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RAPID COMMUNICATION

Prevalence and determinants of delayed gastric emptying in hospitalised Type 2 diabetic patients

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Abstract

AIM: To determine the prevalence of delayed gastric emptying (GE) in older patients with Type 2 diabetes mellitus.

METHODS: One hundred and forty seven patients with Type 2 diabetes, of whom 140 had been hospitalised, mean age 62.3 ± 8.0 years, HbA1c 9.1% ± 1.9%, treated with either oral hypoglycemic drugs or insulin were studied. GE of a solid meal (scintigraphy), autonomic nerve function, upper gastrointestinal symptoms, acute and chronic glycemic control were evaluated. Gastric emptying results were compared to a control range of hospitalised patients who did not have diabetes.

RESULTS: Gastric emptying was delayed (T50 > 85 min) in 17.7% patients. Mean gastric emptying was slower in females (T50 72.1 ± 72.1 min *vs* 56.9 ± 68.1 min, P = 0.02) and in those reporting nausea (112.3 ± 67.3 *vs* 62.7 ± 70.0 min, P < 0.01) and early satiety (114.0 ± 135.2 *vs* 61.1 ± 62.6 min, P = 0.02). There was no correlation between GE with age, body weight, duration of diabetes, neuropathy, current glycemia or the total score for upper gastrointestinal symptoms.

CONCLUSION: Prolonged GE occurs in about 20% of hospitalised elderly patients with Type 2 diabetes when compared to hospitalised patients who do not have diabetes. Female gender, nausea and early satiety are associated with higher probability of delayed GE.

Key words: Autonomic neuropathy; Diabetes mellitus; Gastric emptying; Gastrointestinal symptoms; Glycemic control

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INTRODUCTION

It is now recognised, albeit relatively recently, that disturbances in upper gastrointestinal motility represent a major cause of morbidity in diabetic patients[1] and affect quality of life adversely[2]. Delayed gastric emptying is arguably the most important gastrointestinal complication and has been reported to affect 30%-60% of patients with long-standing Type 1 diabetes[3]. In Type 1 patients gastric emptying (GE) is occasionally faster than in normal during euglycemia[4]. There is less information about the prevalence of gastroparesis in Type 2 diabetes[5,6] and the majority of the cohorts studied have been small[2,7]. There is no information about the prevalence of delayed gastric emptying in older patients with diabetes Type 2 who are in many respects different from Type 1 patients. In Type 1 patients it is recognised that the rate of gastric emptying is modulated by acute changes in blood glucose concentration (gastric emptying is slower during hyperglycemia[8,9] and accelerated during hypoglycemia[10]) and autonomic nerve function. The relationship between gastroparesis and autonomic dysfunction is, however, relatively weak[11,12]. The prevalence of gastroparesis is also dependent on the duration of diabetes and may be higher in females than males[13]. The relationship of upper gastrointestinal symptoms with the rate of gastric emptying in Type 1 patients is poor[11].

The aims of the study were to evaluate the prevalence,

and determinants, of disordered gastric emptying in a large cohort of predominantly hospitalised, Type 2 patients and the relationship of upper gastrointestinal symptoms with gastric emptying. The latter was quantified using a scintigraphic technique, which is considered as the "gold standard"[5,14-16].

MATERIALS AND METHODS

The study was performed in 147 patients with Type 2 diabetes (76 women, 71 men), mean age 62.3 ± 8.0 years, duration of known diabetes 11.4 ± 7.2 years, BMI 31.2 ± 5.5 kg/m^2. One hundred and twenty four patients (84%) had BMI > 25. 72 of the patients (49%) were managed on oral hypoglycemic therapy alone (sulphonylurea and/or metformin, thiazolidindione) and the remaining 75 patients were on insulin. None was on combination of insulin and oral drugs. All but 7 of the 147 patients were hospitalised in patients who were randomly selected from those admitted to the Internal Medicine Department. The primary reasons for hospitalisation are summarised in Table 1.

