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ORIGINAL ARTICLE

# Functional Dyspepsia: Clinical Symptoms, Psychological Findings, and GCSI Scores

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## Abstract

**Background** The GCSI questionnaire measures symptoms of gastroparesis (GP). Symptoms of FD overlap with GP. The ability of the GCSI to discriminate FD from GP is unknown.

**Aims** By prospectively evaluating functional dyspepsia (FD) patients, we aimed to evaluate the ability of the Gastroparesis Cardinal Symptom Index (GCSI) to: (1) distinguish FD from GP; (2) predict symptom severity, anxiety, and depression; (3) correlate symptoms with gastric emptying.

**Methods** FD patients (Rome III criteria) were identified, and upper endoscopy and gastric emptying scan (GES) data recorded. A total of 254 patients were mailed a questionnaire evaluating demographics, FD symptoms, mental well-being; the GCSI was included.

**Results** One hundred and twenty-three patients responded; of them, 75% were women and mean age was 49 (15 SD) years. 44.7% were categorized as postprandial distress subtype (PDS), 34.1% were epigastric pain subtype (EPS), and 21.1% were mixed type. The mean GCSI score was 2.02 (1.1 SD), slightly lower than historical GP controls (2.26–2.56). Mixed EPS–PDS subtype had the lowest GCSI scores (1.79; 0.91 SD). Bloating was the highest GCSI subscore (2.70; 1.53 SD), followed by fullness (2.31; 1.39 SD) and nausea (1.08; 1.19 SD). The GCSI total score did not correlate with anxiety and depression scores or with 4-h gastric emptying.

**Conclusions** In this population of FD patients, GCSI scores were slightly lower than historical gastroparesis control patients, although within the reported range. These results suggest that the GCSI cannot accurately distinguish FD patients from GP patients. A more specific questionnaire is needed to aid in the diagnosis and management of these distinct gastrointestinal disorders.

**Keywords** Dyspepsia · Functional dyspepsia · Gastroparesis · GCSI · Nausea

## Introduction

Gastroparesis (GP) and functional dyspepsia (FD) are the two most prevalent neuromuscular disorders of the upper gastrointestinal tract [1–3]. These disorders are both characterized by chronic recurrent symptoms referable to the gastroduodenal region [4–6]. Functional dyspepsia and GP are both associated with significant decrements in health-related quality of life and a significant negative impact to the healthcare system [7–11].

Gastroparesis (GP) is diagnosed when symptoms of delayed gastric emptying exist in the absence of mechanical obstruction [5]. Typical symptoms of gastroparesis include epigastric pain, early satiety, nausea, vomiting, bloating, and weight loss [5, 12]. Abdominal pain is reported by 90% of gastroparesis patients [13]. A 4-h, solid-phase gastric emptying scan is required to diagnose GP, as symptoms of rapid gastric emptying and functional dyspepsia are similar to, and are often confused with, those of GP [5, 6, 9, 12, 14]. Gastroparesis is categorized into several different subtypes, including diabetic, postsurgical, and idiopathic; the latter group is the most prevalent [15–17].

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Functional dyspepsia is diagnosed using a combination of symptoms, the Rome criteria, and a normal upper endoscopy [18–20]. Upper endoscopy is important to distinguish organic dyspepsia from functional dyspepsia. Typical symptoms include epigastric pain, early satiety, bloating, nausea, and vomiting [18–20]. In addition to significant overlap in symptoms, FD and GP share fundamental pathophysiology [6]. Neither the magnitude nor the quality of symptoms accurately predicts the extent of delay in gastric emptying in either FD or GP patients [21–25].

To facilitate clinical research and therapeutic trials, patient-reported outcome questionnaires have been developed to operationalize symptom clusters. The Gastroparesis Cardinal Symptom Index (GCSI) is a discrete subset of questions from the Patient Assessment of Upper Gastrointestinal Symptom Severity Index (PAGI-SYM) questionnaire that is routinely used to evaluate symptom severity in patients with GP [26, 27]. Patient scores from the GCSI are calculated using a 6-point Likert scale and reported as average subscores for patient responses to 9 questions involving 3 major symptom complexes: bloating (2 questions), nausea (3 questions), and fullness (4 questions). In the initial validation study of the GCSI, total GCSI scores in GP patients were slightly higher than in those with dyspepsia [26, 27].

