Predictors of Delayed Gastric Emptying in Diabetes

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OBJECTIVE — To define the predictors of the rate of gastric emptying in patients with diabetes.

RESEARCH DESIGN AND METHODS — A total of 101 outpatients with diabetes (79 type 1 and 22 type 2) underwent measurements of gastric emptying of a solid/liquid meal (scintigraphy), upper gastrointestinal symptoms (questionnaire), glycemic control (blood glucose concentrations during gastric emptying measurement), and autonomic nerve function (cardiovascular reflexes).

RESULTS — The gastric emptying of solid and/or liquid was delayed in 66 (65%) patients. Solid (retention at 100 min 64 ± 3.2 vs. 50.2 ± 3.6%, $P < 0.005$) and liquid (retention at 100 min 22.7 ± 1.7 vs. 16.0 ± 1.8%, $P < 0.001$) gastric emptying was slower in women than in men. Of all upper gastrointestinal symptoms (including nausea and vomiting), only abdominal bloating/fullness was associated with slower gastric emptying ($P < 0.005$). A multiple regression analysis demonstrated that both abdominal bloating/fullness and female sex were predictors of slower gastric emptying of both solids and liquids.

CONCLUSIONS — We conclude that the presence of abdominal bloating/fullness but not any other upper gastrointestinal symptom is associated with diabetic gastroparesis and that gastric emptying is slower in diabetic women than in diabetic men.

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The application of radioisotopic techniques to quantify gastric emptying has established that delayed gastric emptying (gastroparesis) occurs in 30–50% of patients with longstanding diabetes (1–9), and diabetes and functional dyspepsia represent the two most common disorders associated with chronic gastroparesis (10). Diabetic gastroparesis is also recognized to represent a clinically important problem because of its potential sequelae of upper gastrointestinal symptoms, impaired oral drug absorption, and poor control of blood glucose concentrations (1). However, determinants of the rate of gastric emptying in patients with diabetes are controversial and poorly defined (1–9). Particularly, it is uncertain whether diabetic gastroparesis can be predicted based on clinical, demographic, or biochemical variables. In patients with diabetes, there is also a relatively poor relationship between gastric emptying of solids and gastric emptying of nutrient-containing liquid-meal components (2–4,7); delayed liquid gastric emptying frequently occurs and may be associated with normal solid emptying (7). Hence, the predictors of delay in liquid emptying may potentially differ from those associated with the delayed gastric emptying of solids.

Previous studies have reported a relatively weak relationship between upper gastrointestinal symptoms and the rate of gastric emptying in patients with diabetes (2–7). Accordingly, it has been suggested that gastroparesis cannot be predicted based on symptoms and that objective measurement of gastric emptying is required for diagnosis (1,8). In most of these studies, symptoms have been evaluated using either a global symptom score and/or individual upper gastrointestinal symptoms classified as either "present" or "absent," without considering their severity (2–7). This approach may be relevant to the interpretation of these observations, particularly because recent studies of patients with dyspepsia of unknown origin have demonstrated a close association among specific symptoms, such as postprandial fullness with delayed gastric emptying, particularly when these symptoms are severe enough to influence usual activities (11–13). There is also evidence that gastric emptying in patients with functional dyspepsia may be influenced by demographic factors, such as sex and body weight (11).

Diabetic gastroparesis has traditionally been attributed to irreversible autonomic nerve damage (1), and in support of this concept, some studies have found a relationship between slow gastric emptying and the presence of autonomic neuropathy, as assessed by standardized cardiovascular reflex tests (2,5,8). However, the observed correlations have been relatively weak, and in other studies, no relationship was evident between the rate of gastric emptying and autonomic nerve function (6,9). Moreover, it has now been established that acute changes in blood glucose concentrations affect gastric emptying in patients with diabetes, that gastric emptying is slower during hyperglycemia when compared with euglycemia (14,15), and that gastric emptying is accelerated during hypoglycemia (16). Changes in the blood glucose concentrations that are within the normal postprandial range also influence gastric emptying, and the emptying of both solids and liquids is slower

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Abbreviations: T50, time taken for 50% of the liquid to empty.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

at a blood glucose concentration of 8 vs. 4 mmol/l in both healthy volunteers and patients with uncomplicated type 1 diabetes (17).

