Prevalence and Determinants of Solid and Liquid Gastric Emptying in Unstable Type I Diabetes

Relationship to postprandial blood glucose concentrations

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OBJECTIVE — To compare postprandial blood glucose levels with gastric emptying (GE) time after intake of a solid and a nutrient liquid meal in patients with unstable, type I diabetes.

RESEARCH DESIGN AND METHODS — The subjects studied were 15 patients with long-standing type I diabetes who during the last year repeatedly reported unexplained episodes of instability in their blood glucose regulation, including postprandial hypoglycemia. All patients were on a meal-administered, fast-acting insulin regimen. As control group, 19 healthy subjects were studied. GE was measured at two separate occasions, using a gamma camera after intake of either a solid or a nutrient liquid, isotope-labeled meal. Measurement of GE was done directly after meal completion and at 30-min intervals for 2 h. Insulin was taken 30 min before intake of the meal. Blood glucose was measured 30 min before the meal, after meal completion and at 30, 60, 90, and 120 min after start of the meal. All patients were evaluated for evidence of autonomic neuropathy and were asked for signs of gastrointestinal motor dysfunction.

RESULTS — Seven (44%) of the patients had significantly delayed emptying of the solid meal (three men, four women) ($P < 0.01$), of whom one woman also had delayed emptying of the liquid meal compared with the healthy control subjects. Changes in blood glucose concentration were correlated to GE time with, in the group with delayed GE, a significant fall after the solid meal compared with the liquid meal ($P < 0.05$). The lag phase was prolonged in the women compared with the men, reaching significance in the patient group ($P < 0.01$). The women, patients as well as control subjects, had throughout the study a prolonged emptying time compared with the men after both the solid and the liquid meal. No correlation between GE and blood glucose concentration could be found.

CONCLUSIONS — Delayed GE of a solid meal is commonly found in patients with type I diabetes and may be one cause of unstable blood glucose regulation. Women, patients as well as control subjects, seem to have a more prolonged GE than men. Awareness of gastric function in patients with type I diabetes is essential, especially in patients treated with meal-administered, fast-acting insulin.

Delayed gastric emptying (GE) has been described in 30–50% of both type I and type II diabetes (1–7). As GE has been shown to be a significant determinant of blood glucose response in healthy subjects (8), impaired GE could in type I patients theoretically precipitate postprandial hypoglycemia and impaired glycemic control, especially in patients using meal-administered, fast-acting insulin. In type II patients, on the other hand, a prolonged GE has even been suggested to be of possible advantage (9,10). Emptying of both solid and liquid meals has been shown to be affected to a variable degree, but emptying of the solid component has been suggested to be the most frequently abnormal and prolonged (5,11). Also rapid emptying of liquids has been shown in both type I (5) and type II diabetes (12). Total emptying time is closely dependent on the composition of a mixed meal where the solid components' emptying is dependent on the composition of the liquid part (13). Although GE dysfunction has earlier been considered to be a consequence of autonomic neuropathy, accumulating data suggest gastric motility to be under considerable influence of blood glucose concentration. Hyperglycemia inhibits solid as well as liquid emptying (14–18), whereas insulin-induced hypoglycemia accelerates GE in type I diabetes (19). The importance of these relationships and the implications of delayed GE and different meal compositions on blood glucose regulation in patients with type I diabetes is, however, largely unknown. We have studied a group of patients with type I diabetes treated with meal-administered, fast-acting insulin with unexplained instability in their blood glucose regulation. Postprandial blood glucose response and GE rate was measured using two different meals, solid and nutrient liquid, but with similar caloric composition.

RESEARCH DESIGN AND METHODS

— A group of 15 patients (9 women, 6 men) with, in the majority, long-standing type I diabetes was studied. All patients were treated with meal-administered, short-acting insulin (in the abdominal wall) as well as with long-acting insulin (in the thigh) at nighttime in a standardized way. Patients who during the last year had spontaneously reported or at follow-up had been observed to have episodes of instability in their blood glucose regulation, including postprandial hypoglycemia that was not

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Received for publication 22 November 1995 and accepted in revised form 10 October 1996.

