Relationships between Gastric Emptying, Intragastric Meal Distribution and Blood Glucose Concentrations in Diabetes Mellitus

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The aim of this study was to evaluate the prevalence of disordered intragastric meal distribution and the relationships between gastric emptying, intragastric distribution, glycemic control and gastrointestinal symptoms in diabetes mellitus. **Methods:** Eighty-six patients with diabetes mellitus had measurements of gastric emptying and intragastric distribution of a radioisotopically labeled solid/liquid meal (100 g beef and 150 ml 10% dextrose), glycemic control (plasma glucose concentrations), upper gastrointestinal symptoms (questionnaire) and autonomic nerve function (cardiovascular reflexes). Results were compared to those obtained in 20 normal volunteers. **Results:** Solid and liquid gastric emptying were delayed in the diabetic patients and correlated weakly. Intragastric meal distribution was also often abnormal, with increased retention of both solid and liquid in the proximal stomach and increased retention of solid but not liquid in the distal stomach. In all patients with increased retention of solid in the proximal stomach, emptying from the total stomach was delayed. Gastric emptying of liquid was slower in those subjects who had a mean plasma glucose >15 mmol/liter during the gastric emptying measurement, when compared to the remainder of the group. **Conclusion:** In patients with diabetes mellitus, there is a poor relationship between solid and liquid gastric emptying and intragastric meal distribution is frequently abnormal. Interpretation of the results of gastric emptying measurements should consider meal composition and plasma glucose concentrations.

Key Words: gastric emptying; diabetes mellitus; blood glucose; gastrointestinal symptoms; autonomic nerve function

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The recent application of scintigraphic techniques has demonstrated that disordered gastric emptying, particularly delayed emptying, occurs frequently in patients with diabetes mellitus (*1–5*). Abnormal gastric motor function may have a major effect on the management of diabetic patients by causing upper gastrointestinal symptoms, impaired oral drug absorption and contributing to poor control of blood glucose concentrations (*6*). There is a relatively poor relationship between delay in gastric emptying in patients with diabetes and the presence or absence of upper gastrointestinal symptoms such as nausea and vomiting (*2–4*). Gastrointestinal symptoms may theoretically relate to abnormal intragastric distribution of ingesta rather than delay in total stomach emptying, as has been suggested to be the case in patients with nonulcer dyspepsia (*7*). Although there is some evidence that intragastric distribution of a solid meal is often abnormal in patients with diabetes mellitus (*8*), the prevalence of abnormal intragastric distribution of solid and liquid meal components and the relationship between intragastric distribution and gastrointestinal symptoms has not been evaluated. Nor is it clear whether an analysis of intragastric meal distribution increases the ability of radionuclide methods to detect disordered gastric motility in diabetic patients.

There is inadequate information about the effect of gastric emptying on glycemic control in diabetic patients. The relationship between gastric emptying and blood glucose concentrations is likely to be complex. Whereas the majority of studies which have evaluated gastric motility in diabetes have not monitored (let alone stabilized) blood glucose concentrations during measurements (*3,4,9–11*) and assumed that delayed gastric emptying reflects irreversible autonomic neuropathy (*12*), recent studies have demonstrated that gastric emptying is slowed during hyperglycemia (*13*) and accelerated during hypoglycemia (*14*), i.e., the blood glucose concentration, either directly or indirectly, influences gastric motility. By contrast, in normal subjects it has been established that there is a direct relationship between the rate of gastric emptying and the magnitude of the rise in plasma glucose after an oral glucose load (*15*) i.e., in this situation, gastric emptying "drives" the blood glucose response to oral carbohydrate.

We have sought to shed further light on the above issues

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by evaluating gastric emptying and intragastric distribution of a mixed solid/liquid meal, gastrointestinal symptoms, glycemic control and autonomic nerve function in a large cohort of patients with diabetes mellitus.

MATERIALS AND METHODS

Subjects

Studies were carried out in 86 patients with diabetes mellitus (66 IDDM, 20 NIDDM). The 40 male and 46 female patients had a median age of 46 yr (range 18–77), a median body mass index (BMI) of 24.7 (range 19.9–35.9) and a median body weight of 71 kg (range 46–102). The patients were randomly selected by two endocrinologists (MH, PEH) from ambulant outpatients who were being treated for diabetes mellitus of at least 1 yr known duration [median 14.5 yr (range 1–49)] at the Royal Adelaide Hospital. Some of the patients were included in previous reports (*1,2*). Patients taking any medication known to affect gastrointestinal motility, apart from insulin or oral hypoglycemic drugs, were excluded. No subject had a history of upper gastrointestinal surgery or peptic ulcer disease. The plasma creatinine concentration was required to be within the normal range (0.05–0.12 mmol/liter) in all patients. Gastric emptying results were compared to those obtained in 20 normal volunteers (19 men, 1 woman), median age 36 yr (range 18–63), median body weight 68 kg (range 57–92) and median BMI 22.1 (range 18.0–27.2). None of the control subjects was taking medication that could have influenced gastrointestinal motility, had gastrointestinal symptoms or a history of gastrointestinal disease. Median body mass index ($p < 0.05$) and age ($p < 0.05$) were greater in the patients than in the control subjects. Age ($p < 0.01$) and BMI ($p < 0.01$) were greater in the NIDDM than IDDM patients, while the duration of diabetes was longer in the IDDM group.

Protocol

Each diabetic patient was evaluated for gastrointestinal symptoms and underwent objective assessments for autonomic neuropathy, peripheral neuropathy and retinopathy in addition to measurements of gastric emptying and intragastric distribution of a mixed solid and liquid meal and glycemic control. On the study day, smoking was prohibited and none of the patients took oral hypoglycemic drugs until after the completion of the gastric emptying measurement. On the morning of the test, the IDDM patients administered their usual dose of insulin, usually about 20 min before consumption of the test meal. Written informed consent was obtained from all subjects and the study was approved by the Ethics Committee of the Royal Adelaide Hospital.

