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Original Article

Clinical Characteristics of Esophageal Motility Disorders in Patients With Heartburn

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Background/Aims
Esophageal motility disorders (EMDs) contribute to the pathophysiology of gastroesophageal reflux disease. However, the causes of EMDs and their impact on gastroesophageal reflux disease-associated symptoms remain unknown. This study aims to elucidate clinical features associated with various types of EMDs in patients with heartburn symptoms.

Methods
Of the 511 patients who underwent high-resolution manometry, 394 who were evaluated for heartburn symptoms were examined. Patients subjected to high-resolution manometry were classified into 4 groups: outflow obstruction group, hypermotility group, hypomotility group, and normal motility group. Symptoms were evaluated using 3 questionnaires. Patient characteristics and symptoms for each EMD type were compared with those of the normal motility group.

Results
Of the 394 patients, 193 (48.9%) were diagnosed with EMDs, including 71 with outflow obstruction, 15 with hypermotility, and 107 with hypomotility. The mean dysphagia score was significantly higher in each of the 3 EMD groups compared with those with normal motility. The mean acid reflux and dyspepsia scores were significantly lower in the outflow obstruction group ($P < 0.05$). The mean body mass index and median Brinkman index were significantly higher in the hypermotility group ($P = 0.001$ and $P = 0.018$, respectively), whereas the mean diarrhea and constipation scores were significantly lower in the hypomotility group ($P < 0.05$).

Conclusions
The results of our study indicate that different EMDs have distinct characteristics. Cigarette smoking and high body mass index were associated with esophageal hypermotility. Assessment of the dysphagia symptom scores may help identify patients with EMDs.
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Key Words
Esophageal motility disorders; Gastroesophageal reflux; Manometry

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Introduction

Gastroesophageal reflux disease (GERD) is a condition wherein the gastric contents reflux into the esophagus, causing troublesome symptoms or complications.[1] There are numerous individuals diagnosed with GERD worldwide, with the numbers estimated at 20-30% of the population in Western countries and more than 10% of the population in Asia.[2,3] Proton pump inhibitors (PPIs) are among the first-line treatments for GERD, which may be effective in about 80% to 90% of patients with reflux esophagitis.[4] Contrarily, PPI treatment results in symptom amelioration in only 40-50% of patients with nonerosive disease,[5] suggesting that their symptoms may be attributable to several distinct factors.[6] As such, if PPI treatment does not have a significant impact on GERD symptoms, pathophysiological evaluation using esophageal multichannel intraluminal impedance–pH testing and esophageal high-resolution manometry (HRM) testing have been recommended.[7,8]

The pathophysiology of GERD is complex and multifactorial. The results of the combined multichannel intraluminal impedance-pH and HRM testing can provide an accurate diagnosis of GERD and likewise facilitate the detection of pathological mechanisms, including esophageal motility disorders (EMDs) and lower esophageal sphincter dysfunction. Moreover, HRM testing rules out confounding diagnoses, such as achalasia.[9] GERD-associated symptoms, such as heartburn and regurgitation, are caused by the reflux of gastric contents into the esophagus. However, some patients experience similar symptoms that are unrelated to reflux.[6,10-12] Moreover, some of these patients are ultimately diagnosed with EMDs that include achalasia or jackhammer esophagus requiring a completely different therapeutic approach.[11,13,14] Results from previous studies have documented the frequency of EMDs among GERD patients to be 25-76%.[14-16] As such, in clinical practice, considering the possibility of EMDs is necessary when symptoms do not improve with PPI treatment. Pathophysiological classifications of EMDs have been described previously.[17,18] However, the underlying factors contributing to the pathogenesis of EMDs and their impact on suspected GERD-associated symptoms have not been fully investigated. As such, this study aims to explore clinical features associated with specific types of EMDs in patients with heartburn symptoms.

Materials and Methods

Study Design and Participants

This retrospective cohort study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Out of the 511 patients who underwent HRM testing at our institution between August 2013 and December 2019, 56 patients without heartburn symptoms and 61 patients who had already been diagnosed with achalasia by other test results (endoscopy and/or barium swallow test) were excluded from this study. The remaining 394 patients who were evaluated for suspected GERD-associated symptoms were analyzed. All patients had heartburn symptoms. Patients who had undergone previous esophageal surgery were not included. Demographic data were recorded, including age, sex, body mass index (BMI), cigarette smoking index (Brinkman index: the number of cigarettes smoked per day multiplied by the number of years of smoking), amount of alcohol consumed, comorbidities (hypertension, diabetes mellitus, scleroderma, and allergy), past history of gastrectomy, and *Helicobacter pylori* infection status. Consumption of 60 g or more of pure alcohol per day was defined as heavy drinking, whereas consumption of 0 g to 60 g per day was defined as light drinking. Comorbidities, past history of gastrectomy, and *H. pylori* infection status were investigated by a medical record review. The study was approved by the Research Ethics Committee at our institution (Approval No. 2990) and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients prior to study enrollment.

