Received Date : 27-Jun-2015
Revised Date : 18-Jan-2016
Accepted Date : 21-Jan-2016
Article type : Original Article



# BASELINE FEATURES AND DIFFERENCES IN 48 WEEK CLINICAL OUTCOMES IN PATIENTS WITH GASTROPARESIS AND TYPE 1 VERSUS TYPE 2 DIABETES

**SHORT RUNNING TITLE:** COMPARING GASTROPARESIS BY DIABETIC SUBTYPE

Kenneth L. Koch (Section on Gastroenterology, Wake Forest University, Winston-Salem, NC), William L. Hasler (Division of Gastroenterology, University of Michigan, Ann Arbor, MI), Katherine P. Yates (Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD), Henry P. Parkman (Section of Gastroenterology, Temple University, Philadelphia, PA), Pankaj J. Pasricha (Center for Neurogastroenterology, Johns Hopkins Bayview Medical Center, Baltimore, MD), Jorge Calles-Escandon (Endocrinology Section, MetroHealth Medical Center, Cleveland, OH), William J. Snape (California Pacific Medical Center, San Francisco, CA), Thomas L. Abell (Digestive and Liver Health, University of Louisville, Louisville, KY), Richard W. McCallum (Division of Gastroenterology, Texas Tech University, El Paso, TX), Linda A. Nguyen (Division of Gastroenterology, Stanford University, Palo Alto, CA), Irene Sarosiek (Division of Gastroenterology, Texas Tech University, El Paso, TX), Gianrico Farrugia (Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN), James Tonascia, Linda Lee, Laura Miriel (Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD), and Frank Hamilton (National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD).

For the NIDDK Gastroparesis Clinical Research Consortium (GpCRC)

**ADDRESS CORRESPONDENCE TO:** William L. Hasler, MD
University of Michigan Health System
3912 Taubman Center, SPC 5362
Ann Arbor, MI 48109
Telephone: (734) 936-4780
FAX: (734) 936-7392
E-mail: whasler@umich.edu



**ABSTRACT**

**Background:** In studies of diabetic gastroparesis, patients with type 1 and type 2 diabetes (T1DM, T2DM) are often combined for analyses. We compared gastroparesis severity, healthcare utilization, psychological function, and quality of life in T1DM versus T2DM gastroparesis patients.

**Methods:** Questionnaire, laboratory, and scintigraphy data from patients with gastroparesis and T1DM and T2DM from seven centers of the NIDDK Gastroparesis Clinical Research Consortium (GpCRC) Registry were compared at enrollment and after 48 weeks. Multiple regression models assessed baseline and follow-up differences between diabetes subtypes**.**

**Key Results:** At baseline, T1DM patients (N=78) had slower gastric emptying, more hospitalizations, more gastric stimulator implantations, higher hemoglobin A1c (HbA1c), and more anxiety versus T2DM patients (N=59). Independent discriminators of patients with T1DM versus T2DM included worse GERD, less bloating, more peripheral neuropathy, and fewer comorbidities ($P \leq 0.05$). On follow-up, gastrointestinal (GI) symptom scores decreased only in T2DM ($P<0.05$), but not in T1DM patients who reported greater prokinetic, proton pump inhibitor, anxiolytic, and gastric stimulator usage over 48 weeks ($P \leq 0.03$). GI symptoms at

baseline and 48 weeks with both subtypes were not associated with HbA1c, peripheral neuropathy, psychological factors, or quality of life.

**Conclusions & Inferences:** Baseline symptoms were similar in T1DM and T2DM patients, even though T1DM patients had worse gastric emptying delays and higher HbA1c suggesting other factors mediate symptom severity. Symptom scores at 48 weeks decreased in T2DM but not T1DM patients, despite increased medical and surgical treatment utilization by T1DM patients. Defining causes of different outcomes in diabetic gastroparesis warrants further investigation.

**Key Words:** Gastroparesis, type 1 and type 2 diabetes mellitus, nausea and vomiting, hyperglycemia, gastric emptying.

**KEY MESSAGES**

- This study defined similarities and differences in gastroparesis severity, healthcare utilization, psychological function, and quality of life in patients with type 1 (T1DM) and type 2 (T2DM) diabetes mellitus and gastroparesis.
- At baseline enrollment into the NIDDK Gastroparesis Clinical Research Consortium Registry, T1DM patients had higher hemoglobin A1c (HbA1c) levels and more severe emptying delays, but the severity of GI symptoms was similar to those of patients with T2DM and gastroparesis.
- After 48 weeks of follow-up in the Registry, gastroparesis symptom scores significantly decreased in T2DM patients but not in T1DM patients despite increased use of prokinetic, acid suppressant, anxiolytic, and gastric electrical stimulation therapy in the T1DM group.
- Explanations for these differences in clinical outcomes at 48 weeks in patients with gastroparesis due to T1DM versus T2DM require further investigation.

## INTRODUCTION

Diabetic gastroparesis is associated with nausea, vomiting, fullness, bloating, early satiety, and epigastric discomfort/pain and is diagnosed by documenting delayed gastric emptying (1, 2, 3, 4, 5). However, emptying delays correlate poorly with symptoms, suggesting other pathogenic factors influence symptoms. These factors include: (i) chronic hyperglycemia, which acutely impairs gastric neuromuscular function; (ii) gastric factors ranging from impaired

fundic accommodation and gastric electrical dysrhythmias; and (iii) psychological dysfunction, which is prevalent in diabetic gastroparesis (6, 7, 8, 9, 10, 11, 12). Gastroparesis is thought to contribute to poor glycemic control which results in ketoacidosis and other complications that increase hospitalizations and outpatient visits and costs (13, 14). Longitudinal studies suggest diabetic gastroparesis follows an indolent course with stable gastrointestinal (GI) symptoms and emptying rates over 25 years, although increased mortality has been reported (15, 16, 17). Furthermore, a recently published study observed no differences in overall symptom improvements over 48 weeks in patients with diabetic versus idiopathic gastroparesis (18).

Type 1 diabetes (T1DM) from failed insulin production is distinct from Type 2 disease (T2DM) which is due to insulin resistance and variable insulin release deficits (19, 20). T1DM requires insulin therapy, while T2DM is managed with diet and oral medications in milder cases and insulin in more severe cases. Gastroparesis is reported in 27-58% of T1DM patients versus 20-40% with T2DM; the 10-year incidence of gastroparesis is five times higher with T1DM (5.2% vs. 1.0%)(21, 22, 23, 24). Gastroparesis is associated with increased hemoglobin A1c (HbA1c) levels and diabetic complications (retinopathy, neuropathy) in T1DM, while obesity status has been associated with symptoms in T2DM with gastroparesis (25, 26). Comprehensive comparisons of clinical profiles, comorbidities, disease severity, resource utilization, psychological dysfunction, quality of life, and clinical courses in patients with gastroparesis and T1DM versus T2DM have not been performed.

Our aim was to compare the clinical features of patients with gastroparesis and T1DM and T2DM at baseline enrollment into the NIDDK Gastroparesis Registry and after 48 weeks of follow-up during which time the patients' GI symptoms were managed by gastroenterologists at tertiary centers. We hypothesized that patients with T1DM gastroparesis at baseline have (i) more severe GI symptoms, (ii) more severely delayed gastric emptying, (iii) poorer glycemic control, (iv) more peripheral neuropathy, (v) more healthcare utilization, and (vi) more impaired psychological dysfunction and quality of life compared with patients with T2DM and gastroparesis. We further hypothesized that symptoms, psychological function, and quality of life would show similar longitudinal changes in both subtypes after 48 weeks of management.

## MATERIALS AND METHODS

**Patient Population:**

Seventy-eight patients with T1DM and 59 patients with T2DM and gastroparesis in the Gastroparesis Clinical Research Consortium (GpCRC) Registry were identified. Each patient completed validated surveys and underwent examinations and blood testing on enrollment and at 48-week follow-up visits from January 2007 to May 2011 (ClinicalTrials.gov Identifier: NCT00398801). All subjects reported symptoms associated with gastroparesis for at least 12 weeks duration (not necessarily contiguous weeks) and had gastroparesis defined by scintigraphy (>60% retention at 2 hours and/or >10% retention at 4 hours) within 6 months of enrollment (5). Prokinetics, opiates, anticholinergics, and other agents that affect gut transit were stopped at least 72 hours before gastric emptying testing. Upper endoscopy performed within 1 year of Registry enrollment showed no evidence of organic causes of symptoms. Patients with ulcers, malignancy, mechanical obstruction, active inflammatory bowel disease, eosinophilic gastroenteritis, neurologic disease, hepatic or renal disease, other metabolic disease, or prior gastroesophageal surgery were excluded. The determination of T1DM versus T2DM status and the diagnosis of diabetic gastroparesis were made by each site investigator based upon patient reports and review of records. Studies were approved by Institutional Review Boards at each Clinical Center and Data Coordinating Center. Patients provided written informed consent.

**Data Acquisition:**

Survey completion, examinations, and local laboratory blood testing were performed on enrollment and 48-week follow up visits. Demographic and medical information was collected on Registration and Baseline Medical History forms (Supplemental Methods), including self-reported clinician-diagnosed peripheral neuropathy. Body mass index (BMI) was calculated at both times from physical examination data; numbers and percentages who were overweight or obese ($\geq$25 kg/m$^2$) were calculated. Numbers and percentages with any comorbidity and numbers of comorbidities were determined on enrollment (Supplemental Methods). As inflammatory activation has been identified in some cases of gastroparesis, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured on enrollment as non-specific markers of inflammation (27); numbers and percentages with elevated CRP (>0.8 mg/dl) and ESR values (>20 mm/hr) were determined; any inflammation was defined as either an elevated CRP and/or

elevated ESR. Hemoglobin A1c (HbA1c) was quantified at both visits; numbers and percentages of patients with HbA1c values <8% vs. ≥8% were defined.

Gastroparesis severity was quantified in four ways: 1) investigator-rated gastroparesis severity was assessed on enrollment and at 48 weeks by each principal investigator using an expert consensus stratification (Supplemental Methods)(2); 2) Patient Assessment of Upper Gastrointestinal Disorders Symptoms (PAGI-SYM) questionnaires were used to quantify 20 individual symptoms that the patient scored from 0 (none) to 5 (most severe)(28); 3) overall symptom severity was determined by total scores from the Gastroparesis Cardinal Symptom Index (GCSI)(Supplemental Methods)(29); and 4) percentages of test meal retained at four hours from pre-enrollment scintigraphy studies were used to stratify results into mild (11-20%), moderate (21-35%), and severe (>35% retained) gastric emptying delays (30).