The purpose of this study was to evaluate potential predictors of the rate of gastric emptying of solids and liquids in a large cohort of patients with diabetes.

RESEARCH DESIGN AND METHODS

— A total of 101 patients (44 men and 57 women) with diabetes (79 type 1 and 22 type 2) were studied. Mean age was 45.1 ± 1.4 years, body weight was 76.4 ± 1.5 kg, and BMI was 26.9 ± 0.49 kg/m^2. The patients were randomly selected from ambulant outpatients who were being treated for diabetes at the Royal Adelaide Hospital. Some of the patients have been included in previous reports (2,7,18,19). The mean duration of known diabetes was 16.4 ± 1.1 years. Patients taking medication known to affect gastrointestinal motility were excluded. No subject had a history of upper gastrointestinal surgery or peptic ulcer disease. In 8 (8%) of the 101 patients, plasma creatinine was elevated (normal <0.12 mmol/l, mean 0.088 ± 0.004).

Protocol

After an overnight fast (14-h solids and 12-h liquids), each patient underwent evaluations of gastric emptying of a mixed solid and liquid meal, upper gastrointestinal symptoms, glycemic control, and autonomic nerve function. Smoking was prohibited on the study day, and none of the patients took oral hypoglycemic medication until after the completion of the gastric emptying measurement. Patients with type 1 diabetes administered their usual dose of insulin ~20 min before commencement of the gastric emptying measurement. Written informed consent was obtained from all subjects, and the study protocol was approved by the Ethics Committee of the Royal Adelaide Hospital.

Measurements

Gastric emptying. Details of this dual isotope test, which measures the emptying of solid and liquid meal components simultaneously, have been previously described (20). The solid component of the meal comprised chicken liver labeled in vivo with 20–55 MBq 99 m Tc-sulfur colloid added to 100 g minced beef that was subsequently grilled. The caloric content of the solid meal (25 g protein and 21 g fat) was ~270 kcal. The liquid component of the meal was 150 ml of 10% dextrose (~60 kcal) labeled with either 25–37 MBq ^{113m}Indium DTPA or 8 MBq ^{67}Gallium EDTA (14,18,19). The test meal was consumed at ~10:00 A.M.; the minced beef was eaten over a 5-min period, followed by the liquid, which was consumed within 30 s. Each study was performed in the sitting position with the γ-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 thereafter. Time 0 was defined as the time of meal completion. Radionuclide data were corrected for subject movement, Compton scatter, and radionuclide decay using previously described methods (20). Correction for γ-ray attenuation was done using factors derived from a lateral image of the stomach (20). A region-of-interest was drawn around the total stomach, and the gastric emptying curves (representing percent retention over time) were derived. The amount (percent) remaining in the stomach at 100 min for both solids and liquids and the time taken for 50% of the liquid to empty (T50) were quantified (18,21). Gastric emptying results were compared with an established control range (±2 SD of the mean in normal subjects for solid retention at 100 min [12–61%] and for the liquid T50 [8–31 min]) in 22 healthy subjects (14 men and 8 women, mean age 34 years [range 21–62], mean body weight 76 kg [range 53–92]) (21). Gastric emptying was considered to be abnormal (i.e., delayed or accelerated) when values were outside this range. The amount (percent) of the meal (solid and liquid) remaining in the stomach at 100 min was used to evaluate relationships between gastric emptying and other parameters.

