No Acute Effects of Exogenous Glucose-Dependent Insulinotropic Polypeptide on Energy Intake, Appetite, or Energy Expenditure When Added to Treatment With a Long-Acting Glucagon-Like Peptide 1 Receptor Agonist in Men With Type 2 Diabetes

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OBJECTIVE

Dual incretin receptor agonists in clinical development have shown reductions in body weight and hemoglobin A_{1c} (HbA_{1c}) in patients with type 2 diabetes, but the impact of glucose-dependent insulinotropic polypeptide (GIP) receptor activation remains unclear. Here, we evaluated the effects of high-dose exogenous GIP on energy intake, energy expenditure, plasma glucose, and glucose-regulating hormones in patients with type 2 diabetes treated with a long-acting glucagon-like peptide 1 receptor (GLP-1R) agonist.

RESEARCH DESIGN AND METHODS

In a randomized, double-blind design, men with type 2 diabetes ($n = 22$, mean ± SEM HbA_{1c} 6.8 ± 0.1% [51 ± 1.5 mmol/mol]) treated with metformin and long-acting GLP-1R agonists were subjected to two 5-h continuous infusions (separated by a washout period of ≥3 days): one with GIP (6 pmol/kg/min) and another with saline (placebo). After 60 min of infusion, a liquid mixed-meal test was performed, and after 270 min of infusion, an ad libitum meal was served for evaluation of energy intake (primary end point).

RESULTS

Energy intake was similar during GIP and placebo infusion (648 ± 74 kcal vs. 594 ± 55 kcal, respectively; $P = 0.480$), as were appetite measures and energy expenditure. Plasma glucagon and glucose were higher during GIP infusion compared with placebo infusion ($P = 0.026$ and $P = 0.017$) as assessed by area under the curve.

CONCLUSIONS

In patients with type 2 diabetes, GIP infusion on top of treatment with metformin and a long-acting GLP-1R agonist did not affect energy intake, appetite, or energy expenditure but increased plasma glucose compared with placebo. These results indicate no acute beneficial effects of combining GIP and GLP-1.

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Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are the two known incretin hormones in man (1). In healthy individuals, the two hormones have additive insulinotropic effects and account for 40–70% of the total insulin secretion following an oral glucose tolerance test (1–3). GLP-1 furthermore acts as a satiety-promoting hormone (4), and GLP-1 receptor (GLP-1R) agonists with plasma glucose–lowering and body weight–reducing effects have been developed for the treatment of type 2 diabetes and obesity. In contrast, no GIP receptor (GIPR) agonists are currently available (5). The main obstacle for the utilization of GIPR agonism as a treatment of type 2 diabetes is the diminished insulinotropic effect of GIP observed in patients with type 2 diabetes (6,7), which seems to be driven by the hyperglycemic state (8) and thus appears partly restorable when hyperglycemia is corrected (9,10). Another obstacle is the uncertainty as to whether GIP is an obesity-promoting hormone (5). Hence, diet-induced body weight gain in mice has been prevented both by elimination of GIPR activation as well as by GIP overexpression (11–15). In patients with type 2 diabetes, acute coadministration of GIP and GLP-1 does not induce an additional glucose-lowering effect compared with GLP-1 alone (16–19). Also, GIP infusion does not result in a reduction in energy intake or increase in energy expenditure, which would indicate a later body weight loss (19,20). Nevertheless, a dual GIPR/GLP-1R agonist in clinical development (LY3298176 [tirzepatide]) was recently reported to lower body weight as well as to improve glycemic control compared with GLP-1R agonism alone in patients with type 2 diabetes (21). These results support earlier findings of improved glycemic control in patients with type 2 diabetes treated with dual GIPR/GLP-1R agonist in clinical trials (22,23). Furthermore, the results are in line with an increasing number of rodent studies reporting additive body weight– and plasma glucose–lowering effects of combined GIPR and GLP-1R activation compared with GLP-1R activation alone (22,24,25). Thus, a renewed interest in GIPR agonism as a potentially effective add-on to GLP-1R agonism in type 2 diabetes has been introduced, but the contribution of GIPR activation to the results obtained with the GIPR/GLP-1R dual agonists remains uncertain in humans (5,26). It has been hypothesized that the complementary benefits of dual GIPR/GLP-1R agonism compared with GLP-1R agonism alone might be mediated by an alleviation of GIP resistance following prolonged priming by GLP-1R activation (5). Also, the glycemic control prior to GIPR/GLP-1R activation seems important, as the dual GIPR/GLP-1R agonist NNC0090-2746 was reported to induce the greatest reductions in body weight in patients with baseline hemoglobin A_{1c} (HbA_{1c}) <8.5% (<69 mmol/mol) (23).

In the current study, we evaluated the effects of a 5-h high-dose GIP infusion on energy intake (primary end point), energy expenditure, circulating concentrations of glucose, cholesterols, triglycerides, and glucose-regulating hormones as well as postprandial gastric emptying and gallbladder motility in patients with type 2 diabetes with HbA_{1c} <8.5% (<69 mmol/mol) all in stable treatment with metformin and a long-acting GLP-1R agonist. We hypothesized that prolonged treatment with a long-acting GLP-1R agonist preceding GIP administration would prime the suggested beneficial effects of GIP, i.e., reductions in energy intake and plasma glucose.

