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Euglycaemic hyperinsulinaemia does not affect gastric emptying in Type I and Type II diabetes mellitus

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Summary Hyperglycaemia slows gastric emptying in both normal subjects and patients with diabetes mellitus. The mechanisms mediating this effect, particularly the potential role of insulin, are uncertain. Hyperinsulinaemia has been reported to slow gastric emptying in normal subjects during euglycaemia. The purpose of this study was to evaluate the effect of euglycaemic hyperinsulinaemia on gastric emptying in Type I (insulin-dependent) and Type II (non-insulin-dependent) diabetes mellitus. In six patients with uncomplicated Type I and eight patients with uncomplicated Type II diabetes mellitus, measurements of gastric emptying were done on 2 separate days. No patients had gastrointestinal symptoms or cardiovascular autonomic neuropathy. The insulin infusion rate was 40 $mU \cdot m^{-2} \cdot min^{-1}$ on one day and 80 $mU \cdot m^{-2} \cdot min^{-1}$ on the other. Gastric emptying and intragastric meal distribution were measured using a scintigraphic technique for 3 h after ingestion of a mixed solid/liquid meal and results compared with a range established in normal volunteers. In both Type I and Type II patients the serum insulin concentration had no effect on gastric emptying or intragastric meal distribution of solids or liquids. When gastric emptying during insulin infusion rates of 40 $mU \cdot m^{-2} \cdot min^{-1}$ and 80 $mU \cdot m^{-2} \cdot min^{-1}$ were compared the solid T_{50} was 137.8 ± 24.6 min vs 128.7 ± 24.3 min and liquid T_{50} was 36.7 ± 19.4 min vs 40.4 ± 15.7 min in the Type I patients; the solid T_{50} was 94.9 ± 19.1 vs 86.1 ± 10.7 min and liquid T_{50} was 21.8 ± 6.9 min vs 21.8 ± 5.9 min in the Type II patients. We conclude that hyperinsulinaemia during euglycaemia has no notable effect on gastric emptying in patients with uncomplicated Type I and Type II diabetes; any effect of insulin on gastric emptying in patients with diabetes is likely to be minimal. [Diabetologia (1999) 42: 365–372]

Keywords Type I diabetes, Type II diabetes, euglycaemia, hyperinsulinaemia, gastric emptying.

The delay in gastric emptying which is evident in about 30–50% of outpatients with longstanding Type I (insulin-dependent) or Type II (non-insulin-dependent) diabetes mellitus has been attributed to irreversible autonomic neuropathy [1–5]. It is now recognised, however, that acute changes in the blood glucose concentration have a major effect on gastric emptying as well as motor function in other regions of the gastrointestinal tract [1, 6–14]. The effects of acute hyperglycaemia on gastrointestinal motor function appear to be related directly to the blood glucose concentration [1, 15–19]. Hyperglycaemia slows gastric emptying markedly in patients with Type I and Type II diabetes [1, 7, 8] and healthy subjects [6]. The mechanisms mediating this effect are uncertain but hyperinsulinaemia might be an important factor. In normal subjects, hyperinsulinaemia, under euglycaemic conditions, slows emptying of

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Abbreviations: CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; RoIs, regions of interest; ALP, amylin and amylin-like peptides; T_{50}, 50% emptying times for solid and liquid; R_{100}, amount of solid in the proximal and distal stomach at 100 min; R_{10}, amount of liquid in the proximal and distal stomach at 10 min

both solid and liquid meal components of a meal [20, 21], although in the most recent of these studies [20] the magnitude of this slowing was small, albeit statistically significant. The effects of hyperinsulinaemia on gastric emptying in patients with diabetes mellitus have not been evaluated, although there is some evidence that the magnitude of the delay in gastric emptying associated with acute hyperglycaemia is possibly less in diabetic patients when compared with normal subjects [15, 22]. The effects of hyperglycaemia and hyperinsulinaemia on gastric emptying could also potentially vary between Type I and Type II diabetes; Type I patients having absolute and Type II patients relative insulin deficiency.

The effects of hyperglycaemia (and hyperinsulinaemia) on gastric emptying might be mediated by changes in the secretion of gastrointestinal hormones. There is evidence that cholecystokinin (CCK) [23, 24] and glucagon-like peptide-1 (GLP-1) [25–27] are important in the regulation of gastric emptying. Amylin, which is co-secreted with insulin [28], might slow gastric emptying [29, 30].