Questionnaires

All study participants completed 3 questionnaires, the frequency scale for symptoms of GERD (FSSG),[19] the Gastrointestinal Symptom Rating Scale (GSRS),[20] and the Short Form-8 Health Survey (SF-8),[21] before undergoing HRM in order to evaluate the differences with respect to their symptoms. The FSSG provides a measure of GERD-related symptoms. Of the 12 FSSG questions, 7 are related to symptoms associated with acid reflux, 5 to symptoms associated with gastrointestinal dysmotility, and 1 to symptoms associated with dysphagia (question 9). The patients answered each question based on a scale ranging from 0 (never) to 4 (always) points.[19] The GSRS questionnaire features 15 items and measures gastrointestinal symptoms in 5 categories: acid reflux, abdominal pain, indigestion, diarrhea, and constipation. The score for

each item was calculated as an average, and the total GSRS score was calculated as the average of all 15 items. The acid reflux score consists of 2 questions. One is the frequency of heartburn, and the other is the frequency of acid regurgitation. Scoring was performed using a Likert scale ranging from 1 (least severe gastrointestinal symptoms) to 7 (most severe symptoms).[20] The SF-8 is a measure of the general health which provides a summary of both physical and mental components. The participants were asked 8 questions about their health in the past 4 weeks; the results include 2 scores between 0 and 100, with higher scores indicative of superior health status.[21]

Endoscopic Findings

All patients underwent upper gastrointestinal endoscopy in order to evaluate the presence and degree of erosive esophagitis, hiatal hernia, and/or gastric mucosal atrophy. Erosive esophagitis was graded according to the Los Angeles classification (A-D).[22] Hiatal hernia was defined as an apparent separation of > 1 cm between the lower margin of the esophageal palisade vessels and the diaphragm hiatus on deep inspiration.[23] The severity of gastric mucosal atrophy was evaluated according to the Kimura-Takemoto classification (in order of severity: none, C-1, C-2, C-3, O-1, O-2, and O-3).[24] The status of infection and eradication of *H. pylori* was obtained from the medical records; infection with *H. pylori* was regarded as positive if the record included at least 1 positive result from the urease breath test (Otsuka, Tokyo, Japan) or rapid urease test (Helicocheck; Otsuka) or detection of serum IgG antibody against *H. pylori* (E-Plate "Eiken" *H. pylori* antibody; Eiken Chemical Co, Ltd, Tokyo, Japan).

High-resolution Manometry

All HRM studies were conducted employing the Sandhill System (InSIGHT Ultima; Sandhill Scientific Inc, Milwaukee, WI, USA) with the use of 32 pressure sensors and 16 impedance sensors. Patients were asked to swallow 5 mL of water 10 times while in the supine or semi-Fowler's position; the diagnosis of EMD was made according to the criteria of the Chicago classification, version 3.0.[17] The individual HRM metric types included normal motility, outflow obstruction (achalasia and esophagogastric junction [EGJ] outflow obstruction), hypermotility (distal esophageal spasm and jackhammer esophagus), and hypomotility (absence of contractility, ineffective esophageal motility, and fragmented peristalsis).[25,26]

Statistical Methods

Baseline data are expressed as mean ± standard deviation and median ± interquartile range. The differences in clinical parameter values between the groups were analyzed using Student's *t* test, χ^2 test, and Mann–Whitney *U* test, as appropriate. Moreover, which of the questions might best predict EMDs as well as sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio of symptoms score in predicting EMDs were identified. Receiver operating characteristic curves were used to determine the sensitivity and the specificity of the dysphagia symptom score with respect to predicting EMDs at all possible cutoff points to predict GERD. All statistical analyses were conducted using SPSS 23 (SPSS Inc, IBM, Armonk, NY, USA). A *P*-value of less than 0.05 was considered statistically significant.

Table 1. High-resolution Manometry Test Results

HRM	N = 394
Normal esophageal motility	201 (51.0)
Ineffective esophageal motility	83 (21.1)
Achalasia	38 (9.6)
EGJ outflow obstruction	33 (8.4)
Absent contractility	18 (4.6)
Jackhammer esophagus	9 (2.3)
Distal esophageal spasm	6 (1.5)
Fragmented peristalsis	6 (1.5)

HRM, high-resolution manometry; EGJ, esophageal gastric junction.
Data are presented as n (%).

Results

HRM test results are presented in Table 1. Of the 394 patients included in this study, 193 (48.9%) were diagnosed with EMDs; of these, 71 (36.7%) patients had outflow obstruction, 15 (7.7%) revealed hypermotility, and 107 (55.4%) were diagnosed with hypomotility. The patients' clinical characteristics by type of esophageal motility disorder and comparison with the normal motility group are presented in Table 2.

