Functional Dyspepsia and Gastroparesis in Tertiary Care are Interchangeable Syndromes With Common Clinical and Pathologic Features

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BACKGROUND: The aim of this study was to clarify the pathophysiology of functional dyspepsia (FD), a highly prevalent gastrointestinal syndrome, and its relationship with the better-understood syndrome of gastroparesis. **METHODS:** Adult patients with chronic upper gastrointestinal symptoms were followed up prospectively for 48 weeks in multi-center registry studies. Patients were classified as having gastroparesis if gastric emptying was delayed; if not, they were labeled as having FD if they met Rome III criteria. Study analysis was conducted using analysis of covariance and regression models. **RESULTS:** Of 944 patients enrolled during a 12-year period, 720 (76%) were in the gastroparesis group and 224 (24%) in the FD group. Baseline clinical characteristics and severity of upper gastrointestinal symptoms were highly similar. The 48-week clinical outcome was also similar but at this time 42% of patients with an initial diagnosis of gastroparesis were reclassified as FD based on gastric-emptying results at this time point; conversely, 37% of patients with FD were reclassified as having gastroparesis. Change in either direction was not associated with any difference in symptom severity changes. Full-thickness biopsies of the stomach showed loss of interstitial cells of Cajal and $CD206^{+}$ macrophages in both groups compared with obese controls. **CONCLUSIONS:** A year after initial classification, patients with FD and gastroparesis, as seen in tertiary referral centers at least, are not distinguishable based on clinical and pathologic features or based on assessment of gastric emptying. Gastric-emptying results are labile and do not reliably capture the pathophysiology of clinical symptoms in either condition. FD and gastroparesis are unified by characteristic pathologic features and should be considered as part of the same spectrum of truly "organic" gastric neuromuscular disorders. **CLINICALTRIALS.GOV IDENTIFIER:** NCT00398801, NCT01696747

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Chronic nausea and vomiting, when associated with delayed gastric emptying and with no structural cause of obstruction, is called gastroparesis (Gp). Functional dyspepsia (FD), which is a far more common syndrome, affecting up to 10% of the general population, has traditionally thought to be a distinct clinical entity but its pathogenesis is unknown. However, a significant number of these patients present with symptoms suggestive of Gp (eg, nausea, vomiting, early satiety, and postprandial fullness) but are found to have normal gastric emptying. Apart from "functional dyspepsia," this syndrome has also been described as "gastroparesis-like syndrome" or "chronic unexplained nausea and vomiting."[1,2] We have previously shown that these patients are clinically indistinguishable from those with delayed gastric emptying or Gp.[2] The true nature of FD and its relationship, if any, to Gp is an important issue to resolve, given the lack of insight into the pathogenesis of FD, despite its high prevalence in the general population.[3,4] Our aim in this study was, therefore, to understand this relationship using the largest cohort of such patients available, all of them carefully phenotyped using validated clinical and physiological measures and followed up prospectively over time. The large multi-center Gastroparesis Registry (GpR, GpR2) studies, prospective cohort studies conducted by the National Institute of Diabetes and Digestive and Kidney Diseases–funded Gastroparesis Clinical Research Consortium, have provided the opportunity to study these patients in a more comprehensive, prospective, and systematic manner (ClinicalTrials.gov Identifier: NCT00398801, NCT01696747).

Abbreviations used in this paper: **FD, functional dyspepsia; GCSI, Gastroparesis Cardinal Symptom Index; GES, gastric-emptying scintigraphy; Gp, gastroparesis; GpR, Gastroparesis Registry; ICC, interstitial cells of Cajal.**

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The main questions we asked were as follows: What are the differences and similarities in the symptom profile and clinical course of Gp and FD? Does the diagnosis of Gp or FD by gastric-emptying testing remain consistent over time? and How do enteric neuropathologic changes in Gp and FD compare with each other?

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The relationship of functional dyspepsia (FD) with postprandial distress syndrome to gastroparesis has been unclear and raises the question of the importance of delayed gastric emptying to the pathogenesis of symptoms in these patients.

NEW FINDINGS

In this large prospective study, the two groups were found to be very similar in terms of the nature of their symptoms and their severity, 48-week outcomes and gastric pathology. A significant number of patients in either group change from having delayed emptying to normal emptying (and vice versa), despite no change in symptoms.

LIMITATIONS

These patients were all seen at specialized motility centers and may or may not be representative of patients in the community.

IMPACT

FD is an organic disorder, very similar to gastroparesis both clinically and pathologically. Gastric emptying is not a reliable test to distinguish the two or fully explain their symptoms.

Methods

Patient Population

The National Institute of Diabetes and Digestive and Kidney Diseases–funded GpR studies are prospective cohort studies to investigate the natural history, epidemiology, and clinical course of Gp. Patients were considered for enrollment in the registry if they had symptoms suggestive of Gp, with or without delay in emptying (which may not have been available at the time of screening). We recruited patients with both delayed and normal emptying, generally in an approximately 5:1 ratio, but until the cap was reached (which was generally at a time point that was close to the end of the study), all patients who satisfied the inclusion/exclusion criteria were invited to participate, regardless of gastric-emptying status. A complete list of inclusion and exclusion criteria for the registry is provided in the Supplementary Appendix. In this study, we excluded patients with a history of Nissen or other fundoplication.

For our study, we included 981 adult patients participating in 2 Gp registries from February 2007 through March 2019 with either diabetic (type 1 or type 2) or idiopathic etiology and analyzed gastric-emptying results, symptom profiles, and other patient outcomes over follow-up during which patients received standard-of-care treatment by their physicians. The registries consisted of patients meeting specific entry criteria with symptoms of at least 12- weeks' duration and no abnormality causing obstruction on upper endoscopy. Patients with rapid gastric emptying were excluded from this study. Blood glucose levels were tested before scintigraphy and patients with diabetes with a level of >270 mg/dL were rescheduled and/or received insulin. Gp was defined as percent retention >60% at 2 hours and/or >10% at 4 hours on the gastric-emptying test.[1] FD at baseline was defined as percent retention ≤60% at 2 hours and ≤10% at 4 hours and meeting the criteria for FD using Rome III classification.[1] Thirty-seven patients with normal emptying and symptoms of Gp were excluded due to not being classified as having FD based on Rome III criteria, leaving a total of 944 patients for the final analysis. A diagnosis of idiopathic cause was based on no previous gastric surgery, no history of diabetes, and a normal A1c level.

Institutional Review Board approval was obtained at each clinical site and for the Scientific Data Research Center. All patients provided written informed consent for each registry study of participation. The investigation conforms with the principles outlined in the Declaration of Helsinki. All authors had access to the study data and also reviewed and approved the final manuscript.