The purpose of this study was to evaluate the effects of euglycaemic hyperinsulinaemia on gastric emptying, intragastric meal distribution and serum concentrations of CCK, GLP-1 and amylin in patients with uncomplicated Type I and Type II diabetes.

Subjects and methods

Subjects. We studied six men with Type I diabetes mellitus (weight 72.9 ± 8.7 kg, range 57.3–82.5, BMI 23.5 ± 2.7 kg/m^2, mean ± SD), aged 34.3 ± 9.4 years (range 23–47) and eight men with Type II diabetes mellitus (weight 95.5 ± 11.5 kg, range 82.5–117.2, BMI 31.7 ± 3.8 kg/m^2), aged 43.3 ± 7.9 years (range 31–53). The two groups were not matched. The Type II patients tended to be older ($p = 0.078$) and had a greater BMI ($p = 0.0007$) than the Type I patients. All subjects were ambulatory out patients attending the Diabetic Clinic at Queen's Medical Centre. None reported gastrointestinal symptoms, had a past history of gastrointestinal surgery or was taking medication other than insulin or oral hypoglycaemic agents. Of the Type II patients two were taking insulin and four were on oral hypoglycaemic agents (1 on metformin, 1 on glibenclamide, 1 on gliclazide and 1 on both glibenclamide and metformin). None had autonomic neuropathy, as assessed clinically and by tests of cardiovascular reflexes, including the heart rate response to the valsalva manoeuvre, during deep breathing, and to standing ("30:15" ratio) [31]. In the Type I patients the duration of diabetes was 16.7 ± 10.1 years and in the Type II patients the duration of known diabetes was 4.1 ± 2.1 years ($p < 0.005$). There was no difference in glycosylated haemoglobin (HbA_{1c}) between the two groups (Type I: 7.1 ± 0.6 %, Type II: 7.0 ± 1.4 %). Informed consent was obtained from all patients. The study protocol was approved by the British Department of Health (Administration of Radioactive Substances Advisory Committee) and the Research Ethics Committee of the University Hospital, Queen's Medical Centre, Nottingham.

Protocol. Patients attended the Department of Medical Physics at 0830 h on two separate days after an overnight fast. The two studies were separated by at least a week. Each patient was asked to abstain from smoking, alcohol and any beverage which contained caffeine (including coffee, tea and soft drinks) for at least 18 h prior to each test. The insulin-treated patients (including the two Type II patients who were on insulin) omitted their morning insulin injection and the Type II patients omitted the morning dose of oral hypoglycaemic agent(s). On arrival at the laboratory the fasting blood glucose was less than 10 mmol/l in all patients. One cannula was inserted into an antecubital vein for infusion of glucose and insulin and another, retrogradely, into a vein on the dorsum of the dominant hand. The latter was kept patent with a slow infusion of 0.9 % NaCl and the hand rested in a heated box (55–60 °C) so that "arterialized" venous blood samples could be obtained [20].

