Differences in intragastric pH in diabetic vs. idiopathic gastroparesis: relation to degree of gastric retention

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Gastric acid profiles in patients with idiopathic gastroparesis differ from those with diabetic gastroparesis. The pathophysiological basis for this difference is unexplored. Recently, an ingestible wireless transmitting capsule that measures intraluminal pH, pressure, and temperature was approved by the United States Food and Drug Administration for use in gastric scintigraphy. Gastric pH from the capsule was recorded every 5 s. Basal pH was higher in diabetic (3.64 ± 0.41) vs. control subjects (1.90 ± 0.18) and idiopathic subjects (2.41 ± 0.42; P < 0.05). Basal pH nadirs prior to gastric capsule evacuation were higher in diabetic patients (1.50 ± 0.23) than control subjects (0.58 ± 0.11; P = 0.003). Four-hour gastric retention was similar in diabetic (18.3 ± 0.5%) and idiopathic (19.4 ± 0.5%) patients but higher than control subjects (2.2 ± 0.5%; P < 0.001). Compared with control subjects, those with moderate-severe stasis (>20% retention at 4 h) had higher basal (3.91 ± 0.55) and nadir pH (2.23 ± 0.42) values (P < 0.05). In subgroup analyses, both diabetic and idiopathic patients with moderate-severe gastroparesis exhibited increased pH parameters vs. those with mild/gastroparesis. In conclusion, diabetic patients with gastroparesis exhibit reduced gastric acid output in response to sham feeding is reduced by up to 10.220.33.1 on June 28, 2017 http://ajpgi.physiology.org/ Downloaded from http://ajpgi.org

Diabetic acid secretion is regulated by several factors. Gastric acid output in response to sham feeding is reduced by up to two-thirds in diabetic patients, indicative of vagal neuropathy (8). Other studies have reported variable impairments in acid secretion in response to other stimuli, including pentagastrin (23). However, none of these investigations have related impaired acid secretion to rates of gastric emptying in diabetes. Gastric acid profiles in patients with idiopathic gastroparesis are unexplored. Recently, an ingestible wireless transmitting capsule that measures intraluminal pH, pressure, and temperature was approved by the United States Food and Drug Administration. This device has been shown to quantify gastric emptying with a sensitivity and specificity similar to accepted scintigraphic methods (17).

In this investigation, we employed this pH-sensing capsule to test the hypotheses that 1) gastric pH profiles show differential alteration in diabetic vs. idiopathic gastroparesis and 2) abnormal pH profiles relate to severity of stasis. Intragastric
pH profiles under basal conditions and after standardized meals in diabetic patients with gastroparesis and patients with idiopathic gastroparesis were compared with those of asymptomatic healthy volunteers. Subjects in both gastroparesis groups were stratified into those with severe and those with mild gastroparesis on the basis of concurrently performed gastric scintigraphy, and pH profiles were related to the degree of gastric retention. The findings of this investigation provide novel information on clinical and potential pathophysiological differences in diabetic and idiopathic gastroparesis that may relate to neuropathic defects in the two conditions.

MATERIALS AND METHODS

Human Subjects

Data from 44 patients (9 men, 35 women, mean age 40.0 yr) with documented gastroparesis on prior gastric scintigraphy recruited from the seven participating centers were included in this investigation. Twenty patients had a history of long-standing Type 1 or Type 2 diabetes mellitus that was considered to be the cause of gastroparesis. Twenty-four patients had gastroparesis of an idiopathic nature. All gastroparesis patients reported symptoms of nausea, vomiting, early satiety, and epigastric pain or discomfort for at least 6 mo prior to study enrollment. Exclusion criteria included extreme gastric stasis (>90% retention of radiolabeled egg meal at 2 h), gastric bezoar, peptic stricture or ulcer disease on prior endoscopy, dysphagia, prior gastrointestinal surgery (except appendectomy or cholecystectomy), uncontrolled diabetes (hemoglobin A1c >10%), and severe vomiting (>1 emesis episode per day), constipation (<1 bowel movement every 3 days), or abdominal pain (requiring daily narcotics). Other conditions, including neurological disorders, psychiatric disease, or chronic pain syndromes not requiring daily narcotics (e.g., irritable bowel syndrome, fibromyalgia) were not considered exclusion criteria.

