Natural History of Diabetic Gastroparesis

MARIE-FRANCE KONG, MBCHB, MRCP (U.K.)
MICHAEL HOROWITZ, MBBS, PHD, FRACP
KAREN L. JONES, DIPAPPSCI, PHD
JUDITH M. WISHART, BSC
PHILIP E. HARDING, MBBS, FRACP

OBJECTIVE — The major aim of this study was to evaluate the prognosis of diabetic gastroparesis.

RESEARCH DESIGN AND METHODS — Between 1984 and 1989, 86 outpatients with diabetes (66 type 1, 20 type 2; 40 male, 46 female) underwent assessment of solid and liquid gastric emptying and esophageal transit (by scintigraphy), gastrointestinal symptoms (by questionnaire), autonomic nerve function (by cardiovascular reflex tests), and glycemic control (by HbA_{1c} and blood glucose concentrations during gastric emptying measurement). These patients were followed up in 1998.

RESULTS — Of the 86 patients, solid gastric emptying (percentage of retention at 100 min) was delayed in 48 (56%) patients and liquid emptying (50% emptying time) was delayed in 24 (28%) patients. At follow-up in 1998, 62 patients were known to be alive, 21 had died, and 3 were lost to follow-up. In the group who had died, duration of diabetes ($P = 0.048$), score for autonomic neuropathy ($P = 0.046$), and esophageal transit ($P = 0.032$) were greater than in those patients who were alive, but there were no differences in gastric emptying between the two groups. Of the 83 patients who could be followed up, 32 of the 45 patients (71%) with delayed solid emptying and 18 of the 24 patients (75%) with delay in liquid emptying were alive. After adjustment for the effects of other factors that showed a relationship with the risk of dying, there was no significant relationship between either gastric emptying or esophageal transit and death.

CONCLUSIONS — In this relatively large cohort of outpatients with diabetes, there was no evidence that gastroparesis was associated with a poor prognosis.

Diabetes Care 22:503–507, 1998

Until relatively recently, gastroparesis was thought to be an infrequent complication of diabetes, occurring only in patients with long-standing diabetes who had severe microvascular complications (1–3). We now know that this is not the case. Although there are no true population-based studies of gastric emptying in diabetic patients, cross-sectional studies using radioisotopic methods have established that gastric emptying of solid and/or nutrient liquid meals is delayed in about 50% of outpatients with long-standing type 1 or type 2 diabetes (4–11). Previous methods used to measure gastric emptying in patients with diabetes (e.g., radiographic methods using liquid barium sulfate) are much less sensitive than scintigraphic methods (1,2). Diabetic gastroparesis is clinically important because it may be associated with gastrointestinal symptoms, alterations in glycemic control, and changes in oral drug absorption (12). Gastrointestinal symptoms, however, correlate relatively poorly with measurements of gastric emptying, so that up to 50% of patients with marked delay in gastric emptying have few or no upper gastrointestinal symptoms (4–7,10,11,13). Both symptomatic and asymptomatic gastroparesis may be associated with poor glycemic control by causing a mismatch between the action of insulin (or oral hypoglycemic drug) and absorption of nutrients (8,12). There is relatively little information about the natural history of diabetic gastroparesis (1,14); although it has been considered to be associated with a poor prognosis (1,3,15), its high prevalence suggests that this assumption may be incorrect.

Between 1984 and 1989 we performed radioisotopic measurements of solid and liquid gastric emptying in 86 randomly selected diabetic outpatients; we have reported some of these data previously (4–6,16). We attempted to determine whether these patients were alive or deceased 9 years after their gastric emptying measurement, primarily to evaluate the relationship between delayed gastric emptying and mortality. Those results are reported in this study.