Assessment of Gastrointestinal Symptoms

Upper gastrointestinal symptoms were assessed by questionnaire (*2,16*). Gastric and esophageal symptoms, including anorexia, nausea, early satiety, distension, vomiting, abdominal pain, dysphagia, heartburn and acid regurgitation, were graded as 0 = none, 1 = mild, 2 = moderate, 3 = severe. The frequency and consistency of bowel actions and the presence or absence of nocturnal diarrhea and fecal incontinence were also assessed (*2*).

Assessment of Autonomic and Peripheral Neuropathy and Retinopathy

Autonomic nerve function was assessed by standardized cardiovascular reflex tests (*2,17*). Parasympathetic function was evaluated by the variation (R-R interval) of the heart rate during deep breathing and the immediate heart rate response to standing ("30:15" ratio). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. The result of each of these tests was scored as 0 = normal, 1 = borderline or 2 = abnormal. A total score of ≥3 was taken to indicate definite autonomic nerve damage (*1*). Retinopathy was graded as none (0), background (1) or proliferative (2) on the basis of a recent ophthalmological assessment, which often included fluorescein angiography. Peripheral neuropathy was diagnosed clinically when absent ankle reflexes were associated with either sensory or motor changes (*1*).

Assessment of Glycemic Control

Five-milliliter venous blood samples were taken from an indwelling cannula for subsequent measurement of plasma glucose using a hexokinase technique. Samples were taken immediately before meal ingestion and then at 30, 60, 90 and 120 min. The changes in plasma glucose from immediately before ingestion of the meal were calculated. Hemoglobin A_{1c} (HbA_{1c}) was measured using the initial venous sample and the results expressed as a percentage. The range in normal subjects is 3.5%–6.0%.

Measurement of Gastric Emptying

Details of this dual-isotope test, which measures total, proximal and distal stomach emptying of solid and liquid meal components simultaneously, have been reported (*18,19*). The solid component of the meal comprised chicken liver labeled in vivo with 37–55 MBq ^{99m}Tc-sulphur colloid added to 100 g minced beef which was subsequently grilled. The caloric content of the solid meal (25 g protein, 21 g fat) was about 270 Kcal. The liquid component of the meal was 150 ml 10% dextrose labeled with 25–37 MBq of ^{113m}In-diethylene triaminepentaacetic acid (^{113m}In-DTPA), i.e., approximately 60 Kcal. The test meal was consumed at approximately 10 hr after an overnight fast (15 hr solid, 10 hr liquid). Subjects ate the minced beef over a 5-min period and then drank the liquid within 30 sec. Each study was performed in the sitting position with the gamma camera positioned posteriorly. Data were acquired in dynamic mode for at least 120 min, with 1-min frames for the first hour and 3-min frames subsequently. Time zero was defined as the time of meal completion. Radionuclide data were corrected for subject movement, Compton scatter and radionuclide decay using previously described methods (*18*). Correction for gamma-ray attenuation was made using factors derived from a lateral image of the stomach (*18*). A region of interest was drawn around the total stomach, which was subsequently divided into proximal and distal regions—the proximal region corresponding to the fundus and proximal corpus and the distal region representing the antrum and distal corpus (*19*). Gastric emptying curves for total, proximal and distal stomach (representing the percent retention over time) were derived. From the curves, several parameters were obtained for subsequent statistical analysis. For the solid component, these were the amounts remaining in the total, proximal and distal stomach at 60 and 100 min, expressed as a percentage of maximum counts. For the total stomach, the lag phase, before any of the meal had left the stomach, and the slope of the emptying phase between the end of the lag phase and 100 min were calculated (*2*). The lag phase was determined visually by the frame preceding that in which activity was first seen in the proximal small intestine (*18*). The 50% emptying time (T50) for the proximal stomach and the maximum content of the distal stomach (Dmax) were also derived (*19*). The T50 of the solid component from the total stomach was not used, as in many patients the T50 was not reached in the study period. For the liquid component, the amounts remaining in the total, proximal and distal stomach at 10 and 30 min after meal