Low-activity radioactive anatomical markers (^{99m}Tc) were attached to the surface of the patients' skin, anteriorly and posteriorly. At 0 min (approximately 1100 h) each subject ate, within 10 min, a standard meal consisting of a pancake (46 % carbohydrate, 26 % fat, 10 % protein) labelled with 3 MBq non-absorbable Tc-99m-ion exchange resin, followed by a low fat milkshake (11 % carbohydrate, 4 % fat, 3 % protein) labelled with 0.5 MBq non-absorbable ^{111}In-DTPA, providing a total of 400 kcal (the milkshake containing 69 kcal). While the subject stood, 30 s anterior and posterior images of the stomach were acquired every 10–20 min for 3 h, using an IGE maxi-camera II gamma camera (IGE Medical Systems, Slough, UK) fitted with a medium-energy general purpose collimator [32]. The gamma camera was linked to a dedicated Nuclear Diagnostics computer system. Each subject remained seated between periods of data acquisition. The geometric mean of counts in anterior and posterior gastric regions of interest (ROIs) was calculated and corrected for background radiation, isotope decay and Compton scatter. The total stomach region of interest was subsequently divided into proximal and distal regions – the proximal region corresponding to the fundus and proximal corpus and the distal region representing the antrum and distal corpus [33]. Gastric emptying curves (expressed as percent of the maximum content of the total stomach) were derived for total, proximal and distal stomach regions of interest. For the total stomach the 50 % emptying times for solid and liquid (T_{50}) were obtained. In our laboratory the CV in normal subjects is 13 % for the solid T_{50} and 28 % for the liquid T_{50} [34]. The amount of the solid component of the meal in the proximal and distal stomach at 100 min (R_{100}) and the amount of liquid in the proximal and distal stomach at 10 min (R_{10}) were also calculated. Gastric emptying results were compared with those obtained in 10 healthy male volunteers (weight 79.2 ± 8.2 kg, range 61.8–86.5, BMI 25.5 ± 2.5 kg/m^2, mean ± SD), aged 23.6 ± 3.4 years (20–32) who underwent measurements of gastric emptying during euglycaemic hyperinsulinaemia, with an insulin infusion rate of 40 mU · m^{-2} · min^{-1}. The results of gastric emptying in these subjects have been reported previously [20]. In this latter group the solid T_{50} was 149.6 ± 30.7 min (range 92–195 min) and proximal and distal R_{100} were 53 ± 10 % and 14 ± 5 %. For the liquid component of the meal the T_{50} was 39.8 ± 13.9 min (range 23–66 min) and proximal and distal R_{10} were 61 ± 11 % and 22 ± 5 % respectively. Gastric emptying in the diabetic patients was considered to be abnormal when it was outside the range in the ten control subjects. The control group was younger ($p < 0.05$) and lighter ($p < 0.05$) than the Type II patients, and younger ($p < 0.05$) than the Type I patients.

Euglycaemic, hyperinsulinaemic clamps were carried out according to the method of De Fronzo et al. [35]. Short-acting insulin (Human Actrapid, Novo Nordisk, Copenhagen, Den-

mark) was mixed in 0.9% NaCl, containing 2 ml of the subject's blood, to a concentration of 1 U/ml. The insulin infusion rate was 40 mU · m^{-2} · min^{-1} on one day and 80 mU · m^{-2} · min^{-1} on the other; the order of the two studies was randomised and they were done in single blind fashion. After a 10 min priming infusion, insulin was infused continuously and when the blood glucose concentration reached 5 mmol/l, 20% dextrose was started at 5.56 μmol · kg^{-1} · min^{-1}. The glucose infusion rate was then adjusted to maintain the blood glucose concentration at 4.5–5.0 mmol/l for at least 60 min before each subject ate the test meal, to ensure a steady state glucose infusion rate. After the meal, the rate of glucose infusion was adjusted to maintain the blood glucose concentration within the normal postprandial range (6–10 mmol/l), while the insulin infusion was continued at the same rate. Blood glucose concentrations were measured every 10 min with a glucose oxidase method using a Yellow Springs Analyser (Yellow Springs, Ohio, USA); CV for the assay was 3%. Blood was withdrawn at –30, 0, 20, 30, 40, 60, 90, 120, 150 and 180 min for measurements of serum insulin, CCK, GLP-1 and amylin.

Hormone measurements. Insulin was measured by radioimmunoassay (Diagnostic Products Corporation, Los Angeles, Calif., USA, inter-assay CV 7.4% at 114 mU/l).

C-peptide was measured by an ELISA based on two monoclonal antibodies (Dako Diagnostics Ltd, Ely, Cambridgeshire, UK). The lower limit of detection was less than 0.05 nmol/l. The inter-assay CV was 3.87–8.2%.

Glucagon-like peptide-1 (GLP-1) was measured in extracts of serum by radioimmunoassay with synthetic GLP-1 (7–36) amide (Bachem Ltd., Saffron Walden, Essex, UK) as the assay standard, antibody code R 600–8 (final dilution 1:30 000), and synthetic GLP-1 labelled by chloramine-T method and purified by reverse phase high-performance liquid chromatography. The antiserum used did not cross-react with other known gut or brain peptides. The sensitivity of the assay was 9 pmol/l (30 pg/ml); the inter-assay CV was 11% and the intra-assay CV was 8% at 45 pmol/l (150 pg/ml).