Assessments

A detailed description of the standardized assessments performed on patients is provided in Supplementary Appendix. Patient-reported demographic data was collected at baseline and patient-reported medical histories using face-to-face interviews along with a physical examination were conducted at baseline and at each follow-up visit. Additional assessments included the gastric-emptying scintigraphy (GES) test, a meal-based emptying test at baseline, and, by protocol for GpR2, at 48 weeks,[1] upper gastrointestinal symptom scores using the Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index questionnaire and the related Gastroparesis Cardinal Symptom Index (GCSI), Rome III classification system for functional gastrointestinal disorders and psychological measurements (Patient Assessment of Upper Gastrointestinal Disorders–Quality of Life), the physical and mental components of the Medical Outcomes Study Short-Form V2 (SF-36v2), Beck Depression Inventory, and the State-Trait Anxiety Inventory. For at least 72 hours prior to scintigraphy, patients were instructed to not use opioids, prokinetics, anticholinergics, or cannabinoids.

Full-thickness gastric body biopsy specimens were obtained from 9 patients with idiopathic Gp, 9 patients with FD (nondiabetic) undergoing implantation of a gastric electrical stimulator, and 9 controls without diabetes or Gp symptoms undergoing obesity surgery. There were 8 females and 1 male in each of the 3 subgroups. Tissue collection was done in standardized fashion with established protocols by the participating sites of the Gastroparesis Clinical Research Consortium and was processed and analyzed by the histology core at Mayo Clinic (Rochester, MN). Supplementary Appendix, section on Gastric Pathology, includes details for collection, staining, light microscopy, and quantification of the histologic biomarkers.

Statistical Methods

Two-sample *t* tests or analysis of variance for continuous and Pearson chi-square tests for categorical characteristics were used to compare the FD and Gp subgroups for differences in various characteristics at baseline, including demographic, anthropometric, symptom profiles, clinical evaluations, type of nutrition, and psychological and quality of life assessments. The

Table 1. Baseline Characteristics by Functional Dyspepsia and Gastroparesis

Baseline characteristic	GET status[a] FD Mean (SD) or No. (%) (n = 224)	GET status[a] Gp Mean (SD) or No. (%) (n = 720)	P[b]
Demographics/lifestyle			
Sex: female	199 (89)	603 (84)	.06
Race: White	200 (89)	640 (89)	
Ethnicity: Hispanic	22 (10)	83 (12)	.48
Age at baseline, *y*	42.8 (13.9)	43.0 (13.5)	.80
Age at baseline, ≥50 *y*	64 (29)	208 (29)	.93
Smoked (ever regularly)	71 (32)	225 (31)	.90
Education: college degree or higher	79 (35)	235 (33)	.47
Income, ≥$50,000	119 (53)	357 (50)	.33
Symptom severity (Global and PAGI-SYM[c])			
Global symptom severity (investigator-rated)			**.04**
Mild	37 (17)	117 (16)	
Moderate	150 (67)	423 (59)	
Gastric failure	37 (17)	175 (24)	
Predominant symptom on presentation[c]			.16
Nausea	88 (39)	225 (31)	
Vomiting	41 (18)	158 (22)	
Abdominal pain	40 (18)	140 (19)	
Any other symptom	55 (25)	197 (27)	
GCSI total score	3.0 (0.9)	2.9 (1.1)	.49
Nausea/vomiting subscale	2.2 (1.3)	2.4 (1.4)	.11
Postprandial fullness subscale	3.6 (1.0)	3.4 (1.2)	**.004**
Bloating subscale	3.2 (1.6)	3.1 (1.6)	.43
Abdominal pain moderate/severe[c]	148 (67)	472 (66)	.80
Upper abdominal pain subscale	3.0 (1.4)	3.1 (1.5)	.92
Upper abdominal pain severity score	2.9 (1.5)	3.0 (1.7)	.91
Upper abdominal discomfort score	3.1 (1.4)	3.2 (1.6)	.93
GERD subscale	1.9 (1.3)	2.0 (1.4)	.29
GES			
% Retention at 2 h	33.0 (14.6)	65.0 (18.0)	NA
% Retention at 4 h	4.3 (3.0)	32.2 (22.0)	NA
Delayed emptying at 2 h	0 (0)	455 (63)	NA
Delayed emptying at 4 h[c]	0 (0)	673 (94)	NA
Clinical factors			
Etiology			**.008**
Idiopathic	170 (76)	472 (66)	
Diabetes type 1	22 (10)	125 (17)	
Diabetes type 2	32 (14)	123 (17)	
BMI			
Overweight or obese, BMI >25	117 (52)	406 (56)	.27
Mean BMI, kg/m^2	27.9 (8.7)	27.4 (7.5)	.35
Duration of symptoms at enrollment, *y*	6.1 (7.4)	5.5 (6.8)	.28
Acute onset of symptoms	92 (41)	326 (45)	.27
Initial infectious prodrome	45 (20)	135 (19)	.66
Inflammation[c]	86 (38)	333 (46)	**.04**
CRP, *mg/dL*	1.0 (1.8)	1.9 (6.3)	**.02**
ESR, *mm/h*	15.8 (15.6)	19.7 (20.0)	**.007**
HbA1c, %	6.0 (1.4)	6.4 (1.8)	**.01**
Treatment (current use at baseline)			
Narcotics use	78 (35)	278 (39)	.31
Proton pump inhibitors	150 (67)	541 (75)	**.02**
Prokinetics	66 (29)	329 (46)	**<.001**
Antiemetics	138 (62)	451 (63)	.81
Antidepressants	116 (52)	347 (48)	.35
Anxiolytics	45 (20)	163 (23)	.42

Table 1. Continued

Baseline characteristic	GET status[a] FD Mean (SD) or No. (%) (n = 224)	GET status[a] Gp Mean (SD) or No. (%) (n = 720)	P[b]
Pain modulators	55 (25)	182 (25)	.83
On TPN	7 (3)	52 (7)	**.03**
Gastric electric stimulation device implantation	17 (8)	44 (6)	.43
Psychological and QOL			
BDI score	18.3 (11.5)	18.5 (11.3)	.83
Moderate to severe depression (BDI >20)[c]	91 (41)	296 (41)	.90
STAI			
State anxiety score	43.4 (13.4)	44.2 (13.7)	.44
Severe state anxiety, ≥50[c]	73 (33)	252 (35)	.51
Trait anxiety score	43.0 (12.9)	43.7 (12.6)	.47
Severe trait anxiety, ≥50[c]	69 (31)	237 (33)	.56
QOL total score	2.6 (1.1)	2.6 (1.1)	.98
PAGI-QOL,[c] ≥3	80 (36)	265 (37)	.85
Overall Health Survey,[c] SF-36 v2			
Physical health component subscore	33.8 (11.0)	33.2 (10.6)	.53
Mental health component subscore	40.3 (12.2)	38.9 (13.0)	.15

ANOVA, analysis of variance; BDI, Beck Depression Inventory; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GERD, gastroesophageal reflux disease; GET, gastric-emptying test; NA, not applicable; PAGI-SYM, patient-rated overall GCSI score; QOL, quality of life; SD, standard deviation; STAI, State-Trait Anxiety Inventory; TPN, total parental nutrition.

