



# Hyperglycemia Potentiates the Slowing of Gastric Emptying Induced by Exogenous GLP-1

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## OBJECTIVE

Acute hyperglycemia markedly slows gastric emptying. Exogenous GLP-1 also slows gastric emptying, leading to diminished glycemic excursions. The primary objective was to determine whether hyperglycemia potentiates the slowing of gastric emptying induced by GLP-1 administration.

## RESEARCH DESIGN AND METHODS

Ten healthy participants were studied on 4 separate days. Blood glucose was clamped at hyperglycemia using an intravenous infusion of 25% dextrose (~12 mmol/L; hyper) on 2 days, or maintained at euglycemia (~6 mmol/L; eu) on 2 days, between  $t = -15$  and 240 min. During hyperglycemic and euglycemic days, participants received intravenous GLP-1 (1.2 pmol/kg/min) and placebo in a randomized double-blind fashion. At  $t = 0$  min, subjects ingested 100 g beef mince labeled with 20 MBq technetium-99m-sulfur colloid and 3 g 3-*O*-methyl-glucose (3-OMG), a marker of glucose absorption. Gastric emptying was measured scintigraphically from  $t = 0$  to 240 min and serum 3-OMG taken at regular intervals from  $t = 15$  to 240 min. The areas under the curve for gastric emptying and 3-OMG were analyzed using one-way repeated-measures ANOVA with Bonferroni-Holm adjusted post hoc tests.

## RESULTS

Hyperglycemia slowed gastric emptying (eu/placebo vs. hyper/placebo;  $P < 0.001$ ) as did GLP-1 (eu/placebo vs. eu/GLP-1;  $P < 0.001$ ). There was an additive effect of GLP-1 and hyperglycemia, such that gastric emptying was markedly slower compared with GLP-1 administration during euglycemia (eu/GLP-1 vs. hyper/GLP-1;  $P < 0.01$ ).

## CONCLUSIONS

Acute administration of exogenous GLP-1 profoundly slows gastric emptying during hyperglycemia in excess of the slowing induced by GLP-1 during euglycemia. Studies are required to determine the effects of hyperglycemia on gastric emptying with the subcutaneously administered commercially available GLP-1 agonists in patients with type 2 diabetes.

Gastric emptying is a major determinant of postprandial glycemia in health, as well as in type 1 and type 2 diabetes (1,2), and accounts for ~35% of the variance in the initial glycemic response to oral carbohydrate (1). Accordingly, dietary and pharmacological strategies that slow gastric emptying, including short-acting GLP-1 agonists, are useful interventions to attenuate postprandial glycemic excursions and overall glycemia in type 2 diabetes (3).

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GLP-1 receptor agonists are now incorporated into standard treatment algorithms for the management of type 2 diabetes (4). During fasting, exogenous GLP-1 and GLP-1 agonists lower plasma glucose primarily via effects on the islet cell to increase insulin and reduce glucagon secretion in a glucose-dependent manner (5,6), whereas during the postprandial phase, glucose lowering is predominantly mediated through their effect to slow gastric emptying (7,8). Accordingly, in healthy patients and in those with type 2 diabetes, postprandial insulin concentrations are suppressed, rather than stimulated, during GLP-1 administration (7,9). The magnitude of the deceleration of gastric emptying induced by exogenous GLP-1 and its agonists is dependent on the baseline rate of gastric emptying, so that the emptying rate is markedly slowed in those with relatively rapid gastric emptying before GLP-1 administration, whereas the rate is largely unaffected when gastric emptying is already delayed at baseline (10,11). Furthermore, the reduction in postprandial glycemia induced by these agents is closely related to the magnitude of the slowing of gastric emptying (9–11). Accordingly, when the effect of GLP-1 to slow gastric emptying is attenuated, such as with the concurrent administration of erythromycin (12), the glucose-lowering effect is similarly diminished.

