Received: 5 November 2019 | Revised: 10 December 2019 | Accepted: 18 December 2019

DOI: 10.1111/dom.13956



WILEY

ORIGINAL ARTICLE

# Exenatide once weekly slows gastric emptying of solids and liquids in healthy, overweight people at steady-state concentrations

Karen L. Jones PhD[1,2,3] | Lian Q. Huynh BHlthMedSci[1,2] | Seva Hatzinikolas DipAppSc[1,2] | Rachael S. Rigda BSc[1,2] | Liza K. Phillips PhD[1,2,3] | Hung T. Pham MBBS[1,2] | Chinmay S. Marathe PhD[1,2] | Tongzhi Wu PhD[1,2,3] | Charles H. Malbert PhD[4] | Julie E. Stevens PhD[5] | Kylie Lange BSc[1,2] | Christopher K. Rayner PhD[1,2,6] | Michael Horowitz PhD[1,2,3]

[1]Adelaide Medical School, University of Adelaide, South Australia, Australia

[2]Centre of Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide, South Australia, Australia

[3]Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia

[4]Ani-Scan, Institut National de la Rechercher Agronomique, Saint-Gilles, France

[5]School of Health and Biomedical Sciences, RMIT University, Victoria, Melbourne, Australia

[6]Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide, South Australia, Australia

**Correspondence**
Prof. Karen Jones, University of Adelaide, Adelaide Medical School, Adelaide Health and Medical Sciences Building, Cnr North Tce and George St, Adelaide 5005, South Australia, Australia
Email: karen.jones@adelaide.edu.au

**Funding information**
This study was supported by investigator-initiated funds provided by AstraZeneca Pty Ltd. Study medication (exenatide once weekly and matching placebo) was also provided by AstraZeneca and distributed by staff in the RAH Pharmacy. The salary of K. Jones was supported by the University of Adelaide William T Southcott Research Fellowship. T. Wu was supported by a Royal Adelaide Hospital Research Committee Florey Fellowship, the salary of C. Marathe by a NHMRC Early Career Fellowship, the salary of L. Phillips by a Royal Adelaide Hospital Research Committee Postdoctoral Fellowship and the salary of K. Lange by the NHMRC.

## Abstract

**Aims:** To evaluate the effects of 8 weeks' administration of exenatide (EXE) once weekly on gastric emptying of solids and liquids (using the "gold standard" technique, scintigraphy), glucose absorption and postprandial glycaemia in healthy people.

**Material and methods:** A total of 32 healthy participants were randomized to receive either EXE once weekly (2 mg/wk subcutaneously; six men, 10 women, mean age 59.9 ± 0.9 years, mean body mass index [BMI] 29.6 ± 0.6 kg/m$^2$) or matching placebo (PBO; six men, 10 women, mean age 60.6 ± 1.2 years, mean BMI 29.5 ± 1.0 kg/m$^2$) for 8 weeks. Gastric emptying, nausea (visual analogue scale), and plasma glucose, insulin, C-peptide and glucagon were measured for 120 min after a solid/liquid meal, comprising 100 g ground beef (radiolabelled with 20 MBq $^{99m}$Tc-sulphur colloid) and 150 mL 10% glucose (radiolabelled with 7 MBq $^{67}$Ga-EDTA), and containing 5 g 3-O-methyl-glucose (3-OMG) as a marker of glucose absorption, at baseline and after 8 weeks' treatment.

**Results:** The study treatments were well tolerated. Scores for nausea were consistently low, with no difference between the EXE once weekly and PBO groups. EXE once weekly slowed gastric emptying of solids (area under the curve $[AUC]_{0-120min}$: $P < 0.05$) and liquids ($AUC_{0-120min}$: $P = 0.01$) substantially, and attenuated glucose absorption (3-OMG incremental AUC $[iAUC]_{0-30min}$: $P = 0.001$) and the postprandial rise in plasma glucose ($iAUC_{0-30min}$: $P = 0.008$). Plasma glucagon at 2 h was reduced by EXE once weekly ($P = 0.001$). The magnitude of the reduction in plasma glucose at t = 30 min from baseline to 8 weeks with EXE once weekly was related inversely to the 50% emptying time of the glucose drink ($r = -0.55$, $P = 0.03$).

**Conclusions:** In healthy participants, 8 weeks' administration of the "long-acting" glucagon-like peptide-1 receptor agonist EXE, slowed gastric emptying of solids and liquids substantially, with consequent reductions in glucose absorption and postprandial glycaemia.

  

**Peer Review**
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.13956.

**KEYWORDS**
exenatide, gastric emptying, glycaemia, type 2 diabetes

## 1 | INTRODUCTION

Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) are used widely, and increasingly, in the management of type 2 diabetes[1,2] and, on the basis of their plasma half-life, may be classified as "short-" (eg, exenatide [EXE] twice daily, lixisenatide) or "long-" (eg, EXE once weekly, liraglutide, dulaglutide, semaglutide) acting.[1] Their current use is essentially empirical, rather than "personalized" as is increasingly recommended.[1,2] A number of long-acting GLP-1RAs have been shown to reduce cardiovascular risk.[3,4] The reductions in pre- and postprandial glycaemia in healthy people and those with type 2 diabetes by GLP-1 and its agonists were initially attributed to glucose-dependent insulinotropic and glucagonostatic effects.[5-8] This concept was modified by the recognition that gastric emptying, which exhibits a substantial inter-individual variation in healthy people and is frequently disordered in those with type 2 diabetes,[9,10] is a major determinant of the glycaemic response to oral glucose, and carbohydrate-containing meals, in healthy people and those with type 2 diabetes,[11-13] and that GLP-1 slows gastric emptying.[6,14,15] The relationship of the rise in glycaemia with the entry of carbohydrate into the small intestine is non-linear, so that minor changes in gastric emptying may have a major effect on the glycaemic response[16,17] and, most importantly, that the reduction in postprandial glycaemia induced by acute, intravenous administration of GLP-1 is associated with a decrease, rather than an increase, in postprandial insulin concentrations,[6,7,18,19] so postprandial glucose-lowering by exogenous GLP-1 is attributable primarily to slowing of gastric emptying, rather than its insulinotropic or glucagonostatic properties. However, we and others[20,21] have demonstrated that the slowing of gastric emptying by exogenous administration of GLP-1 is subject to "tachyphylaxis" with sustained exposure;[20,21] for example in healthy people, the slowing of gastric emptying by GLP-1 after 8.5 h'[21] and 24 h'[20] administration, is diminished over time. These observations stimulated the concept that short-acting GLP-1RAs lower postprandial blood glucose primarily by slowing gastric emptying[5,22,23] and, hence, have a dominant postprandial effect, while long-acting GLP-1RAs may have minimal or no effect on gastric emptying with sustained administration as a result of tachyphylaxis, so that their glucose-lowering is preferentially preprandial, reflecting stimulation of insulin and suppression of glucagon.[21,24] This concept is important because, in the large number of people with type 2 diabetes, those whose glycated haemoglobin (HbA1c) is ≥53 mmol/mol (7%) but <64 mmol/mol (8%), postprandial rather than preprandial/fasting, glucose is the dominant determinant of HbA1c; this is the case in both untreated type 2 diabetes and when treatment is instituted, including with insulin.[25] What has apparently received less attention in the two studies with regard to the tachyphylaxis relating to the slowing of gastric emptying by exogenous GLP-1, is that, after continuous administration, GLP-1 still slowed gastric emptying substantially; that is, its effects were not abolished.[20,21]