RESEARCH DESIGN AND METHODS

Approvals and Registrations

The study was conducted at Center for Clinical Metabolic Research, Gentofte Hospital, in accordance with the Declaration of Helsinki. Oral and written consent was obtained from all participants before inclusion. The study was approved by the Scientific-Ethical Committee of the Capital Region of Denmark (identification no. H-16031728, amendment 660103 and 62994) and the Danish Data Protection Agency (journal no. BFH-2017-009) and registered at ClinicalTrials.gov (reg. no. NCT03526289).

Study Participants

Eligible study participants were Caucasian men, age 18–70 years, with type 2 diabetes, HbA_{1c} <8.5% (<69 mmol/mol), and BMI 25–40 kg/m^2, treated for ≥3 months with stable doses of metformin and a long-acting GLP-1R agonist. Exclusion criteria included treatment with other glucose-lowering drugs, other medical treatments that could not be paused for a minimum of 12 h, tobacco smoking, allergy or intolerance to ingredients included in the standardized meals, anorexia, bulimia or binge eating disorder, liver disease, nephropathy or anemia, any current or prior gastrointestinal disease that could interfere with the end points variables, and any physical or psychological condition that the investigator felt would interfere with trial participation.

Experimental Procedures

Each participant underwent two experimental days: one day of GIP infusion and one day of placebo infusion. The two days were performed in a randomized order, blinded for the participant as well as the investigator, and with an interposed washout period of at least 72 h. For a standardized baseline balance of macronutrients, the participants were instructed to abstain from alcohol and strenuous physical exercise 48 h prior to each experimental day and to consume a standardized meal for dinner the evening before each experimental day between 6:00 and 8:00 P.M. (pasta Bolognese, 558 g, with energy content 753 kcal, 44% of energy [E%] from carbohydrates, 37 E% fat, and 16 E% protein). After the meal, the participants were instructed to fast overnight. To uniformize study conditions, we paused all oral agents (including metformin) in the fasting period, whereas the GLP-1R agonist treatment was continued as prescribed. On the experimental days, the participants were placed in a semirecumbent position resting in a hospital bed and cannulas were inserted in the cubital veins: one for infusion and one in the contralateral arm for blood sampling; the latter was wrapped in a heating pad for arterialization of the venous blood. At time point 0 min, infusion of either GIP (8 pmol/kg/min for 10 min followed by 6 pmol/kg/min) or placebo (isotonic sodium chloride) was started (Fig. 1*A*). At time point 60 min, the participants ingested a standardized liquid mixed meal (Nutricia Nutridrink, 200 mL [energy content 300 kcal, with 49 E% from carbohydrates, 35 E% fat, and 16 E% protein]; Nutricia) to which was added 1.5 g acetaminophen dissolved in 100 mL water for evaluation of gastric emptying. At time point 270 min, an ad libitum meal of pasta Bolognese (energy content per 100 g: 135 kcal, with 44 E% from carbohydrates, 37 E% fat, and 16 E% protein) was served together with 500 mL water. The ad libitum serving was weighed before and after meal ingestion, and energy intake was calculated from the weight difference. The participants were allowed 30 min to eat and drink and were instructed to stop when they felt comfortably full.

Infusions

Synthetic human GIP (1-42) (~96% purity) was purchased from Bachem

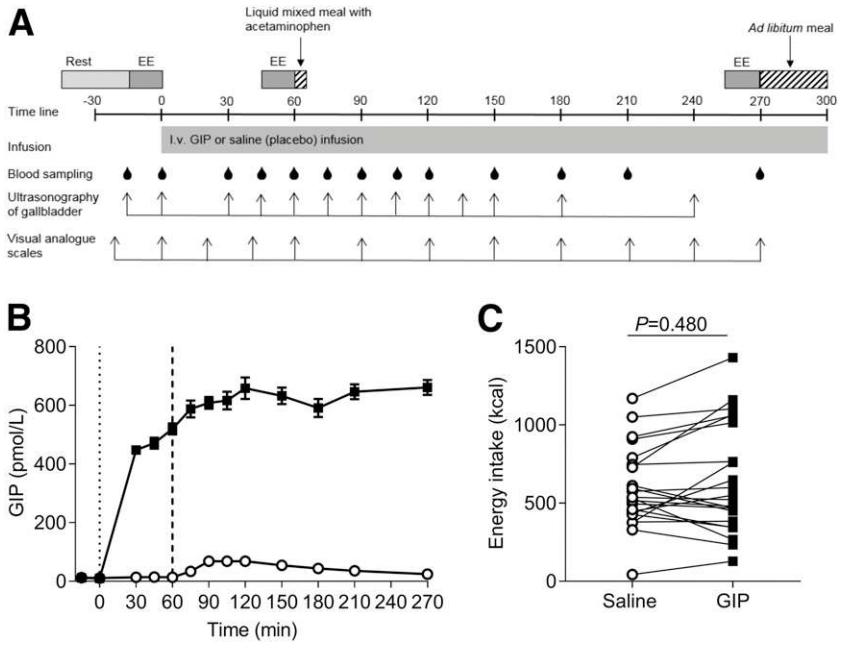

Figure 1—Overview over experimental setup during the two study days (*A*), plasma excursion of total GIP (*B*), and energy intake from the ad libitum meal served after 270 min of infusion (*C*). Data are means ± SEM ($N = 22$). *B* and *C*: ■, infusion with GIP; ○, infusion with saline (placebo). Thin dotted line at time point 0 min indicates time for start of GIP infusion (8 pmol/kg/min from 0 to 10 min and 6 pmol/kg/min for the remainder of the experimental day). Bold dashed line indicates ingestion of the standardized liquid mixed meal. *P* value is from Student paired *t* test with adjustment for multiple testing using the Benjamini-Hochberg procedure. EE, energy expenditure.