Data from 64 healthy volunteers (41 men, 23 women, mean age 31.4 yr) recruited by campus-wide advertisements at each of the seven participating centers were included in this investigation. These individuals reported no gastrointestinal symptoms as screened by the Mayo GI Disease Screening Questionnaire. Healthy subjects additionally had no prior gastrointestinal surgery, were not morbidly obese (body mass index was <35 kg/m^2), were on no medications known to affect gut transit, and reported no cardiovascular, endocrine, renal, or hepatic disease.

Prior to study, any medications that could suppress or neutralize gastric acid and accelerate or delay gut transit were discontinued in both subject groups. Proton pump inhibitors were stopped 7 days before, histamine2 receptor antagonists were stopped 2 days before, and antacids were stopped 1 day before capsule ingestion. Prokinetics such as metoclopramide, erythromycin, domperidone, and tegaserod and antiemetics in the anticholinergic and 5-HT3 receptor antagonist classes were held for 2 days. Opiate agents and nonsteroidal anti-inflammatory drugs were stopped 7 days before study. Women of child-bearing potential underwent urine pregnancy testing on the morning of study prior to capsule ingestion. Diabetic subjects with gastroparesis were instructed to inject half of their normal insulin dose on the morning of study to minimize the risk of hypoglycemia during the testing.

Studies at each of the seven participating centers were approved by the local Institutional Review Board. Prior to study participation, each subject provided written, informed consent.

Experimental Protocol

At approximately 8 AM after overnight fasting, each subject swallowed a pH-sensing, wireless transmitting capsule (SmartPill Corporation, Buffalo, NY) with 50 ml of water. The capsule measures 26.8 mm × 11.7 mm; houses sensors for pH, temperature, and pressure; and transmits sensed data at 434 MHz to a receiver worn by the subject for up to 120 h. Immediately after ingesting the capsule, the subject consumed a standardized low-fat meal (120 g Egg Beaters, 60 kcal; 2 slices of bread, 120 kcal; 30 g of strawberry jam, 74 kcal; and 120 ml of water) radiolabeled with 1 mCi 99mTc-sulfur colloid in 20 min or less. The meal provides a total of 255 kcal and is comprised of 72% carbohydrate, 24% protein, 2% fat, and 2% fiber.

Intragastric pH assessments were obtained every 5 s after capsule ingestion and were able detect pH changes with a sensitivity of ±0.2 pH units. Initial scintigraphy was performed immediately after consumption of the low-fat meal. Subsequent scintiscans were performed at 30-min intervals for 4–6 h. In between images, subjects were ambulatory. Bathroom visits were permitted; however, subjects were not allowed to sleep during the initial 8 h after capsule ingestion to prevent any modulatory effects of sleep on upper gut transit. Six hours after capsule ingestion, subjects consumed a 250-mL liquid nutrient meal (Ensure, Abbott Laboratories, Abbott Park, IL). Fingerstick blood glucose levels were measured in diabetic subjects and insulin was administered according to the subject’s normal protocol. Eight hours after capsule ingestion, subjects were permitted to leave the test facility but continued to wear the receiver unit for ongoing data acquisition. Subjects resumed their normal diets and all medications; however, no alcohol or medications with effects on gut transit were permitted. Strenuous exercise was prohibited. Forty-eight to 72 h after ingestion, subjects returned to the testing facility to return the receiver. A formal protocol involving abdominal radiographs (if needed) was followed to confirm capsule passage.

Data Analysis

Gastric pH parameters. pH data were initially downloaded from the receiver through a docking station via a USB connection to a Windows PC-compatible laptop computer (Dell Latitude, Dell Computer, Round Rock, TX). Digitized data files were then uploaded to a spreadsheet for subsequent analysis (Excel, Microsoft, Redmond, WA). Data from 22 healthy subjects and 16 patients with gastroparesis recruited into the parent study (17) were not included in this investigation. Data from 17 healthy volunteers and 16 gastroparetic patients were excluded because of incomplete pH data during the time the capsule was in the stomach that precluded reliable determination of the various pH parameters (see below). Data from five healthy volunteers were excluded because of abrupt gastric evacuation of the capsule into the duodenum prior to meal completion that precluded quantification of intragastric neutralization and reacidification. It is likely that rapid capsule expulsion in these individuals resulted from ongoing migrating motor complex activity that was present at the time of meal consumption. The beginning of the pH recording was defined as the time that the capsule was swallowed. Capsule passage into the duodenum was defined as the point the pH value abruptly rises at least 2 pH units from the lowest postprandial value to a pH of at least 4 and does not decrease to a value below 4 at any subsequent time in the recording. All healthy subjects and gastroparesis patients satisfied this emptying criterion. The mean time to complete this pH increase was 1.59 ± 0.16 min, which was not different in healthy subjects (1.45 ± 0.15 min) compared with gastroparesis patients (1.82 ± 0.33 min).