Medication use was queried on enrollment and at 48 weeks (Supplemental Methods). Numbers and percentages of T2DM patients taking antidiabetic medications known to cause nausea and vomiting were determined (25). Symptoms were compared in patients who were taking versus not taking these agents on enrollment.

Health utilization parameters were determined. On enrollment, patients reported how many times they were hospitalized over the prior year and for what reasons they were hospitalized. At 48 weeks, they were asked how many times they had required emergency department (ED) evaluation or hospitalization solely for gastroparesis since enrollment (excluding gastric electrical stimulator [GES] implantation). Numbers and percentages of patients on total parenteral nutrition (TPN) and who had undergone GES implantation were determined at baseline and 48 weeks.

Measures of psychological dysfunction and quality of life were quantified. Depression and anxiety were enumerated by the Beck Depression Inventory (BDI) and State and Trait Anxiety Inventory (STAI)(Supplemental Methods)(31, 32). Numbers and percentages with severe depression (BDI score >28), state anxiety (Y1 score ≥50), and trait anxiety (Y2 score ≥50) were calculated. Disease-specific and generic quality of life was assessed by Patient Assessment of Upper Gastrointestinal Disorders Quality of Life (PAGI-QOL) and Short Form-36v2 (SF-36v2) surveys, respectively (Supplemental Methods)(33, 34).

Enrollment (baseline) symptom scores were subtracted from 48-week values to calculate changes in all measures. Baseline BMI, HbA1c, hospitalizations for gastroparesis, patients on

TPN or undergoing GES, BDI, Y1, Y2, and quality of life scores were subtracted from 48-week levels to quantify changes. Numbers and percentages of patients on different medications at baseline were subtracted from 48-week values to estimate changes.

**Statistical Methodologies:**

Number and percentages or means ± SD were reported for enrollment categorical or continuous characteristics. P values were determined from Pearson chi-square or Fisher's exact tests for categorical characteristics and Kruskal-Wallis tests to account for non-normality of continuous distributions (35). Baseline discriminators of diabetes subtype were determined from backward stepwise multiple logistic modeling regressing diabetes subtype on the 46 baseline characteristics, forcing age at enrollment, sex, and white race into the model, with P for exclusion=0.05 (36). Total number rather than individual comorbidities was included; GCSI was excluded due to collinearity. Hosmer-Lemeshow testing revealed adequate fit for the model (P=0.71). Differences between patients completing 48-week follow up versus patients with only enrollment data were assessed using multiple logistic regression of 48-week completion on baseline characteristics (diabetes subtype, demographics, BMI, severity, medications [prokinetics, opiates, antidepressants], healthcare utilization, psychological function, quality of life). Mean changes ± SD at 48 weeks versus enrollment were computed for all characteristics except ED visits (not queried on enrollment). For continuous characteristics, P values were determined using one sample t-tests of the null hypothesis of no difference in means at both visits within diabetes subtype comparisons. For binary characteristics and medication changes, exact McNemar's tests for paired proportions were used to determine P and 95% confidence intervals (CI) which were computed using continuity corrections (37, 38). Multiple regression models of 48-week changes in continuous characteristics, adjusting for enrollment values, assessed changes between diabetes subtype (except for ED visits)(39). Negative binomial regressions (to account for overdispersion) of ED visits over 48 weeks on diabetes subtypes were used. Wald's tests using conditional logistic regression tested if 48-week changes in hospitalizations for gastroparesis or medication use varied by subtype (36). Unconditional exact logistic regression assessed TPN use and GES changes with T2DM. Relative odds of changes in 48-week outcomes were derived from logistic regression models of each indicator at 48 weeks in relation to subtype and enrollment value of the indicator. Models included propensity scores to

adjust diabetes subtype effects for probabilities of being T1DM based on age, sex, and race (40). Outcome indicators defined by 48-week changes from enrollment included any symptom score decrease, no change or decreased BMI, any HbA1c decrease, ≥5 point BDI decrease, any STAI decrease, and any QOL increase. Healthcare utilization reductions were defined as no hospitalizations or ED visits for gastroparesis over 48 weeks.

Given the exploratory nature of our study, P values were two-sided and nominal with significance at the P=0.05 level, *a priori*. Because a goal of these exploratory analyses was to generate new hypotheses to be tested in future confirmatory studies, correction for multiple comparisons was not performed. Such adjustments reduce the power of an investigation to define important differences, are unnecessary if exploratory research questions are unrelated, and are only required for studies which aim to offer decisive proof of a predefined hypothesis to endorse decision-making protocols (41, 42, 43). Stata (Stata Statistical Software, Release v12; StataCorp LP, College Station, TX) and SAS (version 9.3, SAS Institute, Inc., Cary, NC) software were employed.

## RESULTS

### Demographic and Clinical Factors at Baseline:

Demographic and clinical factors and comorbidities for the T1DM and T2DM patients with gastroparesis at baseline are shown in Table 1. T2DM patients with gastroparesis had several expected differences compared with T1DM patients. These T2DM patients were older at enrollment and at the onset of GI symptoms, had higher BMIs, and were more often overweight, obese, or postmenopausal (P<0.001). T1DM patients reported longer durations of diabetes prior to the onset of gastroparesis (P=0.005). On average, HbA1c levels were greater in T1DM patients by 0.9% (P=0.003); T1DM patients comprised larger proportions with HbA1c levels ≥8% (37/53, 69.8%) versus <8% (38/81, 46.9%)(P=0.009). Almost all T1DM (98.7%) and T2DM (98.3%) patients reported ≥1 comorbidity, but numbers of comorbidities were higher with T2DM (5.5±3.4 vs. 4.0±2.8)(P=0.005). Coronary and cerebrovascular disease and interstitial cystitis were significantly more common in T2DM patients (P≤0.05). T2DM patients more often underwent hysterectomies (P<0.001). Similar percentages of T1DM versus T2DM patients reported peripheral neuropathy (43.6% vs. 37.3%, P=0.46).

**Comparisons of Gastroparesis-Related Factors in T1DM versus T2DM at Baseline:**

***Gastroparesis Severity, GCSI Results, and Resource Utilization:***

The most severe symptoms reported by both T1DM and T2DM patients with gastroparesis were nausea and postprandial fullness. Patients with T1DM and gastroparesis were more often assigned by the investigator to the severe gastroparesis category (49% vs. 39%) and less to the mild category (6% vs. 16%) compared with T2DM patients (P=0.05)(Table 2A). However, patient-rated overall GCSI scores were similar in T1DM and T2DM patients (2.8$\pm$1.1 vs. 3.0$\pm$1.0, P=0.28). Individual GI symptoms were also similar, except for higher bloating symptoms in T2DM patients (P=0.04). More T1DM patients had delayed emptying at two hours (P=0.006) and four hours (P<0.001) after ingestion of the meal, and more T1DM patients had severe emptying delays (>35% 4 hour retention) compared with T2DM patients (54% vs. 32%, P=0.001).

Medication use from prokinetics to opiates was similar in the two subtypes, except T2DM patients had more metformin use (P<0.001). Nineteen of 59 T2DM gastroparetics (32%) used metformin on enrollment; none were on other antihyperglycemic agents (exenatide, liraglutide, pramlintide) that cause nausea. Overall, GI symptoms were similar in the T2DM patients who were taking metformin versus those patients not taking metformin (P=0.91), although vomiting scores on average were lower in the group receiving metformin at baseline by 1.0 point (P=0.04)(Supplemental Table 1).

T1DM patients reported more hospitalizations in the year before enrollment solely for gastroparesis (5.1$\pm$6.4 vs. 3.2$\pm$6.6, P=0.003), and were hospitalized more often for nausea and vomiting (P=0.001), abdominal pain (P=0.003), and dehydration (P=0.01) compared with T2DM patients (Table 2A). TPN use at baseline was similar in the T1DM and T2DM patients (P=0.78). More T1DM patients underwent GES implantation before enrollment in the GpCRC Registry (15% vs. 3%, P=0.02).

***Psychological Function and Quality of Life:***

More T1DM patients with gastroparesis reported severe state anxiety (Y1 score $\geq$50) (P=0.04) and though not significant, more severe trait anxiety (Y2 score $\geq$50)(P=0.06) compared

with T2DM patients. Other psychological survey, overall PAGI-QOL, individual PAGI-QOL domain, and SF-36v2 scores were similar in the two diabetes subtypes (Table 2A).

***Relationships Among Gastroparesis Factors, HbA1c Levels, and Peripheral Neuropathy on Subgroup Analysis:***

Table 2B shows investigator-rated severity of gastroparesis and patient-scored GCSI results in the two subgroups according to baseline HbA1c values <8% vs. ≥8% and the presence or absence of peripheral neuropathy. HbA1c groupings had no relationship to investigator ratings of gastroparesis severity, overall GCSI scores and individual GI symptom scores. Delays in gastric emptying at two or four hours were not related to HbA1c status (P=0.96 or P=0.79). GI symptom severities (except for postprandial fullness) were similar whether the T1DM and T2DM patients did or did not report peripheral neuropathy. Investigator-rated gastroparesis severity and delays in gastric emptying were similar regardless of peripheral neuropathy status.

***Characteristics that Discriminated Patients with Gastroparesis and T1DM Versus T2DM at Baseline:***

Forty-six baseline predictors were used in regression analyses to determine clinical characteristics that distinguished the T1DM and T2DM patients. Few baseline characteristics discriminated the subtypes (Table 3). Compared with T2DM gastroparesis patients, T1DM patients were about one-third less likely to have more severe bloating (OR=0.62, P=0.02) and almost twice as likely to have GERD symptoms (OR=1.70, P=0.02). T1DM patients were younger ($OR_{Age\geq 50\ yrs}$=0.07, P<0.001), had more peripheral neuropathy (OR=3.81, P=0.02), had more than 9 times the odds of normal or underweight status (OR=0.11, P<0.001), and reported approximately 25% fewer numbers of comorbidities (OR=0.76, P=0.02) than T2DM patients with gastroparesis.