(Bubendorf, Switzerland). The peptide was dissolved in sterilized water with 0.5% human serum albumin (CSL Behring, Lyngby, Denmark) at the pharmacy of the Capital Region of Denmark, Herlev, Denmark. The solution was dispensed into vials with sufficient peptide per vial for one study day; the vials were tested for endotoxins and sterility and stored at −20°C until use. In the morning of the experimental days, a person not otherwise involved in the study thawed and diluted the peptide solution under sterile conditions in saline (isotone sodium chloride; B. Braun Medical Inc., Melsungen, Germany) with 0.5% human albumin (5% solution) (CSL Behring) to a total of 250 mL or prepared placebo infusate consisting of 250 mL saline with 0.5% human albumin.

Blood Samples and Analyses

Blood samples were drawn regularly throughout the study days. In total, ~250 mL blood was drawn per participant per study day (see Fig. 1*A*). For glucose measurements, blood was sampled into fluoride tubes and centrifuged immediately at 7,400*g* for 45 s at room temperature and measured bedside by the glucose oxidase method (model 2900 STAT Plus analyzer; YSI, Yellow Springs, OH). For measurements of serum insulin and C-peptide, blood was collected into tubes containing serum clot activator and was left to coagulate for at least 20 min at room temperature. For analyses of GIP, GLP-1, glucagon, free fatty acids, and glycerol blood were collected into chilled tubes containing EDTA and a specific dipeptidyl peptidase 4 inhibitor (valine-pyrrolidide [0.01 mmol/L final concentration], a gift from Novo Nordisk A/S, Måløv, Denmark) and placed on ice immediately after sampling. For measurements of triglycerides, cholesterols, and acetaminophen, blood was sampled into lithium-heparin tubes. All tubes were centrifuged for 20 min at ~2,900*g* and 4°C. Serum and plasma samples were stored at −80°C and −20°C, respectively, until batch analyses could be performed. Serum insulin and C-peptide were measured with a two-sided electrochemiluminescence immunoassay (ADVIA Centaur XP; Siemens Healthcare, Ballerup, Denmark). The plasma concentrations of total GIP, total GLP-1, and glucagon were analyzed by radioimmunoassays using the antibodies 80867, 89390, and 4305, respectively (27–29). Plasma concentrations of the GLP-1R agonists were measured using an assay for the N-terminus of the GLP-1 moiety of the agonists against standards of liraglutide (30). Free fatty acids were measured with a NEFA C kit (Wako Chemicals, Neuss, Germany), and glycerol (Boehringer Mannheim, Germany) was measured by enzymatic methods modified to run on a COBAS 6000 automatic analyzer (Roche, Rødovre, Denmark). Plasma triglycerides, total cholesterol, HDL cholesterol, and acetaminophen were analyzed by spectrophotometric methods following hydrolysis and oxidation (Vitros 5.1 FS; Johnson & Johnson, Ortho-Clinical Diagnostics, Raritan, NJ).

Measurement of Gallbladder Volume

Gallbladder volume was assessed by ultrasound scans of the gallbladder using a FlexFocus 500 ultrasound scanner (B&K Medical, Herlev, Denmark). For time points of measurements, see Fig. 1*A*. The measures were performed by the same investigator at all time points. The scans were performed with the participant in a supine position. Three dimensions of the gallbladder (one longitudinal and two cross-sectional diameters) were measured.

Measurements of Energy Expenditure and Respiratory Quotient

Energy expenditure and respiratory quotient were measured by indirect calorimetry using a tight facemask connected to a calorimeter, with measurement of gas exchange breath by breath (MedGraphics CCM Express; Medical Graphics Corporation, St. Paul, MN). The calorimeter was calibrated immediately before each measurement, and the measurements were performed for 15 min each, starting at time point −15 min (baseline measure) and then at 45 min (prior to ingestion of the liquid mixed meal) and 250 min (prior to serving of the ad libitum meal) (Fig. 1*A*).

Appetite and Palatability Ratings

The participants rated their level of hunger, satiety, fullness, prospective food consumption, comfort, nausea, and thirst on 100-mm visual analog scales (VAS) every 20 min from time point −20 min to 60 min and every 30 min thereafter (Fig. 1*A*). Additionally, the participants rated the appearance, smell, taste, off-taste, and overall impression of the ad libitum meal on VAS scores right after the first bite of the ad libitum meal.

Statistical Analyses and Calculations

Results are presented as mean ± SEM unless otherwise stated. Comparisons between the experimental days were