Several pH parameters were quantified for this investigation. The initial basal pH was defined as the lowest pH value recorded immediately after capsule ingestion before acid neutralization by the consumed meal was observed. In all subjects, this value was recorded in the initial 5 min of the study. The peak postprandial pH was defined as the highest peak value obtained after meal ingestion but before the capsule was expelled into the duodenum. This value usually was observed early in the postprandial period, most commonly in the initial 45 min after meal consumption. The nadir postprandial pH was defined as the lowest pH value obtained in the postprandial period after completion of acid neutralization by the meal but before capsule expulsion into the duodenum. This value was always recorded after...
the peak postprandial pH and usually occurred in the final 60–90 min prior to capsule evacuation from the stomach. The times from ingestion of the low-fat meal to the times of peak postprandial pH and nadir pH prior to gastric evacuation of the capsule were quantified. Finally, a summed value for postprandial acid neutralization and reacidification was calculated by quantifying the area under the pH curve. For this measure, all pH values from the time of capsule ingestion to the time of the nadir postprandial pH value were summed and expressed as pH units \( \times \) hours.

**Gastric emptying scintigraphy.** One-minute anterior and 1-min posterior images were taken immediately after meal ingestion and at 30-min intervals for 4 h in the 140-keV \(^{99}\)Tc peak with a 20% window (140 keV \( \pm \) 10%). If 90% of the meal had not emptied after 4 h, an additional image was taken at 6 h. Data were corrected for time decay. The region of interest was drawn around the image of the stomach for each time frame. For each time frame, the geometric mean was calculated as the square root of the product of the counts measured on the anterior and posterior images. For this study, the percent retention of the radiolabeled tracer was quantified at 4 h after consumption of the low-fat meal.

**Statistical Analysis**

All results were expressed as means \( \pm \) SE. Single-factor ANOVA was performed to determine whether there were significant differences in pH values, areas under the pH curve, times to peak and nadir pH, and percent gastric retention in the three subject groups: healthy volunteers, diabetic patients with gastroparesis, and patients with idiopathic gastroparesis. ANOVA also was performed to determine whether there were significant differences in pH values and areas under the pH curve in healthy volunteers, those with moderate-severe gastroparesis, and those with mild gastroparesis. Finally, subgroup analyses comparing diabetic and idiopathic patients with moderate-severe vs. mild gastroparesis were performed by using ANOVA. The Tukey honestly significant difference method was employed to test whether absolute differences between any two sample means were significantly different. A \( P \) value of <0.05 defined statistical significance.

**RESULTS**

**Gastric pH Profiles in Health and Gastroparesis**

Gastric pH measured by the ingested wireless transmitting capsule showed significant differences during the fasting and postprandial periods, as shown in representative tracings from subjects in each of the three groups. In a healthy volunteer under basal conditions, pH was initially low (Fig. 1A). Meal ingestion elicited a temporary increase in pH that quickly reverted to a very acidic nadir pH. Finally, an abrupt increase in pH was observed when the capsule passed from the antrum to the duodenum. A patient with diabetic gastroparesis and a significantly altered gastric acidity profile exhibited an initially higher basal pH (Fig. 1B). Meal ingestion evoked peak and nadir pH levels prior to gastric evacuation of the capsule that were much higher than in the normal control. In this individual, the time for gastric expulsion of the capsule was longer than for the healthy subject. In contrast, a representative patient with idiopathic gastroparesis exhibited a pH profile similar to that of the healthy subject with an initial acidic pH, a brief neutralization, and an abrupt decrease to a very acidic nadir pH despite exhibiting prolonged gastric retention of the capsule similar to the diabetic patient (Fig. 1C).