As well as being a determinant of postprandial glycemia, gastric emptying is itself highly sensitive to acute changes in the blood glucose concentration (13). Acute hyperglycemia (i.e., blood glucose level  $\sim 15$  mmol/L [270 mg/dL]) substantially slows gastric emptying (14). Indeed, even changes within the normal range of postprandial glycemia have marked effects on the rate of gastric emptying, with emptying being slower when blood glucose is clamped at 8 mmol/L (144 mg/dL) compared with emptying rates at 4 mmol/L (72 mg/dL) (15). Conversely, insulin-induced hypoglycemia dramatically accelerates gastric emptying (16).

It also appears that the effect of drugs on gastrointestinal motor function is modified by systemic glucose concentrations. For example, acute hyperglycemia attenuates the gastrokinetic effect of erythromycin (12). Moreover, we recently reported that exogenous GLP-1 attenuates the acceleration of gastric emptying by insulin-induced hypoglycemia ( $\sim 2.6$  mmol/L) (13). Given that the ubiquitous feature in patients with diabetes is hyperglycemia and that GLP-1 agonists are frequently prescribed to this group, it was important to evaluate whether hyperglycemia potentiated or diminished the slowing of gastric emptying induced by GLP-1 administration.

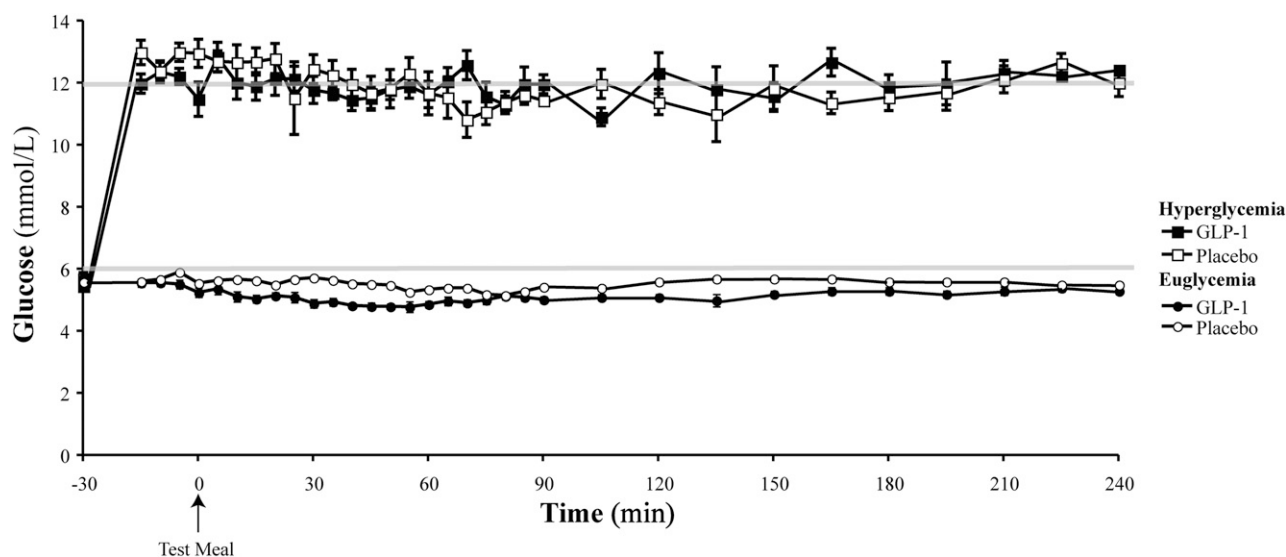
## RESEARCH DESIGN AND METHODS

### Subjects

Participants aged 50–75 years who considered themselves healthy were eligible and attended a screening visit at the Royal Adelaide Hospital. Excluded were participants with known or undiagnosed diabetes ( $HbA_{1c} > 6.5\%$ ; 48 mmol/mol), impaired renal function (estimated creatinine clearance  $< 107$  mL/min), or anemia (hemoglobin  $< 11$  g/dL in females and  $< 13$  g/dL in males), currently smoking, consuming  $> 20$  g of alcohol per day, receiving medication known to affect gastrointestinal motility or glycemia, or with a history of gastric or small-intestinal surgery.