It is clear that short-acting GLP-1RAs slow gastric emptying markedly after sustained administration and that this response is dependent on the baseline rate of gastric emptying and is predictive of the postprandial reduction in glucose.[23] For example, a study using the "gold standard" technique of scintigraphy demonstrated that EXE twice daily slows gastric emptying markedly in type 2 diabetes,[5] and similar observations have been reported for lixisenatide using a stable isotope breath test, an acceptable method for quantifying gastric emptying,[22] as well as scintigraphy.[23] In contrast, the majority of studies relating to the effect of long-acting GLP-1RAs on gastric emptying have hitherto employed suboptimal methods to quantify gastric emptying, for example, plasma kinetics of oral paracetamol absorption,[21,24] a method which is both imprecise and cannot discriminate between effect on gastric emptying of solids and liquids. Even with such techniques, however, it is apparent, albeit not widely appreciated, that liraglutide (1.2–1.8 mg/d) has a sustained effect of slowing gastric emptying in type 2 diabetes, and this correlates with postprandial glucose-lowering.[26,27] Because of the technique used, the magnitude of the slowing of gastric emptying is uncertain. More recently, Halawi et al[28] reported that a higher dose of liraglutide (3.0 mg/d), used in the management of obesity, slowed gastric emptying of a solid meal (measured by scintigraphy) at 16 weeks.

Exenatide once weekly was the first once weekly GLP-1RA to be developed with the inherent convenience of a diminished frequency of injections and independence of the timing of the injection from meals. EXE once weekly reduces postprandial glucose,[29] but, unlike EXE twice daily,[5] the effect of EXE once weekly on gastric emptying has not been characterized adequately. In the comparative study by Drucker et al,[29] the slowing of paracetamol absorption at 14 weeks by EXE once weekly was less than that induced by EXE twice daily. While this suggests that the slowing of gastric emptying by EXE once weekly is less than that of EXE twice daily, this observation does not exclude a significant effect of EXE once weekly.

Evaluation of the effects of a drug on gastric emptying in type 2 diabetes is complicated by the potentially confounding effects of both acute hyperglycaemia, which slows gastric emptying,[30] autonomic neuropathy[10] and the greater variability of gastric emptying.[31] These factors may have contributed to an underestimate of the magnitude of slowing of gastric emptying by long-acting GLP-1RAs. For these reasons, "proof-of-principle" is best established in healthy people.

Upper and lower gastrointestinal symptoms, particularly nausea, are the most commonly reported adverse effects of GLP-1RAs and account for a substantial number of withdrawals from studies.[1] It has been suggested that nausea and vomiting relate to slowing of gastric emptying.[1]

In the present study, we evaluated the effects of 8 weeks' treatment with EXE once weekly on gastric emptying measured by scintigraphy, glucose absorption, postprandial blood glucose concentrations and nausea in healthy people.

## 2 | PARTICIPANTS AND METHODS

### 2.1 | Participants

A total of 70 people were screened for eligibility via telephone or email. Of these, 47 attended the laboratory for a blood test screen for eligibility. Forty participants passed screening and were enrolled in the study but five withdrew prior to study drug allocation, therefore, a total of 35 participants were randomized to receive either placebo (PBO; n = 17) or EXE once weekly (n = 18). One participant from the EXE once weekly group withdrew from the study because of adverse effects, and another due to interstate relocation during the trial. A third participant was randomized to receive PBO, but withdrew just prior to visit 1 (Figure S1). Hence, 32 participants (12 men and 20 women, mean age 60.3 ± 0.7 years, mean body mass index [BMI] 29.6 ± 0.6 kg/m$^2$) completed the study, 16 of whom received PBO and 16 of whom received EXE once weekly. There were no differences in age (EXE vs PBO: 59.9 ± 0.9 vs 60.6 ± 1.2 years; $P$ = 0.68), sex (both groups included six men and 10 women), weight (EXE vs PBO: 85.4 ± 3.0 vs 84.7 ± 3.9 kg; $P$ = 0.89) or BMI (PBO vs EXE: 29.5 ± 1.0 vs 29.6 ± 0.6 kg/m$^2$; $P$ = 0.96) between the two groups. No participant had a history of gastrointestinal disease or surgery, none had significant respiratory, cardiac, hepatic and/or renal disease, alcohol consumption >20 g/day or epilepsy, and none was a smoker or unable to withhold any medication likely to influence gastrointestinal function.

### 2.2 | Protocol

The study (Clinical Trials registration number: ACTRN 1261600055415) followed a prospective, randomized double-blind, PBO-controlled, parallel design. Participants attended the laboratory, after an overnight fast from solids and liquids, for a screening visit, to review their medical history and medications, and record their height and weight. A standardized questionnaire, to quantify gastrointestinal symptoms, comprising six gastric and three oesophageal symptoms, scored as 0 = no symptoms, 1 = mild, 2 = moderate and 3 = severe symptoms, for a total maximum score of 27, was completed.[10] Blood was sampled for complete blood picture, biochemistry, iron studies, follicle-stimulating hormone levels (in women) and HbA1c. Participants who fulfilled the inclusion and exclusion criteria (Supporting Information File S1) and provided informed consent were then randomized.

### 2.3 | Baseline visit (day 0)

Participants attended our clinical research facility at 8:00 AM, having fasted overnight (14 h for solids and 12 h for liquids), for a baseline gastric emptying measurement. An intravenous cannula was placed into a forearm vein for blood sampling, and the forearm kept warm with a heat pack for sampling of "arterialized" blood. Participants were seated in front of a gamma camera and ate a mixed solid/liquid meal comprising a 100 g ground beef patty (270 kcal, 25 g protein, 21 g fat) followed by 150 mL 10% glucose drink within 5 min. The solid component of the meal was labelled with 20 MBq $^{99m}$Tc-sulphur colloid, and the liquid with 7 MBq $^{67}$Ga-EDTA,[32] and included 5 g 3-O-methylglucose (3-OMG; Sigma Aldrich, St Louis, Missouri) as a marker of intestinal glucose absorption. Time zero (t = 0) was taken as the time when the participant finished the meal.

