Relationship Between Glycemic Control and Gastric Emptying in Poorly Controlled Type 2 Diabetes

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BACKGROUND & AIMs: Acute hyperglycemia delays gastric emptying in patients with diabetes. However, it is not clear whether improved control of glycemia affects gastric emptying in these patients. We investigated whether overnight and short-term (6 mo) improvements in control of glycemia affect gastric emptying.

METHODS: We studied 30 patients with poorly controlled type 2 diabetes (level of glycosylated hemoglobin, >9%). We measured gastric emptying using the [13C]-Spirulina platensis breath test on the patients’ first visit (visit 1), after overnight administration of insulin or saline, 1 week later (visit 2), and 6 months after intensive therapy for diabetes. We also measured fasting and postprandial plasma levels of C-peptide, glucagon-like peptide 1, and amylin, as well as autonomic functions.

RESULTS: At visit 1, gastric emptying was normal in 10 patients, delayed in 14, and accelerated in 6; 6 patients had gastrointestinal symptoms; vagal dysfunction was associated with delayed gastric emptying (P < .05). Higher fasting blood levels of glucose were associated with shorter half-times of gastric emptying (t1/2) at visits 1 (r = -0.46; P = .01) and 2 (r = -0.43; P = .02). Although blood levels of glucose were lower after administration of insulin (132 ± 7 mg/dL) than saline (211 ± 15 mg/dL; P = .0002), gastric emptying t1/2 was not lower after administration of insulin, compared with saline. After 6 months of intensive therapy, levels of glycosylated hemoglobin decreased from 10.6% ± 0.3% to 9% ± 0.4% (P = .0003), but gastric emptying t1/2 did not change (92 ± 8 min before, 92 ± 7 min after). Gastric emptying did not correlate with plasma levels of glucagon-like peptide 1 and amylin.

CONCLUSIONS: Two-thirds of patients with poorly controlled type 2 diabetes have mostly asymptomatic yet abnormal gastric emptying. Higher fasting blood levels of glucose are associated with faster gastric emptying. Overnight and sustained (6 mo) improvements in glycemic control do not affect gastric emptying.

Keywords: Gastroparesis; Autonomic; Diabetes Mellitus; DM.

Diabetes mellitus (DM) is associated with abnormal (ie, delayed or rapid) gastric emptying (GE), which frequently is asymptomatic and may affect glycemia control. Although most studies have focused on gastroparesis in type 1 DM, type 2 DM also is associated with GE disturbances. The risk factors for delayed GE in DM are partly understood; autonomic neuropathy, enteropathy, and hyperglycemia are the most frequently implicated mechanisms. Acute hyperglycemia (ie, a blood glucose concentration of 16–20 mmol/L) delayed GE in type 1 DM compared with euglycemia. Moreover, even acute “physiological hyperglycemia” (blood glucose concentration of 8 vs 4 mmol/L) delayed GE in type 1 DM. Although similar assessments have not been performed in type 2 DM, a cross-sectional study observed that the emptying of liquids and the duration of the lag phase, but not overall emptying, for solids were related to the blood glucose concentration in type 2 DM.

The relationship between long-term control of glycemia, as measured by glycosylated hemoglobin (HbA1c),
and GE in DM also is unclear. In cross-sectional epidemiologic studies, increased HbA1c levels were a risk factor for gastrointestinal (GI) symptoms in a cohort of patients with predominantly type 2 DM. However, in another study, HbA1c levels were not significantly different among 3 groups of patients with DM (ie, no GI symptoms, GI symptoms and delayed GE, and GI symptoms and normal GE). In longitudinal studies, intensive control of glycemia reduced the incidence of microvascular (retinopathy and nephropathy) and neuropathic complications in type 1 and type 2 DM. However, the effects of improving glycemia control on GE in DM are essentially unknown. In the only study to assess the question, improved control of glycemia did not improve GE 1 week later in 10 patients with type 2 DM. The Adelaide group assessed the natural history of GE disturbances in DM. Beginning with a cohort of 86 patients, 20 patients (16 had type 1 DM) were reassessed 12 years later, and 13 patients (12 had type 1 DM) were reassessed approximately 25 years after the first study. Despite a reduction in HbA1c level, which was statistically significant at the earlier follow-up point (ie, 8.4% ± 2.3% at baseline, 7.6% ± 1.3% at 12 years mean ± SD), GE was stable over time when assessed for the entire group. Hence, the impact of improving glycemia control on GE in type 2 DM is incompletely understood.

