

# Exogenous glucagon-like peptide-1 attenuates glucose absorption and reduces blood glucose concentration after small intestinal glucose delivery in critical illness

Asaf Miller, Adam M Deane, Mark P Plummer, Caroline E Cousins, Lee-anne S Chapple, Michael Horowitz and Marianne J Chapman

Acute hyperglycaemia in critically ill patients without pre-existing diabetes is associated with substantial increases in morbidity and mortality.<sup>1</sup> For this reason, treatment of hyperglycaemia with a regimen of intravenous insulin is part of standard care.<sup>2</sup> Insulin is an effective drug to treat hyperglycaemia but its use is associated with hypoglycaemia, which leads to short- and long-term harm.<sup>3,4</sup> Hence there is considerable interest in approaches to treat hyperglycaemia in the critically ill which mitigate the risk of hypoglycaemia.<sup>5,6</sup>

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from enteric cells of the distal small intestine and colon in response to luminal fat, carbohydrate, protein and bile acids.<sup>7,8</sup> Endogenous and exogenous GLP-1 lower blood glucose by stimulating insulin secretion, inhibiting glucagon secretion and slowing gastric emptying.<sup>9-11</sup> In terms of glucose-lowering, the slowing of gastric emptying may be physiologically the most important effect. More recently, GLP-1 has been shown to also reduce small intestinal motility, slow luminal intestinal flow and inhibit glucose absorption in healthy people and ambulant patients with type 2 diabetes.<sup>12</sup> These effects may be important in critically ill patients.

The insulinotropic and glucagonostatic effects of GLP-1 are strictly glucose-dependent, so at blood glucose concentrations below about 4 mmol/L, even pharmacological doses of GLP-1 have little or no impact on blood glucose concentration.<sup>13</sup> GLP-1 is rapidly metabolised by dipeptidyl peptidase-4 (DPP-4), predominantly on capillary endothelia, resulting in a short GLP-1 half-life of 1–2 minutes and a stable context-sensitive half-time.<sup>14,15</sup> The rapid, organ-independent metabolism and glucose-dependent safety profile of GLP-1 has generated considerable interest in its use as a novel therapeutic agent for the management of hyperglycaemia in the critically ill.<sup>5,8</sup>

Previous studies in critically ill patients have shown that exogenous infusion of GLP-1 at pharmacological concentrations lowers blood glucose via the known effects of pancreatic alpha and beta cells and the slowing of gastric emptying.<sup>16-21</sup> However, glycaemic control in this population is complex and involves a balance between carbohydrate absorption and counter-regulatory mechanisms. The effect of GLP-1 on small intestinal carbohydrate absorption during critical illness remains unknown.

## ABSTRACT

**Objective:** To evaluate the effect of exogenous glucagon-like peptide-1 (GLP-1) on small intestinal glucose absorption and blood glucose concentrations during critical illness.

**Design, setting and participants:** A prospective, blinded, placebo-controlled, cross-over, randomised trial in a mixed medical-surgical adult intensive care unit, with 12 mechanically ventilated critically ill patients, who were suitable for receiving small intestinal nutrient.

**Interventions:** On consecutive days, in a randomised order, participants received intravenous GLP-1 (1.2 pmol/kg/min) or placebo (0.9% saline) as a continuous infusion over 270 minutes. After 6 hours of fasting, intravenous infusions of GLP-1 or placebo began at T = -30 min (in which T = time), with the infusion maintained at a constant rate until study completion at T = 240 min. At T = 0 min, a 100 mL bolus of mixed liquid nutrient meal (1 kcal/mL) containing 3 g of 3-O-methyl-D-glucopyranose (3-OMG), a marker of glucose absorption, was administered directly into the small intestine, via a post-pyloric catheter, over 6 minutes.

**Main outcome measures:** Blood samples were taken at regular intervals for the measurement of plasma glucose and 3-OMG concentrations.

**Results:** Intravenous GLP-1 attenuated initial small intestinal glucose absorption (mean area under the curve [AUC]<sub>0-30</sub> for 3-OMG: GLP-1 group, 4.4 mmol/L/min [SEM, 0.9 mmol/L/min] v placebo group, 6.5 mmol/L/min [SEM, 1.0 mmol/L/min]; *P* = 0.01), overall small intestinal glucose absorption (mean AUC<sub>0-240</sub> for 3-OMG: GLP-1, 68.2 mmol/L/min [SEM, 4.7 mmol/L/min] v placebo, 77.7 mmol/L/min [SEM, 4.4 mmol/L/min]; *P* = 0.02), small intestinal glucose absorption and overall blood glucose concentration (mean AUC<sub>0-240</sub> for blood glucose: GLP-1, 2062 mmol/L/min [SEM, 111 mmol/L/min] v placebo 2328 mmol/L/min [SEM, 145 mmol/L/min]; *P* = 0.005).

