Impact of Sleep Disorders, Quality of Life and Gastric Emptying in Distinct Subtypes of Functional Dyspepsia in Japan

Hiroshi Yamawaki, Seiji Futagami, * Mayumi Shimpuku, Hitomi Sato, Taiga Wakabayashi, Yuuta Maruki, Yasuhiro Kodaka, Hiroyuki Nagoya, Tomotaka Shindo, Tetsuro Kawagoe and Choitsu Sakamoto

Division of Gastroenterology, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan

Background/Aims
The association between clinical symptoms, gastric emptying, quality of life and sleep disorders in distinct functional dyspepsia (FD) patients has not been studied yet in detail.

Methods
We enrolled 79 FD patients (postprandial distress syndrome [PDS], n = 65; epigastric pain syndrome [EPS], n = 47; EPS-PDS overlap, n = 33) and 44 healthy volunteers. Gastric motility was evaluated. We used Rome III criteria to evaluate clinical symptoms and State-Trait Anxiety Inventory (STAI) scores to determine anxiety status. Sleep disorder was evaluated using the Pittsburgh Sleep Quality Index scores.

Results
There were no significant differences in age, sex and Helicobacter pylori positivity between FD subtypes and healthy volunteers. The scores of Glasgow dyspepsia severity scores (GDSS), SF-8 and Pittsburgh Sleep Quality Index (PSQI) in distinct subtypes of FD patients were significantly different from those in healthy volunteers. However, there were not significant differences in these scores, T_max and T_1/2 among 3 subtypes of FD patients. PSQI score was significantly (P = 0.027, P = 0.002 and P = 0.039, respectively) associated with GDSS among EPS, PDS and EPS-PDS overlap patients. In addition, 8-item short form health survey (SF-8; Physical Component Score and Mental Component Score) was significantly associated with global PSQI score in PDS and EPS-PDS overlap patients. In contrast, SF-8 (Mental Component Score) only was significantly linked to global PSQI score in EPS patients.

Conclusions
Prevalences for sleep disorders, gastric motility and quality of life in 3 subtypes of FD patients were similar levels. In PDS and EPS-PDS overlap patients, SF-8 was significantly associated with global PSQI score.

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Key Words
Dyspepsia; Functional gastrointestinal disorders; Sleep disorders
Introduction

Functional dyspepsia (FD), irritable bowel syndrome (IBS) and gastroesophageal reflux disease (GERD) are highly prevalent and almost endemic gastrointestinal (GI) disorders in the general population. FD has been subclassified into 2 disease categories under the Rome III classification criteria: epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS). Impairment of gastric motility such as gastric emptying is strongly associated with the pathophysiology of FD, one of the most common gastrointestinal disorders. In a previous study, we reported that maximum time (Tmax) value as a marker of gastric emptying in PDS patients was significantly greater compared to healthy volunteers. We also reported that nizatidine significantly improved clinical symptoms by affecting the Tmax value in FD patients with impaired gastric emptying compared to those without impairment of gastric emptying. In addition, acotiamide has been reported to improve significantly clinical symptoms in PDS patients compared to placebo treatment. As for the treatment of FD patients, it might be useful to consider subtypes of FD and classification in view of impairment of gastric emptying. Therefore, we have considered subtypes of FD patients as well as evaluating gastric motility to manage the treatment of FD patients.

Sleep disorder is a common medical problem, and has been associated with several diseases, including pulmonary disease, GERD and fibromyalgia. Sleep disorder, in turn, causes significant morbidity, as evidenced by the increased need for general medical and mental health treatment for emotional problems. However, a number of studies have found an association between sleep disorders and functional GI disorders. Sleep disturbance reported by patients with GERD was substantially improved by the use of proton pump inhibitor (PPI) therapy or anti-reflux surgery. Patients whose treatment protocol included histamine H2 receptor antagonist medication at bedtime in addition to PPI therapy showed overall improvement in GI symptoms and GERD-associated sleep disturbance. In contrast, few studies have focused on the relationship between sleep disorders and functional dyspepsia. We also reported that there was a significant relationship between subjective sleep quality and both Tmax and T1/2 values in FD patients by the 13C-acetate breath test. In this study, we investigated (1) the prevalence and relationship for sleep disorders and status of health-related quality of life (HRQOL) in FD patients according to subtypes and (2) the degree of impairment for gastric emptying in subtypes of FD patients.