Therefore, we evaluated GE on 3 occasions (ie, at baseline, after overnight insulin or saline administration, and after short-term [6 mo] modification of glycemic therapy) to optimize glycemia control in 30 patients with poorly controlled type 2 DM. Our hypotheses were that improved glycemia control will improve GE acutely and after short-term [6 mo] modification. This study was limited to patients with poorly controlled type 2 DM. Our hypotheses were that improved glycemia control will improve GE acutely and after short-term modification (1:1) to overnight insulin or saline infusions. Hence, the impact of improving glycemia control on GE in patients with type 2 DM is incompletely understood.

Therefore, we evaluated GE on 3 occasions (ie, at baseline, after overnight insulin or saline administration, and after short-term [6 mo] modification of glycemic therapy) to optimize glycemia control in 30 patients with poorly controlled type 2 DM. Our hypotheses were that improved glycemia control will improve GE acutely and in the short term. This study was limited to patients with type 2 DM because we sought to reduce heterogeneity in this cohort. Moreover, because, on average, patients with type 1 DM are more likely to have peripheral and autonomic neuropathy, we reasoned that improved glucose control would be more likely to improve GE in patients with type 2 DM.

### Methods

#### Study Design

This was a single-center study, approved by the Mayo Clinic Institutional Review Board, to evaluate whether improving glycemia control affected GE in 30 patients with poorly controlled type 2 DM. The acute intervention comprised balanced single-blind (patient only) randomization (1:1) to overnight insulin or saline infusions. Thereafter, the management of DM was modified as deemed appropriate as part of their clinical management, generally by endocrinologists, for the next 6 months. GE was evaluated at baseline, after the acute intervention 1 week thereafter, and at 6 months. GI symptoms and autonomic functions were assessed at baseline and at 6 months. Plasma hormone concentrations were evaluated concurrently during GE studies at baseline and after the acute intervention.

### Participants

Eligible participants were all patients aged 18 years and older with poorly controlled type 2 DM (HbA1c >9%) in whom the management of DM was scheduled to be modified as part of clinical practice. Exclusion criteria included severe nausea or vomiting before study activities, serum creatinine level greater than 1.5 mg/dL, current or anticipated use of medications most likely to affect GI motility (eg, opiates, metoclopramide, erythromycin, exenatide, or pramlintide) or glycemia control (eg, steroids), serious systemic illness (eg, cardiovascular or pulmonary disorder, psychiatric illness, ongoing systemic cancer) or any prior gastric, intestinal, or colonic resection, consideration of major surgery (eg, pancreas or kidney transplantation, dialysis, bariatric surgery) within the next 6 months, documented serial noncompliance with management, and allergies to eggs, wheat, or milk.

### Assessment of Gastric Emptying by 13C-Octanoate Breath Test

All 3 breath tests were performed in the morning after an overnight fast. GE was evaluated by an established validated 13C-Spirulina platensis breath test. Briefly, S. platensis is a protein-rich, blue-green algae that is sold as a dietary supplement in the United States. The 13C content of Spirulina is increased to 99% by growing it in a closed hydroponics chamber charged with a pure 13C-source. The 13C-labeled S. platensis is incorporated into the egg mix and can be released from the algal cells only after the egg mix is emptied from the stomach, the cells are digested, and the 13C-labeled substrates (algal protein, fat, and carbohydrate) are absorbed and metabolized. The test meal contains 27 grams of freeze-dried egg mix, 6 saltine crackers, and 180 mL of water with a caloric content of 223 kcal (19.2 g carbohydrates, 12 g protein, and 10.9 g fat).

Breath samples were collected at baseline (ie, before the meal) and at 15, 30, 45, 60, 90, 120, 150, 180, and 240 minutes after the meal in glass screwcap Exetainer tubes (Labco Limited, High Wycombe, UK) using a straw to blow into the bottom of the tube to displace contained air. After recapping the tubes, the 13CO2 breath content was determined in a centralized laboratory (AB Diagnostics, Brentwood, TN) by gas isotope ratio mass spectrometry. The 13C enrichment was expressed as the delta per milliliter difference between the 13CO2/12CO2 ratio of the sample and the standard. To calculate the quantity of 13C appearing in breath per unit time, delta over baseline was used as follows: 0.0112372 is the isotopic abundance of the limestone standard, Pee Dee Belemnite, and CO2 production was corrected for age, sex, height, and weight using the algorithms of Schofield.
Plasma samples were placed in ice, centrifuged at 40, 120, 180, and 240 minutes during GE studies at all 3 visits. By standardized methods during visits 1 and 3. Carboxymethylcellulose (PAGI-SYM) at baseline and at the 6-month visits. Assessment of upper gastrointestinal symptom severity were measured during the meal, the 10th to 90th percentile range for GE t_{half} in healthy subjects is 50 to 97 minutes.