**Conclusions:** Short-term administration of exogenous GLP-1 reduces small intestinal glucose absorption for up to 4 hours during critical illness. This is likely to be an additional mechanism for the glucose-lowering effect of this agent.

Our objective was to evaluate the effect of the novel glucose-lowering agent GLP-1 on glucose absorption in critically ill patients.

## Methods

### Study participants

We recruited mechanically ventilated critically ill patients from the Royal Adelaide Hospital intensive care unit, with consent obtained from the surrogate decision maker. Patients were eligible if they were 17 years or older, suitable for or receiving post-pyloric nutrition, and anticipated to remain ventilated for at least 48 hours. Exclusion criteria included a history of diabetes, pregnancy, contraindication to placement of a post-pyloric feeding tube or enteral feeding, having received a prokinetic drug in the preceding 24 hours, previous surgery on the small intestine, or any gastrointestinal surgery during their current hospital admission.

### Protocol

We studied patients on 2 consecutive days, during which they received intravenous synthetic GLP-1-(7-36) amide acetate (Bachem) at 1.2 pmol/kg/min on one day and placebo (0.9% saline) on the other day, in a blinded fashion, with the treatment assignment randomised by the Royal Adelaide Hospital pharmacy department.

The GLP-1 dose was based on previous studies and is known to raise plasma GLP-1 concentrations into the pharmacological range (about 3–4 times higher concentrations compared with concentrations measured after an oral glucose load).<sup>22,23</sup> Twelve hours before the study, a nasoduodenal feeding catheter was inserted, using an electromagnetic guidance technique (Cortrak, Corpak MedSystems), with placement confirmed by abdominal radiograph.<sup>24</sup> No prokinetics were administered during the entire study period.

On each day, enteral feeding was ceased 6 hours before study commencement. Reconstituted GLP-1 and placebo were each infused at a continuous rate of 1 mL/min, via a central or peripheral venous catheter, for 270 min ( $T = -30$  to 240 min [ $T = \text{time}$ ]).<sup>16</sup> At  $T = -6$  min, the test meal, Ensure 100 mL (Abbott), which is a mixed nutrient liquid (64% carbohydrate [maltodextrin], 13% protein and 21% fat [1 kcal/mL]), combined with 3-O-methyl-D-glucopyranose (3-OMG) (Sigma-Aldrich) 3 g dissolved in 5 mL of water, was administered directly into the small intestine over 6 min.<sup>25</sup> The post-prandial period began at  $T = 0$  min. Arterial blood samples were collected every 15–30 min from  $T = -30$  to 240 min for the measurement of plasma glucose and serum 3-OMG concentrations.<sup>26</sup> Once clotted, the samples were centrifuged at 3200 rpm for 15 min. Serum

was then stored at  $-70^{\circ}\text{C}$  for subsequent measurement of 3-OMG concentrations.

The study protocol was approved by the Royal Adelaide Hospital Research Ethics Committee and was conducted according to National Health and Medical Research Council guidelines.

### Measurement of blood glucose

We measured blood glucose concentrations using a portable glucose meter (Optium Xceed, Abbott)<sup>27</sup> with the overall blood glucose concentration indicated by the area under the curve (AUC) for glucose concentration.

### Measurement of glucose absorption

We assessed glucose absorption using serum concentrations of 3-OMG. 3-OMG is a glucose analogue, which uses the same intestinal active transport mechanism as glucose, but is not metabolised by the liver and is cleared unchanged in urine.<sup>28</sup> Hence, when a dose of 3-OMG is administered into the gastrointestinal tract, blood concentrations of 3-OMG indicate the rate of intestinal absorption.<sup>28</sup> The rate of glucose absorption is indicated by the peak concentration, the time to peak,<sup>17</sup> and total glucose absorption calculated by the AUC for 3-OMG concentration over that period of time.

