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Original Article

Development and Validity Assessment of a Self-evaluation Questionnaire for Functional Dyspepsia: A Multicenter Prospective Study in Korea

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Background/Aims

Patient-reported outcomes (PROs) are essential for clinical decision making, conduction of clinical research, and drug application acquisition in functional gastrointestinal disorders. The aim of this study is to develop a PRO instrument and to determine the respondents' perception of the efficacy of therapeutic agents for functional dyspepsia (FD).

Methods

A self-evaluation questionnaire for dyspepsia (SEQ-DYSPEPSIA) was developed and validated through a structured process. The 2-week reproducibility was evaluated, and the construct validity was assessed by correlating the scores of SEQ-DYSPEPSIA (including typical and major FD symptom subscales). Finally, the response to medication was assessed by comparing the changes after 4 weeks of treatment.

Results

A total of 193 Korean patients (age 48.5 ± 13.6 years, 69.4% women) completed the questionnaire. SEQ-DYSPEPSIA with 11 items had a good internal consistency (alpha = 0.770-0.905) and an acceptable test-retest reliability (intraclass correlation coefficient = 0.733-0.859). The self-evaluation questionnaire (SEQ)-major FD score highly correlated with the postprandial fullness/early satiety domain of the Patient Assessment of Gastrointestinal Symptom Severity Index (correlation coefficient $r = 0.741$, $P < 0.001$), Nepean Dyspepsia Index-Korean version (NDI-K) ($r = 0.839$, $P < 0.001$), and NDI-K quality of life ($r = -0.275$ to -0.344, $P < 0.001$). After medical treatment, decrease in the SEQ-typical FD and SEQ-major FD was significantly greater in the responder group than in non-responder group ($P = 0.019$ and $P = 0.009$, respectively).

Conclusion

This study suggests that the Korean version of SEQ-DYSPEPSIA has good reliability and validity, and can be a useful PRO measurement tool in patients with FD.

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Key Words

Dyspepsia; Patient outcome assessment; Surveys and questionnaires; Validation study

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Introduction

Functional dyspepsia (FD) is a symptom complex affecting the upper gastrointestinal (GI) tract, including chronic and recurrent epigastric pain or soreness, postprandial fullness, early satiety, bloating, and nausea, which does not show organic lesions such as peptic ulcers, benign or malignant neoplasms, or pancreato-biliary lesions.[1] The Rome IV criteria define FD as the presence of one or more symptoms among postprandial fullness, early satiety, and upper abdominal pain or soreness, which start at least 6 months before diagnosis and last for > 3 months without any organic disease.[1] FD is classified into 2 subtypes according to the main symptoms: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS).[1,2] The prevalence of FD has been reported to be approximately 15.0-40.0% worldwide.[3,4] In an epidemiological survey of comprehensive medical examinations in Korea, the prevalence of FD according to the Rome III criteria was found to be 8.1% (EPS, 4.6% and PDS, 6.5%).[5] In addition, among patients who visited a tertiary medical center for GI symptoms, FD had the highest prevalence at approximately 37.0%.[6]

FD is not a life-threatening disorder; however, it leads to a poor quality of life (QOL) and places a heavy medical burden on patients.[7,8] The pathophysiology of FD has not yet been fully characterized, although it is known to be caused by a complex of disease processes including delayed gastric emptying, visceral hypersensitivity, impaired gastric accommodation, dysfunction of the duodenum and jejunum, and dysfunction of the brain-gut interaction.[3] Therefore, it is difficult to develop effective drugs for FD that exceed high placebo effects while acting on such diverse mechanisms. The representative drugs for FD are anti-secretory agents including proton pump inhibitors (PPIs) and histamine 2 blockers, as well as prokinetic drugs. In some patients, tricyclic antidepressants or selective serotonin reuptake inhibitors are used to modulate the enteric nervous system and manage psychological comorbidities.[3,9,10]

The Food and Drug Administration provides guidelines for reviewing and evaluating existing or newly developed patient-reported outcomes (PROs) used to support claims in the labeling of medical products.[11] With the establishment of the Rome criteria, clinical trials on the treatment of functional GI diseases are continuously being performed, and recommendations based on clinical trial results are periodically published.[12] To conduct clinical trials, it is essential to develop verified evaluation tools that focus on specific symptoms of FD. In addition, in many countries, a questionnaire for patients with FD written in the local language is developed and verified, and the drug response of FD is measured using a verified symptom assessment questionnaire.[13]

We aim to develop and validate a self-evaluation questionnaire for dyspepsia (SEQ-DYSPEPSIA) that is easily applicable to Korean patients, and can be used in regulated clinical trials for assessing treatment efficacy claims intended for product labeling in FD treatment.

