Effect of dapagliflozin on impaired awareness of hypoglycemia in people with type 1 diabetes

Running title: Effect of dapagliflozin on IAH in type 1 diabetes mellitus

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Clinicaltrials.gov: NCT03556033

Objective About 25% of patients with T1DM have lost the capacity to timely detect hypoglycemia (impaired awareness of hypoglycemia (IAH)). IAH can be reversed by strict avoidance of hypoglycemia for at least 3 weeks. Adjunctive treatment with sodium glucose cotransporter 2 (SGLT-2) inhibitors has been shown to improve glucose control without increasing the risk of hypoglycemia and decrease glucose variability. We hypothesized that dapagliflozin may improve awareness of hypoglycemia in people with T1DM and IAH.

Research Design and Methods Fifteen patients with T1DM and IAH were included in this randomized double-blind, placebo-controlled cross-over trial (age 49.7±14.6 years, 40% males, disease duration 24.1±14.2 years, HbA_{1c} 7.5±0.8% (58.6±8.4 mmol/mol). They were treated with dapagliflozin 10 mg once daily or matching placebo, with a washout period of 2 weeks. At the end of each treatment period, subjects underwent a modified hyperinsulinemic normoglycemic-hypoglycemic glucose clamp (glucose nadir 2.5 mmol/L). Blinded continuous glucose monitors were used in the final treatment weeks.

Results Treatment with dapagliflozin significantly improved HbA_{1c} (-0.32±0.10 vs. 0.22±0.13% (-4.1±0.9 vs. 2.3±1.4 mmol/mol), dapagliflozin vs. placebo, p=0.007) and glucose variability (SD, 2.6±0.2 vs. 3.1±0.3 mmol/L, p=0.029), but did not affect the frequency of hypoglycemia. During the hypoglycemic clamp, dapagliflozin significantly reduced the need for exogenous glucose to maintain hypoglycemia (3.2±0.3 vs. 4.1±0.4 $mg \cdot kg^{-1} \cdot min^{-1}$, p=0.022). Symptom responses to hypoglycemia were numerically higher, but not statistically significant different.

Conclusions Eight weeks of treatment with dapagliflozin ameliorated some components of IAH but did not completely restore hypoglycemic awareness in people with type 1 diabetes and IAH.

Iatrogenic hypoglycemia is the most frequent, acute complication of insulin therapy in people with type 1 diabetes. On average, people with type 1 diabetes experience 2-3 hypoglycemic events per week (1, 2) and each year one severe hypoglycemic event (3), defined by appearance of sufficient cognitive impairment to require external assistance for recovery (4). Timely recognition of (the typical symptoms of) hypoglycemia is critical to prevent severe hypoglycemia. Recurrent hypoglycemia can induce a process of habituation leading to the syndrome of impaired awareness of hypoglycemia (IAH), which affects about 25% of patients with type 1 diabetes (1, 5). These people have lost the capacity to timely detect hypoglycemia, increasing the risk to develop severe hypoglycemia up to six-fold (6).

Risk factors for IAH include a recent history of hypoglycemia, low C-peptide levels and longer diabetes duration (7-9). Marked glucose variability may contribute to both the development and persistence of IAH, possibly mediated by increased incidence of hypoglycemia, following or not following (too aggressive) corrections of recurrent hyperglycemia (1, 10-12). Meticulous avoidance of hypoglycemia for at least 3 weeks has been shown to reverse IAH (13, 14). However, the often associated deterioration of glycemic control (i.e., rise of HbA_{1c}) is an important limitation of this strategy and in daily clinical practice many patients revert back when glucose control is tightened again.

Sodium-glucose co transporter 2 (SGLT-2) inhibitors selectively inhibit SGLT-2 in the proximal tubules of the kidney, leading to decreased reabsorption of filtered glucose and an increase in urinary glucose excursion (15, 16). SGLT-2 inhibitors have been shown to improve glucose control without increasing the incidence of hypoglycemia in people with type 1 diabetes (17, 18). Furthermore, time in range has been reported to increase during treatment with an SGLT-2 inhibitor (19-21), reflecting a reduced glucose variability. More

stability in day-to-day glucose control may ameliorate awareness of hypoglycemia in patients with IAH, as a result of reduced exposure to hypoglycemia. We therefore hypothesized that SGLT-2 inhibition would be helpful in restoring hypoglycemic awareness in people with IAH. To test this hypothesis, we investigated the effect of treatment with the SGLT-2 inhibitor dapagliflozin on counterregulatory responses to insulin-induced hypoglycemia in patients with type 1 diabetes and IAH.