Cholecystokinin (CCK) was measured by radioimmunoassay with synthetic CCK8 (sulphated) (Bachem, UK) as the assay standard, antibody code R7 (3) (final dilution 1:100 000). Serum was extracted using ethanol, shaken, centrifuged and the supernatant dried under an air stream. This was reconstituted in 500 μl assay buffer (phosphate buffer 0.04 mol/l + 0.2g% gelatin and 0.16g% EDTA). Bolton & Hunter [36] labelled ^{125}I-CCK8 s radiolabel (Amersham Life Science Ltd., Little Chalfont, Bucks, UK) and antiserum, raised in rabbit to CCK8s, conjugated to ovalbumin using carbodiimide, were used. The intra-assay CV was 8.2% and 6.6% at 4.37 pmol/l and 13.12 pmol/l respectively and the inter-assay CV was 13.3% and 11.5% at 4.37 pmol/l and 13.13 pmol/l respectively with lower limit of detection of 1.31 pmol/l. The relative crossreactivity with gastrin 17, pentagastrin, CCK/gastrin 4 was less than 0.001.

Amylin and amylin-like peptides (ALP) were measured using two-site sandwich ELISA with capture antibodies F024 and F002 respectively (Amylin Pharmaceuticals Inc., San Diego, USA). Interassay CVs were less than 15% across the assay range. Minimum detectable amylin and ALP concentrations were 1.9 and 2.7 pmol/l.

Statistical analysis. In one subject (in the Type I group) data for liquid gastric emptying were not obtained on one day because of a technical error. Another Type I subject was found to have very high insulin results on both study days, was tested for insulin antibodies and found to have a very high titre. Free insulin concentrations were not measured and his results were, accordingly, excluded from the insulin analysis.

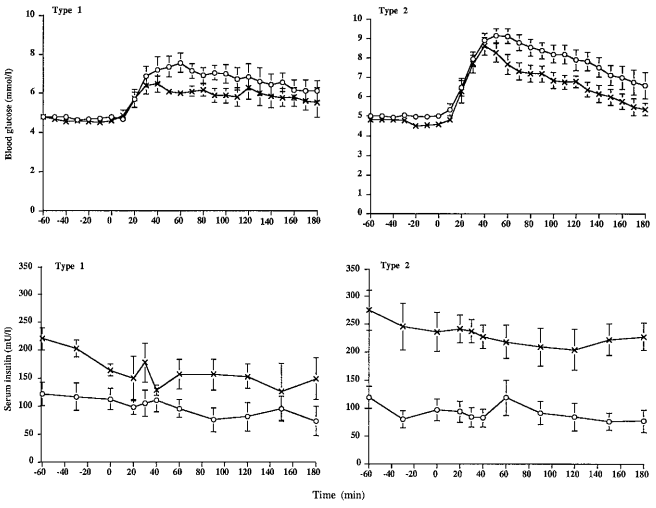

Fig. 1. Blood glucose and insulin profile during the 40 mU · m^{-2} · min^{-1} (-o-) and 80 mU · m^{-2} · min^{-1} (-x-) insulin clamps in the Type I and Type II patients. There were no significant differences in the blood glucose profile on the two experimental days

All biochemical data were analysed using Repeated Measures Analysis of Variance; treatment-time interactions were evaluated to determine the effect of the 40 mU · m^{-2} · min^{-1} insulin infusion rate compared with the 80 mU · m^{-2} · min^{-1} insulin infusion rate over time. The Mann-Whitney U test for non-parametric data was used to compare means between the Type I and Type II diabetic patients. A p value less than 0.05 was considered significant in all analyses. Data are shown as mean values ± SD.

Results

Blood glucose, serum insulin and C-peptide. There were no great differences in the blood glucose profile on the two experimental days (Fig. 1), although postprandial blood glucose concentrations tended to be higher when insulin was infused at 40 mU · m^{-2} · min^{-1} when compared with 80 mU · m^{-2} · min^{-1} ($p = 0.06$ for the Type I group and $p = 0.14$ for the Type II group). In the Type I group the peak blood glucose was 7.6 ± 1.2 mmol/l at 60 min during the 40 mU · m^{-2} · min^{-1} insulin experiment and 6.5 ± 1.0 mmo/l at 40 min during the 80 mU · m^{-2} · min^{-1} insulin experiment. The corresponding values in the Type II group were 9.2 ± 1.0 mmol/l at 50 min and 8.6 ± 1.0 mmol/l at 40 min (Fig. 1).