Materials and Methods

From October 2017 to September 2019, this study was conducted to develop and verify a questionnaire for patients with FD between the ages of 19 and 75 years who first visited the hospital or re-visited the hospital within 6 months. The study protocol was approved by the ethical review committee of each hospital (KUGH 2017-11-037, EUMC 2017-09-037-007, CR-17-146, DKUH 2017-11-007-001, GNAH 2018-01-015-005, DSMC 2017-11-068, and B-1801/442-303). Written informed consent was obtained from all participants.

Patient Selection

Participants for the validation study were enrolled from outpatient clinics in 7 tertiary medical centers in Korea. FD was defined as the Rome IV criteria. Symptoms with a score of at least 2 points (on a scale of 1 to 5 points) in discomfort in daily life are defined as "bothersome" in the Rome criteria.[1] All patients underwent upper GI endoscopy within 6 months before enrollment, which confirmed the absence of an organic cause for upper GI symptoms (UGISs). Patients aged 19-75 years who had the minimum understanding needed to complete the questionnaire were selected as study participants. The following patients were excluded from the study: (1) patients who had undergone GI surgery except appendectomy; (2) patients who were pregnant or lactating; (3) patients with a serious systemic or mental illness; (4) patients requiring continuous treatment for the liver, biliary tract, small intestine, and colon; (5) patients with uncontrolled diabetes mellitus or thyroid disease; and (6) patients who had taken acid secretion inhibitors, including PPIs or GI motility drugs, in the last 2 weeks. The global severity of FD assessed using a five-point Likert scale was evaluated at the first enrollment.

Development of a Self-evaluation Questionnaire for Upper Gastrointestinal Symptoms

First, through a systematic review, published questionnaires and scripted items related to FD were identified and reviewed by

experts (M.G.C. and H.K.J.).[12] By using candidate items including typical and atypical FD symptoms, the SEQ-DYSPEPSIA questionnaire was first developed in English and subsequently translated into Korean. On the basis of a structured translation process, the reverse translation of the translated draft showed that the target version was functionally identical to the original English version. The draft questionnaire was produced at the 6th grade reading level and used words as specifically pronounced by the patients.

The final and validated SEQ-DYSPEPSIA is composed of 11 questions mainly addressing the severity and frequency of FD and UGISs over a 2-week recall period, and is divided into the typical FD, major FD, and other UGISs. The self-evaluation questionnaire (SEQ)-typical FD includes 4 typical FD symptoms (epigastric pain, epigastric soreness, postprandial fullness, and early satiety) corresponding to the Rome IV criteria. The SEQ-major FD includes typical FD symptoms and other frequent dyspeptic symptoms (bloating, belching, and nausea). Other UGISs such as gastroesophageal reflux disease (GERD) symptoms and vomiting were included for the purpose of confirming the overlap or differential diagnosis with other upper GI disorders mimicking FD. This questionnaire required responses based on 5 levels of the Likert scale for frequency (no symptoms to daily symptoms) and severity (not at all or very weak to extremely severe). The scores of SEQ-DYSPEPSIA were calculated into a sum score for each symptom frequency and severity, with higher scores indicating greater severity of symptoms. All 11 items were given equal weight.

Because pictorial expression in the communication of symptoms is known to improve patient understanding and memory, cartoon-style images of the patients' symptoms were added to the SEQ-DYSPEPSIA questionnaire (Supplementary Figure).[14]

Reliability and Validity of the Self-evaluation Questionnaire for Upper Gastrointestinal Symptoms

Test-retest reliability was assessed to determine the stability of SEQ-DYSPEPSIA. The participants were instructed to complete the questionnaire 2 times with a 2-week interval before starting treatment with medication. Quantitative psychometric analyses of SEQ-DYSPEPSIA were conducted together with the Patient Assessment of GI Symptom Severity Index (PAGI-SYM),[15] Nepean Dyspepsia Index-Korean version (NDI-K), and validated NDI-K QOL questionnaires.[16,17]

Evaluation of Therapeutic Response With Self-evaluation Questionnaire for Dyspepsia

