nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01805-3

Check for updates

Empagliflozin add-on therapy to closed-loop insulin delivery in type 1 diabetes: a 2 × 2 factorial randomized crossover trial

Ahmad Haidar[1,2,3], Leif Erik Lovblom[4], Nancy Cardinez[4], Nikita Gouchie-Provencher[2], Andrej Orszag[4], Michael A. Tsoukas[2,3], C. Marcelo Falappa[4], Adnan Jafar[1], Milad Ghanbari[1], Devrim Eldelekli[4], Joanna Rutkowski[1], Jean-François Yale[2,3] and Bruce A. Perkins[4,5] ✉

There is a need to optimize closed-loop automated insulin delivery in type 1 diabetes. We assessed the glycemic efficacy and safety of empagliflozin 25 mg d^{-1} as add-on therapy to insulin delivery with a closed-loop system. We performed a 2 × 2 factorial randomized, placebo-controlled, crossover two-center trial in adults, assessing 4 weeks of closed-loop delivery versus sensor-augmented pump (SAP) therapy and empagliflozin versus placebo. The primary outcome was time spent in the glucose target range (3.9–10.0 mmol l^{-1}). Primary comparisons were empagliflozin versus placebo in each of closed-loop or SAP therapy; the remaining comparisons were conditional on its significance. Twenty-four of 27 randomized participants were included in the final analysis. Compared to placebo, empagliflozin improved time in target range with closed-loop therapy by 7.2% and in SAP therapy by 11.4%. Closed-loop therapy plus empagliflozin improved time in target range compared to SAP therapy plus empagliflozin by 6.1% but by 17.5% for the combination of closed-loop therapy and empagliflozin compared to SAP therapy plus placebo. While no diabetic ketoacidosis or severe hypoglycemia occurred during any intervention, uncomplicated ketosis events were more common on empagliflozin. Empagliflozin 25 mg d^{-1} added to automated insulin delivery improves glycemic control but increases ketone concentration and ketosis compared to placebo.

Closed-loop automated insulin delivery systems (also commonly referred to as artificial pancreases) are progressive technologies designed to treat type 1 diabetes by automating insulin delivery from a portable insulin pump with a wearable glucose sensor and a mathematical dosing algorithm[1]. Commercially available systems are termed hybrid systems because they automate the insulin delivery between meals but require the user to initiate prandial insulin[2–6]. Although these systems improve glucose control compared to SAP therapy, hyperglycemia above 10 mmol l^{-1} is excessive for many patients, on average 6–8 h per day[2–6].

Sodium/glucose cotransporter 2 (SGLT2) inhibitors inhibit glucose reabsorption in the kidney, which allows more glucose to be excreted in the urine and thus lowers blood glucose levels in an insulin-independent manner[7,8]. In type 1 diabetes, SGLT2 inhibitor therapies have been shown to improve HbA1c, weight and blood pressure without increasing hypoglycemia[9,10]. Moreover, post hoc analysis of randomized trials suggests that SGLT2 inhibition provides renal protection to individuals with type 1 diabetes and albuminuria[11,12]. However, due to its mechanism of action, SGLT2 inhibitors can raise ketone concentrations and may potentiate diabetic ketoacidosis[13].

Empagliflozin is a highly selective compound from the SGLT2 inhibitor class that has been tested in phase 3 clinical trials in individuals with type 1 diabetes on either multiple daily insulin injections or conventional insulin pump therapy[14]. Similar to trials of dapagliflozin[15], sotagliflozin[12] and ipragliflozin[16], empagliflozin has been tested at the high doses used in the management of type 2 diabetes (10 mg and 25 mg per day in the case of empagliflozin, associated with a placebo-corrected HbA1c reduction of 0.54%) (ref. [14]). However, a type 1 diabetes-specific dose of 2.5 mg, associated with similar magnitude of glucosuria as observed in individuals with type 2 diabetes on the higher doses[17], was observed to have clinically significant, yet attenuated, HbA1c reduction (0.28%) compared to higher doses.

In this study, we assessed the glycemic efficacy and safety of adding 25 mg d^{-1} empagliflozin to a closed-loop automated insulin delivery system in adults with type 1 diabetes. In a randomized, placebo-controlled, crossover multicenter trial, we compared, in a 2 × 2 factorial design, 4 weeks of each of closed-loop therapy plus empagliflozin, closed-loop therapy plus placebo, SAP therapy plus empagliflozin and SAP therapy plus placebo. The primary outcome was the time spent in the glucose target range (3.9–10.0 mmol l^{-1}) calculated over the entire 4-week period.

Results

Twenty-eight participants were enrolled in the study between 2 August 2019 and 6 January 2021 (CONSORT diagram in Fig. 1). One participant withdrew before randomization due to circumstances surrounding the COVID-19 pandemic. Two (7%) participants withdrew from the study due to symptomatic ketosis (without acidosis), both within the first few days of their first interventions, which were closed-loop therapy plus empagliflozin and closed-loop therapy plus placebo. The data of one participant were excluded from the analysis due to a pharmacy error that prevented accurate

[1]Department of Biomedical Engineering, McGill University, Montreal, Quebec, Canada. [2]The Research Institute of McGill University Health Centre, Montreal, Quebec, Canada. [3]Division of Endocrinology, Department of Medicine, McGill University, Montreal, Quebec, Canada. [4]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada. [5]Division of Endocrinology and Metabolism, Department of Medicine, University of Toronto, Toronto, Ontario, Canada. ✉e-mail: Bruce.Perkins@sinaihealth.ca