At the conclusion of the baseline study, participants received the first dose of EXE once weekly or matched PBO (AstraZeneca Pty Ltd, Sydney, Australia) by subcutaneous injection.

### 2.4 | Intervention period

Commencing on day 0, each participant attended the laboratory once each week for administration of 2 mg EXE or PBO by subcutaneous injection (days 0, 7, 14, 21, 28, 35, 42, 49 and 56); steady-state for EXE once weekly is known to be achieved at 6–7 weeks.[33]

### 2.5 | Final visit

The final visit was scheduled 2 to 5 days after last injection (ie, after day 56) of either EXE or PBO. Participants again attended our facility at 8:00 AM, having fasted overnight, for an identical study as on day 1.

The protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital, and each participant provided written, informed consent. All studies were carried out in accordance with the Declaration of Helsinki.

### 2.6 | Measurements

#### 2.6.1 | Gastric emptying

Gastric emptying data were acquired in 30-s frames for the first 30 min, followed by 3-min frames until t = 120 min. On one of the two study days, at t = 120 min, the participant drank 100 mL of water labelled with 5 MBq of $^{99m}$Tc-sulphur colloid, and a lateral image of the stomach was acquired to derive correction factors for gamma ray attenuation.[34] Gastric emptying curves (expressed as % of the maximum content of the total stomach) were derived and the content of the total stomach at t = 0, 15, 30, 45, 60, 75, 90, 105 and 120 min calculated. The percentage of solid remaining in the stomach at 100 min (T100 min), and the 50% emptying time (T50) for the liquid, were also derived.

#### 2.6.2 | Plasma glucose, insulin, C-peptide, glucagon and serum 3-OMG

"Arterialized" venous blood (14 mL) was sampled immediately before (t = −5 min) and at t = 15, 30, 45, 60, 75, 90, 105 and 120 min after the meal. Blood glucose concentrations were measured using a glucometer on the study day. Plasma and serum were separated from the remainder of each sample and stored at −80°C for subsequent measurements of plasma glucose, insulin, C-peptide and glucagon, and serum 3-OMG

concentrations. Plasma glucose was measured using a glucose oxidase analyser (YSI, Yellow Springs, Ohio). Plasma insulin was measured by ELISA (Diagnostics 10–1113; Mercodia, Uppsala, Sweden). The sensitivity of the assay was 1.0 mU/L and intra- and inter-assay coefficients of variation were 2.9% and 6.7%, respectively.[35]

Plasma C-peptide was measured by ELISA immunoassay (10–1136-01; Mercodia). The sensitivity of the assay was 15 pmol/L and intra- and inter-assay coefficients of variation were 3.7% and 7.7%, respectively.[35]

Plasma glucagon was measured by radioimmunoassay (GL-32 K; Millipore, Billerica, Massachusetts). The minimum detectable limit was 20 pg/mL, and intra- and inter-assay coefficients of variation were 6.4% and 3.2%, respectively.[35]

Serum 3-OMG was analysed by liquid chromatography and mass spectrometry with a sensitivity of 0.0103 mmol/L.[36]

#### 2.6.3 | Nausea

Nausea was evaluated using 100-mm validated visual analogue scale questionnaires immediately prior to study drug administration (t = −33 min) and consumption of the test meal (t = −3 min), and then every 15 min between t = 0 and 120 min.[37]

#### 2.6.4 | Body weight

Body weight was assessed at the baseline visit (visit 1) and at the post-treatment gastric emptying study (visit 2) using the same scales.

### 2.7 | Statistical analysis

Power calculations were performed by a professional biostatistician (K.L.) who also oversaw the data analysis. A minimum sample of 30 participants was required to provide 80% power, with significance set at $P < 0.05$ to detect a 50% increase in gastric retention of the solid at 100 min on EXE once weekly compared to PBO, based on our previous studies.[32] Areas under the curve (AUCs) were calculated for gastric emptying, plasma glucose, insulin, C-peptide, glucagon and 3-OMG using the trapezoidal rule. Data were analysed using analysis of covariance for differences at week 8, with adjustment for baseline values as a covariate. Relationships between variables were assessed by Pearson's linear correlation.

## 3 | RESULTS

The studies were generally well tolerated. Adverse effects were reported in three participants on EXE once weekly. One participant reported sensations of dizziness/lightheadedness, bloating, nausea, vomiting, headache, and lack of sleep, and withdrew from the study. Another participant experienced a transient hive-like rash that resolved after completing the study. The third participant experienced mild "menstrual pain and bleeding", despite apparently being postmenopausal, that was probably unrelated to the study medication. None of the adverse effects were serious and all affected participants made a full recovery.

There was no difference in body weight between the EXE once weekly and PBO groups at baseline (EXE vs PBO: 85.4 ± 3.0 vs 84.7 ± 3.9 kg; $P = 0.89$). After 8 weeks' treatment there was a reduction in body weight with EXE once weekly compared to PBO (EXE vs PBO: −2.1 ± 0.5 vs 0.2 ± 0.5 kg; $P = 0.001$).

### 3.1 | Nausea

Scores for nausea were low, with no difference in the low scores for nausea between the EXE and PBO groups at the baseline (pre-treatment) study ($AUC_{0-120}$: $P = 0.62$) or after treatment ($AUC_{0-120}$: $P = 0.46$).

### 3.2 | Gastric emptying

At baseline, there was no difference in the $AUC_{0-120min}$ for gastric emptying of solids ($P = 0.73$; Figure 1A) or liquids ($P = 0.84$; Figure 1C) between the EXE and PBO groups, nor any difference in the solid retention at 100 min (EXE vs PBO: 41.3 ± 4.2% vs PBO: 43.9 ± 4.0%; $P = 0.63$) or the liquid T50 (EXE vs PBO: 30.4 ± 3.0 vs 29.2 ± 2.0 min; $P = 0.74$).

At the post-treatment visit, EXE once weekly slowed gastric emptying ($AUC_{0-120min}$) of solids ($P = 0.046$; Figure 1B) and liquids ($P = 0.01$; Figure 1D) compared to PBO. EXE once weekly also increased the solid retention at 100 min (EXE vs PBO: 52.0 ± 4.5% vs 36.6 ± 4.5%; $P = 0.02$) with a nonsignificant increase in the liquid T50 (EXE vs PBO: 40.8 ± 4.2 vs 30.3 ± 4.2 min; $P = 0.09$).

### 3.3 | Plasma glucose

At baseline there were no significant differences in fasting plasma glucose, peak glucose, the early rise plasma glucose (incremental AUC $[iAUC]_{0-30min}$), $iAUC_{0-120min}$ or 2-h plasma glucose level between the EXE and the PBO groups (Table 1; Figure 2A).