The degree of symptom improvement was measured using SEQ-DYSPEPSIA before and after treatment with 4 weeks of a PPI (lansoprazole 30 mg, once a day) and a prokinetic agent (mosapride 5 mg, three times a day). In addition, patients with FD were asked to fill out other questionnaires including PAGI-SYM, NDI-K, and NDI-K QOL, before and after medical treatment. The Overall Treatment Evaluation (OTE) scale was a 5-point Likert scale defined as follows: 1 point, disappearance of symptoms; 2 points, greatly improved symptoms more than 50%; 3 points, ≤ 50% disappearance of symptoms; 4 points, no change in symptoms; and 5 points, worsening of symptoms. Patients who showed more than "greatly improved symptoms" (1 or 2 points) after medical treatment were defined as the response group. According to the therapeutic response, the change of the composite score of the SEQ-typical and SEQ-major FD was measured, and the score changes in the PAGI-SYM, NDI-K, and NDI-K QOL questionnaires were also compared.

Statistical Methods

The number of test-retest samples was calculated as 50 by referring to the study in which Park et al[18] conducted cultural validation on GI symptoms questionnaire for functional GI disease. To measure the number of samples to evaluate the treatment response, we referred to the PAGI-SYM survey study through 7-Likert OTE. In the PAGI-SYM study, mean symptom scores between responders and non-responders of satiety and early satiety were found to be −0.10 and −0.91, respectively.[19] Therefore, we estimated a sample size of at least 54 in order to achieve a statistical power of 80.0% at a 5.0% significance level on a 2-sided test. Considering a 20.0% dropout rate or loss to follow-up during the study period, it was estimated that a target enrollment of 68 subjects was needed.[20]

Internal consistency was assessed using Cronbach's alpha, with a value of ≥ 0.7 considered to indicate a high degree of internal consistency. Test-retest reliability was evaluated using intraclass correlation coefficients (ICCs) and Pearson correlation coefficients. An ICC of ≥ 0.7 was considered sufficient to demonstrate reliability.[21] Construct validity was assessed by comparing Pearson's correlation coefficients between the SEQ-typical FD/SEQ-major FD scores and the dyspepsia subscale scores of PAGI-SYM, NDI-K, and NDI-K QOL. Among the valid constructs, discriminant validity was evaluated by comparing the Pearson's correlation coefficients between SEQ-DYSPEPSIA and the PAGI-SYM subscales other than FD symptoms. In contrast, known-group validity was evaluated using an analysis of variance test to compare groups of patients in terms of the scores of SEQ-DYSPEPSIA and FD global severity. The independent *t* test or Mann-Whitney *U* test was used to

compare the differences in changes in the mean SEQ-typical and major FD scores from baseline to 4 weeks according to the OTE scale. The responsiveness index was calculated using effect size (ES) and standardized response mean (SRM) values.[22] ES was calculated by dividing the mean change score by the standard deviation (SD) of the before-treatment scores, and SRM was calculated as the mean change score divided by the SD of the changed scores. The calculated ES or SRM value was categorized as small (0.2), medium (0.5), or large (0.8) (Cohen's thresholds). All statistical analyses were performed using SPSS version 26.0 (IBM Corp, Armonk, NY, USA), and *P*-values < 0.05 were considered statistically significant.

Results

Study Patients and Clinical Characteristics

Among 220 patients with FD, 193 completed the questionnaires and were finally included in the present study. The mean age of the participants was 48.5 years (SD 13.6 years, range 19-75 years), and 69.4% of the patients were women. The proportion of patients with an FD symptom duration of < 1 year was 51.8% (Table 1). For the assessment of test-retest stability, 102 patients completed the SEQ-DYSPEPSIA questionnaire again 2 weeks after their first evaluation. A total of 121 patients underwent treatment with lansoprazole (30 mg, once a day) and mosapride (5 mg, three times a day) for 4 weeks. Finally, 94 patients completed the SEQ-DYSPEPSIA questionnaire for the third time.

The mean SEQ-DYSPEPSIA score for 193 subjects on first questionnaires was 41.51 ± 14.06 (median score 40, range 22-99, maximal score 110). According to the global severity of the patients, 57 (29.5%) reported no or mild symptoms, 79 (40.9%) reported moderate symptoms, and 57 (29.5%) reported severe or very severe symptoms.

