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Small Intestinal Glucose Exposure Determines the Magnitude of the Incretin Effect in Health and Type 2 Diabetes

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The potential influence of gastric emptying on the "incretin effect," mediated by glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), is unknown. The objectives of this study were to determine the effects of intraduodenal (ID) glucose infusions at 2 (ID2) and 4 (ID4) kcal/min (equating to two rates of gastric emptying within the physiological range) on the size of the incretin effect, gastrointestinal glucose disposal (GIGD), plasma GIP, GLP-1, and glucagon secretion in health and type 2 diabetes. We studied 10 male BMI-matched controls and 11 male type 2 patients managed by diet or metformin only. In both groups, GIP, GLP-1, and the magnitude of incretin effect were greater with ID4 than ID2, as was GIGD; plasma glucagon was suppressed by ID2, but not ID4. There was no difference in the incretin effect between the two groups. Based on these data, we conclude that the rate of small intestinal glucose exposure (i.e., glucose load) is a major determinant of the comparative secretion of GIP and GLP-1, as well as the magnitude of the incretin effect and GIGD in health and type 2 diabetes.

It was established in 1964 that the insulin response to oral and enteral glucose is much greater than that to an isoglycemic intravenous glucose infusion (1,2). This "incretin effect," mediated by glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) and calculated by comparing the plasma insulin, or C-peptide, responses to isoglycemic oral and intravenous glucose loads, ranges between 40 and 70% in health (3), independent of glycemia (4), and may be diminished in type 2 diabetes (5).

Gastric emptying, which exhibits substantial interindividual variation in health (1–4 kcal/min) (6) and particularly in type 2 diabetes because of the high prevalence of delayed, and sometimes accelerated, emptying, modulates postprandial glycemic excursions (7). The relationships of the rate of small intestinal glucose delivery, a surrogate of gastric emptying, with glycemic and GLP-1, but not GIP, responses are nonlinear in health and type 2 diabetes (8,9). It has been suggested that both the incretin effect and gastrointestinal glucose disposal (GIGD; which takes into account the actions of the incretin hormones but also changes in glucagon and hepatic glucose uptake [10]) increase with higher glucose loads and are reduced in type 2 diabetes (5,11). However, a fundamental limitation in interpreting these studies has been their failure to account for gastric emptying.

We have now evaluated the effects of different rates of duodenal glucose delivery on the incretin effect and GIGD in health and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

We studied 10 male BMI-matched controls (age 47 ± 3 years; BMI 29.3 ± 1 kg/m^2) and 11 male type 2 patients (age 64 ± 2 years; BMI 31 ± 1.3 kg/m^2; HbA_{1c} 6.9 ± 0.2% [52 ± 2.2 mmol/mol]; duration of known diabetes 4.9 ± 1.3 years) managed by diet or metformin only. Subjects with known gastrointestinal disease, with medical illness(es) apart from diabetes, or taking medication

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known to affect gastrointestinal motility were excluded. Type 2 patients were examined for microvascular complications. The study protocol, which conformed to the principles of the Declaration of Helsinki, was approved by the Royal Adelaide Hospital Research Ethics Committee.

Study Protocol

Each subject attended the laboratory at 0800 h following an overnight fast on 4 separate days. On the first 2 days, subjects received, in randomized order, an intraduodenal glucose infusion at 2 or 4 kcal/min. On the last 2 days, they were given intravenous glucose to match the blood glucose profile of the first two visits.

Intraduodenal Infusion Days

A manometric catheter (Dentsleeve, Ontario, Canada) incorporating an infusion channel opening 12 cm beyond the pylorus was inserted through the nose and positioned in the duodenum by monitoring antral and duodenal transmucosal potential difference (12). Intraduodenal glucose (25 g/100 mL) was infused at 2 (ID2) or 4 (ID4) kcal/min from t = 0 to 120 min, and the catheter was then removed.