### Statistical analysis

We based our sample size on previous studies; a sample size of 12 participants was expected to provide statistical power of 80% to detect an absolute difference of 10 mmol/L/min in the 3-OMG AUC at a two-sided alpha level of 0.05.<sup>17</sup> Initial effects for 3-OMG absorption were calculated as the  $\text{AUC}_{0-30}$ , and overall effects for 3-OMG absorption and blood glucose concentration were calculated as  $\text{AUC}_{0-240}$ . The AUC was calculated using the trapezoidal rule.<sup>20</sup> We used paired Student *t* tests to determine the significance of any observed difference, and report data as means with SEMs unless otherwise specified. We performed statistical analyses using SPSS, version 16.0 (IBM).

## Results

The study protocol was well tolerated in all participants. Demographic data and characteristics of the critically ill patients are summarised in Table 1.

### Blood glucose

On both study days, after test meal administration at  $T = 0$  min, there was an initial linear increase in plasma glucose concentration. The concentration peak occurred at about 30 minutes, followed by a gradual linear decline (Figure 1). The mean baseline blood glucose concentrations

**Table 1. Demographic and medical data of enrolled patients**

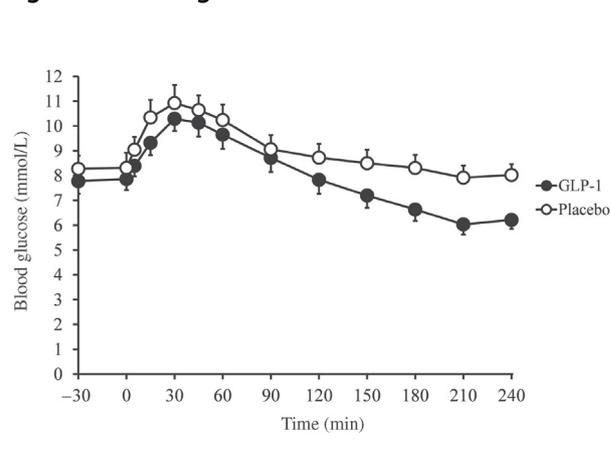
Characteristic	Result
Age, years (SD)	51 (4)
Sex proportion (men:women)	10:2
BMI, kg/m <sup>2</sup> (SD)	28.2 (1.6)
ICU admission APACHE II score (SD)	21 (2)
Admission diagnosis, <i>n</i>	
Trauma	5
ARDS	2
Cardiac arrest	2
Pneumonia	1
Intracranial haemorrhage	1
Sepsis	1
Receiving insulin before study, <i>n</i>	7
Time in ICU before study, days (SD)	6.8 (1.5)
Serum creatinine concentration on day of study, µmol/L (SD)	90.7 (18.6)
Admission HbA <sub>1c</sub> level, % (SD)	5.7% (0.1%)

BMI = body mass index. ICU = intensive care unit. APACHE = Acute Physiology and Chronic Health Evaluation. ARDS = acute respiratory distress syndrome. HbA<sub>1c</sub> = glycated haemoglobin.

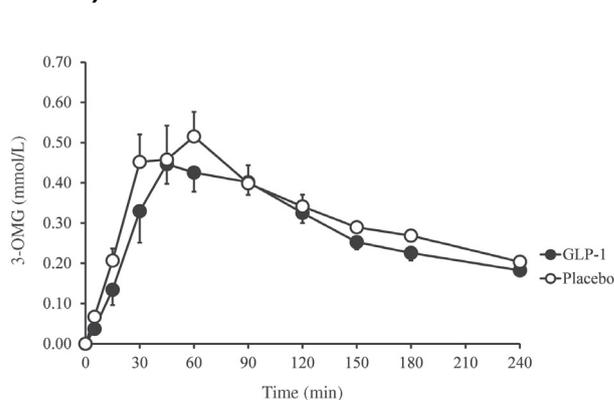
(at T = -30 min) were: GLP-1 group, 7.8 mmol/L (SEM, 0.5 mmol/L) v placebo group, 8.3 mmol/L (SEM, 0.5 mmol/L) ( $P = 0.142$ ). Mean peak blood glucose concentrations were: GLP-1 group, 10.9 mmol/L (SEM, 0.4 mmol/L) v placebo group, 11.4 mmol/L (SEM, 0.6 mmol/L) ( $P = 0.215$ ). The values were similar on the 2 study days. GLP-1 administration reduced the overall blood glucose concentration over the study period, with mean AUC<sub>0-240</sub> values as follows: GLP-1, 2062 mmol/L/min (SEM, 111 mmol/L/min) v placebo, 2328 mmol/L/min (SEM, 145 mmol/L/min) ( $P = 0.005$ ).