Subjects were randomly selected from among all patients with Type 2 diabetes treated with hypoglycemic drugs or insulin and without exclusion criteria. Only one patient was enrolled each day because of limitations in the availability of scintigraphy. Exclusion criteria included previous gastrointestinal disease apart from uncomplicated appendectomy, symptomatic cardiac, hepatic, renal or pancreatic disease, the use of medication known to affect gastrointestinal motility[17-19] and acute derangement of diabetes during the preceding week. Studies were performed on the day after hospital admission.

Protocol

In one day patient underwent assessments of upper gastrointestinal symptoms, gastric emptying, glycemic control and autonomic nerve function. An assessment of diabetic retinopathy was performed within one week. The subjects were studied after an overnight fast and were asked to take their usual dose of insulin or oral hypoglycemic medication about 30 min prior to ingestion of the test meal.

Capillary blood samples for the measurement of blood glucose (enzymatic-amperometric measurement EBIO Plus) were obtained immediately before the meal and at 30, 60, 90 and 120 min. Glycated hemoglobin was measured on one of the blood samples. Each patient also completed a questionnaire relating to upper gastrointestinal symptoms[11]. Ophthalmological examination was performed to assess diabetic retinopathy, unless this diagnosis had already been established.

Autonomic nerve function was assessed after the completion of gastric emptying measurement using power spectral analysis of heart rate variability. The electrocardiogram was recorded under standardised conditions[20] for 5 min (minimum 300 valid R-R intervals) in supine, standing and repeated supine positions using computer-based system VarCor PF6[21]. Spectral analysis using fast Fourier transformation was performed in very low (0.02-0.05 Hz), low (0.05-0.15 Hz) and high (0.15-0.5 Hz) frequency spectral bands. The sum of the overall spectral power in the high and low frequency part of the spectra with patients in all relevant positions and the sum of the spectral power in the low frequency part of the spectra were calculated[22,23]. Values obtained in healthy subjects were used as a standard[22]. Spectral power values less than normal (after adjustment for age) were considered as evidence of cardiovascular autonomic neuropathy (CAN). For the purpose of statistical assessment both borderline and abnormal results were combined.

Table 1 Reasons for hospitalisation in type 2 diabetic (*n* = 147) and nondiabetic (*n* = 34) patients

	Diabetes mellitus *n*	Control group *n*
Diabetes mellitus	80	-
Hypertension	21	12
Ischemic heart disease	16	4
Back pain	6	4
Valvular heart disease	4	-
Colonic polyp	3	-
Anemia	2	-
Peripheral aterosclerosis	2	1
Gout	2	-
Phlebitis	1	3
Chronic bronchitis	1	1
Nontoxic goiter	1	-
Arthrosis	1	1
Atrial fibrilation	-	3
Neurasthenia	-	3
Pacemaker implantation	-	2

Upper gastrointestinal symptoms during the previous 3 mo were assessed using a questionnaire adopted from Horowitz *et al*[11]. Anorexia, nausea, early satiety, vomiting, abdominal pain, bloating and heartburn were recorded and graded as 0 = none, 1 = mild, 2 = moderate, 3 = severe. The global symptom score was calculated as the sum of the number and severity of symptoms.

Written informed consent was obtained from all subjects. Data were evaluated using the Mann-Whitney test, Kruskal-Wallis ANOVA and Spearman correlation, P values < 0.05 were considered as significant.

Measurement of gastric emptying

The test meal consisted of 100 g of boiled rice (560 kJ) flavoured with cinnamon and labelled with 185 mBq ^{99m}Tc sulphur colloid[24,25]. The study was performed in the decubitus position and data were acquired for at least 60 min, in 1 min frames using a Picker Int. one-head camera. Time zero was defined as the time of a meal completion. Data were corrected for radionuclide decay and analysed using the Picker Int. Odyssey computer system. The gastric half-emptying time (T50) was defined as the time for the activity to fall by 50%. In those subjects in whom total gastric activity at the end of investigation was greater than 50% this parameter was computed using software extrapolation. The lag phase was defined as the period from meal ingestion to the peak of the activity within the gastric region of interest.

