Low-Dose Empagliflozin as Adjunct to Hybrid Closed-Loop Insulin Therapy in Adults With Suboptimally Controlled Type 1 Diabetes: A Randomized Crossover Controlled Trial

Melissa-Rosina Pasqua,[1,2,3] Adnan Jafar,[2,4] Alessandra Kobayati,[2,4] Michael A. Tsoukas,[1,2,3] and Ahmad Haidar[1,2,3,4]

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OBJECTIVE

To assess whether low doses of empagliflozin as adjunct to hybrid closed-loop therapy improve glycemia compared with placebo in adults with type 1 diabetes (T1D) who are not able to achieve targets with the system alone.

RESEARCH DESIGN AND METHODS

A double-blind crossover randomized controlled trial was performed in adults with suboptimally controlled T1D (HbA_{1c} 7.0–10.5%) who were not able to achieve a target time in range (3.9–10.0 mmol/L) ≥70% after 14 days of hybrid closed-loop therapy. Three 14-day interventions were performed with placebo, 2.5 mg empagliflozin, or 5 mg empagliflozin as adjunct to the McGill artificial pancreas. Participants were assigned at a 1:1:1:1:1:1 ratio with blocked randomization. The primary outcome was time in range (3.9–10.0 mmol/L). Analysis was by intention to treat, and a *P* value <0.05 was regarded as significant.

RESULTS

A total of 24 participants completed the study (50% male; age 33 ± 14 years; HbA_{1c} 8.1 ± 0.5%). The time in range was 59.0 ± 9.0% for placebo, 71.6 ± 9.7% for 2.5 mg empagliflozin, and 70.2 ± 8.0% for 5 mg empagliflozin (*P* < 0.0001 between 2.5 mg empagliflozin and placebo and between 5 mg empagliflozin and placebo). Mean daily capillary ketone levels were not different between arms. There were no serious adverse events or cases of diabetic ketoacidosis or severe hypoglycemia in any intervention.

CONCLUSIONS

Empagliflozin at 2.5 and 5 mg increased time in range during hybrid closed-loop therapy by 11–13 percentage points compared with placebo in those who otherwise were unable to attain glycemic targets. Future studies are required to assess long-term efficacy and safety.

Type 1 diabetes (T1D) is treated by intensive insulin therapy with a targeted glycated hemoglobin (HbA_{1c}) <7% to reduce the risk of micro- and macrovascular

[1]Division of Endocrinology, Department of Medicine, McGill University, Montréal, Québec, Canada
[2]The Research Institute of McGill University Health Centre, Montréal, Québec, Canada
[3]Division of Experimental Medicine, Department of Medicine, McGill University, Montréal, Québec, Canada
[4]Department of Biomedical Engineering, McGill University, Montréal, Québec, Canada

Corresponding author: Ahmad Haidar, ahmad.haidar@mcgill.ca

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M.A.T. and A.H. contributed equally to this work.

complications (1). Unfortunately, fewer than a quarter of those with T1D achieve this target (2). Currently, the most advanced form of intensive insulin therapy comprises an insulin pump, continuous glucose monitoring (CGM), and an algorithm that modifies the pump's insulin doses based on CGM readings; together they are termed closed-loop therapy. This form of pump therapy reduces HbA_{1c} and increases time in range between 3.9 and 10.0 mmol/L, while reducing hypoglycemia and improving quality of life (3). Unfortunately, this is still insufficient for all patients to reach glycemic targets, because closed-loop therapy results in an average of 5–8 h spent in hyperglycemia per day (4). Even the largest randomized controlled trial to date with hybrid closed-loop therapy demonstrated that 53% of participants after 6 months did not achieve an HbA_{1c} $<7\%$ (4).

Various methods may be used to optimize closed-loop therapy, which include behavioral changes, faster insulins, and adjunctive pharmacotherapy, such as sodium–glucose cotransporter (SGLTi) inhibitors (5–7). SGLT inhibitors block the reabsorption of glucose in the gut (via SGLT1) and in the kidneys (via SGLT2), reducing blood glucose levels independently of insulin. SGLT inhibitors have revolutionized pharmacotherapy for type 2 diabetes as a result of their additional cardiac and renal benefits (8,9). Multiple randomized controlled trials have demonstrated that these agents in T1D reduce HbA_{1c} but increase the risk of diabetic ketoacidosis (10–12); only 2.5 mg empagliflozin (a quarter of the lowest commercial dose) has demonstrated reduction in HbA_{1c} with rates of diabetic ketoacidosis similar to those seen with placebo (12).

Two small pilot studies used dapagliflozin (at two doses of 10 mg) and empagliflozin (at the maximum dose of 25 mg) as adjunct to fully closed-loop therapy (13,14); the focus of both studies was to alleviate carbohydrate counting, although both revealed improved glycemia with SGLT inhibitor use. Our most recent placebo-controlled crossover trial using 25 mg empagliflozin as adjunct to hybrid closed-loop therapy revealed that after 1 month of use, time in range was increased by 7.2 percentage points, but fasting ketone levels also increased (15). The objective of our trial was to assess low doses of empagliflozin, specifically 2.5 and 5 mg, as adjunct to hybrid closed-loop therapy in adults with T1D who do not otherwise obtain time in range $\geq$70 percentage points with the system alone.