Comparison Between the Outflow Obstruction and Normal Motility Groups

The mean dysphagia symptom score in the outflow obstruction group was significantly higher than that in the normal motility group ($P = 0.047$). Contrarily, the mean acid reflux symptoms score (Fig. 1) and mean dyspepsia score on the GSRS questionnaire were significantly lower among those in the outflow obstruction group than among those in the normal motility group ($P =$

Table 2. Baseline Characteristics of Patients by Type of Esophageal Motility Disorder and Comparison With the Normal Motility Group

Characteristics	Total (N = 394)	Outflow obstruction group (n = 71)	Hypermotility group (n = 15)	Hypomotility group (n = 107)	Normal motility group (n = 201)	Outflow vs Normal motility	Hyper vs Normal motility	Hypo vs Normal motility
						P-value	*P*-value	*P*-value
Sex (M/F)	211/183	35/36	8/7	61/46	107/94	0.583	1.000	0.550
Age (yr)	56.2 ± 16.6	59.0 ± 15.6	61.0 ± 13.5	55.7 ± 18.3	55.1 ± 16.1	0.080	0.175	0.790
BMI (kg/m^2)	22.4 ± 3.76	22.3 ± 3.5	25.5 ± 4.7	22.4 ± 3.5	22.2 ± 4.2	0.829	0.001[a]	0.878
Comorbidity								
Hypertension (none/untreated/treating) (%)	77.9/1.7/20.3	71.8/2.8/25.3	60.0/0.0/40.0	79.4/3.7/16.8	80.5/0.4/18.9	0.135	0.151	0.096
Diabetes mellitus (none/untreated/oral medicine/insulin use) (%)	93.1/0.7/5.0/1.0	90.1/2.8/5.6/1.4	80.0/0.0/20.0/0.0	93.4/0.9/2.7/1.8	94.5/0.0/4.9/0.4	0.093	0.060	0.259
Allergy (%)	18.0	18.3	40.0	16.8	16.9	0.716	0.039	1.000
Scleroderma (%)	1.8	1.4	0.0	3.7	1.0	1.000	1.000	0.187
Helicobacter pylori infection status (NE/none/current/past) (%)	74.8/9.6/1.7/13.7	66.1/12/2/10	6.6/6.6/6.6/80.0	76.6/6.5/0.9/14.9	76.1/8.9/1.4/13.4	0.600	0.385	0.744
Medical history								
Gastrectomy (none/distal gastrectomy/others) (%)	98.7/1.2/0.0	100.0/0.0/0.0	93.3/6.6/0.0	100.0/0.0/0.0	98.0/1.9/0.0	0.576	1.000	0.193
Habits								
Smoking, Brinkman index	0.0 (0.0-166.8)	0.0 (0.0-300.0)	435.0 (0.0-780.0)[a]	0.0 (0.0-0.0)	0.0 (0.0-187.5)	0.563	0.018[a]	0.290
Alcohol consumption (NE/none/light/heavy) (%)	1.0/43.9/39.8/15.2	47.8/32.3/19.7	0.0/40.0/26.6/33.3	0.0/49.5/42.0/8.4	1.9/39.8/42.2/15.9	0.284	0.198	0.109
Endoscopic finding								
Erosive esophagitis (NE/none/A/B/C/D) (%)	12.9/47.7/29.2/7.4/2.0/0.7	19.7/52.1/19.7/8.4/0.0/0.0	13.3/73.3/6.6/6.6/0.0/0.0	10.2/48.5/28.9/6.5/4.6/0.9	11.9/43.7/34.3/7.4/1.4/0.9	0.184	0.170	0.443
Hiatal hernia (%)	39.8	16.9[a]	40.0	51.4	41.7	0.005[a]	0.787	0.127
Mucosal atrophy (NE/none/C-1,2,3/O-1,2,3) (%)	14.9/5.8/16.3/20.0	9.8/61.9/8.4/19.7	13.3/53.3/0.0/33.3	11.2/55.1/16.8/16.8	15.9/50.2/16.9/16.9	0.150	0.104	0.933