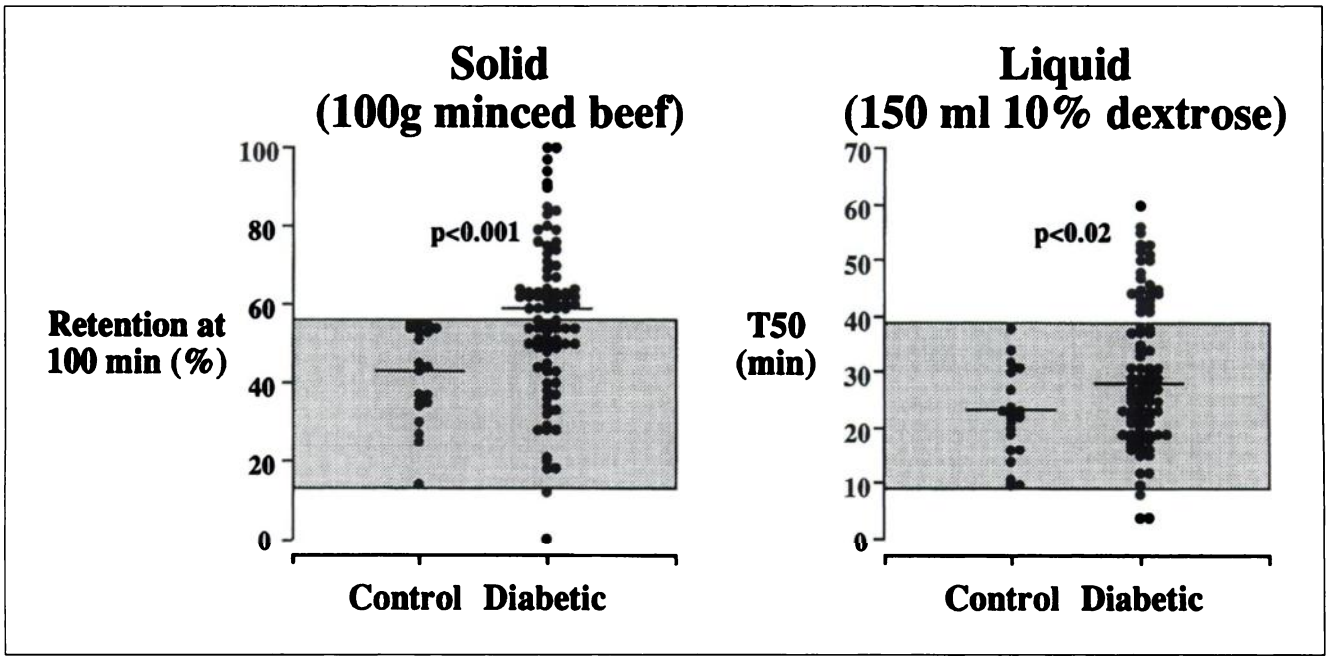

FIGURE 1. Gastric emptying of solid (% retention at 100 min) and liquid (T50) in normal subjects and patients with diabetes mellitus. Horizontal lines represent median values.

completion were calculated. For the total and proximal stomach, the T50 was obtained and for the distal stomach the maximum retention (*19*).

Statistical Analysis

Gastric emptying and intragastric distribution were considered to be abnormal when values were outside the range obtained in the control group. Data are shown as median values and ranges and were evaluated using the Mann-Whitney U-test and linear regression analysis. A p value <0.05 was considered significant.

RESULTS

All subjects tolerated the study well and none became hypoglycemic. In one patient, the plasma glucose results were lost.

Gastrointestinal Symptoms, Diabetic Complications and Glycemic Control

The median score for upper gastrointestinal symptoms was 2 (0–15). Eight patients suffered from constipation (less than two bowel actions/week), six from diarrhea and seven from fecal incontinence. Thirty-six (42%) patients had autonomic neuropathy (total score ≥ 3) and 36 (42%) had peripheral neuropathy. Thirty-one (36%) patients had no retinopathy, 26 (30%) had background retinopathy and 29 (34%) had proliferative retinopathy. The median HbA_{1c} in the diabetic patients was 9.3% (3.6–16.0%). Five patients were within the normal range (3.5–6.0%), 36 patients were in the range 6.1%–9.0%, 33 patients were in the range 9.1%–12.0% and 12 patients had values >12.0%. In 37 (43%) patients, the mean plasma glucose during the gastric emptying measurement was ≤ 15 mmol/liter. There was a significant ($r > 0.22$, $p < 0.05$) relationship between HbA_{1c} and plasma glucose at all time intervals. When patients were divided into those who had a mean plasma glucose ≤ 15 mmol/liter (37 patients) or >15 mmol/liter (48 patients), HbA_{1c} was related to mean plasma glucose in the latter ($r = 0.39$, $p < 0.01$) but not the former ($r = 0.005$, ns) group.

When the diabetic patients were divided into the two subgroups (IDDM and NIDDM), there was no difference in mean plasma glucose concentrations: 17 mmol/liter (5.2–29.7) versus 13.7 mmol/liter (7.7–22.5). Twenty-six of the 65 IDDM patients had a mean plasma glucose ≤ 15 mmol/liter and 11 of the 20 NIDDM patients. There was also no significant relationship between either the duration of diabetes or other diabetic complications and the mean plasma glucose in either group.

Gastric Emptying

Total Stomach. There was a significant delay in gastric emptying of both solid and liquid components of the meal in the patients. For the solid meal, both the lag phase [35 min (7–100)] versus [24 min (3–63)) $p < 0.05$] and retention at 100 min ($p < 0.001$) were delayed (Fig. 1). The retention of the solid meal at 100 min was increased in 49 (57%) patients and decreased in 2. There was a significant relationship between the duration of the lag phase and the retention of the solid meal at 100 min ($r = 0.55$), $p < 0.001$). There was no significant difference (0.68%/min (0.12–1.45) versus 0.75%/min (0.6–1.22), $p = 0.12$) in the slope of the solid emptying phase between the diabetic and control groups. There was no significant difference between the IDDM and NIDDM patients in the retention of the solid meal at 100 min [56% (0–100) versus 60% (28–83)].

The retention of liquid at 10 min was not significantly different between the diabetic and control groups (82%

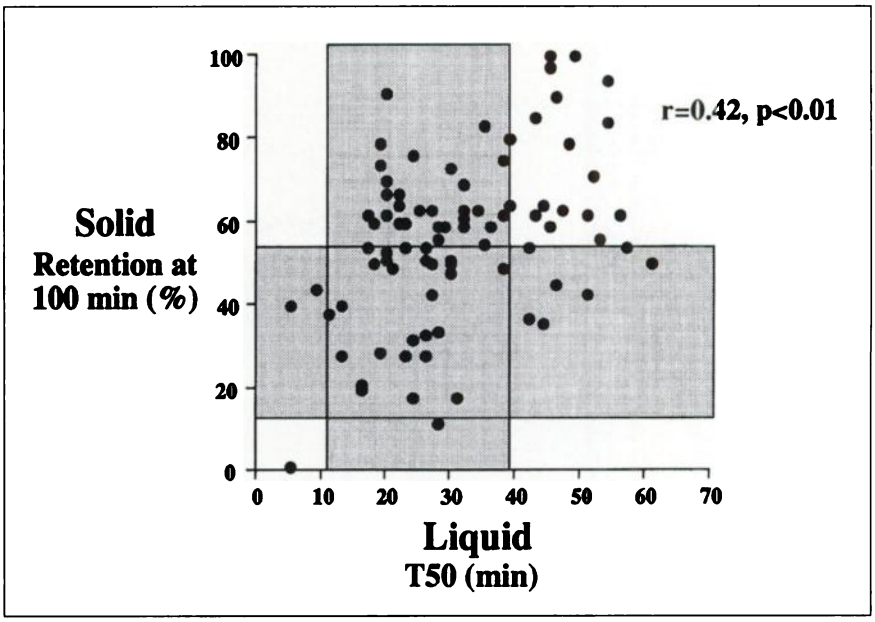

FIGURE 2. Relationship between solid (% retention at 100 min) and liquid (T50) gastric emptying in the diabetic patients. Ranges in normal subjects are shown in the shaded areas.

