

# Impact of Coexisting Irritable Bowel Syndrome and Non-erosive Reflux Disease on Postprandial Abdominal Fullness and Sleep Disorders in Functional Dyspepsia

Seiji Futagami, Hiroshi Yamawaki, Mayumi Shimpuku, Nikki Izumi, Taiga Wakabayashi, Yasuhiro Kodaka, Hiroyuki Nagoya, Tomotaka Shindo, Tetsuro Kawagoe and Choitsu Sakamoto

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

## Abstract

**Background/Aims:** The association between clinical symptoms and sleep disorders in functional dyspepsia (FD)-overlap syndrome has not been studied in detail.

**Methods:** The subjects were 139 patients with FD, 14 with irritable bowel syndrome (IBS), 12 with nonerosive reflux disease (NERD), and 41 healthy volunteers. Gastric motility was evaluated with the <sup>13</sup>C-acetate breath test. We used Rome III criteria to evaluate upper abdominal symptoms, and Self-Rating Questionnaire for Depression (SRQ-D) scores to determine depression status. Sleep disorders were evaluated with Pittsburgh Sleep Quality Index (PSQI) scores.

**Results:** There were no significant differences in age, body-mass index, alcohol intake, and smoking rate between patients with FD alone and those with FD-overlap syndrome. The postprandial abdominal fullness score in patients with FD-NERD-IBS was significantly greater than that in patients with FD-NERD overlap syndrome ( $p < 0.001$ ) or FD alone ( $p < 0.001$ ). The score for the feeling of hunger in patients with FD-NERD-IBS was significantly greater than that in patients with FD alone ( $p = 0.0025$ ), FD-NERD overlap syndrome ( $p = 0.0088$ ), or FD-IBS overlap syndrome ( $p = 0.0057$ ). The heartburn score in subjects with FD-NERD-IBS overlap syndrome was significantly greater than that in subjects with FD alone ( $p = 0.0035$ ) or FD-IBS overlap syndrome ( $p = 0.0026$ ). The T<sub>max</sub> in patients with FD-overlap syndrome or FD alone was significantly higher than that in healthy volunteers. The Pittsburgh Sleep Quality Index score in subjects with FD-NERD-IBS overlap syndrome was significantly greater than that in subjects with FD alone.

**Conclusion:** Symptom scores, such as those for postprandial abdominal fullness, heartburn, and the feeling of hunger, in patients with FD-overlap syndromes are significantly greater than those in patients with FD alone. Further studies are necessary to clarify whether various symptoms are related to sleep disorders in patients with FD-NERD-IBS overlap syndrome.

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**Key words:** functional dyspepsia, gastric motility, sleep disorders, overlap syndrome

## Introduction

Functional dyspepsia (FD), irritable bowel syndrome (IBS), and gastroesophageal reflux disease (GERD) are common gastrointestinal (GI) disorders. Previous studies in Asian populations have found prevalence rates of 8% to 12% for GERD, 8% to 10% for FD, and 10% to 14% for IBS<sup>1,2</sup>. In addition, patients are increasingly reported to also have symptoms attributable to various GI disorders. Under the Rome III classification criteria, FD has been subclassified into 2 new disease categories: epigastric pain syndrome and postprandial distress syndrome<sup>3</sup>. Although the Rome III criteria exclude gastroesophageal reflux symptoms and lower abdominal symptoms from the symptoms of patients with FD, some degree of overlap is inevitable between the symptoms of NERD and FD or between those of IBS and FD. A recent meta-analysis has found that the prevalence of IBS is 8 times higher in patients with dyspepsia and suggests that IBS and dyspepsia share a mechanism of development<sup>4</sup>.