Research Design and Methods

Study design

This was a randomized, double-blind, placebo-controlled cross-over intervention performed at the Radboud university medical center in Nijmegen, the Netherlands. The study was approved by the local institutional review board and performed according to the principles of the Declaration of Helsinki. All participants provided written informed consent.

Study population

Patients with type 1 diabetes were recruited from the outpatient diabetes clinic of the Radboud university medical center. Patients were included between November 2018 and August 2019. Criteria for inclusion were: age 18-75 years, type 1 diabetes duration ≥1 year, BMI 19-40 kg/m^2, insulin treatment according to basal-bolus insulin regimen, HbA_{1c} <9% (75 mmol/mol), and the presence of IAH as assessed by a score of ≥3 on the Dutch modified version of the Clarke questionnaire (22). Key exclusion criteria were current treatment with or known intolerance to SGLT-2 inhibitors, treatment with glucose- or immune-modifying agents other than insulin, history of cardiovascular disease and/or severe kidney failure, diabetes-related complications (except for background retinopathy and asymptomatic

peripheral neuropathy) and history of diabetic ketoacidosis requiring medical intervention within 1 month before screening.

Study procedure

Participants first came for a screening visit, which included medical history and standard physical examination (including body weight, height, blood pressure, pulse rate and screening for peripheral neuropathy). Blood was sampled for determination of HbA_{1c} and serum creatinine.

After inclusion, patients were randomly assigned to treatment with dapagliflozin or matching placebo for 8 weeks in a cross-over fashion, with a 2 week washout period between treatment periods. Participants were enrolled by the investigator and were assigned to dapagliflozin or placebo treatment according to a randomization list that was managed by the pharmacy department of our hospital, to ensure the double-blinded study design. Randomization was done by a computer program with the use of blocks of two subjects, to ensure that equal numbers of participants would be treated with dapagliflozin or placebo first. Before start of the study medication, patients received ketone meters and were advised about how to identify potential symptoms of (normoglycemic) diabetic ketoacidosis (e.g., nausea, vomiting). Patients were instructed to contact the study site in case of (suspected) symptoms of ketoacidosis, and if self-measured blood ketone readings were ≥1.5 mmol/L, irrespective of blood glucose levels. Dapagliflozin and placebo capsules were dosed 10 milligrams once daily. After start of the study medication, patients were instructed to reduce prandial insulin levels by 10% to decrease the risk of hypoglycemia. Participants were asked to perform 4-point daily blood glucose profiles and to keep a glucose diary for the duration of the study. Insulin doses were adjusted according to the glucose profiles, aiming for fasting and pre-meal

blood glucose levels of 4 to 7 mmol/L without the occurrence of hypoglycemia. In weeks 1, 2, 4 and 6, insulin dose adaptations and potential side effects were documented by telephone consultation. Patients recorded any hypoglycemic event in their glucose diary, and whether they needed help from someone. During the final week of each treatment period, subjects completed 7-point glucose profiles, and wore a blinded continuous glucose monitor (CGM) (Dexcom G6; Dexcom Inc., San Diego, CA, USA) for at least five days.

At the end of each treatment period of eight weeks, subjects underwent a hyperinsulinemic euglycemic-hypoglycemic glucose clamp (nadir, 2.5 mmol/L). Participants were asked to come to the clinical research facility after an overnight fast, having abstained from alcohol, caffeine and smoking for 24 hours and from strenuous exercise for 48 hours. Participants were asked to reduce the basal insulin dose to avoid hypoglycemia the day and night before the clamp. The clamps were rescheduled in case of hypoglycemia. After arrival at the research facility, one intravenous cannula was inserted into the antecubital vein for infusion of insulin and glucose, and the other cannula was inserted in a retrograde way in a forearm vein. This forearm was placed in a heated box (55ºC) so that arterialized blood could be obtained. Glucose levels were determined every 5 minutes using Biosen C-Line (EKF Diagnostics, Cardiff, U.K.) (23). Glucose 20% (Baxter B.V., Deerfield, IL) and insulin (insulin aspart; Novo Nordisk, Bagsvaerd, Denmark) were infused in the contralateral arm. Baseline hyperglycemia was corrected as needed with a small bolus of insulin. Subsequently, a hyperinsulinemic (60 $mU \cdot m^{-2} \cdot min^{-1}$) euglycemic-hypoglycemic glucose clamp was initiated. The duration of the euglycemic phase (target glucose, 5.0 mmol/L) was 30 minutes, after which glucose levels were allowed to fall to 2.5 mmol/L over ~35 minutes and maintained there for another 45 minutes. Blood samples were collected at several timepoints (i.e., at baseline, after 30 minutes of euglycemia, after 20 and 45 minutes of hypoglycemia, and after