Symptom Questionnaires

GI symptoms were evaluated by the validated patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM) at baseline and at the 6-month visits. Patients were asked to rate the severity of 20 upper GI symptoms over the preceding 2 weeks.

Autonomic Functions

Cardiovascular and adrenergic functions were evaluated by standardized methods during visits 1 and 3. Cardiovascular functions were evaluated by heart-rate responses to deep breathing (HRDB) and the Valsalva maneuver. HRDB was the heart-rate range with the subject supine and breathing at 6 breaths per minute. For the Valsalva maneuver, the subject was rested and recumbent and was asked to maintain a column of mercury at 40 mm Hg for 15 seconds. The Valsalva ratio is the ratio of maximal-to-minimal heart rate. Vagal functions were scored by the results of the HRDB and Valsalva maneuver. Adrenergic function was evaluated by blood pressure and heart rate responses, monitored continuously (Finapres monitor; Ohmeda, Englewood, CO), to a Valsalva maneuver. The results of the autonomic battery of tests were corrected for confounding effects of age and sex using established norms. The Composite Autonomic Severity Score (CASS) consists of 2 subscores: cardiovagal (CASS-vag, 0–3) and adrenergic (CASS-adr, 0–3). The total score and subset scores provide an evaluation of the severity and distribution of autonomic failure.

Blood Glucose and Plasma Hormone Concentrations

Blood samples were collected before and at 15, 30, 60, 120, 180, and 240 minutes during GE studies at all 3 visits. Plasma samples were placed in ice, centrifuged at 40°C, separated, and stored at -70°C until assay. Plasma glucose concentrations were measured during all 3 GE studies. Because glucagon-like peptide 1 (GLP-1), amylin, and insulin-associated hypoglycemia can delay GE,

\[ C_{\text{peak}} \times (t_{\text{max}} - t_{\text{half}}) \]

plasma concentrations of C-peptide, amylin, and GLP-1 were measured during the first and second GE studies. The plasma glucose level was measured on the Cobas c311 analyzer (Roche Diagnostics, Indianapolis, IN) using a hexokinase reagent. The insulin C-peptide level was measured by a 2-site immune-enzymatic sandwich assay on the Cobas e411 analyzer (Roche Diagnostics). GLP-1 (active) was measured by a quantitative 2-site enzyme immunoassay from Linco Research, Inc (St. Charles, MO). Dipeptidyl peptidase 4 inhibitor (30 μL; Linco Research) was added to these tubes. The total human amylin enzyme-linked immunosorbent assay (EZHAT-51K; Millipore, Bedford, MA) is a monoclonal antibody-based sandwich immunoassay for determining total amylin levels in human plasma.

Statistical Analysis

Analysis of covariance was used to compare post-treatment (ie, acute intervention with insulin vs saline, visit 2) values for GE t_{half}. The baseline t_{half} was included as a covariate. Paired t tests were used to compare baseline and 6-month HbA1c level and GE t_{half}. The postprandial increments in plasma hormone concentrations (eg, first 30 minutes) were compared with zero using a paired t test or signed rank test, as warranted.

Relationships among GE t_{half}, glycemic measures (HbA1c and fasting glucose concentrations), and plasma hormone concentrations were evaluated by Spearman correlation coefficients. The effect of insulin (vs saline) on hormonal responses during GE tests was evaluated by a repeated-measures analysis of covariance (the corresponding mean hormone level from the baseline study was included as the covariate).

Changes in CASS (baseline vs visit 3) were assessed using Bowker’s test for symmetry. The association of GE (fast, slow, overall abnormal) with CASS scores was assessed using contingency table analyses.

All results are presented as means (±SEM).

Post Hoc Sample Size Assessment

In this cohort, the residual between subject standard deviation at study 2 in the analysis of covariance model was 29.5 minutes. With 15 subjects per group, there was approximately 80% power to detect differences between groups in GE t_{half} values of 32 minutes. The observed within-subject SD (baseline vs after 6 months) was 36 minutes. After excluding 1 subject from the 6-month analysis as discussed later, the remaining 29 subjects provided approximately 80% power to detect a difference of ≥19.5 minutes between baseline and 6-month values for t_{half} using a paired t test.

