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Randomized, double-blind, placebo-controlled crossover trial of once daily empagliflozin 25mg for the treatment of postprandial hypoglycaemia after Roux-en-Y gastric bypass

Short running title: Empagliflozin 25mg for postbariatric hypoglycaemia

Clinical trial registration: Clinicaltrials.gov: NCT05057819

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Abstract

Aims

To investigate the effect of empagliflozin on glucose dynamics in individuals suffering from postbariatric hypoglycaemia (PBH) after Roux-en-Y gastric bypass (RYGB).

Methods

Twenty-two adults with PBH after RYGB were randomized to empagliflozin 25 mg or placebo once daily over 20 days in a randomized, double-blind, placebo-controlled, crossover trial. The primary efficacy outcome was the amplitude of plasma glucose excursion (peak to nadir) during a mixed meal tolerance test (MMTT). Outcomes of the outpatient period were assessed using continuous glucose monitoring (CGM) and an event-tracking app.

Results

The amplitude of glucose excursion during the MMTT was 8.1±2.4 mmol/L with empagliflozin vs 8.1±2.6 mmol/L with placebo (mean±SD, p=0.807). CGM-based mean amplitude of glucose excursion (MAGE) during the 20 day-period was lower with empagliflozin than placebo (4.8±1.3 vs 5.2±1.6. p=0.028). Empagliflozin reduced the time spent with CGM values >10.0 mmol/L (3.8±3.5 % vs. 4.7±3.8 %, p =0.009), but not the time spent with CGM values <3.0 mmol/L (1.7±1.6 % vs. 1.5±1.5 %, p=0.457). No significant difference was observed in the quantity and quality of recorded symptoms. Eleven adverse events occurred with empagliflozin (three drug-related) and six with placebo.

Conclusions

Empagliflozin 25 mg reduces glucose excursions but not hypoglycaemia in individuals with PBH.

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Introduction

While bariatric surgery has well-documented beneficial effects on weight and obesity-related comorbidities [1], the anatomical rearrangement of the gastrointestinal tract remarkably alters glucose absorption and insulin kinetics causing an increase in glycaemic variation [2-4]. Etiologically linked is the phenomenon of postbariatric hypoglycaemia (PBH), which is characterised by an early post-meal rise in plasma glucose followed by a rapid fall to hypoglycaemic levels [5]. Accelerated glucose absorption and exaggerated secretion of the incretin hormone GLP-1 are key contributors to excessive insulin exposure and consequently to the rapid drops in glucose levels [6-8]. Prevalence estimates for PBH are uncertain due to diagnostic heterogeneity but may be as high as 30-44% [9,10].

In the absence of approved pharmacotherapies, dietary modifications, in particular carbohydrate restriction, remain the first-line therapy of PBH [11,12]. Although proven effective [13], challenges remain, such as the long-term adherence and inhibition of social life, calling for supportive pharmacological approaches.

As a pharmacological alternative, off-label use of acarbose, which reduces postprandial glucose excursions via inhibition of the intestinal alpha-glucosidase inhibitor, was proven effective in mitigating PBH [14,15 16]. However, gastrointestinal side effects due to incomplete glucose absorption and the inconvenient dosing (e.g. before every meal) underscore the need for alternatives. Empagliflozin is a highly selective inhibitor of the renal sodium-glucose cotransporter 2 (SGLT2) and induces glucose depletion via increased urinary glucose excretion while intestinal glucose absorption remains unaffected [17]. Empagliflozin was shown to reduce glucose exposure and glycaemic variability in patients with diabetes [18] and first insights from a recent study exploring the effects of a single dose of empagliflozin in PBH patients revealed beneficial effects on hypoglycaemia encouraging its further evaluation as a therapeutic option in the population [19].

In this proof-of-concept study, we evaluated the efficacy and safety of once daily empagliflozin 25 mg on glucose excursions and hypoglycaemia burden in patients with PBH after RYGB.