Control values were determined from a group of 34 nondiabetic volunteers. Nineteen women, 15 men, mean age 60.8 ± 8.9 years, mean BMI 30.7 ± 4.7 kg/m^2, 27 subjects

(79%) had BMI > 25. This control group was randomly selected from among hospitalised patients without diabetes and without dyspeptic symptoms using identical exclusion criteria. Reasons for their admission are listed in Table 1. In this group mean T50 was 49.5 ± 23.1 min and lag phase 7.1 ± 5.9 min. The normal range for gastric emptying was defined as mean ± 1.5 SD of the T50. Values outside of this were considered as abnormal.

RESULTS

All of the studies were well tolerated. Mean glycated hemoglobin was 9.1% ± 1.9%. Abnormal autonomic nerve function was evident in 103 of 144 (71.5%) patients (in 3 subjects the assessment was not feasible due to their high age or technical artefacts). Diabetic retinopathy (nonproliferative and proliferative) was evident in 21 (14.3%) cases. 52 patients had upper gastrointestinal symptoms and symptoms were reported more frequently by women (46.0% *vs* 23.9%, $P < 0.01$). The most frequent symptom was bloating (29 subjects), followed by early satiety (10 subjects), pain (8 subjects), nausea and anorexia (6 subjects), heartburn (5 subjects), and vomiting (4 subjects). The median symptom score was 0 (0-9) in the whole group, 2.0 (1-9) in subjects with normal emptying and 3.0 (1-5) in the subgroup with delayed gastric emptying.

The mean T50 was 64.7 ± 70.4 min, and lag phase 9.6 ± 7.9 min, these were related ($P < 0.01$). Gastric emptying was delayed, as assessed by the T50, in 26 subjects (17.7%) and in the whole group was significantly prolonged comparing to the control group (64.7 ± 70.3 min, 49.5 ± 23.4 min, $P = 0.03$). Mean basal (time 0) glucose was 9.9 ± 2.8 mmol/L, at 30 min 10.5 ± 2.8 mmol/L, at 60 min 11.5 ± 2.9 mmol/L, at 90 min 11.7 ± 3.1 mmol/L, and at 120 min 11.6 ± 3.2 mmol/L. The mean rise in blood glucose was significant ($P < 0.01$). The association of gastric emptying with demographic and biochemical variables and gastrointestinal symptoms is summarised in Table 2.

Gastric emptying did not differ between insulin and oral drug treated subjects (68.4 ± 83.7 min, 60.4 ± 50.9 min, $P = 0.47$). Gastric emptying (T50) was slower in females than males ($P = 0.02$). Gastric emptying (T50) was not significantly related to either autonomic nerve function ($P = 0.32$), retinopathy ($P = 0.88$) or upper gastrointestinal symptoms ($P = 0.22$). Gastric emptying was however, slower in those patients who had early satiety ($P = 0.02$) and nausea ($P < 0.01$).

Simple regression analysis showed a weak, but significant, relationship between gastric emptying and glycated hemoglobin ($r = 0.23$; $P = 0.01$), but not between the T50 ($P > 0.35$) or lag phase ($P > 0.07$) and blood glucose levels during the gastric emptying measurement ($P > 0.35$). Significant correlation between gastric emptying rate and glycated hemoglobin was noted in the subgroup treated with hypoglycemic drugs ($r = 0.32$; $P < 0.01$). There was no significant relationship between gastric emptying and either age ($r = -0.05$, $P = 0.55$), duration of diabetes ($r = 0.08$, $P = 0.31$) or body mass index ($r = -0.03$, $P = 0.70$). GE did not differ between obese and non-obese subjects both in the diabetes (66.9 ± 74.6 min, 50.6 ± 28.4 min, $P = 0.16$) and in the control group (48.6 ± 23.4 min, 56.0 ± 24.8 min, $P = 0.25$).

In the insulin treated group (75 subjects) the rise of glycemia between 30-60 min. (16.2% *vs* 5.8%) was greater ($P = 0.048$) in subjects with faster emptying compared to those with delayed GE. In the group treated with oral hypoglycemic drugs the changes were not significantly different.

