Antidiabetic Actions of Endogenous and Exogenous GLP-1 in Type 1 Diabetic Patients With and Without Residual β-Cell Function

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OBJECTIVE—To investigate the effect of exogenous as well as endogenous glucagon-like peptide 1 (GLP-1) on postprandial glucose excursions and to characterize the secretion of incretin hormones in type 1 diabetic patients with and without residual β-cell function.

RESEARCH DESIGN AND METHODS—Eight type 1 diabetic patients with (T1D+), eight without (T1D−) residual β-cell function, and eight healthy matched control subjects were studied during a mixed meal with concomitant infusion of GLP-1 (1.2 pmol/kg/min), saline, or exendin 9-39 (300 pmol/kg/min). Before the meal, half dose of usual fast-acting insulin was injected. Plasma glucose (PG), glucagon, C-peptide, total GLP-1, intact glucose-dependent insulinotropic polypeptide (GIP), free fatty acids, triglycerides, and gastric emptying rate (GE) by plasma acetaminophen were measured.

RESULTS—Incretin responses did not differ between patients and control subjects. Infusion of GLP-1 decreased peak PG by 45% in both groups of type 1 diabetic patients. In T1D+ patients, postprandial PG decreased below fasting levels and was indistinguishable from control subjects infused with saline. In T1D− patients, postprandial PG remained at fasting levels. GLP-1 infusion reduced GE and glucagon levels in all groups and increased fasting C-peptide in T1D+ patients and control subjects. Blocking endogenous GLP-1 receptor action increased endogenous GLP-1 secretion in all groups and increased postprandial glucose, glucagon, and GE in T1D+ and T1D− patients. The insulinogenic index (the ratio of insulin to glucose) decreased in T1D+ patients during blockade of endogenous GLP-1 receptor action.

CONCLUSIONS—Type 1 diabetic patients have normal incretin responses to meals. In type 1 diabetic patients, exogenous GLP-1 decreases peak postprandial glucose by 45% regardless of residual β-cell function. Endogenous GLP-1 regulates postprandial glucose excursions by modulating glucagon levels, GE, and β-cell responsiveness to glucose. Long-term effects of GLP-1 in type 1 diabetic patients should be investigated in future clinical trials. *Diabetes* **60:1599–1607, 2011**

At time of diagnosis and during the first year, prevalence of residual β-cell function in patients with type 1 diabetes is nearly 100% (1,2). After alleviation of initial hyperglycemia with exogenous insulin, patients enter a remission period with improved β-cell function, where insulin treatment can be paused in up to 20–30% of the patients without loss of target glycemic control (3). Persistence of residual insulin secretion is associated with reduced risk of ketosis (4), lower HbA_{1c} levels (5), lower insulin doses, less risk of hypoglycemia, and reduced long-term complications (2,6). However, after disease duration of 5–10 years, the prevalence of residual β-cell function has declined to about 15% (2). Even though lack of insulin is considered to be the most important factor for the hyperglycemia in type 1 diabetic patients, other metabolic disturbances may also play a role: the glucagon response to carbohydrate and protein ingestion has been shown to be abnormal (7) and there is evidence that postprandial hyperglycemia is because of lack of insulin as well as inappropriately elevated glucagon levels (8,9). The gut hormone, glucagon-like peptide 1 (GLP-1), reduces glucagon levels, increases insulin secretion (10), and inhibits gastric emptying rate (GE), thereby reducing postprandial glucose excursions (11). The insulinotropic and the glucagonostatic properties of GLP-1 are glucose dependent (12), and exogenous GLP-1, therefore, does not produce hypoglycemia. Several studies have found lowering of fasting and postprandial glucose by GLP-1 or GLP-1 agonists in type 1 diabetic patients with (13–15) as well as without (16–19) residual β-cell function. Some studies suggested that the glucose lowering effect was because of the enhancement of insulin sensitivity (19), whereas others concluded that delay of gastric emptying (13,14) or reduction of glucagon levels (17) was the most important mechanism. In animal studies, treatment with GLP-1 or GLP-1 agonists has been shown to delay diabetes development or reverse recent onset diabetes in NOD mice (20), ascribed to an improved function of existing β-cells rather than through increments in β-cell mass. However, there is also evidence that GLP-1, in combination with gastrin, increases β-cell mass and restores normoglycemia in recent onset diabetic NOD mice (21) and that GLP-1 combined with gastrin is able to expand β-cell mass of human islets implanted under the renal capsule of immunodeficient diabetic NOD mice (22). In freshly isolated human islets, GLP-1 has been reported to inhibit β-cell apoptosis (23). However, in C-peptide–positive subjects with longstanding type 1 diabetes treated with exenatide for 6 to 9 months with or without daclizumab, insulin dose was significantly reduced, primarily because of the reduction of prandial insulin, but β-cell function was not improved

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(15). Four weeks of treatment with vildagliptin (a DPP-4 inhibitor that increases endogenous GLP-1 levels) in 11 well-controlled type 1 diabetic patients with longstanding disease decreased postmeal glucagon and glucose levels (24), and in adolescents with minimal or no endogenous insulin secretion treated with exenatide, postprandial glucose excursions were reduced despite 20% reduction of insulin dose (25). Therefore, GLP-1–based therapies have potential for treatment of type 1 diabetes alone or—more likely—in combination with insulin.

Because of controversies regarding secretion of incretin hormones in type 1 diabetes (26,27), assessment of the meal-related GLP-1 secretory responses in patients with diabetes is of interest (28). We therefore studied incretin secretion as well as the antidiabetic actions of both endogenously secreted and exogenously infused GLP-1 during a mixed meal in type 1 diabetic patients with and without residual β-cell function.