performed using Student paired *t* test. *P* values were corrected for multiple testing using the Benjamini-Hochberg procedure (31). Adjusted *P* values ≤0.05 were considered statistically significant. SAS, version 9.4 (SAS Institute, Cary, NC), and GraphPad Prism, version 8, for Windows (GraphPad Software, San Diego, CA) were used for statistical analyses. Sample size calculation using an estimated SD of 186 kcal, a two-sided α level of 5%, and a power of 80% showed that 22 men should be included to detect a minimum difference in energy intake from the ad libitum meal of 20% estimated to correspond to 112 kcal. The SD was based on unpublished data from the Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, of patients with type 2 diabetes who had been served an ad libitum meal in a similar experimental setting. It was predefined that in case of dropout, the missing participant should be replaced. Area under the curve (AUC) was calculated using the trapezoidal rule. Insulin secretion rate (ISR) was calculated using ISEC, a mathematical modeling based on deconvolution of C-peptide concentrations, age, height, weight, sex, and population-based variables for C-peptide kinetics (32). Insulin resistance was calculated using the HOMA based on fasting plasma glucose and serum C-peptide values (HOMA2-IR calculator: www.dtu.ox.ac.uk/homacalculator). VLDL cholesterol was calculated as triglycerides × 0.45. LDL cholesterol was calculated as total cholesterol − (HDL cholesterol + triglycerides × 0.45). Gallbladder volume was calculated as: (longitudinal diameter) × (cross-sectional diameter 1) × (cross-sectional diameter 2) × π/6 (33). Gallbladder ejection fraction to each time point (t) was calculated as change from fasting gallbladder volume ($volume_{fasting}$ assessed as the mean of the gallbladder volume at time points −15 and 0 min) using the following formula: 100% × ($volume_{fasting}$ − $volume_t$)/$volume_{fasting}$ (34).

RESULTS

Study Participants

Twenty-two participants completed the two study days and were included in the data analysis. For participant characteristics, see Table 1. Besides the obligatory metformin and GLP-1R agonist treatments, none of the participants were treated with glucose-lowering and/or body weight–lowering agents.

Table 1—Participant characteristics

	n	Mean ± SEM	Range
Men/women	22/0		
Age (years)		61 ± 2	34–70
BMI (kg/m^2)		31.5 ± 0.7	25.3–37.4
Body weight (kg)		103.5 ± 3.0	81.6–129.5
Waist-to-hip ratio		1.04 ± 0.01	0.98–1.17
Duration of diabetes (years)		9.5 ± 1.2	2–21
HbA_{1c} (mmol/mol)		51 ± 1.5	36–61
HbA_{1c} (%)		6.8 ± 0.1	5.4–7.7
Fasting plasma glucose (mmol/L)		7.8 ± 0.2	5.7–9.8
HOMA2-IR		2.1 ± 0.1	1.1–3.0
HOMA2-B (%)		64.2 ± 5.4	31.1–111.2
Metformin (dose, mg/day)	22	1,773 ± 113	1,000–3,000
Liraglutide (dose, mg/day)	21	1.5 ± 0.1	1.2–1.8
Dulaglutide (dose, mg/week)	1	1.5 ± 0	
Cholesterol-lowering drugs (statins)	18 (18)		

HOMA2-IR, HOMA2-calculated insulin resistance; HOMA2-B, HOMA2-calculated β-cell function.

Plasma Concentrations of GLP-1 and GIP

At baseline, plasma concentrations of GIP were similar on the two study days ($P = 0.676$) (Table 2 and Fig. 1*B*). After start of the GIP infusion, the plasma concentration of total GIP rose, and steady state was reached after ∼45 min at ∼600 pmol/L (Table 2 and Fig. 1*B*). During placebo infusion, after ingestion of the liquid mixed meal, plasma GIP rose to a peak concentration of 88 ± 7 pmol/L at time point 117 ± 7 min. All participants adhered to their respective treatment with the long-acting GLP-1R agonist as evaluated by the baseline plasma concentration of the N-terminally modified end of GLP-1 (Tabel 2). The endogenous secretion of GLP-1 was evaluated by measurements of total GLP-1 (i.e., amidated GLP-1 and therefore showing no cross-reaction with the nonamidated agonists), and measurements were similar between the two interventions ($AUC_{0–270\ min}$, $P = 0.914$) (Table 2).

Plasma Acetaminophen

No differences were observed in plasma acetaminophen concentrations between the two interventions ($AUC_{60–270\ min}$, $P = 0.384$) (Table 2 and Fig. 2*A*).

Plasma Glucose

Baseline plasma glucose did not differ between the two study days ($P = 0.553$) (Table 2 and Fig. 2*B*). In the first fasting hour, plasma glucose was reduced more during placebo infusion than during GIP infusion, resulting in different plasma glucose concentrations prior to ingestion of the standardized liquid mixed meal ($P = 0.009$) (Table 2 and Fig. 2*B*). After ingestion of the liquid mixed meal, plasma glucose rose to statistically similar peak values during GIP and placebo infusion ($P = 0.374$) and thereafter declined toward fasting concentrations (Fig. 2*B*). AUC was higher during GIP compared with placebo infusion in both the fasting period ($AUC_{0–60min}$) and the postprandial period ($AUC_{60–270\ min}$) and during the full study day ($AUC_{0–270\ min}$) (Table 2).

Serum Insulin and C-Peptide, ISR, and Plasma Glucagon

There were no differences in baseline concentrations of insulin, C-peptide, ISR, or glucagon on the two study days (Table 2). During the first fasting hour, serum insulin and C-peptide rose during GIP infusion, whereas a small decrease were observed for both parameters during placebo infusion (Table 2 and Fig. 2*C* and *D*). This resulted in higher fasting AUCs for insulin and C-peptide during GIP compared with saline infusion ($P < 0.001$ for $AUC_{0–60\ min}$ for both insulin and C-peptide) and higher insulin and C-peptide concentrations at the time of initiation of the liquid mixed meal (Table 2). After ingestion of the liquid mixed meal, insulin and C-peptide rose and peaked at similar concentrations during the two interventions (Table 2 and Fig. 2*C* and *D*). AUC for the postprandial period ($AUC_{60–270\ min}$) as well as AUC for the full study day ($AUC_{0–270\ min}$) was similar between the interventions (Table 2). Also, the maximal ISRs were similar between the interventions (Table 2 and Fig. 2*E*).