Table 2 Association between demographic variables and gastric emptying in Type 2 patients

		T50 (min)			Lag phase (min)		
	n	mean	1 SD	*P*	mean	1 SD	*P*
Gender				0.02[a]			0.99
Female	76	72.1	72.1		9.1	6.4	
Male	71	56.9	68.1		10.1	9.3	
CAN				0.32			0.66
No	41	64.1	84.4		10.2	8	
Yes	103	65.6	65.3		9.6	8	
Retinopathy				0.88			0.77
No	126	65.7	74.4		9.8	8.2	
Yes	21	58.7	38.9		8.5	6.1	

CAN: Cardiovascular autonomic neuropathy. [a]$P < 0.05$ between male and female.

DISCUSSION

This is the first study to evaluate the prevalence of delayed gastric emptying in a large cohort of elderly predominantly hospitalised patients with Type 2 diabetes. We have established that (1) when compared to a control range obtained in hospitalised patients without diabetes prolonged GE does not occur frequently and (2) female gender and the presence of nausea and early satiety are associated with higher probability of delayed GE.

Delayed GE is said to occur in 30%-70% patients with longstanding Type 2 diabetes[5,7]. Some of the cohorts studied were small, e.g. Tung studied 20 subjects with diabetes[7], and Annese *et al* investigated 35 subjects[2], included otherwise healthy patients with diabetes[5], or patients with upper gastrointestinal symptoms[7], which may not well reflect the situation in general population. We intentionally studied a large cohort of relatively older patients with more severe Type 2 diabetes treated with oral drugs or insulin, of whom the majority had complicated diabetes, and compared them with their age-matched non-diabetic counterparts. In our opinion, this subset of patients corresponds with the status of the older general population. The prevalence of delayed gastric emptying was relatively low and less than we anticipated. Any correlation of our results with other studies is rather difficult due to substantial differences in patient groups and methods used[5]. Alteration of the results due to test food used, however, appears unlikely, given that the mean rate of gastric emptying in the diabetic cohort (8.7 kJ/min) was within the expected "physiological" range (i.e. 8.4 to 12.6 kJ/min)[1,26]. This confirms that test food used by us is sufficient for activation of feedback regulation, which physiologically slows the emptying down. In a previous study, we found that GE was delayed in 42.8% of Type 1 diabetic outpatients[27] us-

ing the same method, and identical control group, a result that is concordant with previous reports[4,14,25]. Also, it is against any possible bias caused by technical errors.

Our group involved a selected set of hospitalised subjects where a selection bias may play a role. Any effect of comorbities on GE has not been so far sufficiently studied. There are some indices that there may exist a certain link between gastric emtying rate and heart, lung, liver diseases or Parkinson's disease[28], occurring frequently in older age. More than 80% of patients screened in this study were treated with other than oral hypoglycemic drugs. Information on the effect of commonly used drugs like beta-blockers, calcium channel blockers, etc. on GE is lacking. Only verapamil and nitrates have been studied so far[29]. The accelerated GE was described in obese patients, e.g. by Bertin[30] and was also documented in obese non-diabetic persons[31]. In spite of the fact that weight in our group was similar to that in Bertin's group, we were not able to confirm any correlation with GE.

There was no significant relationship between the rate of GE and the duration of known diabetes, consistently with previous reports in Type 1 and groups of Type 1 and 2 diabetic patients[6,32]. While, the number of complications increases with the duration of diabetes, their development is highly dependent on glycemic control. This is likely to confound a potential association with the duration of diabetes. In the past autonomic neuropathy was considered to be the main factor causing gastroparesis, but it is clear that any relationship between gastric emptying and cardiovascular autonomic function is weak[5,12,33]. The prevalence of autonomic nerve dysfunction observed in this study is higher than that reported in groups with a similar duration of diabetes (about 65% after 10 years)[34] what is likely to reflect the methodology used. Furthermore, heart rate variability and spectral power is known to decline not only in individuals with diabetic CAN but also in those with ischemic heart disease, poor physical status and/or ageing[23]. It is well known that the presence of diabetic retinopathy correlates with that of CAN[35]. Both retinopathy and CAN are associated with higher mortality while gastroparesis may not be[7,36,37]. Female gender has been reported previously[13] to be associated with an increased rate of diabetic gastroparesis; this is also the case for delayed gastric emptying in functional dyspepsia[38]. The underlying cause(s) remain uncertain.