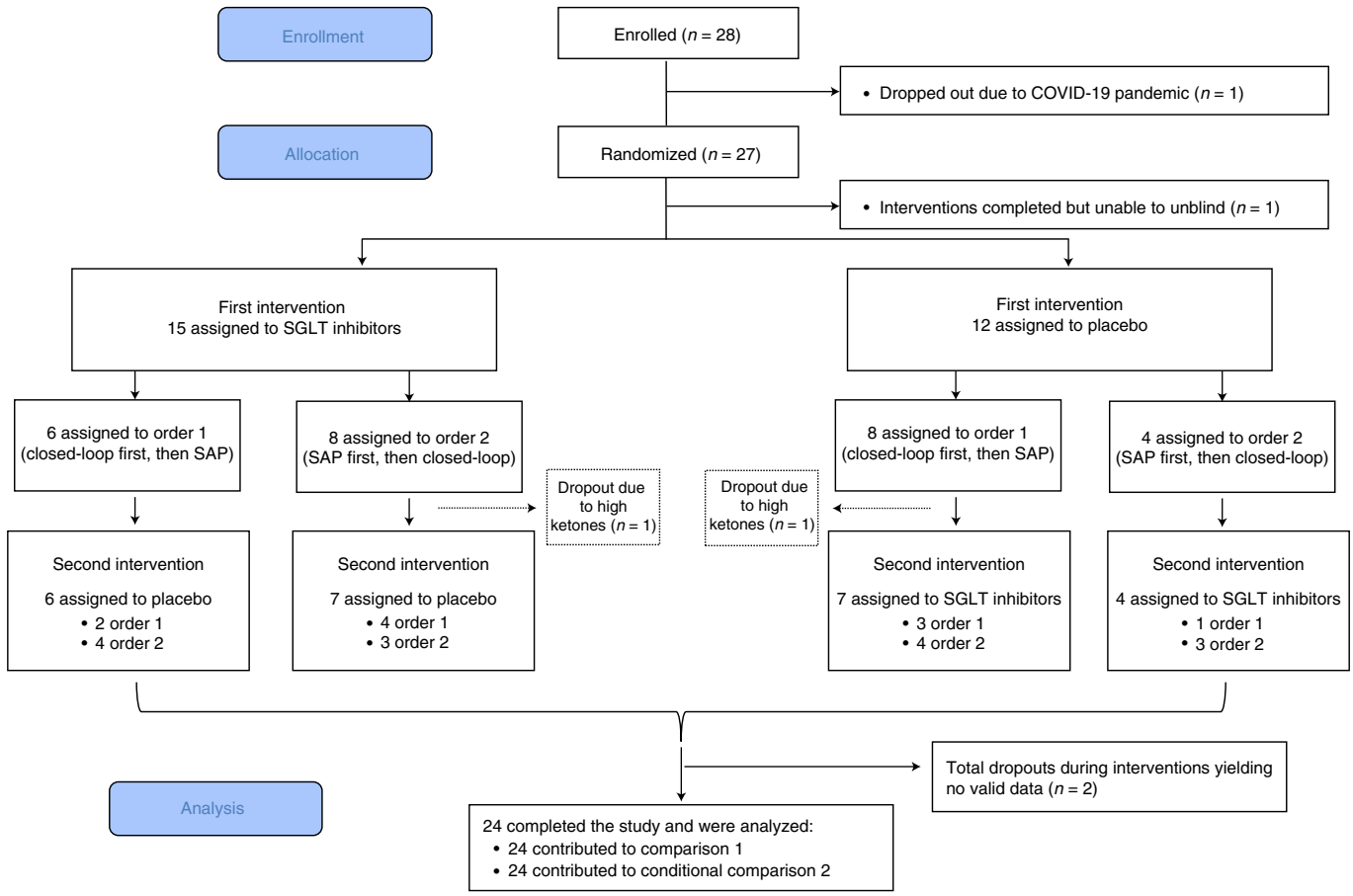


Fig. 1 | CONSORT (Consolidated Standards of Reporting Trials) Diagram Detailing Flow of Trial Participants.

unblinding. Participant characteristics are shown in Table 1: 56% were women, the mean age was 38 ± 15 years, weight was 83 ± 19 kg, body mass index (BMI) was 29.5 ± 6.6 kg m^{-2}, HbA1c was 7.7 ± 0.9% (61 ± 10 mmol mol^{-1}), average duration of diabetes was 24 ± 15 years and average total daily insulin was 0.63 ± 0.21 U kg^{-1}.

Figure 2 shows the comparison glucose profiles during each of the interventions. Glucose sensor readings were available 89 (78–98), 90 (77–94), 88 (82–92) and 88% (78–91) of the time during closed-loop therapy plus empagliflozin, closed-loop therapy plus placebo, SAP therapy plus empagliflozin and SAP therapy plus placebo, respectively. The system was operational in closed-loop mode 86 (77–91) and 89% (73–94) of the time during the closed-loop therapy plus empagliflozin and closed-loop therapy plus placebo interventions, respectively ($P = 0.91$).

The primary outcome of time spent in the target range over the entire 4-week period (3.9–10.0 mmol l^{-1}) was 75.5 ± 8.8, 68.2 ± 9.1, 69.3 ± 10.7 and 57.9 ± 13.2% with closed-loop therapy plus empagliflozin, closed-loop therapy plus placebo, SAP therapy plus empagliflozin and SAP therapy plus placebo, respectively (Table 2). Empagliflozin improved time in range with SAP therapy compared to placebo by 11.4% (7.7–15%, $P < 0.0001$) (corresponding to 2.7 h (1.8–3.6 h)). Empagliflozin also improved time in range with closed-loop therapy compared with placebo ($P < 0.0001$) but by a lower magnitude of 7.2% (3.5–10.9) (1.7 h (0.8–2.6 h)). No treatment-by-period interaction was found and no difference was observed due to the sequence or order of the interventions ($P > 0.87$ for the regression model coefficients). Daytime (6:00–24:00) and nighttime (24:00–6:00) outcomes followed similar patterns (Supplementary Material; Tables 1–3 for daytime and Tables 4–6 for nighttime). HbA1c, blood pressure and estimated glomerular filtration rate (eGFR) outcomes measured at baseline and at the end of drug intervention are reported in Supplementary Table 8.

Table 1 | Baseline characteristics of the 27 randomized participants with type 1 diabetes

Characteristic	Mean ± s.d. or frequency (%)	Range (minimum–maximum)
Female sex	15 (56%)	-
Age (years)	38 ± 15	19–66
Weight (kg)	83 ± 19	53–129
BMI (kg m^{-2})	29.5 ± 6.6	20–42
BMI ≥ 27 kg m^{-2}	14 (52%)	-
HbA1c (%)	7.7 ± 0.9	6–9.4
HBA1c (mmol mol^{-1})	61 ± 10	42–79
Duration of diabetes, years	24 ± 15	3–51
Total daily insulin (U kg^{-1})	0.63 ± 0.21	0.34–1.3
Total daily insulin ≥0.5 U kg^{-1}	17 (63%)	-

To evaluate whether the use of empagliflozin precludes the need for closed-loop therapy, we compared closed-loop therapy plus empagliflozin versus SAP therapy plus empagliflozin (Table 3). On the background of empagliflozin, closed-loop therapy improved time in range compared to SAP therapy by 6.1% (2.5–9.8%; 1.5 h

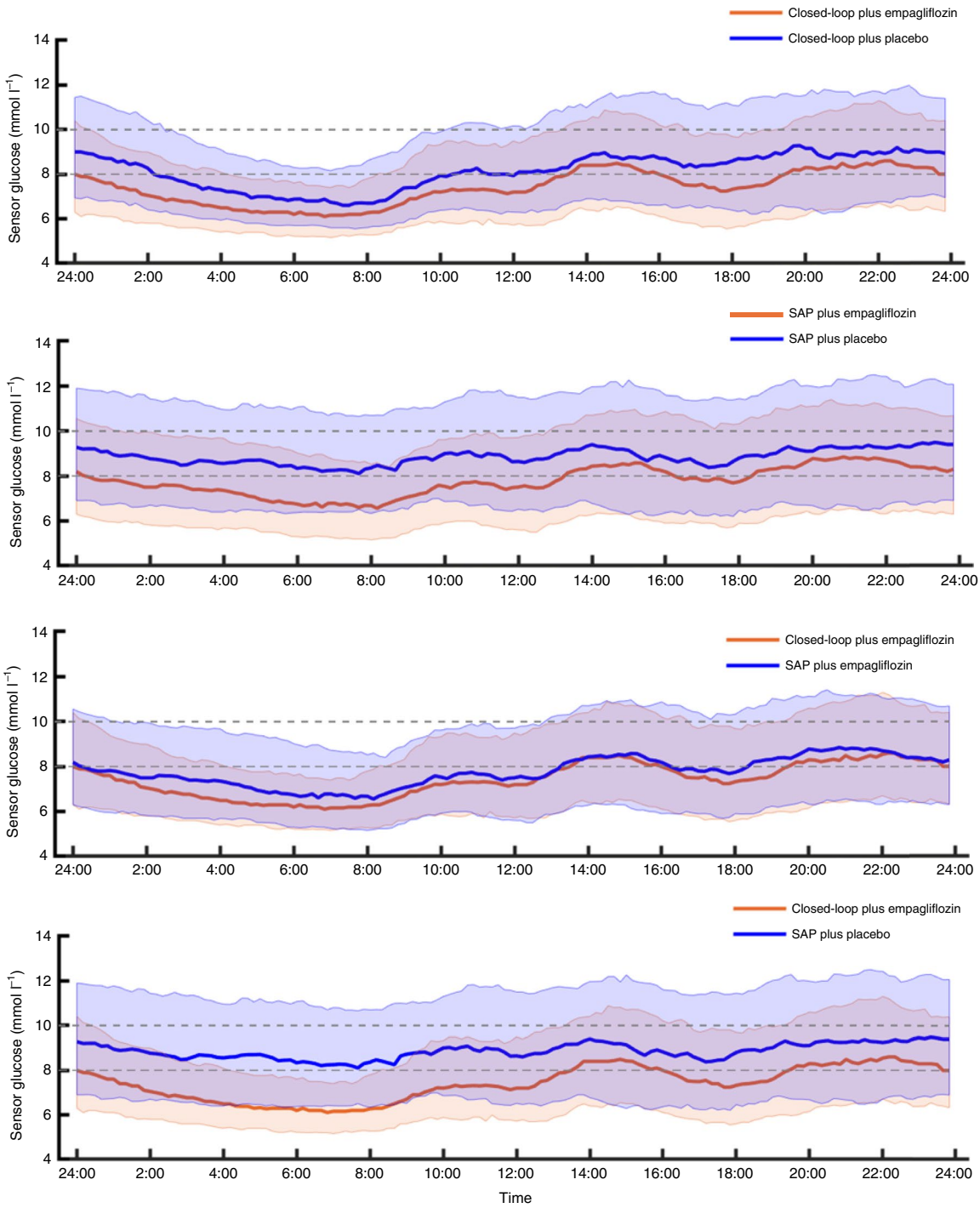


Fig. 2 | The median (IQR) profiles of glucose levels during the interventions from midnight to midnight. $n = 24$ independent participants in each of the four settings. Median values according to time of day are represented by the bold blue and red lines. Interquartile ranges by time of day are represented by the shaded light blue and light red areas. The dashed lines indicate the upper threshold levels for the target ranges analyzed as outcomes, specifically 3.9 to 10.0 mmol l^{-1} and 3.9 to 7.8 mmol l^{-1}.