Upper gastrointestinal symptoms

Upper gastrointestinal symptoms based on the previous 2-week period were assessed by questionnaire immediately before the gastric emptying test (2,18,22). Gastric (anorexia, nausea, early satiation, abdominal bloating/fullness, vomiting, and abdominal pain) and esophageal (dysphagia, heartburn, and acid regurgitation) symptoms were graded as 0 = none, 1 = mild (the symptom could be ignored), 2 = moderate (the symptom could not be ignored but did not influence daily activities), and 3 = severe (the symptom influenced daily activities). A score ≤1 was considered absent/mild, and a score ≥2 was considered to indicate a relevant symptom. A "global" symptom score was also calculated as the total score for both "gastric" and "esophageal" symptoms, so that the maximum score could be 27 (2,18).

Assessment of autonomic nerve function

Autonomic nerve function was assessed by standardized cardiovascular reflex tests (2,7). Parasympathetic function was evaluated by the variation (RR 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 (2,7).

Glycemic control

Venous blood samples were taken from an indwelling cannula immediately before ingestion of the test meal and then at 30, 60, 90, and 120 min thereafter. Blood glucose concentrations were determined immediately using a portable blood glucose meter, and the mean value was calculated. HbA_{1c} was measured using the initial venous sample, and the results were expressed as a percentage. The range in normal subjects was 3.5–6.0%.

Statistical analysis

Data were evaluated using the Mann-Whitney *U* test and a linear regression analysis. Multiple regression was used to determine predictors of the rate of gastric emptying of solids and liquids. Data are shown as mean values ± SEM, unless otherwise stated. $P < 0.05$ was considered significant.

RESULTS

— All subjects tolerated the study well, and none became hypoglycemic during the gastric emptying measurement.

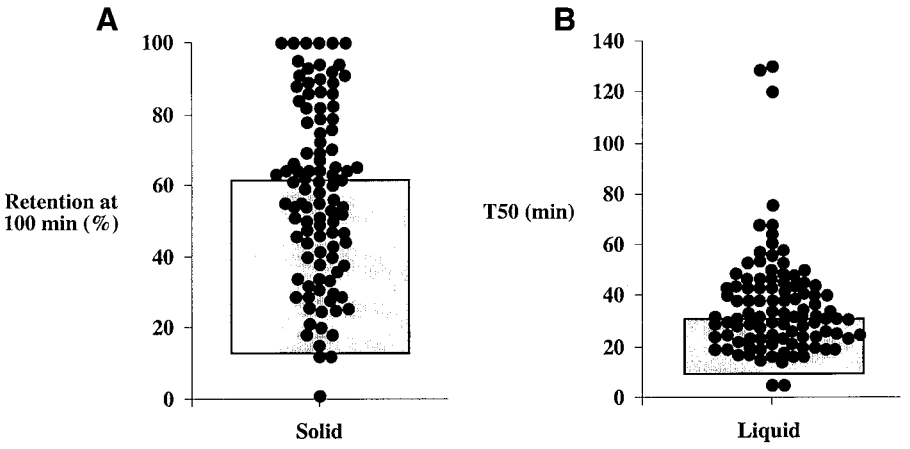

Figure 1—*Gastric emptying of solids (minced beef) (A), shown as the retention at 100 min (percent); and the gastric emptying of liquids (10% dextrose) (B), shown as the 50% emptying time (minutes) in 101 outpatients with diabetes. The normal range is indicated by the shaded area.*

Gastric emptying, upper gastrointestinal symptoms, autonomic nerve function, and glycemic control