Table 2—Difference in plasma and serum substrate and hormonal concentrations, energy expenditure, and respiratory quotient during GIP and saline infusions

	GIP infusion	Saline infusion	Raw *P*	Adjusted *P*	95% CI
Baseline plasma concentration of the GLP-1R agonist (nmol/L)	14.3 ± 1.4	14.1 ± 1.5	0.829	0.914	−1.2 to 1.0
Plasma total GIP					
Baseline (pmol/L)	11 ± 1	12 ± 1	0.352	0.676	−3.5 to 1.3
Steady state (pmol/L) (mean of time point 45–270 min)	599 ± 19	NA	NA	NA	NA
Peak (pmol/L)	747 ± 34	88 ± 7	<0.0001	<0.0001	586–731
Time to peak (min)	200 ± 48	117 ± 7	0.093	0.376	−15 to 180
$AUC_{0–270\ min}$ (nmol/L × min)	153 ± 5	10 ± 1	<0.0001	<0.0001	132–153
Plasma total GLP-1					
Baseline (pmol/L)	23 ± 1.1	22 ± 0.8	0.247	0.553	−1.0 to 3.6
Peak (pmol/L)	38 ± 1.6	41 ± 2.6	0.246	0.553	−8.1 to 2.2
Time to peak (min)	141 ± 9	126 ± 9	0.222	0.553	−10 to 40
$AUC_{0–270\ min}$ (pmol/L × min)	7,834 ± 288	7,781 ± 243	0.810	0.914	−392 to 496
Plasma acetaminophen					
Baseline (μmol/L)	2.6 ± 0.3	2.7 ± 0.4	0.839	0.914	−0.5 to 0.4
Peak (μmol/L)	77.0 ± 4.5	80.3 ± 3.8	0.206	0.531	−8.6 to 2.0
Time to peak (min)	165 ± 8	151 ± 6	0.074	0.374	−2 to 30
$AUC_{60–270\ min}$ (mmol/L × min)	10.7 ± 0.6	11.2 ± 0.4	0.107	0.384	−1.1 to 0.1
Plasma glucose					
Baseline (mmol/L)	7.9 ± 0.3	7.7 ± 0.2	0.232	0.553	−0.1 to 0.3
Time point 60 min (mmol/L)	7.6 ± 0.2	7.0 ± 0.2	0.001	0.009	0.3–0.8
Peak (mmol/L)	10.8 ± 0.4	10.4 ± 0.3	0.088	0.374	−0.1 to 0.8
Time to peak (min)	155 ± 6	142 ± 5	0.098	0.379	−2.6 to 28.5
$AUC_{0–60\ min}$ (mmol/L × min)	460 ± 13	439 ± 12	0.005	0.030	7–35
$AUC_{60–270\ min}$ (mmol/L × min)	1,818 ± 60	1,713 ± 49	0.004	0.026	38–171
$AUC_{0–270\ min}$ (mmol/L × min)	2,394 ± 74	2,260 ± 62	0.002	0.017	57–211
Serum insulin					
Baseline (pmol/L)	114 ± 14	117 ± 15	0.628	0.859	−13 to 8
Time point 60 min (pmol/L)	138 ± 19	96 ± 12	0.0001	0.007	20–63
Peak (pmol/L)	324 ± 52	357 ± 46	0.267	0.582	−94 to 27
Time to peak (min)	156 ± 10	143 ± 5	0.175	0.480	−6 to 32
$AUC_{0–60\ min}$ (nmol/L × min)	8.2 ± 1.1	6.3 ± 0.8	<0.0001	0.0007	1.2 to 2.7
$AUC_{60–270\ min}$ (nmol/L × min)	47.8 ± 7.3	48.6 ± 6.3	0.819	0.914	−7.7 to 6.2
$AUC_{0–270\ min}$ (nmol/L × min)	56.0 ± 8.3	54.9 ± 7.1	0.747	0.914	−6.2 to 8.5
Serum C-peptide					
Baseline (pmol/L)	888 ± 55	876 ± 53	0.653	0.859	−44 to 69
Time point 60 min (pmol/L)	1,083 ± 81	843 ± 56	<0.0001	0.0001	158–322
Peak (pmol/L)	1,946 ± 178	1,875 ± 138	0.462	0.743	−126 to 267
Time to peak (min)	201 ± 8	184 ± 7	0.110	0.384	−4 to 37
$AUC_{0–60\ min}$ (nmol/L × min)	61.3 ± 4.1	51.1 ± 3.3	<0.0001	0.0001	6.7–13.8
$AUC_{60–270\ min}$ (nmol/L × min)	329 ± 29	310 ± 22	0.201	0.531	−10.8 to 48.1
$AUC_{0–270\ min}$ (nmol/L × min)	390 ± 32	361 ± 25	0.076	0.374	−3.2 to 61.1
ISR					
Baseline (pmol/min/kg)	2.3 ± 0.1	2.3 ± 0.1	0.853	0.918	−0.2 to 0.2
Peak (pmol/min/kg)	5.8 ± 0.5	5.5 ± 0.4	0.341	0.674	−0.4 to 1.1
Time to peak (min)	166 ± 14	166 ± 6	0.949	0.977	−30 to 28
Plasma glucagon					
Baseline (pmol/L)	12 ± 1	12 ± 1	0.904	0.961	−2 to 1
Time point 60 min (pmol/L)	16 ± 2	11 ± 1	0.0005	0.006	2–6
$AUC_{0–60\ min}$ (pmol/L × min)	1,060 ± 97	706 ± 69	<0.0001	0.0007	230–478
$AUC_{60–270\ min}$ (pmol/L × min)	3,297 ± 338	2,950 ± 311	0.047	0.266	5.4–690
$AUC_{0–270\ min}$ (pmol/L × min)	4,357 ± 430	3,655 ± 377	0.004	0.026	252–1,151
Energy expenditure					
Baseline, time: −15 to 0 min (kcal/24 h)	1,790 ± 41	1,747 ± 42	0.382	0.705	−57 to 142
Prior to mixed meal, time: 45–60 min (kcal/24 h)	1,751 ± 52	1,785 ± 35	0.435	0.743	−120 to 60
Prior to ad libitum meal, time: 250–265 min (kcal/24 h)	1,799 ± 54	1,777 ± 52	0.734	0.914	−110 to 151
Respiratory quotient					
Baseline, time: −15 to 0 min	0.83 ± 0.01	0.84 ± 0.02	0.481	0.757	−0.03 to 0.02
Prior to mixed meal, time: 45–60 min	0.80 ± 0.01	0.81 ± 0.01	0.448	0.743	−0.03 to 0.01
Prior to ad libitum meal, time: 250–265 min	0.82 ± 0.01	0.86 ± 0.01	0.003	0.023	−0.07 to −0.02