RESEARCH DESIGN AND METHODS

Subjects. Sixteen type 1 diabetic Caucasian patients and eight healthy control subjects were studied. Eight patients had residual β-cell function (T1D+), and eight were without (T1D−). All diabetic subjects were diagnosed between 8 and 40 years old; all were normal or underweight at diagnosis and were treated with multiple daily insulin injections from time of diagnosis. None had other diseases affecting glucose metabolism, overt diabetes complications, or symptoms of autonomic nerve dysfunction. Control subjects were healthy, had a normal oral glucose tolerance test, and no family history of diabetes. Patients and control subjects were matched with respect to age, sex, and BMI. T1D+ and T1D− patients had similar HbA_{1c}, age, and BMI, but T1D− patients had a longer duration of diabetes (10.6 ± 2.2 vs. 3.2 ± 0.7 years [mean ± SEM; $P < 0.05$]) and required more insulin (47.4 ± 3.5 vs. 31.9 ± 3.6 IE/day [mean ± SEM, $P < 0.05$]). Subject characteristics are presented in Table 1. The protocol was approved by the Ethical Committee for Region Hovedstaden and the Danish Data Protection Agency and conducted according to the principles of the Helsinki Declaration 2.

Glucagon test. To assess residual β-cell function, a glucagon stimulation test (GST) was performed at blood glucose levels above 7 mmol/L. Fasting plasma C-peptide concentrations were measured before and 6 min after intravenous bolus-injection of 1 mg glucagon (29). Patients were classified as T1D+ when stimulated plasma C-peptide concentration was ≥200 pmol/L and T1D− if below the detection limit of 0.1 ng/mL (~33 pmol/L) (See Table 1).

Experimental protocol. Patients were investigated after an overnight fast (10 h). The night before, they injected normal dose of long acting insulin. An individual difference in fasting plasma glucose of no more than 3 mmol/L between study days was allowed. Cannulas were inserted in forearms: one for infusions and one for blood sampling with arterialization of the venous blood using the heated hand technique. After basal blood sampling, GLP-1 (1.2 pmol/kg/min), saline, or the GLP-1 receptor antagonist exendin 9-39 (Ex9-39; 300 pmol/kg/min) was infused for 3 h. This dose of Ex9-39 blocks 95% of the insulinotropic and completely antagonizes the glucagonostatic effects of physiological levels of GLP-1 (30). Infusions were randomized and single blinded. Thirty minutes after infusion start (time zero), participants consumed a mixed meal of 2.036 KJ (~485 kcal: 23.6% protein, 15.2% fat, and 45.9% carbohydrates). One gram of acetaminophen was added to the yogurt, which was part of the meal. The whole meal was eaten within 20 min, and the yogurt was eaten within the first 10 min. Before the meal, patients injected half-dose of their usual fast acting insulin (Novorapid was injected at time zero, and Actrapid at time −15 min). For each subject, insulin dose, injection site, as well as exact time until meal completion were identical on the three study days. Blood samples for analysis of plasma glucose, C-peptide, insulin, free fatty acids (FFA), triglycerides (TG), glucagon, intact GIP, total GLP-1, and Ex9-39 were drawn at −45, −40, −35, −30 (infusion start), −20, −10, 0 (meal served), 10, 20 (meal finished), 30, 40, 50, 60, 75, 90, 105, 120, 150, and 180 min.

Analytical methods. Plasma glucose was analyzed bedside with an ABL800 blood gas analyzer (Radiometer, Copenhagen, Denmark). C-peptide responses to the GST were analyzed with solid-phase two-site chemiluminiscent immunometric assay (Immulite 2000), with a detection limit of 0.1 ng/mL (~33 pmol/L). Plasma C-peptide during the meal test was measured by autoDELPHIA automatic flouroimmunoassay (Wallac, Turku, Finland), with a detection limit of 17 pmol/L. Blood was collected in chilled heparinized tubes and centrifuged immediately, and plasma was held on ice and stored at −80°C until analyzed. Blood samples for glucagon, total GLP-1, and intact GIP were sampled in tubes containing EDTA and DPP-4 inhibitor (valpyr). The antiserum of glucagon assay (code no. 4305) is directed against the C-terminus of glucagon and reacts specifically with pancreatic glucagon (31). Unexpectedly, we observed weak cross-reaction with Ex9-39 in concentrations above 10^{-7} mol/L. All glucagon samples were therefore also measured with the LINCO assay (Milipore, Billerica, MA), which did not cross-react with Ex9-39 at all (own results) but had a poorer sensitivity. Total GLP-1 concentrations were measured using antiserum no. 89390, reacting equally with intact GLP-1 (7–36) amide and its primary *N*-terminally truncated metabolite GLP-1 (9–36) amide (32). Intact GIP was measured using antiserum no. 98171, reacting with the *N*-terminus of GIP, but not with the metabolite, GIP 3–42 (33). Detection limits and intra-assay coefficients were 1 and 2 pmol/L and less than 6% for GLP-1 and GIP, respectively. Ex9-39 was measured in EDTA plasma using antibody 3145 obtained from rabbits immunized with exendin 4. It shows 100% cross-reactivity with Ex9-39 but <0.01% cross-reactivity with GIP, glucagon, or GLP-1. Intra-assay coefficient of variation is <6%, with a detection limit of 0.5 pmol/L. Serum non-esterified FFA and TG were measured by oxidase colorimetric methods (Wako Chemicals, Neuss, Germany; and products VITROS Chemistry, Ortho-Clinical Diagnostics, Buckinghamshire, U.K.). Acetaminophen was analyzed by fluorescence polarization immunoassay technology (Abbott Laboratories, Abbot Park, IL).

Insulin secretion rates. For T1D+ patients and control subjects, prehepatic insulin secretion rates (ISR) were calculated through deconvolution of peripheral C-peptide concentrations using two-compartment model of C-peptide kinetics (34,35) and population-based C-peptide kinetics with adjustment for metabolic parameters such as age, sex, and BMI (36). ISR is expressed in units of picomoles × $kilograms^{-1}$ × $minutes^{-1}$.

Insulinogenic index. Insulinogenic index was calculated as the ratio of incremental integral ISR and plasma glucose from start of infusion (−30 min) until termination of the 3-h meal test (180 min), (ISR/PG210) during saline and Ex9-39 infusion, respectively.

