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Longitudinal evaluation of gastric emptying in type 2 diabetes

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ABSTRACT

Aims: To evaluate the natural history of gastric emptying in type 2 diabetes.
Methods: 12 patients with type 2 diabetes (7 female; age 65.6 ± 1.2 years; duration of known diabetes 22.9 ± 1.5 years) were invited to return for repeat measurements of gastric emptying using the same dual-labelled solid and liquid meal, a mean of 14.0 ± 0.5 years after their initial study. Blood glucose levels, glycated haemoglobin, upper gastrointestinal symptoms and autonomic nerve function at baseline and follow up were also compared.
Results: Gastric emptying of solids was more rapid at follow up than at baseline (period effect $P < 0.05$), while emptying of liquids was comparable at baseline and follow up (period effect $P = 0.2$). Gastric emptying of the solid component was abnormally slow (based on T100min) in 6 subjects at baseline and 1 subject at follow up. Liquid emptying was abnormally slow in 6 subjects at baseline, and 5 subjects at follow up. Two patients were insulin treated at baseline, and 6 at follow up. HbA1c was higher at follow up ($P < 0.05$); however, fasting blood glucose ($P = 0.6$), postprandial blood glucose excursions ($P = 0.07$), autonomic nerve function ($P > 0.999$), and total upper gastrointestinal symptom score ($P = 0.1$) did not differ.
Conclusions: In patients with long-term type 2 diabetes, gastric emptying of solids and liquids does not usually become more delayed over time, and abnormally slow gastric emptying of solids may improve.

1. Introduction

Gastric emptying is often disordered in people with type 2 diabetes, with abnormally delayed emptying of solids and/or nutrient liquids observed in 30–50% with longstanding type 2 diabetes [1]. While gastric emptying may be accelerated in early type 2 diabetes [2,3], this has not been a consistent observation [4]. Gastric emptying is a major determinant of postprandial glycaemia, and pharmacological or nutritional therapies that slow gastric emptying, including "short-acting" GLP-1 receptor agonists, pramlintide, acarbose, or nutrient preloads, are effective in lowering postprandial glycaemic excursions [5]. In healthy subjects, there is substantial inter-individual variation in the rate of gastric emptying [6], but the intra-individual variation is modest, so that emptying is highly reproducible [7,8]. In both type 1 and type 2 diabetes,

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the inter-individual variation of gastric emptying is predictably greater than in health because of the higher prevalence of abnormal gastric emptying [1,9]. In type 1 diabetes, the natural history, even over 25 years, is for gastric emptying to remain stable [10,11]. However, little is known about the intra-individual stability of gastric emptying measurements over time in type 2 diabetes. If modulating the rate of gastric emptying is to be developed further as a therapeutic strategy for postprandial glycaemic control, additional information is required about the natural history of gastric emptying in these patients. We therefore aimed to undertake a follow up study in patients with type 2 diabetes who had previously had gastric emptying measured in our department.

2. Materials and methods

We examined the records of 167 patients with diabetes mellitus who had scintigraphic measurement of gastric emptying for research purposes in our laboratory between 2000 and 2005 [12,13]. After excluding 45 patients known to have died (Births Deaths and Marriages Register), 42 who had type 1 diabetes, and 27 whose current address could not be determined, letters of invitation to participate in the study were sent by mail. Twenty-one patients declined to participate, 16 did not respond (either to the original letter or a reminder sent 2 weeks later), and 4 were excluded due to advanced age, iron deficiency, opiate use, and bariatric surgery respectively.

Twelve patients with type 2 diabetes (7 female, 5 male; mean age 65.6 ± 1.2 years; body mass index 31.4 ± 1.0 kg/m^2; duration of known diabetes 22.9 ± 1.5 years) were, therefore, available to undergo repeat measurement of gastric emptying, which was undertaken a mean of 14.0 ± 0.5 years after their initial study. Of the 12 patients, 9 had evidence of chronic kidney disease (stage 2 in 6, stage 3A in 2, and stage 4 in one), while 2 had modest elevation of transaminases at follow up. Two had a history of retinopathy, 3 of peripheral neuropathy, and 2 of macrovascular complications.

One patient who was taking weekly exenatide QW withheld his medication and was studied 2 weeks after the last dose. Other medications, including those for hypertension (angiotensin receptor antagonists or angiotensin converting enzyme inhibitors in 6, beta blockers in 3, and a calcium channel antagonist in one), were withheld on the morning of the study. No patient was a smoker.