At the post-treatment visit fasting plasma glucose was lower after EXE once weekly ($P = 0.03$) compared to PBO (Table 1; Figure 2B). Peak plasma glucose ($P = 0.006$) and the early rise ($iAUC_{0-30min}$) were also lower after EXE once weekly ($P = 0.008$), but there were no differences between EXE once weekly and PBO with regard to $iAUC_{0-120}$ ($P = 0.25$) or plasma glucose at 2 h ($P = 0.84$; Table 1; Figure 2B).

### 3.4 | Plasma insulin, C-peptide and glucagon

At baseline, and post-treatment, there were no statistically significant differences in fasting or postprandial insulin between the EXE and PBO groups (Table 1; Figures 2C,D).

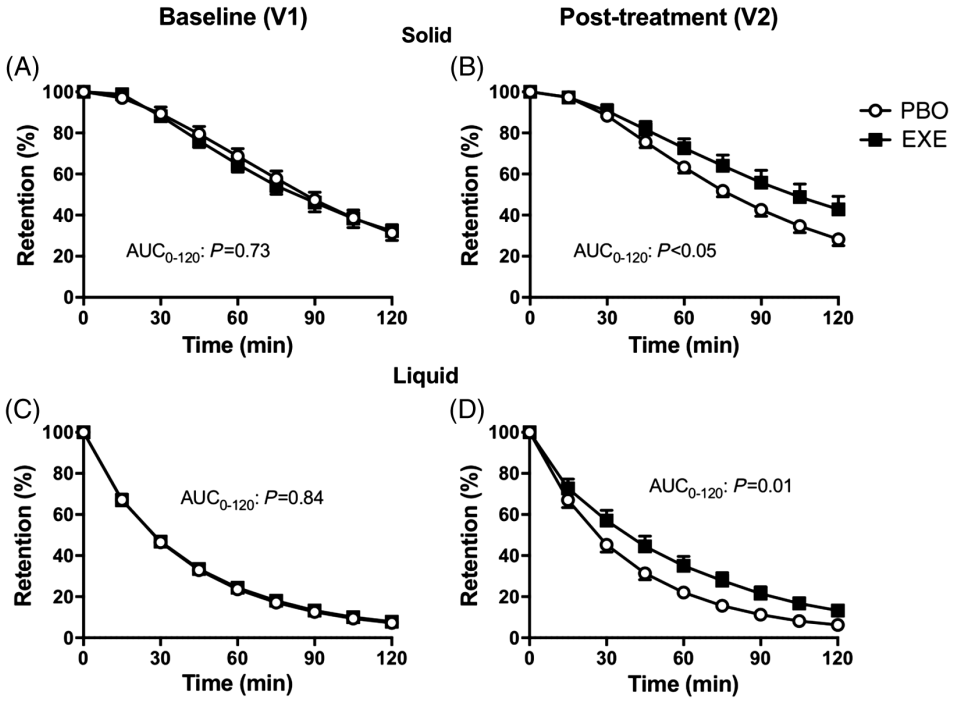


**FIGURE 1** Effects of exenatide once weekly (EXE) and placebo (PBO) on gastric emptying of solid (100 g ground beef) and liquid (150 mL 10% dextrose) meal components at baseline (A) and (C) and post-treatment (B) and (D) in healthy participants; n = 16 in both the EXE once weekly and PBO groups. Data are mean values ± SEM. V1, visit 1; V2, visit 2

**TABLE 1** Baseline variables prior to "treatment" (exenatide once weekly subcutaneously 2 mg or matching placebo), before and after consumption of a test meal comprising 100 g minced beef and 150 mL 10% dextrose in healthy participants

| | Baseline (Visit 1) | | | Post-treatment (Visit 2) | | |
|---|---|---|---|---|---|---|
| Variable | PBO | EXE once weekly | *P* | PBO | EXE once weekly | *P** |
| Fasting glucose, mmol/L | 4.9 ± 0.1 | 5.0 ± 0.1 | 0.67 | 5.0 ± 0.1 | 4.7 ± 0.1 | 0.03 |
| Peak glucose, mmol/L | 7.2 ± 0.2 | 7.3 ± 0.2 | 0.89 | 7.5 ± 0.2 | 6.8 ± 0.2 | 0.006 |
| 2-h glucose, mmol/L | 4.6 ± 0.1 | 4.5 ± 0.1 | 0.32 | 4.6 ± 0.1 | 4.36 ± 0.1 | 0.84 |
| $iAUC_{0-30min}$ | 30.9 ± 2.8 | 33.8 ± 3.7 | 0.55 | 32.9 ± 3.3 | 19.4 ± 3.3 | 0.008 |
| $iAUC_{0-120min}$ | 117.0 ± 11.4 | 98.7 ± 9.9 | 0.23 | 114.7 ± 10.5 | 97.0 ± 10.5 | 0.25 |
| Fasting insulin, mU/L | 3.9 ± 2.7 | 4.6 ± 1.7 | 0.45 | 5.4 ± 0.7 | 6.5 ± 0.7 | 0.24 |
| Peak insulin, mU/L | 30.3 ± 3.9 | 33.1 ± 3.7 | 0.60 | 32.2 ± 3.0 | 37.9 ± 3.0 | 0.18 |
| 2-h insulin, mU/L | 7.9 ± 1.5 | 8.6 ± 1.4 | 0.71 | 10.0 ± 0.8 | 8.5 ± 0.8 | 0.18 |
| $iAUC_{0-30min}$ | 321 ± 35 | 397 ± 67 | 0.33 | 322 ± 37 | 262 ± 37 | 0.27 |
| $iAUC_{0-120min}$ | 1622 ± 173 | 1584 ± 678 | 0.88 | 1670 ± 158 | 1693 ± 158 | 0.92 |
| Fasting C-peptide, pmol/L | 453 ± 38 | 471 ± 36 | 0.73 | 478 ± 32 | 593 ± 32 | 0.02 |
| Peak C-peptide, pmol/L | 1474 ± 107 | 1563 ± 90 | 0.53 | 1530 ± 93 | 1849 ± 93 | 0.02 |
| 2-h C-peptide, pmol/L | 853 ± 53 | 811 ± 286 | 0.19 | 894 ± 48 | 965 ± 48 | 0.30 |
| $iAUC_{0-30min}$ | 10 185 ± 902 | 12 736 ± 1663 | 0.19 | 10 363 ± 1296 | 8388 ± 1296 | 0.30 |
| $iAUC_{0-120min}$ | 75 957 ± 4503 | 77 754 ± 4610 | 0.78 | 78 293 ± 4847 | 78 579 ± 4847 | 0.97 |
| Fasting glucagon, pg/mL | 60.7 ± 4.1 | 57.6 ± 3.4 | 0.57 | 60.6 ± 2.3 | 57.3 ± 2.3 | 0.32 |
| 2-h glucagon, pg/mL | 93.1 ± 8.4 | 84.2 ± 6.2 | 0.40 | 92.4 ± 3.8 | 72.6 ± 3.8 | 0.001 |
| $iAUC_{0-30min}$ | 110 ± 39 | 57.6 ± 22 | 0.25 | 55.2 ± 18.7 | 65.3 ± 18.7 | 0.71 |
| $iAUC_{0-120min}$ | 1252 ± 310 | 1011 ± 799 | 0.52 | 1331 ± 195 | 897 ± 195 | 0.13 |
| Peak 3-OMG, mmol/L | 1.0 ± 0.06 | 1.1 ± 0.04 | 0.85 | 1.1 ± 0.03 | 1.0 ± 0.96 | 0.08 |
| 2-h 3-OMG, mmol/L | 0.84 ± 0.04 | 0.78 ± 0.04 | 0.19 | 0.81 ± 0.02 | 0.83 ± 0.02 | 0.29 |
| $iAUC_{0-30min}$ | 6.7 ± 0.87 | 7.5 ± 0.88 | 0.57 | 7.0 ± 0.62 | 3.7 ± 0.65 | 0.001 |
| $iAUC_{0-120min}$ | 88.0 ± 5.0 | 85.5 ± 12.7 | 0.68 | 87.0 ± 2.1 | 75.2 ± 2.2 | 0.001 |