Table 2. Continued

Characteristics	Total (N = 394)	Outflow obstruction group (n = 71)	Hypermotility group (n = 15)	Hypomotility group (n = 107)	Normal motility group (n = 201)	Outflow vs Normal motility	Hyper vs Normal motility	Hypo vs Normal motility
						P-value	*P*-value	*P*-value
Symptom questionnaire								
FSSG score								
Reflux	11.3 ± 6.5	10.1 ± 6.4	11.5 ± 7.8	12.0 ± 6.6	11.2 ± 6.3	0.281	0.897	0.318
Dysmotility	8.1 ± 4.9	7.7 ± 5.0	8.0 ± 5.5	8.1 ± 4.8	8.2 ± 5.0	0.482	0.912	0.786
Dysphagia	1.6 ± 1.4	2.2 ± 1.5[a]	2.2 ± 1.3[a]	1.6 ± 1.3[a]	1.3 ± 1.2	0.047[a]	0.030[a]	0.022[a]
Total	19.4 ± 10.7	17.9 ± 10.7	19.6 ± 13.1	20.2 ± 10.7	19.5 ± 10.6	0.334	0.961	0.587
GSRS score								
Total	36.3 ± 14.8	33.2 ± 13.6[a]	44.0 ± 18.3	34.8 ± 13.9	37.7 ± 15.3	0.030[a]	0.285	0.121
Average	2.4 ± 1.0	2.2 ± 0.9[a]	2.9 ± 1.2	2.3 ± 0.9	2.5 ± 1.0	0.039[a]	0.285	0.097
Acid reflux	6.2 ± 3.0	4.9 ± 2.5[a]	6.3 ± 3.8	6.4 ± 3.1	6.4 ± 3.0	0.001[a]	0.917	0.867
Abdominal pain	6.9 ± 3.9	6.3 ± 3.7	8.3 ± 5.1	6.8 ± 3.7	7.1 ± 4.0	0.238	0.442	0.601
Dyspepsia	10.1 ± 4.8	8.9 ± 4.1[a]	11.6 ± 5.5	10.0 ± 4.8	10.5 ± 5.0	0.030[a]	0.546	0.370
Diarrhea	5.7 ± 3.7	5.4 ± 3.7	7.9 ± 4.3	4.9 ± 3.1[a]	6.0 ± 3.9	0.249	0.204	0.009[a]
Constipation	7.3 ± 4.2	7.5 ± 4.6	9.8 ± 4.4	6.4 ± 3.6[a]	7.6 ± 4.3	0.943	0.136	0.017[a]
SF-8								
PCS	42.7 ± 8.9	43.5 ± 9.0	41.6 ± 8.7	41.7 ± 8.4	43.0 ± 9.1	0.714	0.600	0.234
MCS	44.1 ± 8.3	43.6 ± 8.7	41.4 ± 8.4	45.3 ± 8.7	43.7 ± 8.0	0.925	0.397	0.127

[a]$P < 0.05$.

M, male; F, female; BMI, body mass index; *H. pylori*, *Helicobacter pylori*; NE, not evaluated; FSSG, frequency scale for symptoms of gastroesophageal reflux disease; GSRS, gastrointestinal symptom rating scale; SF-8, Short Form-8 Health Survey; PCS, physical component summary; MCS, mental component summary.

Data are presented as mean ± SD or median (range).

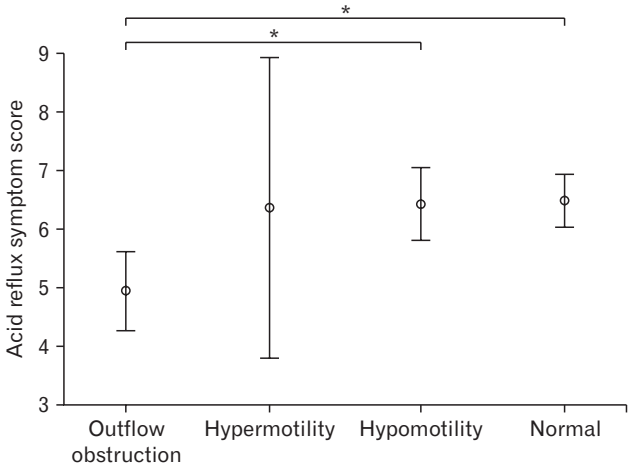

Figure 1. Acid reflux symptom scores by the type of esophageal motility disorder. The reflux symptom score in the outflow obstruction was lower than those in the hypomotility and normal motility groups ($P < 0.001$ and $P = 0.001$, respectively). Points represent mean values. Bars represent confidence intervals for mean values. *$P < 0.05$.

0.001 and $P = 0.030$, respectively). The fraction of patients diagnosed with an esophageal hiatal hernia was significantly lower in the outflow obstruction group ($P = 0.005$). The results of the study of achalasia and EGJ outflow obstruction separately are shown in Table 3. The mean acid reflux symptom score was significantly lower in both achalasia and EGJ outflow obstruction groups than that in the normal motility group ($P = 0.010$ and $P = 0.012$, respectively). However, no significant difference was found in dysphagia symptom score and dyspepsia score between EGJ outflow obstruction and the normal motility groups. Patients with EGJ outflow obstruction was significantly older than those with normal motility ($P = 0.012$).

Comparison Between the Hypermotility and Normal Motility Groups

The mean dysphagia symptom score among patients diagnosed with hypermotility was significantly higher than that reported among patients with normal motility ($P = 0.030$). The mean BMIs among patients in the hypermotility and normal motility groups were 25.5 kg/m^2 and 22.2 kg/m^2, respectively ($P = 0.001$). The median Brinkman indices determined for patients in the hypermotility and normal motility groups were 435.0 and 0, respectively ($P = 0.018$). No significant differences were observed with respect to the degree of abdominal pain, other symptoms, or patient demographic characteristics.

Comparison Between the Hypomotility and Normal Motility Groups

The mean dysphagia symptom scores among those with esophageal hypomotility were significantly higher than among those with normal motility ($P = 0.022$). The mean diarrhea and constipation symptom scores among those in the esophageal hypomotility group were significantly lower than those in the normal motility group ($P = 0.009$ and $P = 0.017$, respectively). No significant differences were observed with respect to any other symptoms, including those associated with reflux.