Methods

Study design

This was a randomized, placebo-controlled, crossover trial conducted at the University Hospital Bern, Switzerland between December 1, 2021 and August 11, 2022. Eligible participants were randomized 1:1 to either empagliflozin 25 mg (Boehringer Ingelheim Laboratories, Germany) once daily followed by placebo, or vice versa. Both periods lasted a minimum of 20 days (periods could be prolonged up to a maximum of 24 days if the visits needed to be postponed), and were separated by 2-6 weeks of washout (Online Supporting Information, Figure S1). At the end of each treatment period, participants underwent standardized mixed-meal tolerance testing (MMTT) in the clinical research unit (CRU) with hormonal and metabolic assessments. Throughout, participants wore a masked continuous glucose monitor (CGM, Dexcom G6, Dexcom Inc, San Diego, US) and were asked to document drug and meal intake, as well as symptoms using an electronic diary.

Empagliflozin was chosen as an intervention on the basis of the promising findings of a previous study [19] and its selectivity for the SGLT2-inhibitor [20], allowing to separate potential effects from the one of the intestinal SGLT1-inhibitor. The dosing regimen was selected to achieve maximal efficacy given the dose-dependent effect of empagliflozin on urinary glucose excretion [21].

The study was conducted in accordance with the principles of the Helsinki Declaration after review and approval of Ethics Commission Bern (approval no. 2021-01187). All participants provided written informed consent before any study-related procedures. This study was preregistered on ClinicalTrials.gov (NCT05057819) and the protocol has been published previously [22].

Study participants

Recruitment was performed by referral from local or collaborating bariatric physicians and endocrinologists. Eligible participants were adults aged 18 years or older who underwent RYGB at least 12 months before screening and had a documented diagnosis of PBH (defined as recurrent symptomatic plasma or sensor glucose levels <3.0 mmol/L within three months prior to screening, relieved by ingestion of glucose). Exclusion criteria were allergic reaction to the study medication, chronic kidney disease (defined as estimated glomerular filtration rate <60

mL/min/1.73m^2), pregnancy, lactation, and/or women of childbearing potential not using effective contraceptive methods, use of any agents known to interfere with glucose metabolism within five half-lives at screening, participation in an overlapping clinical trial, or incapacity to provide informed consent or follow study procedures.

Randomisation and masking

Allocation to the treatment sequence was handled by a person otherwise not involved in the study according to a computer-generated list. Both participants and investigators were blinded to treatment sequence and study drug composition. For safety reasons, investigators had access to point of care glucose results during the MMTT and CGM data during the outpatient period.

Study procedures

In-clinic MMTT

At the end of each treatment period, subjects were admitted to the CRU after an overnight fast for a 150 min MMTT, 2 hours after intake of the last dose of the study drug. After a baseline blood draw, participants consumed a standardized breakfast consisting of bread with butter and jam, and a fruit yogurt (584 kcal, 85 g carbohydrates, 21 g fat and 12 g protein) within 10 min. Postprandial blood sampling was performed after 10, 20, 30, 60, 90, 120, 135 and 150 min. Point-of-care testing for glucose and beta-hydroxy-butyrate was performed with the Accu-Chek Inform II (Roche Diagnostics, Mannheim, Germany) and the Freestyle Precision Neo (Abbott Diabetes Care, Alameda, US) meter. Insulin, C-peptide and glucagon were quantified from plasma aliquots stored at -80°C before batch analysis using commercial immunometric assays (Roche, Siemens and Mercodia, respectively). Rescue dextrose was provided at glucose level <1.5 mmol/L or in case of clinical signs of severe hypoglycaemia [23].