(0.6–2.4 h)), which was significant ($P < 0.0001$) but lower than the improvement on the background of placebo of 10.3% (6.6–14%, $P < 0.0001$) (2.5 h (1.6–3.4h)). Combined closed-loop therapy and empagliflozin compared to SAP therapy plus placebo was associated with the largest improved time in range of 17.5% (13.8–21.2%) (4.2 h (3.3–5.1 h)).

Hypoglycemia outcomes. No severe hypoglycemia was observed in any intervention period. Time spent in hypoglycemia <3.0 mmol l^{-1} was rare in all interventions (<0.7%). Time spent in hypoglycemia <3.9 mmol l^{-1} was 2.5 (2.1–3.8), 2.1 (1.5–2.8), 4.6 (2.4–5.5) and 2.8% (1.3–4.4) with closed-loop therapy plus empagliflozin, closed-loop therapy plus placebo, SAP therapy plus empagliflozin and SAP therapy plus placebo, respectively (Table 2). The difference in time spent <3.9 mmol l^{-1} between empagliflozin and placebo was 0.3 (−0.7 to 1.3, $P = 0.53$) (4.3 min (−10.1 to 18.7)) and 0.9% (−0.1 to 1.9, $P = 0.0368$) (12.1 min (−1.4 to 27.4)) with closed-loop and SAP therapy, respectively.

Table 2 | Comparison of glucose, insulin and safety outcomes between (1) closed-loop therapy plus empagliflozin versus closed-loop therapy plus placebo and (2) SAP therapy plus empagliflozin versus SAP plus placebo

Outcome	Closed-loop therapy plus empagliflozin $n=24$	Closed-loop therapy plus placebo $n=24$	Paired difference, *P*
Percentage time in range (%)			
Target 3.9–10.0	75.5 ± 8.8	68.2 ± 9	7.2 (3.5–10.9), <0.0001
Target 3.9–7.8	53.5 ± 9.1	44.2 ± 8.6	9.3 (5.1–13.4), <0.0001
Below 3.9	2.5 (2.1–3.8)	2.1 (1.5–2.8)	0.3 (−0.7 to 1.3), 0.5337
Below 3.0	0.47 (0.29–0.92)	0.45 (0.27–0.89)	−0.09 (−0.50 to 0.32), 0.8134
Above 7.8	44.2 ± 9.3	53.9 ± 9.4	−9.5 (−14.3 to −4.7), <0.0001
Above 10.0	21.7 ± 8.6	29.3 ± 9.8	−7.5 (−11.7 to −3.2), 0.0001
Above 13.9	4.3 (2.4–7.3)	8.3 (3.8–12.0)	−2.9 (−5.1 to −0.6), 0.0044
Mean glucose (mmol l^{-1})	8.0 ± 0.7	8.7 ± 0.8	−0.7 (−1.1 to −0.3), 0.0002
SD glucose (mmol l^{-1})	3.0 ± 0.6	3.2 ± 0.5	−0.2 (−0.4 to 0), 0.0048
Coefficient of variation (%)	36.7 ± 5.0	36.7 ± 3.8	0 (−1.8 to 1.8), 0.9844
Insulin basal (units)	27.5 ± 15.3	32.4 ± 18.4	−4.9 (−6.8 to −3.1), <0.0001
Insulin bolus (units)	23.5 (14.4–37.5)	22.1 (15.5–38.8)	−0.3 (−3 to 2.3), 0.7826
Total insulin (units)	54.2 ± 28.0	59.8 ± 31.2	−5.3 (−8.4 to −2.1), 0.0003
Fasting ketone level (mmol l^{-1})	0.27 ± 0.15	0.12 ± 0.06	0.14 (0.09–0.19), <0.0001
No. of participants with ketone levels >1.5 mmol l^{-1}	5 (20%)	1 (5%)	–
No. of days with ketone levels >1.5 mmol l^{-1}	9	1	–
Outcome	**SAP therapy plus empagliflozin $n=24$**	**SAP therapy plus placebo $n=24$**	**Paired difference, *P***
Percentage time in range (%)			
Target 3.9–10.0	69.3 ± 10.7	57.9 ± 13.2	11.4 (7.7–15), <0.0001
Target 3.9–7.8	46.3 ± 11.2	35.4 ± 12.5	10.9 (6.7–15), <0.0001
Below 3.9	4.6 (2.4–5.5)	3.0 (1.3–4.3)	0.9 (−0.1 to 1.9), 0.0368
Below 3.0	0.65 (0.32–1.12)	0.61 (0.13–1.19)	0.02 (−0.39 to 0.44), 0.7436
Above 7.8	49.8 ± 12.1	61.7 ± 13.8	−11.8 (−16.5 to −7), <0.0001
Above 10.0	26.6 ± 11.4	39.0 ± 14.4	−12.3 (−16.6 to −8), <0.0001
Above 13.9	5.9 (3.1–9.2)	10.2 (6.9–17.9)	−5.3 (−7.6 to −3.1), <0.0001
Mean glucose (mmol l^{-1})	8.3 ± 0.9	9.3 ± 1.2	−1 (−1.4 to −0.6), <0.0001
SD glucose (mmol l^{-1})	3.1 ± 0.5	3.4 ± 0.5	−0.3 (−0.5 to −0.1), 0.0003
Coefficient of variation (%)	37.0 ± 4.1	36.3 ± 4.2	0.6 (−1.2 to 2.4), 0.4182
Insulin basal (units)	27.3 ± 14.8	28.1 ± 15.0	−0.8 (−2.6 to 1.1), 0.3328
Insulin bolus (units)	22.6 (15.3–36.0)	27.4 (18.3–36.2)	−4.5 (−7.1 to −1.8), 0.0003
Total insulin (units)	54.20 (27.96)	59.24 (29.81)	−5.3 (−8.4 to −2.1), 0.0003
Fasting ketone level (mmol l^{-1})	0.17 (0.08)	0.11 (0.08)	0.06 (0.01–0.1), 0.0100
No. of participants with ketone levels >1.5 mmol l^{-1}	1 (5%)	1 (5%)	–
No. of days with ketone levels >1.5 mmol l^{-1}	1	1	–

P values were derived from a *t*-statistic of the model-based least squares means comparison (two-sided). To control for multiple comparisons of the primary outcome (percentage time in range for the target of 3.9–10.0 mmol l^{-1}), $P<0.025$ was regarded as significant.

Consensus glycemic targets. Extended Data Fig. 1 shows the proportion of participants achieving consensus guidelines of time spent in the target range (>70%), time spent in hypoglycemia <3.9 mmol l^{-1} (<4.0%) and time spent in hypoglycemia <3.0 mmol l^{-1} (<3.0 mmol l^{-1})[18]. The proportion of participants achieving simultaneously all three targets increased approximately twofold between arms and was 8, 17, 30 and 63% in SAP therapy plus placebo, SAP therapy plus empagliflozin, closed-loop therapy plus placebo and closed-loop therapy plus empagliflozin, respectively.