Materials and Methods

Subjects

Seventy-nine consecutive patients presenting typical symptoms of PDS (n = 65), EPS (n = 47) and EPS-PDS overlap (n = 33) were enrolled after upper gastrointestinal endoscopy and abdominal ultrasonography. Patients presented with various types of abdominal symptoms including nausea and upper abdominal discomfort, in addition to the four typical upper abdominal symptoms defined by the Rome III criteria; bothersome postprandial fullness, early satiation, epigastric pain and epigastric burning. Dyspeptic symptoms were defined as pain or discomfort in the upper abdomen for the past 3 months, with symptom onset at least 6 months prior to medical check-up. Patients completed a self-administrated questionnaire for the diagnosis of FD according to the Rome III criteria. Forty-four healthy volunteers with no clinical history of gastroduodenal disease including symptoms of FD, were recruited from our medical staffs and students at Nippon Medical School. Exclusion criteria included severe heart disease, renal or pulmonary failure, liver cirrhosis, severe systemic illness and history of malignant disease. Patients with previous gastroduodenal surgery, duodenal ulcer scars, diabetes mellitus, and recent use of non-steroidal anti-inflammatory drugs, PPIs or anticoagulants at endoscopy were also excluded. Helicobacter pylori infection was determined by both the 13C-acetate breath test and by histological identification. Written informed consent was obtained from all subjects prior to upper gastrointestinal endoscopy and abdominal ultrasonography for evaluation of dyspeptic symptoms. The study protocol was approved by the Ethics Review Committee of Nippon Medical School Hospital.

Clinical Symptoms

Clinical symptoms of FD were evaluated according to the Rome III criteria. Abdominal symptoms were assessed with a previously validated questionnaire. We assessed abdominal symptoms using the modified Glasgow dyspepsia severity score (GDSS), which is based on frequency (never, score 0; on only 1 or 2 days, score 1; on approximately 1 day per week, score 3; on approximately 50% of days, score 4; on most days, score 5), duration (minimum score, 0; maximal score 5), and intensity of symptoms (minimum score, 0; maximal score 5). The degree of anxi-
ety was evaluated by the State-trait Anxiety Inventory (STAI-state/-trait) scores.22

Pittsburgh Sleep Quality Index

A Japanese version of Pittsburgh Sleep Quality Index (PSQI)23 was used to measure the patient’s recent history of sleep quality and the sleep duration during the month immediately preceding the study. The PSQI consisted of 17 items which generated 7 components, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction. Each component score ranged from 0 to 3. The sum of these 7 component scores provides a global PSQI score, which ranges from 0 to 21. Higher scores indicate poorer sleep.23,24 A cut-off score > 5.5 has a sensitivity of 80.0-85.7% for various patient groups, and a specificity of 86.6% for control subjects in the Japanese version of the PSQI.24

Health-related Quality of Life

The 8-item short form health survey (SF-8) was used as a measurement scale for HRQOL, using eight questions scored according to the “Manual of the SF-8 Japanese version.”25,26 Scores for the 8 domains (“general health,” “physical functioning,” “role-physical,” “bodily pain,” “vitality,” “social functioning,” “mental health” and “role-emotional”) and 2 summaries (physical component summary [PCS] and mental component summary [MCS]) were derived. A score < 50 indicates impaired QOL, and an increasingly low score is considered to indicate greater damage to QOL.

Measurement of Gastric Motility

Sodium acetate (water-soluble; $^{13}$C-acetate) for emptying of liquids was used as tracer (Cambridge Isotope Laboratories, Cambridge, MA, USA). The liquid test meal consisted of 100 mg of $^{13}$C-acetate dissolved in 200 mL of a liquid meal (Racol, 1 mL/1 kcal; Otsuka Pharmacia Company, Tokyo, Japan). Breath samples were collected 0, 10 seconds, 5, 10, 15, 20, 30, 40, 50, 60, 75 and 90 minutes after ingestion of the test meal at 10:00 a.m. Patients were instructed not to drink, eat or smoke during the test. Probes were analyzed by non-dispersive infrared spectroscopy (IRIS, Wagner Analyzentechnik, Bremen, Germany). The subject’s own production of 300 mmol CO$_2$ per m$^2$ body surface area and per hour was set as default. We used an Integrated Software Solutions program to calculate the half gastric emptying time (T$_{1/2}$) and the lag phase (T$_{max}$ minutes) as the point of maximum gastric emptying according to Hellmig et al.27 The T$_{1/2}$ represents the time at which 50% of the initial gastric content was emptied.27,28 T$_{max}$ value greater than 60 minutes, representing the mean T$_{max}$ in healthy volunteers plus SD, was defined to represent relative disturbances in gastric emptying according to the diagnostic criteria of the Japan Society of Smooth Muscle Research, and our own study.3,29