(38–100) versus 79% (53–94), $p = 0.21$) but the retention at 30 min [52% (14–100) versus 44% (25–64), $p < 0.05$] was increased in 29 (34%) of the patients. The liquid T50 was delayed in 23 (28%) and more rapid in 3 (3%) of the diabetics (Fig. 1). There was a significant relationship between solid and liquid emptying rates ($r = 0.42$, $p < 0.01$). As assessed by retention of solid at 100 min and the T_{50} for liquid, 16 (19%) patients had delayed solid and liquid emptying, 7 (8%) had normal solid but delayed liquid emptying and 30 (35%) had normal liquid but delayed solid emptying (Fig. 2), i.e., in 62%, either solid and/or liquid gastric emptying was delayed.

Intragastric Distribution. Intragastric meal distribution was frequently abnormal. For the solid component, both proximal stomach retention at 100 min ($p < 0.05$) and proximal stomach T50 [40 min (4–120) versus 26 min (6–65), $p < 0.05$] were delayed. The proximal stomach retention at 100 min was greater than normal in 15 (17%) patients (Fig. 3). The proximal T50 for the liquid component was also delayed ($p < 0.005$) with 28 (33%) patients having values greater than the normal range (Fig. 3). The retention of solid in the distal stomach at 100 min ($p < 0.02$) (Fig. 4) and Dmax [54% (20–89) versus 46% (2–71), $p < 0.05$] were both greater in the patients. The retention in the distal stomach at 100 min was increased in 23 (27%) patients. There was no significant difference between the control subjects and patients in the retention of liquid in the distal stomach at either 10 min (40% (9–65) versus 42%

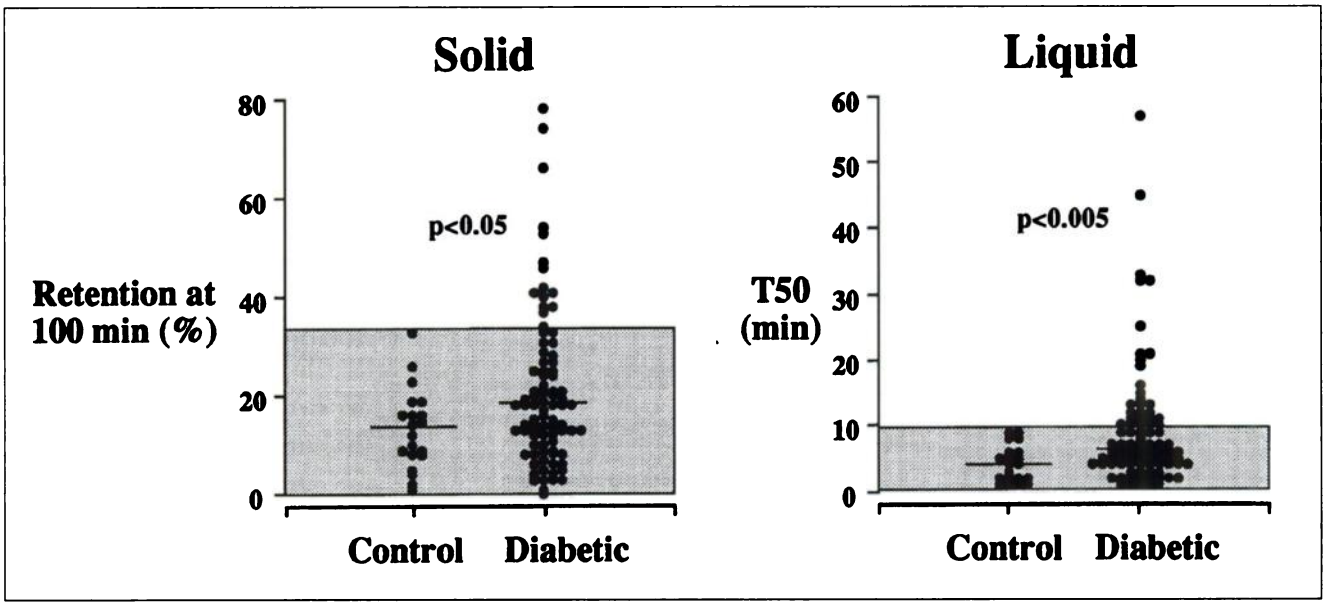

FIGURE 3. Proximal stomach emptying of solid (% retention at 100 min) and liquid (T50) in normal subjects and patients with diabetes mellitus. Horizontal lines represent median values.

