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

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Hasler WL, Coleski R, Chey WD, Koch KL, McCallum RW, Wo JM, Kuo B, Sitrin MD, Katz LA, Hwang J, Semler JR, Parkman HP. Differences in intragastric pH in diabetic vs. idiopathic gastroparesis: relation to degree of gastric retention. Am J Physiol Gastrointest Liver Physiol 294: G1384–G1391, 2008. First published April 10, 2008; doi:10.1152/ajpgi.00023.2008.—Evidence suggests that distinct mechanisms underlie diabetic and idiopathic gastroparesis. Differences in gastric acid in gastroparesis of different etiologies and varying degrees of gastric stasis are uninvestigated. We tested the hypotheses that 1) gastric pH profiles show differential alteration in diabetic vs. idiopathic gastroparesis and 2) abnormal pH profiles relate to the severity of gastric stasis. Sixty-four healthy control subjects and 44 gastroparesis patients (20 diabetic, 24 idiopathic) swallowed wirelessly transmitting capsules and then consumed 99mTc-sulfur colloid-labeled meals for 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). Meals evoked initial pH increases that were greater in diabetic (4.98 ± 0.32) than idiopathic patients (3.89 ± 0.39; P = 0.03) but not control subjects (4.48 ± 0.14). 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, an effect more pronounced in those with severely delayed gastric emptying. Idiopathic gastroparetic subjects exhibit nearly normal acid profiles, although those with severely delayed emptying show reduced acid vs. those with mild delays. Thus both etiology and degree of gastric stasis determine gastric acidity in gastroparesis.

gastric emptying; diabetes mellitus; gastric acid

The pathophysiological basis of the various etiologies of gastroparesis is not well delineated, but is likely multifactorial. Clinical observations suggest that the pathogenesis of diabetic gastroparesis differs from that of idiopathic gastroparesis. Gastroparesis typically complicates poorly controlled diabetes of long duration and is often associated with other diabetic complications including peripheral neuropathy. Many diabetic patients with gastroparesis exhibit evidence of autonomic dysfunction; however, histological studies show inconsistent morphological abnormalities in the vagus and enteric nervous system (16, 21, 33). Idiopathic gastroparesis may present insidiously or abruptly after an apparent viral prodrome (2). In contrast to diabetic disease, idiopathic gastroparesis is rarely associated with other neuropathic defects. However, as in diabetic gastroparesis, histological examination of gastric tissue from patients with idiopathic gastroparesis may reveal variable enteric neuronal damage (9, 34). The most convincing evidence of distinct pathophysiologies for the two etiologies of gastroparesis is provided by the observation that pancreatic polypeptide responses to sham feeding are normal in patients with idiopathic disease but are markedly blunted in diabetic patients with gastroparesis, indicative of greater vagal damage secondary to diabetes (10).

Gastric 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/m²), 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 \( \times \) 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-teusulfur 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 \( \pm 0.2 \) 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 most 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, which 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 \( \pm \) 0.16 min, which was not different in healthy subjects (1.45 \( \pm \) 0.15 min) compared with gastroparesis patients (1.82 \( \pm \) 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 × 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 $^{99m}$Tc peak with a 20% window (140 keV ± 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 radio-labeled tracer was quantified at 4 h after consumption of the low-fat meal.

Statistical Analysis

All results were expressed as means ± 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).

![Image](https://via.placeholder.com/150)

**Fig. 1.** Representative gastric pH tracings from individuals in each of the 3 subject groups are shown. In the top tracing (A) from a healthy volunteer, meal ingestion at time zero produces an abrupt increase from an acidic basal pH to a peak pH value within 15 min. A rapid reacidification phase follows, which reaches a nadir pH prior to capsule evacuation into the duodenum at ~200 min. In the middle tracing (B) from a patient with diabetic gastroparesis, the basal pH is much higher than in the healthy control. Meal ingestion produces a further increase in pH. The reacidification phase in this severely impaired individual is much slower and reaches a nadir pH much higher than for the healthy volunteer. Capsule evacuation is prolonged compared with the control subject. In the bottom tracing (C) from a patient with idiopathic gastroparesis, meal ingestion produces a brief neutralization phase from a low basal pH to a peak pH much less than that of the diabetic patient. Reacidification is rapid and the nadir pH is very acidic. As in the diabetic patient, capsule evacuation is delayed.