Reliability

Internal consistency was calculated using Cronbach's alpha, which ranged from 0.770 (for SEQ-typical FD) to 0.905 (for SEQ-DYSPEPSIA) (Supplementary Table 1). The Cronbach's alpha coefficient of the 4 typical FD symptoms (epigastric pain, soreness, postprandial fullness, and early satiety) was 0.770, and that of the 7 major FD symptoms (epigastric pain, soreness, postprandial fullness, early satiety, bloating, belching, and nausea) was 0.865. SEQ-DYSPEPSIA showed a high test-retest reliability, as confirmed by the ICCs of the different SEQ-DYSPEPSIA subgroups. The ICC of the GERD symptom subgroup (heartburn, retrosternal chest pain, acid regurgitation, and nonacid regurgitation) was 0.841, and that of the bloating and belching subgroup was 0.733 (Table 2).

Validity

The construct validity of SEQ-DYSPEPSIA was evaluated according to its correlation with the PAGI-SYM postprandial fullness/early satiety subscale, NDI-K total and dyspepsia subscale, and NDI-K QOL scores (Table 3). The SEQ-typical FD symptoms highly correlated with the PAGI-SYM postprandial fullness/early satiety subscale ($r = 0.648$, $P < 0.001$), and the SEQ-major FD symptoms showed an even higher correlation with the PAGI-SYM postprandial fullness/early satiety subscale ($r = 0.741$, $P < 0.001$). The SEQ-typical and major FD symptoms also significantly correlated with the NDI-K total scores (SEQ-typical FD, $r = 0.784$, $P < 0.001$; SEQ-major FD, $r = 0.851$, $P < 0.001$) or NDI-K

Table 1. Study Participants and Clinical Characteristics

Variables	N = 193
Female sex	134 (69.4)
Age (yr)	48.5 ± 13.6 (19-75)
BMI (kg/m^2)	23.29 ± 3.59 (16.04-36.85)
Smoking/drinking habits	
Current smoker	22 (11.4)
Alcohol user[a]	32 (16.6)
Coffee user[b]	19 (9.8)
Comorbidities	
Diabetes mellitus	13 (6.7)
Hypertension	26 (13.5)
Chronic lung/heart disease	9 (4.7)
Osteoporosis	12 (6.2)
Other chronic disease[c]	17 (8.8)
Symptom onset	
< 6 mo	73 (37.8)
7 mo-1 yr	27 (14.0)
1-2 yr	21 (10.9)
2-5 yr	28 (14.5)
> 5 yr	44 (22.8)
Global severity grade	
No or mild	57 (29.5)
Moderate	79 (40.9)
Severe or very severe	57 (29.5)

[a]Alcohol user: intake of ≥ 24 g alcohol at least 2 times per week or more.
[b]Coffee user: intake of ≥ 3 cups of coffee per day.
[c]Chronic disease: thyroid disease, hepatitis, Behcet's disease, or hyperlipidemia.
BMI, body mass index.
Data are presented as n (%) or mean ± SD (range).

Table 2. Test-Retest Reliability of Self-evaluation Questionnaire for Dyspepsia

Subscale	No.	ICC	*P*-value	Pearson's *r*	*P*-value
Epigastric pain or soreness	1	0.777	< 0.001	0.659	< 0.001
Postprandial distress (early satiation and postprandial fullness)	2-3	0.736	< 0.001	0.606	< 0.001
SEQ-typical FD (Q1-3)	1-3	0.794	< 0.001	0.679	< 0.001
SEQ-major FD (Q1-6)	1-6	0.831	< 0.001	0.736	< 0.001
Bloating/belching	4-5	0.733	< 0.001	0.599	< 0.001
Nausea/vomiting	6, 11	0.817	< 0.001	0.726	< 0.001
GERD 4 symptoms	7-10	0.841	< 0.001	0.729	< 0.001
SEQ-DYSPEPSIA	1-11	0.859	< 0.001	0.766	< 0.001

ICC, intraclass correlation coefficient; SEQ, self-evaluation questionnaire; FD, functional dyspepsia; GERD, gastroesophageal reflux disease; SEQ-DYSPEPSIA, SEQ for dyspepsia.
Each symptom score is calculated as the sum of the frequency and severity of each subscale.