Gastric emptying of solid and/or liquid was delayed in 66 (65%) patients. A total of 48 (48%) patients had delayed emptying of solids (i.e., retention at 100 min ≥61%), and 58 (57%) patients had slow emptying of liquids (i.e., T50 ≥31 min). Gastric emptying of both solids and liquids was delayed in 40 (40%) patients (Fig. 1). In 28 of the 48 patients with delayed solid emptying, and in 42 of the 58 patients with delayed liquid emptying, gastric emptying was >3 SD outside the normal range. Gastric emptying of solids was abnormally rapid in three (3%) patients, and the gastric emptying of liquid was abnormally rapid in two (2%) patients. There was a positive relationship between the emptying rates of solids and liquids (percent retention) at 100 min ($r = 0.61$, $P < 0.0001$). Solid (retention at 100 min 64.0 ± 3.2 vs. 50.2 ± 3.6%, $P < 0.005$) and liquid (retention at 100 min 22.7 ± 1.7 vs. 16.0 ± 1.8%, $P < 0.001$) gastric emptying were slower in women than in men. There were no significant differences in either solid or liquid gastric emptying in women <50 years of age ($n = 36$) when compared with those ≥50 years of age ($n = 21$).

A total of 84 (83%) patients had upper gastrointestinal symptoms. The mean global symptom score was 4.5 ± 0.4. Abdominal bloating/fullness was the most common of the nine symptoms, occurring in 54 (54%) patients (Table 1). The mean score for abdominal bloating/fullness was greater in women than in men (1.0 ± 0.12 vs. 0.61 ± 0.12%, $P < 0.05$), and there was no difference in any other symptom between men and women. When each upper gastrointestinal symptom was classified according to severity (absent/mild versus relevant), the intragastric retention of both solids (70.9 ± 4.1 vs 53.1 ± 2.8%, $P < 0.005$) and liquids (26.1 ± 2.8 vs 17.3 ± 1.3%, $P < 0.005$) at 100 min was greater in the 28 patients with relevant abdominal bloating/fullness when compared with the other 73 patients. Based on the severity of any other upper gastrointestinal symptom, there were no differences in the gastric emptying of solids or liquids.

A total of 43 (43%) patients had definite evidence of autonomic neuropathy, and the mean score in the whole group was 2.2 ± 0.18%. At least one of the cardiovascular tests was either borderline or abnormal in 75 (74%) patients. The mean HbA_{1c} was 8.6 ± 1.7%; 8 patients had values within the normal range (3.5–6.0%), 55 patients had values in the range of 6.1–9.0%, 35 patients had values in the range of 9.1–12.0%, and 3 patients had values >12.0%. The mean blood glucose concentration during gastric emptying measurement was 14.5 ± 0.48 mmol/l. There was a significant relationship ($r = 0.43$, $P < 0.0001$) between HbA_{1c} and the mean blood glucose concentration.

Determinants of gastric emptying

There was a trend for a relationship between the global symptom score and the gastric emptying of solids ($r = 0.19$, $P = 0.06$) but not for the gastric emptying of liquids ($r = 0.12$, $P = 0.22$). The total score for gastric symptoms correlated weakly with solid gastric emptying ($r = 0.22$, $P < 0.05$) but not with liquid gastric emptying ($r = 0.17$, $P = 0.09$). The score for esophageal symptoms was not related to either solid or liquid gastric emptying. Of the individual symptoms, only abdominal bloating/fullness was related to either solid ($r = 0.29$, $P < 0.005$) or liquid ($r = 0.28$, $P < 0.01$) gastric emptying. There were no significant relationships between the rate of gastric emptying of solids or liquids and BMI, blood glucose, age, or the score for autonomic nerve function.

Multiple regression was used to determine the predictors of the rate of gastric emptying (i.e., solid and liquid at T100 min). When individual gastrointestinal symptoms (scores 0–3), age, sex, BMI, autonomic nerve function, and mean blood glucose were considered, abdominal bloating/fullness ($P < 0.01$), female

Table 1—*Upper gastrointestinal symptoms in 101 patients with diabetes*

Symptom	None	Mild	Moderate	Severe
Gastric				
Anorexia	54	34	12	1
Nausea	66	18	15	2
Vomiting	88	8	2	3
Abdominal bloating/fullness	47	26	26	2
Abdominal discomfort	71	14	16	0
Early satiation	57	21	20	3
Oesophageal				
Dysphagia	91	7	2	1
Heartburn	67	15	17	2
Acid regurgitation	66	24	9	2

Data are *n*.