[a]GpR and GpR2 patients with either idiopathic or diabetic etiology without rapid gastric emptying are included. 37 patients with normal emptying and symptoms of Gp were excluded due to not being classified as having FD based on Rome III criteria (total N = 944). FD defined as percent retention from a GET being ≤60% at 2 h and ≤ 10% at 4 h and meeting the criteria for FD using Rome III classification. Gp defined as percent retention from a GET being >60% at 2 h and/or >10% at 4 h. Percentages or averages for each characteristic determined from patients with nonmissing data for that characteristic. Of the 48 characteristics compared, 3 would be likely be significant (at alpha=.05) due to chance.

[b]*P* value (2-sided) derived from either a *t* test or ANOVA for continuous predictors, or Pearson's chi-square test for categorical predictors. Bold font denotes a $P < .05$.

[c]PAGI-SYM scores report patient-rated severity of symptoms from 0 (none) to 5 (severe) in the past 2 wk. Predominant symptom at presentation (baseline visit) is the main reason for evaluation that the patient reported; it was categorized to report the 3 most frequent issues; the other category includes bloating, early satiety, postprandial fullness, diarrhea, constipation, anorexia, GERD symptoms, poorly managed diabetes or glycemic control, and a weight change (loss or gain). Abdominal pain moderate/severe was defined as either upper abdominal pain or discomfort PAGI-SYM symptom score ≥ 3. The 46 patients without delayed emptying at 4 h (due to missing % retention data) were delayed emptying at 2 h. Inflammation was defined as either C-reactive protein >1.0 mg/dL or erythrocyte sedimentation rate >20 mm/h. BDI >20 indicates moderate or more severe depression. STAI scores ≥ 50 indicate severe state or trait anxiety. PAGI-QOL score increases with increased QOL due to Gp symptoms in past 2 wk. SF-36v2 score increases with increased general QOL in the past 4 wk.

2 subgroups were also compared for 12 patient outcomes during 48 weeks of follow-up using analysis of covariance of the continuous outcomes with adjustment for the baseline value of the outcome and a subgroup (FD or Gp) indicator. Changes in Gp diagnosis during 48 weeks were assessed by classifying each patient by their baseline and 48-week gastric-emptying test diagnosis, then using a Fisher exact text to assess whether the diagnosis changes from baseline to 48 weeks are random. Analysis of covariance, adjusting for the baseline symptom value and an indicator of diagnosis change (change or no change in diagnosis) for each subgroup at baseline, was used to assess whether the changes in each symptom severity during 48 weeks were different based on converter status: if FD at baseline, then symptom changes from baseline were compared between those remaining FD or those with a diagnosis of Gp at 48 weeks, and, if Gp at baseline, symptom changes over 48 weeks were compared between those remaining Gp and those with a diagnosis of FD (normal emptying) at 48 weeks.

For comparison of the histology results per biomarker between the 3 subgroups (Controls, FD, and Gp), *P* values were determined from a mixed multiple linear regression model regressing each patient's biomarker counts on the 3-category subgroup, accounting for the repeated measures per patient and multiple comparisons, and pairwise *P* values from pairwise comparisons of the marginal linear predictions of the margins.

All *P* values are nominal and 2-sided. Also, 95% confidence intervals or standard deviations were provided in all tables except for the binary measures in Tables 1 and 3, so that the amount of variation per measure could be considered in result interpretation. Complete case analysis was used in all tables. Additional details for the statistical methods are provided in Supplementary Appendix.

Table 2. 48-Week Changes From Baseline in Gp Symptoms (GCSI), Anthropometry, Clinical Factors, Depression, and QOL in Patients With Gp and FD

	FD[a] (n = 159)			Gp[a] (n = 456)			P^c	Mean net change: FD-Gp		
Outcome characteristics	Mean Baseline	Mean Δ^b	95% CI	Mean Baseline	Mean Δ^b	95% CI	FD vs Gp	Mean net Δ $\Delta_{FD} - \Delta_{Gp}$	Mean net Δ CI	P^d
Symptom severity										
PAGI-SYM	3.1	-0.40	-0.57,-0.23	2.9	-0.37	-0.47, -0.27	.88	-.03	-0.23, 0.18	.80
Patient-rated improvement in GCSI of 1+ points from baseline	NA	27%	19, 35%	NA	26%	22, 30%	.86	1%	-8%, 9%	.86
Anthropometric										
BMI, *kg/m²*	27.6	0.26	-0.14, 0.67	27.5	0.56	0.31,0.82	.24	-0.30	-0.81,0.22	.26
Weight, *kg*	76.3	0.77	-0.32, 1.87	74.3	1.44	0.78,2.10	.28	-0.67	-2.00,0.66	.32
Clinical factors[e]										
Total hospitalizations, *no.*[f]	1.1	-0.47	-94, 0.0001	2.1	-0.91	-1.26,-0.56	.12	-0.51	-1.14,0.13	.12
On TPN, %	2.8%	2.1%	-1.6,5.8%	7.2%	-2.8%	-5.4,- 03%	.54	4.9%	-0.5,10.2%	.07
Psychological and QOL										
Depression (BDI)	18.3	0.17	-1.23,1.58	18.5	-0.48	-1.40,0.44	.42	0.65	-1.21,2.51	.49
State anxiety total score	43.3	1.03	-0.94,2.99	44.0	0.27	-1.00,1.53	.56	0.76	-1.81,3.33	.56
Trait anxiety total score	43.1	1.16	-0.43,2.75	43.6	0.21	-0.78,1.20	.34	0.95	-1.07,2.98	.36
PAGI-QOL total score	2.5	0.26	0.11,0.42	2.6	0.24	0.15,0.33	.92	0.02	-0.16,0.20	.82
SF-36v2 physical component	33.3	1.51	0.09,2.93	33.5	1.11	0.27,1.95	.54	0.41	-1.33,2.14	.64
SF-36v2 mental component	40.3	0.19	-1.63,2.01	38.7	1.39	0.23,2.55	.57	-1.20	-3.55,1.16	.32