Isoglycemic Intravenous Glucose Infusion Days

An intravenous cannula was placed in an antecubital vein to administer glucose (25 mg/100 mL) at a rate adjusted according to blood glucose measurements every 5 min (5).

Measurements

Blood Glucose and Plasma Hormones

An intravenous cannula was placed in a contralateral antecubital vein for blood sampling. Blood glucose was determined using a glucometer (MediSense Precision QID, Abbott Laboratories, Bedford, MA).

Blood samples were collected at frequent intervals into ice-chilled EDTA tubes for insulin, C-peptide, GLP-1, GIP, and glucagon measurements. Plasma was separated by centrifugation and stored at −70°C until assayed. Plasma insulin and C-peptide were measured by ELISA (10-1113 and 10-1136-01, Mercodia, Uppsala, Sweden) (13). Plasma total GLP-1, total GIP, and glucagon were measured by radioimmunoassay (GLPIT-36HK and GL-32K, Millipore, Billerica, MA for GLP-1 and glucagon and an in-house assay for GIP [13]).

Incretin Effect and GIGD

The incretin effect (percentage) was calculated from incremental area under the curve (iAUC) for plasma C-peptide as $[(iAUC_{ID(0–120)} - iAUC_{IV(0–120)}) / iAUC_{ID(0–120)}] \times 100$ (5). GIGD was calculated as follows: if 25 g intravenous glucose is required to copy a 75 g oral glucose, the GIGD is $100 \times (75 - 25) / 75 = 66\%$ (10).

Statistical Analysis

The sample size was determined by a biostatistician based on previous work (8,9). Peak and iAUC for glucose and hormone concentrations from t = 0 to 120 min were determined. For intragroup data, one-way ANOVA tests were used to analyze baseline values and paired t tests for peak values and iAUC. Unpaired t tests and repeated measures ANOVA were used to analyze intergroup data. Bonferroni adjustment post hoc tests were used when an interaction was evident. Levene F-tests were used to evaluate the variance in incretin effect. Significance was accepted at $P < 0.05$, and data are presented as mean ± SE.

RESULTS

All subjects tolerated the study well. Control subjects were younger than type 2 patients (47 ± 3 vs. 64 ± 2 years; $P < 0.05$), but BMI (29.3 ± 1 vs. 31 ± 1.3 kg/m^2) was comparable. No patient had macrovascular or microvascular complications.

Controls

Blood Glucose and Plasma Insulin, C-Peptide, and Glucagon

There was no difference in the glycemic responses to ID2 and ID4, but for each, insulin and C-peptide responses were greater compared with intravenous glucose loads ($P < 0.05$) and greater with ID4 than ID2 ($P < 0.05$). During ID2, glucagon was lower than baseline at t = 120 min (43.3 ± 5.7 vs. 68.7 ± 11.8 ng/L; $P < 0.05$), while with ID4, glucagon decreased from baseline at t = 60 min (50.4 ± 8.0 vs. 65.6 ± 9.8 ng/L; $P < 0.05$) and then increased until t = 120 min (67.7 ± 14.5 ng/L). Glucagon was suppressed compared with baseline by intravenous isoglycemic infusion corresponding to 2 kcal/min intraduodenal infusion (IV2) and intravenous isoglycemic infusion corresponding to 4 kcal/min intraduodenal infusion (IV4) ($P < 0.05$) (Fig. 1 and Table 1).

Incretin Effect and GIGD

The magnitude of the incretin effect (61.2 ± 3.2 vs. 44 ± 6.2%; $P < 0.05$) and GIGD (63.0 ± 6.6 vs. 42.9 ± 6.2%; $P < 0.05$) was greater for ID4 than ID2 (Table 1).

Plasma GLP-1 and GIP

During ID2, GLP-1 increased transiently, whereas with ID4, the increase was greater and more sustained ($P < 0.05$). The GIP response was much greater with ID4 than ID2 ($P < 0.05$) (Fig. 2 and Table 1).