Daily insulin dose requirements. Empagliflozin reduced average daily insulin dose requirements compared to placebo with closed-loop therapy ($P=0.0003$; Table 2) and SAP therapy ($P=0.0003$; Table 2) by an identical value of −5.3 U d^{-1} (−8.4 to −2.1), corresponding to a relative reduction of 9%. The average daily insulin dose was 54.2 ± 28.0 U d^{-1} with closed-loop therapy plus empagliflozin, 59.8 ± 31.2 U d^{-1} with closed-loop therapy plus placebo, 54.2 ± 28.0 U d^{-1} with SAP therapy plus empagliflozin and 59.2 ± 29.8 U d^{-1} with SAP therapy plus placebo (Table 2). With SAP

Table 3 | Comparison of glucose, insulin and safety outcomes between (1) closed-loop therapy plus empagliflozin versus SAP plus empagliflozin and (2) closed-loop therapy plus empagliflozin versus SAP plus placebo

Outcome	Closed-loop therapy plus empagliflozin $n=24$	SAP therapy plus empagliflozin $n=24$	Paired difference, *P*
Percentage time in range (%)			
Target 3.9–10.0	75.5 ± 8.8	69.3 ± 10.7	6.1 (2.5–9.8), 0.0003
Target 3.9–7.8	53.5 ± 9.1	46.3 ± 11.2	7.2 (3.1–11.4), 0.0002
Below 3.9	2.5 (2.1–3.8)	4.6 (2.4–5.5)	−1.3 (−2.3 to −0.3), 0.0053
Below 3.0	0.47 (0.29–0.92)	0.65 (0.32–1.12)	−0.19 (−0.60 to 0.22), 0.3622
Above 7.8	44.2 ± 9.3	49.8 ± 12.1	−5.6 (−10.4 to −0.8), 0.0092
Above 10.0	21.7 ± 8.6	26.6 ± 11.4	−4.9 (−9.1 to −0.6), 0.0111
Above 13.9	4.3 (2.4–7.3)	5.9 (3.1–9.2)	−1.3 (−3.5 to 0.9), 0.1890
Mean glucose (mmol l^{-1})	8.0 ± 0.7	8.3 ± 0.9	−0.3 (−0.7 to 0.1), 0.0785
SD glucose (mmol l^{-1})	3.0 ± 0.6	3.1 ± 0.5	−0.1 (−0.3 to 0.1), 0.1081
Coefficient of variation (%)	36.7 ± 5.0	37.0 ± 4.1	−0.3 (−2.1 to 1.5), 0.6713
Insulin basal (units)	27.5 ± 15.3	27.3 ± 14.8	0 (−1.8 to 1.9), 0.9809
Insulin bolus (units)	23.5 (14.4–37.5)	22.6 (15.3–36.0)	0.3 (−2.3 to 3), 0.7691
Total insulin (units)	54.2 ± 28.0	54.20 (27.96)	0.4 (−2.8 to 3.5), 0.7919
Fasting ketone level (mmol l^{-1})	0.27 ± 0.15	0.17 (0.08)	0.09 (0.05–0.14), <0.0001
No. of participants with ketone levels >1.5 mmol l^{-1}	5 (20%)	1 (5%)	-
No. of days with ketone levels >1.5 mmol l^{-1}	9	1	-
Outcome	**Closed-loop therapy plus empagliflozin $n=24$**	**SAP therapy plus placebo $n=24$**	**Paired difference, *P***
Percentage time in range (%)			
Target 3.9–10.0	75.5 ± 8.8	57.9 ± 13.2	17.5 (13.8–21.2), <0.0001
Target 3.9–7.8	53.5 ± 9.1	35.4 ± 12.5	18.1 (14–22.3), <0.0001
Below 3.9	2.5 (2.1–3.8)	3.0 (1.3–4.3)	−0.3 (−1.3 to 0.7), 0.4489
Below 3.0	0.47 (0.29–0.92)	0.61 (0.13–1.19)	−0.17 (−0.58 to 0.24), 0.5562
Above 7.8	44.2 ± 9.3	61.7 ± 13.8	−17.4 (−22.2 to −12.6),<0.0001
Above 10.0	21.7 ± 8.6	39.0 ± 14.4	−17.2 (−21.4 to −12.9),<0.0001
Above 13.9	4.3 (2.4–7.3)	10.2 (6.9–17.9)	−6.6 (−8.8 to −4.4), <0.0001
Mean glucose (mmol l^{-1})	8.0 ± 0.7	9.3 ± 1.2	−1.3 (−1.7 to −0.9), <0.0001
SD glucose (mmol l^{-1})	3.0 ± 0.6	3.4 ± 0.5	−0.4 (−0.6 to −0.3), <0.0001
Coefficient of variation, %	36.7 ± 5.0	36.3 ± 4.2	0.3 (−1.5 to 2.1), 0.6998
Insulin basal (units)	27.5 ± 15.3	28.1 ± 15.0	−0.8 (−2.6 to 1.1), 0.3419
Insulin bolus (units)	23.5 (14.4–37.5)	27.4 (18.3–36.2)	−4.1 (−6.8 to −1.5), 0.0007
Total insulin (units)	54.2 ± 28.0	59.24 (29.81)	−4.9 (−8 to −1.8), 0.0007
Fasting ketone level (mmol l^{-1})	0.27 ± 0.15	0.11 (0.08)	0.15 (0.1–0.2), <0.0001
No. of participants with ketone levels >1.5 mmol l^{-1}	5 (20%)	1 (5%)	-
No. of days with ketone levels >1.5 mmol l^{-1}	9	1	-

P values were derived from a *t*-statistic of the model-based least squares means comparison (two-sided). To control for multiple comparisons of the primary outcome (percentage time in range for the target of 3.9–10.0 mmol l^{-1}), $P<0.025$ was regarded as significant.

therapy, the reduction in insulin dose due to empagliflozin was primarily driven by reductions in insulin boluses (−4.5 U d^{-1} (−7.1 to −1.8), $P=0.0003$) rather than insulin basal (−0.8 U d^{-1} (−2.6 to 1.1), $P=0.33$) (Extended Data Fig. 2). On placebo, due to its continuous corrective actions, closed-loop therapy had a higher basal delivery compared to SAP therapy (4.2 U d^{-1} (2.3–6), $P<0.0001$), which led to lower insulin boluses (−3.8 U d^{-1} (−6.5 to −1.1), $P=0.0017$), partially due to the resulting lower daytime glucose levels (−0.6 mmol l^{-1} (−1.0 to −0.3), $P=0.0004$), which impacts correction boluses. However, on empagliflozin, the increase in total daily basal insulin was not observed with closed-loop therapy compared to SAP therapy (0.0 U d^{-1} (−1.8 to 1.9), $P=0.9809$), likely due to reduced need for continuous insulin corrective actions due to the glucose-lowering effect of empagliflozin. The average number of daily meals and snacks announced to the bolus calculator to deliver prandial boluses was similar between interventions. Specifically, these were 3.9 ± 1.0

Table 4 | Glucose, insulin and safety outcomes for each of the four interventions