Written informed consent was obtained from each participant, and the protocol was approved by the Royal Adelaide Hospital Research Ethics Committee.

At the initial study ("baseline"), the mean age was 51.6 ± 1.2 years, body mass index (BMI) was 30.5 ± 0.9 kg/m^2, and duration of known diabetes was 8.9 ± 1.5 years. At follow up, the mean age was 65.6 ± 1.2 years, BMI 31.2 ± 1.0 kg/m^2, and duration of known diabetes 22.9 ± 1.5 years. Insulin was used in the management of diabetes in 2 patients at baseline and 6 patients at follow up (Table 1).

2.1. Measurement of gastric emptying

Gastric emptying was evaluated using a dual isotope scintigraphic method identical to that used at baseline, providing concurrent measurement of solid and nutrient liquid emptying [14]. Patients presented to the department after an overnight fast, and were given their usual insulin dose or antihyperglycaemic medication with the meal. The solid component comprised 100 g minced beef labelled with 20 MBq ^{99m}Tc-sulfur colloid chicken liver (270 kcal), and the liquid component was 150 mL 10% glucose labelled with 7 MBq ^{67}Ga-ethylene-diamine-tetraacetic acid (EDTA) (60 kcal). Studies were performed with the patients seated with their backs against a gamma camera. Data were acquired for 120 min, with 1-minute frames for the first hour, and at 3-minute intervals thereafter. Patients were instructed to consume the meal within 5 min, and time zero (t = 0) was defined as the time of meal completion. The retention (%) of solid and liquid in the stomach at 30, 60, 90, and 120 min was quantified, along with the percentage of solid retained at 100 min (T100 min), and the time taken for 50% of the liquid to empty (T50%). Gastric emptying results were classified as normal or abnormal using a control range (mean ± 2SD) established in 25 healthy volunteers (solid emptying T100min [12–61%], and liquid emptying T50% [8–31 min]) [15].

2.2. Assessment of gastrointestinal symptoms

Symptoms of hunger, desire to eat, and fullness were assessed before and after the meal using validated 100 mm visual analogue scales [16]. Upper gastrointestinal symptoms were assessed by a standardised questionnaire [15]. Gastric (anorexia, nausea, early satiation, abdominal bloating/fullness, vomiting, abdominal pain) and oesophageal symptoms (dysphagia, heartburn, acid regurgitation) 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), or 3 (severe; the symptom influenced daily activities). A total symptom score was calculated as the score for both gastric and oesophageal symptoms, with a potential maximum score of 27.

2.3. Assessment of autonomic neuropathy

Autonomic nerve function was evaluated using standardised cardiovascular reflex tests (variation in heart rate during deep breathing, heart rate response to standing, and fall in systolic blood pressure in response to standing). Each test result was scored as 0 = normal, 1 = borderline, 2 = abnormal. A score ≥ 3 was considered to indicate autonomic dysfunction [17].

2.4. Assessment of glycaemia

At baseline and follow up, glycated haemoglobin (HbA1c) was measured from a fasting blood sample (SA Pathology, Adelaide, Australia), and blood glucose concentrations were measured using a glucometer (Optium Xceed, Abbott Laboratories, Bedford, MA, USA) immediately before ingestion of the meal (−5 min) and then at 30, 60, 90, 120 min after meal ingestion.

2.5. Statistical analysis

Data were evaluated using repeated measures analysis of variance (ANOVA), with "period" (baseline vs follow up) and

Table 1 – Characteristics, gastric emptying and treatment of patients with type 2 diabetes (*indicates patients with delay in solid gastric emptying at baseline but normal solid emptying at follow up; †indicates patients with abnormal gastric emptying for either solid or liquid) B = baseline, F = follow up. Diabetes medications are abbreviated as follows: M = metformin, S = sulfonylurea, A = acarbose, Z = dapagliflozin, P = pioglitazone, D = DPP4 inhibitor, ExQW = exenatide once weekly.