**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 ($P = 0.45$). 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 ($P = 0.45$). 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 (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 not 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 (≤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 \((P = 0.02); \text{Fig. 5}\). Healthy subjects and those with mild gastroparesis showed similar areas under the pH curves \((P = 0.93)\).

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

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

![Fig. 2. Basal, peak, and nadir pH values for each of the 3 subject groups are plotted. Basal pH values in the patients with diabetic gastroparesis were significantly higher than for the healthy volunteers and patients with idiopathic gastroparesis. Peak pH values were significantly higher in the diabetic patients compared with the patients with idiopathic gastroparesis; the healthy control subjects were intermediate. Nadir pH values were much greater in the diabetic patients than in the healthy control subjects, whereas those with idiopathic gastroparesis showed intermediate levels. Results are means ± SE.](http://ajpgi.physiology.org/ by 10.220.33.2 on August 28, 2017)

![Fig. 3. Areas under the pH curves for each of the 3 subject groups are plotted. Patients with diabetic gastroparesis exhibited increases in this parameter compared with both of the other groups. Results in healthy control subjects and patients with idiopathic gastroparesis were similar. Results are means ± SE.](http://ajpgi.physiology.org/ by 10.220.33.2 on August 28, 2017)

![Fig. 4. Basal, peak, and nadir pH values for healthy control subjects are compared with those of individuals with moderate (Mod)-severe (>20% gastric retention at 4 h) and mild (≤20% retention at 4 h) gastroparesis. Those with moderate-severe gastroparesis exhibited greater basal and nadir pH values compared with healthy control subjects and patients with mild gastroparesis. Patients with mild gastroparesis exhibited values similar to the healthy volunteers. Results are means ± SE.](http://ajpgi.physiology.org/ by 10.220.33.2 on August 28, 2017)
Idiopathic patients with moderate-severe gastroparesis showed higher nadir pH levels than those with mild gastroparesis. Results are means ± SE.

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 not 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.
(16, 33). Microscopic examination of gastric specimens re-
sected from diabetic patients with gastroparesis have also re-
vealed smooth muscle degeneration and fibrosis with eosino-
philic 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 progres-
sive 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 com-
pared 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 pa-
in diabetic patients with gastric stasis (10). As in diabetic
patients, histological examination of gastric tissue from pa-
patients with idiopathic gastroparesis may reveal loss of myen-
teric 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
prodromal symptoms (28). 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 gastro-
paresis 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 produc-
tion 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 dysfunc-
tion, such as abnormal heart rate variability and postural
hypotension (27). Another study observed reductions in tetra-
 gastrin-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 re-
sponses depending on the stimulus (1, 22, 32). Basal and
histamine-stimulated acid output was reportedly decreased in
alloxan diabetic rats (24). Nonneuropathic factors may con-
tribute 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 unin-
vestigated.

The findings of the present study provide convincing evi-
dence for significant physiological differences between dia-
betic 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 gas-
troparesis exhibited pH levels that were similar to those of
healthy control subjects. This supports the postulate that dia-
betic 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 inra-
gastric 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 idio-
pathic patients with more severe retention exhibited less gas-
tric acidity than those with milder emptying delays. Diabetic sub-
jects 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 neurophysiological illness that would affect gastric
d 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 influ-
enced results in the diabetic patients. This study was part of a
larger survey of gastric emptying using the wireless transmit-
cing 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 euglyce-
ic 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 gastro-
paresis (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 sub-
jects 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 effects in acid secretion. Likewise, this study did not discriminate patients with idiopathic gastropare-sis 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 gastropare-sis 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.

GRANTS

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DISCLOSURES

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

REFERENCES