Impairment of gastric motility, such as gastric emptying, is strongly associated with the pathophysiology of FD<sup>5</sup>. We have previously reported that the T<sub>max</sub> value, as a marker of gastric emptying, in patients with postprandial distress syndrome is significantly greater than that in healthy volunteers<sup>6</sup>. Interestingly, we have also found that the T<sub>max</sub> value in patients with NERD or postprandial distress syndrome is significantly greater than that in healthy volunteers<sup>6</sup>. In addition, we have reported that prokinetic agents, such as mosapride citrate, improve symptoms by affecting the T<sub>max</sub> value in patients with proton pump inhibitor-resistant NERD and impaired gastric emptying<sup>7</sup>. These findings suggest that the T<sub>max</sub> value is a useful marker for guiding the treatment of NERD and of FD.

In addition, sleep disturbance is more common in patients with FD than in healthy control subjects<sup>8</sup>. Miwa et al have also found that patients with FD-IBS overlap syndrome are significantly less likely to report getting sufficient sleep than are healthy

persons<sup>9</sup>. We have also found a significant relationship between subjective sleep quality and both T<sub>max</sub> and T<sub>1/2</sub> values on the <sup>13</sup>C-acetate breath test in patients with FD<sup>10</sup>.

Therefore, the aim of the present study was to investigate the distribution of symptoms, the prevalence of sleep disorders, and the degree of impairment of gastric emptying in patients with FD-overlap syndrome.

## Materials and Methods

### Subjects

The subjects were 139 consecutive patients with FD alone (n=59), FD-NERD overlap syndrome (n=30), FD-IBS overlap syndrome (n=27), FD-NERD-IBS overlap syndrome (n=23), IBS (n=14), or NERD (n=12), who were enrolled after upper GI endoscopy and abdominal ultrasonography. Patients presented with various abdominal symptoms, including nausea and upper abdominal discomfort, in addition to the 4 typical upper abdominal symptoms defined by the Rome III criteria<sup>11</sup>: 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-administered questionnaire for the diagnoses of FD and IBS according to the Rome III criteria. The diagnosis of IBS was indicated when recurrent abdominal pain or discomfort had been present at least 3 days per month in the last 3 months associated with 2 or more of the following: improvement with defecation, onset associated with a change in stool frequency, or onset associated with a change in stool form. The diagnosis of NERD was indicated by typical heartburn at least once a week without visible esophageal mucosal break on endoscopy<sup>12</sup>. The questions about NERD symptoms concerned the presence or absence of heartburn or acid regurgitation (a bitter or sour fluid coming into the throat or mouth) or both. The diagnoses of FD-NERD overlap syndrome, FD-IBS overlap syndrome, and FD-NERD-IBS overlap syndrome were indicated by the coexistence of symptoms of FD and NERD, of

FD and IBS, and of FD, NERD, and IBS, respectively. In addition, coexistence of NERD and IBS was found to have a slight effect on symptom pattern compared to FD symptom. As control subjects, 41 healthy volunteers, with no clinical history of gastroduodenal disease, including symptoms of FD, were recruited from the medical staff and students at Nippon Medical School.

Exclusion criteria included severe heart disease, renal or pulmonary failure, liver cirrhosis, severe systemic illness, a history of malignant disease, previous gastroduodenal surgery, duodenal ulcer scars, diabetes mellitus, and recent use of nonsteroidal anti-inflammatory drugs, proton pump inhibitors, or anticoagulants at endoscopy.

The presence of *Helicobacter pylori* infection was determined with both the <sup>13</sup>C-urea breath test and histological examination.

Written informed consent was obtained from all subjects before upper GI endoscopy and abdominal ultrasonography for evaluation of dyspeptic symptoms. The study protocol was approved by the Ethics Review Committee of Nippon Medical School Hospital.