recovery from hypoglycemia or 90 minutes after hypoglycemia if not fully recovered) for the measurement of catecholamines, insulin, glucagon, cortisol and growth hormone. Participants were also asked to rate hypoglycemic symptom scores by a validated questionnaire at those timepoints (22). Symptoms were scored from 0 (none) to 6 (severe) and divided into autonomic symptoms (e.g. sweating, trembling and palpitations), neuroglycopenic symptoms (e.g. confusion, blurred vision and difficulty speaking), general symptoms (e.g. nausea and headache) and dummy symptoms (pain in the legs and yellow vision) (22, 23).

At the end of the hypoglycemic phase, participants were asked to estimate the current glucose level, and to eat as much as they thought would be necessary to recover from hypoglycemia. Insulin infusion was stopped at that moment and glucose infusion was tapered until stop over 35 minutes. Glucose levels were measured until 90 minutes after hypoglycemia or until glucose levels reached ≥8.0 mmol/L. A questionnaire on appetite was administered at the abovementioned timepoints during the clamp and after recovery. This questionnaire consisted of a visual analog scale (0-100 mm) on which patients rated hunger, fullness, prospective consumption, desire to eat, and thirst (maximal score 500 mm) (24).

Study outcomes

The primary study endpoint was the symptom score in response to insulin-induced hypoglycemia during the hyperinsulinemic clamp. A power calculation aimed at finding an increase of at least 40% in hypoglycemia-induced autonomic symptom score response with a power of 80% yielded a total number of participants of 15, where drop-outs would be replaced. Differences in symptom scores were calculated between euglycemia and the second hypoglycemic timepoint (after 45 minutes of hypoglycemia). Secondary outcome measures included plasma levels of counterregulatory hormones in response to clamped hypoglycemia,

maximal glucose excursion after hypoglycemia, time until recovery from hypoglycemia (defined as a glucose level above 4.0 mmol/L), glucose infusion rates during euglycemia and hypoglycemia, self-reported appetite scores during and after hypoglycemia, and amount of calories and carbohydrates consumed after hypoglycemia. Other secondary outcomes were the change in total daily insulin dose, body weight, and HbA_{1c}, as well as mean 24-hour glucose levels, glucose variability and percentages of time spent above-, in- and below range, as derived from CGM downloads. Time in range (TIR) was defined as glucose levels between 3.9-10.0 mmol/L, according to predefined Dexcom G6-settings and endorsed by a recent consensus statement (25). Glucose variability was defined by the average standard deviation of 24-hour glucose levels.

Measurements

HbA_{1c} was measured by the TOSOH G8 HPLC-analyzer, distributed by Sysmex. Plasma adrenaline and noradrenaline were analyzed by high-performance liquid chromatography combined with fluorometric detection (23). Plasma insulin was assessed by an in-house radioimmunoassay (26). Plasma glucagon was measured by radioimmunoassay (Eurodiagnostica, Malmö, Sweden). Plasma growth hormone and cortisol were determined using a routine analysis method with an Electrochemiluminescent Immunoassay on a Modular Analytics E170 (Roche Diagnostics, GmbH, Mannheim, Germany).

Statistical analysis

Data were analyzed using IBM SPSS statistics version 25. Missing data were imputed. All data are expressed as the mean ± SEM, unless otherwise specified. A p-value of <0.05 was considered statistically significant. We tested for normality using the Shapiro-Wilk test and QQ plots. Differences in means within groups were analyzed using paired Student *t* tests

(when normally distributed) and Wilcoxon signed rank tests (when not normally distributed). Serial data were analyzed by two-way repeated-measures ANOVA.

Results

A total of 15 patients with type 1 diabetes and IAH were included; two participants withdrew consent (one because of a wish to become pregnant, one because of fear for possible side effects) before start of the study and were replaced. As a result, 15 patients completed the study, baseline characteristics are shown in table 1. Results related to the two hyperinsulinemic hypoglycemic clamps were based on 14 patients because one patient only completed one of the two clamps. The patients were generally well-controlled and the majority was on an insulin pump. Seven patients were on real-time CGM and 3 patients used flash glucose monitoring (FGM).

