD than in healthy subjects [12].

Overall, we conclude that improved gastric motility may explain symptom improvement seen in some patients with FD.

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