RESEARCH DESIGN AND METHODS

— The study group comprised 86 patients with diabetes (66 type 1, 20 type 2) evaluated between 1984 and 1989, as reported previously (4–6,16). The 40 male and 46 female patients had a median age of 46 years (range 18–77), BMI of 24.7 kg/m^2 (19.9–35.9), and body weight of 71 kg (46–102). The patients were randomly selected by two endocrinologists (M.H., P.E.H.) from ambulant outpatients who were being treated for diabetes of a known duration of at least 1 year (median 14.5 years) (1–49) at the Royal Adelaide Hospital. Patients taking medication known to affect gastrointestinal motility were excluded, and none of the study subjects had a history of upper gastrointestinal surgery or gastrointestinal disease unrelated to diabetes (4–6,16). The plasma creatinine concentration was required to be within the normal range (0.05–0.12 mmol/l) in all patients—that is, patient selection was not influenced by the presence or absence of gastrointestinal symptoms or diabetic complications (apart from nephropathy). Gastric emptying results were compared with a range established in 20 healthy volunteers (16). None of the control subjects was taking medication that could have influenced gastrointestinal motility, had gastrointestinal symptoms, or had a history of gastrointestinal disease. All the patients and control subjects were Caucasian.

Protocol

All patients underwent assessments of gastric emptying, gastrointestinal symptoms, retinopathy, esophageal transit, autonomic

From the Department of Medicine, Royal Adelaide Hospital, Adelaide, Australia.
Address correspondence and reprint requests to Michael Horowitz, MBBS, PhD, FRACP, Department of Medicine, University of Adelaide, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia, Australia SA 5000. E-mail: ssuter@medicine.adelaide.edu.au.
Received for publication 5 October 1998 and accepted in revised form 24 November 1998.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

neuropathy, and glycemic control (4–6,16). At the beginning of 1998, we attempted to determine whether patients were alive or deceased by a combination of outpatient case note review, telephone contact, and review of electoral rolls and the Registry of Births, Deaths, and Marriages. In those patients who were deceased, the date of death was identified. The study protocol was approved by the Ethics Committee of the Royal Adelaide Hospital.

Assessment of gastrointestinal symptoms

Upper gastrointestinal symptoms were assessed by questionnaire (4–6). 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, or 3 = severe.

Assessment of autonomic neuropathy and retinopathy

Autonomic nerve function was assessed by cardiovascular reflex tests (4–6,16,17). 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 $\geq$3 was taken to indicate definite autonomic nerve damage (4,16).

Retinopathy was graded as 0 = none, 1 = background, or 2 = proliferative on the basis of a recent ophthalmologic assessment, which often included fluorescein angiography (4,16).

Measurement of gastric emptying

This scintigraphic test measures gastric emptying of solid and liquid meal components simultaneously (18,19). The solid component of the meal comprised 100 g of cooked minced beef, containing 37–55 MBq of ^{99m}Tc-sulfur colloid chicken liver; the liquid component was 150 ml 10% dextrose labeled with 25–37 MBq ^{113m}In-diethylenetriamine pentaacetic acid. Each study was performed at about 10:00 A.M., with the patient in the sitting position and the gamma camera positioned posteriorly; time zero was defined as the time of meal completion. From the emptying curves, the amount of solid remaining in the stomach at 100 min (T_{100}) and the time for half of the liquid to empty (T_{50}) were obtained (4,16). Gastric emptying was considered to be delayed (gastroparesis) when values were greater than the range in the control subjects: solid T_{100} >55%, liquid T_{50} >39 min (16). Of the 86 patients, solid emptying (T_{100}) was delayed in 48 (56%) and liquid emptying (T_{50}) in 24 (28%). Either solid and/or liquid emptying was delayed in 53 (62%).

Measurement of esophageal transit

Immediately before the commencement of the gastric emptying test, the subjects swallowed a 10 g bolus of the solid meal and were then asked to swallow on command every 15 s (4–6). The test was continued until the bolus was seen to enter the stomach or until 20 swallows (300 s) had been performed. The time for 95% (T_{95}) of the radioactivity to enter the stomach was calculated; esophageal transit was considered to be delayed when the T_{95} was >300 s (4–6). Of the 86 patients, esophageal transit was delayed in 29 (35%).