Statistical analyses and calculations. Data are presented as mean ± SEM. Baseline values are calculated as the mean of the four fasting values. Integrated area under the plasma concentration curves (AUC) was calculated using the trapezoidal rule, with subtraction of baseline values when

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TABLE 1
Subject characteristics

	T1D− patients	T1D+ patients	Control subjects
Sex (male/female)	6/2	6/2	6/2
Age (years)	32.1 ± 2.2	26.9 ± 1.0	27.9 ± 5.4
BMI (kg/m^2)	23.5 ± 0.6	24.4 ± 2.8	23.8 ± 0.4
HbA_{1c} (%)	6.93 ± 0.20	6.35 ± 0.20	5.10 ± 0.10
Diabetes duration (years)	10.6 ± 2.2*	3.2 ± 0.7	—
ICA (positive/negative)	3/5	2/6	—
GAD-65 (positive/negative)	6/2	7/1	—
Insulin (IE/day)	47 ± 3.5*	31.9 ± 0.5	—
Meal insulin (IE) (study days)	3.80 ± 0.84*	2.6 ± 0.5	—
Stimulated C-peptide (pM)	<33*	456 ± 221	—

Data are mean ± SEM. Characteristics of type 1 diabetic patients without (−) and with (+) residual β-cell function and control subjects. GAD-65, glutamic acid decarboxylase-65; ICA, islet cell antibody. *$P < 0.05$ vs. T1D+.

calculating the incremental values. Normally distributed data were evaluated using Student *t* test; paired within groups and unpaired between groups and nonnormally distributed data using nonparametric tests. Three or more datasets were evaluated using one-way ANOVA between groups and repeated-measurements ANOVA within groups. Differences resulting in *P* values ≤ 0.05 were considered statistically significant.

RESULTS

GIP. Data are presented in Fig. 1*A–C* and Table 2. With saline, baseline intact GIP (iGIP) concentrations were 14–18 pmol/L and did not differ within or between the three groups on either study day, and peak plasma concentrations were 82 ± 8, 67 ± 7, and 85 ± 8 pmol/L in the T1D−, T1D+, and control subjects, respectively (P = 0.2). When compared with saline, plasma concentration of iGIP was significantly decreased in all three groups during GLP-1 infusion but did not change under Ex9-39 infusion (Table 2). Total $AUC_{0–180\ min}$ of iGIP during saline was 9.3 ± 1.0, 7.5 ± 0.4, and 10.2 ± 0.9 nmol/L × min, in T1D−, T1D+, and control subjects (P = 0.08).

GLP-1. Data are presented in Fig. 1*D–F* and Table 2. Mean baseline concentrations of GLP-1 were 15–20 pmol/L and did not differ within or between the three groups on the 3 study days. On the saline day, peak GLP-1 was 47 ± 5, 44 ± 6, and 54 ± 8 pmol/L (P = 0.5). Infusion of GLP-1 increased mean plasma levels of GLP-1 to ~200 pmol/L in all groups, and steady state plasma levels of GLP-1 were achieved before the meal was served. With saline, total $AUC_{0–180\ min}$ of GLP-1 did not differ between groups (P = 0.5) (Table 2). When compared with saline, Ex9-39 significantly increased secretion of GLP-1, but the GLP-1 response achieved during Ex9-39 did not differ between groups (P = 0.6) (Table 2).

Exendin 9-39. Data are presented in Fig. 2. On Ex9-39 days, plasma levels of Ex9-39 increased to 60 nmol/L in all three groups before the meal was served, corresponding to levels where insulinotropic effects of physiological GLP-1 levels was completely abolished (37). Ex9-39 levels continued to increase reaching plateau levels of 100–120 nmol/L about 120 min after the meal was served. Total $AUC_{0–180\ min}$ of Ex9-39 did not differ between groups; 16.8 ± 1.0, 17.3 ± 2.5, and 19.7 ± 1.3 nmol/L × min in T1D−, T1D+, and control subjects, respectively (P = 0.5). There was no correlation between Ex9-39 and glucagon concentrations.

Glucose. Data are presented in Fig. 3*A–C* and Table 3. Within each group, baseline plasma glucose (PG) did not differ between the 3 study days, but were higher in both diabetic groups compared with control subjects. During saline, peak PG were 6.9 ± 0.2 mmol/L in control subjects and 14.2 ± 0.9 and 16.2 ± 1.5 mmol/L in T1D+ and T1D− patients, respectively, but with GLP-1 infusion, peak PG decreased to 8.6 ± 1.3 and 7.5 ± 0.7 mmol/L in T1D− and T1D+ patients and to 5.8 ± 0.2 mmol/L in the control subjects (P < 0.01 vs. saline for all three groups). GLP-1 infusion decreased peak PG by 45.4 ± 17.7% in the T1D− patients and 45.1 ± 16.2% in the T1D+ patients compared with saline. Peak PGs in both diabetic groups were similar to control subjects receiving saline (P = 0.3). GLP-1 also significantly decreased total and incremental $AUC_{−30\ to\ 180\ min}$ of glucose in all three groups, and in both groups of patients, total $AUC_{−30\ to\ 180\ min}$ did not significantly differ from control subjects receiving saline (Table 3). Ex9-39 significantly increased total and incremental $AUC_{−30\ to\ 180\ min}$ in T1D+ patients, but not in T1D− patients or control subjects (Table 3). However, compared with saline, Ex9-39 significantly increased total $AUC_{0–180\ min}$ from 2.53 ± 0.23 to 2.90 ± 0.21 (P < 0.05) and from 2.19 ± 0.14 to 2.46 ± 0.14 (P < 0.01) mol/L × min in T1D− and T1D+ patients, respectively, whereas no differences were found in control subjects.