Type 2 Patients

Blood Glucose and Plasma Insulin, C-Peptide, and Glucagon

Baseline blood glucose ($P < 0.05$), C-peptide ($P < 0.05$), and glucagon ($P < 0.05$) were greater in type 2 patients than controls, but during both ID2 and ID4, insulin and C-peptide responses were comparable to controls and were greater than for intravenous glucose ($P < 0.05$). Blood glucose, insulin, and C-peptide were greater for ID4 than ID2 ($P < 0.05$), and these rises were comparable with those seen in the control group (Fig. 1 and Table 1).

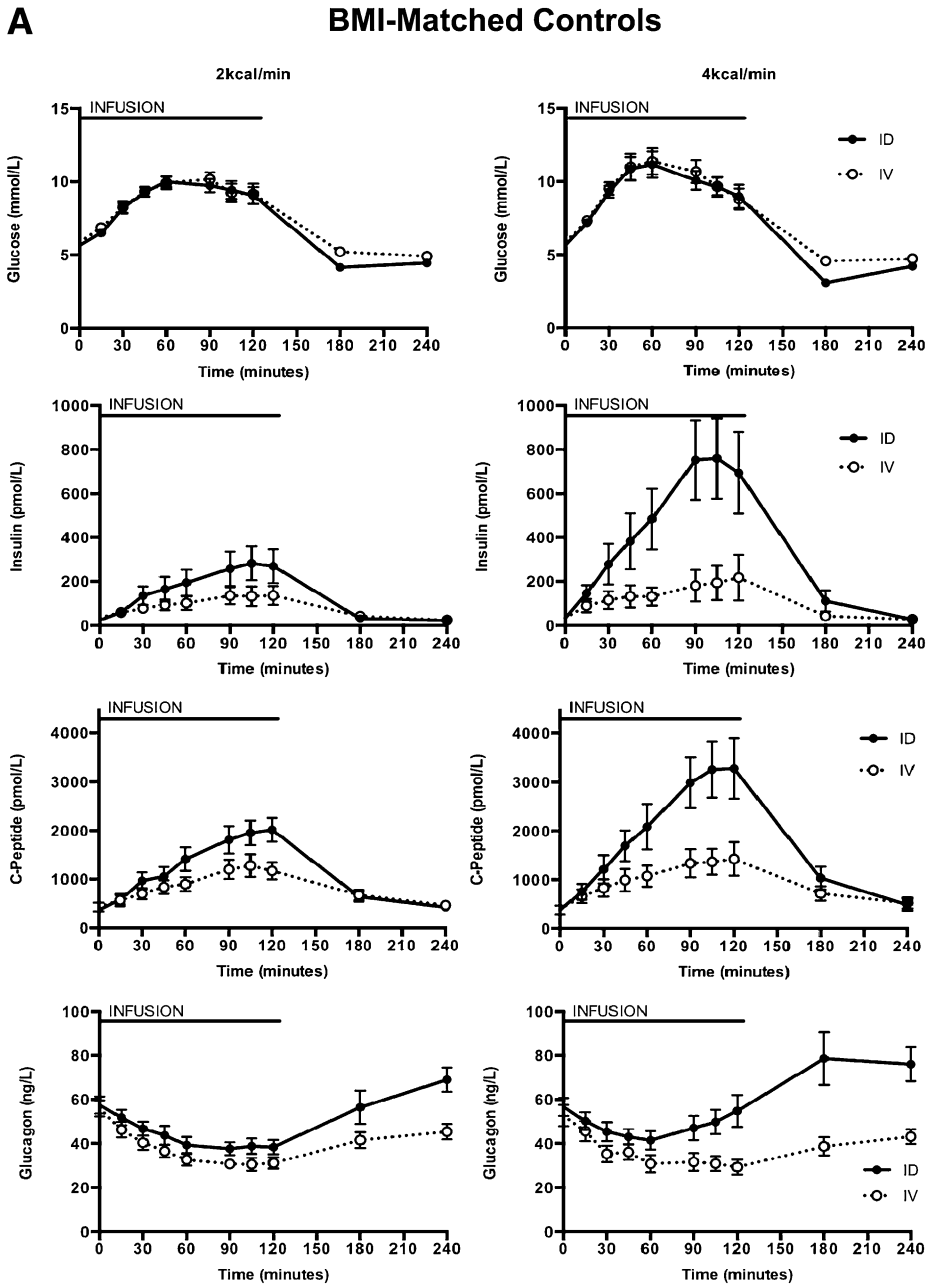

Figure 1—Blood glucose, plasma insulin, C-peptide, and glucagon concentrations at baseline and in response to a 120-min intraduodenal glucose infusion at 2 and 4 kcal/min and corresponding isoglycemic intravenous glucose infusions in (*A*) BMI-matched controls and (*B*) type 2 patients. Data are mean ± SEM. Filled circles with bold line, intraduodenal glucose infusion; empty circles with dotted line, isoglycemic intravenous infusion. ID, intraduodenal; IV, intravenous; T2DM, type 2 diabetes.

During ID2, glucagon decreased from baseline to t = 120 min (82.5 ± 5.2 vs. 57.7 ± 4.3 ng/L; $P < 0.05$), while with ID4, glucagon was unchanged at 120 min (82.6 ± 3.7 vs. 123.1 ± 24.1 ng/L; P = NS). Glucagon was suppressed by both IV2 and IV4, as expected.

Incretin Effect and GIGD

In type 2 patients, the incretin effect (75.2 ± 2.9 vs. 35 ± 13.9%; $P < 0.05$) and GIGD (53.5 ± 4.6 vs. 33.1 ± 4.7%; $P < 0.05$) were greater with ID4 than ID2 and comparable with controls, albeit with greater variance in the incretin effect than controls for ID2 (F = 4.6; $P < 0.05$) but not ID4 (F = 1; P = NS) (Fig. 3 and Table 1).

Plasma GLP-1 and GIP

Baseline plasma GLP-1 ($P < 0.05$), but not GIP, was slightly greater than in controls. There was little change in GLP-1 during ID2, but a greater and sustained GLP-1 response for ID4 ($P < 0.05$), which was marginally less than in controls ($P < 0.05$). The GIP response was much