RESEARCH DESIGN AND METHODS

Study Design

We performed a three-way randomized crossover double-blind trial to compare glycemic control with placebo versus empagliflozin (Boehringer Ingelheim, Ingelheim, Germany) at 2.5 and 5 mg daily, while using hybrid closed-loop insulin therapy, in those who would not otherwise reach target glycemia with the use of hybrid closed-loop therapy over 2 weeks. The study was performed through the Clinique Médicale Hygea, an affiliate of the McGill University Health Centre, in Montréal, Québec, Canada. The protocol was approved by the local research ethics board (Centre for IRB Intelligence; Advarra, Aurora, Ontario, Canada) and Health Canada. The protocol is available in the Supplementary Material.

Participants

Participants were age $\geq$18 years with a clinical diagnosis of T1D for at least 1 year who had been using an insulin pump for $\geq$3 months, with HbA_{1c} levels of 7.0–10.5% (inclusive). Exclusion criteria included recent use of antihyperglycemic agents other than insulin, severe hypoglycemia in the last 3 months, diabetic ketoacidosis in the last 3 years requiring intravenous insulin, active or recurrent infection, severe peripheral vascular disease, osteoporosis, or any severe medical condition threatening the participant's safety during the trial; further detail is available in the protocol (Supplementary Material).

Procedures

Participants attended an admission visit where eligibility was confirmed, consent was obtained, anthropometrics and pump parameters were recorded, and laboratory testing was drawn. This was combined with a training session on the iPancreas closed-loop system (16) (Oregon Health & Science University, Portland, OR) comprising the Dexcom G6 CGM (Dexcom, San Diego, CA), a study pump (a noncommercial t:slim TAP3; Tandem Diabetes Care, San Diego, CA), and a study phone with an application that encompassed the McGill dosing algorithm (17,18). Carbohydrate counting training was not performed, although a quick review of routine diabetes care was discussed during training. If there were any safety concerns about large knowledge gaps, investigators were permitted to withdraw participants from the study; however, this was not required during the trial. This was followed by a 14-day run-in period on hybrid closed-loop therapy; remote follow-up was performed on day 4 (± 2 days) for adjustment of insulin therapy settings (e.g., carbohydrate ratios). The last 10 days were assessed for glycemic outcomes; only those who had time in range between 3.9 and 10.0 mmol/L of $<70\%$ continued in the study. Because of the arrival of commercial hybrid closed-loop systems during the conduct of this study, an amendment was created for those using commercial systems to be enrolled directly if their last 14-day time in range average was $<70\%$. The amendment was created to speed up recruitment and study completion.

Eligible participants underwent three 14-day interventions of hybrid closed-loop therapy in conjunction with either placebo, 2.5 mg empagliflozin daily, or 5 mg empagliflozin daily in a blinded randomized sequence. Carbohydrate ratios were preemptively increased (therefore resulting in a dose decrease) by 10% before the start of each intervention to reduce the risk of hypoglycemia, unless the participant's parameters resulted in sustained hyperglycemia during the prior intervention. Scheduled remote follow-up was performed on day 4 (± 2 days) of each intervention for adjustment of insulin parameters. Study personnel including investigators and nurses were available 24/7 throughout the study for technical and medical assistance. Daily morning and as-needed point-of-care capillary ketone tests were performed by participants in each arm. A subanalysis was performed later to assess levels achieved in the fasting state, which were defined as ketone measurements with no prior bolus in the last 5 h. Interventions were separated by a washout period of 7–21 days; the range allowed flexibility around participants' schedules. The hybrid closed-loop system was initialized using participants' total daily insulin doses, carbohydrate ratios, and programmed basal rates. A new basal rate was calculated every

10 min based on a model predictive control dosing algorithm (17,18), which used the sensor data as input. The computed basal rate was wirelessly communicated to the pump. The system glucose target was set at 6.0 mmol/L for the basal rate changes. Participants were made aware of the exercise feature in the system, which would raise the glucose target by 3.0 mmol/L.

Participants were instructed to manually enter the carbohydrate content of meals and snacks into the closed-loop system, which calculated the prandial boluses. Prandial boluses were calculated using carbohydrate ratios, premeal glucose levels, and insulin on board. Participants could also manually deliver correction boluses through the system at any time. The system had a glucose target of 6.0 mmol/L for the correction boluses. The system did not administer automatic boluses outside mealtimes. The system switched to open-loop mode (delivering the participant's usual basal rates) if communication between the phone and the pump or the sensor was lost for >20 and >30 min, respectively.

Randomization and Masking

Block-balanced randomization was performed with a block size of six. Randomization was assigned to participants after their confirmed inclusion in the study. The randomization sequence was created by a team member not involved in the conduct of the study; the study members conducting the trial were given only a table of which vial to use in which sequence for each participant.