ANCOVA, analysis of covariance; CI, confidence interval; ED, emergency department; GLM, generalized linear model.
[a]Total N determined by the value for the outcome being available at baseline and at 48 wk; total N varies between 449 and 456 for number of patients with gastroparesis, and for those with normal emptying and functional dyspepsia using Rome III (FD), between 130 and 159, and overall total patients between 579 and 615. Patients with Gp have delayed gastric emptying defined as delayed gastric emptying scintigraphy of >60% at 2 h or >10% at 4 h. FD patients have Gp symptoms and normal gastric emptying. Patients with idiopathic or diabetic etiology and without rapid emptying were included.
[b]Mean change of outcome (48 wk–baseline) and 95% CI for the mean change presented, as well as the mean change in the mean changes of each subgroup (mean change of outcome for FD–mean change of outcome for Gp).
[c]*P* values for continuous outcome characteristics determined using ANCOVA of each characteristic of change at 48 wk from baseline in relation to delayed gastric retention indicator (FD vs Gp) with adjustment for the baseline value of the characteristic. *P* for 1+ point improvement in GCSI was determined from a GLM with binomial distribution. *P* for the total hospitalizations in past year determined from a zero-inflated negative binomial regression of total hospitalizations in relation to delay indicator with adjustment for the total hospitalizations in year prior to baseline. *P* value for TPN as a percent was derived from a Wald test to assess whether change in TPN use varied by delayed retention adjusting for the baseline. TPN use using ANCOVA with robust variance.
[d]For continuous variables, mean net change was defined as the difference of the mean change in outcome indicator (value at 48 wk–at baseline) in patients with FD classification minus the mean change in outcome indicator in patients with Gp; 95% CI for the net mean change between gastric retention groups computed from a *t* test. For GCSI 1+ improvement, the difference, 95% CI, and *P* were determined using the 2-subgroup proportion test.
[e]ED visits were not reported at baseline. The total number of ED visits from baseline to 48 wk was: 1.71 ± 4.13 for all patients, 1.38 ± 3.41 for patients with FD, and 1.81 ± 4.33 for patients with Gp ($P = .12$; determined using a zero-inflated negative binomial regression with robust variance).
[f]Total hospitalizations since baseline excluded Enterra placement or removal.

Results

Baseline Characteristics of Patients With FD and Gp are Very Similar

Of a total of 944 patients enrolled during a 12-year period, 720 (76%) met criteria for Gp on scintigraphy whereas 224 (24%) had normal emptying and met the criteria for FD (a detailed classification of the 2 groups based Rome III criteria is provided in Supplementary Table 1). The 2 groups were similar across a broad range of metrics, with only a few statistically significant differences of uncertain clinical significance (Table 1). There was a slightly higher proportion of patients in the idiopathic category (as compared with diabetic Gp) in the group with normal emptying (76% vs 66%; $P = .008$); this was also reflected in the difference in HbA1c (6.0 vs 6.4; $P = .01$). Patients with normal gastric emptying had milder overall severity using a physician-rated scale with 17% of patients with normal emptying classified as "gastric failure" (requiring enteral or parenteral nutrition) as compared with 24% of the Gp group ($P = .01$); only 3% required total parenteral nutrition (as compared with 7% in the Gp group; $P = .03$) The proportion of patients with general markers of inflammation (C-reactive protein and erythrocyte sedimentation rate) was also lower in patients with

Table 3. Change in Diagnosis of Functional Dyspepsia and Gastroparesis at Baseline and 48-wk Follow-up Based on Solid Gastric Emptying

	Total patients (n = 249)[a]		
		48 Wk	
	Baseline	Gp	FD
Diagnosis	Gp (n = 189)	110 (58%)	79 (42%)
	Median at 4 h GE	Median at 4 h GE	Median at 4 h GE
Total patients	24.0% (16.0, 40.0)		
Gp to Gp	25.5% (16.5, 42.0)	23.0% (16.0, 38.0)	
Gp to FD	23.0% (14.7, 35.3)		3.0% (1.9, 5.0)
Diagnosis	FD (n = 60)	22 (37%)	38 (63%)
	Median at 4 h GE	Median at 4 h GE	Median at 4 h GE
Total patients	5.0% (2.5, 8.0)		
FD to FD	6.0% (2.5, 8.0)		3.0% (2.0, 5.1)
FD to Gp	5.0% (2.5, 8.0)	14.6% (12.6, 21.0)	
	% Diagnosis changed	41% ([79 + 22]/249)	
	% Unchanged	59% ([110 + 38]/249)	
	P value[b]	**.005**	

FD, functional dyspepsia; GE, gastric emptying; GP, gastroparesis; IQR, interquartile range.
[a]Idiopathic (n = 182) and diabetic patients (n = 67) with baseline and 48-wk GES test results were included; 7 patients with normal emptying and symptoms of Gp not classified as FD using Rome III were excluded; 34 patients in GpR1, 215 in GpR2. Presented are the number (%) of patients in each diagnosis category, and respective interquartile range (IQR) values of each %-gastric retention at 4 h distribution at baseline and 48 wk. Gp to Gp: patients diagnosed with Gp at baseline and who remained in that category at 48 wk; Gp to FD: patients diagnosed with Gp at baseline and who were classified as FD (normal emptying) at 48 wk; FD to FD: patients diagnosed with normal emptying and FD at baseline and who remained in that category at 48 wk; FD to Gp: patients diagnosed with FD at baseline and who were classified as having Gp at 48 wk. When analyzed separately by etiology subgroup, 75/182 (41%) of the idiopathic subgroup and 26/67 (39%) of the diabetic subgroup changed diagnosis between the baseline and 48-wk GES test ($P = .40$), where P was determined from a logistic regression of the baseline GES diagnosis on the follow-up diagnosis, etiology subgroup, and an interaction term for etiology and follow-up GES diagnosis.
[b]P tests the null hypothesis that the diagnosis changes from baseline to 48 wk are random. P computed using Fisher exact test (2-sided). Bold font denotes a $P < .05$.

normal gastric emptying (38% vs 46%; $P = .04$) with lower mean values for these tests as well. As to be expected, prokinetic use was substantially higher in patients with delayed emptying (46% vs 29%; $P < .001$), whereas the use of proton pump inhibitors was slightly higher (75% vs 67%; $P = .02$). Notably, psychological and quality metrics were equivalent in both groups. When analyzed separately, patients with Gp and those who met Rome III criteria for FD were also similar to the FD (normal emptying) group at enrollment (Supplementary Table 2).

Change in Global Outcomes During the First 48 Weeks in Patients With FD and Gp are Also Similar

Data at 48 weeks of longitudinal follow-up were available for 130–159 patients (depending on the specified outcome) with FD and 449–456 patients with Gp. Clinical improvement at 48 weeks, as previously defined by us (a decrease of 1 or more in the total GCSI score),[5] was seen in 27% and 26% of the FD and Gp groups, respectively, and this did not vary with etiology (idiopathic or diabetic). Also, 48-week GCSI scores, as described in Table 2, improved slightly in both groups by about 0.4 points, which did not meet the threshold for being considered clinically meaningful.

The Diagnosis of Gp or FD Based on Gastric Emptying is Labile Over Time, Can Move in Both Directions, and Has No Impact on Change in Symptoms

Data from gastric scintigraphy performed approximately 48 weeks after enrollment in the study were available in 249 patients. Patients with a gastric-emptying test at 48 weeks were very similar to those patients who did not have a gastric-emptying test when compared on baseline characteristics using a logistic regression. The only difference evident was self-reported ethnicity (identifying as Hispanic/LatinX) was 70% less likely in those without a 48-week GES compared with those with a follow-up GES ($P < .001$) (Supplementary Table 3).