Statistical Methods

For statistical evaluation of group data, Student’s t test for paired data and ANOVA for multiple comparisons were followed by Scheffe’s F test. Mann-Whitney U test was used for analysis of categorical data. The data analysis were performed using a standard software package (SPSS version 13.0; SPSS Inc., Chicago, IL, USA). A P-value of < 0.05 was statistically significant.

Results

Characteristics of EPS, PDS and EPS-PDS Overlap Patients and Healthy Volunteers

We have compared age, sex, H. pylori positivity, STAI-trait/-state score and T$_{max}$ value among EPS, PDS and EPS-PDS overlap patients and healthy volunteers. There were no significant differences in age, sex and H. pylori positivity among EPS, PDS and EPS-PDS overlap patients and healthy volunteers. Although there were significant (P < 0.05) differences in STAI-trait/-state, T$_{max}$ and T$_{1/2}$ values between 3 subtypes of FD patients and healthy volunteers, there were no significant differences in STAI-trait/-state, T$_{max}$ and T$_{1/2}$ values among EPS, PDS and EPS-PDS overlap patients (Table 1).

Comparison of GDSS, SF-8 and Global PSQI Scores Among EPS, PDS and EPS-PDS Overlap Patients and Healthy Volunteers

The scores of GDSS, SF-8 and global PSQI scores in EPS, PDS and EPS-PDS overlap patients were significantly different from those in healthy volunteers (Table 2). Especially, SF-8 (PCS) in EPS, PDS and EPS-PDS overlap patients were significantly lower (P < 0.001, P < 0.001 and P < 0.001) compared to that of healthy volunteers. The ratio of sleep disorders (global PSQI score > 5.5) in EPS, PDS and EPS-PDS overlap patients and healthy volunteers was 36.2%, 35.4%, 33.0% and 19.0%, respectively. However, there was no significant difference in GDSS, SF-8 and global PSQI scores among EPS, PDS and EPS-PDS overlap patients.
### Table 1. Characteristics of Subtypes of Functional Dyspepsia Patients and Healthy Volunteers

|                      | Age (range) | Sex (M:F) | HP positivity (%) | Tmax | T1/2 | STAI-state | STAI-trait |
|----------------------|-------------|-----------|-------------------|------|------|------------|------------|
| PDS (n = 65)         | 24-83       | 23:42     | 35                | 58.80 ± 3.31$^a$ | 96.14 ± 3.29$^b$ | 62.13 ± 3.41$^c$ | 54.71 ± 4.19$^c$ |
| EPS (n = 47)         | 24-83       | 13:34     | 30                | 55.31 ± 4.04$^a$ | 95.19 ± 3.45$^c$ | 61.27 ± 3.87$^b$ | 55.60 ± 4.63$^c$ |
| EPS-PDS overlap (n = 33) | 30-83   | 9:24      | 33                | 58.48 ± 5.39$^a$ | 92.76 ± 4.55$^b$ | 66.04 ± 4.23$^b$ | 58.48 ± 5.39$^c$ |
| Healthy volunteers (n = 44) | 26-81 | 24:20     | 28                | 48.02 ± 1.71 | 73.77 ± 2.33 | 38.51 ± 4.50 | 27.58 ± 3.84 |

$^a$vs. healthy volunteers, $P < 0.05$; $^b$vs. healthy volunteers, $P < 0.01$; $^c$vs. healthy volunteers, $P < 0.001$.

HP, *Helicobacter pylori*; Tmax, the lag phase as the point of maximum gastric emptying; T1/2, half gastric emptying time; STAI, state-trait anxiety inventory; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome.

Values are mean ± SD.