Results

Participants, Study Conduct, and Completion

A total of 123 patients with poorly controlled DM2 and an HbA1c level greater than 9% were assessed for
elibility. Of these, 47 patients were not eligible to participate, 44 patients were eligible but declined to participate, and 2 patients were eligible but were not approached because of language barriers. Hence, 30 patients (17 women: age, 55 [±2] y; body mass index, 34 [±1] kg/m²) were enrolled in the study and all completed the entire study (Table 1).

At baseline, patients had DM for 11 (±1) years and the HbA1c level was 10.6% (±0.3%); 4 patients were not taking any medications for DM, 13 patients were on oral hypoglycemic agents alone, 7 patients were on insulin alone, and 6 patients were being treated with insulin and oral agents. Thirteen patients had nephropathy, 7 patients had retinopathy, and 4 patients had both.

**Relationship Between Blood Glucose and Gastric Emptying**

At baseline, 10 patients had normal GE, 14 patients had delayed GE, and 6 patients had accelerated GE. Vagal dysfunction was associated (P < .05) with delayed GE. Fasting blood glucose concentrations just before the GE study were correlated inversely with GE t½ for the baseline (r = -0.46; P = .01) and postinsulin/saline visits (r = -0.43; P = .02) (ie, higher concentrations were associated with a shorter GE t½) (Figure 1). However, fasting blood glucose concentration was not associated with GE t½ at the 6-month visit (r = 0.04; P = .85). Likewise, the mean blood glucose concentration for the entire GE study was correlated inversely with GE t½ for the baseline (r = -0.51; P = .004) and postinsulin/saline visits (r = -0.36; P = .05) (ie, higher concentrations were associated with shorter GE t½). However, blood glucose concentration was not associated with GE t½ at the 6-month visit (r = -0.18; P = .38).

**Effects of Overnight Insulin or Saline Infusion on Gastric Emptying**

Blood glucose concentrations before saline (325 [±23] mg/dL) and insulin infusions (275 [±20] mg/dL) commenced were not significantly different (P = .11). The blood glucose concentration was lower (P = .0002) after overnight insulin (132 ± 7 mg/dL) than saline (211 ± 15 mg/dL) infusion (Supplementary Figure 1). However, the GE t½ was not significantly different after insulin (91 ± 11 minutes before, 97 ± 10 minutes after) or saline (93 ± 12 minutes before, 81 ± 8 minutes after) infusions (Figure 2). The change in GE was correlated inversely (r = -0.45; P = .01) with the change in fasting blood glucose concentrations between the first and second studies. This indicates that a greater reduction in fasting blood glucose concentration between visits 1 and 2 was associated with a smaller change in GE t½.

Among 14 patients with delayed GE at baseline, blood glucose level decreased from 194 ± 14 mg/dL before to 160 ± 16 mg/dL (P = .03) after overnight infusion of saline or insulin. Among these patients, we also noted that fasting blood glucose concentrations just before GE assessments were correlated inversely with GE t½ for the baseline study (r = -0.56; P = .04) (ie, higher blood glucose concentrations were associated with shorter t½). Moreover, the change in GE was correlated inversely (r = -0.69; P = .007) with the change in fasting blood glucose concentrations between the first and second studies (ie, a larger reduction in fasting blood glucose concentrations was associated with a smaller reduction in GE t½) (Supplementary Figure 1, right panel).

**Effects of Intensive Therapy for 6 Months on Glycemia Control and on Gastric Emptying**

Changes to the diabetes regimen during the 6-month intensive therapy period included lifestyle change only (2 patients), initiation or modification of oral medication only (12 patients), of insulin only (12 patients), initiation of insulin and modification of oral medication (3 patients), and initiation of exenatide (1 patient) (Table 2, Figure 3). Because exenatide delays GE, this patient was not included in the analysis. In the remaining 29 patients, HbA1c concentrations decreased (P = .0003) from 10.6% ± 0.3% before to 9% ± 0.4% at 6 months after modifying therapy. The reduction in HbA1c level was greatest among patients in whom insulin and oral therapy were modified, and least in patients who underwent lifestyle modification only. Despite this improvement in