### Protocol

Participants were studied on four separate occasions separated by a minimum of 4 days. Each participant underwent concurrent measurements of gastric emptying, blood glucose concentrations, and glucose absorption on each of the four occasions: twice with blood glucose concentrations within the euglycemic range (blood glucose  $\sim 6$  mmol/L [108 mg/dL]; eu) and twice during acute hyperglycemia (blood glucose  $\sim 12$  mmol/L [216 mg/dL]; hyper) (Fig. 1). GLP-1 (1.2 pmol/kg/min) or placebo (0.9% saline) was administered intravenously during euglycemia and hyperglycemia. The order of treatment (GLP-1, placebo, euglycemia, and hyperglycemia) was determined by



**Figure 1**—Blood glucose concentrations. Blood glucose (mmol/L) was stabilized using a dextrose infusion to target hyperglycemia (12 mmol/L) or was maintained without intervention at euglycemia (6.0 mmol/L) between  $t = -15$  and 240 min. GLP-1 (1.2 pmol/kg/min) or placebo (0.9% saline) was administered intravenously between  $t = -30$  and 240 min. The test meal was ingested at  $t = -5$  to 0 min. Data are mean  $\pm$  SEM.

the Royal Adelaide Hospital Pharmacy Department using a computer-generated randomization schedule. The investigators performing each study (M.P.P. and C.E.C.) were informed of the glucose target on a particular study day. These investigators had no role in the subsequent analysis of gastric emptying data. All investigators and participants were blinded to the study drug (GLP-1 or placebo), with blinding maintained throughout the entire study period, including analysis of data.

Each subject attended the Department of Nuclear Medicine, PET and Bone Densitometry at the Royal Adelaide Hospital at 0830 h after an overnight fast. Two intravenous cannulae were inserted into the right arm, one in the antecubital vein for an infusion of insulin and 25% dextrose and another in the dorsal vein of the right hand for infusion of the study drug. A third intravenous cannula was inserted into the left antecubital vein for blood sampling. Synthetic GLP-1 amide (Bachem, Weil am Rhein, Germany) was reconstituted by the pharmacy department in 0.9% normal saline. After baseline blood specimens were drawn, GLP-1 (1.2 pmol/kg/min) and placebo (0.9% saline) infusions were commenced 30 min before meal ingestion and infused at a rate of 1 mL/min for the duration of the study (i.e.,  $t = -60$  to 240 min) (13). A 25% dextrose infusion was commenced concurrently to target a blood glucose concentration of 12 mmol/L (216 mg/dL).

After the blood glucose concentration had been stabilized at the desired level for a minimum of 15 min, participants were instructed to eat the test meal as promptly as possible while remaining comfortable. The test meal comprised 100 g lean minced beef, labeled with 20 MBq technetium-99m-sulfur colloid (Pharmalucence Inc., Bedford, MA) (12), followed by 3 g 3-*O*-methyl- $\alpha$ -glucopyranose (3-OMG; Sigma-Aldrich, Sydney, New South Wales, Australia) dissolved in 150 mL water (13). After study completion at  $t = 240$  min, participants were monitored with half-hourly blood glucose concentrations for a further 3 h to detect delayed hypoglycemia before being allowed to leave the laboratory.

The study protocol was approved by the Royal Adelaide Hospital Human Research Ethics Committee and prospectively registered (www.anzctr.com.au;

ACTRN12611000973910). Written informed consent was obtained from all participants before their inclusion.

#### Stabilization of Blood Glucose Concentrations

Hyperglycemia was achieved using a modified glucose clamp technique (12,13). Dextrose (25%) was infused intravenously with an initial rate over 2 min determined using body surface area (DuBois method) (17) and followed with a continuous infusion adjusted between 80 and 300 mL/h to maintain the blood glucose concentration at 12 mmol/L (216 mg/dL) until  $t = 240$  min. On the euglycemic study days, blood glucose was maintained at  $\sim 6$  mmol/L (108 mg/dL) for the duration of the study (i.e.,  $t = -30$  to 240) without external manipulation (13,16). The total amount of 25% dextrose required to maintain the blood glucose on each study day was recorded.