### Symptoms

Symptoms of FD were evaluated according to the Rome III criteria<sup>11</sup>. Abdominal symptoms were assessed with a previously validated questionnaire<sup>13-15</sup>. Abdominal symptoms were assessed with the modified Glasgow dyspepsia severity score<sup>13-16</sup>, which is based on frequency (never, score 0; on only 1 or 2 days per a month, 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; maximum score, 5), and intensity of symptoms (minimum score, 0; maximum score, 3). The coexistence of GERD symptoms and IBS was found to have a minor impact on symptom pattern compared to FD symptom. The status of depression was evaluated with the Self-Rating Questionnaire For Depression (SRQ-D)<sup>17</sup>.

### Pittsburgh Sleep Quality Index (PSQI)

A Japanese version of the Pittsburgh Sleep

Quality Index (PSQI)<sup>18</sup> was used to assess the recent history of sleep quality and sleep duration during the month immediately preceding the study. The PSQI consists of 17 items that generate 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 ranges 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<sup>18,19</sup>. A cut-off score >5.5 has a sensitivity of 80.0% to 85.7% for various patient groups and a specificity of 86.6% for control subjects in the Japanese version of the PSQI<sup>19</sup>.

### Measurement of Gastric Motility

Water-soluble sodium acetate (Cambridge Isotope Laboratories, Cambridge, MA, USA) was used as tracer to assess the gastric emptying of liquids. Probes were analyzed with nondispersive infrared spectroscopy (IRIS, Wagner Analyzentechnik, Bremen, Germany). The subject's own production of 300 mmol CO<sub>2</sub> per m<sup>2</sup> body surface and per hour were set as default. A software program (Integrated Software Solutions, Inc., Malvern, PA, USA) was used to calculate the half gastric emptying time (T<sub>1/2</sub>) and the lag phase (T<sub>max</sub>; min) as the point of maximum gastric emptying according to Hellmig et al<sup>20</sup>. The T<sub>1/2</sub> represents the time at which 50% of the initial gastric content was emptied<sup>20,21</sup>. A T<sub>max</sub> value greater than 60 minutes, representing the mean T<sub>max</sub> plus SD in healthy volunteers, was defined as representing a disturbance in gastric emptying according to the diagnostic criteria of the Japan Society of Smooth Muscle Research, and our own study<sup>6,22</sup>.

### Study Protocol for Gastric Emptying of Liquids

The liquid test meal consisted of 100 mg of <sup>13</sup>C-acetate dissolved in 200 mL of a liquid meal (Racol, 1 kcal/mL; EN Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). Breath samples were collected 0 and 10 seconds and 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

## Comparison of Sleep Disorders and Abdominal Fullness

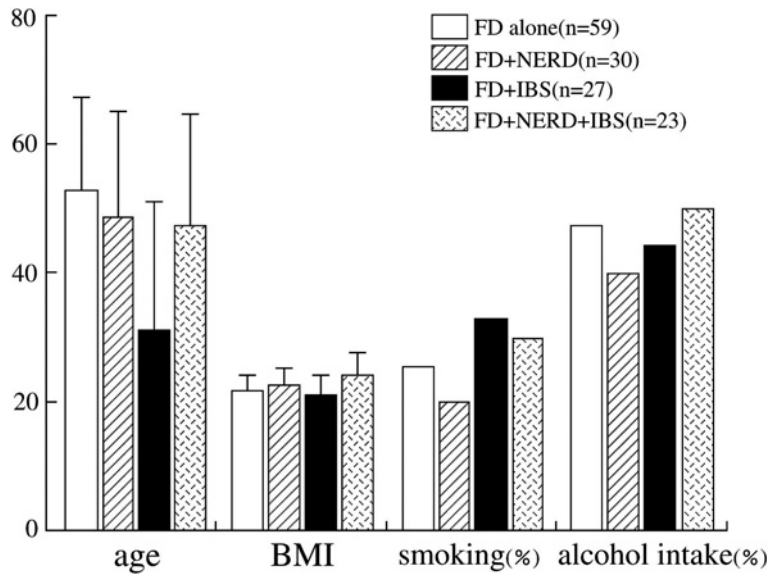


Fig. 1 Characteristics of patients with FD alone and those with FD-overlap syndrome

There were no significant differences in age, BMI, alcohol intake, or smoking rate among patients with FD alone, FD-NERD overlap syndrome, FD-IBS overlap syndrome, or FD-IBS-NERD overlap syndrome. BMI: Body-mass index; FD+NERD: patients with FD-NERD overlap syndrome; FD+IBS: patients with FD-IBS overlap syndrome; FD+NERD+IBS: patients with FD-NERD-IBS overlap syndrome

during the test.