**Table 1. Demographics and Other Baseline Features**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Placebo (saline)</th>
<th>Insulin</th>
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<td>Patients, n</td>
<td>30</td>
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<tr>
<td>Females</td>
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<td>9</td>
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<tr>
<td>Duration of DM, y</td>
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<td>9 ± 1</td>
<td>12 ± 2</td>
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<tr>
<td>HbA1c level at baseline, %</td>
<td>10.55 ± 0.26</td>
<td>11.01 ± 0.43</td>
<td>10.09 ± 0.26</td>
</tr>
<tr>
<td>HbA1c level at 6-month follow-up evaluation, %</td>
<td>8.92 ± 0.37</td>
<td>9.06 ± 0.63</td>
<td>8.79 ± 0.40</td>
</tr>
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<td>Fasting blood glucose level, mg/dL*</td>
<td>222 ± 11</td>
<td>236 ± 13</td>
<td>209 ± 17</td>
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<tr>
<td>Diabetic retinopathy, n</td>
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<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Nephropathy, n</td>
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<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Moderate or severe vagal or adrenergic dysfunction, n</td>
<td>11</td>
<td>5</td>
<td>6</td>
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<tr>
<td>Baseline GE</td>
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</tr>
<tr>
<td>Rapid</td>
<td>6</td>
<td>3</td>
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</tr>
</tbody>
</table>

BMI, body mass index.

*Just before baseline GE study.
HbA1c level, overall GE was not significantly different after 6 months of intensive therapy (Figure 4) and the relationship between changes in HbA1c level and changes in GE were not significant ($r = -0.13; P = .5$). Likewise, the correlation between differences in GE and fasting blood glucose concentrations between the first and third studies was not significant ($r = 0.17; P = .40$).

The relationship between HbA1c level and GE $t_{\text{half}}$ also was considered separately in patients with delayed and normal GE at visit 1. Among patients with delayed GE at the first visit, HbA1c level decreased from $10.2\% \pm 0.3\%$ to $8.9\% \pm 0.4\%$ ($P = .03$) at 6 months. The fasting blood glucose level before the GE study was $194 \pm 14$ mg/dL at baseline and $190 \pm 21$ mg/dL at 6 months. GE $t_{\text{half}}$ decreased ($P = .19$) from $128 \pm 9$ minutes at baseline to $113 \pm 10$ minutes at 6 months. Among patients with normal GE at baseline, HbA1c level decreased from $10.8\% \pm 0.4\%$ to $9.1\% \pm 0.6\%$ ($P = .003$) and GE $t_{\text{half}}$ increased ($P = .09$) from $59 \pm 5$ minutes at baseline to $69 \pm 8$ minutes at 6 months; the fasting blood glucose level before beginning the GE study was $247 \pm 15$ mg/dL at baseline and $205 \pm 23$ mg/dL at 6 months. Hence, after intensive therapy, GE $t_{\text{half}}$ decreased, albeit not significantly, in patients with delayed GE, but increased in patients with normal GE $t_{\text{half}}$ at baseline. Baseline GE was borderline associated ($P = .05$) with the change in $t_{\text{half}}$ from baseline to 6 months.

GE $t_{\text{half}}$ values were correlated significantly between the first and second visits ($r = 0.54; P = .002$) and between the first and third visits ($r = 0.63; P = .0003$). However, among patients with delayed GE at baseline, correlations between GE ($t_{\text{half}}$) values for the first vs second visits ($r = 0.002; P = .99$) and for the first vs third visits ($r = 0.24; P = .40$) were not significant. Among patients who received saline, the difference between the first and second GE values was not related to the average of both studies (ie, the Bland Altman test was negative) (Supplementary Figure 2).
Effects of Intensive Therapy on Autonomic Dysfunction

At baseline, 14 patients had vagal dysfunction, which ranged from mild (n = 8), moderate (n = 6), to severe (n = 4). Eight patients had adrenergic dysfunction, which was mild (n = 6) or moderate (n = 2). Compared with baseline, vagal functions were unchanged in 20 patients, improved by 1 grade in 4 patients, and worsened by 1 grade in 5 patients at 6 months after intensive therapy; 1 patient had frequent extra systoles, precluding a reliable assessment at the 6-month visit. Of these 9 patients with improvement or deterioration, 8 had no or mild dysfunction and 1 had moderately severe vagal dysfunction at baseline. Likewise, adrenergic functions were unchanged in 20 patients. Adrenergic functions improved in 5 patients who had mild (n = 4) or moderate (n = 1) dysfunction at baseline. Adrenergic functions worsened in 2 patients who had no dysfunction at baseline. In the remaining 3 patients, the 6-month assessment was not performed (1 patient) or was incomplete because high intraocular pressure or retinopathy precluded assessment of the Valsalva maneuver (2 patients).