Treatment periods

Compared to placebo, 8 weeks dapagliflozin treatment significantly decreased HbA_{1c} (-0.32±0.10 vs. 0.22±0.13% (-4.1±0.9 vs. 2.3±1.4 mmol/mol), p=0.007). Total daily insulin dose did not change and was not different at the end of the two 8-week treatment periods between dapagliflozin and placebo (35.9±3.2 vs. 37.1±3.5 IU, p=0.28). Compared to placebo, dapagliflozin also reduced body weight (-2.3±0.6 vs. -0.1±0.5 kg, p=0.033). The median number of self-reported hypoglycemic events per person during the 8 weeks of follow-up was 7.0 (3.0, 19.0) with dapagliflozin and 8.0 (2.0, 11.0) with placebo treatment (p=0.70). Two episodes of severe hypoglycemia were recorded, one in each of the treatment periods, both in the same participant.

Mean 24-hour glucose levels during the final dapagliflozin treatment weeks were 7.6±0.3 mmol/L and 8.2±0.4 mmol/L with placebo treatment (difference, -0.6±0.3 mmol/L, p=0.075). Glucose variability was significantly lower during treatment with dapagliflozin as compared to placebo (SD, 2.6±0.2 vs. 3.1±0.3 mmol/L, p=0.029). The percentage of time spent in range was not significantly different after both treatment periods (72.9±3.3 vs. 68.0±4.2%, p=0.19). Although TIR was higher in participants already using real-time CGM (or FGM) than in participants who did not, dapagliflozin did not further improve TIR in either subgroup when compared to placebo. Median percentage of time spent below range (glucose <3.0 mmol/L) and mean percentage of time spent above range (glucose>10.0 mmol/L) also did not differ between treatment periods (0.4 [0.0, 3.7] vs. 1.5 [0.3, 2.1]%, p=0.76 and 20.7±3.3 vs. 26.0±4.1%, p=0.15, respectively).

Hypoglycemic glucose clamps

Before start of the clamp, glucose levels were lower after dapagliflozin than after placebo treatment (7.1±0.6 vs. 10.1±0.8 mmol/L, p=0.002), whereas beta-hydroxybutyrate (BHB) levels were higher (0.65 [0.22, 0.92] mmol/L vs. 0.06 [0.05, 0.37] mmol/L, p=0.003). Beta-hydroxybutyrate levels during hypoglycemia were not different between dapagliflozin and placebo (0.03 [0.03, 0.07] mmol/L vs. 0.03 [0.03, 0.03], p=0.18). During the clamp, mean glucose levels for the euglycemic phase (5.0±0.1 vs. 4.8±0.1 mmol/L, p=0.07) and the hypoglycemic phase (2.8±0.0 vs. 2.8±0.0 mmol/L, p=0.84) were similar for dapagliflozin and placebo, respectively (figure 1), although nadir plasma glucose levels slightly differed (2.5±0.0 vs. 2.4±0.0 mmol/L, p=0.031). Plasma insulin levels were comparable during both clamps. Mean glucose infusion rates (GIR) did not differ between treatments during euglycemia (3.0±0.4 vs. 3.6±0.4 $mg \cdot kg^{-1} \cdot min^{-1}$, p=0.14), but were significantly lower with dapagliflozin than with placebo during hypoglycemia (3.2±0.3 vs. 4.1±0.4 $mg \cdot kg^{-1} \cdot min^{-1}$,

p=0.022) (figure 1). Symptom scores in response to hypoglycemia were numerically higher after treatment with dapagliflozin when compared to placebo treatment, but this difference did not reach statistical significance (mean difference from euglycemia 8.0±3.4 vs. 5.2±1.6, p=0.31) (figure 2). Treatment with dapagliflozin did not alter counterregulatory hormone responses to hypoglycemia, when compared to placebo treatment (figure 3). Participants' estimated glucose level during hypoglycemia was 4.0±0.4 mmol/L after dapagliflozin treatment and 3.6±0.3 mmol/L after placebo treatment (p=0.27). Five participants (35.7%) correctly estimated their glucose level as hypoglycemic after dapagliflozin treatment, and six participants (42.9%) after placebo treatment.

Mean time until glycemic recovery was 17.5±2.1 minutes after dapagliflozin treatment and 21.8±2.1 minutes after placebo treatment (p=0.17). Maximal glucose excursion during recovery after 45 minutes of hypoglycemia was 8.0±0.2 mmol/L after dapagliflozin treatment and 8.0±0.2 mmol/L after placebo treatment (p=0.96). There were no differences in appetite scores at either time point during and amount of carbohydrates and calories consumed after the clamp between the two treatments.