### Statistical Analysis

For statistical evaluation of group data, Student's *t*-test for paired data and analysis of variance for multiple comparisons were followed by Scheffe's *F* test. The Mann-Whitney *U* test was used to analyze categorical data. A *p* value of <0.05 indicated statistical significance.

## Results

### Characteristics of FD Alone and FD-overlap Subjects

We compared age, body-mass index (BMI), smoking, and alcohol intake among patients with FD alone, FD-NERD overlap syndrome, FD-IBS overlap syndrome, or FD-NERD-IBS overlap syndrome. The BMI in patients with FD-NERD-IBS overlap syndrome was higher, but not significantly so, than those in other patients (**Fig. 1**). There were not significant differences in age, BMI, alcohol intake, or smoking rate among patients with FD alone, FD-

NERD overlap syndrome, FD-IBS overlap syndrome, or FD-NERD-IBS overlap syndrome (**Fig. 1**). In addition, the SRQ-D score ( $12.8 \pm 2.8$ ) in patients with FD-NERD-IBS overlap syndrome did not differ significantly from that in patients with FD alone ( $9.6 \pm 2.9$ ). Moreover, there were no significant differences in age, BMI, alcohol intake, or smoking rate among healthy volunteers and patients with FD alone, NERD, or IBS (data not shown).

### Comparison of Symptoms in Healthy Volunteers and Patients with NERD, IBS, FD Alone, FD-NERD Overlap Syndrome, FD-IBS Overlap Syndrome, or FD-NERD-IBS Overlap Syndrome

The postprandial abdominal fullness score in patients with FD alone was significantly ( $p < 0.05$ ) greater than that in healthy volunteers (**Fig. 2A**). The heartburn score in patients with NERD was significantly greater than that in healthy volunteers or patients with FD alone or IBS (**Fig. 2A**). The scores for the feeling of hunger, abdominal discomfort, epigastralgia, and abdominal distention in patients with FD alone were significantly greater