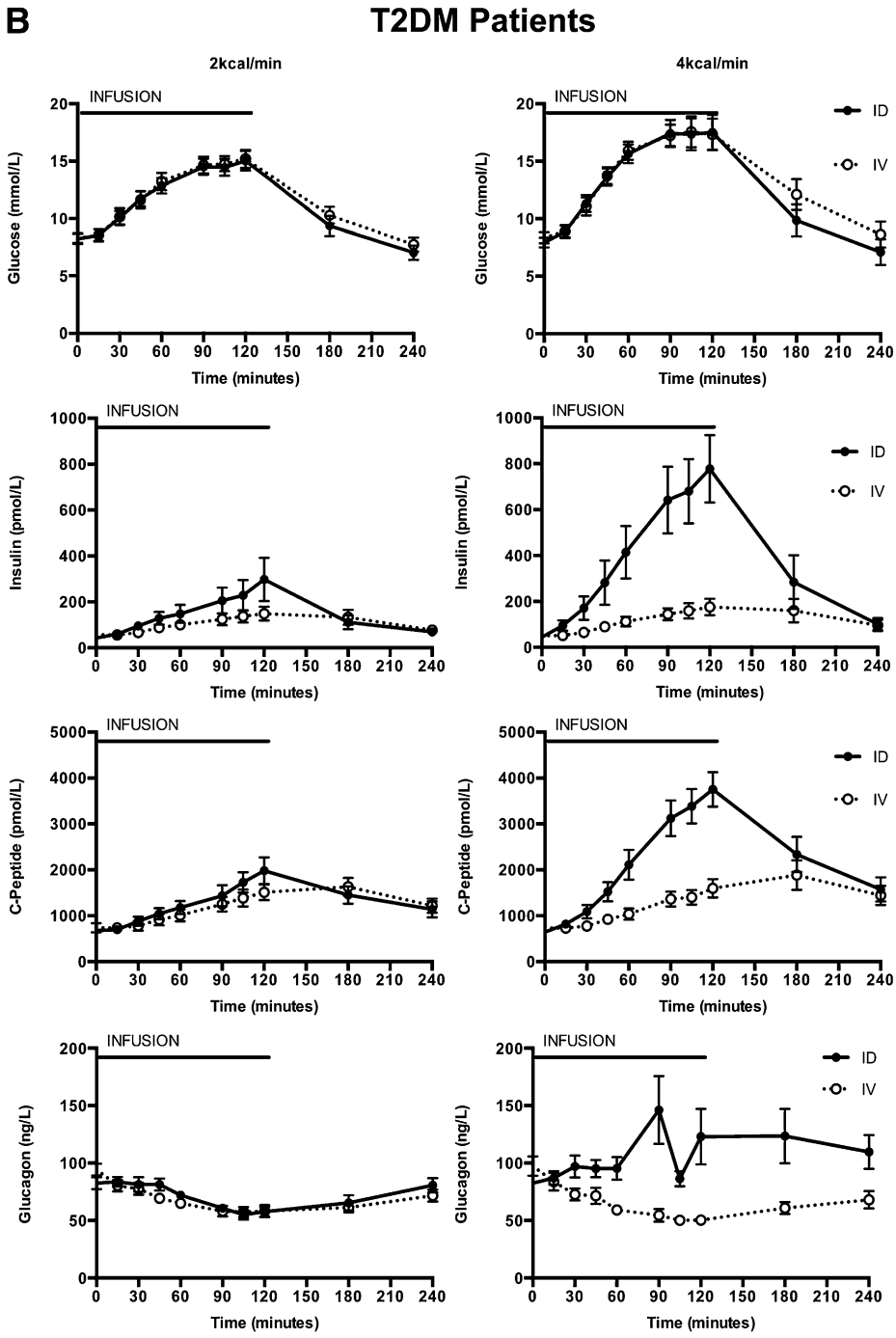

Figure 1—*Continued*.

greater for ID4 than ID2 ($P < 0.05$) and was comparable with controls (Fig. 2 and Table 1).

DISCUSSION

We evaluated the effects of intraduodenal infusion of glucose at 2 and 4 kcal/min on glycemia, insulinemia, glucagonemia, GLP-1, and GIP and compared these responses with the effects of isoglycemic intravenous glucose loads in BMI-matched controls and type 2 patients. The major observations were that in both groups *1*) the rises in plasma insulin and C-peptide and the magnitude of both the incretin effect and GIGD were much greater in response to ID4 than ID2 and *2*) there was sustained suppression of glucagon in response to ID2 and both isoglycemic intravenous infusions, but not for ID4.

While it is well established that the incretin effect represents a major contribution to the postprandial

Table 1—Results for glucose, insulin, C-peptide, glucagon, incretin hormones, incretin effect, and GIGD in BMI-matched controls and type 2 patients