Table 2—*Predictors of delayed gastric emptying of solids (retention at 100 min) in 101 patients with diabetes*

	Coefficient	*t*	*P*
Intercept	1.4	0.08	0.94
Abdominal bloating/fullness	6.7	2.5	0.01
Female sex	11.0	2.3	0.02
Mean blood glucose (mmol/l)	1.0	2.1	0.04
BMI (kg/m^2)	1.1	2.2	0.03

Multiple regression, $r = 0.44$, $P < 0.0005$.

sex ($P < 0.05$), BMI ($P < 0.05$), and mean blood glucose ($P < 0.05$) were independent predictors of slower solid gastric emptying. Together, these predictors accounted for ~19% of the variance ($r = 0.44$, $P < 0.0005$) (Table 2), whereas abdominal bloating/fullness ($P < 0.05$) and female sex ($P < 0.05$) were predictors of slower liquid emptying; together they accounted for ~15% of the variance ($r = 0.39$, $P < 0.001$) (Table 3).

CONCLUSIONS — This study evaluated the potential predictors of the rate of gastric emptying of solids and nutrient-containing liquids in outpatients with diabetes. Two significant observations for this study group were found: *1*) the presence of abdominal bloating/fullness is associated with slower gastric emptying of both solids and liquids, whereas other upper gastrointestinal symptoms do not appear to have any predictive value; and *2*) the gastric emptying of solids and liquids is slower in women than in men. These observations have potential implications for the investigation and management of disordered gastric emptying in patients with diabetes.

The observed relationship between abdominal bloating/fullness and gastric emptying in patients with diabetes is consistent with recent studies of patients with functional dyspepsia (11–13). The total score for gastric symptoms correlated weakly with solid emptying but not with liquid emptying. Furthermore, as in patients with functional dyspepsia, symptoms such as nausea and vomiting, which have been regarded as highly suggestive of gastroparesis, do not appear to be associated with a delay in gastric emptying in patients with diabetes in the absence of abdominal bloating/fullness. This latter observation requires clarification, as it potentially has substantial implications for the investigation of upper gastrointestinal symptoms in patients with diabetes. These issues may also, at least in part, account for the inconsistencies in previous studies that have evaluated the relationship between the magnitude of symptomatic improvement and acceleration of gastric emptying in response to prokinetic therapies in diabetic gastroparesis (21–25) (i.e., the evaluation of symptoms that may not be related to delayed gastric emptying and the absence of any assessment of symptom severity). However, it should be recognized that the relationship between abdominal bloating/fullness and delayed gastric emptying in diabetes was not strong, which is probably indicative of the multifactorial etiology of symptoms in these patients (1,26–28). It has not been established whether the predictive value of postprandial symptoms would be greater compared with the predictive value of fasting (18). It should also be recognized that our observations were obtained in a tertiary referral center, and although the inclusion of subjects was not based on either the presence or absence of gastrointestinal symptoms or the rate of gastric emptying, selection bias cannot be excluded.

Table 3—*Predictors of delayed gastric emptying of liquids (retention at 100 min) in 101 patients with diabetes*

	Coefficient	*t*	*P*
Intercept	13.9	6.8	<0.0001
Abdominal bloating/fullness	3.3	2.4	0.02
Female sex	5.4	2.2	0.03

Multiple regression, $r = 0.34$, $P < 0.005$.