Both participants and investigators were blinded to the study drug used in each intervention; these medications were cut and encapsulated by a compounding pharmacy (Gentès & Bolduc Pharmacists, Saint-Hyacinthe, Québec, Canada), where each vial was demarcated by a separate number (from 1 to 100). The identity of the drug within each vial was provided to the team member performing randomization and hidden from the rest of the team. Unblinding was performed after all participants completed the study.

Outcomes

Study outcomes were compared between placebo versus 2.5 mg empagliflozin, as well as between placebo versus 5 mg empagliflozin. The primary end point was the time in range of glucose levels between 3.9 and 10.0 mmol/L as measured by CGM for the last 10 days of each intervention. Secondary glycemic end points, using the last 10 days of each intervention, included mean glucose level, SD of glucose levels, percent coefficient of variation of glucose levels, proportion of participants with time in range ≥70%, and percentage of time spent in the following glucose ranges: between 3.9 and 7.8 mmol/L, <3.9 and <3.0 mmol/L, and >7.8, >10.0, >13.9, and >16.7 mmol/L. Wherever applicable, outcomes were calculated for the entire period, daytime (0600–2400 h), and nighttime (2400–0600 h). Other secondary end points included total daily insulin requirements and mean daily morning point-of-care ketone levels. Adverse events were also actively and passively collected for safety outcomes during follow-up and by using symptom checklists after each intervention. Adverse events of interest were severe hypoglycemia, diabetic ketoacidosis, genitourinary or other infections, forms of dehydration, and gastrointestinal adverse effects.

Statistical Analysis

Sample size was calculated to detect a difference of 6.25 percentage points (i.e., 90 min per day) in time in range, which is considered a clinically significant difference (17,18). The SD of the paired differences was assumed to be 10 percentage points from our previous studies (17,18). With an aim for power of 80% and 5% significance threshold, a sample size of 23 patients was calculated using the sample size formula for paired Student *t* test. However, to accommodate uncertainty within the power calculation, 25 participants were recruited. Given the crossover design of the study, each participant acted as his or her own comparison between interventions.

A linear mixed-effects model was used to compare the effect of the interventions on the study end points, while accounting for the period effect. Residual values from the regression model were examined for an approximate normal distribution. If residual values were skewed, a transformation or nonparametric analysis (Wilcoxon signed-rank test) was performed. Carryover effect was tested via a model fit with the treatment-by-period interaction term. χ^2 analysis was used for binary outcomes. *P* values <0.05 for the primary end point were regarded as significant (19). Results of the secondary analysis are regarded hypothesis generating and exploratory rather than conclusive, and therefore, no formal multiplicity adjustments were made. Results are reported as median (interquartile range [IQR]) or mean ± SD.

RESULTS

Recruitment took place from November 2020 to November 2021; Supplementary Fig. 1 depicts the CONSORT flowchart. Thirty-five participants with suboptimal HbA_{1c} attended the admission visit: 30 completed the run-in with the closed-loop system, four bypassed the run-in because of their suboptimal glycemic control on a commercial hybrid closed-loop system (MiniMed 670G, *n* = 3; MiniMed 770G, *n* = 1; mean time in range 56 ± 12%), and one dropped out during the run-in because of time constraints. Among the 30 participants who completed the 14-day run-in, nine did not continue in the study because their time in range was ≥70% during the run-in (mean time in range 78 ± 6%), one dropped out because of concerns related to potential adverse effects of the study drug after randomization, and 20 continued in the study because their time in range was <70% (mean time in range 63 ± 6%). Therefore, 24 participants continued in the study, completed the three interventions, and were included in the analysis. Supplementary Table 1 shows baseline characteristics of those 24 participants: 50% were female, with a mean age of 33 ± 14 years, mean duration of diabetes of 21 ± 13 years, mean HbA_{1c} of 8.1 ± 0.5%, and total daily insulin requirement of 0.68 ± 0.2 units/kg. Median washout period between interventions was 7 (IQR = 7, 11.25) days.

Table 1 details glycemic outcomes for the last 10 days of each intervention, with Fig. 1 graphically depicting sensor glucose over a 24-h period. Mean time in range (3.9–10.0 mmol/L) with placebo was 59.0 ± 9.0%, whereas participants spent a greater time in range with 2.5 and 5 mg empagliflozin, at 71.6 ± 9.7% and 70.2 ± 8.0%, respectively ($P <$ 0.0001 for placebo vs. either empagliflozin dose). These increases in time in range with both 2.5 and 5 mg empagliflozin persisted during daytime and nighttime periods (Table 2). Subgroup analysis in those who used hybrid

Table 1—Comparisons between placebo, 2.5 mg empagliflozin, and 5 mg empagliflozin as adjunct to hybrid closed-loop therapy