Relationship Between Gastric Emptying and Plasma Hormone Concentrations

Fasting and peak plasma C-peptide concentrations were ≥200 pmol/L in 29 patients and all 30 patients, respectively, suggesting a relatively preserved endogenous insulin reserve. Plasma concentrations of GLP-1,
Amylin, and C-peptide increased after the GE breath test meal (Supplementary Table 1), and these concentrations differed among postprandial time points (i.e., plasma C-peptide \( P < .0001 \), amylin \( P < .0001 \), and GLP-1 \( P = .06 \)). During the second GE study, the mean postprandial concentrations and the temporal profile were not different between the insulin and saline groups. During the first and second GE studies, postprandial increments in plasma concentrations of GLP-1 and amylin were not correlated with GE (data not shown). There was a significant correlation between plasma concentrations of amylin and C-peptide at corresponding time points (r value range, 0.62–0.83; \( P < .003 \)). Plasma hormone concentrations were not measured during the third GE study.

**Gastrointestinal Symptoms**

At baseline, 6 patients reported GI symptoms. Of these, 5 patients had mild symptoms and 1 patient had severe symptoms; 4 had abnormal (delayed, 3 patients; or accelerated, 1 patient) GE. Symptoms were heartburn/regurgitation (1 patient), nausea/vomiting (1 patient), upper abdominal pain (1 patient), lower abdominal pain (4 patients), and bloating (1 patient). The overall 20-item PAGI-SYM score was 0.4 ± 0.1, for which scores of 0 and 1 reflect no symptoms and very mild symptoms, respectively. At 6 months, 6 patients, including 4 patients who had symptoms at baseline, reported 1 or more mild GI symptoms (nausea/vomiting, 1 patient; lower abdominal pain, 4 patients; postprandial fullness, 1 patient; and bloating, 2 patients); the overall PAGI-SYM score was 0.3 ± 0.1. Four of these 6 patients had abnormal (3 had delayed) GE.

**Discussion**

Although several studies have shown that acute hyperglycemia can delay GE in human beings, the effects of improving glycemia control on GE in DM are unknown. There are 3 main observations from this study. First, contrary to current concepts, higher fasting blood glucose concentrations were associated with shorter \( t_{1/2} \) for GE (i.e., faster emptying) during baseline and after insulin/saline visits in patients with poorly controlled type 2 DM. Second, after overnight treatment with insulin or saline, changes in blood glucose concentrations were correlated inversely with changes in GE \( t_{1/2} \) (i.e., a smaller change in blood glucose concentration was associated with a more pronounced reduction in GE \( t_{1/2} \)). Third, control of glycemia but not GE significantly improved 6 months after more intensive antihyperglycemic therapy.

At baseline, nearly two thirds of patients had abnormal (i.e., delayed, 46%; or rapid, 17%) GE, but most were asymptomatic. Nineteen patients (i.e., nearly two thirds) had autonomic (vagal or adrenergic) dysfunction, which is similar to the prevalence in a prior cohort of patients with DM and symptomatic upper GI motility disorders.\(^5\) Vagal dysfunction was associated with delayed GE in this study. The prevalence of delayed GE in this cohort, which was not selected on the basis of GI symptoms, was higher than previously documented in patients with type 2 DM.\(^{29–33}\) For example, in a study from Olmsted County, only 1% of patients with type 2 DM developed symptoms of
gastroparesis and/or delayed GE over 10 years. However, this figure may be an underestimate because GE disturbances often are asymptomatic and GE was evaluated in only a minority of patients in that study. The present observations reinforce concepts that are well established in type 1 but less so in type 2 DM, which is that DM is associated with frequently asymptomatic delayed or rapid GE.

Compared with euglycemia (blood glucose level, 5–8 mmol/L), acute hyperglycemia (blood glucose level, 16–20 mmol/L) delayed GE in healthy subjects and in type 1 DM. Moreover, acute hyperglycemia for 24 hours induced apoptosis in murine myenteric neurons. Current concepts emphasize the contribution of hyperglycemia to delayed GE. Indeed, consensus guidelines for GE scintigraphy issued by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine recommend that if the blood glucose level is greater than 275 mg/dL on the morning of the test, the glucose level should be lowered with insulin to 275 mg/dL before commencing the test. In contrast, we observed an inverse correlation between fasting glucose concentration and GE, both at baseline and during the second visit, which was preceded by treatment of hyperglycemia. Insulin was not administered for increased fasting blood glucose concentrations just before the GE study because we sought to examine the relationship between the fasting blood glucose concentration and GE. Of interest, 9 of 90 GE studies were preceded by a blood glucose concentration greater than 275 mg/dL. Among these patients, 2 had normal GE, 2 had delayed GE, and 5 had rapid GE. Moreover, among patients with delayed GE at baseline, a smaller reduction in fasting blood glucose concentration was associated with a more pronounced reduction in GE between baseline and second visits.