GE, gastric emptying; HPLC, high-pressure liquid chromatography; ROI, region of interest; T_{50}, time for 50% emptying.

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Table 1—*Clinical characteristics of the study patients*

Sex (M/F)	Age (years)	BMI (kg/m²)	Diabetes duration (years)	HbA_1 (%)	PN	ANPS	ANS	AN score	Retinopathy	Nephropathy	GI score	Diarrhea	Constipation
F	29	31	7	9.2	−	0	0	0	−	−	7	+	+
F	36	23	13	7.0	−	2	0	2	−	−	3	−	−
F	39	26	34	7.6	+	2	1	3	+	+	10	−	+
F	45	33	14	9.1	−	2	1	3	+	−	6	−	+
F	45	22	39	7.4	+	3	0	3	+	+	7	−	+
F	59	24	31	6.5	+	3	1	4	+	+	8	−	+
F	59	24	49	8.8	+	4	2	6	+	+	4	−	−
F	60	28	28	6.7	−	4	1	5	+	−	6	−	+
F	63	24	51	7.5	−	4	2	6	+	−	8	−	−
M	26	25	14	9.6	−	0	0	0	−	−	0	−	−
M	27	23	17	8.4	−	0	0	0	−	−	12	−	−
M	38	22	33	5.9	−	3	0	3	+	−	2	−	−
M	41	32	16	8.6	+	3	0	3	+	+	7	−	−
M	48	21	24	7.1	−	4	0	4	+	+	0	−	−
M	50	21	40	6.2	+	4	0	4	+	+	9	−	−

PN, peripheral neuropathy; AN, autonomic neuropathy; PS, parasympathetic; S, sympathetic; GI, gastrointestinal symptoms.

considered to be caused by overtreatment with insulin or otherwise could be explained, were included. The presence of gastrointestinal symptoms was not considered in subject selection. The group consisted of six men, mean age 38 (range 26–50), mean BMI 24 (range 21–32) with a mean duration of known diabetes of 24 years (range 14–40). The nine women, mean age 48 (range 29–63) and a mean BMI 26 (range 22–33) had a mean duration of their diabetes of 28 years (range 7–51). Patients with laboratory evidence of liver or pancreatic disease, previous peptic ulcer disease or upper gastrointestinal surgery (except cholecystectomy), and any serious disorder other than diabetes were excluded. Medications known to influence gastrointestinal motility, including psychotropic and prokinetic drugs, were discontinued at least 1 week before inclusion. In all diabetic patients, gastrointestinal symptoms, glycemic control, autonomic nerve function, and GE of solid and nutrient liquid meals were evaluated. GE and measurement of blood glucose concentration were also performed in 19 healthy volunteers (12 women, 7 men), mean age 41 (range 27–56) and with a mean BMI 23 (range 20–30) who were nonsmokers and without evidence of gastrointestinal disease. The groups were similar regarding sex and age distribution, but the diabetic women had a higher BMI ($P < 0.05$) than the women in the control group. Informed consent was obtained in all cases, and the study was approved by the ethics committee at the University of Lund, Sweden. Clinical and demographic data for the patients are summarized in Table 1.

Assessment of gastrointestinal symptoms

Presence of chronic gastrointestinal symptoms was assessed at the time of the first GE test, using a standardized protocol (1). Dysphagia, heartburn, regurgitation, chest pain, early satiety, nausea, vomiting, and distention or epigastric fullness were rated on a four-graded scale: 0 = not present, 1 = mild (rare and well tolerated), 2 = moderate (present regularly and weekly), 3 = frequent (influencing daily activities). A maximum score of 18 was possible. Diarrhea was defined as two or more loose bowel actions per day. Constipation was defined as passing three or fewer hard stools per week.