Patient	Sex	Age at follow up (yrs)	Follow up period (yrs)	Duration of Diabetes at follow up (yrs)	Autonomic nerve function score		BMI (kg/m^2)		Fasting Glucose (mmol/L)		HbA1c %		Solid T100min (%) (RR 12–61%)		Liquid T50% (min) (RR 8–31 min)		Treatment	
					B	F	B	F	B	F	B	F	B	F	B	F	B	F
1*	F	63	15	21	1	1	30.9	35.2	9.3	10.2	9.3	8.1	62†	31	32†	39†	Insulin + oral agent (M)	Insulin + oral agent (M)
2	M	62	14	32	1	1	35.6	33.0	9	7.1	6.4	10.2	54	35	33†	43†	Oral agent (S)	Oral agent (M)
3	F	72	15	20	2	2	24.8	32.0	9.7	6	7.9	8.2	36	35	17	30	Oral agent (M)	Insulin + oral agent (M)
4	M	64	15	28	2	2	35.4	37.5	14.3	13	9.1	8.6	27	28	11	26	Insulin + oral agents (M, S, A)	oral agent (M)
5	F	66	14	22	1	1	30.3	29.2	10	11.9	7.9	8.7	59	72†	34†	28	Oral agent (M)	Insulin + oral agents (M, S)
6*	F	59	14	15	1	1	30.2	28.8	7.7	12.5	5.4	8.7	78†	26	28	9	Diet controlled	Oral agents (M, S, Z)
7*	M	65	16	22	2	2	31.0	33.6	5.8	14.9	4.9	10.9	62†	57	60†	39†	Oral agent (M)	Oral agent (M)
8*	F	73	15	28	1	0	29.9	28.5	11.5	6.6	8	8.8	88†	50	58†	21	Oral agents (M, A)	Oral agents (M, A, S, P)
9	F	62	11	27	1	1	27.4	25.0	14	12.7	8.3	8.3	48	41	26	36†	Oral agent (M)	Oral agents (M, S, D)
10	F	66	10	16	2	2	28.0	27.8	7.9	8.7	7.5	8.8	55	30	27	27	Oral agent (M)	Insulin + oral agents (M, S)
11*	M	63	15	23	2	2	29.5	31.0	10.8	9.9	8.6	8.4	98†	51	22	27	Oral agent (M)	Insulin + oral agent (M) + ExQW
12*	M	70	15	20	4	2	32.6	34.8	6.7	10.7	5.6	10.7	83†	59	79†	53†	Oral agents (M, S)	Insulin + oral agent (M)

"time" point within each study as factors, and are shown as mean values ± standard error of the mean. Post hoc comparisons, adjusted for multiple comparisons by Bonferroni correction, were performed if ANOVAs revealed significant interactions between "period" and "time". Incremental areas under the curves (iAUC) for blood glucose concentrations were calculated using the trapezoidal rule. Comparisons between baseline and follow up were evaluated using paired t-tests. Relationships of blood glucose values and HbA1c with gastric emptying of solids and liquids were evaluated using the Pearson correlation coefficient. Analyses were performed using Prism 7.0 (La Jolla, CA, USA). $P < 0.05$ was considered statistically significant.

3. Results

3.1. *Gastric emptying*

As a group, gastric emptying of solids was more rapid at follow up than at baseline (period effect $P < 0.05$, and period*time interaction $P < 0.05$), with significant differences at t = 90 and 120 min ($P < 0.0001$ for both), while emptying of liquids was comparable at baseline and follow up (period effect $P = 0.2$). Gastric emptying of the solid component was abnormally slow (based on T100min) in 6 subjects at baseline and 1 subject at follow up. Liquid emptying was abnormally slow in 6 subjects at baseline, and 5 subjects at follow up; 4 of these subjects had delayed liquid emptying at both baseline and follow up (Fig. 1). Both solid and liquid gastric emptying were delayed in 4 subjects at baseline and none at follow up. No subject had abnormally rapid gastric emptying of either solids or liquids at baseline or follow up.

3.2. *Gastrointestinal symptoms*

Fasting scores for hunger (30.8 ± 8.5 mm at baseline vs 39.7 ± 9.1 mm at follow up, $P = 0.07$), desire to eat (34.8 ± 9.1 mm vs 43.8 ± 10.2 mm, $P = 0.2$), and fullness (9.2 ± 4.1 mm vs 13.5 ± 7.9 mm, $P = 0.6$) did not differ between baseline and follow up. Postprandial scores for hunger (0–120 min) were lower at follow up than at baseline (period*time interaction $P < 0.05$, however post-hoc comparisons were non-significant); ratings of desire to eat ($P = 0.2$) and fullness ($P = 0.5$) were similar (Fig. 2).