Data are presented as mean ± SEM ($N = 22$) unless otherwise indicated. Raw *P* values and 95% CIs are from Student paired *t* tests comparing the days of GIP and saline (placebo) infusion, respectively. Adjusted *P* values are corrected for multiple testing using the Benjamini-Hochberg procedure.

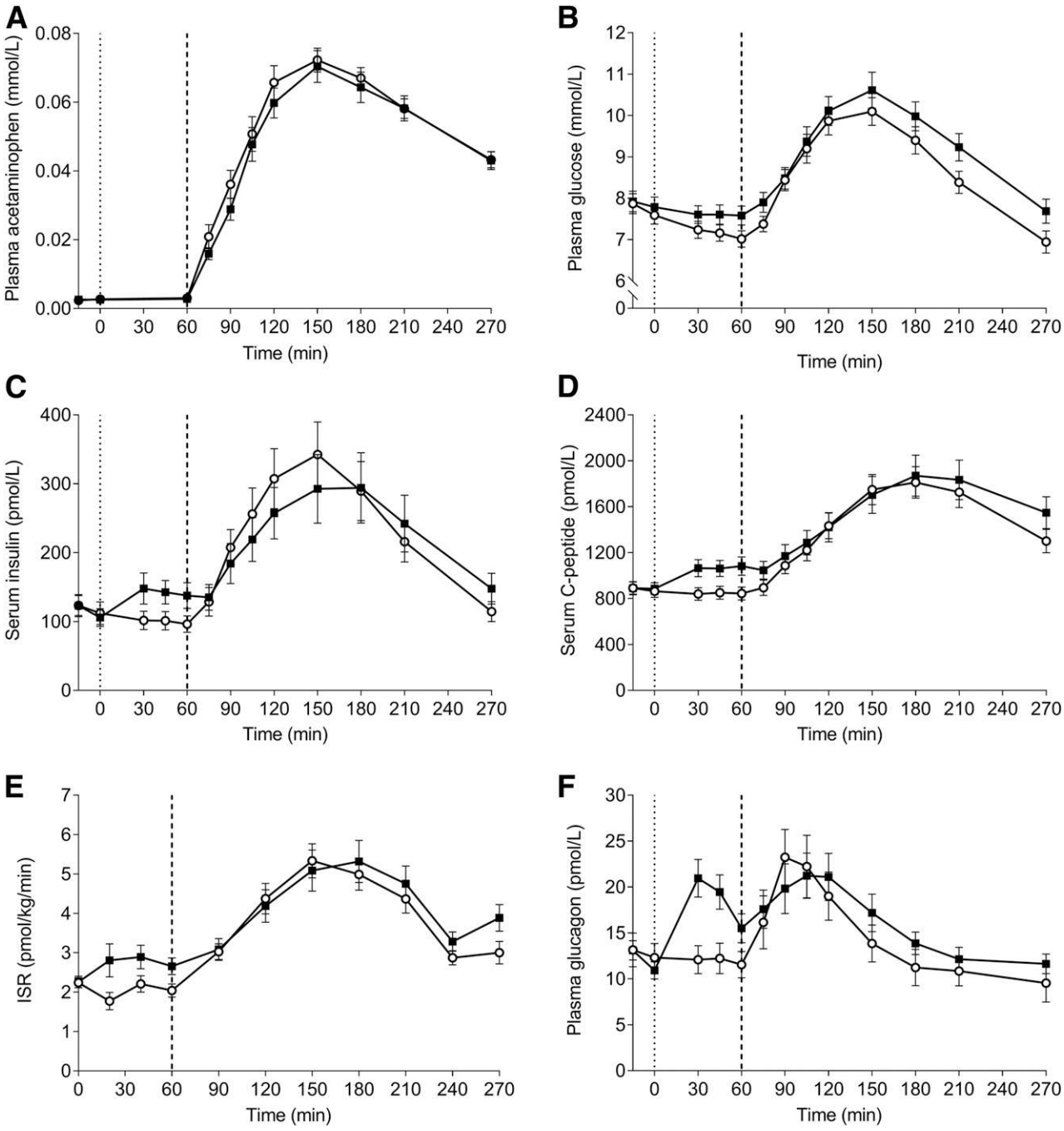

Figure 2—Data are means ± SEM ($N = 22$). Plasma acetaminophen (*A*), plasma glucose (*B*), serum insulin (*C*), serum C-peptide (*D*), ISR (*E*), and plasma glucagon (*F*) during infusion with GIP (■) and saline (placebo) (○). Thin dotted line at time point 0 min indicates time for start of GIP infusion (8 pmol/kg/min from 0 to 10 min and 6 pmol/kg/min for the remainder of the experimental day). Bold dashed line indicates ingestion of the standardized liquid mixed meal.

For plasma glucagon, a pronounced increase was observed right after initiation of the GIP infusion, whereas during placebo infusion, fasting plasma glucagon remained stable at the baseline concentration (Table 2 and Fig. 2*F*). This resulted in significantly higher $AUC_{0–60\ min}$ for glucagon during GIP infusion compared with saline infusion ($P < 0.001$) (Table 2). After ingestion of the liquid mixed meal, plasma glucagon rose during both interventions, resulting in similar postprandial AUCs ($AUC_{60–270\ min}$) ($P = 0.266$), while AUC for the full experimental day ($AUC_{0–270\ min}$) was higher during GIP infusion compared with saline infusion ($P = 0.026$) (Table 2).

Plasma Cholesterols, Triglycerides, Free Fatty Acids, and Glycerol

Baseline concentrations as well as $AUC_{0–270\ min}$ of total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, free fatty acids, and glycerol were similar between the two interventions (Supplementary Table 1 and Supplementary Fig. 1*A*–*G*).

Gallbladder Volume and Ejection Fraction

Baseline gallbladder volumes were similar on the two study days. After ingestion of the liquid mixed meal, gallbladder emptying showed no significant differences

between the interventions (Supplementary Fig. 2*A*). Also, the ejection fractions were similar between the interventions (Supplementary Table 2 and Supplementary Fig. 2*B*).

Energy Expenditure and Respiratory Quotient

Energy expenditure did not differ between the interventions whether measured at baseline, at time point 45–60 min (just prior to ingestion of the mixed meal), or at time point 250–265 min (just prior to serving of the ad libitum meal) (Table 2). The respiratory quotient did not differ between GIP and placebo infusion at baseline or prior to the mixed meal, but at the 250–265 min measure, respiratory quotient was lower during GIP infusion than during placebo infusion ($P = 0.023$) (Table 2).