### Table 2. Comparison of GDSS, SF-8 and PSQI Scores Among Subtypes of Functional Dyspepsia Patients and Healthy Volunteers

| Component | GDSS | SF-8 | PSQI |
|-----------|------|------|------|
| PCS       |      |      |      |
| MCS       |      |      |      |
| PDS       | 2.37 ± 0.12$^a$ | 43.55 ± 1.18$^a$ | 45.47 ± 1.27$^a$ | 5.70 ± 0.44$^a$ |
| EPS       | 2.43 ± 0.14$^a$ | 41.53 ± 1.38$^a$ | 45.51 ± 1.39$^a$ | 5.60 ± 0.49$^a$ |
| EPS-PDS overlap | 2.55 ± 0.19$^a$ | 40.70 ± 1.64$^a$ | 45.40 ± 1.73$^a$ | 5.48 ± 0.57$^a$ |
| Healthy volunteers | 1.85 ± 0.11 | 50.98 ± 0.62 | 49.07 ± 0.93 | 4.52 ± 0.29 |

$^a$vs. healthy volunteers, $P < 0.05$.

GDSS, Glasgow dyspepsia severity score; SF-8, 8-item short form health survey; PCS, physical component summary; MCS, mental component summary; PSQI, Pittsburgh Sleep Quality Index; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome.

Values are mean ± SD.

### Table 3. Comparison of PSQI Scores Among Subtypes of Functional Dyspepsia Patients and Healthy Volunteers

| Component of PSQI score | PDS | EPS | EPS-PDS overlap | HV |
|--------------------------|-----|-----|-----------------|----|
| Subjective sleep quality | 1.29 ± 0.11 | 1.26 ± 0.14 | 1.32 ± 0.16 | 1.25 ± 0.10 |
| Sleep latency            | 1.07 ± 0.13$^a$ | 0.93 ± 0.14$^a$ | 0.92 ± 0.15$^a$ | 0.52 ± 0.10 |
| Sleep duration           | 0.74 ± 0.13$^a$ | 0.74 ± 0.14$^a$ | 0.88 ± 0.16$^a$ | 1.23 ± 0.11 |
| Habitual sleep efficiency| 0.29 ± 0.10$^a$ | 0.35 ± 0.12$^a$ | 0.40 ± 0.15$^a$ | 0.07 ± 0.05 |
| Sleep disturbance        | 0.97 ± 0.08$^a$ | 0.93 ± 0.09$^a$ | 1.00 ± 0.17$^a$ | 0.65 ± 0.08 |
| Use of sleep medication  | 0.81 ± 0.17$^a$ | 0.91 ± 0.20$^a$ | 0.69 ± 0.22$^a$ | 0.07 ± 0.04 |
| Day time dysfunction     | 0.74 ± 0.13 | 0.89 ± 0.16 | 0.81 ± 0.70 | 0.91 ± 0.12 |
| Global PSQI              | 5.70 ± 0.44$^a$ | 5.60 ± 0.49 | 5.48 ± 0.57$^a$ | 4.52 ± 0.29 |

$^a$vs. healthy volunteers, $P < 0.05$.

PSQI, Pittsburgh Sleep Quality Index; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome; HV, healthy volunteers.

Values are mean ± SD.

### Comparison of Each PSQI Score Among EPS, PDS and EPS-PDS Overlap Patients and Healthy Volunteers

Since we previously reported that global PSQI score of FD subjects was significantly higher compared to healthy volunteers, we have compared each PSQI score in distinct subtypes of FD subjects compared to those in healthy volunteers. Sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance and use of sleep medication in 3 subtypes of FD subjects were significantly higher compared to those in healthy volunteers (Table 3). Especially, sleep duration in EPS, PDS and EPS-PDS overlap syndrome was significantly ($P < 0.001$, $P < 0.01$ and $P < 0.05$) lower compared to that of healthy volunteers. However, there was no significant difference in each PSQI score among three subtypes of FD subjects (Table 3).