3-OMG, 3-O-methyl-glucose. *Baseline-corrected post-treatment effects.
Data are mean ± SEM.

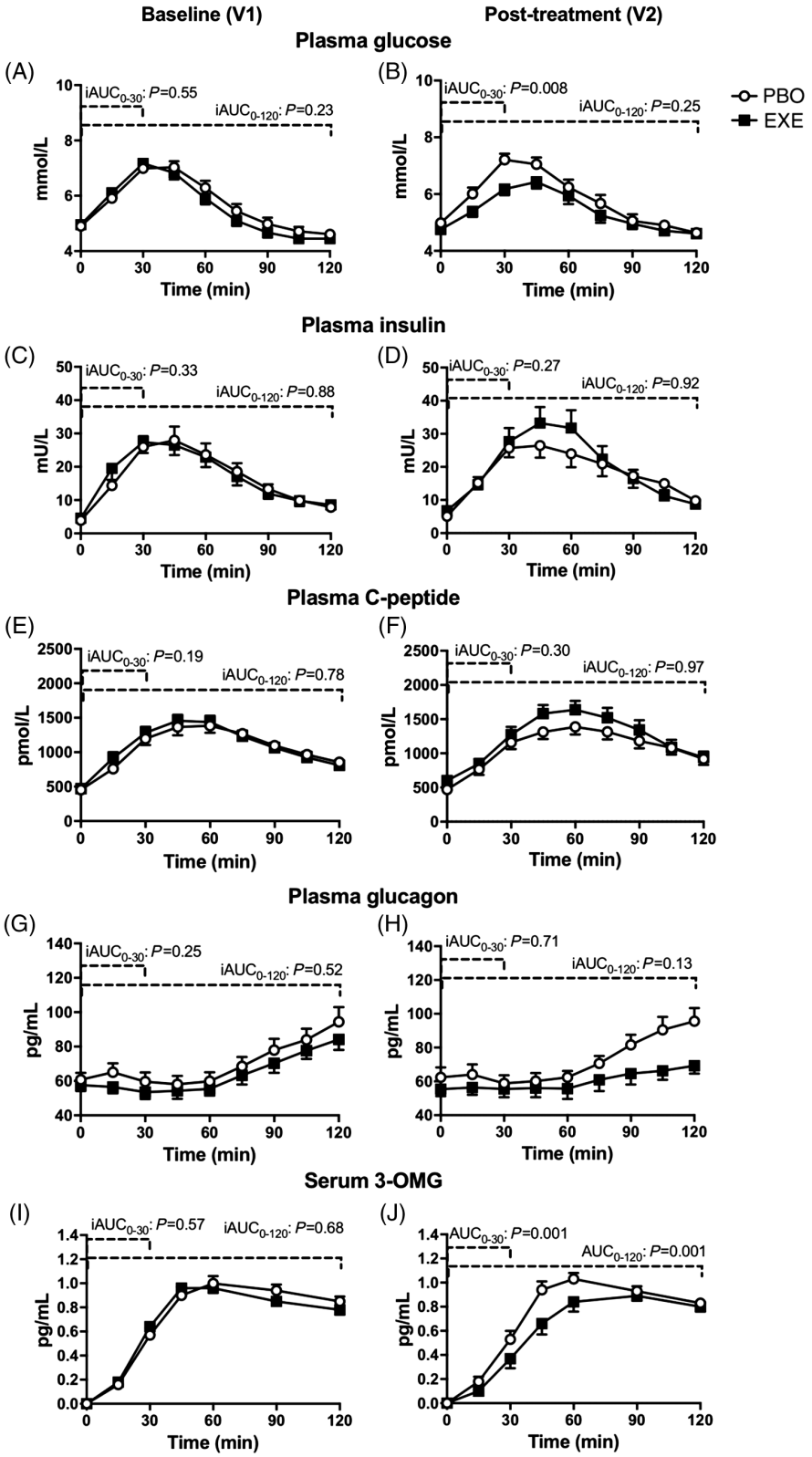


**FIGURE 2** Effects of exenatide once weekly (EXE) and placebo (PBO) on plasma glucose (A) and (B), insulin (C) and (D), C-peptide (E) and (F), glucagon (G) and (H) and serum 3-O-methyl-glucose (3-OMG) (I) and (J) in healthy participants; n = 16 in both the EXE once weekly and PBO groups. Data are mean values ± SEM. iAUC, incremental area under the curve; V1, visit 1; V2, visit 2

At baseline there were no other differences in fasting or postprandial C-peptide between the two groups (Table 1; Figure 2E). At the post-treatment visit, both fasting ($P$ = 0.02) and peak ($P$ = 0.02) C-peptide concentrations were greater after EXE once weekly compared to PBO, with no other differences between the two groups (Table 1; Figure 2F).

At baseline there were no differences in fasting or postprandial glucagon concentrations between the EXE and PBO groups (Table 1; Figure 2G). At the post-treatment visit there were no significant differences in fasting glucagon levels or the $iAUC_{0-30min}$ or $iAUC_{0-120min}$ between the two groups; however, the 2-h glucagon

level was lower ($P$ = 0.001) with EXE once weekly than with PBO (Table 1; Figure 2H).

### 3.5 | Glucose absorption

At baseline there were no differences in glucose absorption (serum 3-OMG levels) between the two groups (Table 1; Figure 2I). At the post-treatment visit, the peak 3-OMG concentration was nonsignificantly lower ($P$ = 0.08) with EXE once weekly (Table 1; Figure 2J). The early rise ($iAUC_{0-30min}$) in 3-OMG ($P$ = 0.001), and the $iAUC_{0-120min}$ ($P$ = 0.001) were both lower after EXE once weekly compared to PBO, with no difference in the 3-OMG concentration at 2 h between the two groups (Table 1; Figure 2J).