Table 3. Construct and Discriminant Validity of Self-evaluation Questionnaire for Dyspepsia Evaluated by Comparing With Patient Assessment of Gastrointestinal Symptom Severity Index, Nepean Dyspepsia Index-Korean Dyspepsia, Nepean Dyspepsia Index-Korean Total, and Nepean Dyspepsia Index-Korean Quality of Life

Variables	SEQ-typical FD (Q1-3)		SEQ-major FD (Q1-6)		SEQ-DYSPEPSIA	
	Pearson's *r*	*P*-value	Pearson's *r*	*P*-value	Pearson's *r*	*P*-value
PAGI-SYM nausea/vomiting	0.289	< 0.001	0.440	< 0.001	0.518	< 0.001
PAGI-SYM postprandial fullness/early satiety	0.648	< 0.001	0.741	< 0.001	0.678	< 0.001
PAGI-SYM bloating	0.489	< 0.001	0.588	< 0.001	0.579	< 0.001
PAGI-SYM upper abdominal pain	0.649	< 0.001	0.598	< 0.001	0.588	< 0.001
PAGI-SYM lower abdominal pain	0.288	< 0.001	0.329	< 0.001	0.338	< 0.001
PAGI-SYM heartburn/regurgitation	0.487	< 0.001	0.568	< 0.001	0.711	< 0.001
NDI-K dyspepsia	0.814	< 0.001	0.839	< 0.001	0.781	< 0.001
NDI-K total	0.784	< 0.001	0.851	< 0.001	0.862	< 0.001
NDI-K QOL						
Tension/sleep	−0.316	< 0.001	−0.351	< 0.001	−0.397	< 0.001
Interference with daily activities	−0.275	< 0.001	−0.295	< 0.001	−0.353	< 0.001
Eating/drinking	−0.336	< 0.001	−0.304	< 0.001	−0.333	< 0.001
Knowledge/control	−0.327	< 0.001	−0.348	< 0.001	−0.350	< 0.001
Work/study	−0.344	< 0.001	−0.385	< 0.001	−0.452	< 0.001

SEQ, self-evaluation questionnaire; FD, functional dyspepsia; SEQ-DYSPEPSIA, SEQ for dyspepsia; PAGI-SYM, Patient Assessment of Gastrointestinal Symptom Severity Index; NDI-K, Nepean Dyspepsia Index-Korean; QOL, quality of life.
Each symptom score is calculated as the sum of the frequency and severity of each subscale.
Data are presented as correlation coefficients and *P*-values.

dyspepsia subscale scores (SEQ-typical FD, $r = 0.814$, $P < 0.001$; SEQ-major FD, $r = 0.839$, $P < 0.001$) (Table 3). Moreover, the SEQ-typical FD/SEQ-major FD symptoms also correlated with NDI-K QOL. As symptom severity increased, the patient-reported NDI-K QOL significantly decreased. The strongest correlations were observed for the SEQ-major FD symptoms and the work/study quality domain of NDI-K QOL ($r = -0.385$, $P < 0.001$).

To confirm discriminant validity for differentiation from other GI symptoms, the results of the SEQ-DYSPEPSIA questionnaire and the association with each subscale of PAGI-SYM other than postprandial fullness/early satiety were analyzed. It showed a high correlation with the postprandial fullness/early satiety subscale (correlation coefficient ≥ 0.6), but a low correlation with nausea/vomiting, and lower abdominal pain (Table 3). In particular, SEQ-typical FD showed poor correlation with nausea/vomiting, lower abdominal pain, and heartburn/regurgitation subscales of PAGI-SYM. In addition, to confirm the degree of discrimination in the questionnaire, the relationship between the SEQ-typical/major FD symptoms and symptoms other than typical FD was also confirmed. Among the various detailed symptoms, acid regurgitation

and nonacid regurgitation modestly correlated with SEQ-typical FD ($r = 0.380$, $P < 0.001$; $r = 0.271$, $P < 0.001$), and vomiting showed the lowest correlation with both the SEQ-typical FD ($r = 0.220$, $P = 0.002$) and SEQ-major FD ($r = 0.310$, $P < 0.001$) composite scores (Supplementary Table 2).

In addition, known-group validity according to the severity of symptoms was also confirmed by examining whether differences in SEQ-typical/SEQ-major FD scores were significantly different according to self-reported global severity. The mean scores of SEQ-typical FD significantly increased according to the global severity of FD (9.42 ± 3.93, no or mild group [n = 57]; 13.20 ± 4.91, moderate group [n = 79]; 14.75 ± 5.65, severe group [n = 57]) ($P < 0.001$). Similarly, the mean scores of the PAGI-SYM postprandial fullness/early satiety subscale (0.93 ± 1.13, no or mild group [n = 57]; 1.65 ± 1.20, moderate group [n = 79]; 2.17 ± 1.25, severe group [n = 57]) ($P < 0.001$), NDI-K dyspepsia subscale (15.53 ± 16.47, no or mild group [n = 57]; 30.81 ± 19.81, moderate group [n = 79]; 39.82 ± 22.26, severe group [n = 57]) ($P < 0.001$), and NDI-K total (26.35 ± 24.88, no or mild group [n = 57]; 44.44 ± 27.47, moderate group [n = 79]; 61.00 ± 36.29, severe group [n = 57]) ($P < 0.001$) were significantly different according to the self-reported global severity (Figure).