The GCSI has been used as a quantitative measure in multiple studies of GP [28–30], some of which remain well-read and well-cited. The GCSI also continues to be used in some clinical trials, although a new version, incorporating a daily diary, has been recently introduced into some protocols [31]. However, the utility of the GCSI has been questioned, because GCSI scores are not associated with gastric retention at 4 h, and the GCSI does not contain any questions about abdominal pain [5, 6, 13, 32]. Despite the marked overlap between FD and GP, and the frequent confusion by clinicians on how to distinguish these two disorders, no study has addressed the ability of the GCSI to distinguish GP patients from FD patients, using Rome III criteria. This is a critical distinction for the optimal development of pharmacologic and other interventional therapeutic options.

We hypothesize that, although the GCSI is common clinical tool, it is not a sufficiently specific instrument to accurately distinguish FD from GP. Our study developed a questionnaire incorporating the GCSI to evaluate symptoms in known FD patients (Rome III) and compared the results with historical GP controls. Our secondary outcomes included assessment of psychometric parameters in FD patients and the relationships between GCSI scores to gastric emptying.

## Methods

The study was approved by our institutions internal review board (IRB) with a waiver of informed consent. Our institution is a Level I academic referral center serving multiple states in the New England region with a busy Department of Gastroenterology and Hepatology. Adult patients previously diagnosed with FD (Rome III criteria; 19) by the institution's expert in functional gastrointestinal disorders were considered eligible to participate in this cross-sectional study. The electronic medical records of 281 patients were examined by the principal investigator for inclusion in this study. Information regarding the subtype of FD (epigastric pain (EPS), postprandial distress (PDS) or mixed EPS/PDS (Rome III criteria)), the result of the most recent 4-h, solid-phase, scintigraphic gastric emptying scan (GES) [14], and the date and result of upper endoscopy (EGD) closest in date to the GES was recorded by a trained research assistant and reviewed by the on-site senior author. The results of the solid-phase gastric emptying scan were classified as delayed if > 10% of the material remained at the end of 4 h, and the results were classified as rapid if < 10% of the material remained at 3 h. Patients were excluded from this study if: there was evidence of organic pathology at the time of EGD (e.g., peptic ulcer disease, gastritis, esophagitis); the EGD and GES results were more than 6 months apart; the patient carried a comorbid diagnosis of GP; the patient had undergone prior surgery to the esophagus or stomach; symptoms were thought secondary to complications of diabetes; and the patient was prescribed opioids or any other class of medication that could delay gastric emptying during the study period. Ultimately, 254 patients were mailed a packet including an explanatory letter, a small participation incentive (a two-dollar bill), and a questionnaire with a unique ID that contained 39 questions. The questionnaire assessed demographic information (8 questions), FD symptom severity and frequency (6 questions), recent tests (EGD and gastric emptying), mental well-being using the validated Hospital Anxiety and Depression Scale (HAD; 14 questions; 33), and the GCSI (9 questions; 26). A prepaid return envelope was included with the questionnaire. The returned questionnaires were manually tabulated and matched to the information that had been retrieved from the electronic medical record by a trained research assistant.

Data were entered manually and statistically assessed using the IBM SPSS Statistics Version 22.0, Chicago, IL. Frequency distributions were evaluated for all categorical variables (e.g., gender). Student's *t* test and analyses of variance (ANOVAs) were performed to evaluate differences in normally distributed continuous measures.

Significant omnibus *F*-tests were further explored using Tukey's HSD tests. Tests for proportionality between groups were made using Chi–square tests. The Pearson correlation coefficient was used to evaluate correlations between continuous measures. Summary statistics included point estimates and standard deviations. All significance levels are set to $P < 0.05$.

## Results

### Demographics

One hundred and twenty-three patients (48%) returned a completed questionnaire. Seventy-five percent were women; the mean (SD) age of all respondents was 49 (15) years. Most respondents were Caucasian (97%). The average (SD) duration of symptoms was 47 (59) months. Using self-reported symptoms (and Rome research questions), 45% of the patients met Rome III criteria for the PDS subtype, while 34% met criteria for the EPS subtype; the remainder were mixed EPS–PDS (21%; see Table 1). FD patients of the EPS subtype reported a mean of 4 days per week with FD symptoms, while patients of the PDS and mixed subtype reported a mean of 5 days per week with symptoms (see Table 1). This difference was not statistically significant. The most bothersome symptom reported was upper abdominal pain (33%) followed by bloating (17%) and upper abdominal discomfort (15%; see Table 1). Analysis of FD subtypes did not reveal a difference in reporting of the most bothersome FD symptom. The second most bothersome symptom (not given in Table 1) reported by FD patients was nausea (23%) followed by bloating (17%). This also did not vary among FD subtypes.