Acute glycemia has been suggested as an important determinant of gastric emptying[14,39]. However, there are studies[25,30], including the present one, which have failed to confirm this relationship. A possible explanation is, that in spite of relatively large variations in glycemia during the studies (3.1-22.3 mmol/L), average values were about 11 mmol/L, and only 10 individuals had blood glucose levels above 15 mmol/L. The present study is also cross-sectional in design, which is not optimal for evaluation of this issue; furthermore, there was a weak relationship between the rate of gastric emptying with HbA1c.

It is clear that the GE rate of carbohydrate influences postprandial glycemia in both Type 1 and Type 2 diabetes[40]-in Type 2 patients the postprandial initial glycemic and insulinemic responses to oral carbohydrate are less when gastric emptying is slower[41]. Hence it is not surprising that the rise in blood glucose after the meal was greater in those with faster gastric emptying in those patients treated with insulin. In contrast there is no difference apparent in the patients treated with oral hypoglycemic agents for which we have no clear explanation.

Previously it was thought that dyspeptic symptoms associated with diabetes were a direct consequence of impaired GE, but the correlation between upper gastrointestinal symptoms and the rate of GE rate is weak[5,11,25] and patients with gastroparesis may not have symptoms at all[3]. Our study confirms that poor correlation between gastrointestinal symptoms and gastric emptying described in Type 1 diabetic patients[4,27] also exists in Type 2 diabetes. Recent studies have found an association between abdominal bloating and fullness, particularly postprandially[6,36,42] and slow GE, especially when the relationship is assessed according to the severity of symptoms. This study confirms that correlations observed between distinct gastrointestinal symptoms (early satiety/fullness) and GE in Type 1 diabetes[4] may also exist in Type 2 diabetes[6]. These relationships should be, however, interpreted with caution and in the context of other variables. For example, postprandial dyspeptic complaints may potentially result from deranged intragastric distribution of ingested food, which however, may not be associated with any in the total GE rate[43]. It is also well established that blood glucose concentrations may modulate sensations arising from the gastrointestinal tract[44]. The authors were not able to confirm any such dependence; nevertheless mean blood glucose levels were not as high as those reported by Jones *et al* (> 15 mmol/L) in their study[45], where the relationship was described.

In conclusion, the present study demonstrates, that delayed GE rate does not occur frequently in elderly hospitalised Type 2 diabetics. Female gender and the presence of nausea and early satiety may predict delayed gastric emptying. Autonomic nerve dysfunction, assessed by means of heart rate variability, however does not correlate with GE rate.

COMMENTS

Background

Delayed gastric emptying is the most important gastrointestinal complication in diabetes. The problem of finding a simple way of identifying persons with gastroparesis is gaining ground in view of the rising proportion of Type 2 diabetic patients. An attractive approach appears to identify groups at risk appropriate for further detailed investigation by using simple criteria. This issue has been studied extensively in Type 1 diabetic patients. In contrast, data have been lacking and study groups are small in patients with diabetes Type 2, who are in many respects different from Type 1 patients.

Research frontiers

To evaluate the prevalence, and determinants (gender, age, BMI, duration of diabetes, control of diabetes, autonomic neuropathy, retinopathy and dyspeptic symptoms) of delayed gastric emptying in older patients with Type 2 diabetes mellitus.

Innovations and breakthroughs

This is the first study evaluating elderly Type 2 diabetic patients with comorbities. Delayed GE rate does not occur frequently in these subjects. They do not differ in predictors of delayed GE from Type 1 diabetes.

Applications

Delayed gastric emptying in old Type 2 diabetic patients may be assumed in

female gender and when nausea and early satiety are present. Presence of diabetic complication (retinopathy, autonomic neuropathy) does not predict disordered gastric emptying.

Peer review

This study explores the presence of dyspeptic symptoms and the timing of gastric emptying in hospitalised elderly patients with Type 2 diabetes treated with oral hypoglycaemic therapy or insulin, compared to hospitalised patients without diabetes. The study is well designed and conducted.

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