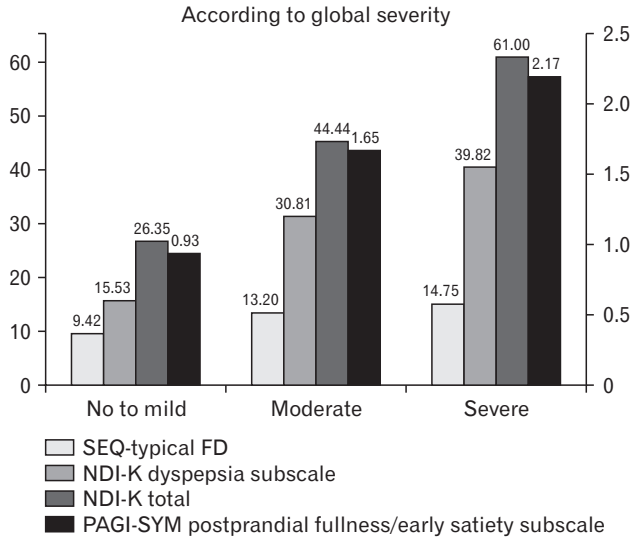

Figure. Results of known-group validity according to the severity of symptoms. The mean scores of the self-evaluation questionnaire (SEQ)-typical functional dyspepsia (FD), Nepean Dyspepsia Index-Korean (NDI-K) dyspepsia subscale, NDI-K total, and Patient Assessment of Gastrointestinal Symptom Severity Index (PAGI-SYM) postprandial fullness/early satiety subscale were significantly different according to the self-reported global severity.

Therapeutic Response Analysis With Self-evaluation Questionnaire for Dyspepsia

Treatment response was evaluated in 94 patients. When the patients were classified according to the definition of therapeutic response, 45 patients were determined to show a favorable treatment response. The posttreatment mean score and the different scores of both SEQ-typical FD and SEQ-major FD significantly decreased in the responder group compared with the non-responder group, and decrease in the SEQ-typical FD and SEQ-major FD was significantly greater in the responder group than in non-responder group ($P = 0.019$ and $P = 0.009$, respectively, Mann-Whitney U test) (Table 4).

Subsequently, the responsiveness index was measured using the ES and SRM values for mean changes in the PAGI-SYM postprandial fullness/early satiety subscale, NDI-K dyspepsia subscale, and NDI-K total scores. After 4 weeks of treatment, it was confirmed that the SEQ-typical/SEQ-major FD domains showed a noninferior responsiveness index compared with other, already validated questionnaires (PAGI or NDI-K) (Supplementary Table 3).

Discussion

SEQ-DYSPEPSIA consists of FD symptoms identified in the Rome criteria as well as additional symptoms identified from the literature.[1,12] It is a highly reliable and valid PRO instrument with a good medication responsiveness index in patients with FD. It is important to develop an accurate diagnostic tool for determining treatment responsiveness that exceeds the high placebo effect in patients with FD.[23]

Currently, a variety of questionnaires are available for measuring outcomes in patients with functional GI disorders, including FD; however, many questionnaires do not meet the Rome criteria or are too complex, resulting in limitations and heterogeneity in evaluating the patients' symptoms and treatment responses.[11] In 2004, the National Institute of Health actively developed patient-generated reports, starting with a system called the PRO Measurement Information System.[24] These patient-generated reports, also known as PROs, are known to be useful for efficiently expressing functional GI disorders and symptoms and for evaluating treatment responses in the viewpoint of patients, rather than evaluating the disease from the viewpoint of physicians.[25] On the basis of important PROs, this study is a patient self-evaluation questionnaire survey that summarizes other symptoms necessary for differential diagnoses, including

Table 4. Changes in the Mean Scores of Self-evaluation Questionnaire for Dyspepsia, Patient Assessment of Gastrointestinal Symptom Severity Index Postprandial Fullness/Early Satiety, and Nepean Dyspepsia Index-Korean According to Overall Treatment Effect