**Table 1** Demographics, FD subtypes, and symptoms ($n = 123$)

| | |
|---|---|
| Mean (SD) age years | 49 (15) |
| Women | 75% |
| Men | 25% |
| Ethnicity | |
| Caucasian | 97% |
| Latino, American Indian | 3% |
| Mean (SD) months with FD symptoms | 47 (59) |
| Mean (SD) days per week with FD symptoms | |
| EPS | 4 (3) |
| PDS | 5 (2) |
| Mixed (EPS/PDS) | 5 (2) |
| FD subtype | |
| PDS | 45% |
| EPS | 34% |
| Mixed EPS–PDS | 21% |
| Most bothersome symptom | |
| Upper abdominal pain | 33% |
| Bloating | 17% |
| Upper abdominal discomfort | 15% |
| Nausea | 14% |
| Heartburn | 5% |
| Early satiety | 5% |
| Regurgitation | 4% |
| Abdominal fullness | 4% |
| Retching or vomiting | 3% |
| Other | 1% |

### GCSI Total Score and Symptoms

The mean (SD) GCSI score for all respondents was 2.02 (1.11). GCSI scores were similar between the EPS subtype (2.09; 1.30 SD) and the PDS subtype (2.01; 0.97 SD); the mean GCSI score for the mixed EPS/PDS subtype was slightly lower (1.79; 0.91 SD), but not statistically significant ($P = 0.548$). Scores for the three symptom subscales (nausea, fullness, and bloating) are given in Table 2. Scores were similar between the 3 FD subgroups (EPS, PDS, and mixed). The bloating scale was the highest subscore for all 3 FD subgroups (range of 2.5–2.83), while the fullness subscore was the second highest for all 3 subgroups (range of 2.22–2.37).

Analysis of individual symptom subscores demonstrated a strong correlation between GCSI subscores of nausea and subscores for both fullness and bloating ($P = 0.01$). Conversely, individual symptom subscores for both fullness and bloating were independently correlated with subscores for nausea ($P = 0.01$) demonstrating the overlap of these symptoms in FD patients.

**Table 2** GCSI symptom scores and subscores

| | |
|---|---|
| Mean (SD) GCSI scores ($n = 123$) | 2.02 (1.11) |
| Nausea subscore | 1.08 (1.19) |
| Fullness subscore | 2.31 (1.39) |
| Bloating subscore | 2.70 (1.53) |
| EPS mean (SD) GCSI ($n = 42$) | 2.09 (1.30) |
| Nausea subscore | 1.12 (1.38) |
| Fullness subscore | 2.23 (1.56) |
| Bloating subscore | 2.83 (1.56) |
| PDS mean (SD) GCSI ($n = 55$) | 2.01 (0.97) |
| Nausea subscore | 1.04 (0.99) |
| Fullness subscore | 2.37 (1.25) |
| Bloating subscore | 2.65 (1.59) |
| Mixed EPS/PDS mean (SD) GCSI ($n = 26$) | 1.79 (0.91) |
| Nausea subscore | 0.95 (1.08) |
| Fullness subscore | 2.22 (1.40) |
| Bloating subscore | 2.50 (1.33) |

### GCSI Scores and Self-Reported Severity Scores

One hundred and nine (89%) of the respondents rated their FD symptoms as mild (32%), moderate (51%), or severe (17%). The GCSI subscore for bloating was the highest for all 3 categories of self-reported symptom severity (2.47–3.04) compared to subscores for fullness (2.28–2.56) and nausea (0.93–1.34) When mean GCSI scores were analyzed based on patient-reported symptom severity, GCSI scores were highest in those with self-reported mild symptoms (2.27; 1.03 SD), followed by severe symptoms (2.10; 1.44 SD) and moderate symptoms (1.89; 1.03 SD). Analysis of the higher GCSI score in those patients with self-reported mild symptoms found that the subscore of bloating (3.04; 1.28 SD) was a driving factor.

### GCSI and Gastric Emptying

A 4-h solid-phase gastric emptying was performed in 76 patients (60%) during the evaluation of their symptoms. Sixty-eight percent of these studies were normal, while 4% identified rapid gastric emptying and 26% were delayed (> 10% of scintigraphic material remaining at 4 h). Mean GCSI scores correlated with gastric emptying at 2 h ($P=0.026$) but not at 4 h ($P=0.137$). GCSI subscores for fullness ($P=0.031$) and bloating ($P=0.049$) were associated with gastric emptying time at 2 h, but not at 4 h. There was no relationship between the GCSI subscore of nausea and the percent of gastric retention at either 2 or 4 h.

### FD Symptom Severity and HAD Scores

A positive association was found between FD symptom severity and higher HAD total scores ($P=0.001$), anxiety subscale scores ($P=0.032$), and depression subscales scores ($P<0.001$). As given in Table 3, the HAD scores were significantly higher in FD patients with self-reported more severe symptoms.