Eleven subjects had upper gastrointestinal symptoms at baseline and 11 at follow up. The mean score for oesophageal symptoms was greater at follow up than at baseline (baseline 0.8 ± 0.3 vs follow up 1.9 ± 0.3, $P = 0.04$), but there were no differences in either gastric ($P = 0.4$) or total upper gastrointestinal symptom scores ($P = 0.1$) between baseline or follow up.

3.3. *Glycaemic assessment*

The mean HbA1c was higher at follow up (9.0 ± 0.3% [73.5 ± 3.5 mmol/mol]) when compared to baseline (7.4 ± 0.4% [56.8 ± 4.5 mmol/mol], $P < 0.05$). Fasting blood glucose concentrations were comparable at baseline (9.7 ± 0.8 mmol/L) and follow up (10.4 ± 0.8 mmol/L) ($P = 0.6$). Blood glucose concentrations increased postprandially, and tended to be higher at

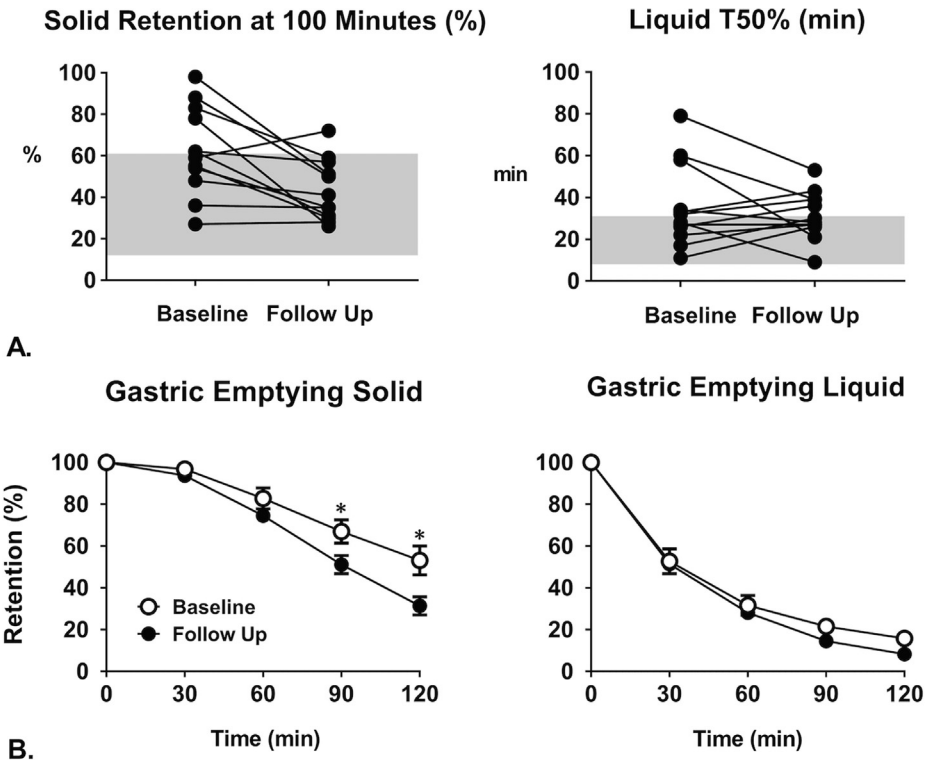

Fig. 1 – A: Gastric emptying of solid (retention at 100 min) and liquid (50% emptying time (T50)) meal components measured at baseline and follow up in 12 patients with type 2 diabetes. Normal ranges are indicated by the shaded areas. B: Gastric emptying (mean ± SEM) of solid and liquid meal components measured at baseline (white circles) and follow up (black circles) in 12 patients with type 2 diabetes. * indicates P < 0.0001 for baseline versus follow up by repeated measures ANOVA.