There are 2 critical implications of the latter observation. First, they suggest that the short-term reproducibility of GE in patients with DM is relatively limited even when the blood glucose concentration is relatively stable between initial and subsequent assessments. Second, they do not support the prevailing concept that hyperglycemia per se up to plasma concentrations observed in this study significantly delays GE in type 2 DM. What might explain these differences between current concepts and the present findings? One possibility is that the effects of hyperglycemia on GE depend on the diabetic phenotype. Indeed, this study was conducted in type 2 DM, whereas the effects of acute hyperglycemia on GE have been studied only in healthy people and in type 1 DM. There are considerable data from animal models (ie, Lepr db/db and nonobese diabetic mice) suggesting that hyperglycemia also is associated with rapid GE. In the Lepr db/db mice, which represent a model for type 2 DM, hyperglycemia induced hyperplasia of the stem cells of interstitial cells of Cajal (ICC) and ICC themselves, which lead to accelerated GE. Hyperplasia of ICC occurred despite reduced signaling by the insulin-like growth factor 1–dependent Kit ligand, which normally sustains ICC. Even in nonobese diabetic mice, which represent a model for type 1 DM, hyperglycemia is associated initially with rapid GE. Subsequently, it is only when oxidative stress and reduced Kit signaling are not offset by mechanisms such as the up-regulation of the antioxidant enzyme heme-oxygenase 1 and mitogen-activated protein kinases, respectively, that ICC are depleted, and GE is delayed. Taken together, these observations suggest the hypothesis that ICC likely are preserved in patients with DM and rapid GE.

Plasma amylin, GLP-1, and C-peptide concentrations increased after the GE meal. Confirming the accuracy of these measurements, plasma concentrations of amylin and C-peptide were correlated strongly, which is consistent with co-secretion of these hormones by the islets. Might hormonal differences explain the different effects of hyperglycemia on GE in type 1 and type 2 DM? Although insulin-induced hypoglycemia (but not euglycemic hyperinsulinemia) accelerated GE in DM, this explanation seems unlikely because patients were euglycemic during overnight insulin administration and infusions (insulin or saline) were discontinued before the GE study. Pharmacologic concentrations of GLP-1 and amylin can delay GE, and impaired hyperglycemia-induced release of amylin, which delays GE, may contribute to rapid GE in DM. However, plasma concentrations of amylin and GLP-1 were not correlated with GE, which argues against the explanation that inadequate release of amylin or GLP-1 is responsible for rapid GE and hyperglycemia. Previous studies have suggested that higher glucagon concentrations in isolation are unlikely to explain rapid GE in type 2 DM.

During the 6-month period, therapy for diabetes was managed per clinical practice, generally by endocrinologists. Thereafter, HbA1c concentrations improved significantly and by a magnitude comparable with the average improvement in HbA1c in randomized trials (eg, 1%–2% for monotherapy with metformin or sulfonylureas, 0.5%–1.4% for monotherapy with thiazolidinediones, and 1.5%–3.5% for insulin). However, improved control of glycemia at 6 months was not associated with a significant improvement in GE either in the overall cohort or in patients who had delayed GE at baseline. Among 14 patients with delayed GE, the mean thalf was 128 minutes. Because the upper range of normal for GE thalf is 97 minutes, a reduction of approximately 35 minutes was required to normalize GE. Fourteen subjects provided 79% power to detect this difference; hence, a type II error is unlikely.