### Relationship Between GDSS Score and PSQI Score in 3 Subtypes of Functional Dyspepsia Subjects

Although we could not get any significant difference in GDSS, SF-8 and global PSQI scores among EPS, PDS and EPS-PDS overlap patients, we have previously reported that there was a significant relationship between clinical symptoms and global PSQI in FD patients. Therefore, we investigated whether there were any differences in GDSS, SF-8 and global PSQI scores in FD subtypes. Total GDSS score in PDS patients was significantly ($P = 0.002$, $r = 0.416$) associated with global PSQI score (Fig. 1A). In EPS patients, total GDSS score was significantly ($P = 0.027$, $r = 0.354$) associated with global PSQI.
Figure 1. Relationship between total Glasgow dyspepsia severity score (GDSS) and global Pittsburgh Sleep Quality Index (PSQI) score among subtypes of functional dyspepsia patients. (A) There was a significant ($P = 0.002, r = 0.416$) relationship between total GDSS and global PSQI score in postprandial distress syndrome (PDS) patients. (B) In epigastric pain syndrome (EPS) patients, there was a significant ($P = 0.027, r = 0.354$) relationship between total GDSS and global PSQI score. (C) In EPS-PDS overlap patients, there was a significant ($P = 0.039, r = 0.408$) relationship between total GDSS and global PSQI score. (D) In healthy volunteers, there was no significant ($P = 0.348, r = 0.148$) relationship between total GDSS and global PSQI score.

Relationship Between Total SF-8 and Global PSQI Score Among EPS, PDS and EPS-PDS Overlap Patients

In our data, quality of life in both subtypes of FD patients was significantly impaired, and we have investigated whether there was any significant correlations between SF-8 score and global PSQI score. In PDS patients, there were significant (PCS and MCS; $P < 0.001, r = -0.524$ and $P < 0.001, r = -0.762$, respectively) correlations between SF-8 score and global PSQI score (Fig. 2A and 2B). In EPS-PDS overlap patients, there were significant (PCS and MCS; $P < 0.013, r = -0.482$ and $P < 0.001, r = -0.720$, respectively) correlations between SF-8 score and global PSQI score (Fig. 2E and 2F). In contrast, in EPS patients, there was no significant ($P = 0.206$) relationship between SF-8 (PCS) score and global PSQI score (Fig. 2C). SF-8 (MCS) in EPS patients was significantly ($P < 0.001, r = -0.629$) associated with global PSQI score (Fig. 2D). In healthy volunteers, there were no significant correlations (PCS and MCS; $P = 0.091, r = -0.265$ and $P = 0.117, r = -0.245$, respectively) between SF-8 and global PSQI score (Fig. 2G and...
Figure 2. Relationship between 8-item short form health survey (SF-8) and global Pittsburgh Sleep Quality Index (PSQI) score among subtypes of functional dyspepsia patients. (A) There was a significant ($P < 0.001$, $r = -0.524$) relationship between SF-8 (physical component summary [PCS]) and global PSQI score in postprandial distress syndrome (PDS) patients. (B) In PDS patients, there was a significant ($P < 0.001$, $r = -0.762$) relationship between SF-8 (mental component summary [MCS]) and global PSQI score. (C) There was no significant ($P = 0.206$, $r = -0.207$) relationship between SF-8 (PCS) and global PSQI score in epigastric pain syndrome (EPS) patients. (D) There was a significant ($P < 0.001$, $r = -0.629$) relationship between SF-8 (MCS) and global PSQI score in EPS patients. (E) There was a significant ($P = 0.013$, $r = -0.482$) relationship between SF-8 (PCS) and global PSQI score in EPS-PDS overlap patients. (F) In EPS-PDS overlap patients, there was a significant ($P < 0.001$, $r = -0.720$) relationship between SF-8 (MCS) and global PSQI score. (G) There was no significant ($P = 0.091$, $r = -0.265$) relationship between SF-8 (PCS) and global PSQI score in healthy volunteers. (H) There was no significant ($P = 0.117$, $r = -0.245$) relationship between SF-8 (MCS) and global PSQI score in healthy volunteers.
Table 4. Multiple Logistic Regression Analysis of Factors Associated With Subtypes of Functional Dyspepsia Patients

| Factor        | Odds ratios (95%CI) | P-value |
|---------------|---------------------|---------|
| GDSS          | 1.195 (0.169-2.234) | 0.211   |
| PSQI          | 2.941 (0.150-4.071) | 0.877   |
| PCS (SF-8)    | 1.389 (0.176-2.096) | 0.269   |
| MCS (SF-8)    | 1.399 (0.193-2.113) | 0.547   |
| STAI-state    | 0.215 (0.097-2.953) | 0.889   |
| STAI-trait    | 0.206 (0.095-2.966) | 0.868   |
| Tmax          | 2.497 (0.110-2.824) | 0.182   |

GDSS, Glasgow dyspepsia severity scores; PSQI, Pittsburgh Sleep Quality Index; PCS, physical component summary; MCS, mental component summary; STAI, State-Trait Anxiety Inventory; Tmax, the lag phase as the point of maximum gastric emptying.