Assessment of diabetic complications

In the diabetic patients, autonomic nerve function was evaluated using standardized cardiovascular reflex tests as described by Ewing and Clarke (20). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. The test was considered abnormal with a fall of 30 mmHg or more. Parasympathetic function was evaluated by *1*) the heart rate variation (R-R-interval) during deep breathing (6 breaths/min) where a mean difference of maximum and minimum heart rates less than 10 beats/min was considered as abnormal; *2*) immediate heart rate response to standing where a 30–15 ratio <1.0 was considered abnormal. The result of each test was scored as 0 = normal, 1 = borderline, or 2 = abnormal with a possible maximum score of 6. Presence of autonomic neuropathy was defined as a score of ≤3 (18,20,21). Retinopathy was graded as none, mild, or proliferative, using stereoscopic fundus photography. A clinical diagnosis of peripheral neuropathy was made when patellar reflexes were absent. The presence of nephropathy was assumed when testing for albuminuria was positive.

Assessment of glycemic control

Plasma glucose concentration was measured with the glucose oxidase method, using a venous cannula to obtain 5-ml blood samples 30 min before and at 0, 30, 60, 90, 120, and 240 min after the start of each meal. Measurement of HbA_{1c} (<5.5%) was done when the patient was admitted for the first meal, using high-pressure liquid chromatography (HPLC), (JASCO, Tokyo, Japan; MonoS HR 5/5 column, Pharmacia LKB-Biotechnology, Uppsala, Sweden; SIC 12, System Instruments, Tokyo, Japan).

Gastric emptying

Measurement of GE and plasma glucose concentration was done on two different occasions when the patient was given either a solid or a liquid meal. The meals were given in a randomized order and with at least 1 week between each meal. To measure the two meals as closely as possible, no

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standardization regarding the menstrual cycle phase was possible in the women. The solid meal consisted of a standardized pancake containing one egg, 35 g wheat-flour, 1 dl medium fat milk, 8 g sugar, 5 g of margarine, 1 ml salt (14 g fat, 14 g protein, 41 g carbohydrate) with a total caloric content of 350 kcal labeled with 10 MBq ^{99}Tc-labeled macroaggregates of human serum albumin (DRN 4368 Techne ScanR Lyo MAA, Mallinckrodt Medical, The Netherlands) added before meal preparation (22). The meal was sweetened with a small amount of strawberry jam. The liquid meal consisted of 275 ml of Semper food enrichener (Semper, Stockholm, Sweden) containing 12 g fat, 14 g protein and 41 g carbohydrate, caloric content 340 kcal and labeled with 10 MBq ^{99}Tc-DTPA (DRN 4362 TechneScanR DTPA, Mallinckrodt Medical). Each meal was consumed at 12:30 P.M. after the subject had fasted for 6 h after breakfast, when it was reasonable to expect the subject's gastric motility to be in a fasting state. Thirty minutes before the test meal, all patients received two-thirds of their usual lunch time dose. The dose was chosen to adjust the insulin dose to the reduced caloric content of the experimental meal, compared to the patient's ordinary lunch time meal. Both meals were consumed over a 5-min period while in a sitting position in front of a scintillation camera (Digital DynaCamera, Picker International, Espelkamp, Germany). Time zero was defined as the time when the meal started. GE of the solid meal was monitored for 120 min and liquid emptying for 90 min. Successive 1-min anterior and posterior images were collected every 5 min for the 1st 30 min and subsequently at 10-min intervals. The gastric outline in each scan was identified as the region of interest (ROI), and the activity of the isotope remaining in the stomach determined in the computer program. To eliminate the influence of anterior-posterior movement within the stomach, the geometric mean of each pair of anterior and posterior images was calculated as the square root of the product of the anterior and the posterior counts.

$$X_{geo} = \sqrt{\text{counts anterior image} \times \text{counts posterior image}} \quad (11)$$