Glucagon. Glucagon data measured by the sensitive RIA (weak cross-reaction with Ex9-39) are presented in

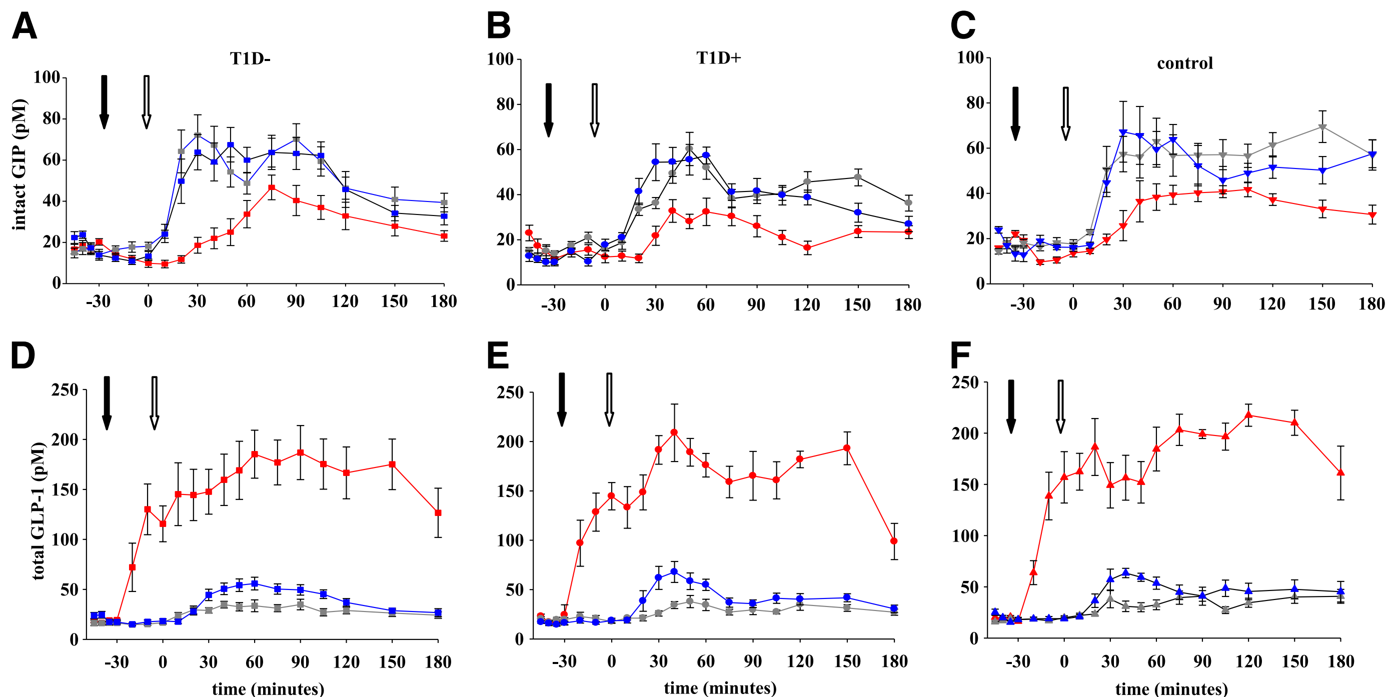

FIG. 1. ***A–C*: Intact GIP (pM). *D–F*: Total GLP-1 (pM) during infusion with GLP-1 (red symbols), saline (gray symbols), and Ex9-39 (blue symbols) in T1D− (■), T1D+ (●), and control subjects (▲) during a mixed meal test. Solid arrow: start of infusion; open arrow: meal start. T1D−: type 1 diabetic patients without residual β-cell function; T1D+: type 1 diabetic patients with residual β-cell function.**

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TABLE 2
Postprandial incretin responses related to infusion type

	T1D− patients	T1D+ patients	Control subjects	P between groups
GIP				
GLP-1	5.13 ± 0.6**	4.13 ± 0.45**	6.04 ± 0.5**	0.07
Saline	9.28 ± 1.0	7.48 ± 0.4	10.20 ± 0.9	0.08
Ex9-39	8.85 ± 1.0	7.15 ± 0.7	9.12 ± 0.7	0.2
GLP-1				
GLP-1	29.60 ± 4.1**	30.30 ± 2.0**	33.76 ± 1.9**	0.5
Saline	5.20 ± 0.5	5.32 ± 0.6	6.16 ± 0.6	0.5
Ex9-39	7.00 ± 0.5**	7.56 ± 0.9**	8.29 ± 1.1*	0.6

Data are mean ± SEM. Total integrated AUC (TAUC; 0–180 min) of total GLP-1 and iGIP (nM × min) during infusion with GLP-1, saline, or Ex9-39 in type 1 diabetic patients without (−) and with (+) residual β-cell function and control subjects. *$P \leq 0.05$ vs. saline; **$P < 0.01$ vs. saline within the same group; no significant differences were found between groups at any infusion type.

Fig. 3*D–F*, Table 3, and described below. Glucagon data measured by the LINCO assay (no cross-reaction with Ex9-39) are presented in Supplementary Table 1 and Fig. 1. Mean baseline glucagon was 5.2 ± 1.5, 8.3 ± 0.6, and 6.2 ± 0.7 pmol/L (P = 0.3) in the T1D−, T1D+, and control subjects. With saline, neither incremental nor total $AUC_{-30 \text{ to } 180 \text{ min}}$ differed between groups (P = 0.9 and P = 0.2, respectively; Table 3). When compared with saline, GLP-1 infusion decreased total and incremental $AUC_{-30 \text{ to } 180 \text{ min}}$ of glucagon in all three groups (Table 3), mainly because of decrements in postprandial levels since GLP-1 also decreased total $AUC_{0\text{–}180 \text{ min}}$ from 1.42 ± 0.24 to 0.55 ± 0.12 (P = 0.001), from 2.27 ± 0.39 to 1.34 ± 0.27 (P = 0.002), and from 1.74 ± 0.36 to 0.86 ± 0.10 (P = 0.016) in T1D−, T1D+, and control subjects, respectively. Ex9-39 significantly increased total and incremental $AUC_{-30 \text{ to } 180 \text{ min}}$ of glucagon in the patients with diabetes regardless of glucagon assay used (Table 3 and Supplementary Data). The increase was mainly due to increments in postprandial levels; total $AUC_{0\text{–}180 \text{ min}}$ increased to 3.38 ± 0.26 ($P < 0.001$), 4.40 ± 0.69 ($P < 0.001$), and 2.74 ± 0.21 (P = 0.018) (vs. saline) in T1D−, T1D+, and control subjects. The supplementary glucagon data (without cross-reaction with Ex9-39) shows that Ex9-39 significantly increased total and incremental AUC of glucagon in both groups of type 1 diabetic patients and increased incremental $AUC_{-30 \text{ to } 180 \text{ min}}$ in control subjects.