Discussion

The major findings of this study are: (1) The scores of STAI-state/-trait and global PSQI in 3 subtypes of FD patients were significantly greater compared to those in healthy volunteers. (2) The scores of SF-8 in 3 subtypes of FD patients were significantly lower compared to that in healthy volunteers. (3) Sleep disorders were similarly observed in distinct subtypes of FD. (4) In PDS and EPS-PDS overlap patients, both SF-8 (PCS) and SF-8 (MCS) were significantly associated with global PSQI score. In contrast, only SF-8 (MCS) in EPS patients was significantly linked to global PSQI score.

H. pylori infection and potent psychological factors. Distinct differences may exist in pathophysiology among the three subgroups, PDS, EPS and EPS-PDS overlap patients. Although following a therapeutic approach for FD in line with pathophysiology of each subgroup is appropriate, it is very difficult to investigate the factors of each FD patient at clinical investigations, including primary care hospitals. Therefore, in this study, we tried to clarify whether there were any differences such as sleep disorders, quality of life and gastric motility among 3 subgroups. Sleep disorders are common medical problems, and have been associated with several diseases, including GERD and pulmonary disease.6 In addition, an epidemiological survey on insomnia demonstrated that almost 20% of the general Japanese population suffer from sleep disorders.24,30,31 Higher prevalence of sleep disorders in FD patients has been reported by other studies conducted in Japan and in the USA.16,32 Miwa32 have also re-
ported that the distribution of subjects who thought that they got enough sleep was significantly lower for the FD-IBS overlap subjects than that for control subjects. In our study, prevalence of sleep disorder in EPS (36.2%), PDS (35.4%) and EPS-PDS overlap patients (33%) was significantly higher than that in healthy volunteers (19%). We have first reported the ratio of sleep disorders in distinct subtypes in functional dyspepsia. Sleep disorders distribution in three FD subtypes was significantly higher compared to that in healthy volunteers.

Moreover, it is possible that both sleep disorders and functional GI disturbances may be the result of some other underlying problem, such as depression, anxiety or other psychological conditions. Studies have shown that the prevalence of psychological disorders is significantly higher in patients with FD than in the general population. Lee et al have reported a significant correlation between clinical depression and FD. We have also reported that Self-Rating Questionnaire for Depression scores in FD patients are relatively higher than that in healthy volunteers. Some studies have suggested that the presence of anxiety can modulate the gut function and produce gastrointestinal disorders. In EPS patients, there was a significant correlation between the mental component score and global PSQI score. In contrast, sleep disorders in PDS and EPS-PDS overlap patients were significantly associated with psychological factors as well as physical factors. These results suggest that psychological factors significantly affect sleep disorders compared to physiological factors in EPS patients. In addition, in our study, STAI scores in subtypes of FD patients were significantly higher compared to that in healthy volunteers. We have first demonstrated STAI scores in subtypes of FD patients. Further studies will be needed to clarify the reason why psychological factors strongly affected on sleep disorders, especially in EPS patients.

Tack et al have reported that we could better select a treatment for FD patients based on the classification of subtypes of FD. They recommended anti-acid therapy for EPS patients and prokinetics for PDS patients were recommended. Therefore, treatment for FD patients based on subtypes of FD or impairment of gastric emptying might be very important for the effective treatment of FD patients. However, we could not find significant differences in gastric motility, sleep disorders, anxiety and quality of life among EPS, PDS and EPS-PDS overlap patients. Although it is very much important for the effective treatment of FD patients to classify FD, precise diagnosis for the subtypes of FD is sometimes difficult because it depends on subjective complaints. Further studies will be needed to determine the certain tools for classifying the distinct subtypes of FD.

Taken together, prevalences for sleep disorders, gastric motility and quality of life in subtypes of FD patients were similar level. However, there is the limitation of sample size and evaluation of sleep disorders in this study.