Symptoms That Predict Esophageal Motility Disorders

A full analysis of the aforementioned examinations revealed that the mean dysphagia scores of patients in each of the 3 EMD groups were all higher than those of patients with normal motility (Fig. 2). Furthermore, the dysphagia scores of those in the outflow obstruction group were significantly higher than those in the hypomotility group ($P = 0.013$). The sensitivity and specificity of the dysphagia symptom score with respect to predicting EMDs were determined. A dysphagia score ≥ 1 predicted EMDs with a sensitivity of 52.9% and specificity of 63.7%, with a positive predictive value of 76.5%, a negative predictive value of 37.6%, a positive likelihood ratio of 1.37, and a negative likelihood ratio of 0.73. A dysphagia score ≥ 2 predicted EMDs with a sensitivity of 57.3% and specificity of 61.0%, with a positive predictive value of 57.7%, a negative predictive value of 60.7%, a positive likelihood ratio of 1.46, and a negative likelihood ratio of 0.69. A dysphagia score ≥ 3 predicted EMDs with a sensitivity of 63.5%, a specificity of 57.7%, a positive predictive value of 34.8%, a negative predictive value of 82.6%, a positive likelihood ratio of 1.37, and a negative likelihood ratio of 0.63.

Discussion

This study evaluated the clinical characteristics and symptoms of patients diagnosed with EMDs. Among our findings, we demonstrated that different EMDs have distinct characteristics and symptoms. We also revealed for the first time that cigarette smoking and high BMI are associated with esophageal hypermotility in patients with GERD symptoms. Furthermore, our findings identified dysphagia symptoms as characteristic of all EMDs; as such, an assessment of the dysphagia symptom score on the FSSG questionnaire may be useful with respect to the diagnosis of EMDs.

Table 3. Comparison Between Achalasia and Normal Motility Groups, and Esophageal Gastric Junction Outflow Obstruction and Normal Motility Groups

Characteristics	Achalasia (n = 38)	EGJ outflow obstruction (n = 33)	Normal motility (n = 201)	Achalasia vs Normal motility	EGJ outflow obstruction vs Normal motility
				P-value	*P*-value
Sex (M/F)	19/19	16/17	107/94	0.714	0.613
Age (yr)	55.8 ± 16.2	62.7 ± 14.2[a]	55.1 ± 16.1	0.081	0.012[a]
BMI (kg/m^2)	22.9 ± 4.5	21.4 ± 3.8	22.2 ± 4.2	0.344	0.167
Comorbidity					
Hypertension (none/untreated/treating) (%)	71.0/5.2/23.6	72.7/0.0/27.2	80.5/0.4/18.9	0.041[a]	0.519
DM (none/untreated/oral medicine/insulin use) (%)	92.1/0.0/5.2/2.6	87.8/6.0/6.0/0.0	94.5/0.0/4.9/0.4	0.414	0.006[a]
Allergy (%)	15.7	21.2	16.9	0.855	0.449
Scleroderma (%)	0.0	3.0	1.0	0.537	0.335
H. pylori infection status (NE/none/current/past) (%)	55.2/23.6/5.2/15.7	78.7/9.0/0.0/12.1	76.1/8.9/1.4/13.4	0.444	0.888
Medical history					
Gastrectomy (none/distal gastrectomy/others) (%)	100.0/0.0/0.0/0.0	100.0/0.0/0.0	98.0/1.9/0.0	0.380	0.414
Habits					
Smoking, Brinkman index	0.0 (0-337.5)	0.0 (0-60.0)	0.0 (0.0-187.5)	0.136	0.749
Alcohol consumption (NE/none/light/heavy) (%)	0.0/47.3/36.8/15.7	0.0/48.4/27.2/24.2	1.9/39.8/42.2/15.9	0.721	0.202
Endoscopic finding					
Erosive esophagitis (NE/none/A/B/C/D) (%)	28.9/60.5/10.5/0.0/0.0/0.0	9.0/42.4/30.3/18.1/0.0/0.0	11.9/43.7/34.3/7.4/1.4/0.9	0.015[a]	0.346
Hiatal hernia (%)	5.2[a]	30.3	41.7	< 0.001[a]	0.300
Mucosal atrophy (NE/none/C-1,2,3/O-1,2,3) (%)	13.1/55.2/10.5/21.0	6.0/69.6/6.0/18.1	15.9/50.2/16.9/16.9	0.540	0.165
Symptom questionnaire					
FSSG score					
Reflux	9.9 ± 6.2	10.3 ± 6.7	11.2 ± 6.3	0.330	0.496
Dysmotility	8.4 ± 5.7	7.1 ± 4.3	8.2 ± 5.0	0.904	0.247
Dysphagia	2.0 ± 1.4[a]	1.5 ± 1.5	1.3 ± 1.2	0.015[a]	0.593
Total	18.3 ± 11.5	17.5 ± 10.2	19.5 ± 10.6	0.615	0.349
GSRS score					
Total	32.0 ± 12.6	34.3 ± 14.5	37.7 ± 15.3	0.070	0.253
Average	2.1 ± 0.8	2.2 ± 0.97	2.5 ± 1.0	0.070	0.253
Acid reflux	4.8 ± 2.4[a]	5.0 ± 2.7[a]	6.4 ± 3.0	0.010[a]	0.012[a]
Abdominal pain	6.8 ± 3.5	6.0 ± 3.9	7.1 ± 4.0	0.723	0.172
Dyspepsia	8.5 ± 3.3[a]	9.3 ± 4.7	10.5 ± 5.0	0.010[a]	0.203
Diarrhea	5.0 ± 3.4	5.7 ± 4.0	6.0 ± 3.9	0.174	0.678
Constipation	6.8 ± 4.6	8.1 ± 4.6	7.6 ± 4.3	0.389	0.486
SF-8					
PCS	43.7 ± 10.1	43.4 ± 8.2	43.0 ± 9.1	0.724	0.838
MCS	42.9 ± 8.0	44.2 ± 9.2	43.7 ± 8.0	0.613	0.754