### 3.6 | Relationship between glycaemia and gastric emptying

When the data for both the EXE once weekly and PBO groups were pooled at the baseline visit, there was an inverse relationship between the intragastric retention of the liquid at t = 30 min with the early rise in plasma glucose from 0 to 30 min ($iAUC_{0-30min}$; $r$ = −0.41, $P$ = 0.02); when gastric emptying was faster, the rise in plasma glucose was greater. Similarly, at the post-treatment visit, there were inverse relationships between the intragastric retention of the liquid at t = 30 min and the rise in plasma glucose from 0 to 30 min ($iAUC_{0-30min}$) after both PBO ($r$ = −0.54, $P$ = 0.03) and EXE ($r$ = −0.76, $P$ = 0.001).

In the EXE once weekly group, the magnitude of glucose-lowering at t = 30 min from the baseline visit (visit 1) to the post-treatment visit (visit 2) was inversely related to the increase in T50 for liquid gastric emptying (ie, magnitude of the slowing of gastric emptying) between visits 1 and 2 ($r$ = −0.55, $P$ = 0.03; Figure 3).

There were no significant relationships between postprandial glycaemia and solid emptying.

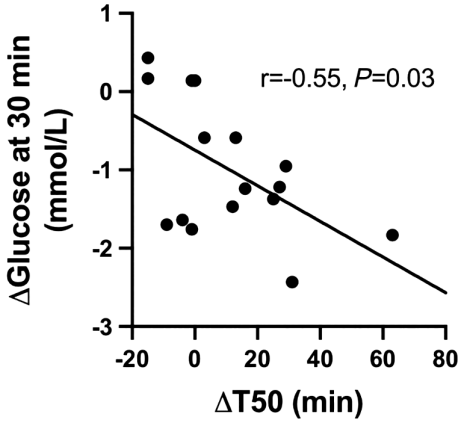


**FIGURE 3** Correlation between the change in plasma glucose concentrations at t = 30 min post-treatment (Visit 2) and change in liquid gastric 50% emptying time (T50) in the exenatide (EXE) once weekly group

### 3.7 | Relationship between weight loss, glycaemia and gastric emptying

There were no significant relationships between changes in either postprandial glycaemia or gastric emptying and weight loss.

## 4 | DISCUSSION

The present study established that, after 8 weeks' administration, EXE once weekly slows gastric emptying of a solid/liquid meal substantially and that this is related to a delay in absorption of ingested glucose and a reduction in postprandial glycaemia in healthy people. The demonstration that EXE once weekly, a long-acting GLP-1RA, delays gastric emptying is contrary to current thinking and has implications for its use in the management of type 2 diabetes.

That treatment with EXE once weekly slows gastric emptying of both solid and liquid meal components substantially is perhaps surprising; in the DURATION 1 study, comparing EXE twice daily and once weekly, without a PBO arm, EXE twice daily slowed paracetamol absorption markedly at 14 weeks, whereas EXE once weekly had no significant effect.[29] However, as alluded to, the paracetamol technique is associated with major deficiencies and, from our perspective, should not be used clinically. The present study did not include a comparison with EXE twice daily, but it is probable that the slowing of gastric emptying by EXE twice daily would be greater than with EXE once weekly. It is now appreciated that the relationship between gastric emptying and glycaemia is bi-directional, such that gastric emptying is not only a major determinant of, but is also determined by, the postprandial rise in blood glucose[11,12,30,38]; that is, acute hyperglycaemia (~15 mmol/L), and even changes within the normal postprandial range (4–8 mmol/L), slow gastric emptying in healthy people and those with diabetes.[30,38] Furthermore, hyperglycaemia potentiates the slowing of gastric emptying induced by acute administration of exogenous GLP-1 in healthy participants.[39] EXE once weekly also slowed oral glucose absorption, consistent with the delay in gastric emptying. Potentially, changes in small intestinal motility induced by EXE once weekly may have contributed to this effect.[40]

As expected, EXE once weekly reduced both fasting and postprandial plasma glucose, as is the case with other long-acting GLP-1RAs.[1] Comparative studies of EXE once weekly with EXE twice daily in type 2 diabetes indicate that EXE once weekly is associated with greater reductions in fasting/preprandial glucose, while EXE twice daily leads to greater reductions in postprandial glucose.[1,29] This is also the case when liraglutide is compared to lixisenatide.[41] In the present study, while plasma insulin levels did not differ, EXE once weekly increased both fasting and postprandial C-peptide concentrations, and stimulation of insulin secretion may have contributed to the glucose-lowering effect of EXE once weekly. EXE once weekly had no effect on plasma glucagon in the fasting state, but reduced the 2-h glucagon level, attesting to a glucagonostatic effect; however, changes in glucagon by EXE once weekly are unlikely to account for changes in glycaemia in the early postprandial period. It is likely that the effects of EXE once

weekly in increasing insulin secretion and suppressing glucagon will be greater in type 2 diabetes, given that the insulinotropic and glucagonostatic effects of GLP-1[2] GLP-1RAs[1] are glucose-dependent, requiring a threshold blood glucose of ≥8 mmol/L. Moreover, type 2 diabetes is associated with elevated fasting and impaired postprandial suppression of plasma glucagon.[2] We observed that the rise in plasma glucose between 0 and 30 min at baseline and in both treatment groups at the post-treatment visit, was inversely related to the rate of gastric emptying of liquids (carbohydrate-containing meal component), consistent with previous studies establishing gastric emptying as a major determinant of early postprandial glycaemia.[11,12] This is despite the predictably modest glycaemic response in healthy participants. Importantly, the magnitude of postprandial glucose-lowering by EXE once weekly was related to the magnitude of slowing of gastric emptying, an effect shown in studies of short-acting GLP-1RAs.[23] It has been recently appreciated that in contrast to poorly controlled type 2 diabetes (HbA1c >8.0%) associated with established microvascular complications,[31] gastric emptying is usually normal, or modestly accelerated[42] in people with type 2 diabetes who have reasonable glycaemic control, which provides an additional rationale for the use of interventions that slow gastric emptying to improve glycaemic control in type 2 diabetes. We deliberately studied a cohort of healthy people to avoid the potential confounding effects of marked hyperglycaemia and autonomic neuropathy for a "proof-of-principle" study. The selection of participants aged >50 years was based on ethical restrictions relating to the use of scintigraphy in healthy participants; however, this also typically represents the age of people with type 2 diabetes usually studied in clinical trials and, therefore, does not represent a limitation. Our observations should, ideally, be confirmed in people with type 2 diabetes. Given that blood glucose concentrations will inevitably be higher and gastric emptying probably more variable in this group, the outcomes are likely to be stronger. It should also be appreciated that, in the present study, the lowering of glycaemia by EXE once weekly, albeit modest, may have led to an underestimate in the magnitude of the slowing of gastric emptying.