![Fig. 1. Representative gastric pH tracings from individuals in each of the 3 subject groups are shown.](http://ajpgi.physiology.org/)

**Gastric pH Parameters**

Several gastric pH parameters were compared in the three subject groups. Between-group comparisons revealed a significant difference between the three subject groups in basal intragastric pH (\( P = 0.002 \)), peak postprandial pH after consuming the low-fat meal (\( P = 0.04 \)), and nadir pH prior to capsule evacuation from the stomach (\( P = 0.004 \); Fig. 2). Compared with recordings from healthy volunteers, basal pH levels were significantly higher in patients with diabetic gastroparesis (\( P = 0.001 \)). Basal pH levels in patients with idiopathic gastroparesis were similar to those of the healthy control subjects (\( P = 0.45 \)) and were less than those of the diabetic subjects (\( P = 0.04 \)). Peak pH values were higher in diabetic patients than in idiopathic gastroparesis patients (\( P = 0.03 \)). Healthy volunteers exhibited peak postprandial pH levels that were intermediate between the two gastroparesis patient groups and were not statistically significantly different from either (\( P = \) not significant). Nadir pH values were higher in diabetic subjects with gastroparesis than healthy volunteers (\( P = 0.003 \)), while patients with idiopathic gastroparesis exhibited values intermediate to and not significantly different from the two other groups (\( P = \) not significant). Between-group comparisons revealed a significant difference between the three subject groups in times to peak postprandial pH after meal ingestion and times to nadir pH prior to gastric capsule evacuation.
evacuation (Table 1). Times to peak postprandial pH were greater in the diabetic patients compared with the healthy control subjects ($P = 0.02$) and patients with idiopathic gastroparesis ($P = 0.04$) but were similar in the healthy volunteers and idiopathic gastroparesis patients ($P = 1.00$). Times to nadir pH were longer in the diabetic gastroparesis group than in healthy subjects ($P = 0.02$) but were not significantly greater than for the patients with idiopathic gastroparesis ($P = 0.59$). Times to nadir pH were not different in the idiopathic gastroparesis group compared with the healthy control subjects ($P = 0.23$). Finally, between-group comparisons revealed a significant difference between the three subject groups in the areas under the pH curves representing a summation of postprandial neutralization and reacidification (Fig. 3). Areas under the pH curves were higher in diabetic patients than in healthy control subjects ($P = 0.04$) and patients with idiopathic gastroparesis ($P = 0.02$). Values in healthy control subjects and those with idiopathic gastroparesis were different ($P = 0.74$).

**Relation to Gastric Emptying Scintigraphy**

Intragastric pH parameters were related to results of scintigraphic assessments of gastric emptying. Between-group comparisons revealed a significant difference between the three subject groups in percentages of gastric retention of the low-fat meal at 4 h. Gastric retention was increased in patients with diabetic ($18.3 \pm 4.9\%$) and idiopathic ($19.4 \pm 4.7\%$) gastroparesis compared with the healthy control subjects ($2.2 \pm 0.5\%; P < 0.001$). However, gastric retention values were similar in diabetic subjects compared with those with idiopathic disease ($P = 0.97$). Subjects in both gastroparesis groups were stratified into those with moderate to severe ($>20\%$ retention at 4 h) and mild ($\leq 20\%$ retention at 4 h) gastroparesis. Between-group comparisons revealed a significant difference between the healthy volunteers and those with mild and moderate-severe gastroparesis in the various pH parameters (Figs. 4 and 5). Compared with healthy volunteers, subjects with moderate-severe gastroparesis exhibited significantly higher basal pH ($P = 0.001$) and nadir pH ($P < 0.001$) levels (Fig. 4). In contrast, those with mild gastroparesis showed basal ($P = 0.14$), peak postprandial ($P = 0.24$), and nadir ($P = 0.74$) pH values that were no different from those of healthy control subjects. Subjects with mild gastroparesis exhibited lower basal ($P = 0.05$), peak ($P = 0.02$), and nadir ($P < 0.001$) pH values than those with moderate-severe gastroparesis. Similarly, areas under the pH curves were greater for subjects with moderate-severe gastroparesis than in healthy volunteers ($P = 0.02$) or patients with mild gastroparesis ($P = 0.02$; Fig. 5). Healthy subjects and those with mild gastroparesis showed similar areas under the pH curves ($P = 0.93$).