Assessment of glycemic control

Immediately before meal ingestion and at 30, 60, 90, and 120 min, 5-ml venous blood samples were taken via an indwelling cannula for measurement of plasma glucose using a hexokinase technique (4–6,16). HbA_{1c} was measured on the initial venous sample and the results were expressed as a percentage. The range in normal subjects is 3.5–6.0% (4).

Statistical analysis

Statistical analysis was carried out with Statview (version 4.51; Abacus Concepts, Berkeley, CA) and SAS packages (20). The Mann-Whitney *U* test was used to evaluate results in those patients who had died compared with those who were alive. The χ^2 test was used to evaluate the prevalence of delayed gastric and esophageal emptying in these two groups. Data were also analyzed by the log rank test for univariate analysis of potential predictors. When considering all-cause mortality, the Cox proportional hazards model for multivariate analysis was used (21). Univariate results were calculated for both continuous and absolute values. Data are shown as median values and range. A P value <0.05 was considered significant in all analyses.

RESULTS — In 1998, 62 patients were known to be alive (72%), 21 had died (24%), and 3 were lost to follow-up (2 had moved overseas and 1 had moved interstate). The median time of death was 6 years (range 1–12) from the initial measurement. The major causes of death were cardiovascular or renal disease. None of the deaths was due to trauma. Of the 62 living patients, gastric solid emptying (T_{100}) was delayed in 32 (52%); liquid emptying (T_{50}), in 18 (29%); and esophageal transit, in 17 (27%). In those patients who had died, the duration of diabetes (P = 0.048) and scores for autonomic neuropathy (P = 0.046), retinopathy (P = 0.017), and esophageal transit (P = 0.032) were greater than in the patients who were alive. There were no significant differences between the two groups in other parameters, including upper gastrointestinal symptoms, HbA_{1c}, and solid or liquid gastric emptying (Table 1). When

Table 1—*Results at baseline (1984–1989) in 83 outpatients with diabetes known to be alive or deceased in 1998*

	Alive	Deceased	*P* value
n	62	21	—
Age at baseline (years)	45 (18–77)	50 (31–69)	NS
Duration of diabetes	12 (1–49)	18 (5–27)	0.048
Gastrointestinal symptoms (score)	2 (0–13)	2 (0–15)	NS
HbA_{1c} (%)	9.4 (3.6–16.0)	9.1 (5.3–15.7)	NS
Mean plasma glucose during gastric emptying measurement (mmol/l)	16.9 (5.2–29.7)	16.6 (6.0–22.4)	NS
Autonomic nerve dysfunction (score)	2 (0–6)	3 (0–6)	0.046
Retinopathy (score)	1 (0–2)	2 (0–2)	0.017
Esophageal transit (s)	60 (12–450)	135 (15–450)	0.032
Solid retention at 100 min (%)	55 (12–100)	60 (0–94)	NS
Liquid 50% emptying time (min)	28 (5–61)	35 (5–57)	NS

Data are median values (range).