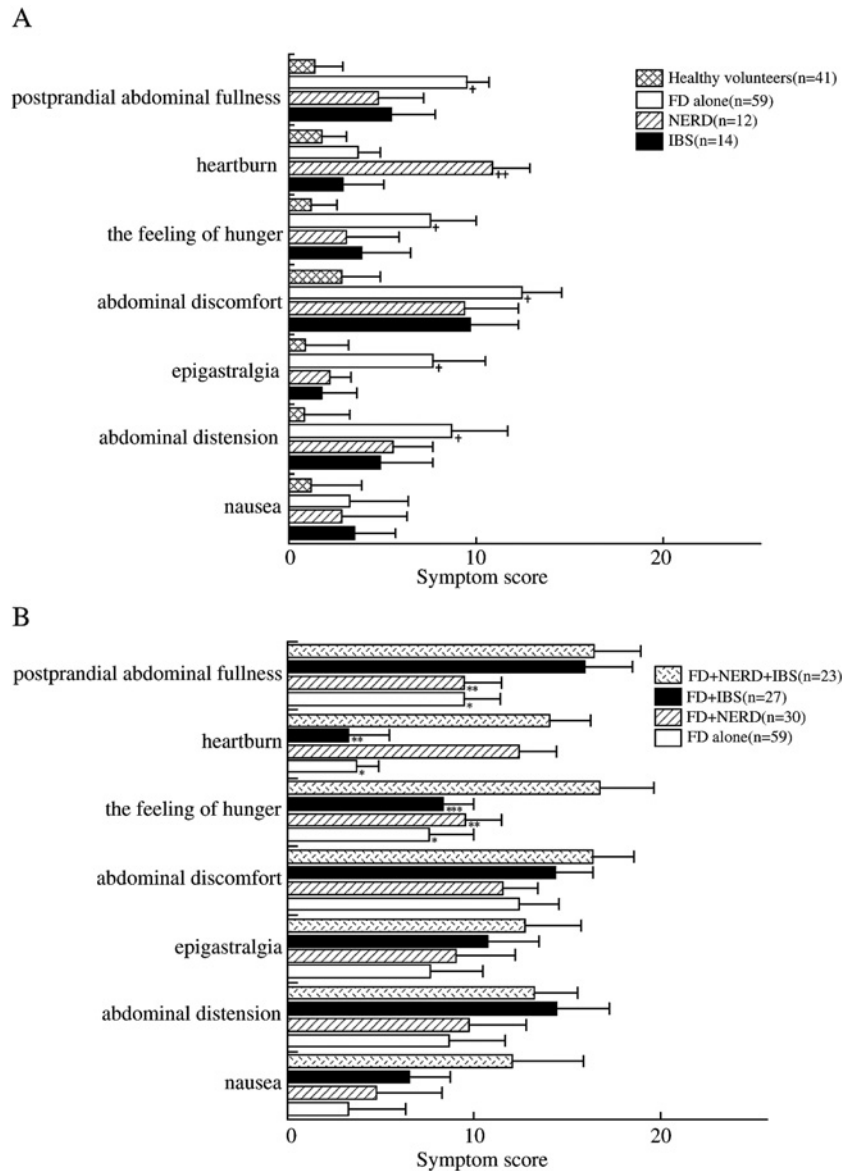


Fig. 2 Comparison of symptoms in healthy volunteers and patients with NERD, IBS, FD alone, FD-NERD overlap syndrome, FD-IBS overlap syndrome, or FD-NERD-IBS overlap syndrome

**A.** Comparison of symptoms among healthy volunteers and patients with NERD, IBS, or FD alone.

The postprandial abdominal fullness score in patients with FD alone was significantly ( $p < 0.05$ ) greater than that in healthy volunteers. The heartburn score in patients with NERD was significantly greater than that in healthy volunteers, patients with FD alone, or patients with IBS. The scores for the feeling of hunger, abdominal discomfort, epigastralgia, and abdominal distension in patients with FD alone were significantly greater than those in healthy volunteers. †  $p < 0.05$ , patients with FD alone vs healthy volunteers; ††  $p < 0.05$ , patients with NERD vs healthy volunteers, patients with IBS, or patients with NERD

**B.** Comparison of symptoms in patients with FD alone, FD-NERD overlap syndrome, FD-IBS overlap syndrome, or FD-NERD-IBS overlap syndrome.

The postprandial abdominal fullness score in patients with FD-NERD-IBS was significantly greater than that in patients with FD-NERD overlap syndrome ( $p < 0.001$ ) or FD alone ( $p < 0.001$ ). The score for the feeling of hunger in patients with FD-NERD-IBS was significantly greater than that in patients with FD alone ( $p = 0.0025$ ), FD-NERD overlap syndrome ( $p = 0.0088$ ), or FD-IBS overlap syndrome ( $p = 0.0057$ ). The heartburn score in patients with FD-NERD-IBS overlap syndrome was significantly greater than that in patients with FD alone ( $p = 0.0035$ ) or FD-IBS overlap syndrome ( $p = 0.0026$ ).