**Clinical Factors at 48 Weeks:**

Ninety of 137 enrolled patients (66%) completed the 48 week visit: 44 patients with T1DM (56% of baseline cohort) and 46 patients with T2DM (79% of the baseline cohort). Compared to those with only enrollment data, patients completing follow-up were more often male, white race and overweight and less likely to have GES surgery (P≤0.05); diabetic subgroup

was not associated with completing follow-up with adjustment for all other characteristics (OR T1DM vs. T2DM=0.35, P=0.09)(Supplemental Table 2).

BMI did not change significantly over the 48 weeks in these T1DM and T2DM patients as shown in Table 4. HbA1c levels increased similarly, but not significantly, compared with baseline over the 48 weeks in both T1DM and T2DM patients (P=0.51). Three patients with T1DM and one with T2DM died during the 48-week period.

**Comparisons of Gastroparesis-Related Factors in T1DM versus T2DM at 48 Weeks:**

***Gastroparesis Severity, GCSI Results, and Resource Utilization:***

GI symptom severity did not decrease at 48 weeks in the patients with T1DM as measured by GCSI and individual scores (Figure 1A). In contrast, overall GCSI scores and all individual symptoms (except postprandial fullness and visible distention) decreased significantly at 48 weeks in the T2DM patients (Figure 1B). Figure 1C shows the changes in patient-reported symptoms (±95% CI) at 48 weeks for both subtypes. Investigator-rated gastroparesis severity ratings showed similar reductions from baseline within T1DM (mean change=-0.33, P=0.009) and T2DM (mean change=-0.30, P=0.02) patients; however, these changes were not different between the subtypes ($P_{T1DM\ vs\ T2DM}$=0.23)(Table 4).

Increased use of prokinetic drugs (+15.9%), proton pump inhibitor/other GI agents (+13.6%), and anxiolytic drugs (+25.0%) was recorded in T1DM patients (P≤0.03), whereas increased use of opiates (+17.4%) was documented in T2DM patients (P=0.04) at 48 weeks compared with baseline (Table 4). Percentages of patients hospitalized for gastroparesis during the 48-week follow-up decreased 15.1% in the T1DM patients (P=0.04), but did not significantly change for T2DM patients; however, decreases in hospitalizations for T1DM versus T2DM patients were not significantly different (P=0.26). Numbers of ED visits and changes in TPN use over 48 weeks were not different between diabetes subtypes. Implantation of GES devices increased 20.5% over 48 weeks in patients with T1DM (P=0.01) and increased 10.9% in T2DM patients (P=0.06). Including those who were implanted before enrollment, more T1DM patients were receiving GES after 48 weeks of follow-up compared with patients with T2DM and gastroparesis (31.9% vs. 10.9%)(P=0.02).

***Psychological Function and Quality of Life:***

No changes in any psychological or quality of life parameter in either subtype or between subtypes were observed at 48 weeks of follow-up (Table 4).

***Factors Associated with Changes in Gastroparesis-Related Outcomes at 48-Weeks:***

Multiple regression analyses were used to assess the relationship of eight clinical factors to outcomes at 48 weeks in the T1DM and T2DM groups with gastroparesis (Table 5). T1DM patients were less likely to report decreased vomiting (OR =0.21, 95% CI: 0.05-0.87; P=0.03), but more likely to have reductions in loss of appetite scores (OR=4.25, 95% CI: 1.07-16.92; P=0.04) compared to T2DM patients. When data from both diabetic subtypes were pooled, no reduction in any parameter of gastroparesis severity was related to initial HbA1c levels or presence of peripheral neuropathy on enrollment (Supplemental Table 3). Except for decreases in abdominal pain scores in T2DM patients whose HbA1c increased over 48 weeks (P=0.02), changes in symptom severity over 48 weeks were similar in T1DM and T2DM patients whose HbA1c levels either worsened or decreased (Supplemental Table 4). Reduction or no reduction in HbA1c levels did not vary significantly between diabetic subgroups over the 48 week period (data not shown).

## DISCUSSION

Our findings delineate many clinical similarities in patients with T1DM and T2DM and gastroparesis and confirm several demographic differences. GI symptoms rated at baseline were remarkably similar in intensity between diabetic subtypes, including nausea and stomach fullness, with only greater bloating in T2DM patients and increased GERD in T1DM patients being significantly different. Our results also showed the HbA1c levels and the severity of gastric emptying delay did not correlate with the symptoms associated with gastroparesis in either patients with T1DM or T2DM; even though gastric retention severity was higher in T1DM, symptoms were not correspondingly increased at enrollment.

The poor relation of symptom severity to gastric emptying in T1DM versus T2DM patients is consistent with recent literature, and suggests other pathophysiologic abnormalities mediate GI symptom genesis (8, 44). Factors such as poor fundic accommodation, heightened

sensitivity to gastric distention, gastric dysrhythmias, and pyloric dysfunction warrant study as potential causes of GI symptoms associated with diabetic gastroparesis (45, 46, 47).

Despite reporting similar GI symptom intensity as T2DM patients, hospitalizations for gastroparesis and for GES implantations were higher in T1DM patients at baseline. It is likely that factors other than gastrointestinal symptoms such as poor glycemic control, as well as dehydration and electrolyte disturbances brought on by acute vomiting may be more relevant drivers of hospitalizations in T1DM patients. Despite this greater resource use in T1DM, overall medication use profiles and quality of life scores were similar to T2DM gastroparetics at baseline.

The clinical perception that patients with T1DM and gastroparesis are frequently underweight is not supported by our findings. We found almost half of T1DM patients with gastroparesis were overweight or obese and only 3% were underweight, while T2DM patients with gastroparesis were even heavier as in prior reports (19, 20). Baseline TPN use was noted by less than 10% of patients in both subgroups reflecting the ability of most patients to sustain intake by oral or enteral routes. However, these findings do not rule out significant nutritional impairments. Our group previously reported mean daily caloric intakes of less than 1200 calories with deficiencies in essential nutrients including vitamin $B_6$, vitamin K, and iron in patients with gastroparesis (48).

An infectious prodrome was noted in 14% of T1DM and T2DM patients. A similar incidence of infectious prodrome has been observed with idiopathic gastroparesis, suggestive of a potential viral etiology in these non-diabetic patients (8). The role of infections as cofactors in triggering the onset of diabetic gastroparesis could be the focus of additional study.

A new finding of this investigation is the difference in gastrointestinal symptoms in the two groups at the 48 week follow up visits. Symptom scores decreased only in the T2DM patients while symptom severity was mostly unchanged in those with T1DM. It is possible the lack of reduction in GI symptom scores at 48 weeks in T1DM patients may reflect irreversible diabetes-related damage to the stomach wall. However, in ultrastructural studies from full thickness gastric biopsies, no differences were observed in the loss of enteric neurons, depletion of interstitial cells of Cajal, or in myenteric immune cell infiltration in specimens from T1DM versus T2DM patients (49). This differential outcome in GI symptoms in T1DM versus T2DM patients occurred despite aggressive management over the 48 weeks of follow-up. Patients with

T1DM more often were prescribed prokinetic agents, proton pump inhibitors, and anxiolytics, and had more GES implants compared with T2DM patients. These interventions had little positive impact on symptoms in the T1DM subgroup, suggesting these patients had a refractory and end-stage condition. However, investigator ratings of gastroparesis severity improved in both diabetic groups at 48 weeks; it is possible this divergence of clinician and patient ratings stemmed from decreases in hospitalizations observed in the T1DM patients. Nevertheless, future studies of investigational therapies of diabetic gastroparesis may need to consider differential responses in the two subtypes.

Our results showed no relationship between HbA1c levels and patient-reported GCSI scores or investigator-rated gastroparesis severity at 48 weeks. Furthermore, the decrease in GI symptoms reported by the T2DM patients occurred even though HbA1c values increased slightly over the 48 weeks. Thus, chronic glycemic control did not appear to influence GI symptoms in either group of diabetic patients with gastroparesis. Efforts for tighter glycemic control in patients with long-standing diabetes are important for many reasons, but these findings suggest that symptom reductions (particularly in T2DM patients) can occur without improved glucose control. Ongoing studies employing intensive insulin therapy will more rigorously determine if improved glycemia has additional symptom benefits. Although the presence of peripheral neuropathy was a discriminator of gastroparesis in T1DM versus T2DM on regression analysis, neuropathy did not relate to GCSI scores suggesting that peripheral and visceral complications of diabetes may not necessarily be linked. This finding also raises the possibility that gastroparesis in diabetes is not primarily neuropathic in origin, as suggested by histopathologic investigations performed by the GpCRC (26).

Medication use over 48 weeks differed in the diabetic subtypes. Nearly half of the patients in the subgroups were receiving opioid agents at baseline, but T2DM patients more often were given new opiate prescriptions over 48 weeks of follow up. Abdominal pain is the predominant symptom in 20% of gastroparesis patients, irrespective of etiology (4). The mechanisms for abdominal pain and the reasons for starting narcotics in T2DM patients are likely to be multifactorial; these could not be discerned from our analyses. In general, opiates slow gastric emptying and may worsen symptoms associated with gastroparesis. However, the reductions in GI symptom scores in the T2DM patients suggest that narcotics did not adversely affect these patients from an overall perspective. Many oral antidiabetic drugs such as

metformin can cause nausea and vomiting (25). Unexpectedly, metformin use was actually associated with less vomiting in T2DM patients. Nevertheless, metformin intake should be considered among the causes of unexplained GI symptoms in T2DM patients.

Psychological dysfunction and quality of life are poor in patients with gastroparesis (11). These measures were equally poor in T1DM and T2DM patients at baseline, although more T1DM patients had severe anxiety. Psychological and quality of life parameters remained unchanged at 48 weeks of follow-up despite decreases in GI symptom scores in gastroparesis patients with T2DM. These findings suggest that GI symptom severity is not the only factor influencing either psychological distress or poor quality of life, at least in T2DM patients.

GES therapy was employed more often for gastroparesis in T1DM patients compared to T2DM patients, but the T1DM group did not report a decrease in GI symptoms. Although differences did not reach significance, GES use also was higher over 48 weeks in the T2DM patients (change=11%, P=0.06). GES therapy decreases nausea and vomiting in some but not all studies of diabetic gastroparesis (50). Future controlled investigations assessing GES efficacy in diabetic gastroparesis should be performed to contrast benefits in T1DM versus T2DM patients.