[a]$P < 0.05$.

EGJ, esophageal gastric junction; M, male; F, female; BMI, body mass index; DM, diabetes millitus; *H. pylori, Helicobacter pylori*; NE, not evaluated; FSSG, frequency scale for symptoms of gastroesophageal reflux disease; GSRS, gastrointestinal symptom rating scale; SF-8, Short Form-8 Health Survey; PCS, physical component summary; MCS, mental component summary.

Data are presented as mean ± SD or median (range).

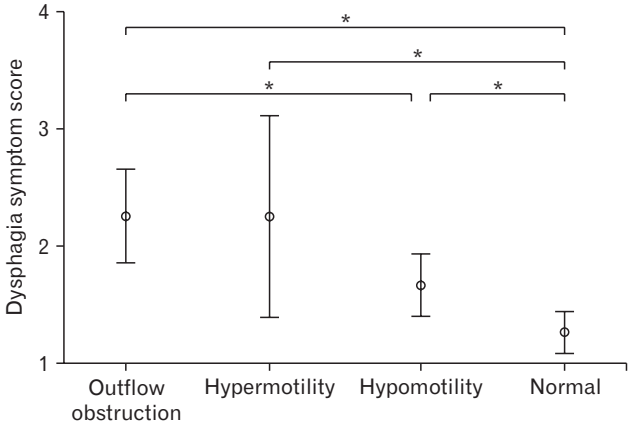

Figure 2. Dysphagia symptom scores by the type of esophageal motility disorder. The dysphagia scores in the outflow obstruction, hypermotility, and hypomotility groups were higher than those in the normal motility group. The score in the outflow obstruction group was also significantly higher than that in the hypomotility group ($P = 0.013$). Points represent mean values. Bars represent confidence intervals for mean values. *$P < 0.05$.

EMDs include several dysmotility types. In order to evaluate the characteristics of the different EMDs, we categorized them as those with primarily outflow obstruction, those with hypermotility, and those with hypomotility; the responses and characteristics were compared with those with normal motility, as reported in previous studies.[25,26] We evaluated the relationship between EMDs and detailed clinical histories of 394 patients presenting with heartburn symptoms; these characteristics included smoking habits, alcohol consumption, comorbidities, past medical histories, and endoscopic findings. In addition, we used 3 questionnaires in order to examine the association between symptoms and EMDs; these questionnaires focused not only GERD symptoms but also on non-GERD-associated symptoms, including irritable bowel syndrome (IBS), and quality of life. Among our results, we revealed that mean acid reflux and dyspepsia scores were significantly lower among those in the outflow obstruction group, whereas mean diarrhea and constipation scores were significantly lower among those with hypomotility. Significantly lower mean scores for acid reflux in the outflow obstruction group may be related to diminish acid reflux due to impaired EGJ relaxation. This result was similar when achalasia and EGJ outflow obstruction groups were separately compared with the normal motility group. On the other hand, the significantly lower score of dysphagia was found only in patients with achalasia. Moreover, the significantly lower mean scores for diarrhea and constipation in the hypomotility group may be due to the fact that more patients were categorized in the normal motility group. In other words, although the relationship between IBS and EMDs is still controversial,[27-29] our results suggest the possibility of less EMDs in GERD patients who also experience symptoms associated with IBS.