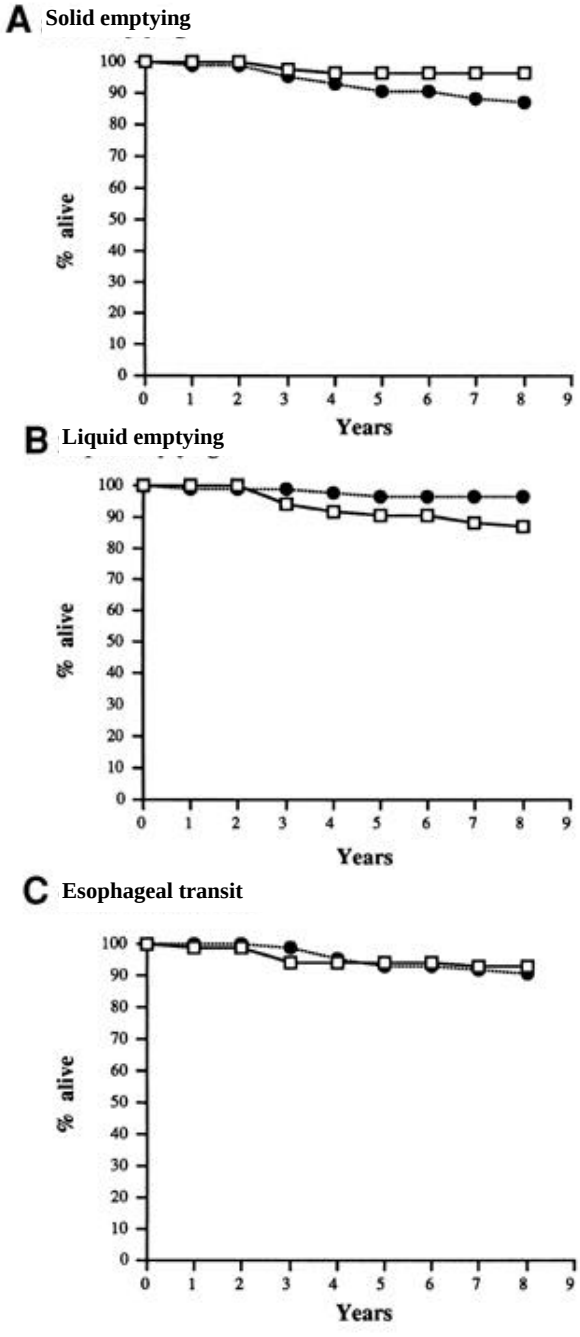

Figure 1—*Calculated 9-year survival according to whether gastric emptying (A,B) or esophageal transit (C) were normal (□) or delayed (●).*

esophageal transit and solid and liquid gastric emptying were classified as either normal or delayed, relatively more patients with delayed (as opposed to normal) esophageal transit had died (χ^2 4.65, P = 0.031), whereas there was no difference for solid or liquid emptying. In the total group of 83 patients, 32 of the 45 (71%) patients with delayed solid emptying, 18 of the 24 patients (75%) with delayed liquid gastric emptying, and 17 of the 29 patients (59%) with delayed esophageal transit were alive.

At 9 years, 19 of the 83 patients had died. The percentage alive was not affected by the rate of solid or liquid gastric emptying or esophageal transit (Fig. 1).

When all-case mortality was considered, there were significant relationships between risk of death and age (P = 0.03) and duration of diabetes (P = 0.02), and a nonsignificant trend for a relationship between risk of death and the score for autonomic nerve dysfunction (P = 0.17). There was no significant relationship with any other parameter (including esophageal transit, solid and liquid gastric emptying, and upper gastrointestinal symptoms) and death. After adjustment for the effects of other factors that showed a significant relationship with the risk of dying, there was still no significant relationship between either gastric emptying or esophageal transit and the risk of death.

Exclusion of type 2 patients from the analysis did not affect the results significantly (data not shown).

CONCLUSIONS — We demonstrated that in a relatively large cohort of outpatients with long-standing diabetes the majority of patients with gastroparesis were alive after a period of 9–14 years and that the risk of death was not related to the rate of solid or liquid gastric emptying. These observations suggest that gastroparesis per se is, at least in most cases, not associated with a major increased risk of mortality.

The techniques used to quantify gastric emptying in patients with diabetes before the advent of scintigraphy were insensitive, and the prevalence of gastroparesis was grossly underestimated (1,2). Scintigraphic measurements of gastric emptying in patients with diabetes are reproducible (22), but there is considerable variation in the criteria used to define delay in gastric emptying—for example, values greater than mean + 1.5 SD (11) and mean + 2 SD (5) of a control range have been used. We were conservative and considered gastric emptying to be delayed when values were greater than the upper limit of the normal range for either solid or liquid emptying (16). Hence all of our patients with gastroparesis had a marked delay in gastric emptying.