Our study had some limitations. First, determination of diabetic subtype was dependent on subject report and review of the medical records by the investigator. Second, referral bias may have influenced the findings because the patients were referred to the tertiary motility centers of the GpCRC. Thus, our patients may not reflect typical patients managed in the community and they may have had clinical features that were unfavorable for symptom reductions over 48 weeks of follow up. However, given the similarities in baseline GI symptoms in the T1DM and T2DM patients, it is likely referral bias was similar for both diabetic subtypes. Nevertheless, more T1DM patients had GES therapy which probably reflects the refractory nature of symptoms in this group. Third, assessments of healthcare utilization did not include costs or address length of stay, outpatient visits, and missed work. Fourth, 48 weeks may be an inadequate time period to detect symptom score reductions in T1DM patients or differentiate resource utilization. The numbers of patients available for study at 48 weeks may have precluded some smaller differences not being detected; however, our study had 80% power to detect a minimal difference of 0.6 SD units in GCSI between the two subtypes. Finally, we had some concerns about non-significant trends to higher dropouts over 48 weeks of follow-up in the T1DM patients. Although several minor differences were observed in patients who did versus

did not attend their 48 study visits, the lack of relation of 48 week visit attendance and GCSI scores, diabetes subtype, and hospitalizations confirmed that the different outcomes of T1DM and T2DM patients were not due to differential study compliance. We believe these limitations are countered by the significant strengths of the study including the large numbers of patients with gastroparesis and T1DM and T2DM, use of standardized tests and protocols and comprehensive collection of clinical, psychological, quality of life, and healthcare usage data.

In conclusion, our findings challenge several clinical axioms about gastroparesis in the two diabetic subtypes. First, baseline gastrointestinal symptoms associated with gastroparesis were remarkably similar in T1DM versus T2DM patients, even though T1DM patients had more severe gastric emptying delays and higher hemoglobin A1c values. These observations suggest the presence of other gastric or extragastric pathogenic factors may mediate gastroparesis symptom severity. Second, symptoms associated with gastroparesis in both diabetic subtypes did not correlate with HbA1c levels or severity of gastroparesis; and last, after 48 weeks of follow-up, most GI symptom scores decreased only in T2DM patients even though T1DM patients showed increased medical and surgical treatment utilization. These similarities and differences in patients with T1DM and T2DM form a basis for further research to improve clinical outcomes with novel drugs, gastric stimulation parameters, and insulin dosing regimens for symptoms associated with gastroparesis.

**ACKNOWLEDGMENTS, FUNDING, AND DISCLOSURES**

**Members of the Gastroparesis Clinical Research Consortium:**

***Clinical Centers:***

*Johns Hopkins University, Baltimore, MD:* Pankaj Jay Pasricha, MD (Principal Investigator); John Clarke, MD; Yale Kim, MHS MS

*Stanford University, Stanford, CA:* Linda Nguyen, MD (Principal Investigator); Nighat Ullah, MD

*California Pacific Medical Center, San Francisco, CA:* William Snape, MD (Principal Investigator); Nata DeVole, RN; Mary Greene (2009-2011); Candice Lee; Courtney Ponsetto (2009-2010); Katerina Shetler, MD

*Temple University, Philadelphia, PA:* Henry P. Parkman, MD (Principal Investigator); Steven Kantor; Vanessa Lytes, MSN CRNP; Amiya Palit, MD; Kellie Simmons, NP

*Texas Tech University Health Sciences Center, El Paso, TX:* Richard W. McCallum, MD (Principal Investigator); Reza Hejazi, MD (2009-2011); Kathy Roeser (2008-2009); Irene Sarosiek, MD; Denise Vasquez, RN; Natalia Vega, RN

*University of Louisville, Louisville, KY:* Thomas Abell, MD (Principal Investigator); Karen Beatty, RN; Lisa Hatter, RN; Ronna Howard; Lindsay Nowotny, PA-C

*University of Mississippi Medical Center, Jackson, MS:* Shou Tang, MD (Principal Investigator); Om S Amin, MD (2010-2011); Olivia Henry, MS RD; Archana Kedar, MD; Valerie McNair (2008-2012); Susanne Pruett, RN (2007-2008); Margaret Smith, RN; Danielle Spree, RN (2007-2010)

*University of Michigan, Ann Arbor, MI:* William Hasler, MD (Principal Investigator); Michelle Castle (2008-2011); Radoslav Coleski, MD (2007-2009); Sophanara Wootten

*Wake Forest University, Winston-Salem, NC:* Kenneth Koch, MD (Principal Investigator); Lynn Baxter; Anya Brown; Samantha Culler (2009-2012); Judy Hooker; Paula Stuart, PA

***Resource Centers:***

*Mayo Clinic College of Medicine (Pathology Analyses Center), Rochester, MN:* Gianrico Farrugia, MD (Principal Investigator); Cheryl Bernard, Matthew Lurken

*MetroHealth Medical Center, Cleveland, OH:* Jorge Calles-Escandon, MD

*National Institute of Diabetes, Digestive and Kidney Diseases, Bethesda, MD:* Jose Serrano, MD, PhD (Program Official); Frank Hamilton, MD, MPH (Project Scientist); Steven James, MD; Rebecca Torrance, RN MSN; Rebekah Van Raaphorst, MPH

*Johns Hopkins University, Bloomberg School of Public Health (Data Coordinating Center), Baltimore, MD:* James Tonascia, PhD (Principal Investigator); Patricia Belt; Erin Corless Hallinan, MHS; Ryan Colvin, MPH (2007-2010); Michele Donithan, MHS; Mika Green, MA (2009-2012); Milana Isaacson; Wana Kim (2009-2011); Linda Lee, MD; Patrick May, MS; Laura Miriel; Alice Sternberg, ScM; Mark Van Natta, MHS; Ivana Vaughn, MPH; Laura Wilson, ScM; Katherine Yates, ScM

**Specific Author Contributions:**

| | |
|---|---|
| Kenneth L. Koch: | Study design, subject recruitment, data collection, data analysis, manuscript preparation, approval of final manuscript version |
| William L. Hasler: | Study design, subject recruitment, data collection, data analysis, manuscript preparation, approval of final manuscript version |
| Katherine P. Yates: | Study design, statistical analysis, manuscript preparation, approval of final manuscript version |
| Henry P. Parkman: | Study design, subject recruitment, data collection, contribution to manuscript preparation, approval of final manuscript version |
| Pankaj J. Pasricha: | Study design, subject recruitment, data collection, contribution to manuscript preparation, approval of final manuscript version |
| Jorge Calles-Escandon: | Study design, contribution to manuscript preparation, approval of final manuscript version |
| William J. Snape: | Study design, subject recruitment, data collection, contribution to manuscript preparation, approval of final manuscript version |
| Thomas L. Abell: | Study design, subject recruitment, data collection, contribution to manuscript preparation, approval of final manuscript version |

| | |
|---|---|
| Richard W. McCallum: | Study design, subject recruitment, data collection, contribution to manuscript preparation, approval of final manuscript version |
| Linda A. Nguyen: | Study design, subject recruitment, data collection, contribution to manuscript preparation, approval of final manuscript version |
| Irene Sarosiek: | Study design, subject recruitment, data collection, contribution to manuscript preparation, approval of final manuscript version |
| Gianrico Farrugia: | Study design, contribution to manuscript preparation, approval of final manuscript version |
| James Tonascia: | Study design, statistical analysis, contribution to manuscript preparation, approval of final manuscript version |
| Linda Lee: | Study design, statistical analysis, contribution to manuscript preparation, approval of final manuscript version |
| Laura Miriel: | Contribution to manuscript preparation, approval of final manuscript version |
| Frank Hamilton: | Study design, grant administration, contribution to manuscript preparation, approval of final manuscript version |



**Funding:**

This project received support from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (grants U01DK073983, U01DK073975, U01DK073985, U01DK074007, U01DK073974, U01DK074008) as part of its funding of the Gastroparesis Clinical Research Consortium.

**Disclosures:**

None of the authors report any financial, professional, or personal conflicts of interest that are relevant to this manuscript.

**Competing Interests:**

The authors have no competing interests.



**REFERENCES**


1. Camilleri M. Clinical practice. Diabetic gastroparesis. *N Engl J Med* 2007; **356**: 820-29.
2. Abell TL, Bernstein VK, Cutts T, Farrugia G, Forster J, Hasler WL, McCallum RW, Olden KW, *et al*. Treatment of gastroparesis: a multidisciplinary clinical review. *Neurogastroenterol Motil* 2006; **18**: 263-83.
3. Hasler WL, Wilson LA, Parkman HP, Nguyen L, Abell TL, Koch KL, Pasricha PJ, Snape WJ, *et al*. Bloating in gastroparesis: severity, impact, and associated factors. *Am J Gastroenterol* 2011; **106**: 1492-502.
4. Hasler WL, Wilson LA, Parkman HP, Koch KL, Abell TL, Nguyen L, Pasricha PJ, Snape WJ, *et al*. Factors related to abdominal pain in gastroparesis: contrast to patients with predominant nausea and vomiting. *Neurogastroenterol Motil* 2013; **25**: 427-38.
5. Tougas G, Eaker EY, Abell TL, Abrahamsson H, Boivin M, Chen J, Hocking MP, Quigley EM, *et al*. Assessment of gastric emptying using a low fat meal: establishment of international control values. *Am J Gastroenterol* 2000; **95**: 1456-62.
6. Pasricha PJ, Colvin R, Yates K, Hasler WL, Abell TL, Unalp-Arida A, Nguyen L, Farrugia G, *et al*. Characteristics of patients with chronic nausea and vomiting and normal gastric emptying. *Clin Gastroenterol Hepatol* 2011; **9**: 567-76.
7. Janssen P, Harris MS, Jones M, Masaoka T, Farré R, Törnblom H, Van Oudenhove L, Simrén M, *et al*. The relation between symptom improvement and gastric emptying in the treatment of diabetic and idiopathic gastroparesis. *Am J Gastroenterol* 2013; **108**: 1382-91.
8. Soykan I, Sivri B, Sarosiek I, Kiernan B, McCallum RW. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow up of patients with gastroparesis. *Dig Dis Sci* 1998; **43**: 2398-404.
9. Fraser RJ, Horowitz M, Maddox AF, Harding PE, Chatterton BE, Dent J. Hyperglycemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1990; **33**: 675-80.