Outcome	Placebo	2.5 mg empagliflozin	5 mg empagliflozin	2.5 mg empagliflozin vs. placebo*		5 mg empagliflozin vs. placebo†	
				Paired difference	*P*	Paired difference	*P*
Time in range (%) of glucose (mmol/L)							
Target 3.9–10.0	59.0 ± 9.0	71.6 ± 9.7	70.2 ± 8.0	12.6 ± 9.8	<0.0001	11.2 ± 8.8	<0.0001
Target 3.9–7.8	36.1 ± 10.5	46.7 ± 12.5	45.0 ± 8.9	10.5 ± 11.9	0.00036	8.9 ± 8.4	<0.0001
<3.9	1.0 (0.4, 1.6)	0.8 (0.3, 2.7)	1.5 (0.5, 3.2)	0.0 (−0.7, 0.9)	0.44	0.3 (−0.2, 1.3)	0.0051
<3.0	0.1 (0, 0.4)	0.0 (0.0, 0.4)	0.1 (0.0, 0.7)	0 (−0.2, 0.1)	0.98404	0 (−0.1, 0.3)	0.29372
>7.8	64 ± 11	53 ± 13	55 ± 10	−11 ± 13	0.00069	−9 ± 8	<0.0001
>10.0	40 ± 9	27 ± 10	28 ± 8	−13 ± 11	<0.0001	−12 ± 9	<0.0001
>13.9	13 ± 6	7 ± 5	7 ± 5	−6 ± 6	<0.0001	−7 ± 6	<0.0001
>16.7	5 ± 3	2 ± 3	2 ± 2	−2 ± 3	0.00060	−3 ± 3	0.00030
Mean glucose (mmol/L)	9.6 ± 0.9	8.6 ± 1.0	8.6 ± 0.7	−1.0 ± 1.0	<0.0001	−1.0 ± 0.8	<0.0001
SD (mmol/L)	3.5 ± 0.5	3.1 ± 0.6	3.0 ± 0.6	−0.4 ± 0.4	<0.0001	−0.5 ± 0.5	0.00011
Coefficient of variation (%)	36.6 ± 4.2	35.7 ± 5.7	34.8 ± 5.4	−0.9 ± 4.8	0.44	−1.8 ± 4.2	0.052
Time in 3.9–10.0 mmol/L ≥70%	2 (8.3)	15 (62.5)	11 (45.8)	—	<0.001	—	0.003
Basal insulin (units/day)	33.7 ± 14.2	30.3 ± 12.5	30.5 ± 13.4	−3.5 ± 4.3	0.0010	−3.3 ± 2.6	<0.0001
Bolus insulin (units/day)	25.5 ± 11.9	23.8 ± 10.3	22.5 ± 11.2	−1.7 ± 5.4	0.067	−3.0 ± 4.2	0.0018
Total insulin (units/day)	59.2 ± 23.3	54.0 ± 20.5	52.9 ± 22.2	−5.2 ± 7.7	0.0025	−6.3 ± 4.4	<0.0001
Total insulin (units/kg/day)	0.73 ± 0.24	0.66 ± 0.21	0.65 ± 0.24	−0.07 ± 0.09	0.0015	−0.08 ± 0.05	<0.0001
Mean daily point-of-ketone level (mmol/L)	0.15 ± 0.23	0.15 ± 0.10	0.17 ± 0.10	0.02 ± 0.06	0.28	0.00 ± 0.04	0.25
N of participants with ketone levels ≥0.6 mmol/L	4	4	6	—		—	
N of days with ketone levels ≥0.6 mmol/L	8	6	13	—		—	
N of participants with ketone levels ≥1.5 mmol/L	1	3	0		—		—
N of days with ketone levels ≥1.5 mmol/L	1	3	0		—		—

Data are given as mean ± SD, median (IQR), or *n* (%) for *N* = 24 participants. *2.5 mg empagliflozin minus placebo. †5 mg empagliflozin minus placebo.

closed-loop therapy before the study or not showed similar outcomes (Supplementary Table 2).

Median times spent in hypoglycemia thresholds were low and comparable for all interventions (Table 1). Although rates of hypoglycemia for 5 mg empagliflozin demonstrated differences compared with placebo that were statistically significant, the absolute difference was minimal (7 min/day in hypoglycemia) and not clinically important, with rates substantially lower than those recommended by international consensus guidelines (20). Similar results were seen for daytime hypoglycemia outcomes, but there were no statistical differences in median times spent in hypoglycemia overnight (Table 2).

Mean times spent above all thresholds of hyperglycemia (7.8, 10, 13.9, and 16.7 mmol/L) were significantly reduced with both empagliflozin doses compared with placebo at all thresholds. Specifically, times spent >10 mmol/L for placebo and 2.5 and 5 mg empagliflozin were, respectively, 40 ± 9, 27 ± 10, and 28 ± 8%. During daytime and nighttime hours, both empagliflozin doses demonstrated similar reductions in hyperglycemia (Table 2).

A higher proportion of participants achieved time in range ≥70% when using empagliflozin compared with placebo: 8.3% (two of 24) with placebo compared with 62.5% (15 of 24) and 45.8% (11 of 24) with 2.5 and 5 mg empagliflozin, respectively. Mean glucose level was also reduced by empagliflozin at both doses, with 9.6 ± 0.9, 8.6 ± 1.0, and 8.6 ± 0.7 mmol/L for placebo and 2.5 and 5 mg empagliflozin, respectively ($P < 0.001$ for both comparisons with placebo).