Outpatient procedures

Throughout all treatment periods, participants used an electronic diary and a masked Dexcom G6 CGM. Participants were prompted to calibrate their CGM based on finger stick testing with the Contour Next glucometer (Ascensia Diabetes Care, Basel, Switzerland) after 24 and 72 h during stable euglycaemia (3.9-10.0 mmol/L). The diary was used to record any perceived symptoms using pre-defined categories (gastrointestinal, autonomic,

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neuroglycopenic and other). Symptom intensity was indicated on a visual analogue scale ranging from zero to 10. Participants were asked to log the timing and carbohydrate content of the meals (< or ≥30 g [24]). Assistance was provided using an electronic lookup guide for carbohydrate quantities. Study drug intake was also recorded in the diary, and adherence was additionally monitored via accounting of returned study drug containers. A 24 h urine collection was performed during the day before the in-clinic MMTT. The study did not interfere with or specify dietary habits or any other aspect of daily living.

Outcomes

The primary endpoint was the amplitude of the decrease in plasma glucose during the 150 min MMTT (from peak to nadir) based on the intention-to-treat analysis. Secondary endpoints included peak and nadir plasma glucose during the MMTT, proportion of participants with plasma glucose <3.0 mmol/L during the MMTT, CGM-based glucose endpoints and frequency of recorded symptoms during the outpatient period. CGM-based outcomes were mean amplitude of glucose excursion (MAGE) [25], percentage time spent with sensor glucose values >10.0 mmol/L, <3.0 mmol/L, <2.8 mmol/L and coefficient of variation of sensor glucose. Exploratory outcomes were hormonal responses during the MMTT (insulin, C-peptide and glucagon), fasting and postprandial beta-hydroxy butyrate, 24 h glucosuria and meal frequency.

Safety outcomes included frequency and nature of adverse events. As part of the clinical examination, body weight and blood pressure were assessed at baseline and after each treatment period.

Participants' treatment preference

At the end of the study (before unblinding the study medication), participants were asked about their treatment preference in terms of the general well-being during each period.

Statistical analysis

The sample size was calculated based on the primary outcome and preliminary findings [19]. We aimed at recruiting 22 participants in order to achieve 90% power to detect a decrease

in the post MMTT peak to nadir plasma glucose amplitude of 0.30 mmol/L (SD 0.35 mmol/L) at a 5% alpha-level using a two-tailed test and accounting for a drop-out rate of 20%. Normality assumptions were assessed using the Shapiro-Wilk test. Stata 16.1 (Stata Corp. LLC, College Station, TX) was used for data analysis.

The trial statistician was blinded to the allocated sequence. The primary efficacy endpoint was examined using standard linear mixed-effect models for crossover designs. Treatment, treatment sequence, and treatment period were considered fixed effects, while subjects within sequence were treated as random effect. Analysis of secondary and exploratory endpoints paralleled the analysis of the primary endpoint except for safety outcomes and the quality and intensity of symptoms, which were summarised descriptively. All outcomes were calculated according to an intention-to-treat principle (ITT). In addition, a sensitivity analysis according to protocol adherence (per protocol) was carried-out. Non-adherence was a-priori defined as: in any of the two treatment periods, 1) more than two non-consecutive days with missed intake of the study drug; or 2) more than four missed doses of the study drug; or 3) missed intake of the study drug on the day of the MMTT.

Results

Participants

Participant baseline characteristics are reported in Table 1. Fifty-two participants were approached, of these, 22 met eligibility criteria, provided informed consent and were randomized. Of the 22 participants who completed the trial, outcomes from in-clinic assessment were available for 18 participants (data of three participants needed to be excluded from the analysis due to inability to ingest and keep down the meal). In addition, one participant did not meet the adherence criteria and was excluded from the per-protocol analysis. The Consort Flow diagram is provided in the Online Supplemental Information (Figure S2). Three participants (13.6%) had a history of Level 3 Hypoglycaemia[23] and 12 participants (54.5%) were treated with an off-label medication and/or revisional surgery or endoscopic intervention due to PBH. No participant had a past or present diagnosis of diabetes. Off-label medication for PBH was stopped before joining the trial with adequate wash-out periods. Three participants (13.6%) were on antihypertensive treatment during the study period (all three received angiotensin-

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converting enzyme inhibitors and one subject was additionally treated with a beta-blocker).