There are several published studies that have documented the association between EMDs and patient clinical histories and characteristics.[30-33] For example, Lee et al[30] reported that age was directly associated with esophageal dysmotility. Similarly, Spechler et al[31] considered the possibility of an association linking eosinophilic esophagitis with achalasia and other EMDs. With regard to BMI, Tanaka et al[32] reported that BMI was negatively associated with the distal contractile integral (DCI) determined by HRM, whereas Côté-Daigneault et al[33] reported that 85.0% of EMDs diagnosed in obese patients (BMI > 29 kg/m^2) involved hypomotility. Contrarily, Rogers et al[26] reported that EMDs were diagnosed less frequently in obese patients (BMI > 30 kg/m^2), including the esophageal hypermotility type. In our study, we found no association between BMI and esophageal hypomotility, although there was a distinct association between BMI and esophageal hypermotility. The discrepancies between these sets of results may be related to the differences in the range of BMIs and/or sample sizes; there may be other confounding factors as well. Taken together, the relationship between BMI and EMDs remains unclear; thus, further investigation of this point will be needed.

With regard to cigarette smoking, it is well known that cigarette smoking reduces lower esophageal sphincter pressure and is one of the major risk factors for the development of GERD.[34,35] Furthermore, results of a large prospective cohort study indicated that cessation of cigarette smoking was associated with diminished symptoms of reflux in normal-weight individuals.[36] Tanaka et al[32] reported that the Brinkman index was correlated with DCI. Since patients with normal IRP and high DCI (> 8000 mmHg·sec·cm) are diagnosed with hypermotility, the results of this study are consistent with those previously reported. To the best of our knowledge, previously published reports focusing on the relationship between cigarette smoking and esophageal hypermotility were not found. In the future, it will be necessary to conduct a prospective evaluation in order to determine whether cessation of cigarette smoking and/or weight reduction could improve esophageal motility.

In the present study, the dysphagia score was significantly higher in all EMD groups when compared with that observed among patients with normal esophageal motility. Reddy et al[25] examined 211 patients who underwent HRM testing and who were categorized into outflow obstruction, hypermotility, and hypomotility groups, which resulted in a gradient of decreasing dysphagia

and increasing reflux burden. Our results were similar to those presented in this study. However, contrary to their methods, we also examined the sensitivity and specificity of dysphagia symptom scores for predicting EMDs. Although the sensitivity and specificity were low, the negative predictive value of a dysphagia score of ≥ 3 was relatively high (82.6%). These results suggest that an assessment of the dysphagia symptom score may be beneficial for excluding a diagnosis of EMD. While various guidelines include recommendations for HRM testing of patients with PPI-refractory GERD, this is not yet a common diagnostic tool; only a few facilities are capable of conducting HRM testing at this time. The opportunity to predict the overall likelihood of EMDs would certainly be clinically useful. The results presented here would assist clinicians with disease-associated predictions.

This study has several limitations. First, although the relationship between EMDs and symptoms was evaluated, reflux monitoring was not performed in all patients, and the relationship between reflux and these symptoms was not explored. As such, EMDs cannot be identified as directly associated with these symptoms. Second, there were only 15 patients in the hypermotility group; as such, this study may have been underpowered with respect to the differences between patients with hypermotility and normal esophageal motility. Esophageal hypermotility is a comparatively uncommon diagnosis; more information on the characteristics of patients with this disorder needs to be collected and verified at multiple centers. Third, all patients in this study exhibited GERD symptoms; no symptom-free individuals were included. Given the reports of peristaltic disorders observed in subjects who report no symptoms,[15] it will be necessary to incorporate this group in future studies so as to have an accurate measure of the association between EMDs and associated symptoms.

In conclusion, we demonstrated here that different EMDs present with distinct characteristics and symptoms depending on the type of disorder. The underlying factors associated with the pathogenesis of EMDs remain unknown. Our results may be useful toward a larger understanding of the pathophysiology of EMDs and the development of new treatments for GERD in the future.

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References

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101:1900-1920.
2. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2005;54:710-717.
3. Goh KL. Changing epidemiology of gastroesophageal reflux disease in the Asian-pacific region: an overview. J Gastroenterol Hepatol 2004;19(suppl 3):S22-S25.
4. Dekkers CP, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Double-blind comparison [correction of double-blind, placebo-controlled comparison] of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. The European Rabeprazole Study Group. Aliment Pharmacol Ther 1999;13:49-57.
5. Fass R. Erosive esophagitis and nonerosive reflux disease (NERD): comparison of epidemiologic, physiologic, and therapeutic characteristics. J Clin Gastroenterol 2007;41:131-137.
6. Mainie I, Tutuian R, Shay S, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut 2006;55:1398-1402.
7. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon consensus. Gut 2018;67:1351-1362.
8. Iwakiri K, Kinoshita Y, Habu Y, et al. Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2015. J Gastroenterol 2016;51:751-767.
9. Garbarino S, Horton A, Patel A. The utility of esophageal motility testing in gastroesophageal reflux disease (GERD). Curr Gastroenterol Rep 2019;10;21:37.
10. Matsumura T, Ishigami H, Fujie M, et al. Endoscopic-guided measurement of mucosal admittance can discriminate gastroesophageal reflux disease from functional heartburn. Clin Transl Gastroenterol 2017;8:e94.
11. Ponce J, Ortiz V, Maroto N, Ponce M, Bustamante M, Garrigues V. High prevalence of heartburn and low acid sensitivity in patients with