Commencing 30 min before the meal (i.e.,  $t = -30$  min), venous blood samples for measurement of glucose were taken at 5-min intervals until  $t = 90$  min and then every 15 min until study completion at  $t = 240$  min. Blood glucose concentrations were measured using a portable electrochemical coulometric glucose dehydrogenase glucose meter with a coefficient of variation of 3.8% in the targeted range (Optium Xceed; Abbott Laboratories, Bedford, MA) (18).

#### Measurement of Gastric Emptying

On all study days, the radiolabeled beef mince test meal was consumed within 5 min, followed by ingestion of the 3-OMG-labeled water. Scintigraphic data were acquired with a gamma camera (Digirad, Poway, CA) placed over the participant's abdomen to obtain a left anterior oblique image. Subjects were supine with the upper body at an angle of  $\sim 30^\circ$ . Data were acquired from meal completion ( $t = 0$  min) in 1-min frames for 240 min and corrected for radionuclide decay,  $\gamma$ -ray attenuation, and subject movement (12). Radioisotopic data were analyzed by an experienced nuclear medicine scientist (K.L.J.) who was blinded to the treatment arm and the glycemic period assigned. A region of interest was drawn around the total stomach and a gastric emptying curve, expressed as intragastric retention over time, derived (12). From these curves

the following variables were considered: duration of the lag phase, determined visually as the time immediately before any of the solid meal had entered the small intestine, and total area under the curve  $t = 0$  to 240 min ( $AUC_{0-240}$ ).

#### Measurement of Glucose Absorption

Serum 3-OMG was used as an index of intestinal glucose absorption (10) and was measured using liquid chromatography/mass spectroscopy, with an assay sensitivity of 0.0103 mmol/L (10). Blood samples were collected at  $t = 15, 30, 45, 60, 90, 120, 150, 180, 210,$  and 240 min and, once clotted, centrifuged at 3,200 rpm for 15 min. Serum was stored at  $-70^\circ\text{C}$  for subsequent measurement of 3-OMG concentrations, with the rate of glucose absorption indicated by the 3-OMG concentration AUC (10).

#### Statistical Analysis

Sample size was determined using previous data relating to the effect of exogenous GLP-1 on gastric emptying in health, and we calculated that 10 participants completing all 4 study days would provide 80% power to detect a 25% difference in gastric emptying, the latter defined as the total gastric emptying AUC (9). Overall effects for gastric emptying and glucose (3-OMG) absorption were calculated as  $AUC_{0-240}$ . Data are shown as mean values  $\pm$  SEM, with the difference between groups ( $\Delta$ ) reported as median (interquartile range). Data were evaluated using one-way repeated-measures ANOVA, with Bonferroni-Holm adjusted post hoc tests for multiple comparisons. Given that we have reported an association between glucose absorption and gastric emptying (13), we tested for this relationship. This correlation was evaluated adjusted for repeated measures. The null hypothesis was rejected at the 0.05 significance level. Statistical analyses were performed using SPSS 6.0 software (SPSS, Chicago, IL). All analyses were supervised by an independent professional biostatistician.

#### RESULTS

Ten healthy participants (5 men, age 71 [5] years, BMI 26 [2.8] kg/m<sup>2</sup>) completed the 4 study days without significant adverse effects. However, five participants experienced leg cramping during the hyperglycemic study days. No participant experienced nausea or

vomited. Blood glucose concentrations were effectively clamped at hyperglycemic and euglycemic targets on GLP-1 ( $11.9 \pm 0.2$  and  $5.1 \pm 0.1$  mmol/L) and placebo ( $12.0 \pm 0.1$  and  $5.5 \pm 0.1$  mmol/L) study days (Fig. 1). GLP-1 markedly increased the intravenous glucose required to maintain hyperglycemia (hyper/GLP-1 vs. hyper/placebo;  $\Delta 91$  [24] g;  $P < 0.001$ ) (Fig. 2).