MMTT outcomes

Metabolic responses to the MMTT at the end of each treatment period are shown in Table 2 (results of the per-protocol analysis are reported in the Supporting Information). The plasma glucose profile is shown in Figure 1. Plasma glucose concentration alongside the profiles of insulin, C-peptide and glucagon are also illustrated in Figure S3. The primary endpoint was not met, neither in the ITT nor in the per-protocol analysis. Similarly, secondary endpoints assessed during the MMTT did not reveal any significant difference. Fasting glucose was significantly lower with empagliflozin compared to placebo (4.9 ± 0.3 vs 5.1 ± 0.3 mmol/L, p = 0.004). In the per-protocol- analysis, empagliflozin additionally lowered postprandial insulin exposure (insulin AUC) by 18.7% (p = 0.018). Fasting and postprandial glucagon exposure did not significantly differ between empagliflozin and placebo. Beta-hydroxy-butyrate concentrations were low and comparable between the periods. The glucose profile assessed using CGM during the MMTT (see Supporting Information, Table S2 and S3) showed significantly lower peak glucose (mean difference 1.1 ± 1.0 mmol/L, p = 0.019), indicating that plasma sampling may have missed the maximal excursion.

Outpatient outcomes

Outcomes collected in the outpatient setting during each treatment period are shown in Table 3 (results of the per-protocol analysis are reported in the Supporting Information). Empagliflozin resulted in a lowered MAGE compared with placebo (4.8 ± 1.3 vs. 5.2 ± 1.6 mmol/L, mean difference 0.4 ± 0.4 mmol/L, p = 0.028). In addition, empagliflozin significantly lowered time spent with sensor glucose values >10.0 mmol/L by 0.9 ± 1.4 percentage points (p = 0.009). The quantity and quality of recorded symptoms did not significantly differ between empagliflozin and placebo (p = 0.248). Detailed results of the reported symptoms are shown in the Supporting Information (Table S5). Likewise, we did not observe any significant differences in meal patterns, neither in terms of meal frequency nor carbohydrate categories (<30 vs. ≥30 g). As expected, empagliflozin induced

glucosuria with mean daily excretions of 33.1 ± 13.0 g at the end of the 20 day-treatment period.

Safety outcomes and findings of the clinical examination

Treatment-emergent adverse events were reported in 11 and 6 participants during the empagliflozin and the placebo period, respectively (Table 4). There were no treatment-related serious adverse events and no patient withdrawals. One serious adverse event (hospitalization due to COVID-19 infection) occurred during the empagliflozin period and was not considered study-related. In this participant the treatment was prematurely stopped. The control period was performed after full recovery.

Overall, empagliflozin was well tolerated in all participants. Three participants experienced genital mycotic infections, which were deemed related or possibly related to the study drug. Full recovery was observed in all participants following a local treatment without the need for stopping the study drug.

Body weight during the treatment period decreased by 0.9 ± 1.4 kg with empagliflozin and increased by 0.8 ± 1.5 kg with placebo ($p < 0.001$ for the between treatment difference). Study treatments did not significantly alter office systolic and diastolic blood pressure measured before and after each period.

Participants' treatment preference

Two participants were not reachable at the end of the study. Consequently, data regarding treatment preference were available from 20 participants. When asked about their preferred treatment period, 10 of 20 participants (50%) preferred the period with the empagliflozin as compared to four (20%) who preferred the placebo period. Six (27.3%) participants reported no difference between treatments.