The time for each pair of images was defined as the start of the posterior image. After correction for ^{99}Tc-radionuclide decay the count rate of the ROI was converted to percent of the maximum count rate recorded for each study and plotted against time as previously described (23). From the time-activity curves of each emptying test, the following parameters were derived for subsequent analysis. For the solid meal, this was the lag phase before the meal left the stomach (defined as the time when ~10% of isotope activity had left the stomach and the beginning of the linear emptying phase), the percentage remaining at 60, 90, and 120 min after the start of the meal, the time for 50% emptying (T_{50}) as well as postlag emptying rate. For the liquid meal, this was the percentage remaining at 30, 60, 90, and 120 min after the start of the meal and T_{50}. Early liquid emptying was evaluated measuring percentage emptied during the first 15 min after start of the meal.

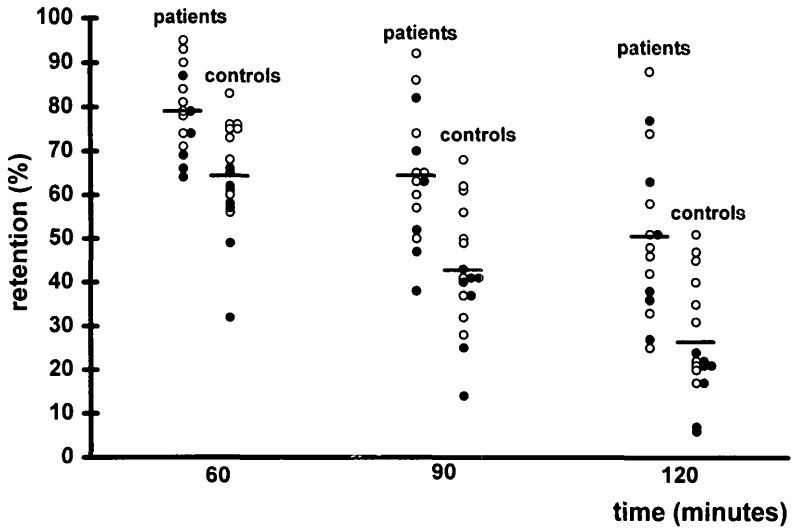

Figure 1—*Retention and mean of the solid meal at 60, 90, and 120 min after meal intake in patients and healthy control subjects. ○, women; ●, men.*

Statistical methods

Data between groups and intra-individual comparisons were evaluated using the Mann-Whitney *U*, Wilcoxon's rank-sum W test, Fisher's exact test, and χ^2 with Yates' correction when appropriate. A *P* value of <0.05 was considered as significant. All results are presented as the mean and the standard deviation. Gastric emptying was classified as abnormal if values for retention at 120 min and T_{50} reached more than two standard deviations outside the range obtained in the control subjects (1,5).

RESULTS

Clinical features

All clinical features have been summarized in Table 1. The mean HbA_{1c} was 7.6 mmol/l (range 5.9–9.6) with no difference between the sexes. Eleven of the patients had definite evidence of autonomic neuropathy (total score ≥3), and two had a score of 2. The mean score for gastroesophageal symptoms was 6 (range 0–12). Three patients had constipation, one patient diarrhea, and one patient complained of both constipation and diarrhea.

Gastric emptying

Control subjects. Emptying of the solid meal was characterized by an initial lag phase preceding the emptying curve, which approximated a linear pattern. The lag phase for the male control subjects was 22 ± 7 min compared with 27 ± 9 min for the female control subjects (NS). GE of the liquid meal was significantly faster than the solid meal ($P < 0.05$), was without any lag phase, and approximated a linear pattern similar to the postlag emptying curve of the solid meal. The percentage remaining in the stomach at 60, 90, and 120 min was 50 ± 12, 27 ± 14, and 11 ± 10 for the liquid meal. Also the corresponding half emptying times (T_{50}) differed significantly between the two meals ($P < 0.01$). The emptying rate for the liquid meal approximated an emptying of 3.0 kcal/min (men 3.2, women 2.9 kcal/min), and the corresponding emptying rate for the solid postlag phase was 2.5 kcal/min (men 3.0, women 2.3 kcal/min). GE of the solid meal was significantly slower in the female control subjects compared with the male control subjects ($P < 0.05$) (Fig. 1).