Type 2 diabetes is associated with an increased prevalence of gastrointestinal symptoms which affect quality of life adversely.[43] Gastrointestinal adverse effects, particularly nausea, are associated with EXE once weekly and other GLP-1RAs and may lead to discontinuation of therapy.[1] A limitation of the majority of previous studies in this area is that symptoms were assessed by "self-report", which is unreliable. In the present study, EXE once weekly was very well tolerated, with no differences in low scores for nausea (assessed using a validated measure), between the two groups. Hence, the slowing of gastric emptying cannot be attributed to nausea and, conversely, induction of slower gastric emptying did not induce nausea. The observed weight loss (~2 kg) with EXE once weekly is consistent with studies of longer duration with EXE once weekly[29] as well as other long-acting GLP-1RAs.[27,28]

Strengths of the present study include the use of scintigraphy to measure gastric emptying of both solids and liquids, the assessment of gastric emptying at stable, steady-state concentrations of the drug (expected to be achieved at 6 weeks), and the randomized, double-blind, PBO-controlled study design. We cannot exclude the possibility that the slowing of gastric emptying by EXE once weekly diminishes after 8 weeks, but this appears unlikely, nor can we conclude whether measurements of gastric emptying before steady-state, for example, at 2 weeks, would have shown a more potent slowing. Restrictions in the use of dual isotope scintigraphy did not permit the latter assessment in this study; however, future studies using a single isotope would allow more frequent gastric emptying measurements to be performed. Given the observed slowing of gastric emptying achieved by EXE once weekly, the period of data acquisition should ideally be extended, possibly to 4 h, to provide more precise information about gastric emptying dynamics. It is also unclear whether our observations would apply to other long-acting GLP-1RAs.

In conclusion, EXE once weekly slows gastric emptying after steady-state administration in healthy people, and this is related to the reduction in postprandial glucose. Hence, it is plausible that the lowering of postprandial glucose in type 2 diabetes by EXE once weekly is mediated, at least in part, by retardation of gastric emptying, an effect which should be greater in individuals with faster gastric emptying at baseline. Accordingly, routine measurement of gastric emptying (scintigraphy, breath test or ultrasonography) may allow the use of EXE once weekly and other GLP-1RAs to be more personalized and effective.

## ACKNOWLEDGMENTS

The authors thank Radiology SA for their generous donation of a research-dedicated gamma camera to perform the scintigraphic measurements, and Scott Standfield and Judith Wishart of the CRE in Translating Nutritional Science to Good Health for performing the gut hormone assays.

## CONFLICTS OF INTEREST

K.L.J. has received research funding from Sanofi and AstraZeneca, and study medication from Merck Sharp & Dohme. L.K.P. has received research funding from Sanofi and Glaxo Smith Kline and has participated in symposia for Novo Nordisk, Merck Sharp and Dohme and Novartis and has received honoraria for this activity. T.W. has received research funding from Novartis and AstraZeneca. C.K.R. has received research funding from AstraZeneca, Merck Sharp & Dohme, Eli Lilly, Novartis and Sanofi. M.H. has participated in advisory boards and/or symposia for Novo Nordisk, Sanofi, Novartis, Eli Lilly, Merck Sharp & Dohme, Boehringer Ingelheim and AstraZeneca, and has received honoraria for this activity. None of the other authors has any personal or financial conflict of interest to declare.

## AUTHOR CONTRIBUTIONS

K.L.J was involved in the conception, design, and coordination of the study, scintigraphic data analysis, data interpretation, statistical analysis and writing of the manuscript. L.Q.H. was involved in data collection, data interpretation and statistical analysis. S.H. was involved in participant recruitment, data collection, scintigraphic data analysis and data interpretation. R.S.R was involved in participant recruitment, data collection and data interpretation. H.T.P. assisted with data collection

and was involved in data interpretation. L.P., C.S.M., T.W., J.E.S., C.K.R. and M.H. were involved in the conception and design of the study and data interpretation. C.-H.M. wrote purpose-built software to perform scintigraphic data analysis and was involved in data interpretation. K.L. performed the statistical analysis and was involved in data interpretation. K.L.J. and M.H. 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.

## ORCID

*Karen L. Jones* https://orcid.org/0000-0002-1155-5816
*Tongzhi Wu* https://orcid.org/0000-0003-1656-9210
*Christopher K. Rayner* https://orcid.org/0000-0002-5527-256X