10. Hebbard GS, Samsom M, Sun WM, Dent J, Horowitz M. Hyperglycemia affects proximal gastric motor and sensory function during small intestinal triglyceride infusion. *Am J Physiol* 1996; **271**: G814-9.
11. Hasler WL, Parkman HP, Wilson LA, Pasricha PJ, Koch KL, Abell TL, Snape WJ, Farrugia G, *et al*. Psychological dysfunction is associated with symptom severity but not disease etiology or degree of gastric retention in patients with gastroparesis. *Am J Gastroenterol* 2010; **105**: 2357-67.
12. Kashyap P, Farrugia G. Diabetic gastroparesis: what we have learned and had to unlearn in the past 5 years. *Gut* 2010; **59**: 1716-26.
13. Ramzan Z, Duffy F, Gomez J, Fisher RS, Parkman HP. Continuous glucose monitoring in gastroparesis. *Dig Dis Sci* 2011; **56**: 2646-55.
14. Hyett B, Martinez FJ, Gill BM, Mehra S, Lembo A, Kelly CP, Leffler DA. Delayed radionucleotide gastric emptying studies predict morbidity in diabetics with symptoms of gastroparesis. *Gastroenterology* 2009; **137**: 445-52.
15. Jung HK, Choung RS, Locke GR, Schleck CD, Zinsmeister AR, Szarka LA, Mullan B, Talley NJ. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmstead County, Minnesota, from 1996 to 2006. *Gastroenterology* 2009; **136**: 1225-33.
16. Jones KL, Russo A, Berry MK, Stevens JE, Wishart JM, Horowitz M. A longitudinal study of gastric emptying and upper gastrointestinal symptoms in patients with diabetes mellitus. *Am J Med* 2002; **113**: 449-55.
17. Chang J, Rayner CK, Jones KL, Horowitz M. Prognosis of diabetic gastroparesis—a 25 year evaluation. *Diabet Med* 2013; **30**: e185-8.
18. Pasricha PJ, Yates KP, Nguyen L, Clarke J, Abell TL, Farrugia G, Hasler WL, Koch KL, *et al*. Outcomes and factors associated with reduced symptoms in patients with pastroparesis. *Gastroenterology* 2015; doi: 10.1053/j.gastro.2015.08.008.
19. Daneman D. Type 1 diabetes mellitus. *Lancet* 2006; **367**: 847-58.
20. Lyssenko V, Jonsson A, Almgren P, Pulizzi N, Isomaa B, Tuomi T, Berglund G, Altshuler D. Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N Engl J Med* 2008; **359**: 2220-32.

21. Horowitz M, Maddox AF, Wishart JM, Harding PE, Chatterton BE, Shearman DJ. Relationships between esophageal transit and solid and liquid gastric emptying in diabetes mellitus. *Eur J Nuc Med* 1991; **18**: 229-34.
22. Keshavarzian A, Iber FL, Vaeth J. Gastric emptying in patients with insulin-requiring diabetes mellitus*. Am J Gastroenterol* 1987; **82**: 29-35.
23. Horowitz M, Harding PE, Maddox AF, Wishart JM, Akkermans LM, Chatterton BE, Shearman DJ. Gastric and esophageal emptying in patients with type 2 (noninsulin-dependent) diabetes mellitus. *Diabetologia* 1989; **32**: 151–9.
24. Choung RS, Locke GR, Schleck CD, Zinsmeister AR, Melton LJ, Talley NJ. Risk of gastroparesis in subjects with type 1 and type 2 diabetes in the general population. *Am J Gastroenterol* 2012; **107**: 82-8.
25. Dickman R, Kislov J, Boaz M, Ron Y, Beniashvili Z, Raz I, Baigel I, Niv Y, *et al*. Prevalence of symptoms suggestive of gastroparesis in a cohort of patients with diabetes mellitus. *J Diab Comp* 2013; **27**: 376-9.
26. Kofod-Andersen K, Tarnow L. Prevalence of gastroparesis-related symptoms in an unselected cohort of patients with type 1 diabetes. *J Diab Comp* 2012; **26**: 89-93.
27. Grover M, Farrugia G, Lurken MS, Bernard CE, Faussone-Pellegrini MS, Smyrk TC, Parkman HP, Abell TL, *et al*. Cellular changes in diabetic and idiopathic gastroparesis. *Gastroenterology* 2011; **140**: 1575-85.
28. Rentz AM, Kahrilas P, Stanghellini V, Tack J, Talley NJ, de la Loge C, Trudeau E, Dubois D, *et al*. Development and psychometric evaluation of the patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM) in patients with upper gastrointestinal disorders. *Qual Life Res* 2004; **13**: 1737-49.
29. Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, Tack J. Development and validation of a patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. *Aliment Pharmacol Ther* 2003; **18**: 141-50.
30. Abell TL, Camilleri M, Donohoe K, Hasler WL, Lin HC, Maurer AH, McCallum RW, Nowak T, *et al*. Consensus recommendations for gastric emptying scintigraphy. A joint report of the Society of Nuclear Medicine and The American Neurogastroenterology and Motility Society. *Am J Gastroenterology* 2008; **103**: 753-63.

31. Richter P, Werner J, Heerlein A, Kraus A, Sauer H. On the validity of the Beck Depression Inventory. A review. *Psychopathology* 1998; **31**: 160–8.
32. Spielberger C, Gorsuch R, Lushene R. Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press, 1970.
33. De la Loge C, Trudeau E, Marquis P, Kahrilas P, Stanghellini V, Talley NJ, Tack J, Revicki DA, *et al*. Cross-cultural development and validation of a patient self-administered questionnaire to assess quality of life in upper gastrointestinal disorders: the PAGI-QOL. *Qual Life Res* 2004; **13**: 1751-62.
34. Ware JE, Kosinski M, Dewey JE. How to score version 2 of the SF-36® Health Survey. QualityMetric Incorporated, 2000.
35. Agresti A. Categorical Data Analysis, Second Edition. John Wiley and Sons, Inc., 2002.
36. Hosmer DW, Lemeshow S. Applied Logistic Regression, Second Edition. John Wiley and Sons, Inc., 2000.
37. McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika* 1947; **12**: 153-7.
38. Fleiss JL, Leven B, Paik MC. Statistical Methods for Rates and Proportions, Third Edition. John Wiley and Sons, Inc., 2003: 374-80.
39. Draper N, Smith H. Applied Regression Analysis, Third Edition. John Wiley and Sons, Inc., 1998.
40. Rosenbaum PR. Observational Studies, Second Edition. Springer, 2010.
41. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ* 1998; **316:** 1236-8.
42. Cao J, Zhang S. Multiple comparison procedures. *JAMA* 2014; **312:** 543-4.
43. Bender R, Lange S. Adjusting for multiple testing: when and how? *J Clin Epidemiol* 2001; **54:** 343-9.
44. Parkman HP, Yates K, Hasler WL, Nguyen L, Pasricha PJ, Snape WJ, Farrugia G, Koch KL, *et al*. Similarities and differences between diabetic and idiopathic gastroparesis. *Clin Gastroenterol Hepatol* 2011; **9**: 1056-64.
45. Kumar A, Attaluri A, Hashmi S, Schulze KS, Rao SS. Visceral hypersensitivity and impaired accommodation in refractory diabetic gastroparesis. *Neurogastroenterol Motil* 2008; **20**: 635-42.

46. Koch KL, Stern RM, Stewart WR, Vasey MW. Gastric emptying and gastric myoelectrical activity in patients with diabetic gastroparesis: effect of long-term domperidone treatment. *Am J Gastroenterol* 1989; **84**: 1069-75.
47. Mearin F, Camilleri M, Malagelada JR. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. *Gastroenterology* 1986; **90**: 1919-25.
48. Parkman HP, Yates KP, Hasler WL, Nguyan L, Pasricha PJ, Snape WJ, Farrugia G, Calles J, *et al.* Dietary intake and nutritional deficiencies in patients with diabetic or idiopathic gastroparesis. *Gastroenterology* 2011; **141**: 486-98.
49. Grover M, Bernard CE, Pasricha PJ, Lurken MS, Faussone-Pellegrini MS, Smyrk TC, Parkman HP, Abell TL, *et al*. Clinical-histological associations in gastroparesis: results from the Gastroparesis Clinical Research Consortium. *Neurogastroenterol Motil* 2012; **24**: 531-9.
50. Hasler WL. Methods of gastric electrical stimulation and pacing : a review of their benefits and mechanisms of action in gastroparesis and obesity. *Neurogastroenterol Motil* 2009; **21** : 229-43.
1.

**ABBREVIATIONS**

GpCRC—Gastroparesis Clinical Research Consortium
T1DM—type 1 diabetes mellitus
T2DM—type 2 diabetes mellitus
NIDDK—National Institute of Diabetes and Digestive and Kidney Diseases
HbA1c—hemoglobin A1c
GERD—gastroesophageal reflux disease
GI—gastrointestinal
BMI—body mass index
CRP—C-reactive protein
ESR—erythrocyte sedimentation rate
PAGI-SYM—Patient Assessment of Upper Gastrointestinal Disorders Symptoms
GCSI—Gastroparesis Cardinal Symptom Index
ED—emergency department