### HAD Scores and Relationship to GCSI and Gastric Emptying

The mean (SD) HAD score for all FD respondents was 13.30 (7.49). HAD scores tended to be numerically lower for the mixed subgroup (10.54) compared to both the EPS (13.55) and PDS subgroups although this was not statistically significant (14.36; $P=0.113$). The mean (SD) anxiety subscore for all respondents was 8.14 (4.27), with the mixed group having a lower overall score (6.33) compared to both the EPS (8.24) and the PDS (8.87) subgroups ($P=0.051$), although this was not statistically significant. The mean (SD) depression subscore for all respondents was 5.13 (3.99); there were no significant differences with the scores (mixed EPS/PDS group score of 4.21 compared to the EPS (5.31) and PDS (5.42) groups ($P=0.444$)). There was no correlation between HAD scores and GCSI mean scores or subscores, nor was there correlation between HAD scores and gastric emptying times at either the 2- or 4-h mark (Table 4).

## Discussion

Gastroparesis affects approximately 8–10 million adult Americans [1, 2]. Many GP patients suffer from chronic, persistent symptoms (nausea, vomiting, early satiety, abdominal pain, and weight loss) which can be quite debilitating. The substantial effect of this chronic disorder is highlighted by its negative impact on quality of life and its significant burden to our healthcare system [11, 26, 34–36]. Nearly 15 years ago, the Gastroparesis Cardinal Symptom Index

**Table 3** Association of FD severity with anxiety and depression

| | FD severity | | | |
|---|---|---|---|---|
| | Mild | Moderate | Severe | *P* value |
| Anxiety—mean (SD) | 7.03 (3.53) | 8.76 (4.05) | 10.00 (5.64)[a] | 0.032 |
| Depression—mean (SD) | 3.76 (3.53) | 5.42 (3.48) | 8.26 (4.93)[ab] | < 0.001 |
| HADs total—mean (SD) | 10.78 (6.36) | 14.25 (6.57) | 18.26 (9.89)[ab] | 0.001 |

[a]Significantly different from mild

[b]Significantly different from moderate

**Table 4** Association of FD subtype with anxiety and depression

| | FD subtype | | | |
|---|---|---|---|---|
| | EPS | PDS | Mixed | *P* value |
| Anxiety—mean (SD) | 8.24 (4.37) | 8.87 (4.24) | 6.33 (3.75) | 0.051 |
| Depression—mean (SD) | 5.31 (4.54) | 5.42 (3.58) | 4.21 (3.83) | 0.444 |
| HADs total—mean (SD) | 13.55 (8.20) | 14.36 (7.10) | 10.54 (6.58) | 0.113 |

was developed in an attempt to better characterize symptom severity in GP patients [26]. In the interim, our understanding of the etiology, pathophysiology, and symptom expression in patients with gastroparesis and functional dyspepsia has advanced considerably. Once thought to represent two distinct disorders, there is significant overlap with regard to both symptoms and pathophysiology between FD and GP [4–6]. The substantial overlap calls into question whether the GCSI remains a sufficiently specific tool to accurately characterize GP patients and distinguish them from FD patients.

In this novel study of well-characterized FD patients (Rome III criteria), mean GCSI scores were quite similar to historical patients with GP originally characterized by Revicki and colleagues [26]. Coincidentally, the patients described in the original report of the GCSI (mean age 46 years; 77% women; the majority of patients (85%) were Caucasian) were quite similar demographically to the patients in the current study. In the initial validation study of the GCSI, total GCSI scores in patients with documented GP ($N = 169$; 2.56; 1.05 SD at baseline; 2.26, 1.1 SD at 8-week follow-up) were slightly higher than in those with dyspepsia recruited from the PAGI-SYM cohort ($N = 760$; 1.82; 0.87 SD; $P < 0.0001$; 26,27). The GCSI score at the 8-week follow-up point is remarkably similar to our mean GCSI score of 2.02 (1.1 SD) in 123 FD patients characterized using Rome III criteria. A comparison of GCSI subscores between the two studies also revealed many similarities. As an example, the GCSI subscore for bloating in our cohort of FD patients (2.70; 1.53 SD) was identical to the bloating subscore reported by the GP patients in the original study describing the GCSI (2.69; 1.51 SD; 26). Of note, bloating was a critical factor in patient reporting of overall symptoms as mild, moderate, or severe, more so than fullness or nausea.