On day 4 of the interventions upon the scheduled remote follow-up with the research team, a third of participants did not require change to their carbohydrate ratios, although there were more participants requiring increased ratios (i.e., decreased insulin prandial dosing) with empagliflozin interventions and decreased ratios with placebo (Supplementary Table 3). By day 14, there were incrementally higher carbohydrate ratios as the dose of empagliflozin increased (Supplementary Table 4).

Accompanying the reductions in mean glucose levels, total daily insulin doses were also reduced by empagliflozin compared with placebo (−5.2 ± 7.7 units/day with 2.5 mg empagliflozin; $P = 0.025$ vs. placebo; −6.3 ± 4.4 units/day with 5 mg empagliflozin; $P < 0.001$ vs. placebo). Both basal and bolus insulin were reduced with empagliflozin, although the bolus reduction with 2.5 mg was not significant (Table 1). Daytime and nighttime insulin requirements were also reduced (Table 2).

Mean daily point-of-care ketone levels were low and similar between interventions (0.15–0.17 mmol/L), with most ketone levels within the normal range (Table 1 and Supplementary Fig. 2). Subanalysis revealed 81% of morning

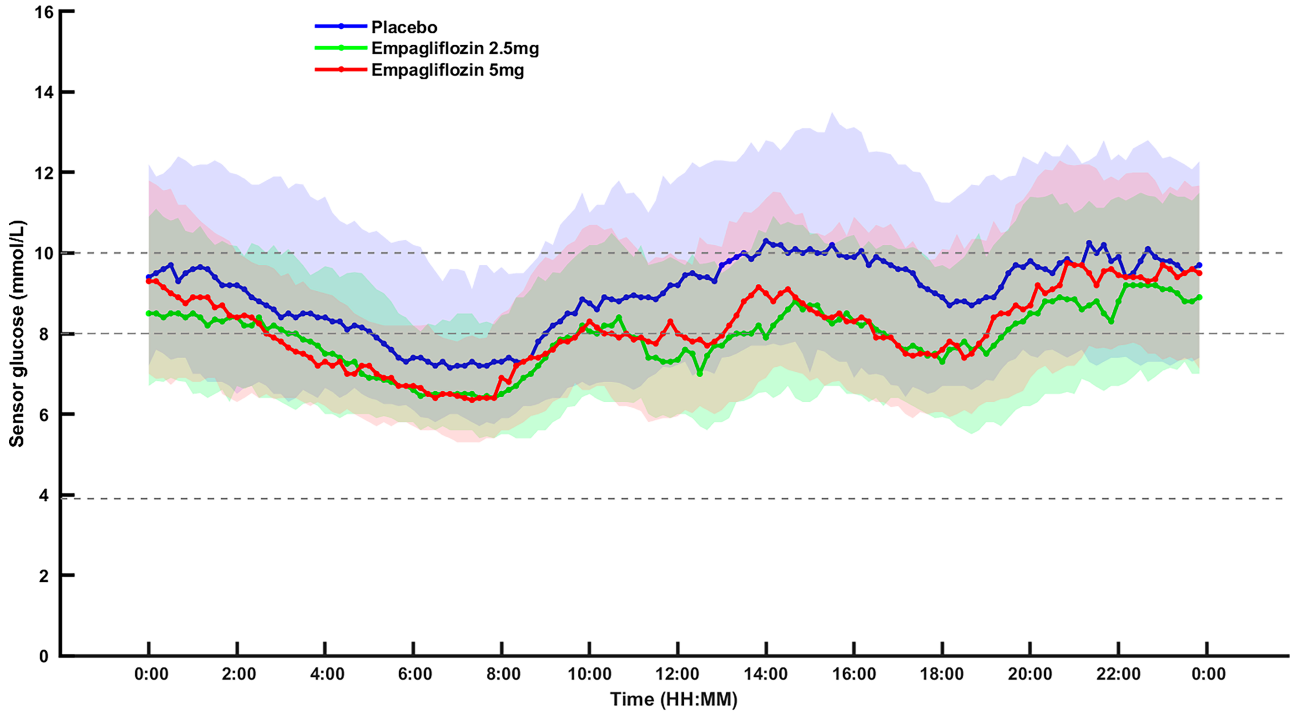

Figure 1—Median (IQR) glucose levels (mmol/L) as measured by CGM data over a 24-h period of placebo (blue), 2.5 mg empagliflozin (green), and 5 mg empagliflozin (red) as adjunct to hybrid closed-loop therapy (N = 24).

measurements were performed during fasting (>5 h since last bolus), and mean fasting levels were also not different between arms (Supplementary Table 6). Events of ketosis ≥0.6 mmol/L were few, with slightly more with 5 mg empagliflozin (Table 1). Ketone levels ≥1.5 mmol/L were rare (placebo, n = 1; 2.5 mg empagliflozin, n = 3; 5 mg empagliflozin, n = 0) and all related to catheter malfunction; none resulted in ketoacidosis or required urgent medical care. All four levels ≥1.5 mmol/L were measured when glucose was ≥18 mmol/L. The most common adverse events (Table 3) were increased urination, increased thirst, and nausea. One female participant developed urinary tract infection with 5 mg empagliflozin and developed genital mycotic infection with both empagliflozin doses. Another female participant developed genital mycotic infection with 5 mg empagliflozin. No serious adverse events occurred during the study.