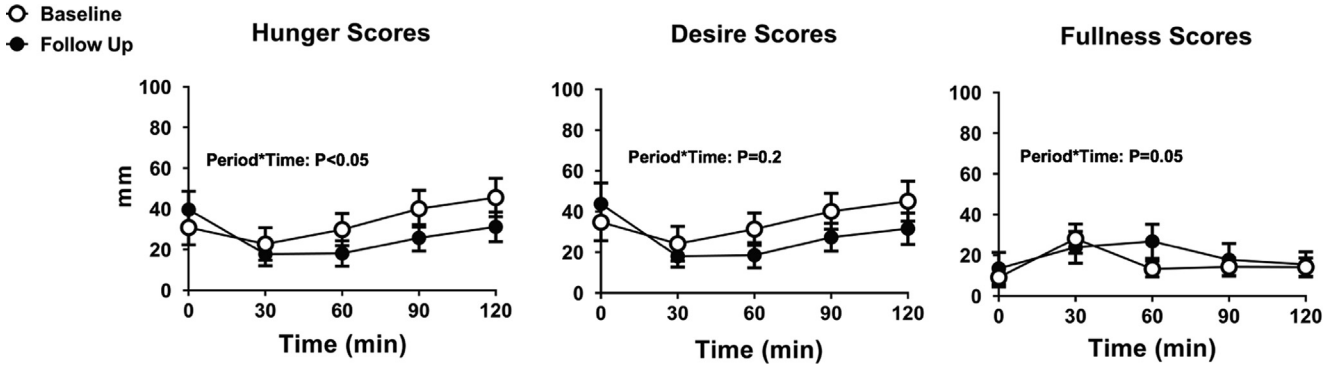

Fig. 2 – Visual analog scores for hunger, desire to eat, and fullness at baseline (white circles) at follow up (black circles). Repeated-measures ANOVA was used to determine significance between baseline and follow up for hunger (P < 0.05), desire to eat (P = 0.2), and fullness (P = 0.5).

follow up than at baseline (P = 0.07 for period * time interaction; P = 0.1 for comparison of iAUC (baseline 223.8 ± 34.73 mmol/L.min vs follow up 300 ± 54.17 mmol/L.min) (Fig. 3).

There were no relationships evident between fasting blood glucose or HbA1c and the rate of gastric emptying of both solids and liquids, either at baseline or follow up in the 12 patients studied twice, or in the entire original cohort. However, there was a strong relationship between the increment in blood glucose 30 min after the meal and the liquid half-emptying time in the 12 patients at baseline (r = −0.77, P = 0.004), as well as the whole original cohort (r = −0.48, P = 0.008), i.e., the faster the liquid emptying, the greater the blood glucose increment at 30 min. This relationship was not statistically significant in the 12 patients at their follow up visit.

3.4. *Autonomic neuropathy*

Seven subjects had evidence of cardiovascular autonomic neuropathy at baseline, and 6 at follow up; five of these had abnormal tests at both baseline and follow up. The mean

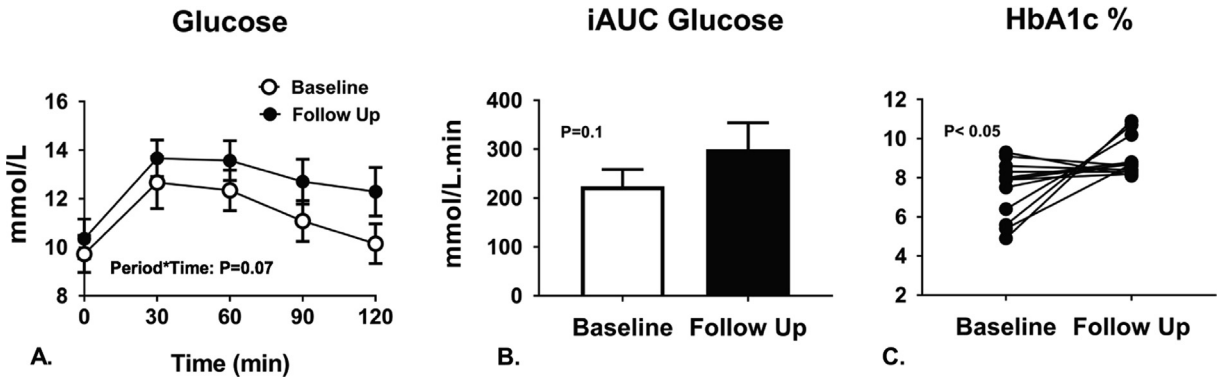

Fig. 3 – A. Postprandial blood glucose concentrations (Period * Time P = 0.07, repeated measures ANOVA) B: iAUC for postprandial blood glucose concentrations (mean values ± SEM, paired *t*–test baseline and follow up, P = 0.1), and C: HbA1c (values for individual patients at baseline and follow up, paired *t* test baseline vs follow up, P < 0.05).

score for autonomic nerve function score did not change between baseline and follow up (P > 0.999).