Variables	Responders (n = 45)	Non-responders (n = 49)	*P*-value
SEQ-typical FD (Q1-3)			
Baseline	13.36 ± 4.23	13.98 ± 5.56	0.889
At 4 weeks	8.69 ± 2.97	11.63 ± 5.02	0.001
Difference	−4.67 ± 4.84	−2.35 ± 4.59	0.019
SEQ-major FD (Q1-6)			
Baseline	26.49 ± 7.88	27.31 ± 8.44	0.629
At 4 weeks	17.00 ± 5.09	22.78 ± 8.61	< 0.001
Difference	−9.49 ± 8.28	−4.53 ± 7.50	0.009
SEQ-DYSPEPSIA			
Baseline	43.27 ± 11.15	44.37 ± 13.21	0.840
At 4 weeks	29.33 ± 7.15	37.29 ± 12.61	< 0.001
Difference	−13.93 ± 11.44	−7.08 ± 10.94	0.001
PAGI-SYM postprandial fullness/early satiety			
Baseline	1.64 ± 1.32	2.04 ± 1.33	0.177
At 4 weeks	0.76 ± 0.89	1.41 ± 1.37	0.016
Difference	−0.89 ± 1.33	−0.62 ± 1.35	0.320
NDI-K dyspepsia			
Baseline	30.42 ± 19.79	34.22 ± 20.80	0.322
At 4 weeks	12.07 ± 13.61	23.73 ± 21.03	0.002
Difference	−18.36 ± 19.08	−10.49 ± 15.66	0.031
NDI-K total			
Baseline	45.24 ± 27.04	50.55 ± 31.41	0.356
At 4 weeks	17.62 ± 20.38	36.04 ± 34.05	0.001
Difference	−27.62 ± 27.23	−14.51 ± 21.89	0.017

SEQ, self-evaluation questionnaire; FD, functional dyspepsia; SEQ-DYSPEPSIA, SEQ for dyspepsia; PAGI-SYM, Patient Assessment of Gastrointestinal Symptom Severity Index; NDI-K, Nepean Dyspepsia Index-Korean.
P-values were calculated using the independent *t* test or Mann-Whitney *U* test.

typical FD symptoms highlighted in Rome IV. For patient-reported questionnaires on FD, several indices (Dyspepsia Symptom Severity Index, GI symptom score, and NDI) have been validated in previous studies.[26-28] However, although a Korean version of a questionnaire that records the patients' symptoms in an intuitive manner, other than being a QOL assessment questionnaire, has been developed in patients with GERD, very limited instruments are available for patients with FD.[29-31] In the case of FD, 4 distinct symptoms are mentioned in the Rome IV criteria;[1] however, other additional symptoms (belching, nausea, and bloating) may be present in patients with FD. In a factor and cluster analysis study conducted by Piessevaux et al[32] in the general population, symptoms of bloating, belching, nausea, and vomiting, in addition to the main symptoms of epigastric discomfort, pain, fullness, and early satiety in patients with FD, were also analyzed. In a total of 378 participants, mild to severe symptoms were accompanied by bloating in 68.0%, belching in 50.0%, nausea in 38.9%, and vomiting in 23.3% of patients. In addition to the 4 typical symptoms mentioned in the Rome IV criteria, additional symptoms such as bloating, nausea, belching, and vomiting were confirmed in patients with FD. In a study analyzing the heterogeneity of symptom patterns, Fischler et al[33] observed similar results among the types of symptoms, except for heterogeneity that did not show vomiting symptoms in 71.2% (311/438) of patients. On the basis of the results of previous studies,[1,32-34] the present study identified bloating, belching, and nausea as the main symptoms of FD along with the 4 typical symptoms (epigastric pain, epigastric soreness, postprandial fullness, and early satiety). In the full questionnaire, vomiting was also included to discriminate against other diseases and to confirm validity, as well as to discriminate GERD. GERD is difficult to clearly distinguish from FD, especially because it frequently overlaps with FD (approximately 9.0-30.0%),[35] and the present study showed that the correlation between FD and reflux symptom was low to moderate (Pearson's correlation coefficient 0.271-0.507). Therefore, each item in SEQ-

DYSPEPSIA can be used for research purposes.