Postprandial abdominal fullness: \* $p < 0.001$ , FD alone vs FD+NERD+IBS; \*\* $p < 0.001$ , FD+NERD vs FD+NERD+IBS. The feeling of hunger: \* $p = 0.0025$ , FD alone vs FD+NERD+IBS; \*\* $p = 0.0088$ , FD+NERD vs FD+NERD+IBS; \*\*\* $p = 0.0057$ , FD+IBS vs FD+NERD+IBS. Heartburn: \* $p = 0.0035$ , FD alone vs FD+NERD+IBS; \*\* $p = 0.0026$ , FD+IBS vs FD+NERD+IBS.

FD+NERD: patients with FD-NERD overlap syndrome; FD+IBS: patients with FD-IBS overlap syndrome; FD+NERD+IBS: patients with FD-NERD-IBS overlap syndrome

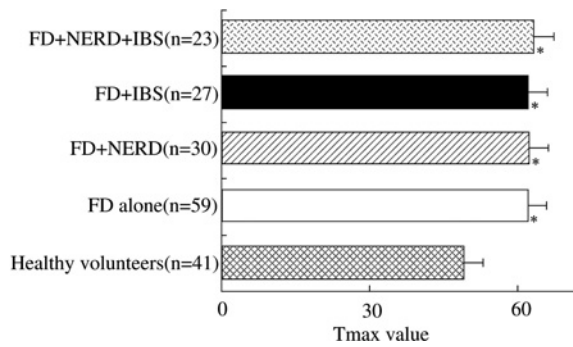


Fig. 3 Comparison of Tmax values in healthy volunteers and patients with FD alone, FD-NERD overlap syndrome, FD-IBS overlap syndrome, or FD-NERD-IBS overlap syndrome. The Tmax value in patients with FD-overlap syndrome was significantly greater than that in healthy volunteers ( $p < 0.05$ ). \* $p < 0.05$  vs healthy volunteers. There was no significant difference in Tmax among patients with FD alone, FD-NERD overlap syndrome, FD-IBS overlap syndrome, or FD-NERD-IBS overlap syndrome.

than those in healthy volunteers (**Fig. 2A**).

The postprandial abdominal fullness score in patients with FD-NERD-IBS overlap syndrome was significantly greater than that in patients with FD-NERD overlap syndrome ( $p < 0.001$ ) or FD alone ( $p < 0.001$ ) (**Fig. 2B**). The score of the feeling of hunger in patients with FD-NERD-IBS overlap syndrome was significantly greater than that in patients with FD alone ( $p = 0.0025$ ), FD-NERD overlap syndrome ( $p = 0.0088$ ), or FD-IBS overlap syndrome ( $p = 0.0057$ ) (**Fig. 2B**). In addition, the heartburn score in patients with FD-NERD-IBS overlap syndrome was significantly greater than that in patients with FD alone ( $p = 0.0035$ ) or FD-IBS overlap syndrome ( $p = 0.0026$ ). However, there were no significant differences in other symptoms, such as epigastralgia, nausea, abdominal discomfort, and abdominal distension, among patients with FD-overlap syndrome (**Fig. 2B**).

**Comparison of Tmax in Healthy Volunteers and Patients with FD Alone, FD-NERD Overlap Syndrome, FD-IBS Overlap Syndrome, or FD-NERD-IBS Overlap Syndrome**

Since we have previously reported that Tmax value in NERD subjects as well as FD subjects was significantly greater compared to that of healthy

volunteers, we compared Tmax among healthy volunteers and patients with FD alone, FD-NERD overlap syndrome, FD-IBS overlap syndrome, or FD-NERD-IBS overlap syndrome. The Tmax in patients with FD-overlap syndrome was significantly ( $p < 0.05$ ) greater than that in healthy volunteers (**Fig. 3**). However, we found no significant difference in Tmax among patients with FD alone, FD-NERD overlap syndrome, FD-IBS overlap syndrome, or FD-NERD-IBS overlap syndrome (**Fig. 3**).

**Comparison of PSQI Score among Subjects with Overlap Syndromes**

The global PSQI score did not differ significantly among healthy volunteers and patients with FD alone, NERD, or IBS (**Fig. 4A**). However, the PSQI score in patients with FD-NERD-IBS overlap syndrome was significantly greater than that in patients with FD alone (**Fig. 4B**).