Table 4. Changes in Gp Symptom Scores by Changes in Gastric-Emptying Diagnosis During 48 Weeks of Follow-up

	FD at baseline[a] (n = 60)			Gp at baseline[a] (n = 189)		
	FD at 48 wk (n = 43)	Gp at 48 wk (n = 22)	P^b	Gp at 48 wk (n = 110)	FD at 48 wk (n = 79)	P^b
Changes in PAGI-SYM symptom severity (0–5) scores at 48 wk from baseline:						
GCSI[c]	-0.2 (1.2)	-0.4 (0.6)	.82	-0.3 (1.0)	-0.4 (1.1)	.21
Nausea severity	0.0 (1.3)	-0.2 (1.7)	.84	-0.3 (1.5)	-0.7 (1.5)	.11
Retching severity	0.3 (1.6)	0.2 (1.1)	.78	-0.4 (1.6)	-0.5 (1.8)	.27
Vomiting severity	0.4 (1.6)	0.2 (0.9)	.75	-0.3 (1.8)	-0.5 (1.8)	.25
Nausea subscale[c]	0.2 (1.2)	0.1 (0.8)	.70	-0.4 (1.3)	-0.6 (1.4)	.13
Feeling of stomach fullness severity	-0.3 (1.2)	-0.7 (1.1)	.45	-0.3 (1.5)	-0.3 (1.7)	.70
Inability to finish meal severity	-0.8 (1.7)	-0.9 (0.8)	.70	-0.4 (1.6)	-0.5 (1.7)	.43
Excessively full after meal severity	-0.4 (1.3)	-0.5 (1.0)	.78	-0.3 (1.5)	-0.3 (1.6)	.65
Loss of appetite severity	-0.8 (1.7)	-1.5 (1.2)	.32	-0.3 (1.7)	-0.5 (1.7)	.45
Post-prandial fullness subscale[c]	-0.6 (1.2)	-0.9 (0.7)	.43	-0.3 (1.2)	-0.4 (1.3)	.48
Visibly larger stomach severity	-0.2 (2.1)	0.1 (1.1)	.86	-0.2 (1.7)	-0.1 (1.5)	.58
Bloating severity	-0.4 (1.7)	-0.5 (1.1)	.71	-0.3 (1.5)	-0.3 (1.6)	.42
Bloating subscale[c]	-0.3 (1.8)	-0.2 (.9)	.44	-0.2 (1.5)	-0.2 (1.5)	.61
Upper abdominal pain	-0.2 (1.5)	-0.9 (1.4)	.68	-0.3 (1.7)	-0.5 (1.6)	.23
Upper abdominal discomfort	-0.4 (1.4)	-0.7 (1.2)	.85	-0.2 (1.7)	-0.6 (1.4)	.08
Upper abdominal pain subscale[c]	-0.3 (1.3)	-0.8 (1.3)	.77	-0.3 (1.6)	-0.6 (1.4)	.12
GERD subscale[c]	-0.1 (0.9)	-0.2 (1.1)	.78	-0.3 (1.1)	-0.5 (1.1)	.11

[a]Data for symptom changes presented are means ± SDs. PAGI-SYM severity scores range from 0–5 indicating symptom severity of none to very severe during the past 2 wk. Positive change in symptom severity at 48 wk from baseline indicates worsening of the symptom and negative change indicates a decrease in severity.
[b]Symptom changes were analyzed between converter status within 2 subgroups (FD or Gastroparesis (Gp) at baseline) using an ANCOVA regressing the change in symptom score on the subgroup indicator (change in DX at 48 weeks, or no change), adjusting for the baseline value of the symptom.
[c]Definitions: Gastroparesis Cardinal Symptom Index = (nausea subscale + postprandial fullness subscale + bloating subscale)/3 where: nausea subscale = (nausea + retching + vomiting)/3; postprandial fullness/early satiety subscale = (stomach fullness + inability to finish meal + excessively full + loss of appetite)/4; bloating subscale = (bloating + large stomach)/2; GERD subscale = (heartburn day + heartburn lying down + chest discomfort day + chest discomfort night + reflux day + reflux night + bitter taste)/7; and upper abdominal pain subscale = (upper abdominal pain + upper abdominal discomfort)/2.

Overall 41% of this cohort could be categorically transferred from one group to the other after 48 weeks (Table 3). Of 189 patients with a diagnosis of Gp at baseline, 79 (42%) had normal emptying at 48 weeks, thus no longer satisfying the definition of Gp. Conversely, of the 60 patients with FD (normal gastric emptying at baseline), 22 (37%) showed delayed emptying at 48 weeks, thus qualifying for the diagnosis of Gp. These findings hold true irrespective of cause because 41% of the idiopathic and 39% of the diabetic population underwent a change in the diagnosis of FD or Gp after 48 weeks ($P < .40$).

We also analyzed whether patients with Gp with milder delays in emptying were more likely to have normal emptying at 48 weeks and hence may represent "outliers" that were misclassified using scintigraphy. When classified according to severity of delay at baseline by 4-hour retention as "mild" (>10%; n = 169), "moderate" (>20%; n = 104), "severe" (>35%; n = 54), and "very severe" (>50%; n = 26), the conversion rates to normal emptying at 48 weeks were 41%, 39%, 40%, and 27%, respectively ($P = .64$).

Furthermore, analysis of symptom scores in these patients showed mild improvements after 48 weeks, consistent with those reported for the larger cohorts, regardless of whether gastric emptying had improved or worsened enough to change the initial diagnosis (Table 4). The correlation between gastric retention values and GCSI total scores at baseline and at 48 weeks (grouped according to initial GES diagnosis), along with the medians and range, are shown in Figure 1. Corresponding medians and range for GCSI subclusters are shown in Supplementary Figure 1. No significant correlations between emptying and symptom severity were seen at either time point and in either group, confirming previously published results from our group.[2] These changes in diagnosis were not accompanied by any significant changes in HbA1c levels, medication use, total parenteral nutrition, or electrical stimulator use (Table 5). Serum glucose test results are provided in Supplemental Table 4 and Rome III classifications at baseline and at 48 weeks for these patients are provided in Supplementary Figure 2.

FD and Gp Share the Same Characteristic Neuropathology

We have previously shown that the most prominent pathologic changes in Gp are a loss of interstitial cells of