In the Type I group mean postprandial insulin concentrations were 92.8 ± 13.6 mU/l and 150.5 ± 16.2 mU/l during the 40 mU · m^{-2} · min^{-1} and 80 mU · m^{-2} · min^{-1} insulin infusions respectively ($p = 0.013$); for the Type II group the mean postprandial insulin concentrations were 89.4 ± 13.6 mU/l and 224.4 ± 12.7 mU/l ($p = 0.0002$). During the 80 mU · m^{-2} · min^{-1} infusion serum insulin concentrations were higher ($p = 0.03$) in the Type II than the Type I

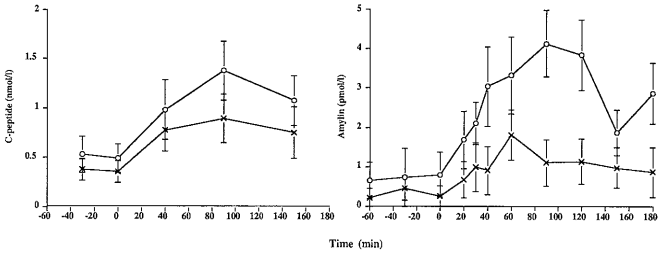

Fig. 2. C-peptide and amylin results in the Type II patients. C-peptide concentrations were low before the meal and rose ($p = 0.0002$) after it, the response being greater ($p = 0.0001$) during the 40 mU · m^{-2} · min^{-1} insulin infusion (-o-) compared with the 80 mU · m^{-2} · min^{-1} infusion (-x-). There was a rise in serum amylin ($p < 0.0001$) after the meal and this response was greater when the insulin infusion rate was 40 mU · m^{-2} · min^{-1}(-o-) ($p = 0.002$)

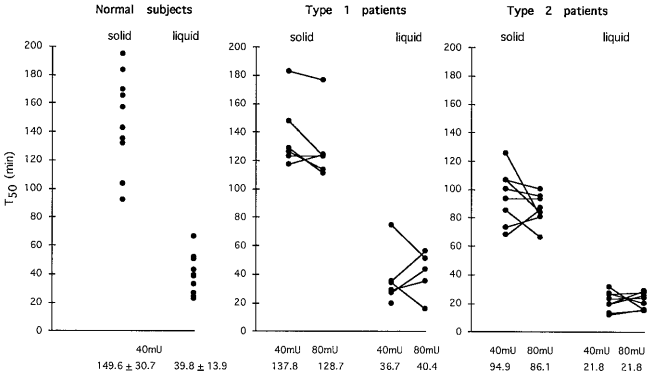

Fig. 3. Solid and liquid half-emptying times (T_{50}) for the normal subjects, Type I and Type II patients at an insulin infusion rate of 40 mU · m^{-2} · min^{-1} and for the Type I and Type II patients at an insulin infusion rate of 80 mU · m^{-2} · min^{-1}. There was no significant difference in gastric emptying of solid or liquid between the Type I patients and the control subjects when the insulin infusion rate was 40 mU · m^{-2} · min^{-1}. Gastric emptying was within the control range in all Type I patients

patients whereas there was no difference between the two groups during the 40 mU · m^{-2} · min^{-1} infusion. There was no significant change in serum insulin following the meal in either the Type I or Type II patients.

In the Type II patients C-peptide concentrations were low before the meal and rose ($F = 10.8$, $p = 0.0002$, treatment-time interaction) after it, the response being greater ($F = 881.3$, $p = 0.0001$, treatment factor) during the 40 mU · m^{-2} · min^{-1} insulin infusion when compared with the 80 mU · m^{-2} · min^{-1} infusion (Fig. 2).

Solid and liquid gastric emptying. The comparisons of gastric emptying between the Type I and Type II patients and control subjects are presented as these data are of interest and only tentative conclusions are drawn from these observations. There was no important difference in gastric emptying or intragastric distribution of solid or liquid between the Type I patients and the normal volunteers when the insulin infusion rate was 40 mU · m^{-2} · min^{-1}. Gastric emptying was within the control range in all patients. In contrast, in the Type II patients gastric emptying of both solids ($p < 0.008$) and liquids ($p < 0.05$) was faster than in both normal volunteers and Type I patients (Fig. 3). In three of the Type II patients solid emptying (T_{50}) was faster than the control range; in four patients liquid emptying (T_{50}) was more rapid. In the Type II patients the retention of solid in the proximal stomach at 100 min (R_{100}) was less ($p < 0.05$) than in both the control and Type I patients, whereas there was no difference in the retention in the distal stomach at that time. There was no difference in intragastric distribution of the liquid meal between the Type II patients and the two other groups.