To date there has been little information about the natural history of diabetic gastroparesis. In a retrospective study of 35 patients with "diabetic gastropathy" Zitomer et al. (1) reported that 12 (34.3%) of the patients died within 3 years of diagnosis, but in that study gastric emptying was evaluated by barium meal. It is therefore likely that only those patients with grossly delayed gastric emptying were identified. It has been suggested that the development of gastric symptoms, particularly if associated with evidence of gastric atony on barium meal, is a late manifestation of autonomic

neuropathy and associated with a poor prognosis (3). A more recent study using scintigraphy provided evidence that delay in gastric emptying may not signify a poor prognosis (14); 10 of 13 type 2 patients who had delayed gastric emptying of a nutrient liquid meal were alive at 3–5 years. However, only limited conclusions can be drawn: the number of patients studied was small, patients with type 1 diabetes were not evaluated, the duration of follow-up was short, and gastric emptying of solids (which may be more sensitive than measurement of nutrient liquid emptying) was not assessed (14). Because gastric emptying of liquid barium is delayed in only a small percentage of patients with diabetes (1), it is possible that very severe gastroparesis is associated with high mortality. It should be recognized that our patients were selected at random; there was no information about the prognosis of those patients who presented with significant gastrointestinal symptoms and gastroparesis. Nevertheless, our observations support the concept that in the majority of patients, both gastroparesis and the presence of upper gastrointestinal symptoms are not associated with a poor prognosis.

Rundles (2) suggested in 1945 that the cause of diabetic gastroparesis was vagal damage, occurring as part of a more generalized autonomic neuropathy. Although animal models of diabetes are associated with marked changes in the neural innervation of the gut (23), histopathological studies in humans have failed to show consistent abnormalities (24). Moreover, the relationship between the rate of gastric emptying and autonomic nerve function, as assessed by tests of cardiovascular autonomic function, is relatively weak (6,10,11,25). It has recently been established that acute changes in blood glucose concentration affect gastric emptying as well as motor function in other regions of the gastrointestinal tract; for example, acute hyperglycemia (blood glucose of ~15 mmol/l) slows gastric emptying in normal subjects and diabetic patients (5,19,26,27). During our gastric emptying measurements, blood glucose concentrations were not maintained in the euglycemic range and, at the time when the study was performed, the impact of the blood glucose concentration on gastric emptying had not been recognized. Although the prevalence of delayed gastric emptying in patients with diabetes during euglycemia has not been evaluated, it is likely to be less than that reported in all previous studies in which the blood glucose concentrations were not stabilized during measurements of gastric emptying (4–11,25).

Esophageal radionuclide transit is delayed in 30–40% of patients with long-standing diabetes and may be associated with symptoms such as dysphagia and delayed esophageal transit of medications, with consequent risks of mucosal ulceration and delayed drug absorption (4,5,28–31). In this study, esophageal transit of a solid bolus was slower in those patients who died, although there was no significant relationship between esophageal transit and death (presumably because most deaths occurred some time after the baseline measurements). Esophageal motor dysfunction may be more closely related to autonomic neuropathy than delay in gastric emptying (4,5,32), although esophageal motility is also affected by acute changes in the blood glucose concentration (33).

Diabetic neuropathy (34), retinopathy (35), and symptomatic autonomic neuropathy (15) are associated with increased mortality. In contrast, asymptomatic autonomic dysfunction, characterized by abnormal cardiovascular reflexes, occurs frequently and appears to be associated with either no (15) or only a modest (36) increase in the risk of death. It is, therefore, perhaps not surprising that delay in gastric emptying, which is now recognized to occur in ~50% of outpatients with diabetes, may not be associated with a substantial increased risk of mortality in the majority of cases. However, it should also be recognized that both symptomatic and asymptomatic gastroparesis may decrease quality of life and affect glycemic control.