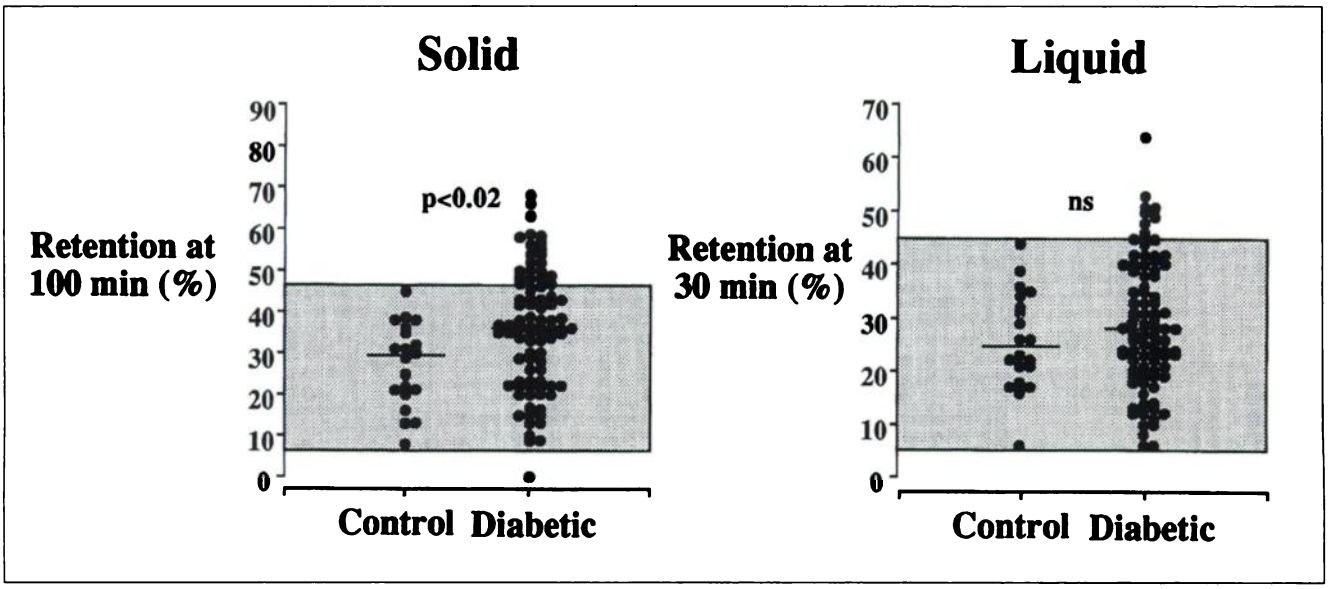

FIGURE 4. Distal stomach retention of solid (% retention at 100 min) and liquid (% retention at 30 min) in normal subjects and patients with diabetes mellitus. Horizontal lines represent median values.

(18–65), ns) or 30 min (25% (6–44) versus 28% (6–64), ns) (Fig. 4). For the solid meal, there was an inverse relationship between the proximal stomach T50 and both the retention in the distal stomach at 100 min ($r = -0.35$, $p < 0.001$) and Dmax ($r = -0.45$, $p < 0.0001$). There was also a significant relationship between the proximal stomach T50 and Dmax for the liquid meal ($r = 0.27$, $p < 0.05$).

Relationships between Total Stomach Emptying and Intragastric Distribution. There was a relationship between the lag phase and retention of the solid meal in the proximal stomach at 100 min ($r = 0.53$, $p < 0.001$). At 100 min, there were significant relationships between the retention of the solid meal in the total and both the proximal ($r = 0.70$, $p < 0.0001$) and distal stomach ($r = 0.62$, $p < 0.0001$) (Figs. 5 and 6). There was also a relationship between retention of solid in the total stomach at 100 min and solid Dmax ($r = 0.35$, $p < 0.001$). At 100 min, both total and proximal stomach emptying were delayed in 15 (17%) of the patients. Thirty-two (37%) had normal proximal stomach but delayed total stomach emptying. In all patients with normal total stomach emptying, the retention in the proximal stomach was also normal (Fig. 5). At 100 min, total and distal stomach emptying of solids were both delayed in 21 (24%) of the patients. Twenty-five (29%) patients had normal retention in the distal stomach but delayed total stomach emptying and there was normal total stomach emptying but marginally increased retention in the distal stomach in two patients (Fig. 6).

There were significant relationships between the total stomach T50 for liquid and both the proximal stomach T50 ($r = 0.48$, $p < 0.001$) (Fig. 5) retention in the distal stomach at 30 min ($r = 0.71$, $p < 0.001$) (Fig. 6) and Dmax ($r = 0.27$, $p < 0.05$). For the total and proximal stomach, the T50 for liquid was delayed in 12 (14%) patients. Nine (10%) patients had delayed total but normal proximal stomach emptying and 15 (17%) with normal total stomach emptying had delayed emptying from the proximal stomach. In three subjects, delayed emptying from the total stomach was associated with normal proximal stomach emptying (Fig. 5). At 30 min, both total and distal stomach emptying were delayed for liquid in 10 (12%) patients. Sixteen (19%) patients had delayed total stomach emptying but normal retention in the distal stomach. None of the patients with normal total stomach emptying of liquid had abnormal retention in the distal stomach. Three (3%) of the patients with normal distal stomach retention had delayed emptying of liquid from the total stomach (Fig. 6).

Relationship between Diabetic Complications, Gastrointestinal Symptoms and Gastric Emptying. Gastrointestinal symptoms ($r = 0.26$, $p < 0.05$), retinopathy ($r = 0.47$, $p < 0.001$) and peripheral neuropathy ($r = 0.38$, $p < 0.001$) were all related to the duration of known diabetes. The score for autonomic nerve dysfunction was related to age ($r = 0.28$, $p < 0.01$) but not the duration of diabetes ($r = 0.18$, ns). There were significant relationships between solid lag phase and retention at 100 min, but not the postlag emptying phase or liquid, gastric emptying and the scores for autonomic nerve function ($r > 0.35$, $p < 0.001$), peripheral neuropathy ($r > 0.31$, $p < 0.01$) and gastrointestinal symptoms ($r > 0.32$, $p < 0.01$). The retention of solid in the distal ($r = 0.22$, $p < 0.05$) but not the proximal ($r = 0.20$, $p < 0.1$) stomach at 100 min was also related to the score for gastrointestinal symptoms. The retention of solid in the proximal ($r = 0.31$, $p < 0.005$) but not in the distal stomach ($r = 0.15$, ns) at 100 min was related to the score for autonomic nerve dysfunction. There was no significant relationship between intragastric distribution of liquid and gastrointestinal symptoms.