In both Type I and Type II patients there was no difference in gastric emptying or intragastric distribution of solids or liquids between the two experiments,

Table 1. Gastric emptying and intragastric meal distribution in Type I, Type II patients and control subjects at an insulin infusion rate of 40 mU · m^2 · min^{-1} and in Type I and Type II patients at an insulin infusion rate of 80 mU · m^2 · min^{-1}

	Insulin infusion rate of 40 mU · m^2 · min^{-1}			Insulin infusion rate of 80 mU · m^2 · min^{-1}	
	Normals	Type I	Type II	Type I	Type II
Total stomach					
T_{50} solid (min)	149.6 ± 30.7	137.8 ± 24.6	94.9 ± 19.1[b]	128.7 ± 24.3	86.1 ± 10.7 [d]
T_{50} liquid (min)	39.8 ± 13.9	36.7 ± 19.4	21.8 ± 6.9[a]	40.4 ± 15.7	21.8 ± 5.9 [c]
Proximal stomach					
$R_{100\,prox}$ solid (%)	53 ± 10	44 ± 6	33 ± 8[e]	42 ± 6	24 ± 5[e]
$R_{10\,prox}$ liquid (%)	61 ± 11	59 ± 15	53 ± 16	58 ± 13	51 ± 14
Distal stomach					
$R_{100\,distal}$ solid (%)	14 ± 5	18 ± 5	13 ± 4	17 ± 8	17 ± 5
$R_{10\,distal}$ liquid (%)	22 ± 5	23 ± 9	22 ± 5	24 ± 14	25 ± 8

T_{50} – 50% emptying time, R_{100} – amount of solid in the proximal and distal stomach at 100 min, R_{10} – amount of liquid in the proximal and distal stomach at 10 min

[a] $p < 0.05$, [b] $p < 0.0005$ vs control, [c] $p < 0.05$, [d] $p < 0.005$, [e] $p < 0.0005$ vs Type I patients, data are mean ± SD

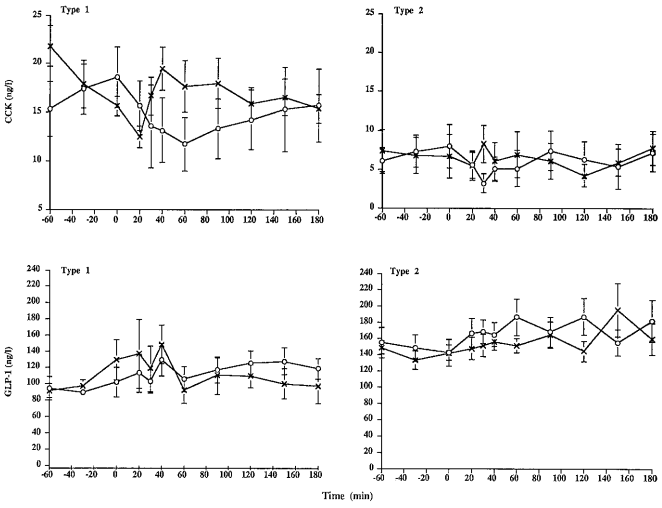

Fig. 4. CCK and GLP-1 results in the Type I and Type II patients. In both the Type I and Type II patients the insulin infusion rate had no effect on serum concentrations of CCK or GLP-1

that is, the serum insulin concentration had no effect on gastric emptying.