![Image 1](http://ajpgi.physiology.org/)

**Table 1. Time course of meal-induced neutralization and reacidification**

<table>
<thead>
<tr>
<th>Time to peak pH, min</th>
<th>Healthy Volunteers</th>
<th>Diabetic Gastroparesis Patients</th>
<th>Idiopathic Gastroparesis Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.9 ± 2.7</td>
<td>37.8 ± 6.6</td>
<td>21.5 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>Time to nadir pH, min</td>
<td>192.0 ± 6.5</td>
<td>245.7 ± 20.7</td>
<td>222.9 ± 23.1</td>
</tr>
</tbody>
</table>

![Image 2](http://ajpgi.physiology.org/)

![Image 3](http://ajpgi.physiology.org/)

![Image 4](http://ajpgi.physiology.org/)
GASTRIC pH IN DIABETIC VS. IDIOPATHIC GASTROPARESIS

In subgroup analyses, between-group comparisons revealed a significant differences in basal pH (P = 0.001), peak postprandial pH (P = 0.017), nadir pH (P = 0.001), and areas under the pH curve (P = 0.001) between diabetic and idiopathic patients with moderate-severe vs. mild gastroparesis (Figs. 6 and 7). Within the diabetic group alone, those with >20% gastric retention exhibited greater nadir pH values (P = 0.03) and areas under the pH curves (P = 0.005) than patients with ≤20% retention. Basal (P = 0.32) and peak postprandial (P = 0.44) pH levels were similar in the two groups. Within the group of patients with idiopathic gastroparesis, those with moderate-severe gastroparesis showed higher nadir pH levels (P = 0.03) and a trend to higher basal pH levels (P = 0.06) compared with those with idiopathic disease, although peak pH levels (P = 0.18) and areas under the pH curves (P = 0.61) were no different. Among those with moderate-severe gastroparesis, patients with diabetes exhibited higher areas under the pH curves (P = 0.01) than patients with idiopathic gastroparesis although basal (P = 0.49), peak postprandial (P = 0.67), and nadir (P = 0.55) pH values were not different in the two groups. Among those with mild gastroparesis, patients with diabetes showed higher basal pH levels (P = 0.03) but no difference in peak postprandial pH (P = 0.17), nadir pH (P = 0.50), and areas under the pH curves (P = 0.47).

DISCUSSION

Gastroparesis is a clinical disorder with objective delays in gastric emptying that produces symptoms of gastric retention and has extragastrointestinal consequences. The condition may develop as complications of several systemic diseases, occur after selected surgeries on the stomach, or present without warning as an isolated disorder of gastric function. In a series of 146 gastroparesis patients seen at a large tertiary center, 29% of cases had underlying diabetes, 13% developed symptoms after gastric surgery, and 36% were idiopathic (30). In a population-based survey, 18% of diabetic subjects reported upper gastrointestinal symptoms (3). The prevalence of delayed emptying among individuals with longstanding Type 1 diabetes ranges from 27 to 58% (12). Likewise, gastroparesis is present in up to 30% of patients with Type 2 diabetes (11). Idiopathic gastroparesis is as common as diabetic gastroparesis in most case series (30). Patients typically are young or middle aged and up to 90% are women.

The pathophysiological mechanisms responsible for diabetic and idiopathic gastroparesis are incompletely characterized, but several observations suggest that the two disorders are very different. Diabetic gastroparesis typically develops gradually in the setting of other diabetic complications such as neuropathy, suggesting the disorder may have a chronic neuropathic basis. Indeed, measures of dysautonomia, including postural hypotension and loss of vagotonic cardiac reflexes, are prominent in diabetic patients with gastroparesis (21). Histological studies of vagus nerves from diabetic subjects with gastroparesis provide contradictory results with some studies revealing myelin degeneration and others showing normal morphology.
Microscopic examination of gastric specimens reacted from diabetic patients with gastroparesis have also revealed smooth muscle degeneration and fibrosis with eosinophilic inclusion bodies in one study and disruption of gastric networks of interstitial cells of Cajal in a second investigation, indicating nonneuronal deficits as well (6, 9). Most patients with idiopathic gastroparesis also exhibit a gradually progressive course without a clear triggering event for its onset, but do not have other associated neuropathic symptoms. A lesser dependence on vagal damage in idiopathic gastroparesis compared with diabetic disease comes from the observation that plasma pancreatic polypeptide responses to sham feeding are normal in patients with idiopathic gastroparesis but are blunted in diabetic patients with gastric stasis (10). As in diabetic patients, histological examination of gastric tissue from patients with idiopathic gastroparesis may reveal loss of myenteric neurons, damage to interstitial cells, or smooth muscle fibrosis (29, 34). However, one quarter of cases of idiopathic gastroparesis present acutely, often in association with viral fibrosis (29, 34). Prominent eosinophilic infiltrates were noted in the gastric smooth muscle layers and around nerve fibers in tissues from two patients (19). Another patient with idiopathic gastroparesis exhibited increases in myenteric CD4+ and CD8+ T lymphocytes (5). These findings point to a prominent inflammatory basis for some cases of idiopathic gastroparesis. The female predominance of idiopathic gastroparesis also suggests possible roles for genetic or hormonal factors. Although most cases of diabetic gastroparesis occur in women, men do not uncommonly develop this condition, indicating important roles for gender-neutral, diabetes-related factors. Finally, many patients with idiopathic disease exhibit disease resolution of disease over 1–3 yr whereas most cases of diabetic gastroparesis show a persistent or worsening course (2, 13, 28).