	BMI-matched controls (n = 10)	Type 2 diabetes (n = 11)	ANOVA P values		
			Visit main effect	Group main effect	Interaction
Glucose					
Baseline					
ID2	5.7 ± 0.2	8.2 ± 0.5	0.199	<0.001	0.752
ID4	5.7 ± 0.1	7.9 ± 0.4			
IV2	5.9 ± 0.2	8.3 ± 0.4			
IV4	5.9 ± 0.2	8.3 ± 0.5			
Peak					
ID2	10.4 ± 0.7	15.1 ± 0.8	0.003	<0.001	0.144
ID4	11.7 ± 0.7	18.3 ± 1.2			
IV2	10.7 ± 0.4	15.5 ± 0.8			
IV4	12.0 ± 0.8	18.3 ± 1.2			
iAUC (0–120)					
ID2	377 ± 34.7	478 ± 31.3	<0.001	0.007	0.009
ID4	461 ± 63.5	751 ± 68.3			
IV2	366 ± 36.7	489 ± 51.2			
IV4	462 ± 63.1	709 ± 56.4			
Insulin					
Baseline					
ID2	4.1 ± 1.1	7.1 ± 1.2	0.006	0.167	0.801
ID4	5.5 ± 2.2	7.4 ± 1.3			
IV2	5.9 ± 1.7	9.5 ± 1.8			
IV4	5.6 ± 1.4	8.5 ± 1.1			
Peak					
ID2	53.7 ± 13.5	49.7 ± 15.7	<0.001	0.793	0.806
ID4	137 ± 30.8	130. ± 24.4			
IV2	25.6 ± 7.1	25.4 ± 4.9			
IV4	40.6 ± 17.1	30.2 ± 5.9			
iAUC (0–120)					
ID2	19,101 ± 5,535	13,081 ± 4,156	<0.001	0.424	0.900
ID4	52,769 ± 12,746	44,835 ± 11,384			
IV2	7,805 ± 2,281	5,099 ± 1,281			
IV4	12,800 ± 5,339	7,304 ± 1,810			
C-peptide					
Baseline					
ID2	369 ± 74.5	676 ± 95.3	0.109	0.018	0.765
ID4	379 ± 92.8	644 ± 70.7			
IV2	430 ± 91.8	741 ± 101			
IV4	400 ± 84	734 ± 79			
Peak					
ID2	2,137 ± 253	1,980 ± 294	<0.001	0.845	0.170
ID4	3,553 ± 572	3,754 ± 377			
IV2	1,320 ± 227	1,533 ± 183			
IV4	1,510 ± 339	1,599 ± 203			
iAUC (0–120)					
ID2	114,500 ± 16,647	65,360 ± 12,942	<0.001	0.132	0.620
ID4	199,946 ± 35,116	178,167 ± 26,861			
IV2	58,598 ± 7,967	38,504 ± 9,270			
IV4	77,602 ± 16,472	44,739 ± 8,410			
Glucagon					
Baseline					
ID2	57.4 ± 4	82.5 ± 5.2	0.454	<0.001	0.203
ID4	56.5 ± 4	82.5 ± 3.7			
IV2	56 ± 3.6	94.4 ± 5.2			
IV4	52.6 ± 4.8	94.7 ± 8.2			
Δ (0–60 min)					
ID2	−22.6 ± 5	−10.5 ± 4	0.016	0.037	0.607
ID4	−7 ± 9	12.8 ± 8			

Continued on p. 2673

Table 1—Continued

	BMI-matched controls (n = 10)	Type 2 diabetes (n = 11)	ANOVA P values		
			Visit main effect	Group main effect	Interaction
GLP-1					
Baseline					
ID2	23.3 ± 3.3	33.2 ± 3.7	0.052	0.041	0.537
ID4	20.2 ± 2.5	31.6 ± 4			
iAUC (0–120)					
ID2	222 ± 61	224 ± 64	<0.001	0.902	0.897
ID4	2,490 ± 514	2,586 ± 536			
GIP					
Baseline					
ID2	19.3 ± 2	25.8 ± 2.9	0.749	0.225	0.065
ID4	21.1 ± 2.3	23.2 ± 2.5			
iAUC (0–120)					
ID2	3,428 ± 325	3,341 ± 359	<0.001	0.535	0.210
ID4	5,268 ± 651	6,075 ± 431			
Incretin effect (%)					
C-peptide					
ID2	44 ± 6.2	35 ± 13.9	<0.001	0.591	0.126
ID4	61.2 ± 3.2	75.2 ± 2.9			
GIGD (%)					
ID2	42.9 ± 6.2	33.1 ± 4.7	<0.01	0.132	0.985
ID4	63 ± 6.6	53.5 ± 4.6			