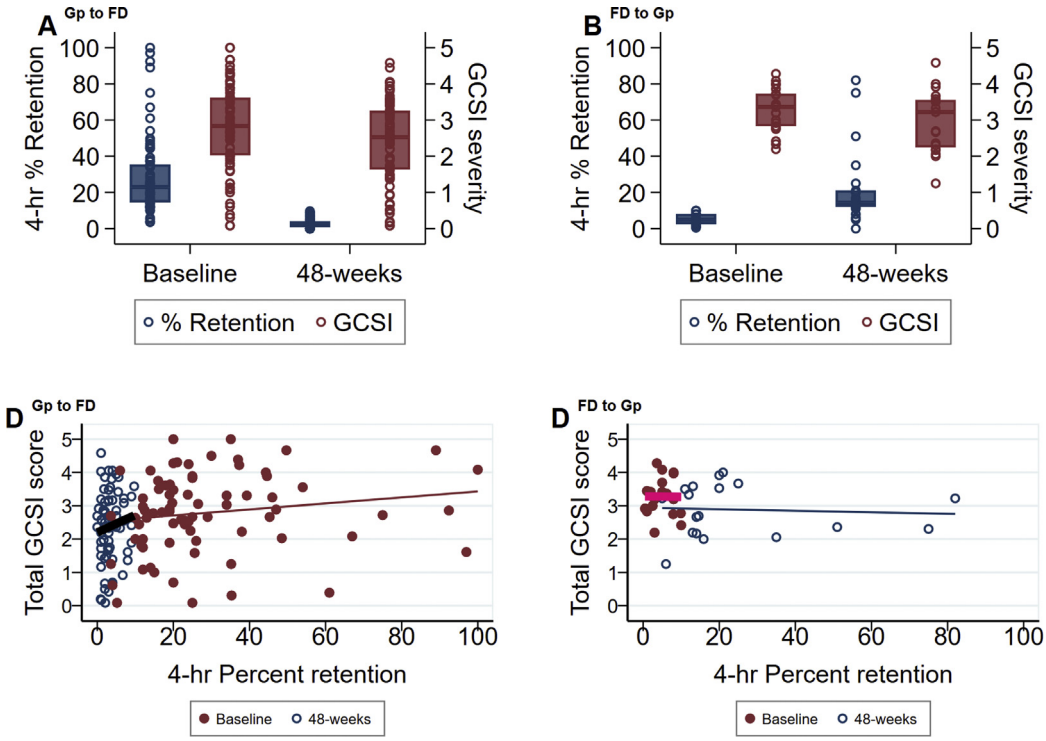

Figure 1. Seventy-nine patients with Gp and 22 patients with Gp symptoms, normal gastric retention, and FD using the Rome III classification at enrollment are compared based on 4-hour % gastric retention and severity of the total GCSI score (0–5) at baseline and at 48 weeks of follow-up. Boxplots and dot plot distributions of total GCSI (*blue*) and % gastric retention (*maroon*) are displayed. Each dot represents a patient's values. (*A*) Seventy-nine patients with Gp at baseline had normal gastric retention at 48 weeks (Gp converters) and (*B*) 22 patients without delayed retention (FD) at baseline had delayed gastric emptying at 48 weeks (FD converters). Total GCSI remained similar at both time points. Scatterplots and fitted regression lines at baseline (*maroon*, *pink regression line*) and 48 weeks (*blue*) are displayed. (*C*) Gp converters: $y = 2.53 + 0.009*x$, $r = 0.16$ at baseline and $y = 2.20 + 0.05*x$, $r = 0.13$ at 48 weeks, and (*D*) FD converters: $y = 3.28 - 0.001*x$, $r = -0.01$ at baseline and $y = 2.94 - 0.002*x$, $r = .07$, where y = GCSI score an x = % gastric retention.

Cajal (ICC), which set the electrical rhythm and transduce neuromuscular signals and reduced numbers of anti-inflammatory C206^{+} macrophages.[6,7] Full-thickness gastric body biopsy specimens were surgically obtained in a subset of patients with FD and Gp and compared with matched controls (n = 9 each; all nondiabetic) for histologic changes as previously described. The median retention at 4 hours (Q1,Q3) was 2.0% (1.0,4.0) and 24% (20.0,60.0) for the FD and Gp groups, respectively. A detailed comparison of the baseline clinical and other characteristics for these 18 patients is described in Supplementary Table 5; as can be seen, the 2 groups were very similar. As compared with controls, a significant loss of ICC along with a decrease in myenteric plexus CD206-positive staining was seen in both patient subgroups (Figure 2). Protein Gene Product 9.5 (a marker for neurons) counts/high-power field were similar in all 3 groups as were a variety of other histologic markers (Supplementary Table 6).

Discussion

In this study, we hypothesized that FD and Gp may be part of the same clinicopathologic spectrum of gastric neuromuscular dysfunction and that the classical biomarker, gastric emptying, may not be useful in separating these 2 disorders. We first performed a cross-sectional analysis of baseline characteristics of patients in the 2 groups (Table 1). Although some of the symptoms were of milder severity in the FD as compared with the Gp group, these differences were minor and of equivocal clinical significance. We then examined changes in symptom severity and other outcomes after a year of follow-up (Table 2) and found no significant differences between the 2 groups, with only a minority of patients showing clinically important improvement, regardless of the initial diagnosis. Thus, these results show no significant or meaningful differences across multiple metrics, attesting to the clinical similarities of the 2 groups.

The striking clinical similarities among the 2 groups prompted us to reconsider the significance of an abnormal gastric-emptying test in these patients, with the hypothesis that gastric emptying is not a reliable marker to distinguish them. We tested this by examining changes in gastric emptying over time and found that in a large number of patients (41% of the idiopathic and 39% of the diabetic population) gastric-emptying testing would have reclassified the patients into the alternative group after a year. Smaller studies have suggested that gastric emptying remains on average stable over prolonged periods of time in

Table 5. Changes in HbA1c Level and Medication Use by Changes in Gastric-Emptying Diagnosis During 48 Weeks of Follow-up

Changes in HbA1c and medication use during 48 wk of follow-up[a]	FD at baseline (n = 60)			Gp at baseline (n = 189)		
	FD at 48 wk (n = 38)	Gp at 48 wk (n = 22)	*P*	Gp at 48 wk (n = 110)	FD at 48 wk (n = 79)	*P*[b]
HbA1c (%)[c]	0.12 (0.83)	0.60 (1.55)	.40	0.29 (1.25)	0.18 (1.71)	.77
Medication use during 48 wk (%)						
Narcotics use	13.9% (54.3)	22.7% (42.9)	.80	15.7% (43.6)	11.0% (35.6)	.37
Proton pump inhibitors	-2.8% (50.6)	-9.1% (52.6)	.74	2.8% (48.3)	-8.2% (46.4)	.12
Prokinetics	-2.8% (56.0)	0% (43.6)	.26	6.5% (49.8)	5.5% (0.50)	.43
Antiemetics	2.8% (37.7)	9.1% (29.4)	.62	11.1% (43.9)	5.5% (46.8)	.20
Antidepressants	-22.2% (54.0)	-9.1% (52.6)	.27	-10.2% (51.0)	0% (60.1)	.18
Anxiolytics	11.1% (57.5)	13.6% (35.1)	.95	14.8% (47.0)	15.1% (43.0)	.48
Pain modulators	5.6% (53.2)	9.1% (61.0)	.95	9.3% (39.9)	6.8% (25.4)	.40
Cannabinoids	0% (33.8)	4.5% (21.3)	.46	2.8% (25.4)	9.6% (29.6)	.22
Treatment use during 48 wk (%)						
On TPN	-2.8% (16.7)	-4.5% (21.3)	.33	0.9% (21.6)	-5.5% (28.3)	.54
Gastric electric stimulation device implantation	8.3% (43.9)	4.5% (37.5	.34	13.0% (41.2)	9.6% (37.9)	.72