3.5. *Comparison with patients not followed up*

When the baseline characteristics of our patient group were compared with those of the type 2 diabetes patients who had died, refused to participate, or were otherwise lost to follow up, there were no differences in age (51.6 ± 1.2 versus 52.7 ± 1.6 years), BMI (30.5 ± 0.9 versus 31.4 ± 0.6 kg/m^2), HbA1c (7.4 ± 0.4 versus 7.2 ± 0.3%), fasting blood glucose (9.7 ± 0.8 versus 9.6 ± 0.7 mmol/L), or gastric emptying for solids (T100min 64.1 ± 5.9 versus 63.2 ± 4.7) or liquids (t50% 35.6 ± 5.7 versus 29.1 ± 3.7 min).

4. Discussion

This study has evaluated of the natural history of gastric emptying in patients with type 2 diabetes. During a mean follow-up of 14 years, gastric emptying of solids tended to improve in those who had abnormally slow emptying at baseline. Emptying of nutrient liquids was stable over time, such that if it was abnormally slow at baseline, it was also slow at follow up. Moreover, for both solids and liquids, emptying that was initially in the normal range generally did not become slower over time.

We previously evaluated the natural history of gastric emptying using scintigraphy in patients with predominantly type 1 diabetes, and observed no overall change over time in the rate of emptying of either solids or liquids. Jones et al studied twenty patients with diabetes – 16 type 1 and 4 type 2 – and reported no differences in either solid or liquid gastric emptying over a period of 12 years [11]. Similarly, Chang et al evaluated the same group 25 years after the initial study and found that gastric emptying remained stable over that period [10]. Our findings in patients with type 2 diabetes suggest similar stability in those with normal solid emptying, and in those with either slow or normal liquid emptying on the initial study. However, our finding that initially slow solid emptying can became more rapid over time in type 2 diabetes contrasts with these longitudinal studies of predominantly type 1 patients. The reasons for this difference are unclear.

Prevailing blood glucose concentrations influence gastric emptying, such that acute hyperglycaemia – even at physiological postprandial levels – is associated with slowing of gastric emptying compared with euglycemia, in both health and type 1 diabetes [18,19]. In our study, the delay in solid gastric emptying at baseline compared to follow up is not attributable to differences in blood glucose concentrations, which were similar during the fasting state on both occasions and tended to be higher postprandially at follow up. Moreover, we did not observe a relationship between fasting blood glucose and gastric emptying of liquids or solids, at either baseline or follow up. This is consistent with the observations of other investigators that the rate of gastric emptying in type 2 diabetes was not related to fasting glucose or HbA1c [20,21]. However, in the DCCT/EDIC cohort of patients with type 1 diabetes, slow gastric emptying at long term follow up was found to be related to a high baseline HbA1c [22], suggesting that hyperglycaemia early in the course of type 1 diabetes is relevant to the development of disordered gastric function. Other than the reversible influence of acute hyperglycaemia, the pathophysiology of delayed gastric emptying is complex and heterogeneous. Irreversible autonomic neuropathy potentially contributes, but its relationship with the rate of gastric emptying is, at best, weak, particularly in type 2 diabetes [1]. In our patients, autonomic neuropathy was present in 3 of 6 patients who had delayed gastric emptying at baseline, and we did not observe a relationship between autonomic function scores and solid gastric emptying.

In contrast to the lack of effect of fasting blood glucose on gastric emptying, there was a strong relationship between the rate of emptying of the liquid phase (which contained virtually all the carbohydrate) and the increment in blood glucose 30 min after the meal. A similar observation has been reported previously in health [23] as well as type 2 diabetes [4]. However, such a relationship was not apparent on the follow up study, possibly because many more patients were using exogenous insulin at follow up than at baseline (6 versus 2).

In response to the same meal, postprandial hunger scores overall were lower at follow up compared with baseline. This finding was not unexpected, as aging is known to be associated with some degree of physiological anorexia [24]. Oeso-

phageal symptoms such as dysphagia, heartburn, and acid regurgitation worsened over time, however there were no significant changes in total upper gastrointestinal symptoms between baseline and follow up. That symptoms should not improve over time despite a normalisation of delayed solid emptying is not entirely unexpected; although there is some relationship between upper gastrointestinal symptoms and delayed gastric emptying [25], and symptoms may improve with prokinetic drugs [26], the relationship between symptoms and delayed gastric emptying is known to be weak [15].