GES—gastric electrical stimulator

TPN—total parenteral nutrition

BDI—Beck Depression Inventory

STAI—State and Trait Anxiety Inventory

PAGI-QOL—Patient Assessment of Upper Gastrointestinal Disorders Quality of Life

SF-36v2—Short Form-36v2



## TABLES

**Table 1: COMPARISON OF BASELINE DEMOGRAPHIC AND CLINICAL FACTORS IN T1DM VERSUS T2DM**

| Category | Characteristic | | Type 1 Diabetics (N=78) | | Type 2 Diabetics (N=59) | | P Value* |
|---|---|---|---|---|---|---|---|
| | | | N | % or Mean±SD | N | % or Mean±SD | |
| Demographic/ Clinical | Demographic | Female sex | 55 | 70.5% | 45 | 76.3% | 0.56 |
| | | Age (years) | 78 | 39±11 | 59 | 53±11 | ***<0.001*** |
| | | White race | 60 | 76.9% | 45 | 76.3% | 1.00 |
| | | Hispanic ethnicity | 7 | 9.0% | 5 | 8.5% | 1.00 |
| | | Married | 42 | 53.9% | 38 | 64.4% | 0.23 |
| | | College degree | 15 | 19.2% | 12 | 20.3% | 1.00 |
| | | Income >$50K | 36 | 46.2% | 25 | 42.4% | 0.73 |
| | | Ever smoked regularly | 23 | 29.5% | 23 | 39.0% | 0.28 |
| | Medical History | Age at symptom onset (years) | 78 | 34±10 | 59 | 49±11 | ***<0.001*** |
| | | Time from diabetes onset to initial symptoms (years) | 78 | 14.0±11.0 | 59 | 8.4±8.0 | ***0.005*** |
| | | Symptom duration (years) | 78 | 6.2±6.3 | 59 | 3.9±3.3 | 0.13 |
| | | Peripheral neuropathy | 34 | 43.6% | 22 | 37.3% | 0.46 |
| | | Acute onset | 46 | 59.0% | 27 | 45.8% | 0.11 |
| | | Initial infectious prodrome | 11 | 14.1% | 8 | 13.6% | 1.00 |
| | | Postmenopausal (if female) | 12 | 21.8% | 28 | 62.2% | ***<0.001*** |
| | Anthropometric | BMI ($kg/m^2$) | 78 | 26±6 | 59 | 33±8 | ***<0.001*** |
| | | Underweight | 2 | 3% | 0 | 0% | ***<0.001*** |
| | | Normal | 37 | 47% | 8 | 14% | |
| | | Overweight or obese | 39 | 50% | 51 | 86% | |
| | Laboratory | CRP (mg/dl) | 78 | 0.9±1.5 | 58 | 0.7±0.6 | 0.10 |

| Category | Characteristic | | Type 1 Diabetics (N=78) | | Type 2 Diabetics (N=59) | | P Value* |
|---|---|---|---|---|---|---|---|
| | | | N | % or Mean±SD | N | % or Mean±SD | |
| | | CRP elevated >0.8 mg/dl | 20 | 25.6% | 19 | 32.8% | 0.36 |
| | | ESR (mm/hr) | 78 | 26±24 | 59 | 28±25 | 0.53 |
| | | ESR elevated >20 mm/hr | 37 | 47.4% | 30 | 50.9% | 0.69 |
| | | Hemoglobin A1c (%) | 78 | 8.3±2.0 | 59 | 7.4±1.7 | ***0.003*** |
| Comorbidities | Peptic ulcer disease | | 3 | 3.9% | 5 | 8.5% | 0.29 |
| | GERD | | 41 | 52.6% | 38 | 64.4% | 0.16 |
| | Gallstones/gallbladder disease | | 21 | 26.9% | 25 | 42.4% | 0.06 |
| | Coronary artery/cerebrovascular disease | | 6 | 7.7% | 11 | 18.6% | ***0.05*** |
| | Endometriosis | | 4 | 5.1% | 7 | 11.9% | 0.21 |
| | Interstitial cystitis | | 0 | 0.0% | 4 | 6.8% | ***0.03*** |
| | Prior hysterectomy | | 9 | 16.4% | 22 | 48.9% | ***<0.001*** |
| | Migraine headaches | | 19 | 24.4% | 22 | 37.3% | 0.10 |
| | Chronic fatigue syndrome | | 4 | 5.1% | 2 | 3.4% | 0.70 |
| | Fibromyalgia | | 5 | 6.4% | 7 | 11.9% | 0.26 |
| | Major depression | | 22 | 28.2% | 19 | 32.2% | 0.61 |
| | Severe anxiety | | 8 | 10.3% | 5 | 8.5% | 0.72 |

*P (2-sided) determined from either a chi-squared test or Fisher's exact test for categorical characteristics or a Kruskal-Wallis test to account for non-normality of the continuous variables.

**Table 2: COMPARISON OF BASELINE SEVERITY, HEALTHCARE USE, PSYCHOLOGICAL FUNCTION, AND QUALITY OF LIFE IN T1DM VERSUS T2DM**

***Table 2A: BETWEEN DIABETIC SUBTYPES***

| Category | Characteristic | | Type 1 Diabetics (N=78) | | Type 2 Diabetics (N=59) | | P Value* |
|---|---|---|---|---|---|---|---|
| | | | N | % or Mean±SD | N | % or Mean±SD | |
| Gastroparesis severity | Investigator-rated | Grade 1 | 4 | 5.8% | 9 | 15.5% | ***0.05*** |
| | | Grade 2 | 36 | 46.2% | 27 | 46.6% | |
| | | Grade 3 | 38 | 49.4% | 23 | 39.0% | |
| | Patient-rated | Overall GCSI | 78 | 2.8±1.1 | 59 | 3.0±1.0 | 0.28 |
| | | Nausea | 78 | 3.4±1.3 | 59 | 3.2±1.2 | 0.20 |
| | | Retching | 78 | 2.4±1.7 | 59 | 2.5±1.7 | 0.99 |
| | | Vomiting | 78 | 2.7±1.8 | 59 | 2.4±1.7 | 0.30 |
| | | Stomach fullness | 78 | 3.2±1.6 | 59 | 3.6±1.0 | 0.27 |
| | | Unable to finish meal | 78 | 2.9±1.5 | 59 | 3.2±1.2 | 0.43 |
| | | Postprandial fullness | 78 | 3.3±1.5 | 59 | 3.5±1.3 | 0.80 |
| | | Loss of appetite | 78 | 2.8±1.6 | 59 | 2.8±1.4 | 0.96 |
| | | Bloating | 78 | 2.8±1.7 | 59 | 3.4±1.4 | ***0.04*** |
| | | Visible distention | 78 | 2.5±1.8 | 59 | 2.9±1.7 | 0.19 |
| | | Upper abdominal pain | 78 | 2.8±1.9 | 59 | 2.8±1.7 | 0.84 |
| | | Upper abdominal discomfort | 78 | 2.9±1.8 | 59 | 3.2±1.5 | 0.47 |
| | | Lower abdominal pain | 78 | 2.3±1.7 | 59 | 1.8±1.4 | 0.09 |
| | | Lower abdominal discomfort | 78 | 2.3±1.6 | 59 | 1.9±1.5 | 0.15 |
| | | GERD | 78 | 2.0±1.4 | 59 | 1.9±1.3 | 0.86 |
| | | Constipation | 78 | 2.3±1.7 | 59 | 2.4±1.6 | 0.71 |
| | | Diarrhea | 78 | 2.0±1.8 | 59 | 1.8±1.6 | 0.48 |
| | Gastric function | 2 hour retention | 78 | 71±20% | 59 | 61±22% | ***0.006*** |
| | | 4 hour retention | 78 | 47±27% | 59 | 33±24% | ***<0.001*** |
| | | Mild retention (11-20% 4 hour retention) | 14 | 18.0% | 26 | 44.1% | ***0.001*** |
| | | Moderate retention (21-35% 4 hour retention) | 22 | 28.2% | 14 | 23.7% | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Severe retention (>35% 4 hour retention) | 42 | 53.9% | 19 | 32.2% | |
| Medications | | Prokinetics | 54 | 69.2% | 38 | 64.4% | 0.55 |
| | | Antiemetics | 55 | 70.5% | 40 | 67.8% | 0.73 |
| | | Proton pump inhibitors/other GI agents | 62 | 79.5% | 49 | 83.1% | 0.60 |
| | | NSAIDs | 42 | 53.9% | 40 | 67.8% | 0.10 |
| | | Opiates | 36 | 46.2% | 28 | 47.5% | 0.88 |
| | | Pain modulators | 21 | 26.9% | 17 | 28.8% | 0.81 |
| | | Antidepressants | 33 | 42.3% | 21 | 35.6% | 0.43 |
| | | Anxiolytics | 7 | 9.0% | 12 | 20.3% | 0.06 |
| | | Antidiabetics | 74 | 94.9% | 56 | 94.9% | 1.00 |
| | | Metformin | 2 | 2.6% | 19 | 32.2% | ***<0.001*** |
| Health care utilization | Hospitalized for gastroparesis in past year | | 57 | 73.1% | 27 | 45.8% | ***0.001*** |
| | Number of hospitalizations for gastroparesis in past year | | 78 | 5.1±6.4 | 59 | 3.2±6.6 | ***0.003*** |
| | Reason for hospitalization | Nausea/vomiting | 54 | 72.0% | 25 | 43.9% | ***0.001*** |
| | | Abdominal pain | 33 | 61.1% | 15 | 31.9% | ***0.003*** |
| | | Dehydration | 39 | 65.0% | 22 | 40.7% | ***0.01*** |
| | | GI hemorrhage | 6 | 22.2% | 3 | 8.6% | 0.16 |
| | On TPN | | 8 | 10.3% | 5 | 8.5% | 0.78 |
| | Underwent GES | | 12 | 15.4% | 2 | 3.4% | ***0.02*** |
| Psychological function | BDI | | 78 | 22±13 | 59 | 19±10 | 0.78 |
| | BDI score >28 | | 20 | 25.6% | 10 | 17.0% | 0.22 |
| | Y1 state anxiety | | 78 | 48±14 | 59 | 45±13 | 0.19 |
| | Y1 score ≥50 | | 37 | 47.4% | 18 | 30.5% | ***0.04*** |
| | Y2 trait anxiety | | 78 | 47±13 | 59 | 44±13 | 0.08 |
| | Y2 score ≥50 | | 35 | 44.9% | 17 | 28.8% | 0.06 |
| Quality of life | Overall PAGI-QOL | | 78 | 2.4±1.1 | 59 | 2.6±1.2 | 0.23 |
| | PAGI-QOL subscore | Daily activities | 78 | 2.2±1.3 | 59 | 2.4±1.2 | 0.21 |
| | | Clothing | 78 | 3.0±1.7 | 59 | 3.0±1.7 | 1.00 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Diet | 78 | 1.7±1.2 | 59 | 1.8±1.3 | 0.71 |
| | | Relationship | 78 | 2.8±1.7 | 59 | 3.1±1.5 | 0.28 |
| | | Psychological | 78 | 2.4±1.5 | 59 | 2.8±1.4 | 0.08 |
| | SF-36v2 physical | | 78 | 33±10 | 59 | 30±9 | 0.11 |
| | SF-36v2 mental | | 78 | 34±12 | 59 | 37±13 | 0.16 |

*P (2-sided) determined from either a chi-squared test or Fisher's exact test for categorical characteristics or a Kruskal-Wallis test to account for non-normality of the continuous variables.