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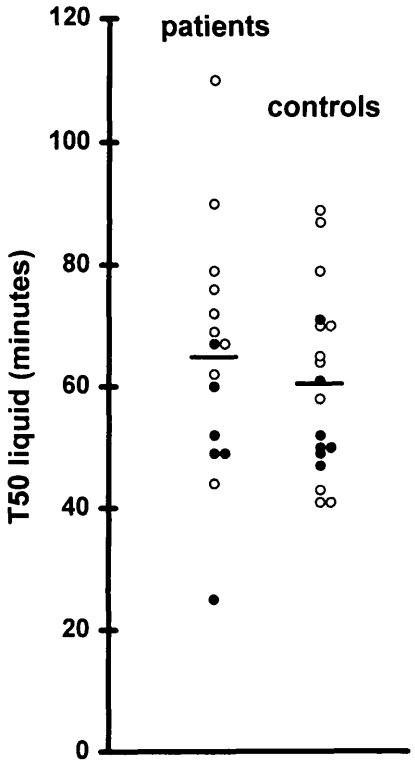

Figure 2—*Gastric emptying time of the nutrient liquid meal, expressed as T_{50} (half emptying time) and mean in patients and control subjects. ○, women; ●, men.*

Diabetic patients

Solid meal. GE of the solid meal was delayed in diabetic patients as compared with the control group both at 60, 90, and 120 min ($P < 0.01$) (Fig. 1). In seven patients (three men, four women), GE of the solid meal was outside the control range (retention 120 min and T_{50}). The lag phase was prolonged in six women and two men; female patients had a significantly longer lag phase compared with both the control subjects and the male patients (women 50 ± 26 min, men 32 ± 6 min, $P < 0.01$). The postlag emptying rate was 2.0 kcal/min (men 1.9, women 2.1 kcal/min).

Liquid meal. No difference in mean GE of the liquid meal was seen between the patients and the control subjects (Fig. 2). However, emptying was significantly slower in female patients than in male patients, with T_{50} values of 74 ± 15 compared with 50 ± 14 ($P < 0.05$). One woman had a prolonged emptying of the liquid meal as well as delayed solid emptying. Two of the men had an increased early emptying rate, although the total retention values were within normal limits. In four patients (one man, three women), liquid emptying resembled that of solid emptying with an initial lag phase between 30 and 45 min. Emptying rate approximated 3.0 kcal/min for the female patients and 3.5 kcal/min for the male patients. There was no correlation between GE and diabetes duration, other diabetic complications, or gastrointestinal symptoms. There was no significant correlation regarding emptying pattern between the two meals in either the patient or the control group.

Plasma glucose concentration during the study

At the start of the solid meal the mean blood glucose concentration for all the patients was 8.6 ± 3.7 mmol/l and 10.5 ± 3.9 mmol/l at the start of the liquid meal (NS). No correlation between this value and the patient's HbA_{1c} was found. Changes in blood glucose concentration during the 2 h after the meal was correlated to the rate of GE and meal composition with a mean postprandial increase after the liquid meal and an initial fall in postprandial mean levels after the solid meal. This difference in postprandial blood glucose concentration response between the solid and the liquid meal was significant in the patients with delayed solid emptying ($P < 0.05$) (Fig. 3*A*). No correlation between blood glucose levels at the start of the meal or the mean blood glucose concentration during the registration and GE rate was found. In the control group, blood glucose concentration was measured in nine subjects (Fig. 3*C*). The postprandial glucose curve was characterized by a postprandial rise at 30 min, reaching a plateau phase within or at 60 min. The blood glucose response was more pronounced and prolonged after the solid meal compared with the liquid meal.