A gender difference in gastric emptying has been reported in healthy control subjects in some (29–33) but not all (34,35) studies; in patients with functional dyspepsia, gastric emptying appears to be slightly slower in women than in men (11). Hence, our observation that gastric emptying is slower in women with diabetes, albeit novel, is not surprising. The etiology of this difference remains speculative. The higher prevalence of abdominal bloating/fullness in women with diabetes is also consistent with observations in nondiabetic subjects (36) and outpatients with type 1 diabetes (37). Multiple regression analysis showed a weak relationship between BMI and gastric emptying of solids but not between BMI and gastric emptying of liquids. In healthy subjects, there is evidence that the rate of gastric emptying may be influenced by body weight per se (35,38,39) as well as previous patterns of nutrient intake (40,41). In healthy subjects, obesity has been associated with both slower (35) and more rapid (38,39) gastric emptying, whereas in patients with functional dyspepsia, delayed gastric emptying has been associated with low body weight (11). Hence, the observed association between higher BMI and slower gastric emptying of solids in our study should be viewed circumspectly, and it awaits confirmation from future studies.

The observed relationship between blood glucose concentration and gastric emptying of solids was anticipated. Previous studies have demonstrated a dose-dependent inverse relationship between the rate of gastric emptying and the blood glucose concentrations in both healthy subjects and patients with uncomplicated diabetes (14–16). The blood glucose concentration also influences the effect of prokinetic therapy on gastric emptying (42,43). However, it is not known whether the effects of variations in blood glucose concentration on gastric emptying are influenced by either the rate of gastric emptying during euglycemia or autonomic nerve function. In relation to the latter, we did not find that cardiovascular autonomic nerve dysfunction was independently associated with the rate of gastric emptying, which is contrary to the suggestion of some (2,5,8) but not all (6,9) studies. This may potentially reflect the fact that many of our patients had evidence of autonomic dysfunction, and thus using cardiovascular reflex tests as a surrogate markers of gastrointestinal autonomic nerve function has inherent limitations (1).