Adverse effects

One patient had a genital infection during dapagliflozin treatment, treated with antimycotic therapy, another had a urinary tract infection during placebo treatment, treated with antibiotics. One participant suffered from flu-like symptoms for 3 days during dapagliflozin treatment, which were self-limiting. Other adverse events included food poisoning, shoulder bursitis and an ankle fracture. Diabetic ketoacidosis did not occur during both treatment periods.

Conclusions

The main finding of this study is that eight weeks of treatment with dapagliflozin ameliorated some components of IAH but did not completely restore hypoglycemic awareness in people with type 1 diabetes and IAH. Indeed, treatment with dapagliflozin reduced the need for exogenous glucose to maintain hypoglycemia during the clamp, reflecting greater endogenous glucose appearance. Dapagliflozin also reduced HbA_{1c} and improved glucose variability without increasing the frequency of hypoglycemia or the time spent below the range of normoglycemia.

This is the first study specifically examining the effect of treatment with an SGLT-2 inhibitor in people with type 1 diabetes and IAH. Our data of improved glucose control and reduced glucose variability are in line with previous studies that investigated SGLT-2 inhibitor treatment in people with type 1 diabetes (18, 19, 27-32). Remarkably, these improvements were achieved against a background of already reasonably-well glucose control and – similar to previous studies – without increasing the risk of (severe) hypoglycemic events or the time spent in hypoglycemia (17-20, 27-29). In other words, treatment with dapagliflozin shifted the inverse relationship between HbA_{1c} and incidence of hypoglycemia to the left, but contrary to our aims, this effect was entirely due to a change in the first rather than the second component.

Symptom scores in response to clamped hypoglycemia were numerically higher after dapagliflozin treatment when compared to placebo, but this difference was not statistically significant. Dapagliflozin treatment was associated with a reduced GIR during the hypoglycemic condition of the clamp, reflecting lower external glucose requirements and consequently greater endogenous glucose rising capacity to maintain the same blood glucose level. Since no single counterregulatory hormone response was enhanced by dapagliflozin,

this effect may be due to the composite glucose-increasing effect of all counterregulatory hormones combined or to increased beta-adrenergic sensitivity, reduction of which has been associated with IAH (33, 34). Beta-hydroxybutyrate levels before start of the clamps were higher after dapagliflozin than after placebo treatment. However, although ketones may be used as an alternative for glucose, these levels were almost completely suppressed during hypoglycemia, thus unlikely to explain the differences in glucose requirements.

Apart from reduced need for exogenous glucose to maintain hypoglycemia, treatment with dapagliflozin was not better than placebo in enhancing counterregulatory hormone responses to or symptomatic awareness of hypoglycemia during the clamp. The most obvious explanation for these results is that dapagliflozin did not affect hypoglycemia event rates, presumably because the participants were more concerned about (reducing) hyper- than hypoglycemic excursions (35). Although this study cannot claim clear beneficial effects of dapagliflozin on IAH, there are several points to consider. First, the frequency of hypoglycemia in our study was around one episode per week, which is very low for a population with IAH. The proportion of time spent below range was similarly low, averaging 0.4 and 1.5% for dapagliflozin and placebo treatment, respectively. Second, the TIR of around 70% in both study-arms was much higher than observed in other studies on SGLT-2 inhibitor treatment (19, 27, 28, 30-32) and close to the target recommended by current guidelines (25). Both points may be related to quite optimal treatment with the majority already on both pump and CGM, suggesting that participants were already able to avoid hypoglycemia despite decreased awareness, perhaps as an effect of the CGM use. Theoretically, addition of an SGLT-2 inhibitor may be more effective in people with type 1 diabetes and IAH not using CGM, although our data were too limited to show this. Although speculative, we would posit that participants were able to reduce the incidence of hypoglycemia and improve awareness to

a certain point under both study conditions, whereas dapagliflozin enabled them to improve overall glucose control on top of that.

Impaired awareness of hypoglycemia is a complex clinical syndrome that is difficult to reverse. Although various agents and interventions have been shown to enhance counterregulatory responses to hypoglycemia (36-39), few have been tried in longer-term studies and none were effective in restoring hypoglycemic awareness. This includes CGM, although its use effectively reduces the risk of severe hypoglycemia as the main consequence of IAH (40). One explanation for the failure to resolve IAH may relate to many people with IAH being more concerned about hyperglycemia and associated complications and prone to underestimating the risks of hypoglycemia (35, 41). Use of SGLT-2 inhibitors may play a role in improving IAH, although its use should be carefully balanced against the risk of diabetic ketoacidosis (42). The risk of ketoacidosis remains a controversial issue when it comes to approving treatment with SGLT-2 inhibitors for patients with type 1 diabetes (43, 44).