Acknowledgments — This work was supported by the National Health and Medical Research Council of Australia and the Wellcome Trust, U.K.

We wish to thank K. Willson (biostatistician) for assistance with the statistical analyses.

This paper has been published in abstract form: M-F Kong, M Horowitz, KL Jones, JM Wishart, PE Harding: Prognosis of diabetic gastroparesis (Abstract). *Diabetologia* 41 (Suppl. 1):A268, 1998.

References

1. Zitomer BR, Gramm HF, Kozak GP: Gastric neuropathy in diabetes mellitus: clinical and radiologic observations. *Metabolism* 17:199–211, 1968
2. Rundles RW: Diabetic neuropathy. *Medicine* 24:111–160, 1945
3. Ewing DJ, Campbell IW, Clarke BF: The natural history of diabetic autonomic neuropathy. *Q J Med* 193:95–108, 1980
4. Horowitz M, Harding PE, Maddox A, Maddern GJ, Collins PJ, Chatterton BE, Wishart J, Shearman DJC: Gastric and oesophageal emptying in insulin-dependent diabetes mellitus. *J Gastroenterol Hepatol* 1:97–113, 1986
5. Horowitz M, Harding PE, Maddox AF, Wishart JM, Akkermans LM, Chatterton BE, Shearman DJ: Gastric and oesophageal emptying in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 32:151–159, 1989
6. Horowitz M, Maddox AF, Wishart JM, Harding PE, Chatterton BE, Shearman DJC: Relationships between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. *Eur J Nucl Med* 18:229–234, 1991
7. Keshavarzian A, Iber FL, Vaeth J: Gastric emptying in patients with insulin-requiring diabetes mellitus. *Am J Gastroenterol* 82:29–35, 1987
8. Lyrenas E, Olsson E, Arvidsson U, Örn TJ, Spjuth JH: Prevalence and determinants of solid and liquid gastric emptying in unstable type 1 diabetes: relationship to postprandial blood glucose concentrations. *Diabetes Care* 20:413–418, 1997
9. Wegener M, Börsch G, Schaffstein J, Luerweg C, Leverkus F: Gastrointestinal transit disorders in patients with insulin treated diabetes mellitus. *Dig Dis Sci* 8:23–26, 1990
10. 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 of gastric emptying in diabetic patients: validation and relationship to gastric symptoms and cardiovascular autonomic function. *Diabetologia* 39:823–830, 1996
11. Merio R, Festa A, Bergmann H, Eder T, Eibl N, Stacher-Janotta G, Weber U, Budka C, Heckenberg A, Bauer P, Francesconi M, Schernthaner G, Stacher G: Slow gastric emptying in type 1 diabetes: relation to autonomic and peripheral neuropathy, blood glucose and glycemic control. *Diabetes Care* 20:419–423, 1997
12. Horowitz M, Fraser R: Disordered gastric motor function in diabetes mellitus. *Diabetologia* 37:543–551, 1994
13. Iber FL, Parveen S, Vandrunen M, Sood KB, Reza F, Serlovsky R, Reddy S: Relation of symptoms to impaired stomach, small bowel and colon motility in longstanding diabetes. *Dig Dis Sci* 38:45–50, 1993
14. Chaudhuri TK, Fink S: Prognostic implication of gastroparesis in patients with diabetes mellitus. *Clin Auton Res* 2:221–224, 1992
15. Sampson MJ, Wilson S, Karagiannis P,