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References

1. Horowitz M, Fraser R: Disordered gastric motor function in diabetes mellitus. *Dia-*

betologia 37:543–551, 1994
2. Horowitz M, Maddox AF, Wishart JM, Harding PE, Chatterton BE, Shearman DJ: Relationships between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. *Eur J Nucl Med* 18: 229–234, 1991
3. Keshavarzian A, Iber FL, Vaeth J: Gastric emptying in patients with insulin-requiring diabetes mellitus. *Am J Gastroenterol* 82:29–35, 1987
4. Wegener M, Borsch G, Schaffstein J, Luerweg C, Leverkus F: Gastrointestinal transit disorders in patients with insulin-treated diabetes mellitus. *Dig Dis Sci* 8:23–26, 1990
5. Ziegler D, Schadewaldt P, Pour Mirza A, Piolot R, Schommartz B, Reinhardt M, Vosberg H, Brosicke H, Gries FA: ^{13}C octanoic acid breath test for non-invasive assessment in diabetic patients: validation and relationship to gastric symptoms and cardiovascular autonomic function. *Diabetologia* 39:823–830, 1996
6. Annese V, Bassotti G, Caruso N, De Cosmo S, Gabbrielli A, Modoni S, Frusciante V, Andriulli A: Gastrointestinal motor dysfunction, symptoms and neuropathy in noninsulin-dependent (type 2) diabetes mellitus. *J Clin Gastroenterol* 29: 171–177, 1999
7. Jones KL, Horowitz M, Wishart J, Maddox AF, Harding PE, Chatterton B: Relationship between gastric emptying, intragastric meal distribution and blood glucose concentrations in diabetes mellitus. *J Nucl Med* 36:2220–2228, 1995
8. Buysschaert M, Moulart M, Urbain JL, Pauwels S, de Roy L, Ketelslegers JM, Lambert AE: Impaired gastric emptying in diabetic patients with cardiac autonomic neuropathy. *Diabetes Care* 10:448–452, 1987
9. Cotroneo P, Grattagliano A, Rapaccini GL, Manto A, Mancini L, Magnani P, Pompili M, Vccioli L, Greco AV, Ghirlanda G: Gastric emptying rate and hormonal response in type II diabetics. *Diabetes Res* 17:99–104, 1991
10. Horowitz M, Fraser RJ: Gastroparesis: diagnosis and management. *Scand J Gastroenterol* 213 (Suppl.):7–16, 1995
11. Stanghellini V, Tosetti C, Paternicò A, Barbara G, Morselli-Labate AM, Monetti N, Marengo M, Corinaldesi R: Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* 110:1036–1042, 1996
12. Stanghellini V, Tosetti C, Paternico A, Barbara G, Morselli-Labate AM, Monetti N, Marengo M, Corinaldesi R: Predominant symptoms identify different subgroups in functional dyspepsia. *Am J Gastroenterol* 94:2080–2085, 1999
13. Tack J, Piessevaux H, Coulie B, Geypens B, Caenepeel P, Ghoos Y, Janssens J: Symptom pattern and gastric emptying rate assessed by the octanoic acid breath test in functional dyspepsia (Abstract). *Gastroenterology* 114:G1233, 1998
14. Fraser R, Horowitz M, Maddox A, Chatterton B, Harding P, Dent J: Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 30:675–680, 1990
15. Samsom M, Akkermans LM, Jebbink RJ, van Isselt H, vanBerge-Henegouwen GP, Smout AJ: Gastrointestinal motor mechanisms in hyperglycemia induced delayed gastric emptying in type I diabetes mellitus. *Gut* 40:641–646, 1997
16. Schvarcz E, Palmer M, Aman J, Lindkvist B, Beckman KW: Hypoglycaemia increases gastric emptying rate in patients with type 1 diabetes mellitus. *Diabet Med* 10:660–663, 1993
17. Schvarcz E, Palmer M, Aman J, Horowitz M, Stridsberg M, Berne C: Physiological hyperglycaemia slows gastric emptying in normal subjects and patients with insulin-dependent diabetes mellitus. *Gastroenterology* 113:60–66, 1997
18. Jones KL, Horowitz M, Berry M, Wishart JM, Guha S: Blood glucose concentration influences postprandial fullness in IDDM. *Diabetes Care* 20:1141–1146, 1997
19. Jones KL, Wishart JM, Berry MK, Abitbol J-L, Horowitz M: Effects of fedotozine on gastric emptying and upper gastrointestinal symptoms in diabetic gastroparesis. *Aliment Pharmacol Ther* 14:937–943, 2000
20. Collins PJ, Horowitz M, Cook DJ, Harding PE, Shearman DJ: Gastric emptying in normal subjects: a reproducible technique using a single scintillation camera and computer system. *Gut* 24:1117–1125, 1983
21. Horowitz M, Maddox A, Harding PE, Maddern GJ, Chatterton BE, Wishart J, Shearman DJ: Effect of cisapride on gastric and esophageal emptying in insulin-dependent diabetes mellitus. *Gastroenterology* 92:1899–1907, 1987