Discussion

In the present proof-of-concept study, 20 days of once daily empagliflozin 25 mg did not lower the amplitude of the plasma glucose decrease following a standardized mixed meal. Despite not meeting the primary endpoint, our results provide evidence that empagliflozin reduces glucose excursions by approximately 10% in unrestricted outpatient conditions, as

indicated by a significantly lower mean amplitude of sensor glucose excursions compared with placebo. Empagliflozin, however, did not reduce exposure to hypoglycaemia, neither during the in-clinic visit nor the outpatient period. These observations are notably in discordance with a recently published pilot study, which found that a single dose of empagliflozin 10 mg significantly lowered the incidence of hypoglycaemic episodes during a MMTT [19]. There are several factors that may account for the discrepant findings. First, the mixed meal was liquid in the previous study and solid in the present study, leading to different postprandial glycaemic response patterns (steeper rise and fall in the former). Second, hypoglycaemia in the previous study was defined by the presence of symptoms requiring glucose administration rather than a standardised cut-off glucose concentration. Third, although the dose was lower in the previous study (10 vs 25 mg), acute vs sustained SGLT2-inhibition may lead to more pronounced attenuations of glycaemic excursions. In line with findings of other studies, sustained glucose depletion with repetitive dosing may lower plasma glucose concentration and consequently renal glucosuria [18,26]. Fourth, empagliflozin-induced weight loss in the present study may have increased insulin sensitivity and consequently decreased fasting and postprandial glucose nadir values. A short 3-day regimen of empagliflozin 25mg once daily was further evaluated in an open label non-randomised study, which included people after RYGB and vertical sleeve gastrectomy with and without self-reported symptoms of hypgolycaemia [27]. The substantial differences in the study population, design and outcomes does not allow any meaningful comparison with our study and the one by Hepprich et al [19].

An important finding of the present work is the significant reduction of glucose excursions with empagliflozin in the outpatient period, as quantified using CGM. The attenuation of glycaemic excursions was mainly achieved by lowering peak glucose excursions, in line with significantly less time spent with sensor glucose values >10.0 mmol/L.

Of note, previous studies demonstrated a relationship between glucose excursions and activation of oxidative stress [28,29]. Oxidative stress is one of the main mechanisms that leads to vascular damage [30,31]. This is corroborated by evidence that short-term glycaemic variability might adversely affect plaque stability in individuals with or without diabetes [32].

Acute daily glucose fluctuations were also shown to be associated with an impaired of cognitive functioning, independent of overall glycaemic exposure [33].

The use of empagliflozin 25 mg once daily resulted in a mean urinary glucose excretion of 33.1 g/day after 19 days of treatment, which is compatible with the concomitantly observed weight loss in the absence of recorded alterations in dietary habits. In contrast with previous work in patients with diabetes, empagliflozin did not significantly increase glucagon concentrations [34], although a tendency towards higher levels was noticeable. Although comparison of recorded symptoms during the empagliflozin versus placebo period did not reveal any significant differences, it is notable that 50% of the participants preferred the treatment period with empagliflozin, suggesting possible positive effects on subjective well-being. The impact of empagliflozin on the change in quality of life is currently under investigation in an ongoing trial (NCT05036317).

The use of the highly selective action of empagliflozin for the renal SGLT2 allowed us to disentangle the contribution of increased glucosuria on glucose excursions in patients with PBH. Although our results suggest beneficial effects in terms of lower glucose variability, more potent effects may be achieved by additionally targeting the intestinal SGLT1. Indeed, recent work on the use of high-dose canagliflozin in RYGB-subjects support the therapeutic potential of less selective SGLT2-inhibitor for the treatment of PBH [35 36]. Thus, the present study alongside with recently published work suggest that the use of SGLT 2 inhibitors may broaden the pharmacological options for the treatment of PBH.