CONCLUSIONS

In this study, 2.5 and 5 mg empagliflozin increased time in range by 11–13 percentage points compared with placebo when used as adjunct to hybrid closed-loop therapy in adults with T1D who did not otherwise reach glycemic targets. Low-dose empagliflozin also allowed more participants to achieve standardized targets of time in range ≥70% as per the international consensus guidelines (20). This is the second published study to assess 5 mg empagliflozin in T1D and as adjunct to hybrid closed-loop therapy (21). In the study by Garcia-Tirado et al. (21), the improvement in daytime time in range with 5 mg empagliflozin with Control-IQ (compared with no empagliflozin) was close to that achieved in our study (+9.9 percentage points), although this was a nonblinded trial without drug crossover. Surprisingly, the improvement in time in range seen with low-dose empagliflozin was greater than that demonstrated in our recent double-blind randomized controlled trial using 25 mg empagliflozin as adjunct to hybrid closed-loop therapy, where time in range increased only by 7.2 percentage points compared with placebo (15). This may have been due to the inclusion in our current study of participants with HbA_{1c} >7% who did not achieve glycemic targets with hybrid closed-loop therapy, thus removing a possible ceiling effect. This also emphasizes that those farthest from glycemic goals benefit most from novel therapies (22).

Although we did not characterize why participants did not achieve target time in range during the run-in, it is well established that the weakness of closed-loop therapy is postprandial hyperglycemia. In many large trials assessing hybrid closed-loop therapy, the average percentage of target time in range was ∼70% (4,23,24), meaning that approximately half of participants were <70% and not achieving targets. As per prior studies assessing predictors of achieving target time in range (25,26), the elevated HbA_{1c} at baseline in our population decreased the chance of achieving this.

In the EASE (Empagliflozin as Adjunctive to Insulin Therapy) trials, there was a dose-dependent reduction in HbA_{1c} from the 2.5- to 10-mg doses, but glycemic outcomes were saturated thereafter because the HbA_{1c} reduction with 25 mg was similar to that of the 10-mg dose (12). In our study, the 5- and the 2.5-mg doses had similar effects on glycemia, insulin doses, and ketone levels. Therefore, our study and the EASE data suggest that the dose-response relationship for the metabolic effects of empagliflozin is nonlinear, and saturation occurs approximately between 5 and 10 mg. However, data from other SGLT2 inhibitors indicate that nonglycemic cardiorenal

Table 2—Comparisons between placebo, 2.5 mg empagliflozin, and 5 mg empagliflozin as adjunct to closed-loop therapy over day and night periods