Appetite Ratings

Hunger, satiety, fullness, prospective food consumption, and thirst were statistically similar between the interventions (Supplementary Fig. 3*A*–*E*). Also, comfort and nausea were similar during GIP and placebo infusions with high ratings of comfort (mean ± SEM comfort score 8.8 ± 0.3 and 8.8 ± 0.3, $P = 0.987$, respectively, with 10 equaling "very comfortable") and low ratings of nausea (mean nausea score 0.3 ± 0.2 and 0.2 ± 0.1, $P = 0.705$, respectively, with 0 equaling "no nausea") (Supplementary Fig. 3*F* and *G*).

Energy Intake and Palatability

Energy intake from the ad libitum meal (primary end point of the study) was similar during GIP and placebo infusion, respectively (648 ± 74 vs. 594 ± 55 kcal, $P = 0.171$, adjusted $P = 0.480$, mean difference 53 kcal, 95% CI −25 to 132) (Fig. 1*C*) (one participant had a small energy intake on both study days; post hoc analyses of the data without the data from this participant did not change the results [data not shown]). Water intake also did not differ during GIP and placebo infusion (414 ± 24 vs. 375 ± 31 mL, $P = 0.236$, adjusted $P = 0.553$, mean difference 39 mL, 95% CI −27 to 104). The overall impression of the ad libitum meal as well as the look, scent, and taste of the meal was at or above average (mean scores ≥5 on a scale from 1 to 10), with no difference between the scores obtained during GIP and placebo infusions (data not shown).

CONCLUSIONS

We report that a 5-h high-dose GIP infusion in patients with type 2 diabetes on stable treatment with metformin and a long-acting GLP-1R agonist did not influence energy intake, appetite, or energy expenditure but lowered the respiratory quotient and increased plasma concentrations of glucagon and glucose compared with placebo.

The applied GIP dose resulted in clearly supraphysiological plasma concentrations of total GIP. Accordingly, the lack of effect on energy intake and energy expenditure does not seem to be caused by insufficient dosing of GIP, though we cannot exclude an effect of different GIP–to–GLP-1 dose ratios.

The participants had an HbA_{1c} between 5.4 and 7.7% (36–61 mmol/mol) with a mean HbA_{1c} of 6.8 ± 0.1% (51 ± 1.5 mmol/mol). Hence, they were well regulated. This might be important, as the effect of GIP on insulin secretion is severely diminished in patients with type 2 diabetes with poor glycemic control but seems to be somewhat restored during near normoglycemia (9). Similarly, poor metabolic control could diminish other GIP functions, as suggested by a study demonstrating that the effect of exogenous GIP on subcutaneous adipose tissue blood flow is impaired in obese compared with lean individuals but seems to be somewhat restored following weight loss (35,36).