idiopathic achalasia. Dig Dis Sci 2011;56:773-776.
12. Matsumura T, Arai M, Suzuki T, et al. Clinical utility of salivary pepsin measurement in patients with proton pump inhibitor-refractory gastroesophageal reflux disease symptoms: a prospective comparative study. Esophagus 2020;17:339-347.
13. Gyawali CP, Fass R. Management of gastroesophageal reflux disease. Gastroenterology 2018;154:302-318.
14. Kasamatsu S, Matsumura T, Ohta Y, et al. The effect of ineffective motility on gastroesophageal reflux disease. Digestion 2017;95:221-228.
15. Daum C, Sweis R, Kaufman E, et al. Failure to respond to physiologic challenge characterizes esophageal motility in erosive gastro-esophageal reflux disease. Neurogastroenterol Motil 2011;23:517-e200.
16. Izawa S, Funaki Y, Iida A, et al. The role of gastroesophageal reflux in relation to symptom onset in patients with proton pump inhibitor-refractory nonerosive reflux disease accompanied by an underlying esophageal motor disorder. Digestion 2014;89:61-67.
17. Kahrilas PG, Bredenoord AJ, Fox M, et al. The Chicago classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015;27:160-174.
18. Savarino E, Bredenoord AJ, Fox M, et al. Expert consensus document: advances in the pathological assessment and diagnosis of GERD. Nat Rev Gastroenterol Hepatol 2017;14:665-676.
19. Kusano M, Shimoyama Y, Sugimoto S, et al. Development and evaluation of FSSG: frequency scale for the symptoms of GERD. J Gastroenterol 2004;39:888-891.
20. Svedlund J, Sjödin I, Dotevall G. GSRS – a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci 1988;33:129-134.
21. Turner-Bowker DM, Bayliss MS, Ware Jr JE, Kosinski M. Usefulness of the SF-8 health survey for comparing the impact of migraine and other conditions. Qual Life Res 2003;12:1003-1012.
22. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45:172-180.
23. Hanada Y, Hoshino S, Hoshikawa Y, et al. Endoscopic diagnosis of hiatus hernia under deep inspiration is not consistent with esophageal manometric diagnosis. J Gastroenterol 2018;53:712-717.
24. Kimura K, Satoh K, Ido K, Taniguchi Y, Takimoto T, Takemoto T. Gastritis in the Japanese stomach. Scand J Gastroenterol Suppl 1996;214:17-20; discussion 21-23.
25. Reddy CA, Patel A, Gyawali CP. Impact of symptom burden and health-related quality of life (HRQOL) on esophageal motor diagnoses. Neurogastroenterol Motil 2017;29:e12970.
26. Rogers BD, Patel A, Wang D, Sayuk GS, Gyawali CP. Higher esophageal symptom burden in obese subjects results from increased esophageal acid exposure and not from dysmotility. Clin Gastroenterol Hepatol 2020;18:1719-1726.
27. Lee OY. Asian motility studies in irritable bowel syndrome. J Neurogastroenterol Motil 2010;16:120-130.
28. Soffer EE, Scalabrini P, Pope 2nd CE, Wingate DL. Effect of stress on oesophageal motor function in normal subjects and in patients with the irritable bowel syndrome. Gut 1988;29:1591-1594.
29. Thomaidis T, Goetz M, Gregor SP, et al. Irritable bowel syndrome and organic diseases: a comparative analysis of esophageal motility. World J Gastroenterol 2013;19:6408-6415.
30. Lee J, Anggiansah A, Anggiansah R, Young A, Wong T, Fox M. Effects of age on the gastroesophageal junction, esophageal motility, and reflux disease. Clin Gastroenterol Hepatol 2007;5:1392-1398.
31. Spechler SJ, Konda V, Souza R. Can eosinophilic esophagitis cause achalasia and other esophageal motility disorders? Am J Gastroenterol 2018;113:1594-1599.
32. Tanaka Y, Ihara E, Nakamura K, et al. Clinical characteristics associated with esophageal motility function. J Gastroenterol Hepatol 2016;31:1133-1140.
33. Côté-Daigneault J, Leclerc P, Joubert J, Bouin M. High prevalence of esophageal dysmotility in asymptomatic obese patients. Can J Gastroenterol Hepatol 2014;28:311-314.
34. Dennish GW, Castell DO. Inhibitory effect of smoking on the lower esophageal sphincter. N Engl J Med 1971;284:1136-1137.
35. Kahrilas PJ, Gupta RR. The effect of cigarette smoking on salivation and esophageal acid clearance. J Lab Clin Med 1989;114:431-438.
36. Ness-Jensen E, Lindam A, Lagergren J, Hveem K. Tobacco smoking cessation and improved gastroesophageal reflux: a prospective population-based cohort study: the HUNT study. Am J Gastroenterol 2014;109:171-177.