Outcome	Placebo	2.5 mg empagliflozin	5 mg empagliflozin	2.5 mg empagliflozin vs. placebo*		5 mg empagliflozin vs. placebo†	
				Paired difference	*P*	Paired difference	*P*
Daytime (0600–2400 h)							
Time in range (%) of glucose (mmol/L)							
Target 3.9–10.0	58.4 ± 9.3	70.9 ± 9.4	68.5 ± 8.7	12.5 ± 10.2	<0.0001	10.1 ± 9.0	<0.0001
Target 3.9–7.8	36.6 ± 10.1	46.0 ± 12.1	43.7 ± 9.7	10.4 ± 11.9	0.00039	8.1 ± 7.2	<0.0001
<3.9	0.7 (0.4, 1.7)	0.8 (0.2, 3.0)	1.1 (0.3, 3.3)	0.1 (−0.5, 2.6)	0.19	0.6 (−0.1, 1.4)	0.0065
<3.0	0.0 (0.0, 0.4)	0.0 (0.0, 0.4)	0.1 (0, 0.6)	0 (0, 0.2)	0.26272	0 (0, 0.2)	0.13362
>7.8	65 ± 10	53 ± 13	56 ± 11	−11 ± 13	0.00069	−9 ± 7	<0.0001
>10.0	41 ± 10	27 ± 10	30 ± 9	−13 ± 11	<0.0001	−11 ± 9	<0.0001
>13.9	14 ± 6	7 ± 5	7 ± 5	−7 ± 6	<0.0001	−7 ± 7	<0.0001
>16.7	5 ± 3	2 ± 2	2 ± 2	−3 ± 3	0.00023	−3 ± 3	0.00022
Mean glucose (mmol/L)	9.7 ± 0.9	8.6 ± 0.9	8.7 ± 0.8	−1.1 ± 1.0	<0.0001	−1.0 ± 0.8	<0.0001
SD (mmol/L)	3.6 ± 0.5	3.0 ± 0.6	3.1 ± 0.6	−0.5 ± 0.5	<0.0001	−0.5 ± 0.6	0.00063
Coefficient of variation (%)	36.8 ± 4.3	35.6 ± 6.2	35.0 ± 5.7	−1.2 ± 5.7	0.39	−1.8 ± 4.9	0.11
Time in 3.9–10.0 ≥70%	2 (8.3)	13 (54.2)	13 (53.2)	—	<0.001	—	0.001
Basal insulin (units/day)	24.9 ± 10.4	22.6 ± 9.6	22.6 ± 10.3	−2.3 ± 3.0	0.0013	−2.3 ± 2.3	<0.0001
Bolus insulin (units/day)	24.3 ± 11.7	22.5 ± 9.9	21.6 ± 10.9	−1.8 ± 5.1	0.043	−2.7 ± 4.0	0.0032
Total insulin (units/day)	49.1 ± 19.6	45.0 ± 17.1	44.1 ± 19.0	−4.1 ± 7.1	0.0049	−5.0 ± 4.1	<0.0001
Overnight (2400–0600 h)							
Time in range (%) of glucose (mmol/L)							
Target 3.9–10.0	61.5 ± 15.0	73.7 ± 15.8	75.2 ± 12.4	12.2 ± 14.5	0.00062	13.7 ± 12.5	<0.0001
Target 3.9–7.8	38.1 ± 15.1	48.8 ± 20.4	48.8 ± 14.0	10.7 ± 18.3	0.011	10.7 ± 14.0	0.0019
<3.9	0.3 (0.0, 2.6)	0.4 (0.0, 1.2)	1.0 (0.0, 2.2)	0.0 (−1.2, 0.4)	0.40	0.0 (−0.9, 0.4)	0.57
<3.0	0.0 (0.0, 0.4)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0 (−0.1, 0)	0.44726	0 (−0.3, 0)	0.3843
>7.8	62 ± 16	51 ± 21	51 ± 15	−10 ± 20	0.026	−10 ± 15	0.0037
>10.0	37 ± 16	25 ± 16	23 ± 13	−12 ± 16	0.0022	−13 ± 13	<0.0001
>13.9	12 ± 8	8 ± 8	5 ± 7	−4 ± 9	0.043	−7 ± 8	0.00038
>16.7	3 ± 4	3 ± 5	2 ± 3	0 ± 4	0.62	−2 ± 3	0.020
Mean glucose (mmol/L)	9.4 ± 1.3	8.6 ± 1.6	8.4 ± 1.0	−0.8 ± 1.6	0.031	−1.0 ± 1.1	0.00017
SD (mmol/L)	3.2 ± 0.7	2.8 ± 1.0	2.6 ± 0.8	−0.3 ± 0.7	0.021	−0.5 ± 0.7	0.0036
Coefficient of variation (%)	33.9 ± 6.0	32.8 ± 9.1	31.3 ± 6.9	−1.1 ± 8.2	0.55	−2.6 ± 7.2	0.10
Time in 3.9–10.0 ≥70%	6 (25.0)	14 (58.3)	16 (66.7)	—	0.019	—	0.004
Basal insulin (units/day)	8.9 ± 4.3	7.7 ± 3.4	7.9 ± 3.7	−1.1 ± 2.2	0.027	−0.9 ± 1.7	0.014
Bolus insulin (units/day)	1.2 ± 1.4	1.3 ± 1.7	0.9 ± 1.1	0.1 ± 1.3	0.30	−0.3 ± 1.1	0.077
Total insulin (units/day)	10.1 ± 4.6	9.0 ± 4.0	8.8 ± 4.0	−1.0 ± 1.7	0.0083	−1.3 ± 2.2	0.011

Data are given as mean ± SD, median (IQR), or *n* (%) for *N* = 24 participants. *2.5 mg empagliflozin minus placebo. †5 mg empagliflozin minus placebo.

benefits continue to be dose dependent even after glycemic effects are saturated (10,27). Taken together, low-dose SGLT inhibitors could be considered for additional studies in T1D, given their glycemic benefits and the lower risk of diabetic ketoacidosis, but the introduction of continuous ketone monitoring could allow for safety reassurance when using higher doses to maximize the nonglycemic benefits of SGLT2 inhibitors (28).

Several studies have reported comparable CGM outcomes when an SGLT inhibitor was added to routine insulin delivery. EASE-3 showed an increased placebo-adjusted time in range with 2.5, 10, and 25 mg empagliflozin by 4.3, 10.7, and 7.4 percentage points, respectively, with no statistical difference for the lowest dose. Increased time in range from 7 to 13.4 percentage points was seen in the DEPICT (Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes) and inTandem trials with dapagliflozin and sotagliflozin, respectively (29,30). Note that SGLT2 inhibitors have also been shown to reduce glycemic variability (12,29,30). Although coefficient of variation was not reduced in our study, this may be due to similar reductions in both mean glucose and SD, which are components of the coefficient of variation calculation.

A pertinent concern of SGLT inhibitor use with closed-loop systems is the risk of diabetic ketoacidosis. In our previous study with high-dose 25 mg empagliflozin, mean daily ketone level was increased compared with placebo with open-loop therapy, but hybrid closed-loop therapy further amplified this increase by an additional twofold, likely because of automated insulin reductions and suspensions (15). However, this study with low-dose SGLT2 inhibitors did not affect daily ketone levels, similar to findings from larger studies of open-loop therapy (12), but alternatively, the findings in our study could be due to lack of statistical power. Ketone levels ≥1.5 mmol/L were associated with overt hyperglycemia, which would have prompted concern for catheter malfunction as per standard of care for pump therapy. There were in total 28 (3%) of 1,008 days in which ketone levels were ≥0.6 mmol/L, which may reflect catheter failure rates previously measured (31).