C-peptide. C-peptide data are presented in Fig. 3*G–I* and Table 3. None of the T1D− patients displayed C-peptide levels above 33 pmol/L. During GLP-1 infusion, total and incremental $AUC_{-30 \text{ to } 180 \text{ min}}$ of C-peptide decreased significantly in T1D+ patients (Table 3). However, fasting C-peptide increased transiently with incremental $AUC_{-30 \text{ to } 0 \text{ min}}$ of 0.60 ± 0.24 (saline) vs. 4.39 ± 2.02 (GLP-1) nM × min (P = 0.02). Ex9-39 decreased total and tended to decrease incremental $AUC_{-30 \text{ to } 180 \text{ min}}$, of C-peptide ($P$ = 0.05 and P = 0.06, respectively), and total $AUC_{0\text{–}180 \text{ min}}$ also significantly decreased from 103.8 ± 33.6 (saline) vs. 90.6 ± 30 (Ex9-39) (P = 0.02).

In control subjects, C-peptide showed the same pattern as in T1D+ patients; GLP-1 decreased total $AUC_{-30 \text{ to } 180 \text{ min}}$ (Table 3), but increased fasting incremental $AUC_{-30 \text{ to } 0 \text{ min}}$ of C-peptide from −0.61 ± 1.13 (saline) to 7.68 ± 2.7 (GLP-1) nM × min ($P < 0.01$). There were no significant differences in fasting or postprandial C-peptide responses between Ex9-39 and saline, but C-peptide tended to be lower during Ex9-39 (Table 3).

ISR. In T1D+ patients, Ex9-39 tended to decrease incremental $AUC_{-30 \text{ to } 180 \text{ min}}$ of ISR from 0.28 ± 0.9 to 0.22 ± 0.1 nmol × kg^{-1} (P = 0.06; vs. saline) but no difference was found in the control subjects (P = 0.5). However, in T1D+ patients, the insulinogenic index, calculated as the ratio of incremental integral ISR and PG from −30 to 180 min (ISR/PG210), decreased with Ex9-39:

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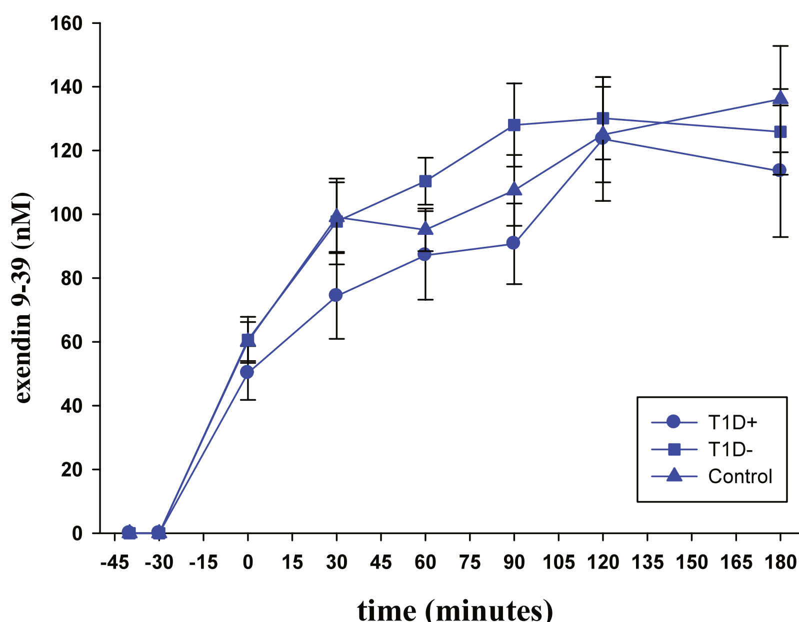

FIG. 2. Plasma Ex9-39 (nM) on the day assigned to Ex9-39 infusion (blue symbols) in T1D− (■), T1D+ (●) and control subjects (▲). Solid arrow: start of infusion; open arrow: meal start. T1D−: type 1 diabetic patients without residual β-cell function; T1D+: type 1 diabetic patients with residual β-cell function.