Gastric acid secretion is regulated by vagal neural input and by nonneuronal factors. Evidence showing impaired acid production in diabetes is conflicting. Acid output with sham feeding is reduced by two-thirds in diabetic subjects, reflecting impaired vagal responsiveness (8). Elevated gastrin levels in diabetic subjects have been correlated with measures of vagal dysfunction, such as abnormal heart rate variability and postural hypotension (27). Another study observed reductions in tetragastrin-evoked acid output in diabetic patients with autonomic neuropathy (23). However, some have reported normal basal and stimulated acid output in Type 2 diabetic patients (20, 27). Likewise, studies of acid secretion in animal models report variable findings. Acid output in animals with streptozotocin-induced diabetes show increased, normal, or decreased responses depending on the stimulus (1, 22, 32). Basal and histamine-stimulated acid output was reportedly decreased in alloxan diabetic rats (24). Nonneuropathic factors may contribute to reduced acid secretion in diabetes as well, since up to 25% of patients with Type 1 diabetes exhibit antiparietal cell antibodies (4). To date, no study has quantified abnormalities in gastric acidity in diabetic patients with gastroparesis. Gastric acid levels in patients with idiopathic gastroparesis are uninvestigated.

The findings of the present study provide convincing evidence for significant physiological differences between diabetic and idiopathic gastroparesis relating to gastric acidity. They further correlate gastric acidity with the severity of gastric retention in both types of gastroparesis. Increases in basal and postprandial gastric pH were observed in patients with diabetic gastroparesis whereas those with idiopathic gastroparesis exhibited pH levels that were similar to those of healthy control subjects. This supports the postulate that diabetic patients with gastroparesis exhibit impaired gastric acid secretion. Times to peak postprandial pH were selectively prolonged in the diabetic patients, which may reflect poor trituration and mixing of the ingested food with delayed intragastric buffering. Times to nadir pH also were longer in the diabetic group, possibly reflecting retardation of acid secretion. When both patient groups were analyzed, those with moderate to severe food retention on gastric scintiscans exhibited higher gastric pH levels under fasting and fed conditions than those with lesser degrees of gastroparesis. Within-group analyses of selected pH parameters suggested that both diabetic and idiopathic patients with more severe retention exhibited less gastric acidity than those with milder emptying delays. Diabetic subjects with both moderate-severe and mild gastroparesis showed trends to less gastric acidity than idiopathic patients with comparable degrees of gastric retention. These findings suggest the presence of two independent factors that relate to reduced gastric acidity-diabetes and moderate to severe gastric retention.

The probable explanation for these findings is that diabetic patients have neural defects that impair gastric acid release, whereas those with idiopathic gastroparesis do not exhibit as striking a neuropathic illness that would affect gastric acidity. Furthermore, acid secretory defects in both subject groups are more severe in those with moderate to severe gastric retention. This suggests a second independent factor in the impairment of acid secretion related to the magnitude of gastric stasis which suggests that, even among idiopathic patients, reduced acidity can occur albeit to a lesser degree than in the diabetic patients. An alternate possibility is that autoimmune factors leading to atrophic gastritis might be causative of reduced gastric acidity in the diabetic patients. Such a phenomenon is more common in those with diabetes of an immune basis, including many Type I patients (4). Unfortunately, patients were not stratified according to type of diabetes in the present study and mucosal biopsies were not obtained. Thus this possibility could not be addressed. A second alternate explanation for our findings is the possibility that poor glycemic control might have influenced results in the diabetic patients. This study was part of a larger survey of gastric emptying using the wireless transmitting capsule method and did not control for plasma glucose levels. Acute hyperglycemia can reduce acid secretion as well as pancreatic polypeptide release in response to sham feeding in healthy volunteers (18). Future studies employing euglycemic clamping techniques could resolve this issue.