### Solid Emptying

In all cases, gastric emptying approximated a linear pattern after an initial lag phase (Fig. 3). The lag phase and gastric retention (%) over time were markedly different across study days ( $P < 0.001$ ). There were trends toward longer lag phases during clamped hyperglycemia with placebo (eu/placebo  $14.1 \pm 3.1$  vs. hyper/placebo  $24.3 \pm 5.3$  min;  $P = 0.12$ ), during euglycemia with GLP-1 compared with placebo (eu/placebo  $14.1 \pm 3.1$  vs. eu/GLP-1  $57 \pm 17.9$  min;  $P = 0.09$ ), and with GLP-1 during hyperglycemia compared with euglycemia (eu/GLP-1  $57 \pm 17.9$  vs. hyper/GLP-1  $98.4 \pm 20.6$  min;  $P = 0.12$ ).

### Total Stomach

During placebo infusions, the intragastric retention of the radioisotope was  $\sim 80\%$  greater during hyperglycemia compared with euglycemia ( $AUC_{240}$ , eu/placebo vs. hyper/placebo;  $P < 0.001$ ) (Fig. 3). At euglycemia, the administration of GLP-1 increased intragastric retention more than twofold ( $AUC_{240}$ , eu/placebo vs. eu/GLP-1;  $P < 0.001$ ), and at  $t = 240$ , more than 60% of contents were retained in the stomach compared with complete emptying during placebo. The rate of gastric emptying during GLP-1 administration at euglycemia was slower than the rate of

emptying during placebo at hyperglycemia ( $AUC_{240}$ , hyper/placebo vs. eu/GLP-1;  $P = 0.01$ ). During hyperglycemia, GLP-1 slowed gastric emptying more than GLP-1 administered during euglycemia ( $AUC_{240}$ , hyper/GLP-1 vs. eu/GLP-1;  $P < 0.01$ ) so that there was only minimal emptying with GLP-1 administration during hyperglycemia (hyper/GLP at  $t = 240$  mean emptying of  $15 \pm 3\%$ ).

### Serum 3-OMG Concentrations

Serum 3-OMG concentrations are shown in Fig. 4. The initial ANOVA for all four curves was significant ( $P < 0.001$ ). During the placebo studies, there was an initial steep linear rise in the 3-OMG concentration that peaked at 30 min on the hyperglycemic day and at 60 min on the euglycemic day, followed by a gradual linear decline. During euglycemic GLP-1 studies, a linear rise occurred in the 3-OMG concentration to 45 min, followed by a gradual increase to 120 min, which then plateaued for the remainder of the study. In contrast, during the hyperglycemic GLP-1 studies, there was minimal 3-OMG absorption for the duration of the study, with a gradual increase over 150 min, which then plateaued for the remainder of the study. Overall hyperglycemia decreased 3-OMG concentrations ( $AUC_{0-240}$ , hyper/placebo vs. eu/placebo;  $P = 0.01$ ). GLP-1 markedly reduced 3-OMG concentrations during euglycemia ( $AUC_{0-240}$ , eu/GLP-1 vs. eu/placebo;  $P < 0.01$ ). During hyperglycemia, GLP-1 decreased 3-OMG absorption substantially more than GLP-1 administered during euglycemia ( $AUC_{0-240}$ , hyper/GLP-1 vs. hyper/placebo;  $P < 0.01$ ).

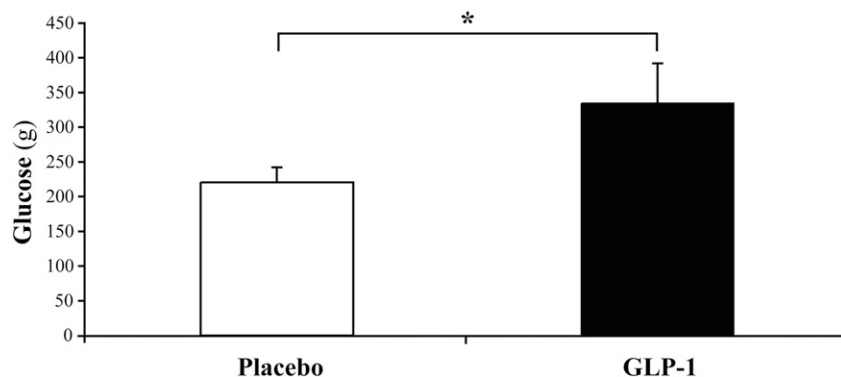
### Relationships Between Glucose Absorption and Gastric Emptying

There was a strong association between 3-OMG absorption and gastric emptying ( $AUC_{0-240}$  % gastric retention and  $AUC_{0-240}$  3-OMG;  $r = -0.80$ ,  $P < 0.001$ ).