Edmonds M, Watkins PJ: Progression of diabetic autonomic neuropathy over a decade in insulin-dependent diabetics. *Q J Med* 278:635–646, 1990
16. Jones KL, Horowitz M, Wishart JM, Maddox AF, Harding PE, Chatterton BE: Relationships between gastric emptying, intragastric meal distribution and blood glucose concentrations in diabetes mellitus. *J Nucl Med* 36:2220–2228, 1995
17. Ewing DJ, Clarke BF: Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 285:916–918, 1982
18. Collins PJ, Horowitz M, Cook DJ, Harding PE, Shearman DJC: Gastric emptying in normal subjects: a reproducible technique using a single scintillation camera and computer system. *Gut* 24:1117–1125, 1983
19. Fraser RJ, Horowitz M, Maddox AF, Harding PE, Chatterton BE, Dent J: Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 33:675–680, 1990
20. SAS Users Guide: *Statistics. Version 6.12 Edition*. Cary, NC, SAS Institute, 1997
21. Cox DR: Regression models and life tables. *J R Stat Soc Ser B* 187–220, 1972
22. Lartigue S, Bizais Y, Bruley des Varannes S, Murat A, Pouliquen B, Galmiche JP: Inter- and intrasubject variability of solid and liquid gastric emptying parameters: a scintigraphic study in healthy subjects and diabetic patients. *Dig Dis Sci* 39:109–115, 1994
23. Takahashi T, Nakamura K, Itoh H, Sima AA, Owyang C: Impaired expression of nitric oxide synthase in the gastric myenteric plexus of spontaneously diabetic rats. *Gastroenterology* 113:1535–1544, 1997
24. Yoshida MM, Schuffler MD, Sumi SM: There are no morphologic abnormalities of the gastric wall or abdominal vagus in patients with diabetic gastroparesis. *Gastroenterology* 94:907–914, 1988
25. 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
26. Samsom M, Akkermans LMA, Jebbink RJA, van Isselt H, vanBerge-Henegouwen GP, Smout AJPM: Gastrointestinal motor mechanisms in hyperglycemia induced delayed gastric emptying in type 1 diabetes mellitus. *Gut* 40:641–646, 1997
27. Schvarcz E, Palmer M, Aman J, Horowitz M, Stridsberg M, Berne C: Physiological changes in blood glucose affect gastric emptying in normal subjects and patients with insulin-dependent diabetes. *Gastroenterology* 113:60–66, 1997
28. Keshavarzian A, Iber FL, Wasrallah S: Radionuclide oesophageal emptying and manometric studies in diabetes mellitus. *Am J Gastroenterol* 82:625–631, 1987
29. Channer KS, Jackson PC, O'Brien I, Corrall RJ, Coles DR, Davies ER, Virjee JP: Oesophageal function in diabetes mellitus and its association with autonomic neuropathy. *Diabet Med* 2:378–382, 1985
30. Jermendy G, Fornet B, Koltai MZ, Pogatsa G: Correlation between oesophageal dysmotility and cardiovascular autonomic dysfunction in diabetic patients without gastrointestinal symptoms of autonomic neuropathy. *Diabetes Res* 16:193–197, 1991
31. Frusciante V, Modoni S, Bonazza A, Cosmo SD, Barbano F, Lucentini L, Vettori PG: Scintigraphic oesophageal clearance in diabetics: clinical usefulness. *Nucl Med Commun* 9:955–964, 1988
32. Hollis JB, Castell DO, Braddom RL: Esophageal function in diabetes mellitus and its relation to peripheral neuropathy. *Gastroenterology* 73:1098–1102, 1977
33. De Boer SY, Masclee AA, Lam WF, Lamers CB: Effect of acute hyperglycemia on oesophageal motility and lower oesophageal sphincter pressure in humans. *Gastroenterology* 103:775–780, 1992
34. Gall M-A, Borch-Johnsen K, Hougaard P, Nielsen FS, Parving H-H: Albuminuria and poor glycemic control predict mortality in NIDDM. *Diabetes* 44:1303–1309, 1995
35. Miettinen H, Haffner S, Lehto S, Ronnemaa T, Pyörälä K, Laakso M: Retinopathy predicts coronary heart disease events in NIDDM patients. *Diabetes Care* 19:1445–1448, 1996
36. Rathmann W, Ziegler D, Jahnke M, Haastert B, Gries FA: Mortality in diabetic patients with cardiovascular autonomic neuropathy. *Diabet Med* 10:820–824, 1993