Gastrointestinal hormones. In both the Type I and Type II patients the insulin infusion rate had no effect on serum concentrations of CCK or GLP-1. In contrast, in the Type II patients there was a rise in serum amylin ($F = 15.2$, $p < 0.0001$, treatment-time interaction) and ALP ($F = 16.5$, $p < 0.0001$, treatment-time interaction, data not shown) after the meal and this response was greater when the insulin infusion rate was $40\ mU \cdot m^{-2} \cdot min^{-1}$ ($F = 7.5$, $p = 0.04$ for ALP and $F = 8.8$, $p = 0.02$ for amylin, treatment factor). As expected, the Type I subjects had undetectable amylin and ALP values and there was no response following the meal on either day. At both insulin infusion rates serum CCK was greater ($p < 0.005$) while serum GLP-1 was less ($p < 0.05$) in the Type I patients than the Type II patients.

Discussion

Our study is the first to evaluate the effect of variations in the serum insulin concentration on gastrointestinal motor function in patients with diabetes. The results indicate that hyperinsulinaemia per se, in the absence of hyperglycaemia, has no significant effect on gastric emptying in patients with uncomplicated Type I or Type II diabetes. This suggests that the substantial retardation of gastric emptying induced by hyperglycaemia in both normal subjects [6] and patients with diabetes mellitus [1, 7, 8] is not mediated by an increase in insulin secretion.

The effects of insulin on gastrointestinal motor function are controversial [16, 20, 21, 37–40]. The serum insulin concentrations that we evaluated are comparable with those achieved during "marked" and "physiological" hyperglycaemia in normal subjects [16, 20, 21]. In the healthy volunteers, the postprandial serum insulin concentrations during the saline infusion approximated the serum insulin concentrations in the diabetic patients during the $40\ mU \cdot m^{-2} \cdot min^{-1}$ insulin infusion and in the diabetic patients, the serum insulin concentrations during the $80\ mU \cdot m^{-2} \cdot min^{-1}$ insulin infusion approximated the postprandial serum insulin concentrations in the healthy volunteers during the $40\ mU \cdot m^{-2} \cdot min^{-1}$ insulin infusion (which included endogenous insulin secretion). Not surprisingly, there was a non-significant trend for lower blood glucose concentrations during the $80\ mU \cdot m^{-2} \cdot min^{-1}$ insulin infusion when compared with the $40\ mU \cdot m^{-2} \cdot min^{-1}$ insulin infusion, and a modest postprandial increase in blood glucose concentrations. These issues are unlikely to have influenced the results. A non-hyperinsulinaemic control (saline infusion) study was not included because the inevitable occurrence of marked hyperglycaemia would have precluded interpretation as hyperglycaemia is known to slow gastric emptying under these conditions [1, 7, 8]. We cannot exclude the possibility that serum insulin concentrations that are lower or higher than those evaluated may affect gastric emptying, or that the effects of insulin differ between normal subjects and patients with diabetes. Our observations, however, are consistent with the majority of previous studies that have evaluated the effects of insulin on gut motor function in normal subjects; in most cases in which an effect of insulin was evident, its magnitude was relatively small [20, 39]. Furthermore, it has been shown that the effects of hyperglycaemia on gastric emptying, antral motility [1,15–17], gallbladder emptying [19] and anorectal motility [18] are related directly to the blood glucose concentration, e.g. postprandial antral motility is suppressed more at a blood glucose of 230 mg/dl (12.8 mmol/l) compared with 175 mg/dl (9.7 mmol/l) [16]. These observations reinforce the concept that insulin concentrations lower than those examined would almost certainly not affect gastric emptying in patients with diabetes.

In our previous study which assessed the effect of euglycaemic hyperinsulinaemia on gastric emptying in normal subjects, gastric emptying of both solids and liquids was slower during hyperinsulinaemia, but the difference, albeit statistically significant, was modest (solid T_{50} 149.6 ± 30.7 vs 129 ± 26.2 min, liquid T_{50} 39.8 ± 13.9 vs 30.1 ± 12.5 min). It has been reported that in normal subjects postprandial antral motility is suppressed by hyperglycaemia, but not euglycaemic hyperinsulinaemia [16]. In contrast to this another study reported that in normal subjects hyperinsulinaemia per se abolishes antral phase III and shortens duodenal phase III [37]. The slowing of

small intestinal transit by marked hyperglycaemia [11, 12] is not replicated by hyperinsulinaemia [39] and, similarly, it has been reported that acute hyperglycaemia, but not secondary hyperinsulinaemia, blunts mechanoreceptor-mediated gastrocolonic responses [40], and the rectoanal inhibitory reflex [38].