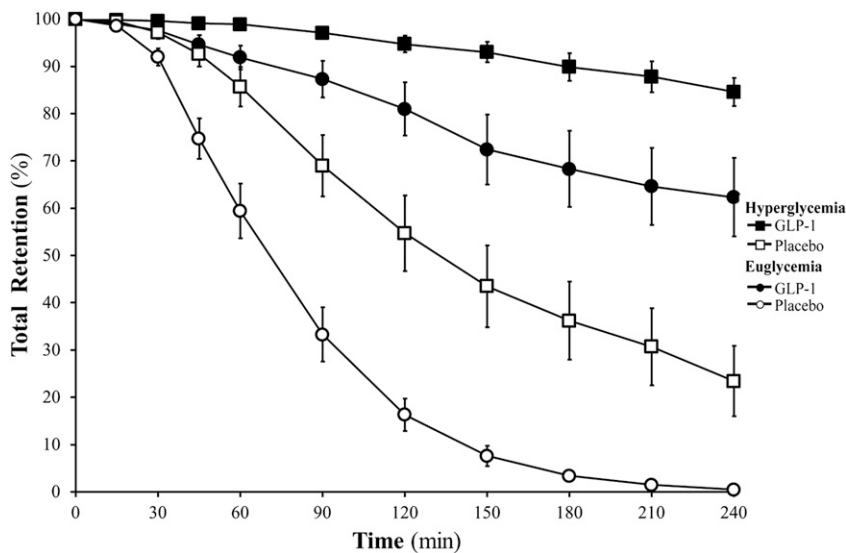
### CONCLUSIONS

The key finding of our study is that even during hyperglycemia, the administration of GLP-1 ( $1.2$  pmol/kg/min) retains its profound effect to slow gastric emptying and further limits the rate of small-intestinal carbohydrate absorption. The implication of our observation in healthy participants is that GLP-1 agonists could well retain their potent effect to slow gastric emptying in patients with diabetes and preprandial hyperglycemia, because, at least in health, there appears to be a supplementary effect of GLP-1 during hyperglycemia to slow gastric emptying.

The novelty of our study is that, to the best of our knowledge, it is the first study to evaluate the effect of a drug that slows gastric emptying during hyperglycemia in humans. That acute hyperglycemia markedly slows the rate of gastric emptying is well established. This phenomenon was initially observed in healthy participants (12) and then confirmed in patients with diabetes (19). Gastric emptying of solids consists of two phases: the lag phase, corresponding to meal transportation from the fundus to the antrum (20), and the postlag phase, corresponding to the propulsion of solid food particles through the pylorus (20). Hyperglycemia slows gastric emptying of solids by prolonging the lag phase and decreasing the postlag emptying rate (14) via reduced proximal gastric tone (21), suppression of antral pressure waves (22), and stimulation of pyloric contractions (23). The magnitude of deceleration of emptying, the prolongation of the lag phase, and the slowing of the postlag emptying rate that we observed during hyperglycemia are consistent with these previous studies (20,22,23). Purported mechanisms governing this response include nitrergic pathways (24), direct stimulation of glucose-dependent neurons within the myenteric plexus (25), and suppression of vagal cholinergic activity, which has been demonstrated via reduced pancreatic polypeptide levels during hyperglycemia (26).