It has been postulated that accelerated gastric emptying may precede the development of type 2 diabetes, and/or contribute to worsening of glycaemic control [2,3]. Rapid gastric emptying has also been demonstrated in adolescents with type 1 diabetes [27], and is predictably associated with a greater rise in postprandial blood glucose. Similarly, studies evaluating patients with longstanding type 2 diabetes have reported abnormally rapid gastric emptying in approximately 20% [28]. No patient in our study had abnormally rapid emptying of solid or liquid at either baseline or follow up. It is well established that the relationship between liquid and solid gastric emptying in type 2 diabetes is weak, such that those with severe gastroparesis of solids may have normal gastric emptying of liquids, while up to 24% of those with delayed emptying of a nutrient liquid have normal solid emptying [15,29]. In our study, all 6 patients with delayed liquid gastric emptying at follow up demonstrated normal emptying of solids, while emptying of the liquid component – which contained almost all of the carbohydrate content – remained stable over time. It is likely that the deterioration in glycaemic control evident in our patients at follow up, as reflected in the HbA1c, was attributable to progressive beta cell failure, an established feature of type 2 diabetes, although we did not confirm this by measuring plasma insulin concentrations. That we did not observe any significant difference in postprandial incremental glucose concentrations over time in our patients, is consistent with the lack of change in liquid emptying.

Potential mechanisms by which initially slow gastric emptying could become more rapid over time may include the development of impaired proximal gastric accommodation to a meal, or a loss of factors that inhibit emptying [30,31]. An example of the latter is amylin, a pancreatic hormone co-secreted with insulin, which often reaches low or undetectable plasma concentrations in patients with type 1 or late-stage type 2 diabetes [32,33]. Accordingly, relative amylin deficiency could potentially contribute to an increase in the rate of gastric emptying over time in longstanding type 2 diabetes [34]; however, we did not measure plasma amylin concentrations in our patients.

There are limitations to our study. The number of patients was small, so that larger cohorts should be studied to confirm our findings. At baseline, patients had already been diagnosed with diabetes for a mean of almost 9 years, so our study does not provide information about changes in gastric emptying early in the disease course. Moreover, they had relatively suboptimal glycaemic control at follow up (mean HbA1c 9.0%), so our observations may not generalise to a better controlled population. We did not assess patients under identical fasting glucose conditions, but this seems unlikely to account for the changes in solid meal emptying over time. At follow up, a number of patients had developed renal impairment, and diabetes medications had changed in many. While these factors may have influenced gastric emptying, they would be more likely to slow than accelerate it, so they appear unlikely to account for our observations. We acknowledge that selection of study participants was potentially biased, since they had previously participated in research studies concerning experimental therapies for gastroparesis within our department [12,13]. However, a strength is that follow up measurement of gastric emptying was by invitation from the investigators, rather than being performed for clinical indications; the latter might have biased the outcomes. Moreover, the baseline characteristics of the patients whom we were able to follow up did not differ from those of the patients who could not be studied again due to death, refusal, or inability to contact, suggesting that our follow up data ought to be representative of the entire original cohort. We used a meal that differs from that advocated by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine [29], but it was essential that we used the same meal at follow up as at baseline. Our data highlight that there is frequently inconsistency between solid and liquid gastric emptying; in our opinion, this supports our practice of measuring both. We evaluated gastric retention over 2 h rather than 4, but the correlation between retention at these time points is reported to be good [35]. Our reference range to define "normal" gastric emptying represents 2 standard deviations on either side of the mean, derived from 25 healthy volunteers [15]. We could have used a more conservative range defined by the 10th and 90th percentiles from this sample, which would categorise 9 patients as having abnormally slow solid emptying at baseline and 3 at follow up, and 8 patients having abnormally slow liquid emptying at baseline and 9 at follow up; however, this would not change the interpretation of our observations substantially. We acknowledge that various validated scoring systems have been developed to evaluate gastrointestinal symptoms in diabetes (eg. the Gastroparesis Cardinal Symptom Index [36]), but as for gastric emptying measurement, it was important for the purposes of this study to use an identical questionnaire at baseline and follow up.

The main clinical implication of our findings relates to the relative stability of gastric emptying in type 2 diabetes, particularly if gastric emptying is within the normal range on initial evaluation. These patients would be candidates for pharmacological or dietary therapies that slow gastric emptying in order to improve postprandial glycaemic excursions. Patients with initially slow emptying of solids, on the other hand, do not inexorably progress and indeed may improve over time, so that they may merit re-evaluation if such therapies were to be considered later in the course of their management.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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