Opposite to the glucose-lowering effects observed from dual GIPR/GLP-1R agonists (21–23), we observed higher plasma glucose levels during GIP infusion compared with placebo infusion—a difference seemingly driven by a pronounced glucagonotropic effect of GIP. These findings are in line with previous studies in patients with type 2 diabetes reporting increased glucagon concentrations (37,38) and worsened postprandial plasma glucose excursions during GIP infusion (37). Also, our findings are in line with a study reporting that GIP antagonizes the glucagonostatic effect of GLP-1 when GIP and GLP-1 are infused concomitantly to patients with type 2 diabetes (16). A study in critically ill patients has also shown that GIP infusion to GLP-1 infusion increases glucagon concentrations in the fasting state; however, no effects on plasma glucose or insulin were observed in that study (39). In the current study, we observed slightly higher fasting insulin and C-peptide concentrations during GIP compared with placebo infusion. Whether this is due to a direct insulinotropic effect of GIP or caused by the pronounced increase in plasma glucagon and ensuing elevation in fasting plasma glucose concentration cannot be inferred from this study. Interestingly, the dual GIPR/GLP-1R agonist tirzepatide has been shown to reduce glucagon more than the GLP-1R agonist dulaglutide (21). Though the long-term effect of GIP on glucagon concentrations remains unexplored in humans, the current study shows that during prolonged GLP-1R activation, acute administration of GIP stimulates glucagon secretion. This finding does not lend support to the notion that the GIPR-activating component of dual GIPR/GLP-1R agonists is important for their glucose-lowering effect in humans.

We here report that GIP infusion did not affect energy expenditure (as also previously reported in patients with type 2 diabetes [19]) but lowered the respiratory quotient compared with placebo—the latter seemingly caused by a lack of rise in respiratory quotient following the liquid mixed meal during GIP infusion compared with placebo infusion. The higher plasma glucose concentration and unchanged free fatty acid concentration observed during GIP infusion would be expected to increase the respiratory quotient. Hence, the lower respiratory quotient during GIP infusion compared with placebo could indicate that GIP induces a shift toward fat oxidation in humans. Preclinical studies have reported that the dual GIPR/GLP-1R agonist tirzepatide mainly reduces body weight through a reduction in energy intake, resulting in more fat oxidation, but also seems to increase energy expenditure with a slower onset (40). Whether the present finding of acute GIP-induced lowering of the respiratory quotient with no effect on energy expenditure will be sustained during longer-term GIPR activation and/or translate into clinically relevant effects on body weight remains unknown.

GLP-1R activation has been suggested to prime the beneficial metabolic effects of GIPR activation by yet unknown mechanisms (5,13). Thus, initial priming by GLP-1 could facilitate the complementary benefits reported from dual GIPR/GLP-1R activation. Hence, all participants in the current study were in stable treatment for ≥3 months with a long-acting GLP-1R agonist and the treatment was

continued during the study. Data from mice have suggested that administration of GLP-1 results in an initial weight loss, whereas GIP administration results in a delayed body weight loss (13). In this perspective, the acute study design of the current study would be considered a limitation. We found a nonsignificant mean increase in energy intake of 53 kcal during GIP compared with saline infusion (95% CI −25 to 132 kcal, raw $P = 0.171$, adjusted $P = 0.480$). Based on these findings, we cannot exclude that a clinically relevant increase in energy intake might have been overlooked due to a lack of power. Nevertheless, based on the present results, long-term GLP-1R activation does not seem to prime any relevant acute energy intake–lowering effects of GIP. We recently reported that whereas GIP infusion did not affect energy intake, short-term infusion of GIP and GLP-1 during isoglycemic conditions resulted in higher caloric intake from an ad libitum meal compared with GLP-1 administration alone in overweight/obese men without diabetes (20). This discrepancy could be due to different study conditions and populations (20). Furthermore, the slightly higher plasma glucose levels at the time of the ad libitum meal during GIP infusion (<1 mmol/L) in the current study may have influenced the results.

In conclusion, we here show that a 5-h infusion of GIP (resulting in clearly supraphysiological plasma concentrations) administered to well-regulated patients with type 2 diabetes treated with metformin and long-acting GLP-1R agonists did not lower energy intake or significantly influence appetite, energy expenditure, gastric emptying, gallbladder motility, or plasma lipids but lowered the respiratory quotient, increased plasma glucagon and fasting serum insulin and C-peptide concentrations, and increased plasma glucose compared with placebo. These findings do not indicate acute metabolic benefits of GIP administration on top of stable GLP-1R agonism in men with type 2 diabetes.

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Author Contributions. N.C.B. was involved in planning of the study, conduct of the clinical experiments, statistical analyses, and writing of the manuscript. L.S.G. was involved in planning of the study, statistical analyses, and writing of the manuscript. S.M.H. and L.S.L.K. were involved in conduct of the clinical experiments. B.H. and J.J.H. analyzed plasma samples for GIP, GLP-1, and glucagon. F.D. analyzed plasma samples for free fatty acids and glycerol. L.J., M.B.C., T.V., and A.L. were involved in planning of the study. F.K.K. conceptualized the study and was involved in planning of the study, the statistical analyses, and writing of the manuscript. All authors critically reviewed the manuscript and approved the version to be published. N.C.B. and F.K.K. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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