**Discussion**

The major findings of this study were: 1) the postprandial abdominal fullness score in patients with FD-NERD-IBS overlap syndrome was significantly greater than to those in patients with FD-NERD overlap syndrome or FD alone, 2) the Tmax in patients with FD overlap syndrome or FD alone was significantly higher than that in healthy volunteers, and 3) the global PSQI score in patients with FD-NERD-IBS overlap syndrome was significantly greater than that in patients with FD alone.

Sleep disorders are common and have been associated with several diseases, including pulmonary disease, GERD, and fibromyalgia<sup>23</sup>. In addition, an epidemiological survey of insomnia has found that from 17.3% to 22.3% of the general Japanese population have sleep disorders<sup>19,24,25</sup>. Sleep disorders are strongly associated with NERD<sup>26</sup>. In addition, Yi et al have reported that patients with NERD have higher PSQI scores than do healthy control subjects<sup>27</sup>. Fujiwara et al have reported that NERD is significantly associated with sleep dysfunction compared to erosive reflux disease using PSQI score<sup>28</sup>. Elsenbruch et al have shown using

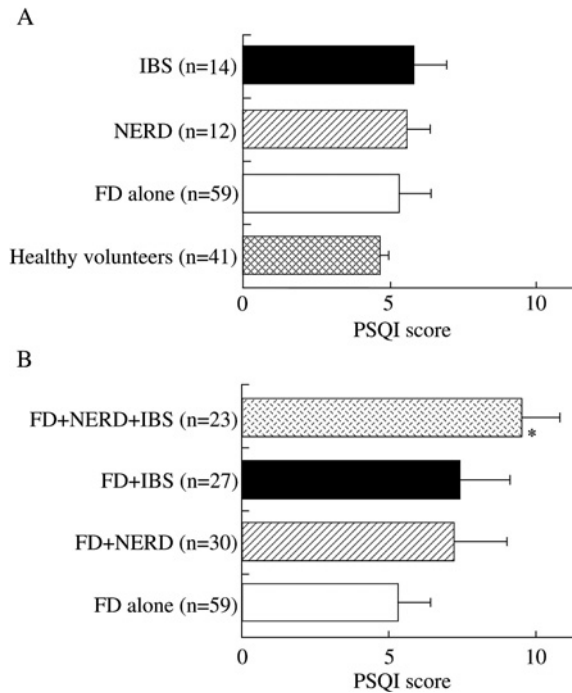


Fig. 4 Comparison of PSQI scores among patients with overlap syndromes

- A.** PSQI scores among patients with IBS, NERD, or FD alone and healthy volunteers. There was no significant difference among patients with IBS, NERD, or FD alone and healthy volunteers.
- B.** PSQI scores among patients with FD alone, FD-NERD overlap syndrome, FD-IBS overlap syndrome, or FD-NERD-IBS overlap syndrome.

The global PSQI score in patients with FD-NERD-IBS overlap syndrome was significantly greater than that in patients with FD alone. \* $p < 0.05$ , FD+NERD+IBS vs FD alone

PSQI scores that IBS is also associated with sleep disorders<sup>29</sup>. However, in the present study, we found no significant difference in PSQI score among healthy volunteers and subjects with FD alone, NERD, or IBS. The healthy volunteers in the present study were recruited from the medical staff and students of our medical school. Schaefer et al have reported that medical staff tend to have sleep disorders because shift work is an inherent part of their duties<sup>30</sup>. Therefore, we should consider the possibility that the prevalence of sleep disorders was higher among our healthy volunteers than among the general population. In contrast, few studies have focused on the relationship between sleep disorders