Relationships between Plasma Glucose Concentrations, Gastric Emptying and Gastrointestinal Symptoms. Liquid,

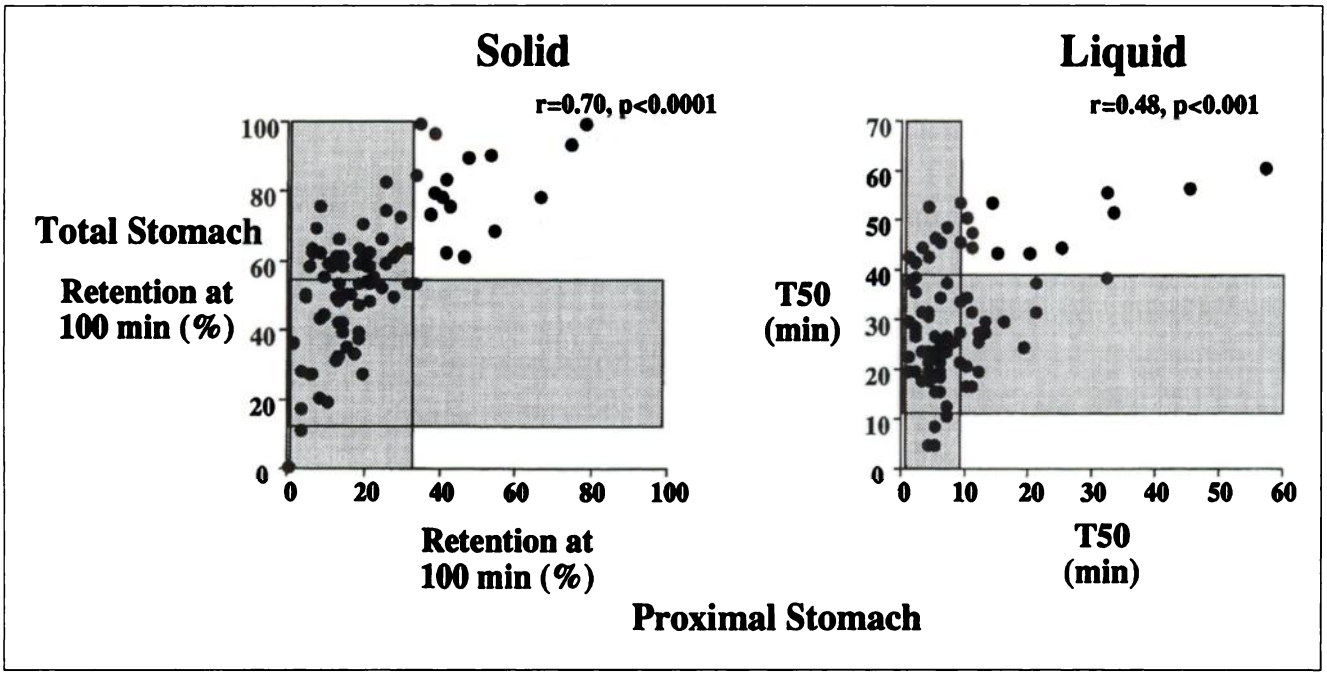

FIGURE 5. Relationship between retention in the total and proximal stomach for the solid (% retention at 100 min) and liquid (T50) meals in patients. The ranges in normal subjects are shown in the shaded areas.

but not solid, emptying from the total ($p < 0.05$) and proximal ($p < 0.01$) stomach was slower in those patients with a mean plasma glucose >15 mmol/liter when compared to those with a mean glucose ≤15 mmol/liter (Table 1). The retention of liquid in the distal stomach at 30 min was not different between these two groups. In those patients with a mean plasma glucose ≤15 mmol/liter, there was a strong inverse relationship between liquid (T50) but not solid emptying and the change in plasma glucose from baseline at both 30 ($r = -0.70$, $p < 0.001$) and 60 min ($r = -0.53$, $p < 0.001$) (Fig. 7). Similarly, plasma glucose at 30 min was inversely related to the retention of liquid in both

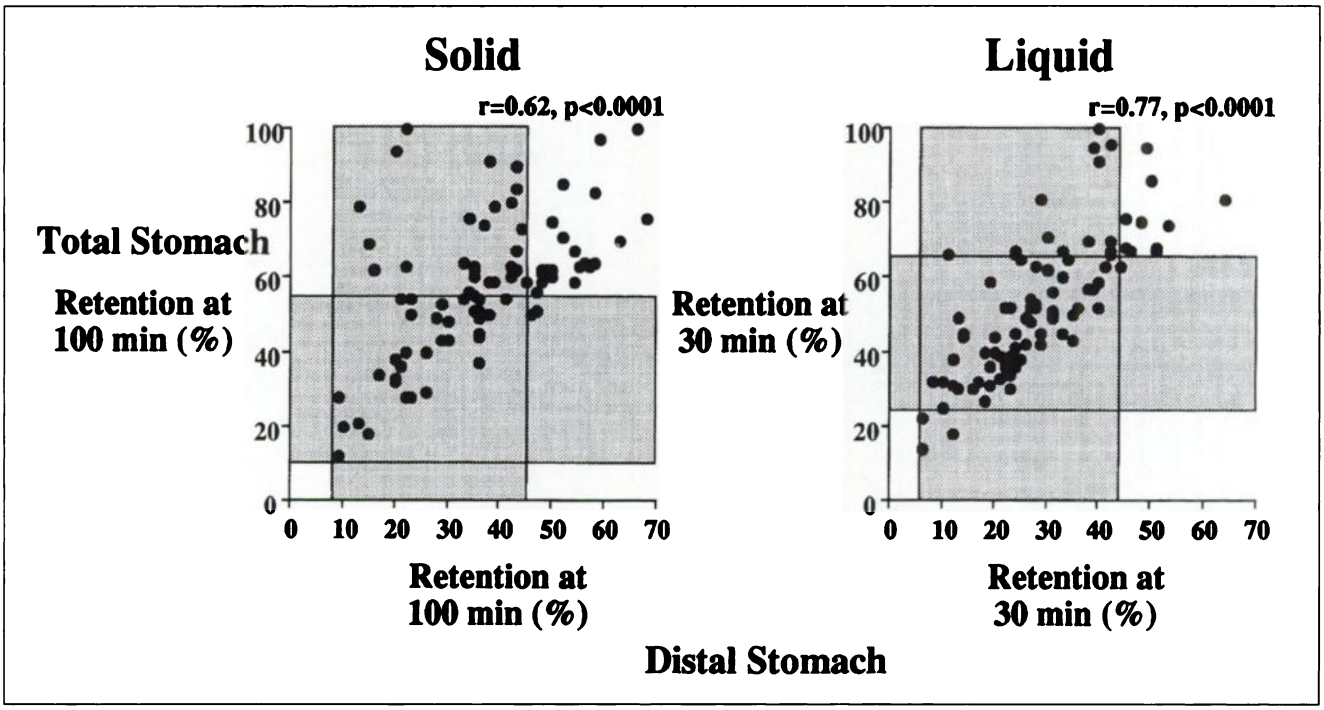

FIGURE 6. Relationship between retention in the total and distal stomach for the solid (% retention at 100 min) and liquid (% retention at 30 min) meals in patients. Ranges in normal subjects are shown in the shaded areas.