Outcome	Closed-loop therapy plus empagliflozin $n=24$	Closed-loop therapy plus placebo $n=24$	SAP therapy plus empagliflozin $n=24$	SAP therapy plus placebo $n=24$
Percentage time in range (%)				
Target 3.9–10.0	75.5 ± 8.8	68.2 ± 9	69.3 ± 10.7	57.9 ± 13.2
Target 3.9–7.8	53.5 ± 9.1	44.2 ± 8.6	46.3 ± 11.2	35.4 ± 12.5
Below 3.9	2.5 (2.1–3.8)	2.1 (1.5–2.8)	4.6 (2.4–5.5)	3.0 (1.3–4.3)
Below 3.0	0.47 (0.29–0.92)	0.45 (0.27–0.89)	0.65 (0.32–1.12)	0.61 (0.13–1.19)
Above 7.8	44.2 ± 9.3	53.9 ± 9.4	49.8 ± 12.1	61.7 ± 13.8
Above 10.0	21.7 ± 8.6	29.3 ± 9.8	26.6 ± 11.4	39.0 ± 14.4
Above 13.9	4.3 (2.4–7.3)	8.3 (3.8–12.0)	5.9 (3.1–9.2)	10.2 (6.9–17.9)
Mean glucose (mmol l^{-1})	8.0 ± 0.7	8.7 ± 0.8	8.3 ± 0.9	9.3 ± 1.2
Glucose management indicator	6.8 ± 0.3	7.0 ± 0.4	6.9 ± 0.4	7.3 ± 0.5
SD glucose (mmol l^{-1})	3.0 ± 0.6	3.2 ± 0.5	3.1 ± 0.5	3.4 ± 0.5
Coefficient of variation (%)	36.7 ± 5.0	36.7 ± 3.8	37.0 ± 4.1	36.3 ± 4.2
Insulin basal (units)	27.5 ± 15.3	32.4 ± 18.4	27.3 ± 14.8	28.1 ± 15.0
Insulin bolus (units)	23.5 (14.4–37.5)	22.1 (15.5–38.8)	22.6 (15.3–36.0)	27.4 (18.3–36.2)
Total insulin (units)	54.2 ± 28.0	59.8 ± 31.2	54.20 (27.96)	59.24 (29.81)
Fasting ketone level (mmol l^{-1})	0.27 ± 0.15	0.12 ± 0.06	0.17 (0.08)	0.11 (0.08)
No. of participants with ketone levels >1.5 mmol l^{-1}	5 (20%)	1 (5%)	1 (5%)	1 (5%)
No. of days with ketone levels >1.5 mmol l^{-1}	9	1	1	1

and 3.7 ± 1.0 meals and snacks during closed-loop therapy plus empagliflozin and closed-loop therapy plus placebo, and 4.0 ± 1.1 and 4.3 ± 1.1 during SAP therapy plus empagliflozin and SAP therapy plus placebo, respectively. The average meal and snack size announced was 42 g carbohydrate in all 4 arms.

Adverse events, ketone levels and ketoacidosis. There were no severe hypoglycemia or diabetic ketoacidosis events in any interventional period. Two (7%) participants withdrew within the first few days on closed-loop therapy plus placebo intervention and closed-loop therapy plus empagliflozin intervention, respectively, due to symptomatic ketosis (1.8 and 3.7 mmol l^{-1}, respectively) without acidosis. These were 1 male and 1 female participant with a baseline daily insulin dose of 26 U (0.34 U kg^{-1}) and 27 U (0.56 U kg^{-1}), BMI of 24.8 kg m^{-2} and 18.7 kg m^{-2} and baseline HbA1c of 5.1% (32 mmol mol^{-1}) and 7.5% (58 mmol mol^{-1}), respectively. Among participants who completed the study, five (20%) experienced ketosis (>1.5 mmol l^{-1}) on closed-loop plus empagliflozin compared to one participant (5%) in each of the other interventions (Table 2).

Empagliflozin increased mean fasting ketone level with SAP therapy from 0.11 ± 0.08 mmol l^{-1} to 0.17 ± 0.08 mmol l^{-1} ($P=0.0100$) and with closed-loop therapy from 0.12 ± 0.06 mmol l^{-1} to 0.27 ± 0.15 mmol l^{-1} ($P<0.0001$). Compared to the baseline mean fasting ketone level with SAP therapy plus placebo, the increase with closed-loop therapy plus empagliflozin (0.15 mmol l^{-1} (0.1–0.2), $P<0.0001$) was double the additive increase with closed-loop therapy plus placebo (0.01 mmol l^{-1} (−0.04 to 0.06)) and SAP therapy plus empagliflozin (0.06 mmol l^{-1} (0.01–0.1)), suggesting a synergic impact of empagliflozin and closed-loop therapy on ketone levels. When the data from the closed-loop and SAP therapy interventional arms were combined, the mean fasting ketone level was 0.24 ± 0.14 mmol l^{-1} in women compared to 0.18 ± 0.10 mmol l^{-1} in men ($P=0.19$).

In the post hoc analysis, BMI was inversely correlated to mean ketone level, particularly in the empagliflozin arms (Extended Data Fig. 3). When assessing mean ketone level in the empagliflozin arms (closed-loop and SAP therapy interventional arms combined) with regard to the BMI cutoff in the approved indication of SGLT2 inhibitors in several countries (27 kg m^{-2}) (ref. [19]), the mean fasting level was lower in participants with a BMI > 27 kg m^{-2} (0.15 ± 0.05 mmol l^{-1}) than participants with a BMI < 27 kg m^{-2} (0.27 ± 0.16 mmol l^{-1}, $P=0.0057$). Moreover, the increase in mean ketone level with empagliflozin (closed-loop and SAP therapy interventional arms combined) relative to placebo was lower in participants with a BMI > 27 kg m^{-2} (difference 0.07 mmol l^{-1} (0.05–0.10), $P<0.0001$) than participants with a BMI < 27 kg m^{-2} (difference 0.13 mmol l^{-1} (0.06–0.20), $P<0.0001$).

Two female participants in the closed-loop therapy plus empagliflozin arm reported an episode of genital mycotic infection, each mild in severity. In the SAP therapy plus empagliflozin arm, one participant reported an ear infection (mild severity) and one participant had an upper respiratory tract infection (mild severity). In the closed-loop therapy plus placebo arm, one participant reported flu-like symptoms. Two days after the end of the closed-loop therapy plus placebo arm, one participant was hospitalized with chest pain following a traumatic stress, diagnosed as Takotsubo cardiomyopathy unrelated to the study interventions. In the SAP therapy plus placebo arm, one participant reported a common cold.

Discussion

In this study, we assessed, using a factorial crossover design, the individual and combined efficacy of the SGLT2 inhibitor empagliflozin (compared to placebo) and closed-loop automated insulin delivery (compared to SAP) on glycemic control in type 1 diabetes. The efficacy of empagliflozin compared to placebo on the background of closed-loop therapy led to an increase in time spent in the glucose target range of 7.2% compared to closed-loop therapy alone. As per international consensus guidelines[18], an increase of more than 5% is considered clinically meaningful. Despite this substantive contribution to glycemic control, the increase in time in range when empagliflozin was added to closed-loop therapy was

lower than that when empagliflozin was added to SAP therapy (7.2 versus 11.4%). This is likely because, as opposed to SAP therapy, both empagliflozin and closed-loop therapy work in a continuous glucose-responsive manner that might have led to a partial overlap in their action. However, we emphasize that the combination of closed-loop therapy and empagliflozin was associated with 17.5% greater time in range compared to SAP therapy and placebo.

In our study, no episode of diabetic ketoacidosis was observed with empagliflozin in either SAP or closed-loop therapy interventions, probably due to daily ketone monitoring, the mitigation and education strategies put into place in the trial (Extended Data Fig. 4 and 5), the relatively small sample size and the short duration of the interventions. Nevertheless, the mean fasting ketone level was increased when empagliflozin was added to SAP therapy; closed-loop therapy amplified this empagliflozin-induced increase by twofold. Moreover, more participants experienced ketosis ($>1.5\,mmol\,l^{-1}$) with the closed-loop therapy plus empagliflozin intervention compared to the other interventions. Taken together, these results indicate that efforts must be taken to prevent ketoacidosis when adding a 25-mg empagliflozin dose to closed-loop therapy[20], including enhanced patient education, minimization of insulin reductions, clinical follow-up and ketone monitoring. Technologies for continuous ketone monitoring could provide people with diabetes constant surveillance with an alarm in the context of ketosis as an additional measure to prompt self-management interventions to prevent progression to diabetic ketoacidosis[18,20,21]. Although of potential benefit to all people with type 1 diabetes for ketoacidosis prevention, uptake and use could first be targeted toward those with the greatest magnitude of risk (such as those using adjunct-to-insulin SGLT2 inhibitors), in combination with clinical risk mitigation strategies[22,23] to reduce the risk of diabetic ketoacidosis[24,25].