The strength of the study was its randomised double-blind placebo controlled design and the exploration of potential drug effects on multiple outcomes under both controlled in-clinic and non-restricted daily life conditions. However, we acknowledge important limitations. The primary endpoint analysis was challenged by the exclusion of three participants due to imbalanced meal ingestion and the fact that blood sampling frequency was not optimally tailored to the postprandial glucose dynamics. In retrospect, we would recommend 3-5 min intervals at times of expected peak and nadir values to more accurately represent the postprandial plasma glucose profile. These circumstances may have masked potential drug effects. Thus, the CGM-based outpatient outcomes are likely

to provide more representative insights into treatment effects. Although men and women were eligible, the study population was predominantly female, in line with sex distribution of the bariatric surgery population and previous studies in patients with PBH [37]. Recorded carbohydrate intake was often low to moderate (e.g. on average 2 meal per day with carbohydrate contents < 30g/d) and benefits of empagliflozin may be greater when increasing the amounts of ingested carbohydrates, especially those with a high glycaemic impact. However, the study was not designed to interfere with or specify participants' eating habits and our study cohort displayed glycaemic patterns and characteristics in agreement with that of previous analyses of patients with PBH [38] and guidelines for nutritional management in people with PBH [24].

In conclusion, empagliflozin 25 mg once daily administered for 20 consecutive days in patients with PBH, was well tolerated and had positive effects on ambulatory glucose excursions. However, empagliflozin did not reduce the burden of hypoglycaemia. Whilst the reduction of glycaemic variability and other, glucose-independent, protective effects [39,40] may offer potential benefits to patients with PBH, the exact therapeutic role of SGLT2 inhibitors in this population require further investigation.

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Author contribution statement

D.H. and L.B. (study sponsor investigator) conceptualized the study. D.H., A.M., C.N., A.V., and L.B. contributed to the protocol draft and planning of the study. A.F., K.A.S., N.P., P.N., P.G., J.Z., D.G., and L.B. contributed to the recruitment of participants, A.F. and L.B.

screened and enrolled participants. A.F. conducted the study visits and collected the data. J.G. contributed to the laboratory analyses. L.C. and A.Fa. procured the eDiary platform. A.F, D.H., L.C., D.G.F., A.Fa., C.M. and L.B. reviewed and prepared the data for analysis, A.F., C.T.N., D.H. and L.B. analyzed and interpreted the data. M.H. and M.Y.D. contributed to data interpretation. A.F., D.H., and L.B. wrote the manuscript. All authors critically reviewed the manuscript. L.B. 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. All authors approved the final draft of the manuscript for submission.

Authors' disclosure

Authors report no potential conflict of interest relevant to this article. M.Y.D. is listed as an inventor on a patent owned by University Hospital Basel covering the use of SGLT-2 inhibitors or IL-1R antagonists for reduction of hypoglycemia after bariatric surgery.

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Data sharing

The dataset generated and analysed in this work is available from the corresponding author upon reasonable request.

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Diabetes Technology and Therapeutics
Randomized, double-blind, placebo-controlled crossover trial of once daily empagliflozin 25 mg for the treatment of postprandial hypoglycaemia after Roux-en-Y gastric bypass (DOI: 10.1089/dia.2023.0036)
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Table 1: Participant baseline characteristics

	Mean or n	SD
Age (years)	43.7	13.6
Sex (female/male)	16 / 6	-
Current body weight (kg)	74.3	15.0
Current BMI (kg/m^2)	26.4	4.9
Time since primary surgery (years)	5.5	3.0
Pre-surgery body weight (kg)	118.1	16.5
Pre-surgery BMI (kg/m^2)	41.2	4.3
Nadir body weight (kg)	68.1	13.6
Total weight loss (%)	36.9	10.8
Patients with pharmacotherapy interfering glucose metabolism at enrolment	10 (45.5%)	-
Patients with previous invasive interventions due to PBH	5 (22.7%)	-
Patients with history of severe hypoglycaemia*	3 (13.6%)	-
Charlson Comorbidity Score	0.7	1.2

BMI, body mass index; PBH, postbariatric hypoglycaemia; time since primary surgery defined as: date of surgery – date of baseline visit; off-label pharmacotherapy due to PBH included acarbose (n=6), GLP1-analogues (n=2) and metformin (n=2); Level 3 (severe) hypoglycaemia defined as: requirement of third-party assistance to take corrective action (n=3); invasive intervention includes: pouch revision (n=4) and endoluminal surgery using a endoscopic suturing device (n=3). *hypoglycaemic event leading to unconsciousness and requiring third party assistance to treat.