Other factors are less likely to explain differences in the diabetic and idiopathic patients. *Helicobacter pylori* infection can reduce gastric acidity (7). However, other studies have reported no increase in *Helicobacter* infection in diabetes and have not shown that infection correlates with or causes gastroparesis (14, 15). Also, it would not be expected that the prevalence of *Helicobacter* infection in this diabetic population would be that much greater than in the healthy control subjects and idiopathic patients to cause such striking differences. Acid suppressant use probably had little effect on our findings. All subjects discontinued proton pump inhibitors 1 wk prior to study. It is unlikely that significantly more diabetic subjects...
used such agents than those with idiopathic disease or that recovery of acid secretion after their discontinuation would be a selective factor in the diabetic patients. However, reliable records were not obtained relating to chronic use of acid suppressants prior to study enrollment. Thus this issue cannot be addressed. A third possibility is that diabetic but not idiopathic patients might have retained food that would have buffered any acid in the stomach. This also is unlikely because retained food on endoscopy was an exclusion criterion for this study and rates of emptying were comparable in the two groups. A fourth concern that many of the idiopathic patients might have experienced disease resolution at the time of study is also not supported by the similar gastric retention results in the two groups. A fifth potential issue is that the reduced acidity in the diabetic patients contributes to delayed emptying. Indeed, proton pump inhibitors do delay gastric emptying in subjects without underlying gastroparesis (26). However, this cannot be the explanation for the idiopathic patients since their acidity levels were nearly normal. Finally, demographic characteristics of the groups show differences in age and percent-ages of women subjects. Indeed, gastroparesis patients exhibited a significantly greater female predominance than the healthy volunteers. However, there were no differences in age or gender in those with diabetic vs. idiopathic gastroparesis despite prominent differences in acidity in the two groups. Thus these factors are unlikely to represent explanations for the differential acid profiles in the different subject groups.

Other questions are raised by our findings that would be topics of future study. Because Type 1 and Type 2 diabetic patients have different clinical characteristics, it is reasonable to postulate differential defects in acid secretion. Likewise, this study did not discriminate patients with idiopathic gastropa-resis and a history of prior viral infection from those without such a history. It is possible that those with postviral disease might exhibit differences in gastric pH profiles from those who have no prior infection. Thirdly, this investigation quantified pH which can be an imperfect measure of acid secretion. Future investigations to measure secretion using validated techniques of intragastric titration would be needed to address this issue.

Finally, it is uncertain whether differences in gastric acidity pertain to any symptomatic manifestations of diabetic vs. idiopathic gastroparesis. Even though these diabetic patients exhibited abnormally high pH levels, acid-related esophageal disease can be prominent in patients with diabetic gastroparesis (25). There is significant overlap in symptoms and gastric function testing in patients with idiopathic gastroparesis compared with those with functional dyspepsia (31). In controlled trials, significant benefits have been demonstrated for proton pump inhibitors in functional dyspepsia. The efficacy of acid suppressing medications such as proton pump inhibitors in reducing symptoms in each form of gastroparesis has not been investigated. From the findings of this study, one might speculate that aggressive acid suppression might have greater effects in those with idiopathic gastroparesis than in patients with diabetes.

In conclusion, diabetic patients with gastroparesis exhibit reduced gastric acidity whereas patients with idiopathic gastroparesis show nearly normal pH profiles. Patients in both subject groups with severe gastric retention exhibit higher pH levels than those with mildly delayed gastric emptying. Thus both etiology and degree of gastric stasis determine gastric acidity in patients with gastroparesis.

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DISCLOSURES
Drs. Hasler, Chey, Koch, McCallum, Wo, Kuo, Siriin, Katz, and Parkman are consultants for the SmartPill Corporation. Ms. Hwang and Mr. Semler are employees of the SmartPill Corporation.

REFERENCES