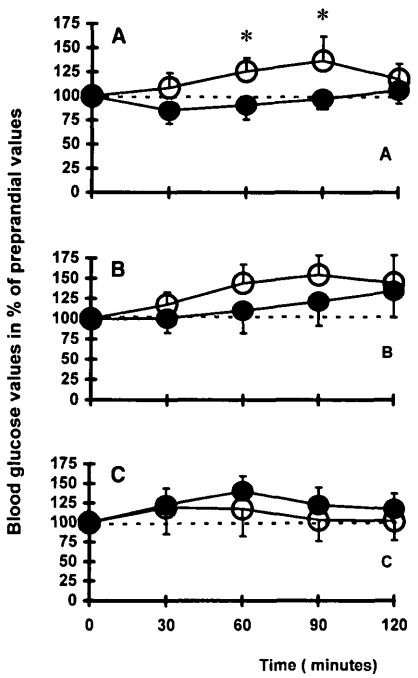

Figure 3—*Blood glucose values in percentage of preprandial values in patients with delayed solid emptying (n = 7) (A), patients with normal solid emptying (n = 9) (B); healthy control subjects (C). ●, solid meal; ○, liquid meal. *P < 0.05.*

CONCLUSIONS — This study is the first to separately compare solid and nutrient liquid GE with postprandial blood glucose concentration in patients with type I diabetes and with unexplained instability in their blood glucose regulation on a four-dose insulin regimen. We have shown that GE of a solid meal was delayed in a significant portion of the patients compared with the healthy control subjects and that the diabetic women had a significant prolonged lag phase compared with the diabetic men. The emptying pattern after the calorically identical nutrient liquid meal did not differ between the two groups, although the women continued to be significantly slower compared with the men in each group. The results also indicate that the postprandial blood glucose curve is dependent on the rate of GE with, in the presence of delayed GE, falling blood glucose levels during the first 60 min postprandially after a solid meal. This finding stands in contrast to the increase in blood glucose seen after the nutrient liquid meal, an increase that was, although exaggerated and prolonged, similar to the physiological curve seen in healthy volunteers after both the solid and liquid meal. These results are in agreement with recent findings of altered postprandial insulin requirement in type I diabetes gastroparesis (24) and with earlier suggestions that delayed GE could contribute to poor glycemic control (25,26).

Delayed GE is a common finding in both type I and type II diabetes (1–7,17). Both solid and liquid meals have been shown to be affected to a variable degree, although emptying of the solid phase has been suggested to be the most frequently abnormal (5,11). However, in no earlier study have the two components of the meal, identical in nutrient content, been studied separately and compared with the blood glucose response. In the present study, seven patients (44%) had abnor-