Additionally, aspects of patient selection could further mitigate the risk of diabetic ketoacidosis. Post hoc analysis of randomized trials showed that a higher BMI shifts the benefits versus risk profile of SGLT2 inhibitors with a reduced risk of diabetes ketoacidosis[15], probably due to lower rates of lipolysis in this population compared to lean individuals and the requirement of higher doses of insulin compared to those of lower body mass[26,27]. In the current study, mean ketone levels with empagliflozin in participants with a BMI $\geq 27\,kg\,m^{-2}$ was significantly lower than in those with a BMI $< 27\,kg\,m^{-2}$. Moreover, combined empagliflozin and closed-loop therapy remained effective in improving time in range when analysis was restricted to participants with high BMI (Supplementary Table 7). Dedicated long-term studies in this subpopulation are warranted.

Even though we tested one specific closed-loop system with the McGill automated insulin dosing algorithm, the results of our study likely generalize to other available and commercialized closed-loop systems. Acknowledging that comparison between systems across studies is complex due to differences in baseline patient characteristics and study designs that can influence study outcomes[28], our closed-loop system plus placebo in this study performed similarly to current commercial systems tested in other studies. The time in range with our closed-loop system plus placebo was 68.2%, which approximated the targets observed with other systems in randomized trials (67–71%; refs. [2–6]). Moreover, when compared to SAP therapy, our closed-loop system plus placebo improved time in range by 10.3% (Table 4), which is within what is observed with other systems (9–12%; refs. [2–6]). However, with the introduction of new rapid-acting insulins and glucagon or pramlintide in dual-hormone systems, closed-loop systems will continue to improve. It is unknown if adding SGLT2 inhibitors will continue to provide a 7.2% improvement in time in range. Irrespective of the glycemic benefits, the potential cardiorenal protective benefits with SGLT2 inhibitors could justify using this class of drug in type 1 diabetes[29], especially since mortality from any cause or from cardiovascular causes is still high compared to the general population even in those who achieve HbA1c below 7.0% (ref. [30]).

Despite the use of a randomized 2×2 factorial design, the inclusion of two sites and the outpatient setting of the interventions, this study has some limitations. As is customary with device technologies, the closed-loop therapy intervention could not be blinded, while the SGLT2 inhibitor intervention was blinded to participants and investigators. We did not test low-dose options for SGLT2 inhibitors in this study. Longer and substantively larger studies are needed to quantify the diabetic ketoacidosis risk with closed-loop therapy plus empagliflozin intervention. Two earlier studies assessed SGLT2 inhibitors and closed-loop therapy in type 1 diabetes but were small and pilot in nature and in highly supervised settings. Biester et al. compared 10 mg dapagliflozin twice daily to placebo under fully closed-loop conditions in a 24-h inpatient study[31]. Haidar et al. assessed empagliflozin 25 mg once daily under 3 prandial insulin strategies with closed-loop therapy in 9–14-h supervised interventions[32]. Both studies demonstrated improved control with the addition of SGLT2 inhibitors. This study builds on these proof-of-concept smaller studies and was conducted in an outpatient free-living setting over four weeks without remote monitoring; thus, it allowed more robust assessment of efficacy and safety outcomes.

Our study showed that combining high-dose empagliflozin with closed-loop therapy brings synergic benefits to glucose control during the day and night in patients with type 1 diabetes, although it amplifies the increase in ketone levels and ketosis. Clinical use of empagliflozin as an adjunct therapy to closed-loop systems could be appropriate in individuals with a low risk of diabetic ketoacidosis and implementing strategies for early ketoacidosis detection.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-022-01805-3.

Received: 21 September 2021; Accepted: 28 March 2022;
Published online: 12 May 2022

References

1. Haidar, A. The artificial pancreas: how closed-loop control is revolutionizing diabetes. *IEEE Control Syst.* **36**, 28–47 (2016).
2. Brown, S. A. et al. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N. Engl. J. Med.* **381**, 1707–1717 (2019).
3. Thabit, H. et al. Use of an artificial beta cell in type 1 diabetes. *N. Engl. J. Med.* **373**, 2129–2140 (2015).
4. Collyns, O. J. et al. Improved glycemic outcomes with Medtronic MiniMed Advanced Hybrid Closed-Loop delivery: results from a randomized crossover trial comparing automated insulin delivery with predictive low glucose suspend in people with type 1 diabetes. *Diabetes Care* **44**, 969–975 (2021).
5. Benhamou, P.-Y. et al. Closed-loop insulin delivery in adults with type 1 diabetes in real-life conditions: a 12-week multicentre, open-label randomised controlled crossover trial. *Lancet Digit. Health* **1**, e17–e25 (2019).
6. Bergenstal, R. M. et al. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. *Lancet* **397**, 208–219 (2021).
7. Heerspink, H. J. L., Perkins, B. A., Fitchett, D. H., Husain, M. & Cherney, D. Z. I. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation* **134**, 752–772 (2016).
8. Mudaliar, S. et al. Remogliflozin etabonate, a selective inhibitor of the sodium-glucose transporter 2, improves serum glucose profiles in type 1 diabetes. *Diabetes Care* **35**, 2198–2200 (2012).
9. Taylor, S. I., Blau, J. E., Rother, K. I. & Beitelshees, A. L. SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: balancing benefits and risks. *Lancet Diabetes Endocrinol.* **7**, 949–958 (2019).