### Glucose absorption

On both placebo and GLP-1 study days, there was an initial linear rise in 3-OMG concentrations, which reached a peak 30–60 min after the meal, and then a gradual linear decline (Figure 2). There was no difference in peak 3-OMG concentrations (GLP-1, 0.57 mmol/L [SEM, 0.07 mmol/L] v placebo, 0.61 mmol/L [SEM, 0.05 mmol/L];  $P = 0.483$ ) or time to peak (GLP-1, 37.5 min [SEM, 3.5 min] v placebo, 33.8 min [SEM, 2.7 min];  $P = 0.191$ ). However, GLP-1 administration reduced the mean initial 3-OMG concentrations (AUC<sub>0-30</sub>: GLP-1, 4.4 mmol/L/min [SEM, 0.9 mmol/L/min] v placebo, 6.5 mmol/L/min [SEM, 1.0 mmol/L/min];  $P = 0.01$ ) and mean overall 3-OMG concentrations (AUC<sub>0-240</sub>: GLP-1, 68.2 mmol/L/min [SEM, 4.7 mmol/L/min] v placebo, 77.7 mmol/L/min [SEM, 4.4 mmol/L/min];  $P = 0.02$ ). 3-OMG concentrations had not returned to baseline at 240 min.

**Figure 1. Blood glucose concentrations over time\***

GLP-1 = glucagon-like peptide-1. \* Peak blood glucose concentrations and time to peak concentrations were similar, regardless of study drug.

**Figure 2. Glucose absorption (concentrations of 3-OMG)\***

3-OMG = 3-O-methyl-D-glucopyranose. GLP-1 = glucagon-like peptide-1. \* Peak 3-OMG concentrations and time to peak concentrations were similar between GLP-1 and placebo study days.

### Discussion

GLP-1 agonists are increasingly being used for the management of hyperglycaemia in people with diabetes in the community. Both synthetic GLP-1 and its agonists have the potential for use during critical illness. It is therefore important to understand the mechanisms by which this agent reduces blood glucose concentrations. Our key finding is that in critically ill patients, short-term exogenous administration of GLP-1 at 1.2 pmol/kg/min reduces glucose absorption. In addition, and consistent with previous studies, post-prandial glycaemic excursions in the critically ill were diminished during GLP-1 administration. Our study shows that one of the mechanisms by which GLP-1 reduces

the blood glucose concentration during critical illness is to reduce glucose absorption.

GLP-1 reduces blood glucose concentration by several established mechanisms. It increases insulin, and suppresses glucagon secretion, but only when glucose concentrations are elevated. This latter quality makes it attractive in the management of hyperglycaemia in critical illness as it does not cause hypoglycaemia. GLP-1 also slows gastric emptying and, in the ambulant patient, reduces food intake. In the critically ill, exogenous GLP-1 markedly attenuates glycaemic excursions after intragastric<sup>17</sup> and small intestinal nutrient administration.<sup>16,18</sup> It also reduces the rate of glucose absorption when the nutrient liquid is administered directly into the stomach.<sup>17</sup> However, it is not clear if this reduction in the rate of glucose absorption is due to the effect of GLP-1 on gastric emptying, as the rate of gastric emptying is a major determinant of nutrient absorption and the post-prandial glycaemic response to the presence of carbohydrate.<sup>11,26,29</sup> Therefore, in order to investigate whether glucose absorption is reduced by GLP-1, independent of its effect to slow gastric emptying, we administered the nutrient liquid directly into the small intestine.

The rate and extent of glucose absorption depend on a number of factors. In addition to the rate of gastric emptying, variables such as small intestinal transit time, the available contact surface area (length and height of surface villi) and the number and function of intestinal transporters are all important.<sup>25,30</sup> Previous data from animals and ambulant humans indicate that GLP-1 has the capacity to reduce glucose absorption via effects on small intestinal motility and luminal flow of intestinal contents.<sup>12</sup> In rats, supra-pharmacological doses of GLP-1 cause dose-dependent slowing of small intestinal transit,<sup>31</sup> and in fasted humans, pharmacological doses of GLP-1 reduce the frequency of small intestinal migrating motor complexes.<sup>32</sup> More recently, it was reported that in ambulant patients with type 2 diabetes, duodenal pressure waves and antegrade flow events were fewer after the administration of the GLP-1 agonist exenatide, and that these motility features were associated with a modest reduction in glucose absorption.<sup>12</sup>