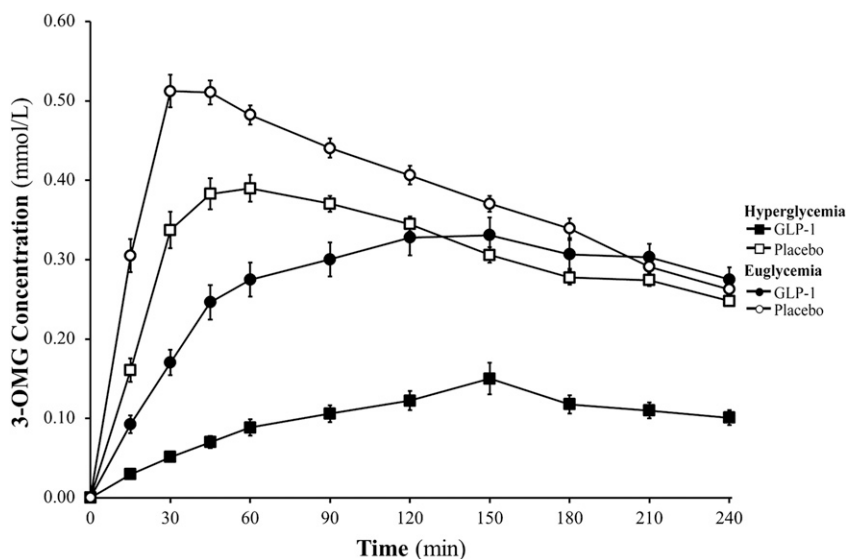
**Figure 2**—Exogenous glucose requirements during hyperglycemic clamps. GLP-1 markedly increased the amount of intravenous glucose required to maintain hyperglycemia (12 mmol/L) (hyper/GLP-1 vs. hyper/placebo;  $\Delta 91$  [24] g).  $*P < 0.001$ . Data are median (interquartile range).



**Figure 3**—Gastric retention (%) of test meal in participants with blood glucose clamped at hyperglycemia (12 mmol/L) or euglycemia ( $\sim 6.0$  mmol/L), with or without intravenous GLP-1 (1.2 pmol/kg/min). Data are mean  $\pm$  SEM.

Gastric emptying is the major rate-limiting step for glucose absorption from the gastrointestinal tract and therefore the primary determinant of postprandial glucose excursions (2,27). Acute GLP-1 administration at pharmacological doses has been shown to dose-dependently relax the gastric fundus, increase gastric compliance, inhibit antral motility, and increase pyloric tone (28,29), thereby slowing gastric emptying and attenuating postprandial glycemic excursions (9). Similar effects

have been reported with the commercially available “short-acting” GLP-1 agonists (11,30). The “long-acting” GLP-1 agonists, such as exenatide sustained release/long-acting release, compared with the “short-acting” GLP-1 agonists have diminished effect to slow emptying (31,32), which is thought to reflect the development of rapid tachyphylaxis to sustained exposure to supraphysiological concentrations of GLP-1 (33). The mechanisms underlying tachyphylaxis are uncertain—Nauck et al. (34) have



**Figure 4**—Glucose absorption (3-OMG concentrations). Serum 3-OMG (mmol/L) concentrations in participants with blood glucose maintained at hyperglycemia (12 mmol/L) or euglycemia ( $\sim 6.0$  mmol/L), with or without intravenous GLP-1 (1.2 pmol/kg/min). Data are presented as mean  $\pm$  SEM.

proposed a role for vagal pathways. The relative importance of the plasma GLP-1 concentration, as opposed to the duration of its elevation, is also uncertain. It should also be recognized that with prolonged GLP-1 receptor stimulation the slowing of gastric emptying is attenuated but not abolished (31,33,34).

Although the magnitude of the slowing of gastric emptying that we observed during euglycemia on GLP-1 is consistent with previous studies using acute administration of GLP-1 (13,28,29), this was dramatically potentiated during hyperglycemia, such that mean gastric emptying was only  $\sim 15\%$  at 4 h. The mechanisms underlying the inhibitory effect of GLP-1 are incompletely understood; however, a number of studies indicate a putative role of vagal cholinergic pathways (28,35), and nitric oxide has been implicated as an important efferent neurotransmitter in GLP-1-induced gastric relaxation (36). Accordingly, there appears to be substantial overlap between the mechanisms governing slower gastric emptying during GLP-1 stimulation and hyperglycemia, which we speculate may account for the summative interaction observed in our study.