TABLE 1
Gastric Emptying in 85 Patients with Diabetes Mellitus with Mean Blood Glucose Concentration ≤15 mmol/liter or >15 mmol/liter.

	≤15 mmol/liter	>15 mmol/liter	p
Number of subjects	37	48	
Total stomach emptying			
Solid retention at 100 min (%)	59 (0–100)	59 (18–100)	ns
Solid lag phase (min)	33 (9–100)	38 (7–100)	ns
Slope of solid G.E. (%/min)	0.72 (0.12–1.26)	0.67 (0.33–1.45)	ns
Liquid retention at 30 min (%)	45 (14–95)	58 (18–100)	<0.01
Liquid 50% emptying time (min)	27 (5–61)	32 (5–57)	<0.05
Proximal stomach retention			
Solid retention at 100 min (%)	16 (0–78)	20 (1–74)	ns
Liquid retention at 30 min (%)	18 (7–56)	25 (6–60)	<0.01
Liquid T50 (min)	6 (1–57)	7 (1–45)	<0.05
Distal stomach retention			
Solid retention at 100 min (%)	36 (0–68)	35 (13–66)	ns
Liquid retention at 30 min (%)	28 (6–53)	27 (10–64)	ns

Data are median values and ranges in parentheses.
G.E. = gastric emptying.

the total ($r = -0.41$, $p < 0.01$) and proximal ($r = -0.32$, $p < 0.05$) stomach but not to solid emptying. Similar correlations were evident in the IDDM and NIDDM subgroups, with significant relationships between the liquid T50 and the rise in plasma glucose from baseline at 30 min ($r = -0.25$, $p < 0.05$ and $r = 0.71$, $p < 0.001$, respectively). In patients with a mean plasma glucose >15 mmol/liter there was no significant relationship between gastric emptying and either the change in plasma glucose from baseline or the absolute plasma glucose concentration (Fig. 7). Gastrointestinal symptoms were related to solid ($r = 0.38$, $p < 0.05$) but not liquid ($r = 0.30$, ns) emptying in patients whose mean plasma glucose was ≤15 mmol/liter. Similarly, in those patients with mean plasma glucose levels >15 mmol/liter,

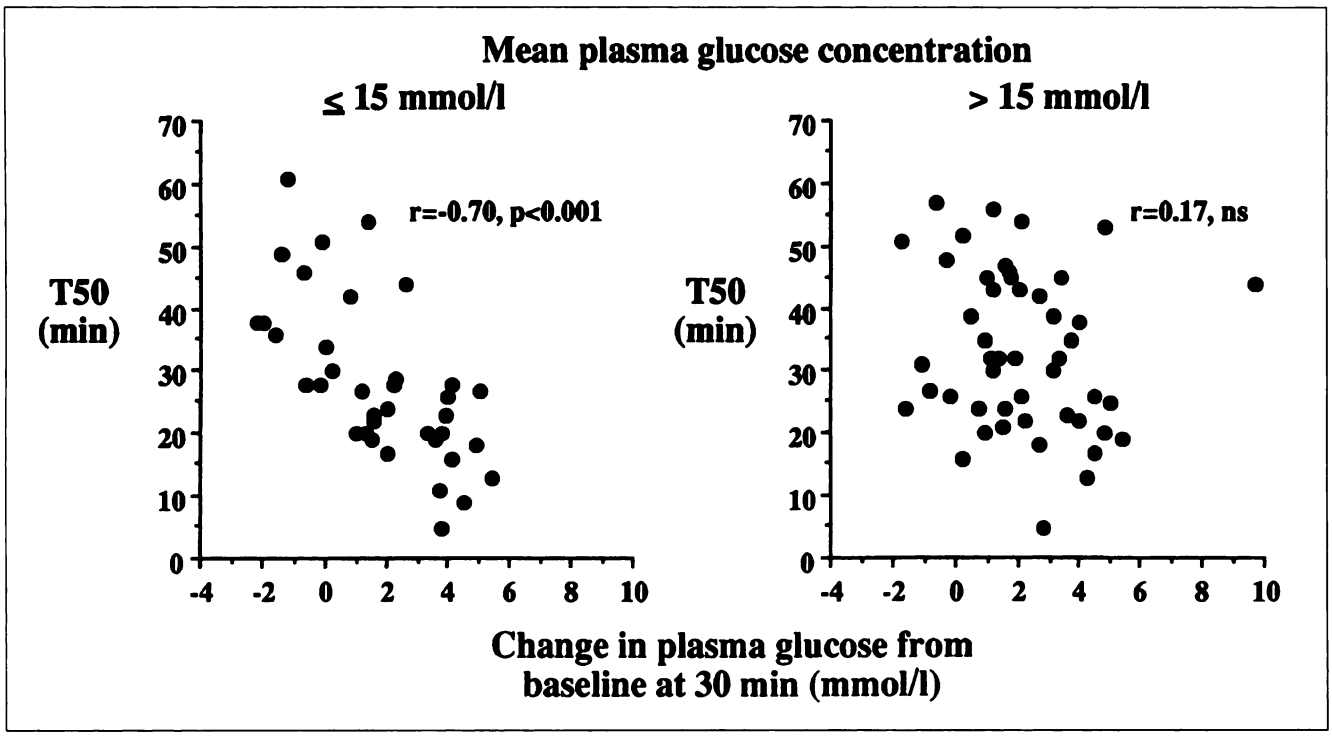

FIGURE 7. Relationship between the change in plasma glucose from baseline at 30 min and gastric emptying of liquid (T50) in diabetic patients: those with a mean plasma glucose concentration during gastric emptying ≤15 mmol/liter or >15 mmol/liter.

symptoms were related to solid ($r = 0.28$, $p < 0.05$) but not liquid ($r = 0.004$, ns) emptying.