Some diabetes guidelines recommend that the target HbA1c value for nonpregnant patients is less than 7%. However, a systematic review of large randomized controlled trials in patients with type 2 diabetes suggests that “tight control of glycemia burdens patients with complex treatment programs, hypoglycemia, weight gain, and costs and offers uncertain benefits in return.” For example, the United Kingdom Prospective Diabetes Study...
metformin trial reported that tight control of glycemia reduced mortality risks, whereas the Action to Control Cardiovascular Risk in Diabetes trial reported that tight control increased these risks. Moreover, it is unlikely the substantial improvement in HbA1c concentrations reported in these trials can be replicated in clinical practice. For example, a systematic review of 52 studies that implemented care management models in clinical practice observed a statistically significant but trivial reduction of HbA1c values (weighted difference in means, -0.21%; 95% confidence interval, -0.40 to -0.03; \( P < .03 \)) with intensive therapy.\(^4\) Similar to other complications of DM (eg, microvascular disease, nephropathy, neuropathy), it is conceivable that a more pronounced and/or long-term improvement in control of glycemia is necessary to restore GE,\(^12\) assuming that delayed GE is not a result of irreversible mechanisms (eg, loss of ICC). Alternatively, similar to the phenomenon of metabolic memory for autonomic neuropathy in type 1 DM, it is conceivable that intensive control of glycemia will improve GE only if it is instituted relatively early in the disease.\(^49\) Indeed, a recent study showed a striking improvement, indeed normalization, of GE 3 months after improving control of glycemia in 30 women with recently diagnosed type 2 DM.\(^50\) However, the improvement in HbA1c concentration from an average of 10.5% to 5.8% at 2 to 3 months after beginning glipizide in that trial far exceeds the effect of monotherapy in other trials.\(^46\)

These findings have implications on clinical practice. First, consideration should be given to assessing GE, even in asymptomatic patients with type 2 DM, because GE disturbances may at least partly explain impaired control of glycemia.\(^43\) The \(^{13}\)C-spirulina breath test, which has been validated extensively in healthy subjects and disease, provides an effective and noninvasive approach to measure GE without radiation exposure. Second, because GE assessments in DM may be variable, consideration should be given to re-evaluating GE when indicated in patients with type 2 DM. To emphasize, higher variability in GE was associated with a smaller change in blood glucose concentrations between the first and second visits. Third, the recommendation to cancel GE assessment in patients with type 2 DM when the fasting blood glucose level is greater than 275 mg/dL should be revisited.\(^38\) Fourth, although better control of glycemia generally is beneficial, long-term studies are necessary to clarify whether improved control of glycemia improves GE in type 2 DM. Because these patients were mostly asymptomatic, the extent to which these findings are applicable to symptomatic patients with poorly controlled type 2 DM is unclear.

In summary, these observations show that nearly two thirds of patients with poorly controlled type 2 DM had, mostly asymptomatic, delayed (46%) or rapid GE. Although overnight insulin infusion and subsequent therapy (6 months) improved control of glycemia, neither significantly affected GE in patients with poorly controlled type 2 DM. Higher fasting blood glucose concentrations were associated with a shorter \(t_{\text{half}}\) for GE (ie, faster emptying), and after treatment with insulin or saline the changes in blood glucose concentrations were correlated inversely with changes in GE \(t_{\text{half}}\).

**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org), and at [http://dx.doi.org/10.1016/j.cgh.2014.06.034](http://dx.doi.org/10.1016/j.cgh.2014.06.034).

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Figure 1. Comparison of effects of insulin and saline on blood glucose concentrations. (Left panel) Blood glucose concentrations decreased significantly during overnight saline and insulin infusions and were lower after insulin than saline. (Right panel) Note the inverse relationship between the change in fasting blood glucose concentration and GE t_{1/2} between the first and second visits.

Supplementary Figure 2. Comparison of GE results in patients who received saline infusion between the first and second studies. (Left panel) GE measurements deviated considerably from the line of equality. (Right panel) Differences between the first (GE1) and second (GE2) gastric emptying values were not related to the average of these 2 studies (ie, the Bland Altman test was negative).

Supplementary Table 1. Fasting and Postprandial Hormone Concentrations

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Visit 1</th>
<th>Visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting concentration</td>
<td>Postprandial increment</td>
</tr>
<tr>
<td>GLP-1, pg/mL</td>
<td>4.2 ± 0.9</td>
<td>5.4 ± 0.9^a</td>
</tr>
<tr>
<td>IAPP, pmol/L</td>
<td>21.1 ± 3.8</td>
<td>4.8 ± 0.7^a</td>
</tr>
<tr>
<td>C-peptide, pmol/L</td>
<td>1010 ± 100</td>
<td>110 ± 20^a</td>
</tr>
</tbody>
</table>

NOTE. The postprandial increment reflects the difference in the peak postprandial concentration minus the fasting concentration.

IAPP, islet amyloid polypeptide.

^aP < .0001 vs 0.