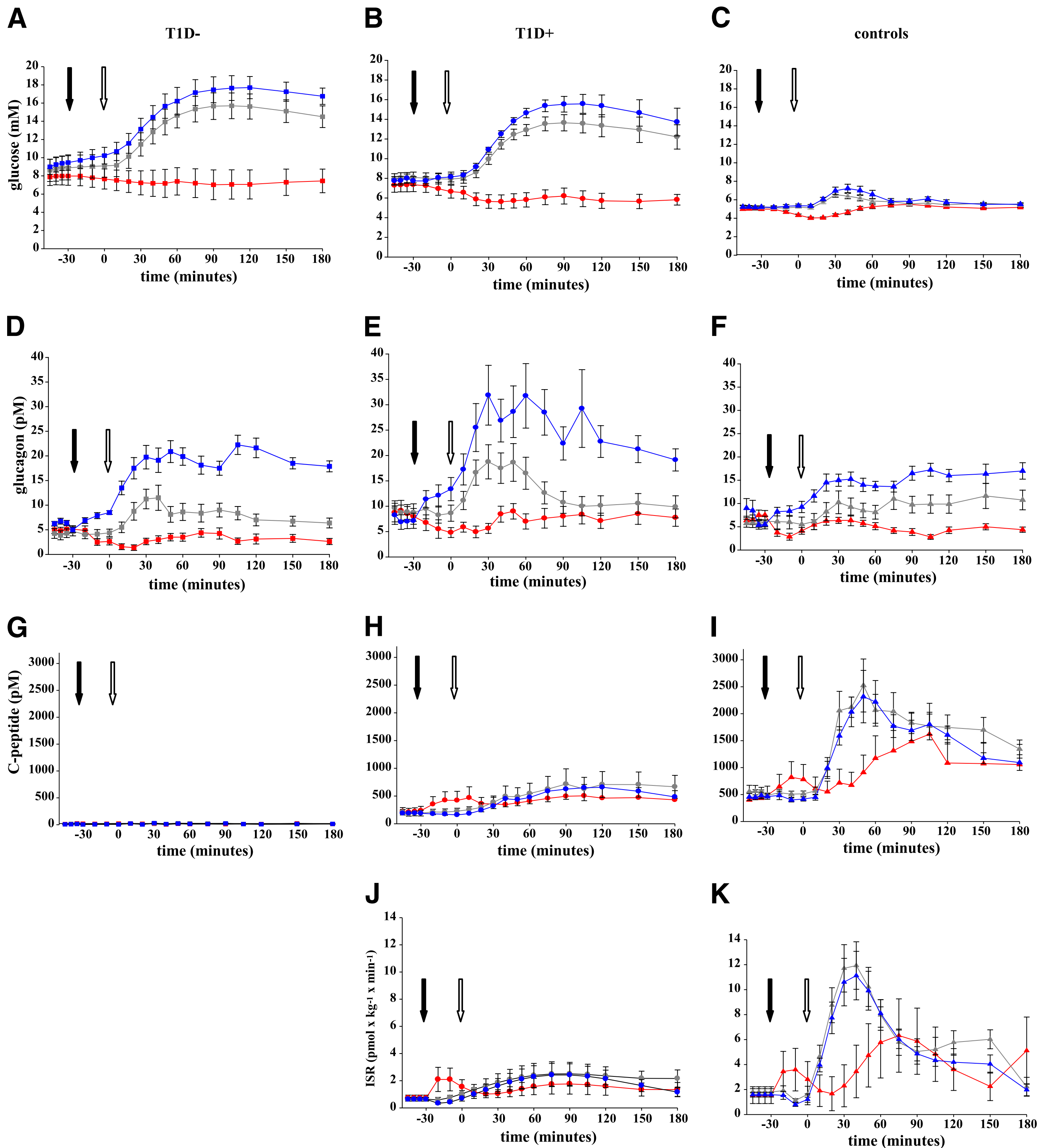

FIG. 3. ***A–C*****: Plasma glucose (mM).** ***D–F*****: Plasma glucagon (pM).** ***G–I*****: Plasma C-peptide (pM).** ***J*** **and** ***K*****: ISR (pmol × kg^{-1} × min^{-1}) during infusion with GLP-1 (red symbols), saline (gray symbols), and Ex9-39 (blue symbols) in T1D− (■), T1D+ (●), and control subjects (▲) during a mixed meal test. Solid arrow: start of infusion; open arrow: meal start. T1D−: type 1 diabetic patients without residual β-cell function; T1D+: type 1 diabetic patients with residual β-cell function.**

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0.44 ± 0.17 (saline) vs. 0.24 ± 0.11 (Ex9-39) pmol × kg^{-1} × min^{-1}/mmol × L^{-1} (P < 0.01). In control subjects the change in (ISR/PG210) was not significant (P = 0.4). Time courses of ISR for T1D+ and control subjects are shown in Fig. 3*J* and *K*.

GE. With saline, time to peak of plasma acetaminophen was 60 ± 8, 62 ± 13, and 82 ± 14 min (P = 0.5) and $AUC_{0–180\ min}$ was 7.91 ± 0.51, 7.92 ± 0.32, and 8.62 ± 0.80 nmol/L × min (P = 0.6) in T1D−, T1D+, and control subjects, respectively. With GLP-1, $AUC_{0–180\ min}$ decreased to 1.99 ± 0.90,

TABLE 3
Hormone responses

	T1D− patients			T1D+ patients			Control subjects		
	GLP-1	Saline	Ex9-39	GLP-1	Saline	Ex9-39	GLP-1	Saline	Ex9-39
Glucose									
IAUC	−0.14 ± 0.10**†	0.93 ± 0.20	1.17 ± 0.13 (NS)	−0.27 ± 0.11**†	0.73 ± 0.14	1.07 ± 0.10*	−0.01 ± 0.03**	0.08 ± 0.03	0.14 ± 0.03 (NS)
TAUC	1.54 ± 0.30**¶	2.80 ± 0.30	3.16 ± 0.23 (P = 0.06)	1.27 ± 0.13***¶	2.43 ± 0.15	2.70 ± 0.15*	1.04 ± 0.02***	1.18 ± 0.01	1.24 ± 0.04 (NS)
Glucagon									
IAUC	−0.39 ± 0.1**	0.66 ± 0.18	2.31 ± 0.23***	−0.27 ± 0.14*	0.64 ± 0.19	3.21 ± 0.47***	−0.48 ± 0.09**	0.70 ± 0.22	1.78 ± 1.44***
TAUC	0.67 ± 0.14***	1.55 ± 0.25	3.59 ± 0.27***	1.53 ± 0.31**	2.53 ± 0.44	4.74 ± 0.75**	0.99 ± 0.12**	1.92 ± 0.41	2.98 ± 0.23*
C-peptide									
IAUC	—	—	—	43.7 ± 19.2*	70.1 ± 26.9	56.0 ± 22 (P = 0.06)	121 ± 43 (NS)	209 ± 34.6	187 ± 20.2 (NS)
TAUC	—	—	—	90.2 ± 33.7*	110 ± 35.0	95.8 ± 31*	213 ± 75*	321 ± 44.9	284 ± 27.7 (NS)
ISR									
IAUC	—	—	—	0.16 ± 0.1*	0.28 ± 0.9	0.22 ± 0.1 (P = 0.06)	0.47 ± 0.1 (NS)	0.83 ± 0.2	0.72 ± 0.1 (NS)
TAUC	—	—	—	0.32 ± 0.1*	0.41 ± 0.1	0.35 ± 0.1*	0.80 ± 0.1*	1.21 ± 0.2	1.05 ± 0.1 (NS)

Data are mean ± SEM. TAUC and incremental integrated AUC (IAUC), respectively (−30 to 180 min), of plasma glucose (M × min), C-peptide (nM × min), ISR (nmol × kg^{-1}), and glucagon (nM × min) during infusion with GLP-1, saline, or Ex9-39 in type 1 diabetic patients without (−) and with (+) residual β-cell function and control subjects. NS, nonsignificance vs. saline in the same group. *$P \le 0.05$ vs. saline; **$P < 0.01$ vs. saline; ***$P < 0.001$ vs. saline within the same group; †$P \le 0.05$ vs. control subjects with saline; ¶P = NS vs. control subjects with saline.