It should be recognized that we studied a relatively small number of patients who were selected to have uncomplicated diabetes mellitus and good glycaemic control; gastric emptying was not delayed in any patient. It seems most unlikely that hyperinsulinaemia would affect gastric emptying in diabetic patients who have gastroparesis or autonomic neuropathy or both but we did not address this issue.

There were substantial differences in gastric emptying and serum concentrations of CCK, GLP-1 and amylin between the Type I and Type II patients. Only tentative conclusions should be drawn from these observations, however, as both Type I and Type II patients were highly selected and there were substantial differences between the two groups as well as between these groups and the normal volunteers. For example, the Type II patients were, not surprisingly, heavier and tended to be older than the Type I patients. Furthermore, the number of control subjects was relatively small. Our observations that gastric emptying from the total and proximal stomach was faster in the Type II patients than in both Type I patients and control subjects is, however, consistent with the concept that gastric emptying is frequently accelerated in "early" Type II diabetes [41–43]. While the prevalence of delayed gastric emptying in patients with longstanding Type II diabetes appears comparable with that in Type I diabetes [2, 4, 7], there is substantial controversy as to the prevalence of disordered gastric emptying in patients with so-called "early" Type II diabetes [41–44] and a number of studies have suggested that gastric emptying may be more rapid in this group [41–43]. It should, however, be recognised that a substantial deficiency of all studies which have evaluated the prevalence of disordered gastric emptying in Type II diabetes is that blood glucose concentrations were not stabilised in the euglycaemic range [41–44].

CCK plays a role in the regulation of gastric emptying [23, 24] and appetite [45, 46]. In normal subjects, acute hyperglycaemia does not affect CCK secretion induced by intraduodenal fat [11]. Reports on the effects of diabetes mellitus on CCK secretion are controversial. It has been reported that both basal and postprandial CCK concentrations are normal in Type I and Type II diabetic patients without autonomic neuropathy [47] and that the CCK response to a meal is increased in patients with autonomic neuropathy [47–49]; in contrast, it has been reported that postprandial CCK concentrations are lower in Type II patients when compared with normal subjects [50]. We observed that serum CCK concentrations were lower in the Type II than the Type I patients; accordingly the possibility that more rapid gastric emptying in Type II diabetes mellitus might be related to a reduction in CCK secretion warrants evaluation. The higher serum GLP-1 concentrations in the Type II patients has been noted previously [51, 52]; it has been suggested that the reduction in the incretin effect in these patients possibly reflects insensitivity of the beta-cell to GLP-1 [53].

There was a notable rise in both C-peptide and amylin after the meal in the Type II patients, the response being greater when the insulin infusion rate was $40\ mU \cdot m^{-2} \cdot min^{-1}$. As amylin is co-secreted with insulin, these observations are indicative of an increase in endogenous insulin secretion despite the absence of significant change in serum insulin concentrations. It has been demonstrated in normal subjects that raising serum insulin does not prevent endogenous insulin release [20, 21]. It should be acknowledged that we did not look at the effect of an insulin infusion rate of $80\ mU \cdot m^{-2} \cdot min^{-1}$ in our healthy volunteers so we cannot be sure that very high insulin concentrations would not suppress the beta-cell. The demonstration that postprandial concentrations of both C-peptide and amylin were lower at an insulin infusion rate of $80\ mU \cdot m^{-2} \cdot min^{-1}$ suggests that in Type II diabetes serum insulin concentrations influence insulin secretion. On the other hand, the higher blood glucose concentrations at an insulin infusion rate of $40\ mU \cdot m^{-2} \cdot min^{-1}$ could potentially account for a higher secretory drive on both endogenous insulin and amylin.

We conclude that euglycaemic hyperinsulinaemia has little or no effect on gastric emptying of a solid and liquid meal in patients with uncomplicated Type I and Type II diabetes mellitus. Another potential mechanism by which hyperglycaemia slows gastric emptying is possibly a central nervous system effect which is supported by animal and human studies; a direct effect on smooth muscle seems unlikely as both smooth muscle stimulation (pylorus, small intestine) [10, 12] and inhibition (proximal stomach, antrum) [9, 13, 14, 16] occur during hyperglycaemia. Changes in vagal activity and the secretion of other gastrointestinal hormones (motilin, glucagon, GIP) and myogenic mechanisms could be important.

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