10. Lu, J., Tang, L., Meng, H., Zhao, J. & Liang, Y. Effects of sodium-glucose cotransporter (SGLT) inhibitors in addition to insulin therapy on glucose control and safety outcomes in adults with type 1 diabetes: a meta-analysis of randomized controlled trials. *Diabetes Metab. Res. Rev.* **35**, e3169 (2019).
11. Groop, P.-H. et al. Effect of dapagliflozin as an adjunct to insulin over 52 weeks in individuals with type 1 diabetes: post-hoc renal analysis of the DEPICT randomised controlled trials. *Lancet Diabetes Endocrinol.* **8**, 845–854 (2020).
12. Musso, G., Gambino, R., Cassader, M. & Paschetta, E. Efficacy and safety of dual SGLT 1/2 inhibitor sotagliflozin in type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* **365**, l1328 (2019).
13. Taylor, S. I., Blau, J. E. & Rother, K. I. SGLT2 inhibitors may predispose to ketoacidosis. *J. Clin. Endocrinol. Metab.* **100**, 2849–2852 (2015).
14. Rosenstock, J. et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE trials. *Diabetes Care* **41**, 2560–2569 (2018).
15. Mathieu, C. et al. Benefit/risk profile of dapagliflozin 5 mg in the DEPICT-1 and -2 trials in individuals with type 1 diabetes and body mass index ≥27 kg/m^2. *Diabetes Obes. Metab.* **22**, 2151–2160 (2020).
16. Kaku, K., Isaka, H., Sakatani, T. & Toyoshima, J. Efficacy and safety of ipragliflozin add-on therapy to insulin in Japanese patients with type 1 diabetes mellitus: a randomized, double-blind, phase 3 trial. *Diabetes Obes. Metab.* **21**, 2284–2293 (2019).
17. Pieber, T. R. et al. Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). *Diabetes Obes. Metab.* **17**, 928–935 (2015).
18. Battelino, T. et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. *Diabetes Care* **42**, 1593–1603 (2019).
19. Danne, T. et al. Efficacy and safety of adding sotagliflozin, a dual sodium-glucose co-transporter (SGLT)1 and SGLT2 inhibitor, to optimized insulin therapy in adults with type 1 diabetes and baseline body mass index ≥27 kg/m^2. *Diabetes Obes. Metab.* **23**, 854–860 (2021).
20. Singh, S., Rushakoff, R. J. & Neinstein, A. B. A case report of diabetic ketoacidosis with combined use of a sodium glucose transporter 2 inhibitor and hybrid closed-loop insulin delivery. *J. Diabetes Sci. Technol.* **13**, 605–606 (2019).
21. Zhang, J. Y., Shang, T., Koliwad, S. K. & Klonoff, D. C. Continuous ketone monitoring: a new paradigm for physiologic monitoring. *J. Diabetes Sci. Technol.* **15**, 775–780 (2021).
22. Goldenberg, R. M., Gilbert, J. D., Hramiak, I. M., Woo, V. C. & Zinman, B. Sodium-glucose co-transporter inhibitors, their role in type 1 diabetes treatment and a risk mitigation strategy for preventing diabetic ketoacidosis: the STOP DKA Protocol. *Diabetes Obes. Metab.* **21**, 2192–2202 (2019).
23. Garg, S. K., Peters, A. L., Buse, J. B. & Danne, T. Strategy for mitigating DKA risk in patients with type 1 diabetes on adjunctive treatment with SGLT inhibitors: a STICH Protocol. *Diabetes Technol. Ther.* **20**, 571–575 (2018).
24. Alva, S., Castorino, K., Cho, H. & Ou, J. Feasibility of continuous ketone monitoring in subcutaneous tissue using a ketone sensor. *J. Diabetes Sci. Technol.* **15**, 768–774 (2021).
25. Nguyen, K. T. et al. Continuous Ketone Monitoring Consensus Report 2021. *J. Diabetes Sci. Technol.* https://doi.org/10.1177/19322968211042656 (2021).
26. Cifuentes, M., Albala, C. & Rojas, C. V. Differences in lipogenesis and lipolysis in obese and non-obese adult human adipocytes. *Biol. Res.* **41**, 197–204 (2008).
27. Herring, R. A. et al. Metabolic effects of an SGLT2 inhibitor (dapagliflozin) during a period of acute insulin withdrawal and development of ketoacidosis in people with type 1 diabetes. *Diabetes Care* **43**, 2128–2136 (2020).
28. Schoelwer, M. J. et al. Predictors of time-in-range (70–180 mg/dL) achieved using a closed-loop control system. *Diabetes Technol. Ther.* **23**, 475–481 (2021).
29. Pasqua, M.-R., Tsoukas, M. A. & Haidar, A. Strategically playing with fire: SGLT inhibitors as possible adjunct to closed-loop insulin therapy. *J. Diabetes Sci. Technol.* **15**, 1232–1242 (2021).
30. Lind, M. et al. Glycemic control and excess mortality in type 1 diabetes. *N. Engl. J. Med.* **371**, 1972–1982 (2014).
31. Biester, T. et al. Add-on therapy with dapagliflozin under full closed loop control improves time in range in adolescents and young adults with type 1 diabetes: the DAPADream study. *Diabetes Obes. Metab.* **23**, 599–608 (2021).
32. Haidar, A. et al. Reducing the need for carbohydrate counting in type 1 diabetes using closed-loop automated insulin delivery (artificial pancreas) and empagliflozin: a randomized, controlled, non-inferiority, crossover pilot trial. *Diabetes Obes. Metab.* **23**, 1272–1281 (2021).

Methods

The study was approved by the local ethics committees (Mount Sinai Hospital Research Ethics Board, approval no. 18-0165-A, and McGill University Health Center's Research Ethics Board, approval no. 2019-4946) and Health Canada.

Participants. From 2 August 2019 to 6 January 2021, participants were enrolled at Mount Sinai Hospital, Toronto and the Research Institute of McGill University Health Centre, Montreal, Canada. Participants were adults aged 18 years or older, diagnosed with type 1 diabetes for more than 1 year, had used an insulin pump for more than 3 months and had an HbA1c ≤ 10%. Exclusion criteria included reduced eGFR (< 60 ml min 1.73 ml^{-2}), use of non-insulin antihyperglycemic drugs (for example, glucagon-like peptide-1 analogs or metformin), use of loop diuretics, pregnancy, diabetic ketoacidosis in the last 3 months, recent history of genital or urinary infection and use of hydroxyurea medications. Participants provided written informed consent.

Study design. We conducted a randomized, crossover, placebo-controlled, 2×2 factorial trial in 28 adults with type 1 diabetes. Each participant entered an open-loop 14-d therapy optimization period, was then randomized to empagliflozin 25 mg d^{-1} or placebo and (within each empagliflozin and placebo intervention) allocated to closed-loop and SAP therapy in random order. Each intervention lasted four weeks; on average, the total study duration was five months per participant. The interventions were separated by 11 d (8–13) when switching drugs (empagliflozin and placebo) and 1 d (0–2) when switching insulin delivery method (closed-loop and SAP therapy) to eliminate the effects of empagliflozin and insulin delivery method between interventions. (The half-lives of empagliflozin and insulin are around 12 h (ref. [33]) and 50 min[34], respectively.) The trial was registered at ClinicalTrials.gov (identifier NCT03979352) and the study protocol is provided in the supplementary materials.

Randomization, concealment and masking. We used blocked randomization with equal ratios of size eight (separate blocks for each site) to generate the allocation sequences. Sequences were generated by the Mount Sinai Hospital pharmacy and were placed in opaque envelopes, which were distributed to both sites and opened by the study coordinators after the therapy optimization period. The order of drug interventions (empagliflozin and placebo) was randomized and so was the order of the insulin delivery method (closed-loop and SAP therapy) within each drug intervention. The empagliflozin and placebo doses were placed in identical capsules. Participants and investigators were blinded to the allocation of the drug but were not blinded to the allocation of the insulin delivery method.

Study procedures. After study entry, participants had an optimization period of 14 d with a glucose sensor (Dexcom G5 or G6; Dexcom) and using their own pump. During this optimization, a member of the team reviewed the participant's pump and sensor data and adjusted their pump settings if substantial hyperglycemia or hypoglycemia were observed. Dexcom G5 was discontinued in Canada during the study; thus, the last three participants used Dexcom G6.

On the SAP therapy arms, participants used the Dexcom glucose sensor and their own pump for four weeks. On the closed-loop therapy arms, participants used the iPancreas system[35] (Oregon Health & Science University) with our dosing algorithm (the McGill dosing algorithm, version Lucie-3.9.0) (refs. [36,37]) for four weeks. The system consists of a Dexcom glucose sensor, a noncommercial t:slim TAP3 insulin pump (Tandem Diabetes Care) and a smartphone. After the optimization period, participants were trained on how to use the iPancreas system. The iPancreas system was the same in both closed-loop therapy interventions (placebo and empagliflozin).

The closed-loop system was initialized using participants' total daily insulin dose, carbohydrate ratios and programmed basal rates. A new basal rate was calculated every 10 min based on a model predictive control dosing algorithm[36,37], which used the sensor data as an input. The computed basal rate was communicated wirelessly to the pump. The system glucose target was set at 6.0 for the basal rate changes. Participants were made aware of the exercise feature in the system, which would raise the glucose target by 3 mmol l^{-1}.

Participants were instructed to manually enter the carbohydrate content of the meals and snacks into the iPancreas system, which calculated the prandial boluses. Prandial boluses were calculated using the carbohydrate-to-insulin 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^{-1} for the correction boluses. The system does not administer automatic boluses outside mealtimes. The system switches to open-loop mode (delivering the participant's usual basal rates) if communication between the phone and pump or sensor is lost for more than 20 and 30 min, respectively.

If a participant's HbA1c was less than 8% before the start of a closed-loop or SAP therapy intervention, then the programmed basal rates, carbohydrate ratios and insulin sensitivity factors were altered, based on the investigators' judgment, to deliver 10% less insulin to account for the glycemic lowering effect of empagliflozin. Since the participants and investigators were masked to the drug intervention, these initial adjustments were made regardless of drug assignment (empagliflozin or placebo). Participants were subsequently contacted on the first 3 d of closed-loop and SAP therapy interventions, as well as once weekly afterward to discuss any unexpected events or technical problems. Downloads of glucose and insulin data on days 3 (±2) and 7 (±2) were also reviewed by the research team during both closed-loop and SAP therapy interventions and further adjustments to insulin therapy parameters were made if necessary. Thus, even if the systems were the same in both closed-loop therapy interventions (placebo and empagliflozin), the adjustable parameters (for example, carbohydrate ratios) were generally different between the two closed-loop therapy interventions.