[a]Data for changes in HbA1c and any medication use presented are mean changes ± SDs. Positive change in Hba1c value or medication use at 48 wk from baseline indicates worsening of the HbA1c and increasing use of medications. Patients included in this analysis had paired (baseline and 48 wk) GETs and follow-up history case reports.
[b]Change in HbA1c was analyzed between converter status within 2 subgroups (FD or Gp at baseline) with an ANCOVA, regressing HbA1c change on baseline HbA1c, and converter subgroup. *P* values for medication and treatment use changes during follow-up as percentages were derived from a Wald test to assess whether change in use varied by converter status adjusting for the baseline use by each subgroup using ANCOVA with robust variance.
[c]HbA1c required at baseline for all patients and at follow-up for diabetics, and, if available, for nondiabetics. For FD converters, n = 9 and 11 patients with both values at follow-up, and for Gp converters, there were n = 36 and n = 21 patients with paired HbA1c values at follow-up. There are 2 patients without paired GES and medication use data in the FD converter subgroup (n = 36 and 22) and 8 patients without paired data for analysis in the Gp converter subgroup (n = 108 and 73).

diabetic Gp.[8] In one of these, gastric emptying (not using currently accepted standardized methodology) was delayed at baseline in 8 of 13 patients, with 3 of these normalizing during a 25-year period without change in symptoms.[9] Other investigators have also shown that over time many patients initially diagnosed with Gp may normalize emptying.[10] Our study shows that movement between the 2 groups can be in both directions: patients with normal emptying can exhibit delayed emptying when tested at a later time point and vice versa. Further, patients with Gp across the spectrum of delay were similar in their frequency of conversion to FD and, therefore, this was not a phenomenon confined to those close to the cusp between delayed and normal emptying. Our findings indicate a significant lack of reproducibility of gastric emptying, either due to intrinsic limitations in the test methodology or because gastric emptying in a given patient may vary highly over time. A recent study examined the reproducibility of scintigraphic measurement of gastric emptying by repeating the test an average of 15 days later and showed significantly high coefficients of variation: 2 hours, 4 hours, and $T_{1/2}$ of 23%, 20%, and 20%, respectively.[11] In 30% of the cohort of 60 patients that included both diabetic and idiopathic patients, the interpretation of gastric emptying as normal, rapid, or delayed was different between the 2 time points. These results, along with ours, provide strong support for the conclusions that gastric emptying is not a reliable method to discriminate between the 2 conditions.

Equally if not more importantly, symptom severity remained on average unchanged despite the change in gastric-emptying status. The relationship between gastric emptying has remained a point of controversy in the literature with some investigators arguing that the discrepancy has been due to nonstandardized assays and the fact that most studies have not measured symptoms at the same time as measuring gastric emptying.[10,12] The results of our present study add a new and different kind of evidence to support our previous findings that symptom severity does not correlate with rates of gastric emptying, which is also in keeping with other reports in the literature, as discussed previously.

Recognizing that pathologic changes in the target tissue is required to ultimately prove that the 2 conditions are indeed similar, we proceeded to examination of full-thickness gastric biopsy specimens obtained from a subset of patients with FD and Gp and compared them with matched controls. We have previously shown patients with Gp exhibit loss of ICC (these cells are important for setting the electrical rhythm and neuromuscular coupling) accompanied by a shift in the myenteric macrophage phenotype indicated by a reduction in the CD206-expressing population that normally play an anti-inflammatory role.[6,7] Our