insulin response, the reasons for its low intraindividual and substantial interindividual variation have not been determined, although it has been suggested that its regulation "occurs primarily at the level of the gastrointestinal tract" (4). The incretin effect is reported to be reduced in longstanding type 2 diabetes, attributed to a reduced insulinotropic capacity of GIP (14) rather than an absolute reduction in postprandial GIP or GLP-1 secretion (15). The current study indicates that in both health and type 2 diabetes, the incretin effect is dependent on the rate of gastric emptying, with the inference that modulating emptying would impact on its magnitude. This observation has important implications for future studies evaluating the incretin effect. That GIGD is also dependent on duodenal glucose exposure attests to the importance of the rate of gastric emptying for glucose disposal, which has hitherto not been established.

It has been suggested that the incretin hormones GIP and GLP-1 make a comparable contribution to the incretin effect in health (16), but our observations (8,9,13) and those of others (17) suggest that GIP is the major contributor to the incretin effect when gastric emptying of glucose is ≤2 kcal/min and that the importance of GLP-1 is greater at loads ≥3 kcal/min (13). The current study confirmed that at rates of duodenal infusion ≤2 kcal/min, any GLP-1 release is modest and transient (9,18) while GIP increases in linear proportion to the rate of duodenal delivery (8,9). At higher duodenal glucose loads, the maximal rate of proximal small intestinal glucose absorption is probably exceeded so that a greater length, and more distal regions, of the gut—with a higher density of GLP-1-secreting L cells—are exposed (7). Postprandial GLP-1 secretion is exaggerated after gastric bypass surgery (19), which is associated with markedly accelerated gastric emptying of nutrient liquids (20).

In response to ID2, glucagon was suppressed, but with ID4, initial glucagon suppression was followed by a rise in controls, and there was no suppression in type 2 patients. The reason(s) underlying these discrepant responses is uncertain but could relate to *1*) divergent effects of GLP-1 to suppress glucagon and GIP and GLP-2 (cosecreted with GLP-1) to stimulate its release (21) or *2*) to gut-derived glucagon secretion (22).

While there was no difference in the incretin effect or GIGD between the two groups, the variance in the incretin response to ID2 was greater in the type 2 patients; the three patients who exhibited no incretin effect may have been less responsive to the insulinotropic effect of GIP. It would be of interest to evaluate patients with longstanding, complicated type 2 diabetes and determine whether chronic glycemic control impacts on the incretin effect. Interestingly, baseline GLP-1 levels were marginally greater in type 2 patients, although the overall GLP-1 response was slightly less.

In interpreting our observations, potential limitations should be recognized. We have assumed that the rate of duodenal glucose delivery is indicative of the effects of a comparable gastric emptying rate following oral ingestion of glucose, and it would be of interest to compare the incretin effect between individuals known to empty an oral glucose load at different rates. It would also be of interest to determine the effects of a combination of macronutrients, including fat, which is a potent stimulus for incretin hormone secretion (23). We included only