***Table 2B: BY BASELINE HEMOGLOBIN A1c LEVEL AND PERIPHERAL NEUROPATHY STATUS***

| Category | Characteristic | | Hemoglobin A1c | | | | | Peripheral Neuropathy | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | A1c<8% (N=81) | | A1c≥8% (N=53) | | P Value* | Neuropathy (N=56) | | No Neuropathy (N=81) | | P Value* |
| | | | N | % or Mean±SD | N | % or Mean±SD | | N | % or Mean±SD | N | % or Mean±SD | |
| Gastroparesis severity | Investigator-rated | Grade 1 | 9 | 11.1% | 3 | 5.8% | | 4 | 7.3% | 8 | 9.9% | |
| | | Grade 2 | 36 | 44.4% | 25 | 48.1% | 0.63 | 21 | 38.2% | 42 | 51.9% | 0.20 |
| | | Grade 3 | 36 | 44.4% | 24 | 46.2% | | 30 | 54.6% | 31 | 38.3% | |
| | Patient-rated | Overall GCSI | 81 | 2.9±1.0 | 53 | 3.0±1.0 | 0.56 | 56 | 2.8±1.1 | 81 | 3.0±1.0 | 0.36 |
| | | Nausea | 81 | 3.3±1.3 | 53 | 3.5±1.2 | 0.43 | 56 | 3.2±1.4 | 81 | 3.5±1.2 | 0.15 |
| | | Retching | 81 | 2.3±1.8 | 53 | 2.7±1.6 | 0.33 | 56 | 2.3±1.8 | 81 | 2.5±1.6 | 0.48 |
| | | Vomiting | 81 | 3.4±1.3 | 53 | 3.3±1.4 | 0.86 | 56 | 2.3±1.8 | 81 | 2.7±1.8 | 0.21 |
| | | Stomach fullness | 81 | 3.1±1.5 | 53 | 3.0±1.3 | 0.54 | 56 | 3.1±1.6 | 81 | 3.5±1.2 | 0.35 |
| | | Unable to finish meal | 81 | 3.4±1.4 | 53 | 3.3±1.4 | 0.79 | 56 | 2.9±1.7 | 81 | 3.1±1.2 | 0.56 |
| | | Postprandial fullness | 81 | 3.0±1.5 | 53 | 2.6±1.5 | 0.18 | 56 | 3.0±1.7 | 81 | 3.6±1.2 | ***0.04*** |
| | | Loss of appetite | 81 | 2.8±1.6 | 53 | 3.1±1.6 | 0.61 | 56 | 3.1±1.6 | 81 | 2.7±1.4 | 0.12 |
| | | Bloating | 81 | 2.6±1.8 | 53 | 2.8±1.7 | 0.43 | 56 | 2.9±1.6 | 81 | 3.1±1.6 | 0.52 |
| | | Visible distention | 81 | 2.9±1.0 | 53 | 3.0±0.9 | 0.56 | 56 | 2.7±1.7 | 81 | 2.6±1.8 | 0.96 |
| | | Upper abdominal pain | 81 | 2.8±1.8 | 53 | 2.8±1.9 | 0.94 | 56 | 2.6±1.9 | 81 | 2.9±1.8 | 0.46 |
| | | Upper abdominal discomfort | 81 | 3.1±1.6 | 53 | 3.0±1.8 | 0.71 | 56 | 3.0±1.8 | 81 | 3.1±1.6 | 0.94 |
| | | Lower abdominal pain | 81 | 2.1±1.7 | 53 | 2.1±1.4 | 0.98 | 56 | 2.1±1.8 | 81 | 2.0±1.4 | 0.95 |
| | | Lower abdominal discomfort | 81 | 2.2±1.7 | 53 | 2.2±1.4 | 0.85 | 56 | 2.3±1.7 | 81 | 2.1±1.4 | 0.56 |
| | | GERD | 81 | 2.0±1.4 | 52 | 2.0±1.3 | 0.99 | 55 | 2.1±1.5 | 81 | 2.0±1.3 | 0.77 |
| | | Constipation | 81 | 2.6±1.7 | 53 | 2.0±1.6 | 0.06 | 56 | 2.5±1.8 | 81 | 2.3±1.6 | 0.54 |
| | | Diarrhea | 81 | 1.8±1.7 | 53 | 2.0±1.7 | 0.57 | 56 | 1.7±1.8 | 81 | 2.0±1.7 | 0.27 |
| | Gastric function | 2 hour retention | 81 | 67±21% | 53 | 67±22% | 0.96 | 56 | 68±21% | 81 | 66±21% | 0.43 |
| | | 4 hour retention | 81 | 41±27% | 53 | 41±27% | 0.79 | 56 | 41±26% | 81 | 40±27% | 0.98 |
| | | Mild retention (11-20% 4 | 25 | 30.9% | 14 | 26.4% | 0.90 | 17 | 30.4% | 23 | 28.4% | 0.97 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | hour retention) | | | | | | | | | | |
| | | Moderate retention (21-35% 4 hour retention) | 20 | 24.7% | 14 | 26.4% | | 15 | 25.0% | 22 | 27.2% | |
| | | Severe retention (>35% 4 hour retention) | 36 | 44.4% | 25 | 47.2% | | 25 | 44.6% | 36 | 44.4% | |

*P (2-sided) determined from either a chi-squared test or Fisher's exact test for categorical characteristics or a Kruskal-Wallis test to account for non-normality of the continuous variables.

**Table 3: BASELINE CLINICAL DISCRIMINATORS OF DIABETES SUBTYPE (T1DM VERSUS T2DM) IN PATIENTS WITH GASTROPARESIS**

| Category | Characteristic | OR* | 95% CI | P Value† |
|---|---|---|---|---|
| Demographic | Age (≥50 vs. <50 years) | 0.07 | 0.02, 0.24 | ***<0.001*** |
| | Sex (female vs. male) | 1.39 | 0.47, 4.07 | 0.17 |
| | Race (white vs. non-white) | 2.78 | 0.84, 9.20 | 0.40 |
| Clinical | Peripheral neuropathy (yes vs no) | 3.81 | 1.28, 11.35 | ***0.02*** |
| | Overweight or obese (BMI ≥25 vs. <25 kg/m$^2$) | 0.11 | 0.04, 0.36 | ***<0.001*** |
| | Number of comorbidities | 0.76 | 0.63, 0.92 | ***0.02*** |
| Symptom severity | Bloating | 0.62 | 0.42, 0.91 | ***0.02*** |
| | GERD | 1.70 | 1.08, 2.67 | ***0.02*** |

* A total of 136 diabetic patients with delayed emptying were included in the analysis: T1DM=78, T2DM=58; one T2DM patient has missing data for the GERD subscale on enrollment.

† P derived from a backward stepwise multiple logistic model regressing diabetes subtype (T1DM vs. T2DM on the candidate set of 46 baseline predictors included in Tables 1 and 2A (P for exclusion=0.05), where age, sex, and white race were forced into the model. GCSI was not included due to collinearity with its components. One measure of inflammation was used (either a high CRP and/or a high ESR). Total numbers of comorbidities were included instead of individual comorbidities. A two category symptom duration (≥5 vs. <5 years) was used due to small numbers in the categories. Final model is presented. Hosmer-Lemeshow Goodness of fit $\chi^2$ (d.f.=86)=3.77, P=0.71.

**Table 4: COMPARISON OF 48 WEEK CHANGES IN SEVERITY, HEALTHCARE USE, PSYCHOLOGICAL FUNCTION, AND QUALITY OF LIFE IN T1DM VERSUS T2DM**

| Category | Characteristic | Type 1 Diabetics (N=44*) | | | | Type 2 Diabetics (N=46*) | | | | T1DM vs. T2DM P Value‡ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean Baseline | Mean Δ (48 Weeks vs. Baseline) | 95% CI | P Value† | Mean Baseline | Mean Δ (48 Weeks vs. Baseline) | 95% CI | P Value† | |
| Clinical | BMI (kg/m$^2$) | 27.2 | 0.67 | -0.18, 1.53 | 0.12 | 34.1 | 0.55 | -0.32, 1.42 | 0.21 | 0.44 |
| | Hemoglobin A1c (%) | 8.1 | 0.47 | -0.32, 1.27 | 0.23 | 7.2 | 0.44 | -0.03, 0.92 | 0.07 | 0.51 |
| Gastroparesis severity | Investigator-rated | 2.5 | -0.33 | -0.57, -0.09 | ***0.009*** | 2.2 | -0.30 | -0.55, -0.05 | ***0.02*** | 0.23 |
| Medications | Prokinetics | 70.5% | 15.9% | 2.8, 30.0% | ***0.01*** | 71.7% | 8.7% | -3.6, 21.0% | 0.22 | 1.00 |
| | Antiemetics | 70.5% | 4.5% | -13.1, 22.2% | 0.77 | 67.4% | 4.3% | -13.7, 22.4% | 0.79 | 0.95 |
| | Proton pump inhibitors/other GI agents | 81.8% | 13.6% | 1.2, 26.0% | ***0.03*** | 80.4% | 4.3% | -6.3, 15.0% | 0.63 | 1.00 |
| | NSAIDs | 52.3% | 2.3% | -21.8, 17.2% | 1.00 | 76.1% | -17.4% | -35.9, 1.1% | 0.08 | 0.21 |
| | Opiates | 47.7% | 13.6% | -2.1, 29.4% | 0.11 | 43.5% | 17.4% | 1.3, 33.4% | ***0.04*** | 0.84 |
| | Pain modulators | 29.6% | 4.5% | -10.3, 19.3% | 0.73 | 34.8% | -2.2% | -13.9, 9.5% | 1.00 | 0.43 |
| | Antidepressants | 40.9% | 9.1% | -8.4, 26.6% | 0.39 | 39.1% | 13.1% | -5.8, 31.8% | 0.21 | 0.91 |
| | Anxiolytics | 15.9% | 25.0% | 9.9, 40.1% | ***0.001*** | 21.7% | -2.1% | -17.1, 12.8% | 1.00 | 1.00 |
| | Antidiabetics | 93.2% | 0% | -2.3, 2.3% | 1.00 | 95.3% | -2.2% | -13.9, 9.5% | 1.00 | 1.00 |
| | Metformin | 2.3% | -2.3% | -8.9, 4.4% | 1.00 | 32.6% | -2.2% | -16.0, 11.3% | 1.00 | 1.00 |
| Health care utilization | Hospitalization in past year (%) | 70.5% | -15.1% | -30.6 -1.1% | ***0.04*** | 43.5% | -8.7% | -25.4, 8.0% | 0.39 | 0.26 |
| | Number of hospitalizations for | 4.8 | -1.55 | -3.16, 0.07 | 0.06 | 2.4 | -0.74 | -2.22, 0.74 | 0.32 | 0.70 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | gastroparesis | | | | | | | | | |
| | Number of ED visits | NA | 4.86 | 2.78, 6.95 | NA | NA | 2.46 | 1.04, 3.88 | NA | 0.07 |
| | % on TPN | 4.5% | 2.3% | -7.7, 12.2% | 1.00 | 8.7% | -8.7% | -19.0, -1.6% | 0.13 | 0.13 |
| | % undergoing GES | 11.4% | 20.5% | 4.73, 36.2% | ***0.01*** | 0.0% | 10.9% | -0.3, 22.0% | 0.06 | 0.16 |
| Psychological function | BDI | 21.3 | -1.18 | -4.91, 2.56 | 0.53 | 18.8 | 0.51 | -2.42, 3.44 | 0.73 | 0.69 |
| | Y1 state anxiety | 44.4 | 0.85 | -3.96, 5.66 | 0.72 | 44.4 | 0.64 | -3.70, 4.99 | 0.77 | 0.97 |
| | Y2 trait anxiety | 44.1 | 2.20 | -1.80, 6.20 | 0.27 | 44.0 | 0.58 | -3.26, 4.42 | 0.77 | 0.53 |
| Quality of life | PAGI-QOL | 2.5 | 0.22 | -0.14, 0.58 | 0.22 | 2.6 | 0.15 | -0.11, 0.42 | 0.25 | 0.84 |
| | SF-36v2 physical | 32.6 | 1.28 | -1.72, 4.27 | 0.39 | 29.7 | 1.82 | -0.52, 4.16 | 0.12 | 0.80 |
| | SF-36v2 mental | 35.3 | 1.55 | -2.95, 6.05 | 0.49 | 36.6 | 0.65 | -2.96, 4.26 | 0.72 | 0.86 |