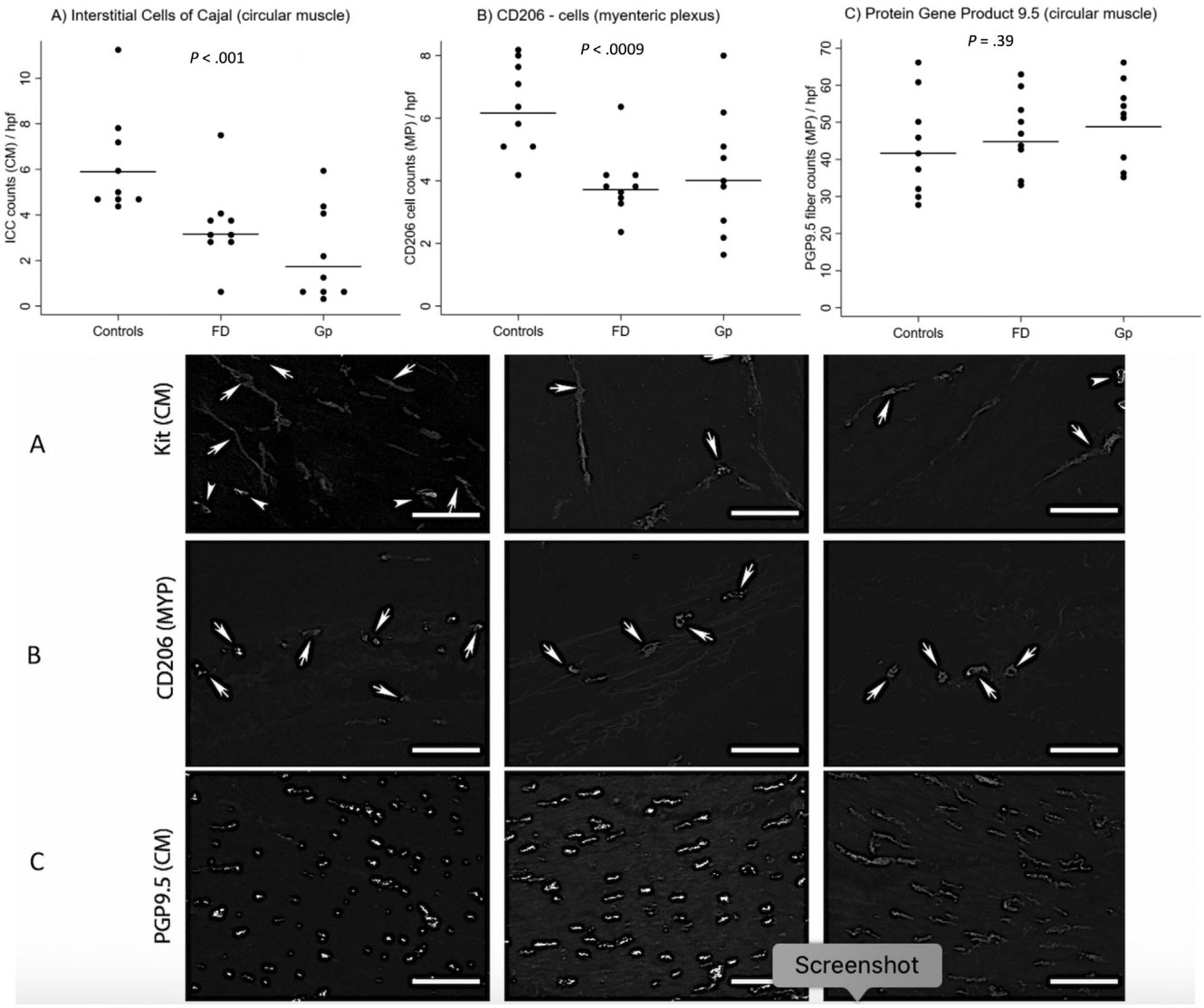

Figure 2. Three histologic biomarkers were analyzed over 3 subgroups, each with 9 nondiabetic patients' samples per group: controls, FD and normal emptying, and Gp. The biomarkers were determined using stained stomach tissue slides, with multiple counts per circular field under high-powered focus (hpf) per patient. The number of counts per patient varied by the histologic biomarker and patient. Each figure displays individual patient's mean count (*dots*) and the adjusted mean count per subgroup (*horizontal line*). *P* (2-sided) was determined using a mixed multiple linear regression model regressing each patient's biomarker counts on the 3-category subgroup, accounting for the repeated measures per patient. (*Top*) (*A*) ICC (expressing c-Kit) in circular muscle showing decreased cell count numbers in FD and Gp in a linear trend from controls ($P \leq .0001$), with no difference seen between the 2 syndromes. (*B*) CD206 (myenteric plexus)–positive macrophage counts showing decreased numbers in both FD and Gp ($P \leq .0009$), with no difference seen between the 2 syndromes (*C*) Neuronal counts (as measured using Protein Gene Product 9.5 [PGP9.5] staining) in circular muscle showed no difference between any of the 3 groups ($P = .39$). (*Bottom*) Images of histologic changes in control patients and patients with FD and idiopathic Gp. (*A*) c-Kit (circular muscle) showing decreased immunoreactivity in FD and idiopathic Gp (*arrows* [*horizontal lines*] indicate ICC with slender bodies and 2–3 processes; *arrowheads* indicate mast cells with larger, rounded bodies and no processes. (*B*) CD206 staining of myenteric plexi showing decreased immunoreactivity in both FD and Gp. (*C*) PGP9.5 staining for neurons. Images obtained at 20x magnification (scale = 20 μm).

findings confirmed our previous results in Gp but, more importantly, indicated the stomach of patients with FD had the same characteristic pathology (ie, loss of ICC and CD206-expressing macrophages). As previously shown by us in Gp by itself, no overt loss of neurons was seen in the FD group either. Although a previous study had also shown loss of ICC in patients with FD,[13] our results extend that to include the neuronal and macrophage population and we are the first to report a head-to-head comparison in the 2 patient groups.

These findings have significant impact because patients with Gp and so-called functional disorders of the stomach represent a large component of clinical practice, affecting 10%–30% of the population.[14] These diagnoses are suspected in patients who present with chronic symptoms (typically exacerbated by a meal) including nausea,

vomiting, early satiety/fullness, bloating, and epigastric pain in the absence of any other condition that could account for them on routine clinical testing. Traditionally, these disorders have further been classified into 1 of 2 categories, based on the results of gastric emptying: Gp (if emptying is delayed) and FD (if emptying is normal). FD in turn, has 2 subtypes: postprandial distress syndrome and epigastric pain syndrome.

Although these classifications have become enshrined with time, it has been apparent that this approach remains unsatisfactory for several reasons, even prior to the current report. First, there is almost complete overlap between the symptoms of Gp and FD of the postprandial distress syndrome type.[2] Second, symptom severity correlates poorly, if at all, with delays in gastric emptying.[10] Further, trials with drugs that simply accelerate gastric emptying ("prokinetic" drugs) have generally failed to improve symptoms,[15] although a counterargument has been made recently.[16] Third, such a classification has led to a perspective that although Gp is an "organic" disease, FD is not; this has led to significant consequences for patients with FD, who often feel stigmatized or dismissed as having a "psychosomatic disorder" (often loosely interchanged with the term "functional" by many physicians) despite symptoms that can be disabling. In this regard, it is important to note that there were no differences in psychological scores between the 2 groups at baseline or at 48 weeks. On the other hand, there is considerable evidence to support common pathophysiologic mechanisms between the 2 conditions including impaired gastric accommodation and visceral hypersensitivity.[10,17] This has led many experts to consider blurring the distinction between them; as an example, up to a third of European patients diagnosed as having FD have delayed gastric emptying, albeit mild.[10] Our results reinforce the concept that gastric-emptying studies are of limited utility in patients presenting with symptoms suggestive of Gp/FD. However, we realize that this is an area of considerable controversy and corroborative studies by other investigators are encouraged to provide validation (or not) of this statement. At the same time, we would like to emphasize that we do believe that both Gp and FD represent neuromuscular disorders of the stomach even if gastric-emptying measurements do not capture the pathophysiology adequately. This also raises the question of the effectiveness of so-called "prokinetic" drugs; however, many of these drugs probably have effects on gastric motility beyond acceleration of gastric emptying and, therefore, may still have a therapeutic role.

This study has several limitations that can inform the interpretation of the results. First, the number of patients on whom full-thickness biopsies were performed is small, given the invasive nature of this procedure. In the future, the adoption of endoscopic procedures to obtain such tissue may provide an opportunity for further validation of these findings. It should also be noted that these patients presented with predominant nausea or vomiting, which is a subset of the larger group presenting with upper gastrointestinal symptoms. A second potential criticism of this study is that the patient cohort may be skewed in its phenotype because of the tertiary referral nature of the clinical sites. Thus, it is possible that patients with FD seen at such centers represent a far more severe phenotype than usual. However, just as there may be many "FD" patients in the community with less severe symptoms, there may also proportionately be as many patients with "Gp" who have equally mild symptoms. There is, therefore, no a priori reason to think that these patients with less severe symptoms (with or without delayed gastric emptying) comprise a distinct syndrome, as opposed to occupying a different position on the same spectrum. Nevertheless, we acknowledge this potential bias, which can only be settled by performing similar studies on patients that are more representative of those seen in the community. It should also be noted that our findings do not necessarily apply to other forms of secondary Gp such as that seen after fundoplication or Parkinson's disease. Finally, we acknowledge that the new Rome IV criteria may have classified these patients differently (eg, chronic idiopathic nausea) but regardless of the nomenclature, our results suggest that these patients share common clinical and pathologic features with Gp.

In conclusion, our results provide an important and unifying perspective on FD and Gp. We have shown that patients initially classified as one or the other are not distinguishable by clinical features or by follow-up assessment of gastric emptying, which is labile and does not capture the pathophysiologic basis of symptoms in these patients. Instead, both disorders are unified by characteristic pathologic features, best summarized as a macrophage-driven "cajalopathy" of the stomach. Future improvements in diagnostic ability may reveal subtle differences between these 2 syndromes but for now it is reasonable to conclude that FD and Gp are part of the same spectrum of pathologic ("organic") gastric neuromuscular dysfunction as has been previously suggested.[18] This has profound implications for our diagnostic and therapeutic approach to these patients and for future directions of research in disease etiology, pathogenesis, diagnosis, drug development, and therapy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2021.01.230.

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Conflicts of interest
The authors disclose no conflicts.

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