Even minor variations in duodenal delivery of glucose (i.e., rate of gastric emptying) have major effects on postprandial glycemia (27), and postprandial glycemia is a major determinant of overall glycemic control (37). The marked additional slowing of gastric emptying that we observed during hyperglycemia compared with euglycemia on GLP-1 study days highlights a role for short-acting GLP-1 agonist in patients with type 2 diabetes who are hyperglycemic at the time of meal ingestion (38). Furthermore, patients with type 2 diabetes frequently are prescribed one or more medications that are ingested, and the protracted period of gastric slowing (for up to 4 h) induced by GLP-1 during hyperglycemia may have significant effects on the absorption of concomitant oral drugs, particularly modified-release or enteric-coated formulations.

There are, however, limitations to our study. We elected to evaluate the effects of GLP-1 on the response to hyperglycemia in healthy participants, rather than in patients with diabetes. We chose a healthy cohort for this proof-of-principal study because patients

with diabetes have the potential for variable glycemic control, autonomic neuropathy, and abnormally slow gastric emptying (39). The latter variable may be particularly important because the capacity for GLP-1 to slow gastric emptying depends on the underlying rate of gastric emptying (10,11). However, patients with diabetes and autonomic neuropathy have impaired relaxation of the proximal stomach in response to exogenous GLP-1 (40), and no studies have evaluated the effect of exogenous GLP-1 on gastric emptying in patients with gastroparesis.

In addition, our study design was somewhat artificial in that synthetic GLP-1 was administered acutely as a continuous intravenous infusion over 4 h at a dose representative of pharmacological concentrations (8) rather than as a subcutaneous administration of a commercially available GLP-1 agonist. This was to ensure predictable plasma concentrations of GLP-1 across the 4 study days; however, the response may potentially be more variable with the subcutaneous route and the magnitude of slowing of gastric emptying possibly attenuated with prolonged administration (33). Furthermore, increasing blood glucose acutely to a set level of 12 mmol/L (216 mg/dL) is not representative of the chronic hyperglycemia seen in most patients with well-to-moderately controlled type 2 diabetes.

Notably, exogenous GLP-1 was well tolerated, with no episodes of nausea or vomiting during euglycemia or hyperglycemia, even with profound intragastric retention of the meal at 4 h. This is consistent with previous reports of the low incidence of gastrointestinal side effects with intravenous GLP-1 (8) and the weak relationship between nausea and vomiting and delayed gastric emptying (11,31). However, we emphasize that gastrointestinal symptoms may be greater when commercially available GLP-1 agonists are used. Studies are now warranted to determine if the potentiated effect of hyperglycemia to slow gastric emptying persists with prolonged infusions of intravenous GLP-1 and chronic administration of short- and long-acting GLP-1 agonists.

In conclusion, our study establishes that acute administration of exogenous GLP-1 in a healthy older population profoundly slows gastric emptying during hyperglycemia in excess of the

slowing induced by GLP-1 during euglycemia and by physiological hyperglycemia. This effect is associated with a substantial reduction in small intestinal carbohydrate absorption. The clinical relevance of our observations will be clarified further by studies with subcutaneous administration of commercially available short- and long-acting GLP-1 agonists in the target population of patients with type 2 diabetes stratified according to chronic glycemic control.

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**Author Contributions.** M.P.P. was responsible for study conception and design, acquisition of data, statistical analysis, interpretation, and drafting the manuscript. K.L.J. was responsible for analysis and interpretation of the scintigraphic data and contributed to the study design and critical revision of the manuscript for important intellectual content. C.E.C. and L.G.T. contributed to the acquisition and interpretation of data. J.J.M., M.J.C., and M.H. contributed to the study design and to critical revision of the manuscript for important intellectual content. A.M.D. was responsible for the study conception and design, obtaining funding, acquisition of data, interpretation, and critical revision of the manuscript for important intellectual content. M.P.P. is the guarantor of this work and, as such, had full 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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