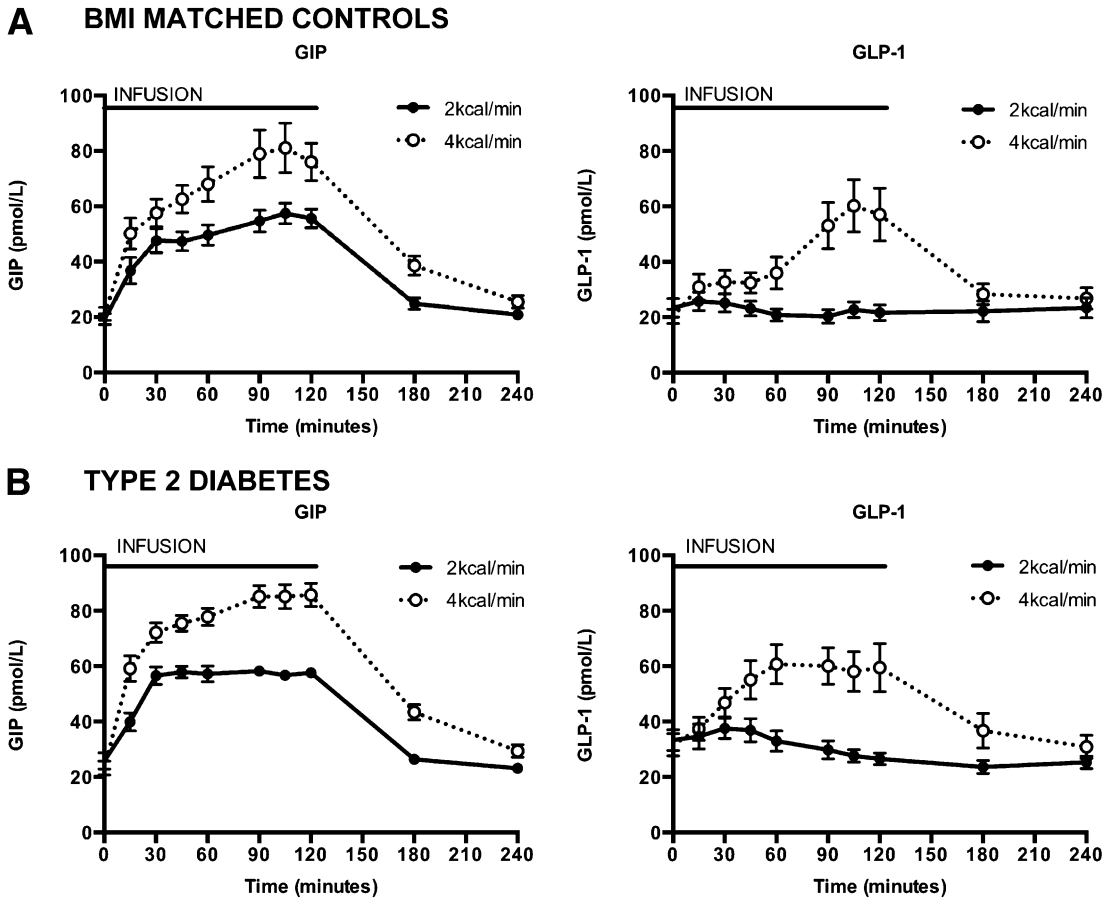

Figure 2—Plasma GIP and GLP-1 concentrations at baseline and in response to a 120-min intraduodenal glucose infusion at 2 and 4 kcal/min in (*A*) BMI-matched controls and (*B*) type 2 patients. Data are mean ± SEM. Filled circles with bold line, intraduodenal glucose infusion at 2 kcal/min; empty circles with dotted line, intraduodenal glucose infusion at 4 kcal/min.

males to exclude confounding effects of the menstrual cycle on gut motility and hormone secretion (7). While our type 2 patients were older than the controls, incretin responses are known to be comparable in healthy younger and older subjects (13).

In conclusion, in health and well-controlled type 2 diabetes, the magnitude of the incretin effect is dependent on the rate of small intestinal glucose exposure, implying that gastric emptying is a major determinant of the incretin effect in both health and type 2 diabetes.

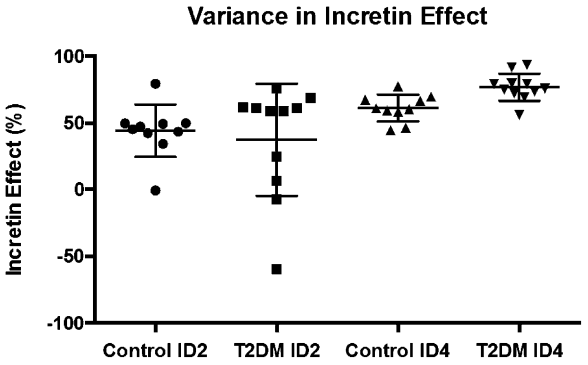

Figure 3—Variance in incretin effect in BMI-matched controls and type 2 patients. Data are mean ± SEM. T2DM, type 2 patients.

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access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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