The reliability and reproducibility of the questionnaire was confirmed by dividing it into typical FD symptoms, major FD symptoms, and other atypical symptoms among the symptoms of FD, with a total of 11 questions. In particular, Cronbach's alpha was high at 0.865 when evaluating the major FD symptoms compared with the typical FD symptoms. The correlation coefficients with other, already validated subscales (PAGI-SYM postprandial fullness/early satiety, NDI-K dyspepsia, and NDI-K total) were very high (0.648-0.851), and the correlation coefficient was higher in SEQ-major FD than in SEQ-typical FD.

In studies assessing the treatment response of FD, various drugs such as rabeprazole, lansoprazole, mosapride, acotiamide, itopride, and rikkunshito were used, and various questionnaires such as the Leuven Postprandial Distress Scale,[36] Leeds Dyspepsia Questionnaire,[37] 8-symptom dyspepsia questionnaire,[38] Hong Kong index questionnaire,[39] NDI,[40] and PAGI-SYM[41] were also used. Among these, in the validation study of the Leuven Postprandial Distress Scale conducted by Carbone et al,[36] a comparative analysis using the PAGI-SYM and NDI questionnaires was conducted to evaluate the treatment response to itopride, which showed a significant change in the PDS type of FD. Similarly, in this study, to evaluate the treatment response using SEQ-DYSPEPSIA, the NDI and PAGI-SYM questionnaires were also evaluated. After 4 weeks of treatment, the SEQ-DYSPEPSIA questionnaire survey was conducted again to evaluate the treatment response, and it was confirmed that the FD symptoms significantly improved in the treatment response group. Similar findings were found for the NDI-K dyspepsia subscale, but not for the PAGI-SYM postprandial fullness/early satiety subscale.

The PAGI-SYM postprandial fullness/early satiety subscale is primarily limited to symptoms of postprandial fullness and early satiety, and epigastric pain or discomfort is divided into different measures of the upper abdominal pain subscale. These epigastric pain or discomfort items showed a significant difference from the NDI-K and SEQ-DYSPEPSIA questionnaires used in this study, and it was judged that the PAGI-SYM postprandial fullness/early satiety subscale did not show statistically meaningful results in the treatment response evaluation.

The NDI-K dyspepsia subscale is similar to the SEQ-major FD subscale; however, in NDI, items that are difficult to distinguish, such as epigastric pain, discomfort, or soreness, are divided, and similar items exist including a sense of epigastric pressure and bloating. In addition, the NDI questionnaire confirmed the level of discomfort along with frequency and intensity. However, with respect to the level of discomfort expressed by the actual patients, many overall global evaluations are available and some components are difficult to objectively express. In consideration of these points, in the questionnaire in this study, except for the level of discomfort, epigastric pain, discomfort, and soreness symptoms were combined into 1 question, and each symptom was simply investigated on the basis of frequency and intensity. Owing to these differences, SEQ-DYSPEPSIA in this study showed more statistically meaningful differences in the treatment response evaluation than the PAGI-SYM and NDI questionnaires, and was confirmed to be useful in evaluating the treatment response.

To confirm the degree of treatment response, the ES and SRM values were checked, and when patients with a much improved condition ($> 50.0\%$) was used as the response group, the response index was confirmed to be > 0.8 for both ES and SRM, and the ratio was "large."[22] In the case of the non-response group, the responsiveness index was 0.4-0.5 (ES), which was categorized as "small to medium." When the PAGI-SYM postprandial fullness/early satiety, NDI-K dyspepsia, and NDI-K total scores were also considered, a better responsiveness index (0.67-1.02) was obtained in the responder than in the non-responder group, and all items of the typical FD and major FD symptoms in SEQ-DYSPEPSIA well reflected the subjective symptoms and treatment response of patients with FD.

This study had some limitations. First, it is possible that the response to symptom evaluation was low because many patients with severe FD were not included. In addition, because this study did not use placebo as a double-blind comparator for the evaluation of treatment response, the response index could be compared only between the treatment response group and the non-response group. As the placebo effect is high in pharmaceutical research in patients with dyspepsia, further studies on symptom changes that include a placebo group can be helpful.

In conclusion, this study suggests that SEQ-DYSPEPSIA, including typical FD and seven major FD symptoms, has a high degree of reliability and validity, compared with the PAGI-SYM postprandial fullness/early satiety subscale, NDI-K dyspepsia subscale, and NDI-K total score. Moreover, this verified questionnaire was also found to be useful and accurate for treatment response evaluation.

Supplementary Materials

Note: To access the supplementary tables and figure mentioned in this article, visit the online version of *Journal of Neurogastroen-*

terology and Motility at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm20250.

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