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Table 2: Study outcomes (in-clinic, intention-to-treat)

	Empagliflozin Mean ± SD or relative frequency (n=19)	**Placebo** Mean ± SD or relative frequency (n=19)	**P-value**
Amplitude plasma glucose (mmol/L)*	8.1 ± 2.4	8.1 ± 2.6	0.807
Peak plasma glucose (mmol/L)	11.4 ± 2.3	11.8 ± 2.6	0.345
Nadir plasma glucose (mmol/L)	3.3 ± 0.5	3.7 ± 1.1	0.094
Postprandial AUC plasma glucagon (min x pmol/L)	919.6 ± 834.2	790.3 ± 704.7	0.123
Postprandial AUC plasma insulin (min x pmol/L x 10^3)	99.5 ± 66.9	115.5 ± 93.5	0.138
Number of participants with plasma glucose <3.0 mmol/L (n)	8/19	4/19	0.146
Fasting plasma glucose (mmol/L)	4.9 ± 0.3	5.1 ± 0.3	**0.004**
Fasting plasma insulin (pmol/L)	7.2 ± 3.3	8.0 ± 4.9	0.410
Fasting plasma C-peptide (pmol/L)	4.5 ± 2.7	4.3 ± 0.7	0.715
Fasting plasma glucagon (pmol/L)	6.5 ± 3.5	6.0 ± 2.3	0.555
Fasting plasma beta-hydroxy butyrate (mmol/L)	0.3 ± 0.2	0.3 ± 0.3	0.606

*primary outcome; AUC, area under the curve

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Table 3: Study outcomes (outpatient, intention-to-treat)

	Empagliflozin Mean ± SD or relative frequency (n=22)	**Placebo** Mean ± SD or relative frequency (n=22)	**P-value**
MAGE (mmol/l)	4.8 ± 1.3	5.2 ± 1.6	**0.028**
CV of sensor glucose (%)	29.8 ± 5.1	30.2 ± 5.9	0.593
Time spent with sensor glucose >10.0 mmol/l (%)	3.8 ± 3.5	4.7 ± 3.8	**0.009**
Time spent with sensor glucose <3.0 mmol/l (%)	1.7 ± 1.6	1.5 ± 1.5	0.457
Time spent with sensor glucose <2.8 mmol/l (%)	1.2 ± 1.3	1.1 ± 1.1	0.531
Frequency of daily postprandial symptoms (n)	0.4 ± 0.5	0.4 ± 0.6	0.763
Average daily frequency CHO ingestion <30g/24h (n)	2.2 ± 2.4	2.2 ± 2.3	0.938
Average daily frequency of CHO ingestion >30g/24h (n)	1.3 ± 0.9	1.3 ± 0.9	0.459
Daily excreted urine glucose (g/24h)	33.1 ± 13.0	0.3 ± 0.8	**<0.001**

MAGE, mean amplitude of glycaemic excursions; CV, coefficient of variation; CHO, carbohydrate

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Table 4: Safety outcomes

	Baseline (n=22)	**Empagliflozin** (n=22)	**Placebo** (n=22)
Total number of SAEs	**0**	**1**	**0**
COVID-19-infection	-	1	-
Total number of AEs	**0**	**10**	**6**
Genital mycotic infection	-	3	-
Diarrhoea	-	1	3
Generalised pruritus	-	1	-
Left upper abdominal pain	-	1	-
Toothache	-	1	1
External ear canal infection	-	-	1
Itching at sensor site	-	1	-
Flank pain	-	1	-
Clear vomit	-	1	1