Strengths of our study include the study design (randomized, double-blind and placebo-controlled), the use of glucose clamps to measure awareness of hypoglycemia and the use of (blinded) CGMs. Our study also has limitations. The duration of the study was relatively short when compared to other studies. However, 3 weeks of hypoglycemia avoidance is reportedly sufficient to improve hypoglycemic awareness (13, 14) and we showed meaningful results with respect to glucose variability and HbA_{1c}, so that a longer study duration is unlikely to have produced different results. The cross-over design may have influenced the results by carry-over effects, despite the 2-week washout period (plus in fact an additional eight weeks non-active treatment) between the treatment periods. This study design was chosen because the high statistical power allowing substantially fewer study participants than parallel

designed studies, particularly given the intensity of the interventions scheduled (particularly hypoglycemic clamps). Cross-over studies generally result in more homogeneous study populations. Moreover, we used block randomization to minimize the impact of carry-over effects, which was not found by formal testing.

In conclusion, eight weeks of treatment with dapagliflozin ameliorated some components of IAH but did not completely restore hypoglycemic awareness in people with type 1 diabetes and IAH. Treatment with dapagliflozin lowers HbA_{1c} without increasing the risk of hypoglycemia, and decreases glucose variability in people with type 1 diabetes and IAH. In theory this should result in less time in hypoglycemia when aiming at a stable HbA_{1c}, but larger studies, including more subjects with and without CSII and CGM, are needed to determine the exact value of adding SGLT-2 inhibitors on hypoglycemia awareness.

Acknowledgments

The authors thank Karin Saini, Eveline Otters-van Bodegom, Sanne Houba, Anja Rasing and Jordi van Unnik (Clinical Research Center Nijmegen) for assistance during the glucose clamps. We also thank Clementine Verhulst, Julia van Heck and Anneke Hijmans for assistance during the clamps and for performing laboratory experiments. The authors also thank all the volunteers for their participation.

Duality of Interest

The authors have no other conflicts to disclose that are relevant to this manuscript.

Author Contributions

C.J.T., B.E.d.G. and L.A.v.M. designed the study. L.A.v.M. performed the experiments and collected the data. L.A.v.M. analyzed the data and wrote the first version of the manuscript. All authors discussed the results and implications and commented on the manuscript at all stages. The guarantor accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Tables

Table 1. Baseline characteristics

	n = 15
Age, years	49.7 ± 14.6
Male gender, n (%)	6 (40)
Weight, kg	77.5 ± 13.1
BMI, kg/m²	25.1 ± 3.0
Score on modified Clarke questionnaire	3.0 [3.0, 4.0]
Complications, n (%)	
Retinopathy	0 (0)
Neuropathy	1 (6.7)
Nephropathy	0 (0)
Duration of diabetes, years	24.1 ± 14.2
Insulin therapy, n (%)	
CSII	9 (60)
MDI	6 (40)
Insulin dose, IU/day	42.4 ± 19.4
Insulin dose, IU/kg	0.55 ± 0.2
HbA1c, % (mmol/mol)	7.5 ± 0.8 (58.6 ± 8.4)
Creatinin, µmol/L	71.9 ± 16.9

Data are presented as number (%), mean±SD or median [IQR]. CSII=continuous subcutaneous insulin infusion; MDI= multiple daily injections.