References

1. Tack J, Talley NJ, Camilleri M, et al. Functional gastroduodenal disorders. Gastroenterology 2006;130:1466-1479.
2. Quigley EM. Gastric emptying in functional gastrointestinal disorders. Aliment Pharmacol Ther 2004;20(suppl 7):S6-60.
3. Shindo T, Futagami S, Hirasuka T, et al. Comparison of gastric emptying and plasma ghrelin levels in patients with functional dyspepsia and non-erosive reflux disease. Digestion 2009;79:65-72.
4. Futagami S, Yamawaki H, Izumi N, et al. Impact of sleep disorders in Japanese patients with functional dyspepsia (FD): nizatidine improves clinical symptoms, gastric emptying and sleep disorders in FD patients. J Gastroenterol Hepatol 2013;28:1314-1320.
5. Matsueda K, Hongo M, Tack J, Saito Y, Kato H. A placebo-controlled trial of acetamide for meal-related symptoms of functional dyspepsia. Gut 2012;61:821-828.
6. Parish JM. Sleep-related problems in common medical conditions. Chest 2009;135:563-572.
7. Weissman MM, Greenwald S, Niño-Murcia G, Dement WC. The morbidity of insomnia uncomplicated by psychiatric disorders. Gen Hosp Psychiatry 1997;19:245-250.
8. Fass R, Fullerton S, Tung S, Mayer EA. Sleep disturbances in clinic patients with functional bowel disorders. Am J Gastroenterol 2000;95:1195-2000.
9. Jarrett M, Heitkemper M, Cain KC, Burr RL, Hertig V. Sleep disturbance influences gastrointestinal symptoms in women with irritable bowel syndrome. Dig Dis Sci 2000;45:952-959.
10. Goldsmith G, Levin JS. Effect of sleep quality on symptoms of irritable bowel syndrome. Dig Dis Sci 1993;38:1809-1814.
11. David D, Mertz H, Fefer L, et al. Sleep and duodenal motor activity in patients with severe non-ulcer dyspepsia. Gut 1994;35:916-925.
12. Vakil N, van Zanten SV, Kabirillas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101:1900-1920.
13. Orr WC, Goodrich S, Robert J. The effect of acid suppression on sleep patterns and sleep-related gastro-oesophageal reflux. Aliment Pharmacol Ther 2005;21:103-108.
14. Rackoff A, Aprawal A, Hila A, Mainie I, Tutuiai R, Castell DO. Histamine-2 receptor antagonists at night improve gastroesophageal reflux disease symptoms for patients on proton pump inhibitor therapy. Dis Esophagus 2005;18:370-373.
15. Vege SS, Locke GR 3rd, Weaver AL, Farmer SA, Melton LJ 3rd, Talley NJ. Functional gastrointestinal disorders among people with sleep disturbances: a population-based study. Mayo Clin Proc 2004;79:1501-1506.
16. Lacy BE, Everhart K, Crowell MD. Functional dyspepsia is associated with sleep disorders. Clin Gastroenterol Hepatol 2011;9:410-414.
17. Drossman DA. The functional gastrointestinal disorders and the Rome III process. Gastroenterology 2006;130:1377-1390.
18. Futagami S, Shimpuki M, Song JM, et al. Nizatidine improves clinical symptoms and gastric emptying in patients with functional dyspepsia accompanied by impaired gastric emptying. Digestion 2012;86:114-121.
19. McColl K, Murray L, El-Omar E, et al. Symptomatic benefit from eradicating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. N Engl J Med 1998;339:1869-1874.
20. Portincasa P, Altonare DF, Moschetta A, et al. The effect of acute oral erythromycin on gallbladder motility and on upper gastrointestinal symptoms in gastrectomized patients with and without gallstones: a randomized, placebo-controlled ultrasonographic study. Am J Gastroenterol 2000;95:3444-3451.
21. Shimpuku M, Futagami S, Kawagoe T, et al. G-protein β3 subunit 825CC genotype is associated with postprandial distress syndrome with impaired gastric emptying and with the feeling of hunger in Japanese. Neurogastroenterol Motil 2011;23:1073-1080.
22. Spielberg CD, Goursuch RL, Lushene RE. Manual for the State Trait Anxiety Inventory. Mountain View: Consulting Psychologist Press. 1983.
23. Doi Y, Minowa M, Okawa M. Development of the Japanese version of the Pittsburgh Sleep Quality Index. Jpn J Psychiatr Treat 1998;13:755-763. [Japanese]