*****N determined by value for medication or outcome being available at enrollment and at 48 weeks; for T1DM, between 31 and 44; for T2DM, between 36 and 46.

† Mean change of outcome or % medication use (48 weeks – baseline) or mean number of events in 48 weeks for emergency department (ED) visits, since baseline for ED visits unavailable. For continuous outcomes, P value determined using one sample t-test of the null hypothesis of no difference in means at follow-up and baseline. For binary outcomes (hospitalized, TPN, GES) and medication use, an exact McNemar's test for paired proportions was used to determine P, and 95% confidence intervals (C.I.) determined using a continuity correction.

‡ P values for continuous outcomes determined using multiple regression of each outcome in relation to diabetes subtype with adjustment for the baseline value of the outcome. P value for ED visits was determined using a negative binomial with robust variance to account for overdispersion. P values for binary outcomes and medication use were derived from Wald tests to assess whether change in medication use varied by diabetes subtype using conditional logistic regression. Unconditional exact logistic regression was used to assess changes in TPN use or GES implantation, since no T2DM patients had those treatments at either enrollment (GES) or 48 weeks (TPN).

NA was defined as not applicable (the number of ED visits in the past year was not queried at baseline).

§ Total hospitalizations for gastroparesis since baseline exclude GES placement.

**Table 5: RELATIVE ODDS OF CHANGE IN CLINICAL 48 WEEK OUTCOMES IN RELATION TO DIABETES SUBTYPE (T1DM VERSUS T2DM) IN PATIENTS WITH GASTROPARESIS**

| Category | Change at 48 Weeks from Baseline* | | Type 1 Diabetics N (% Improved) | Type 2 Diabetics N (% Improved) | OR† | 95% CI | P Value‡ |
|---|---|---|---|---|---|---|---|
| Clinical measures | BMI ($kg/m^2$)(same or lower vs. higher BMI | | 42 (31%) | 44 (27%) | 1.86 | 0.51, 6.80 | 0.35 |
| | Hemoglobin A1c (%)(any decrease) | | 28 (25%) | 36 (42%) | 0.80 | 0.19, 3.30 | 0.76 |
| Gastroparesis severity | Investigator-rated severity (≥1 point decrease) | | 43 (33%) | 46 (37%) | 0.68 | 0.21, 2.13 | 0.50 |
| | Patient-rated (any decrease) | Overall GCSI | 40 (60%) | 45 (62%) | 1.10 | 0.32, 3.71 | 0.88 |
| | | Nausea | 40 (35%) | 45 (51%) | 0.54 | 0.18, 1.64 | 0.28 |
| | | Retching | 40 (48%) | 45 (56%) | 0.45 | 0.10, 2.10 | 0.31 |
| | | Vomiting | 40 (33%) | 45 (53%) | 0.21 | 0.05, 0.87 | ***0.03*** |
| | | Stomach fullness | 40 (40%) | 45 (44%) | 1.71 | 0.53, 5.53 | 0.37 |
| | | Unable to finish meal | 40 (35%) | 45 (42%) | 1.13 | 0.33, 3.81 | 0.85 |
| | | Postprandial fullness | 40 (48%) | 45 (40%) | 2.65 | 0.78, 9.02 | 0.12 |
| | | Loss of appetite | 40 (50%) | 45 (42%) | 4.25 | 1.07, 16.92 | ***0.04*** |
| | | Bloating | 40 (38%) | 45 (40%) | 1.68 | 0.50, 5.63 | 0.40 |
| | | Visible distention | 40 (30%) | 45 (36%) | 1.15 | 0.32, 4.13 | 0.83 |
| | | Upper abdominal pain | 40 (38%) | 45 (47%) | 1.81 | 0.48, 6.75 | 0.38 |
| Health care utilization | Hospitalizations for gastroparesis (none over 48 weeks vs. any) | | 44 (45%) | 46 (65%) | 0.85 | 0.26, 2.77 | 0.78 |
| | ED visits (none over 48 weeks vs. any) | | 44 (27%) | 46 (50%) | 0.43 | 0.14, 1.29 | 0.13 |
| Psychological function | BDI (≤5 point decrease) | | 40 (35%) | 45 (40%) | 0.91 | 0.28, 2.90 | 0.87 |
| | Y1 state anxiety (any decrease) | | 40 (45%) | 45 (49%) | 0.85 | 0.25, 2.95 | 0.80 |
| | Y2 trait anxiety (any decrease) | | 40 (38%) | 45 (49%) | 0.45 | 0.14, 1.44 | 0.18 |
| Quality of life | PAGI-QOL (any increase) | | 39 (51%) | 43 (56%) | 0.87 | 0.29, 2.54 | 0.80 |
| | SF-36v2 physical (≥1 point increase) | | 40 (50%) | 43 (53%) | 1.70 | 0.50, 5.81 | 0.40 |
| | SF-36v2 mental (≥1 point increase) | | 40 (53%) | 43 (51%) | 1.19 | 0.39, 3.66 | 0.76 |

* Each outcome indicator is defined as change in the characteristic score at 48 weeks compared to baseline. Outcome indicators based on change in value at 48 weeks from value at enrollment included: symptom score reduction (any decrease in total GCSI or in individual GCSI scores), BMI (same or lower), hemoglobin A1c (any decrease), psychological function (BDI decreased

by 5 or more points; Y1 state-anxiety, Y2 trait-anxiety any decrease), and QOL (PAGI-QOL any increase; SF-36v2 physical and SF-36v2 mental components, increase of at least one point).

† OR = Relative odds of change in T1DM versus T2DM.

‡ OR's derived from logistic regression models of each indicator of change in characteristic score at 48 weeks in relation to diabetes type and baseline value of the indicator. Models included a propensity score to adjust the diabetes type effect for the probability of being T1DM based on age, sex, and race (white vs. not white).

**FIGURE LEGENDS**

**Figure 1:** Patient-rated symptom scores at baseline and at 48 week follow-up. (A) T1DM patients exhibited moderate to severe baseline symptom severities (clear bars)(data expressed as mean±upper limit of 95% CI). Symptom scores did not decrease over 48 weeks (dark bars). (B) T2DM patients exhibited baseline symptom severities in the moderate to severe range (clear bars). However, a reduction in symptoms was observed at 48 weeks for all symptoms except postprandial fullness and visible distention (dark bars). (C) Mean changes in symptoms ± 95% CI are plotted with P values for baseline versus 48 week values for T1DM and T2DM patients. No symptom changed significantly for T1DM patients. Overall symptom scores decreased and 8 of 10 individual symptoms significantly decreased in T2DM gastroparetics at 48 week follow-up (all $P \leq 0.05$).

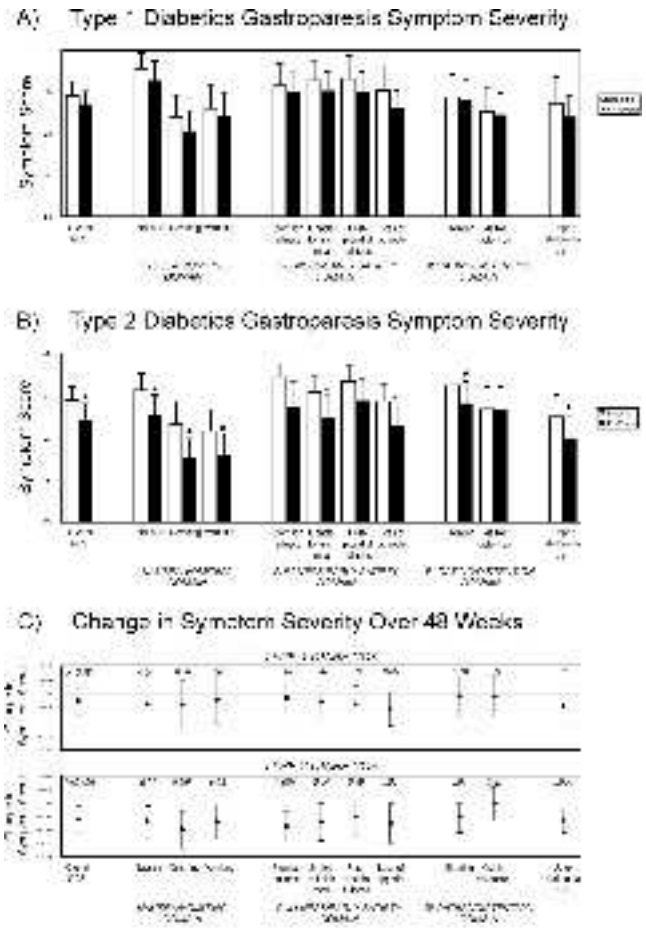


**Figure 1**

nmo_12800_f1.tif