Legends to figures

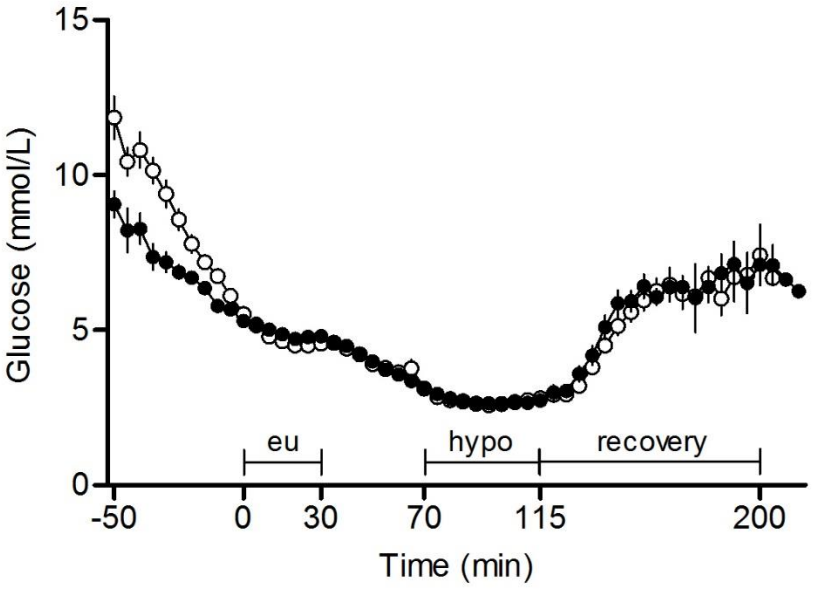
Figure 1: (a) Glucose levels and (b) glucose infusion rate (GIR) during the hyperinsulinemic clamps after treatment with dapagliflozin (closed circles) or placebo (open circles). Eu, 30 min euglycemic phase; Hypo, 45 min hypoglycemic phase; Recovery, recovery phase after hypoglycemia.

Figure 2: (a) Autonomic and (b) neuroglycopenic symptom scores during clamped euglycemia (white bars) and hypoglycemia (black bars), after dapagliflozin and placebo treatment.

Figure 3: (a-e) Levels of counterregulatory hormones during hyperinsulinemic clamps after treatment with dapagliflozin (closed circles) or placebo (open circles). Hypo, 45 min hypoglycemic phase; Rec, recovery phase after hypoglycemia.

Figures

(a)



(b)

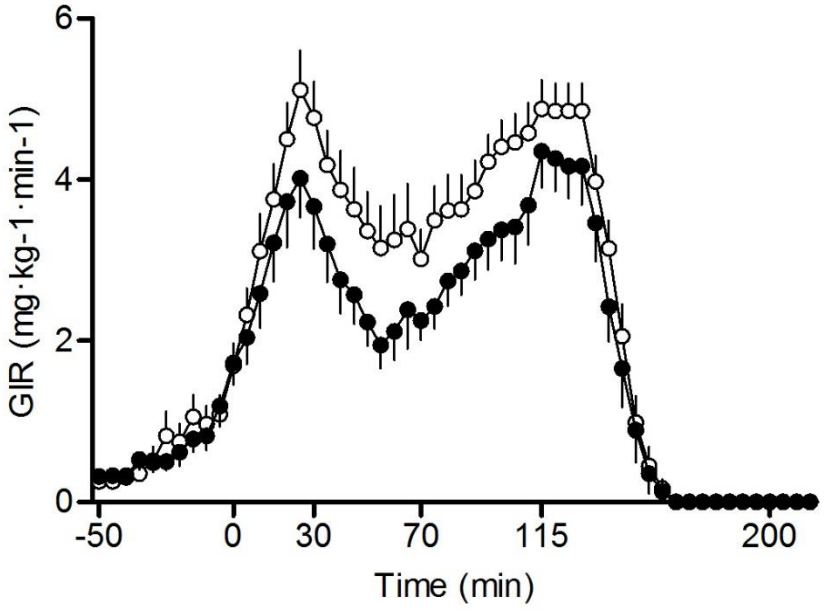
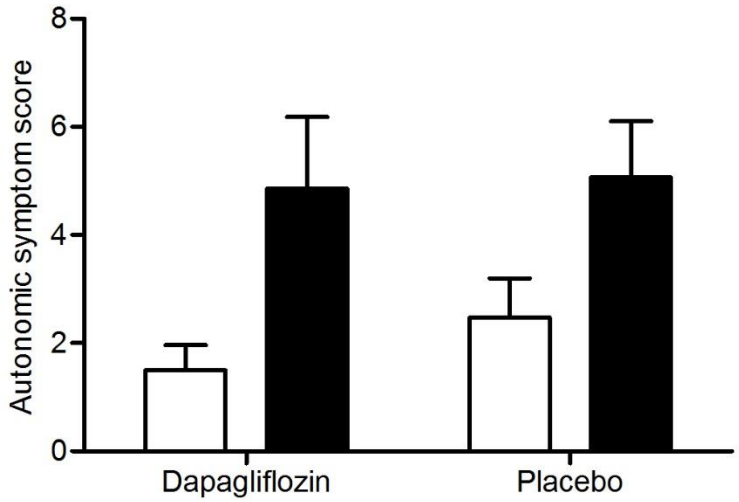