2.09 ± 0.48, and 4.61 ± 1.22 nM × min ($P < 0.01$, $P < 0.01$, and $P < 0.05$ vs. saline) in T1D−, T1D+, and control subjects, respectively. Time-to-peak increased to 159 ± 14, 140 ± 17, and 150 ± 15 min ($P < 0.05$ compared with saline). Ex9-39 decreased time-to-peak by about 20 min in all three groups, but the difference reached significance only in the T1D− group. However, when the two diabetic groups were considered together, Ex9-39 shifted $AUC_{0–180\ min}$ from 7.9 ± 0.3 to 8.6 ± 0.8 nmol/L × min (P = 0.046) and time-to-peak from 61 ± 7 to 42 ± 5 min (P = 0.02 compared with saline).

Effect of endogenous and exogenous GLP-1 on plasma lipids. Data are presented in Fig. 4*A–F*. Fasting TG concentrations tended to be higher in the healthy subjects (1.1 ± 0.2 mmol/L) than in T1D+ (0.7 ± 0.09 mmol/L) and T1D− (0.6 ± 0.08 mM) patients, on the saline day (P = 0.08). Neither GLP-1 nor Ex9-39 infusions significantly affected TG concentrations. Fasting FFA did not differ within or between groups (fasting FFA ~0.4–0.5 mmol/L) except for T1D+ subjects on the day assigned to Ex9-39 where fasting FFA levels were almost twice as high (~0.7 mmol/L). FFA concentrations decreased in all groups after ingestion of the meal regardless of infusion type.

DISCUSSION

We conclude that incretin responses to a mixed meal test are similar between type 1 diabetic patients with as well as without residual β-cell function and healthy subjects. This is in contrast with results from Lugari et al. (26), who reported absence of postprandial GLP-1 responses in type 1 diabetes, but in agreement with data from Vilsbøll et al. (27), who found incretin responses in type 1 diabetic patients equal to that of lean healthy controls. We have no clear explanation for this discrepancy other than differences in methodology or subject characteristics (28). Our study confirms that chronic hyperglycemia in lean type 1 diabetic patients in otherwise good metabolic control does not decrease L-cell secretory response to a mixed meal. Blocking the effect of endogenous GLP-1 with Ex9-39 increased postprandial GLP-1 consistent with earlier findings in healthy subjects (38) and in type 2 diabetic patients (39). This could theoretically be the result of *1*) increases in GE (with more nutrients reaching the intestine and the L-cells [40]), *2*) blockade of a negative feedback system between the GLP-1 and the L-cell (41), *3*) changes in plasma clearance of GLP-1 (because the GLP-1 receptor [GLP-1R] is expressed in tubular cells of the kidneys and might be involved in the very high renal extraction of GLP-1 [42]), and *4*) cross-reactions with Ex9-39 in the GLP-1 assay as previously described (37), but this was excluded in the current study. During infusion of saline, GIP increased to the same extent in the three groups but was clearly decreased during GLP-1 infusion, presumably because of delayed GE.

GLP-1 infusion, despite a 50% dose-reduction of usual fast-acting prandial insulin, effectively reduced postprandial glucose-excursions in T1D+ and T1D− patients. In T1D+ patients postprandial glucose decreased and became indistinguishable from those of healthy subjects receiving saline, and in T1D− patients, it remained at fasting values. This clearly antidiabetic effect is in accordance with a previous study (19), where GLP-1 infusion decreased the isoglycemic meal-related insulin requirement by 50%, which was thought to be because of increased glucose utilization as well as a decrease in glucagon release. However, another study did not find evidence of an

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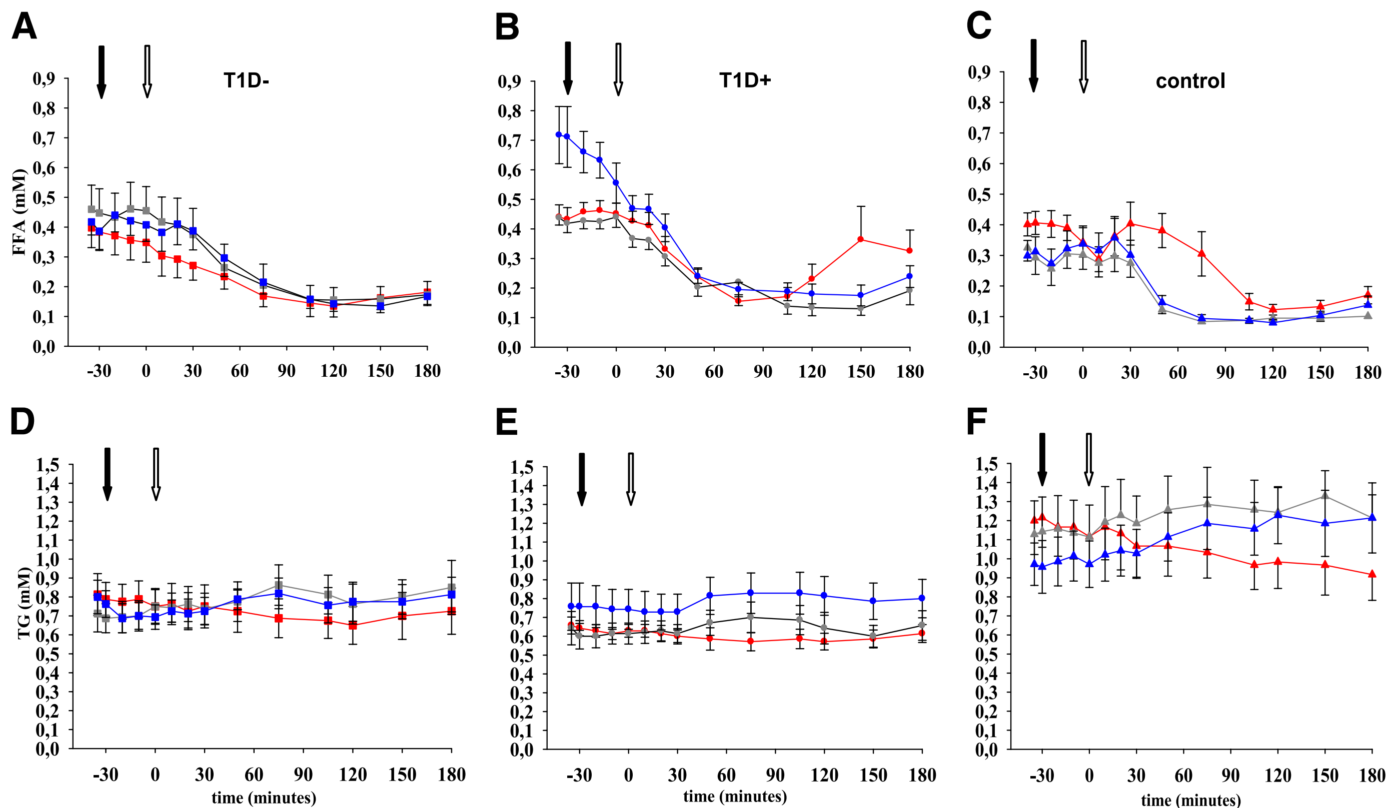