SAEs, serious adverse events; AEs, adverse events

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Figure Legend

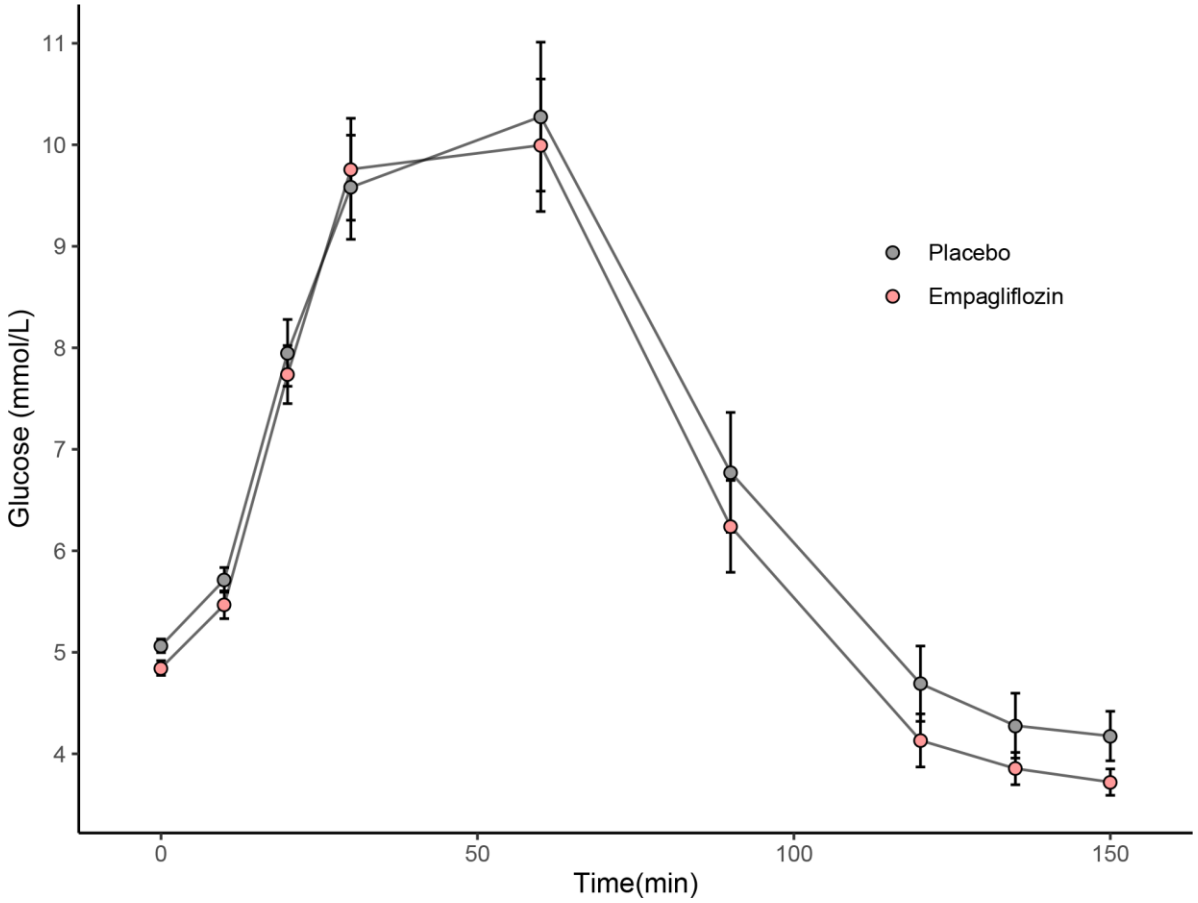

Figure 1. Glucose profiles during the Mixed Meal Tolerance Test. Points and error bars represent mean and standard errors, respectively.