Figure 1

(a)


Autonomic symptom score
8
6
4
2
0
Dapagliflozin
Placebo

(b)

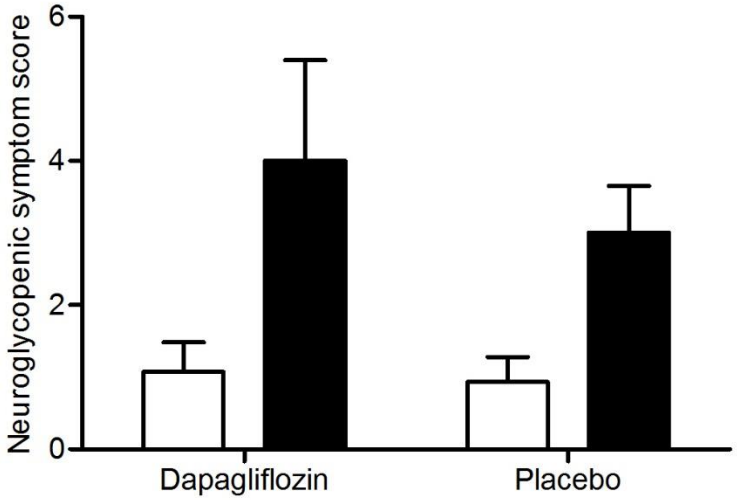
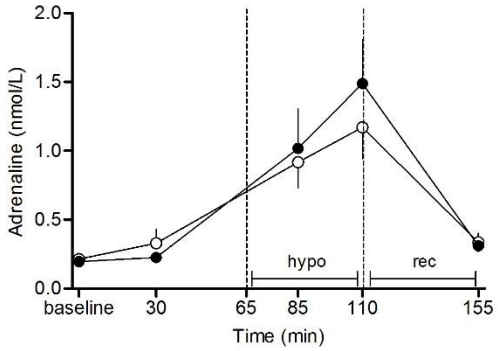

Neuroglycopenic symptom score
6
4
2
0
Dapagliflozin
Placebo

Figure 2

(a)



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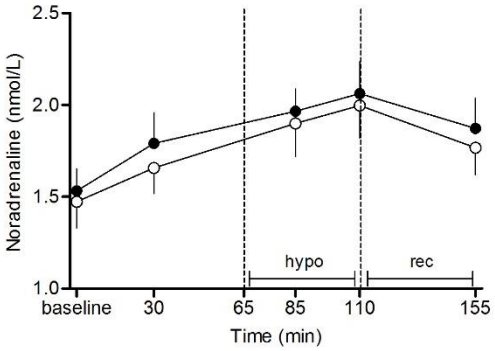

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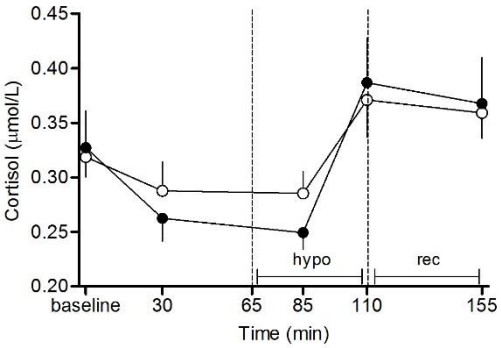

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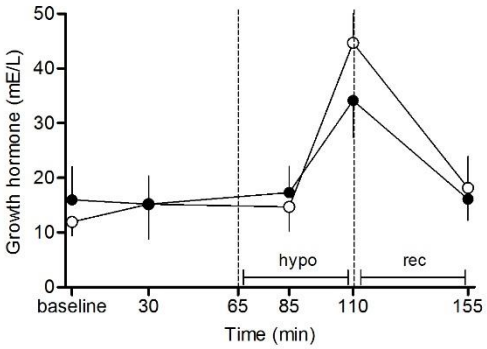

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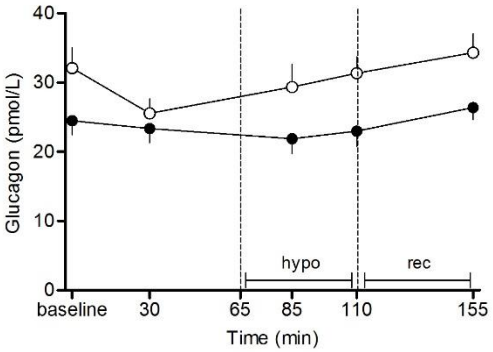

Figure 3