Two case reports have previously been published where SGLT2 inhibitor use

Table 3—Adverse events during the interventions

Adverse event	Placebo	2.5 mg empagliflozin	5 mg empagliflozin
Most common			
Increased urination	4 (17)	4 (17)	8 (33)
Increased thirst	4 (17)	4 (17)	5 (21)
Nausea	2 (8)	2 (8)	4 (17)
Less common			
Emesis	2 (8)	0	1 (4)
Dizziness	2 (8)	2 (8)	3 (12.5)
Genital mycotic infection	0	1 (4)	2 (8)
Headache	3 (12.5)	0	1 (4)
Neuroglycopenic symptoms (in absence of hypoglycemia)	0	1 (4)	1 (4)
Pruritus	2 (8)	1 (4)	1 (4)
Rash	2 (8)	1 (4)	1 (4)
Upper respiratory tract infection	0	1 (4)	1 (4)
Dysuria (in absence of genitourinary infection)	0	2 (8)	0
Rare (experienced by 1 participant only)			
Abdominal pain	0	1 (4)	1 (4)
Acne	1 (4)	1 (4)	1 (4)
Arthralgias*	0	0	1 (4)
Constipation	0	0	1 (4)
Dry skin	1 (4)	1 (4)	1 (4)
Dysgeusia*	0	0	1 (4)
Fever*	0	0	1 (4)
Flexor tenosynovitis	1 (4)	1 (4)	1 (4)
Nocturia	1 (4)	1 (4)	1 (4)
Oral blisters	1 (4)	0	1 (4)
Pulsatile tinnitus	0	1 (4)	0
Stye	0	0	1 (4)
Urinary tract infection	0	0	1 (4)
Vaginal discomfort	0	1 (4)	1 (4)
Vaginal bleeding	0	0	1 (4)
Weight loss	0	0	1 (4)

Data are given as *n* (%) for *N* = 24 participants. *Occurred immediately after COVID-19 vaccine administration.

resulted in ketoacidosis when concomitantly used with hybrid closed-loop therapy, specifically the MiniMed 670G (32) and 770G (33). In both cases, the patients used a higher empagliflozin dose than that in our study (10 and 12.5 mg) and had a relatively low carbohydrate intake (maximum 125 g/day carbohydrates but dropping to $<$100 g/day before presentation). In the report by Visser et al. (33), insulin requirements dropped by 49%, and in that by Singh et al. (32), there was a catheter malfunction; both events are known risk factors for diabetic ketoacidosis in pump users (32–34). Whether the use of closed-loop therapy per se increased the risk of diabetic ketoacidosis in these two case reports is unknown.

These findings have pertinent implications as commercial hybrid closed-loop therapy emerges into clinical practice worldwide (3). As clinicians and individuals with T1D gain more experience with these devices, it becomes apparent that these technologies improve but do not perfect diabetes management. Even in large randomized controlled trials, there remains a subgroup of individuals who do not obtain target HbA_{1c} or time in range as per guidelines, with postprandial glycemia being the predominant concern (4,5). Low doses of empagliflozin may be an avenue for future studies for those who require additional improvements after optimization on hybrid closed-loop therapy. Whether this medication can introduce nonglycemic benefits that cannot be provided by automated insulin delivery, such as vascular protection, is to be assessed (7).

Despite the positive findings, our study has several limitations. First, the duration of the interventions was relatively short. Although use of CGM over 14 days has been shown to correlate strongly with 3 months of mean glucose, time in range, and hyperglycemia metrics (35,36), we used only the last 10 days for statistical analysis. However, outcomes from the last 10 days are comparable to the full 14 days of data (Supplementary Table 5). Another limitation resulting from the short duration of the interventions is that participants had less time to optimize system parameters and habits. Second, we used one particular research-based hybrid closed-loop system rather than a commercial system. Because the exact algorithms of insulin suspensions and basal insulin reductions may be different between systems, dynamic ketone production may consequently be affected differently. Finally, the frequency of point-of-care ketone testing in this study can be considered both a strength and weakness, because this is not routine clinical practice, but it provides further information on the safety of low doses of empagliflozin compared with higher doses. The increased supervision in our study is less representative of real-life clinical practice.

In conclusion, our crossover double-blind randomized controlled trial revealed that low doses of empagliflozin as adjunct to our hybrid closed-loop therapy significantly improved glycemic control in adults with T1D who did not initially reach glycemic targets. This may have future implications for those who, despite using advanced commercial closed-loop systems, face difficulties in improving glucose levels. Longer studies with larger populations are required to confirm long-term efficacy and safety.

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Author Contributions. M.-R.P., A.K., M.A.T., and A.H. conducted the study. M.-R.P., M.A.T.,

and A.H. designed the study. M.-R.P. and A.H. verified the underlying data. A.J. and A.H. performed the data analysis, including the statistical analyses. M.A.T. and A.H. supervised the study. A.H. designed the dosing algorithm. All authors had full access to all of the data, read and approved the final version of the manuscript, and accept responsibility for the decision to submit for publication. M.A.T. and A.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.

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