FIG. 4. *A–C*: FFA (mM). *D–F*: TG (mM) during infusion with GLP-1 (red symbols), saline (gray symbols), and Ex9-39 (blue symbols) in T1D− (■), T1D+ (●), and control subjects (▲) during a mixed meal test. Solid arrow: start of infusion; open arrow: meal start. T1D−: type 1 diabetic patients without residual β-cell function; T1D+: type 1 diabetic patients with residual β-cell function.

improvement of insulin sensitivity by GLP-1 in type 1 diabetic patients (43). In yet another study of type 1 diabetic patients with residual β-cell function who omitted their prandial insulin, postprandial glucose elevations were completely prevented without stimulation of endogenous insulin, whereas glucagon and pancreatic polypeptide (PP) were suppressed (13). Six to nine months of exenatide treatment in patients with longstanding type 1 diabetes and measurable C-peptide levels decreased preprandial insulin by 30% but did not affect β-cell function or glucagon levels (15). The patients' C-peptide level in that study was relatively small (mean stimulated of about 270 pmol/L). Our T1D+ patients had stimulated C-peptide levels about twice as high, which could explain the difference in effect of GLP-1 treatment on glucose metabolism. However, we also found a strong GLP-1–induced glucose lowering effect in our T1D− patients. The remaining β-cells in our T1D+ patients responded well to GLP-1 stimulation, as clearly shown in the premeal period (where PG levels were still above 6 mmol/L), and improved insulin secretion may have contributed to the reduction of postprandial glucose excursions. It is possible that the glucose lowering effect observed here—regardless of residual insulin secretion—is mainly caused by the combination of reduced glucagon levels and inhibition of GE. The observation that DPP-4 inhibition reduces postprandial glucose excursions in type 1 diabetic patients through β-cell independent suppression of glucagon (24) but has no or little effect on GE (44), supports a particular role for glucagon suppression. Blocking the effect of endogenous GLP-1 decreased postprandial (0–180 min) C-peptide level in the T1D+ patients despite slightly elevated PG values, suggesting that endogenously secreted GLP-1 might affect β-cell responsiveness to glucose. Accordingly, Ex9-39 significantly decreased the insulinogenic index (PG/ISR210) in the T1D+ patients and increased postprandial glucagon levels most pronounced in the patients with diabetes. Thus endogenous GLP-1 seems to participate in the regulation of postprandial glucagon secretion in type 1 diabetic patients and enhances the β-cell responsiveness to glucose during a mixed meal. The absence of an effect of GLP-1R blockade on glucose excursions and β-cell function in control subjects may be because of the low glycemic index of the meal resulting in modest glucose excursions and therefore reduced insulinotropic effects of incretin hormones. Furthermore, because insulinotropic effect of GIP is severely impaired in type 1 diabetes (45), but explains about half of the incretin effect in healthy humans (46), Ex9-39 (which only antagonizes GLP-1, but does not affect insulinotropic action of GIP) might abolish the incretin effect relatively more in the patients as observed.

As expected, GLP-1 strongly decreased GE in all groups accompanied by a reduction of GIP secretion. Ex9-39 accelerated GE in type 1 diabetic patients but did not significantly affect GE rate in control subjects. Using the same antagonist but scintigraphy for detection of emptying rates, Deane et al. (47) found accelerated GE in healthy humans, influencing glucose absorption and postprandial glycemia. Therefore, insufficient statistical power may be partly responsible for the insignificant effect observed here. Furthermore, in healthy subjects and in type 1 diabetic patients, hyperglycemia decelerates GE, whereas hypoglycemia increases it (48–51), and differences in glucose levels by infusion type may therefore indirectly have affected GE in our patients.

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FFA decreased during the meal in all three groups regardless of infusion type, but we have no explanation for the elevated fasting FFA in the T1D+ patients on the Ex9-39 day other than natural variation. It has been shown that treatment with GLP-1 and DPP-4 inhibitors reduces intestinal lipid production and absorption, preventing postprandial rise in TG (52,53). In our study, TG was unaffected by the meal as well as by infusion type, except for a weak (nonsignificant) trend of lower postprandial values during GLP-1 infusion in all groups. The tendency of lower TG levels in the patients compared with control subjects is probably the result of exogenous insulin (52). In a recent study, GLP-1R signaling was found to be essential for the control of postprandial lipoprotein biosynthesis and secretion at least in rodents (54), but our results suggest that this may not apply to humans.

Conclusions. We conclude that type 1 diabetic patients have normal incretin responses to a mixed meal and that infusion of GLP-1 at the rate we used decreases peak postprandial glucose by approximately 45% in type 1 diabetic patients regardless of β-cell function. Endogenously secreted GLP-1 plays a role in the regulation of postprandial glucose excursions in type 1 diabetes by modulating glucagon levels, GE rate, and β-cell responsiveness to glucose. We suggest that long term effects of GLP-1–based therapies should be investigated in future clinical trials of type 1 diabetic patients with as well as without residual β-cell function.

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U.K. researched data and wrote the manuscript. J.J.H. and S.M. reviewed and edited the manuscript and contributed to discussion.

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