DISCUSSION

Our results indicate that in patients with diabetes mellitus:

1. There is a relatively weak relationship between gastric emptying of solid and nutrient-containing liquid meal components.
2. Evaluation of intragastric meal distribution does not have a major effect on the ability of radionuclide techniques to detect disordered gastric motility or predict gastrointestinal symptoms.
3. The relationship between gastric emptying and blood glucose concentrations may be direct or inverse, depending on the blood glucose concentration.

Scintigraphic measurement of gastric emptying is presently the most precise and clinically applicable method to evaluate gastric motility in patients with diabetes (*6,20*). We have confirmed that gastric emptying is abnormal in more than 50% of patients and that there is a poor relationship between solid and liquid emptying (*2,3*). The latter observation indicates the need to use a test meal containing discretely labeled solid and nutrient liquid components when gastric emptying is evaluated in patients with diabetes. Our diabetic and control groups were not ideally matched, but it is unlikely that the differences in age, body weight and sex influenced our observations (*2–4*). In particular, with our methodology, there is no significant difference in gastric emptying between men and women (*21,22*). The suggestion that disordered gastric motility in patients with diabetes predominantly affects gastric emptying of solids (*5,23*) probably reflects the use of non-nutrient liquids, such as water, in the test meal, which do not stimulate mechanisms which retard gastric emptying.

The demonstration that the intragastric distribution of solid and liquid components is frequently abnormal in patients with diabetes is not unexpected. In a relatively small cohort of patients with diabetes, Urbain et al. (*8*) found that the retention of a solid meal in the proximal stomach was increased, which is consistent with our observations. In our study, abnormal intragastric distribution of solids in most of the patients was associated with delay in emptying from the total stomach. In contrast, evaluation of retention of liquid in the proximal (but not the distal) stomach increased the detection of disordered gastric motility in that increased retention of liquid in the proximal stomach was associated with normal emptying from the total stomach in 17% of patients. It should be recognized that measurement of the retention of isotope in the distal stomach has limitations in that it is influenced by the rate of emptying into the small intestine as well as filling from the proximal stomach.

The mechanical dysfunctions leading to delayed gastric emptying in patients with diabetes are poorly understood. The rate of gastric emptying is related to the relationship between contractions generated by the fundus, antrum, pylorus and proximal small intestine (*24*). It is now clear that the gastric motor abnormalities in diabetic gastroparesis are widespread, may reflect the blood glucose concentration and do not involve just the antrum (*9,10,25–27*). Because no studies have measured motor events in the proximal stomach, antrum, pylorus and duodenum simultaneously with transpyloric flow, there is considerable uncertainty about the relative contribution of regional abnormalities of motor function to disordered gastric emptying. It is therefore difficult to speculate on the etiology of the poor relationship between gastric emptying of solid and nutrient liquid meal components in diabetic patients. Solid food is normally ground into small particles (<1 mm in size) before entering the small intestine and the time taken for trituration appears to be a major rate-limiting step, so that solids can be considered to empty from the stomach at maximum rates (*28*). In contrast, feedback from small intestinal luminal receptors is the major factor regulating gastric emptying of nutrient-containing liquids and triturated solids (*29,30*). Interestingly, gastric emptying of solid but not liquid was related to the severity of cardiovascular autonomic nerve dysfunction (albeit weakly), suggesting that irreversible autonomic neuropathy may affect the grinding function of the antrum. This concept is supported by the observation that the severity of autonomic nerve dysfunction was related to the duration of the lag phase for the solid meal but not the postlag emptying rate or gastric emptying of liquid.

In diabetes, the etiology of upper gastrointestinal symptoms, which are presumed to result primarily from disordered gastrointestinal motility, is poorly understood. Despite the frequent occurrence of gastrointestinal symptoms, both total stomach emptying and intragastric meal distribution correlated weakly with symptom severity and only for the solid component of the meal. This observation is not surprising (*1–5*) and inevitably leads to the conclusion that abnormal gastric emptying and intragastric meal distribution should be regarded as markers of gastroduodenal motor abnormality rather than the direct cause of symptoms. In considering the etiology of symptoms abnormal gastric myoelectrical activity (*31*), disordered esophageal and intestinal motility (*2,3*), psychiatric dysfunction (*32*) and abnormal sensory feedback from luminal receptors in the stomach or small intestine (*24*) may all play a role.

Our observations support the concept that the blood glucose concentration has a major influence on gastric motility in diabetes (*2,13,14,20*). Significant hyperglycemia (~15 mmol/liter) has been shown to suppress antral pressure waves and stimulate pressure waves that are localized to the pylorus (*33*). Gastric emptying and motility may be influenced by more modest elevation of plasma glucose within the physiological range (*15,34*). Clearly, studies of gastric emptying in diabetic patients must take into account blood glucose concentrations, which should ideally be stabilized in the euglycemic range (*27*).

In addition to these previously described effects of blood

glucose on gastric motility and emptying in patients with diabetes, we have shown a reciprocal effect of gastric emptying on blood glucose in both IDDM and NIDDM patients. Although our liquid meal contained only a relatively small amount of carbohydrate (15 g dextrose) and all IDDM patients took their normal insulin dose before consumption of the test meal, there was a strong relationship between the rate of liquid gastric emptying and the rise in blood glucose in those subjects in whom the mean blood glucose during gastric emptying measurements was ≤15 mmol/liter. Because of deficient counter-regulatory responses, gastric emptying would be expected to have a greater effect on oral glucose tolerance in diabetic patients, particularly IDDM patients, than in normal subjects (*15*) and such a relationship is likely to be more evident when preprandial blood glucose concentrations are low and meal carbohydrate content is high.

CONCLUSION

Our observations are consistent with the hypotheses (*6*) that the rate of gastric emptying plays a significant role in determining glycemic response to meals in patients with diabetes mellitus and that disordered gastric emptying may contribute to, as well as result from, poor glycemic control.

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