## REFERENCES

1. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2012;8:728-742.
2. Phillips LK, Deane AM, Jones KL, Rayner CK, Horowitz M. Gastric emptying and glycaemia in health and diabetes mellitus. *Nat Rev Endocrinol*. 2015;11:112-128.
3. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular Actions and Clinical Outcomes With Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors. *Circulation*. 2017;136:849-870.
4. Bethel MA, Patel RA, Merrill P, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6:105-113.
5. Linnebjerg H, Park S, Kothare PA, et al. Effect of exenatide on gastric emptying and relationship to postprandial glycemia in type 2 diabetes. *Regul Pept*. 2008;151:123-129.
6. Little TJ, Pilichiewicz AN, Russo A, et al. Effects of intravenous glucagon-like peptide-1 on gastric emptying and intragastric distribution in healthy subjects: relationships with postprandial glycemic and insulinemic responses. *J Clin Endocrinol Metab*. 2006;91:1916-1923.
7. Meier JJ, Gallwitz B, Salmen S, et al. Normalization of glucose concentrations and deceleration of gastric emptying after solid meals during intravenous glucagon-like peptide 1 in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2003;88:2719-2725.
8. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*. 1993;36:741-744.
9. Horowitz M, Maddox AF, Wishart JM, Harding PE, Chatterton BE, Shearman DJ. Relationships between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. *Eur J Nucl Med*. 1991;18:229-234.
10. Jones KL, Horowitz M, Wishart JM, Maddox AF, Harding PE, Chatterton BE. Relationships between gastric emptying, intragastric meal distribution and blood glucose concentrations in diabetes mellitus. *J Nucl Med*. 1995;36:2220-2228.
11. Horowitz M, Edelbroek MA, Wishart JM, Straathof JW. Relationship between oral glucose tolerance and gastric emptying in normal healthy subjects. *Diabetologia*. 1993;36:857-862.
12. Jones KL, Horowitz M, Carney BI, Wishart JM, Guha S, Green L. Gastric emptying in "early" noninsulin-dependent diabetes mellitus relationship to oral glucose tolerance and appetite. *J Nucl Med*. 1996;37:1643-1648.
13. Mourot J, Thouvenot P, Couet C, Antoine JM, Krobicka A, Debry G. Relationship between the rate of gastric emptying and glucose and insulin responses to starchy foods in young healthy adults. *Am J Clin Nutr*. 1988;48:1035-1040.
14. Trahair LG, Horowitz M, Stevens JE, et al. Effects of exogenous glucagon-like peptide-1 on blood pressure, heart rate, gastric emptying, mesenteric blood flow and glycaemic responses to oral glucose in older individuals with normal glucose tolerance or type 2 diabetes. *Diabetologia*. 2015;58:1769-1778.
15. Delgado-Aros S, Kim DY, Burton DD, et al. Effect of GLP-1 on gastric volume, emptying, maximum volume ingested, and postprandial symptoms in humans. *Am J Physiol Gastrointest Liver Physiol*. 2002;282:G424-G431.
16. Ma J, Pilichiewicz AN, Feinle-Bisset C, et al. Effects of variations in duodenal glucose load on glycaemic, insulin, and incretin responses in type 2 diabetes. *Diabet Med*. 2012;29:604-608.
17. Pilichiewicz AN, Chaikomin R, Brennan IM, et al. Load-dependent effects of duodenal glucose on glycemia, gastrointestinal hormones, antropyloroduodenal motility, and energy intake in healthy men. *Am J Physiol Endocrinol Metab*. 2007;293:E743-E753.
18. Nauck MA. Is glucagon-like peptide 1 an incretin hormone? *Diabetologia*. 1999;42:373-379.
19. Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol*. 1997;273:E981-E988.
20. Umapathysivam MM, Lee MY, Jones KL, et al. Comparative effects of prolonged and intermittent stimulation of the glucagon-like Peptide 1 receptor on gastric emptying and glycemia. *Diabetes*. 2014;63:785-790.
21. Nauck MA, Kemmeries G, Holst JJ, Meier JJ. Rapid tachyphylaxis of the glucagon-like peptide 1-induced deceleration of gastric emptying in humans. *Diabetes*. 2011;60:1561-1565.
22. Lorenz M, Pfeiffer C, Steinstrasser A, et al. Effects of lixisenatide once daily on gastric emptying in type 2 diabetes–relationship to postprandial glycemia. *Regul Pept*. 2013;185:1-8.
23. Jones KL, Rigda RS, Buttfield MDM, et al. Effects of lixisenatide on postprandial blood pressure, gastric emptying and glycaemia in healthy people and people with type 2 diabetes. *Diabetes Obes Metab*. 2019;21:1158-1167.
24. Jelsing J, Vrang N, Hansen G, Raun K, Tang-Christensen M, Knudsen LB. Liraglutide: short-lived effect on gastric emptying – long lasting effects on body weight. *Diabetes Obes Metab*. 2012;14:531-538.
25. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care*. 2003;26:881-885.
26. Flint A, Kapitza C, Hindsberger C, Zdravkovic M. The once-daily human glucagon-like peptide-1 (GLP-1) analog liraglutide improves postprandial glucose levels in type 2 diabetes patients. *Adv Ther*. 2011;28:213-226.
27. Horowitz M, Flint A, Jones KL, et al. Effect of the once-daily human GLP-1 analogue liraglutide on appetite, energy intake, energy expenditure and gastric emptying in type 2 diabetes. *Diabetes Res Clin Pract*. 2012;97:258-266.
28. Halawi H, Khemani D, Eckert D, et al. Effects of liraglutide on weight, satiation, and gastric functions in obesity: a randomised, placebo-controlled pilot trial. *Lancet Gastroenterol Hepatol*. 2017;2:890-899.
29. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet*. 2008;372:1240-1250.
30. Fraser RJ, Horowitz M, Maddox AF, Harding PE, Chatterton BE, Dent J. Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia*. 1990;33:675-680.
31. Horowitz M, Harding PE, Maddox AF, et al. Gastric and oesophageal emptying in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*. 1989;32:151-159.
32. Chang J, Russo A, Bound M, Rayner CK, Jones KL, Horowitz M. A 25-year longitudinal evaluation of gastric emptying in diabetes. *Diabetes Care*. 2012;35:2594-2596.

33. Wysham C, Grimm M, Chen S. Once weekly exenatide: efficacy, tolerability and place in therapy. *Diabetes Obes Metab*. 2013;15:871-881.
34. Collins PJ, Horowitz M, Cook DJ, Harding PE, Shearman DJ. Gastric emptying in normal subjects–a reproducible technique using a single scintillation camera and computer system. *Gut*. 1983;24:1117-1125.
35. Wu T, Zhang X, Trahair LG, et al. Small intestinal glucose delivery affects the lowering of blood glucose by acute vildagliptin in type 2 diabetes. *J Clin Endocrinol Metab*. 2016;101:4769-4778.
36. Wu T, Xie C, Wu H, Jones KL, Horowitz M, Rayner CK. Metformin reduces the rate of small intestinal glucose absorption in type 2 diabetes. *Diabetes Obes Metab*. 2017;19:290-293.
37. Sepple CP, Read NW. Gastrointestinal correlates of the development of hunger in man. *Appetite*. 1989;13:183-191.
38. Schvarcz E, Palmer M, Aman J, Horowitz M, Stridsberg M, Berne C. Physiological hyperglycemia slows gastric emptying in normal subjects and patients with insulin-dependent diabetes mellitus. *Gastroenterology*. 1997;113:60-66.
39. Plummer MP, Jones KL, Cousins CE, et al. Hyperglycemia potentiates the slowing of gastric emptying induced by exogenous GLP-1. *Diabetes Care*. 2015;38:1123-1129.
40. Thazhath SS, Marathe C, Wu T, et al. Effects of the glucagon-like peptide-1 (GLP-1) receptor agonist, exenatide, on small intestinal motility, flow and glucose absorption in healthy subjects and type 2 diabetes. *United Eur Gastroenterol J*. 2014;2:A29.
41. Meier JJ, Rosenstock J, Hincelin-Mery A, et al. Contrasting effects of lixisenatide and liraglutide on postprandial glycemic control, gastric emptying, and safety parameters in patients with type 2 diabetes on optimized insulin glargine with or without metformin: A randomized, open-label trial. *Diabetes Care*. 2015;38:1263-1273.
42. Watson LE, Xie C, Wang X, et al. Gastric emptying in patients with well-controlled type 2 diabetes compared to non-diabetic young and older controls. *J Clin Endocrinol Metab*. 2019;104:3311-3319.
43. Talley NJ, Young L, Bytzer P, et al. Impact of chronic gastrointestinal symptoms in diabetes mellitus on health-related quality of life. *Am J Gastroenterol*. 2001;96:71-76.


## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Jones KL, Huynh LQ, Hatzinikolas S, et al. Exenatide once weekly slows gastric emptying of solids and liquids in healthy, overweight people at steady-state concentrations. *Diabetes Obes Metab*. 2020;22:788–797. https://doi.org/10.1111/dom.13956