22. Horowitz M, Harding PE, Chatterton BE, Collins PJ, Shearman DJ: Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. *Dig Dis Sci* 30:1–9, 1985
23. Sturm A, Holtmann G, Gerken G: Prokinetics in patients with gastroparesis: a systematic analysis. *Digestion* 60:422–427, 1999
24. Drenth J, Engels LG: Diabetic gastroparesis: a critical appraisal of new treatment strategies. *Drugs* 44:537–553, 1992
25. Janssens J, Peeters TL, Vantrappen G, Tack J, Urbain JL, De Roo M, Muls E, Bouillon R: Improvement of gastric emptying in diabetic gastroparesis by erythromycin: preliminary studies. *N Engl J Med* 322:1028–1031, 1990
26. Mearin F, Malagelada JR: Gastroparesis and dyspepsia in patients with diabetes mellitus. *Eur J Gastroenterol Hepatol* 7: 717–723, 1995
27. Rayner CK, Su YC, Doran SM, Jones KL, Malbert CH, Horowitz M: The stimulation of antral motility by erythromycin is attenuated by hyperglycemia. *Am J Gastroenterol* 95:2233–2241, 2000
28. Bytzer P, Talley NJ, Jones MP, Horowitz M: Oral hypoglycaemic drugs and gastrointestinal symptoms in diabetes mellitus. *Aliment Pharmacol Ther*. 15:137–142, 2001
29. Datz FL, Christian PE, Moore J: Gender-related differences in gastric emptying. *J Nucl Med* 28:1204–1207, 1987
30. Hermansson G, Sivertsson R: Gender related differences in gastric emptying rate of solid meal. *Dig Dis Sci* 41:1994–1998, 1996
31. Mones J, Carrio I, Calabuig R, Estorch M, Sainz S, Berna L, Vilardell F: Influence of the menstrual cycle and of menopause on the gastric emptying rate of solids in female volunteers. *Eur J Nucl Med* 20:600–602, 1993
32. Knight LC, Parkman HP, Brown KL, Miller MA, Trate DM, Maurer AH, Fisher RS: Delayed gastric emptying and decreased antral conctractility in normal premenopausal women compared with men. *Am J Gastroenterol* 92:968–975, 1997
33. Bennink R, Peeters M, Van den Maegdenbergh V, Geypens B, Rutgeerts P, De Roo M, Mortelmans L: Comparison of total and compartmental gastric emptying and antral motility between healthy men and women. *Eur J Nucl Med* 25:1293–1299, 1998
34. Horowitz M, Maddern GJ, Chatterton BE, Collins PJ, Harding PE, Shearman DJ: Changes in gastric emptying rates with age. *Clin Sci* 67:213–218, 1984
35. Horowitz M, Collins PJ, Cook DJ, Harding PE, Shearman DJ: Abnormalities of gastric emptying in obese patients. *Int J Obes* 7:415–421, 1983
36. Talley NJ, Zinsmeister AR, Melton LJ III: Irritable bowel syndrome on a community: symptom subgroups, risk factors and healthcare utilization. *Am J Epidemiol* 142:76–83, 1995
37. Schvarcz E, Palmer M, Ingberg CM, Aman J, Berne C: Increased prevalence of upper gastrointestinal symptoms in long-term type 1 diabetes mellitus. *Diabet Med* 13: 478–481, 1996
38. Tosetti C, Corinaldesi R, Stanghellini V, Pasquali R, Corbelli C, Zoccoli G, Di Febo G, Monetti N, Barbara L: Gastric emptying of solids in morbid obesity. *Int J Obes* 20:200–205, 1996
39. Teff KL, Alavi A, Chen J, Pourdehnad M, Townsend RR: Muscarinic blockade inhibits gastric emptying of mixed nutrient

meal: effect of weight and gender. *Am J Physiol* 276:R707–R714, 1999
40. Horowitz M, Cunningham KM, Wishart JM, Jones KL, Read NW: The effect of short-term dietary supplementation with glucose on gastric emptying of glucose and fructose and oral glucose tolerance in normal subjects. *Diabetologia* 39:481–486, 1996
41. Corvilain B, Abramowicz M, Fery F, Schoutens A, Verlinden M, Balasse E, Horowitz M: Effect of short-term starvation on gastric emptying in humans: relationship to oral glucose tolerance. *Am J Physiol* 269:G512–G517, 1995
42. Jones KL, Berry M, Kong MF, Kwiatek MA, Samsom M, Horowitz M: Hyperglycemia attenuates the gastrokinetic effect of erythromycin and affects the perception of postprandial hunger in normal subjects. *Diabetes Care* 22:339–344, 1999
43. Petrakis IE, Vrachassotakis N, Sciacca V, Vassilakis SI, Chalkiadakis G: Hyperglycaemia attenuates erythromycin-induced acceleration of solid-phase gastric emptying in idiopathic and diabetic gastroparesis. *Scand J Gastroenterol* 34:396–403, 1999