24. Doi Y, Minowa M, Okawa M, Uchiyama M. Prevalence of sleep disturbance and hypnotic medication use in relation to sociodemographic factors in the general Japanese adult population. J Epidemiol 2000;10:79-86.
25. Ware JE, Kosinski M, Dewey JE, Gandek B. How to score and interpret single-item health status measures: a manual for users of the SF-8 health survey. Lincoln: Quality Metric Inc. 2001.
26. Fukuhara S, Suzukamo Y. [Manual of the SF-8 Japanese version.] Kyoto: Institute for Health outcomes & Process Evaluation Research 2004. [In Japanese]
27. Hellings S, Von Schöning F, Gadow C, et al. Gastric emptying time of fluids and solids in healthy subjects determined by 13C breath tests: influence of age, sex and body mass index. J Gastroenterol Hepatol 2006;21:1832-1838.
28. Ghoos YF, Maes BD, Geypens BJ, et al. Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. Gastroenterology 1993;104:1640-1647.
29. Futagami S, Shindo T, Kawagoe T, et al. Migration of eosinophils and CCR2-CD68-double positive cells into the duodenal mucosa of patients with postinfectious functional dyspepsia. Am J Gastroenterol 2010;105:1835-1842.
30. Kim K, Uchiyama M, Okawa M, Liu X, Oghara R. An epidemiological study of insomnia among the Japanese general population. Sleep 2000;23:41-47.
31. Kim K, Uchiyama M, Liu X, et al. Somatic and psychological complaints and their correlates with insomnia in the Japanese general population. Psychosom Med 2001;63:441-446.
32. Miwa H. Life style in persons with functional gastrointestinal disorders—large-scale internet survey of lifestyle in Japan. Neurogastroenterol Motil 2012;24:464-471, e217.
33. Lee HJ, Lee SY, Kim JH, et al. Depressive mood and quality of life in functional gastrointestinal disorders: differences between functional dyspepsia, irritable bowel syndrome and overlap syndrome. Gen Hosp Psychiatry 2010;32:499-502.
34. Haug TT, Svelbak S, Wilhelmsen I, Berstad A, Urisin H. Psychological factors and somatic symptoms in functional dyspepsia. A comparison with duodenal ulcer and healthy controls. J Psychosom Res 1994;38:281-291.
35. Wu JC. Psychological co-morbidity in functional gastrointestinal disorders: Epidemiology, mechanisms and management. J Neurogastroenterol Motil 2012;18:13-18.
36. Miwa H, Ghoshal UC, Gonlachanvit S, et al. Asian consensus report on functional dyspepsia. J Neurogastroenterol Motil 2012;18:150-168.
37. Eisenbruch S, Thompson JJ, Hamish MJ, Exton MS, Orr WC. Behavioral and physiological sleep characteristics in women with irritable bowel syndrome. Am J Gastroenterol 2002;97:2306-2314.
38. Geeraerts B, Vandenbergh J, Van Oudenhove L, et al. Influence of experimentally induced anxiety on gastric sensorimotor function in humans. Gastroenterology 2005;129:1437-1444.
39. Lorena SL, Timois E, Brunetto SQ, Camargo EE, Mesquita MA. Gastric emptying and intragastric distribution of a solid meal in functional dyspepsia: influence of gender and anxiety. J Clin Gastroenterol 2004;38:230-236.
40. Mönnikes H, Tebbe JJ, Hildebrandt M, et al. Role of stress in functional gastrointestinal disorders. Evidence for stress-induced alterations in gastrointestinal motility and sensitivity. Dig Dis 2001;19:201-211.
41. De la Roca-Chiapas JM, Solís-Ortiz S, Fajardo-Araujo M, Sosa M, Córdova-Fraga T, Rosa-Zarate A. Stress profile, coping style, anxiety, depression, and gastric emptying as predictors of functional dyspepsia: a case-control study. J Psychosom Res 2010;68:73-81.
42. Miwa H. Osada T, Nagahara A, et al. Effect of a gastro-protective agent, rebamipide, on symptom improvement in patients with functional dyspepsia: a double-blind placebo-controlled study in Japan. J Gastroenterol Hepatol 2006;21:1826-1831.
43. Chen JD, Ke MY, Liu XM, Wang Z, Zhang M. Cisapride provides symptomatic relief in functional dyspepsia associated with gastric myoelectrical abnormality. Aliment Pharmacol Ther 2000;14:1041-1047.