Revicki and colleagues [26] noted a wide range in GCSI scores based on bed-disability days and restricted activity days. For gastroparesis patients with 14 or more bed-disability days, the mean GCSI score was 3.2, while for those with 14 or more restricted activity days the mean GCSI score was 3.1. In contrast, those with zero bed-disability days had a GCSI score of 2.0 and those with zero restricted activity days had a GCSI score of 1.9. Our study did not assess either bed-disability days or restricted activity days. However, an analysis of GCSI scores using a patient self-reported severity scale demonstrated GCSI scores (1.89–2.27) that fell within this range. The overlap of these scores, from patients with differing degrees of self-reported symptom severity, highlights the substantial overlap in FD and GP symptom reporting using the GCSI.

In the current study, the total mean HAD score fell within historical normal limits for the general population [33]. Mean anxiety subscores for our patient cohort (8.14) were above general population control values and fell within the range categorized as mild anxiety; mean depression subscores fell within normal limits. This confirms a prior study demonstrating that anxiety, measured by the HAD, is more common in FD patients and is associated with disordered sleep [37]. The modest elevation in HAD scores in our study did not correlate with GCSI scores, indicating that anxiety is not a driving factor in symptom expression in our cohort of FD patients. Unsurprisingly, HAD scores were not related to gastric emptying measured at either 2 or 4 h.

In our cohort of FD patients, 26% were identified as having delayed gastric emptying at 4 h. This finding is consistent with other large studies, demonstrating that 20–30% of patients with FD have a delay in gastric emptying [18, 38, 39]. The delay in gastric emptying, which was generally mild, was not associated with mean GCSI scores or subscores. This finding is not completely unexpected, since data from a large study of 560 FD patients (Rome III criteria) found little relationship between FD subgroups (EPS, PDS, and mixed), FD symptoms, and underlying pathophysiology [25]. This finding also highlights the overlap between FD and gastroparesis and illustrates why the GCSI lacks sufficient discriminant ability to accurately distinguish FD from gastroparesis. Although the majority of FD patients in our study underwent a gastric emptying scan, not all patients did. This is consistent with clinical practice and clinical guidelines, however, as a gastric emptying scan is not required to make the diagnosis of FD.

Our patients reported FD symptoms on average 4–5 days per week, fulfilling both Rome III and Rome IV criteria [4, 19]. The most bothersome symptoms were those of upper abdominal pain/discomfort (39% of respondents) and bloating (17% of respondents). Although abdominal pain is reported by up to 90% of patients with gastroparesis [5, 12, 13], that cardinal symptom is not included in the GCSI. In contrast, the Nepean Dyspepsia Index, commonly used in FD research studies, includes questions on abdominal pain and also includes questions on nausea and vomiting [40]. Given the significant overlap of symptoms and pathophysiology in FD and gastroparesis, the NDI may be a better overall instrument to assess symptoms. Bloating was the second most bothersome symptoms reported by FD patients (17%) and led to the highest GCSI subscore (2.70). Interestingly, in patients who reported their symptoms as mild, bloating was a driving factor resulting in elevated GCSI scores. The symptom of bloating is including in both the NDI and the GCSI.

All research studies have limitations; ours is no exception. One, respondents were primarily from the New England area and thus these results may not be generalizable to patients in other parts of the world. Two, our respondents were primarily Caucasian. That said, large prospective studies have not demonstrated that symptom expression in FD patients is dramatically different in patients of different ethnicities.

Thus, we believe that these results are generalizable. Three, the data presented in this study were collected from patients categorized as having FD using Rome III criteria, as the questionnaire was mailed prior to the release of the Rome IV criteria. However, given the frequency, intensity, and expression of symptoms, patients in the current study would also meet Rome IV criteria. Four, not every patient underwent a 4-h solid-phase gastric emptying scan. However, a GES is not required in the evaluation of all patients with dyspeptic symptoms and thus these findings mirror clinical practice in the community. Five, the GCSI data from our patients were compared with historical controls from a well-designed, well-validated study. This is a commonly accepted practice; however, a future trial would be improved by comparing a current cohort of gastroparesis patients from the same institution.

In summary, FD patients report symptoms, using the GCSI, similar in intensity and quality to patients with GP. This finding, in conjunction with the inability of the GCSI to accurately measure abdominal pain, a cardinal symptom of GP, highlights the incapacity of the GCSI to accurately distinguish FD patients from gastroparesis patients, using data from historical controls. Moving forward, a similar study investigating the ability of the GCSI-DD (daily diary; 31) to distinguish these two conditions would be important. A validated questionnaire that evaluates abdominal pain and which accurately distinguishes FD from GP patients will markedly improve future gastroparesis research trials.

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## Compliance with ethical standards

**Conflict of interest** None of the authors have any conflicts of interest to disclose with regard to the production of this manuscript.

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