and FD<sup>10,31</sup>. Miwa et al have also found that that patients with FD-IBS overlap syndrome are significantly less likely to report getting sufficient sleep than are healthy persons<sup>9</sup>. Lacy et al have reported that PSQI scores are higher in patients with FD who have moderate or severe symptoms<sup>32</sup>. In the present study, we also found that PSQI scores in patients with FD-NERD-IBS overlap syndrome who complained of various symptoms were significantly greater than scores in patients with FD alone. In addition, Holtmann et al have reported that patients with overlap syndromes are less able to tolerate balloon distention of the stomach, duodenum, and rectum than are control subjects<sup>33</sup>. Corsetti et al have also reported that patients with overlap syndrome are more likely to exhibit hypersensitivity to gastric distention than are patients with FD alone<sup>34</sup>. Previous studies and our results suggest that hypersensitivity in overlap syndrome is associated with sleep disorders.

Among subjects with FD, IBS, or NERD, the pathophysiology is complexed. Camilleri et al have reported that many aspects of pathophysiology seem to be shared by FD and IBS<sup>35</sup>. They have suggested that certain mechanisms, such as visceral hypersensitivity, upper GI dysmotility, lower GI dysmotility, genetics, psychiatric comorbidities, infection are linked to the basis of both diseases<sup>35</sup>. Wang et al have reported that patients with FD-IBS overlap syndrome or FD-NERD-IBS overlap syndrome have higher severity scores for postprandial fullness than do patients with FD alone<sup>36</sup>. They have also shown that postprandial fullness is a risk factor for FD-IBS overlap syndrome<sup>36</sup>. We have confirmed that postprandial abdominal fullness scores in patients with FD-IBS overlap syndrome or FD-NERD-IBS overlap syndrome are significantly higher than those in patients with FD alone. Tack et al have found that symptoms of FD in patients with FD-IBS overlap syndrome, who have a greater prevalence of hypersensitivity to gastric distention, are more severe than those in patients with FD alone<sup>37</sup>. Because we failed to find a significant difference in gastric emptying between patients with FD alone and those with FD-overlap syndrome, further

studies are needed to clarify how mechanisms might affect postprandial abdominal fullness in patients with FD-NERD-IBS overlap syndrome and patients with FD-IBS overlap syndrome.

Comorbid psychiatric and psychological conditions, including anxiety, neuroticism, and somatization, have been reported in both FD and IBS<sup>38</sup>. However, these abnormalities have not been established to cause either FD or IBS<sup>38</sup>. Lee et al have reported that patients with overlap syndromes and those with FD alone show higher Beck Depressive Inventory scores than do healthy persons, whereas patients with IBS alone show no differences in scores from healthy persons<sup>39</sup>. In the present study, the SRQ-D score, as a marker of depression, was greater in patients with FD-NERD-IBS overlap syndrome than in patients with FD alone. The depressive state in patients with FD-NERD-IBS overlap syndrome might affect severe sleep disorders. In contrast, Lynn et al have shown that abdominal pain interferes with normal sleep patterns and awakens patients from sleep<sup>40</sup>. Kusano et al have shown that sleep disorders, such as inability to sleep, difficulty falling asleep, and awakening during the night, are present in 56.3% of patients with heartburn<sup>41</sup>. Although arousal from sleep has several protective roles, such as accelerating esophageal clearance and preventing aspiration via airway reflexes, it also impairs sleep quality<sup>42</sup>.

Taken together, in the present study, we have demonstrated that symptom scores, such as those for postprandial abdominal fullness, heartburn, and the feeling of hunger, are significantly greater in patients with FD-overlap syndromes than in patients with FD alone. The PSQI score in patients with FD-NERD-IBS overlap syndrome is also significantly greater than that in patients with FD alone. It will be useful to consider whether patients with FD alone should be distinguished from those with FD-overlap syndromes to understand the relationship between sleep disorders and various symptoms in FD-overlap syndromes.

**Conflict of Interest:** The authors have no financial conflicts of interest to declare with regard to the publication of this article.

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