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mally prolonged emptying of the solid meal, but only one had a delayed liquid emptying, whereas two had a rapid early emptying. Prolonged solid emptying and rapid early liquid emptying in diabetic patients, as reported by others (5,11,27), has also been described in postvagotomy patients (28,29) and has been suggested to be the result of autonomic neuropathy in the diabetic patient (5,30–32). Accumulating data show, however, that GE is also influenced by the blood glucose concentration in both healthy individuals (14–17) and in both type I and type II diabetes patients (2,18), indicating that diabetic gastroparesis may result not only from autonomic neuropathy but also from poor glycemic control. In such hyperglycemic patients, delayed GE has also been shown but without evidence of autonomic neuropathy (33). The close regulation of gastroduodenal caloric liquid flow of 2.5 kcal/min (34,35) and nutrient liquids' delay of solid emptying (13) compared with low or noncaloric liquid may also have an impact on the interpretation of earlier results, regarding the prevalence of abnormal GE, particularly of liquids, in type I diabetes patients (1,2,5,11,27,36). The normal emptying rate of nutrient liquid in our patients and the high incidence of delayed solid emptying indicate a preserved regulation of gastroduodenal caloric flow and support recent findings of gastric motor dysfunction, such as postprandial antral hypomotility as one cause of delayed solid emptying (37–39). The patients in the present study had been under close control regarding blood glucose regulation and showed also a mean HbA_{1c} that was lower compared with other studies, indicating a better metabolic control. The risk for hypoglycemia increases with improved glycemic control, but we could not find any evidence for insulin overdose or impaired hypoglycemic awareness in our patients. Differences in injection sites in the abdominal wall have recently been shown to influence insulin absorption rates and the plasma glucose–lowering effect (40,41). As the study was standardized also regarding the site of insulin injection, a major influence of variations in insulin absorption therefore seems unlikely. Insulin-induced hypoglycemia has been suggested to increase the rate of GE in type I diabetes patients (19). An impaired gastric motor response, resulting in a defective counterregulation of hypoglycemia, could be one factor explaining our patients' instability in blood glucose regulation. Although the mean levels of glucose were moderately raised in our patients (8.6 ± 3.7 mmol/l at the start of the solid meal, 10.5 ± 3.9 mmol/l at the start of the liquid meal), no significant correlation between blood glucose concentration and GE could be found. The blood glucose levels were, however, clearly lower compared with the study of Fraser et al. (18), where induced hyperglycemia between 16 and 20 mmol/l was shown to prolong GE compared with euglycemia. It is not possible, however, from our results to exclude either an influence of the blood glucose levels (15) or the presence of irreversible autonomic neuropathy, of which a combination is also possible. As virtually all our patients had positive findings of autonomic neuropathy, no comparison was possible with GE. In our study, 69% of the patients described significant gastrointestinal symptoms but no correlation to gastric motor dysfunction was found, a finding similar to earlier reports (1,3,11). Of the patients with gastroparesis, two of seven were asymptomatic also confirming that asymptomatic gastroparesis is regularly found (5,31,32,42).

Our results have several important implications. For the clinician attending patients with type I and type II diabetes, it is important to bear in mind that although the blood glucose concentration is dependent on insulin action and postprandial GE, accumulating data suggest that this emptying rate is also closely dependent on the blood glucose concentration. In patients with meal-administered, fast-acting insulin, a prolonged GE may explain poor metabolic control, although such an explanation is probably oversimplistic. Fluctuations in GE secondary to variations in blood glucose concentration may be more important, making the relationship between insulin delivery and nutrient absorption unpredictable and may also contribute to upper gastrointestinal symptoms. Whatever the causes, delayed GE may precipitate postprandial hypoglycemia and jeopardize the intention of meal-administered, fast-acting insulin treatment. Would a change of meal composition to more nutrient liquids or adjusting the time of insulin injection to after meal completion be of any benefit to a patient with established prolonged solid emptying? In some of our patients such changes have indeed been seen to improve glycemic control and quality of life (E.B.L., T.J.Ö., J.H.S., unpublished observations). With our present knowledge of the postpyloric regulation of gastric nutrient liquid emptying and gastric motor dysfunction, more information is needed in the diabetic patient, regarding the metabolic events after meals with different nutrient contents of the liquid and solid phase. The significance of the persistent findings of prolonged GE rate in the women, control subjects as well as patients, compared with the men remains uncertain. Both nutrient liquid emptying rate and solid lag phase were slower in the women than in the men, indicating a difference in both gastric motor function and postpyloric caloric flow regulation. If confirmed, further studies regarding gastroduodenal motility, meal composition, and postprandial blood glucose response between the two sexes are needed. In conclusion, evaluation of gastric motor function in relation to blood glucose concentration and meal composition in the diabetic patient may give further information in the overall assessment of clinical problems such as poor glycemic control and upper gastrointestinal symptoms when present.

Acknowledgments— This work was supported by grants from the Swedish Diabetes Association, the Swedish Pediatric Diabetes Foundation, and the Swedish Hoechst Foundation.

The authors thank Jonas Ranstam, Department of Community Medicine, University of Lund, Sweden, for help with the statistical analysis.

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