### Study limitations

Our study has several limitations. First is the uncertain clinical importance of a small, though statistically significant, reduction in carbohydrate absorption. A reduction in glucose absorption may be beneficial in terms of blood glucose concentration but detrimental in terms of nutritional requirements. Both hyperglycaemia and reduced nutrient delivery are associated with increased mortality.<sup>33</sup> It is therefore possible that impaired carbohydrate absorption may adversely affect important clinical outcomes.<sup>34</sup> However, interventional studies have not shown a benefit

with increasing or decreasing carbohydrate delivery.<sup>35,36</sup>

We evaluated only a short (4-hour) period of administration, and a tachyphylactic response (rapidly decreasing response to successive drug doses) to the gastrointestinal effects after prolonged stimulation of the GLP-1 receptor has been reported. Slowing of gastric emptying becomes less evident with prolonged exposure to the agent.<sup>29,37</sup> Hence, the results of our study may not be representative of longer term effects. Also, as we studied only a 4-hour period, only the extent of glucose absorption over 4 hours, not total glucose absorption, can be reported.

We evaluated the effect of only a single dose of GLP-1 (1.2 pmol/kg/min). This was a decision based on previous studies and, given that the gastrointestinal effects of GLP-1 are dose-dependent,<sup>38</sup> effects may vary with different dosing. In addition, we did not assess mechanistic reasons for the reduced glucose absorption; specifically, we did not evaluate small intestinal motility, nor concentrations of insulin or glucagon. However, as the observed effect of GLP-1 on glucose absorption is consistent with effects seen in healthy people and patients with diabetes, it is likely the underlying mechanisms will be the same.<sup>12</sup>

Finally, we evaluated the effects in a relatively small, heterogeneous cohort of critically ill patients, at various times after their admission, but this limitation may have been of greater relevance if the study outcome had been negative, rather than positive.

There is a plausible rationale for the use of GLP-1 as a novel glucose-lowering therapy in the critically ill. When compared with insulin administration, the proposed advantages of GLP-1 include avoidance of hypoglycaemia, attenuation of glycaemic variability, putative beneficial cardiac effects, and a reduction in nursing workloads.<sup>8,39</sup> Our results provide an additional mechanistic reason for the glucose-lowering effect of GLP-1. However, as the effects of GLP-1 on the small intestine are modest, it is likely to be a more effective glucose-lowering agent when the patient is receiving intragastric rather than small intestinal feeding.

The attenuation of glucose absorption appeared relatively small, but the prolonged administration of GLP-1 agonists to ambulant patients with type 2 diabetes and to people who are overweight or obese results in weight reduction,<sup>40</sup> probably via centrally mediated effects on appetite suppression. Given the concerns relating to the magnitude and impact of weight loss and sarcopenia after critical illness,<sup>41</sup> further evaluation of the impact of glucose-lowering drugs on body composition would be of benefit.

### Conclusion

GLP-1 at 1.2 pmol/kg/min reduces blood glucose concentration in critically ill patients, partly by reducing glucose absorption.

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## Competing interests

None declared.

## Author details

Asaf Miller, Intensivist<sup>1,2</sup>

Adam M Deane, Intensivist<sup>2,3,4</sup>

Mark P Plummer, Trainee Intensivist<sup>3,5</sup>

Caroline E Cousins, Research Assistant<sup>2</sup>

Lee-anne S Chapple, Dietitian and PhD Candidate<sup>2</sup>

Michael Horowitz, Endocrinologist<sup>4,6</sup>

Marianne J Chapman, Intensivist<sup>2,3,4</sup>

1 Assaf Harofeh Medical Center, Israel.

2 Intensive Care Unit, Royal Adelaide Hospital, Adelaide, SA, Australia.

3 Discipline of Acute Care Medicine, University of Adelaide, Adelaide, SA, Australia.

4 NHMRC Centre of Research Excellence in the Translation of Nutritional Science into Good Health, University of Adelaide, Adelaide, SA, Australia.

5 Neurosciences and Trauma Critical Care Unit, Addenbrooke's Hospital, Cambridge, UK.

6 Discipline of Medicine, University of Adelaide, Adelaide, SA, Australia.

**Correspondence:** Marianne.Chapman@sa.gov.au

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