Study teams were on call throughout the interventions to provide technical support. For both closed-loop and SAP therapy interventions, sensor alarm thresholds were determined by the participants. Participants were asked to treat hypoglycemia as per their usual practice. Participants were instructed to measure their blood ketone levels using a capillary ketone meter every morning during the interventions, as well as in case of any symptoms of diabetic ketoacidosis, irrespective of glucose levels, and were instructed to contact the research team if their blood ketone levels were >0.6 mmol l^{-1} at any time. Participants were given a brochure for the management of ketone levels while on empagliflozin (Supplementary Information and Extended Data Figs. 4 and 5).

Study outcomes. The primary comparisons were aimed at assessing the benefits of empagliflozin as an adjunct therapy to both closed-loop and SAP therapy. Therefore, the two primary comparisons were the percentage of times that the sensor glucose readings were in the target range (3.9–10.0 mmol l^{-1}) (refs. [15,16]) between (1) closed-loop therapy plus empagliflozin versus closed-loop therapy plus placebo and (2) SAP therapy plus empagliflozin versus SAP therapy plus placebo. If the primary comparisons were achieved, then we aimed to assess (1) whether the use of empagliflozin with SAP therapy could overcome the need for a closed-loop system and (2) the benefits of combining both closed-loop therapy and empagliflozin. Therefore, the two conditional comparisons were the percentage of times that the sensor glucose readings were in the target range between closed-loop therapy plus empagliflozin versus SAP therapy plus (1) empagliflozin and (2) placebo. Secondary outcomes included the time spent below and above the target range, glucose variability and insulin delivery[15,16]. Analysis was by intention to treat. Outcomes were calculated for the entire four-week study period. For the closed-loop therapy arms, outcomes included all available data including when the system was in open-loop mode; 5-min glucose sensor data were used in the calculations. If glucose sensor values were missing for less than 2 h, then missing values were interpolated.

Statistical analysis. We aimed to recruit 28 participants (14 per site), a reduction from the initial planned recruitment owing to funding decisions before and during the pandemic. Assuming an s.d. in time spent in the target range of 13 and 15% for the empagliflozin arms and a correlation between arms of 0.50, 28 participants would give 73% and 60% power to detect 8% and 7% differences in time in range, respectively, at a significance level of 2.5%. After the filing of the protocol, preliminary data became available that indicated that we had overestimated the s.d. in time in range during exposure to empagliflozin and we felt confident that power was substantially higher.

Analyses were performed on an intention-to-treat basis. The effect of the interventions was estimated using a linear mixed-effects model: specifically, least squares mean estimates of treatment effect were determined and two-sided tests of the resulting t-statistic were applied. To examine for carryover effect, a model was fitted with the treatment-by-period interaction term. The model accounted for repeated observations as well as the period and randomization sequence. Residual values were examined for normality; if skewed, data were transformed using the square root function or the Wilcoxon signed-rank test was used. The two primary comparisons shared an overall Alpha level of 0.05 (that is, $P < 0.025$ was regarded as significant). Since testing the 2 conditional comparisons was conditional on the rejection of the 2 primary hypotheses (that is, prespecified ordering of the null hypotheses, with 2 sequential testing), we did not further adjust for multiple comparisons and a 5% significance level was shared between the 2 conditional comparisons (that is, $P < 0.025$ was regarded as significant). The results of the secondary analysis are regarded as hypothesis-generating and exploratory rather than conclusive; therefore, no formal multiplicity adjustments were made. Results are reported as the median (interquartile range (IQR)) or mean (s.d.). SAS v.9.4 (SAS Institute) was used for the statistical analysis.

Data sharing. The raw data (that is, insulin delivery, glucose levels and individual participant data) and informed consent form will be shared by the corresponding author, for academic purposes, subject to a material transfer agreement and approval of the Mount Sinai Hospital Research Ethics Board and McGill University Health Center's Research Ethics Board. All data shared will be deidentified.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Code availability

The code used for analysis is available from the corresponding author. The predictive control algorithm cannot be made publicly available because it is

proprietary intellectual property. The control algorithm cannot be used in routine practice in the outpatient setting because regulatory approval has not yet been granted.

References

33. Ndefo, U. A., Anidiobi, N. O., Basheer, E. & Eaton, A. T. Empagliflozin (Jardiance): a novel SGLT2 inhibitor for the treatment of type-2 diabetes. *P T* **40**, 364–368 (2015).
34. Haidar, A., Duval, C., Legault, L. & Rabasa-Lhoret, R. Pharmacokinetics of insulin aspart and glucagon in type 1 diabetes during closed-loop operation. *J. Diabetes Sci. Technol.* **7**, 1507–1512 (2013).
35. Castle, J. R. et al. Randomized outpatient trial of single- and dual-hormone closed-loop systems that adapt to exercise using wearable sensors. *Diabetes Care* **41**, 1471–1477 (2018).
36. Haidar, A., Messier, V., Legault, L., Ladouceur, M. & Rabasa-Lhoret, R. Outpatient 60-hour day-and-night glucose control with dual-hormone artificial pancreas, single-hormone artificial pancreas, or sensor-augmented pump therapy in adults with type 1 diabetes: an open-label, randomised, crossover, controlled trial. *Diabetes Obes. Metab.* **19**, 713–720 (2017).
37. Haidar, A. et al. Comparison of dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional insulin pump therapy for glycaemic control in patients with type 1 diabetes: an open-label randomised controlled crossover trial. *Lancet Diabetes Endocrinol.* **3**, 17–26 (2015).

Acknowledgements

This research was supported by the Juvenile Diabetes Research Foundation and by Diabetes Action Canada, a Canadian Institutes for Health Research (CIHR) Strategy for Patient-Oriented Research Network in Chronic Disease (grant no. 4-PAR-2017-327-A-N to A.H. and B.A.P.). B.A.P. holds the Sam and Judy Pencer Family Chair in Diabetes Clinical Research, University of Toronto and acknowledges research program support from the Menkes Fund and the David Wright Fund. A.H. holds the Canada Research Chair in Artificial Pancreas Systems (950-231305). We thank P. Jacob for providing the iPancreas research platform. No funder had any role in study design, data collection or interpretation, or writing of the manuscript. The study investigators had final responsibility for the decision to submit for publication.

Author contributions

A.H., N.C., A.O., L.E.L., J.R., J.-F.Y. and B.A.P. designed the study. A.H., N.C., N.G.-P., A.O., M.A.T., C.M.F., J.-F.Y. and B.A.P. conducted the study. A.H., L.E.L., A.J., M.G. and D.E. carried out the data and statistical analyses. A.H. and B.A.P. are the guarantors of this work and, as such, had full access to the data and take responsibility for the integrity of the data analysis. All authors read and approved the final version of the manuscript.

Competing interests

A.H. received research support/consulting fees from Eli Lilly, Medtronic, AgaMatrix, Tandem, Adocia and Dexcom, and has pending patents in the artificial pancreas area. M.A.T. received research support from AgaMatrix, consulting fees from Sanofi and speaker honoraria from Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Janssen and AstraZeneca. J.-F.Y. received research support from Sanofi, Bayer and Novo Nordisk, and consulting fees and speaker honoraria from Sanofi, Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Janssen, Takeda, Abbott, Merck and AstraZeneca. B.A.P. received speaker honoraria from Abbott, Medtronic, Insulet and Novo Nordisk, research support to his research institute from Boehringer Ingelheim and the Bank of Montreal, and has served as a consultant to Boehringer Ingelheim, Abbott and Novo Nordisk. N.C. has received speaker honoraria from AstraZeneca and consultation fees from Novo Nordisk and Antibody Research Corporation. L.E.L. received support from a CIHR Canada Graduate Scholarship Doctoral Award. The other authors declare no competing interests.

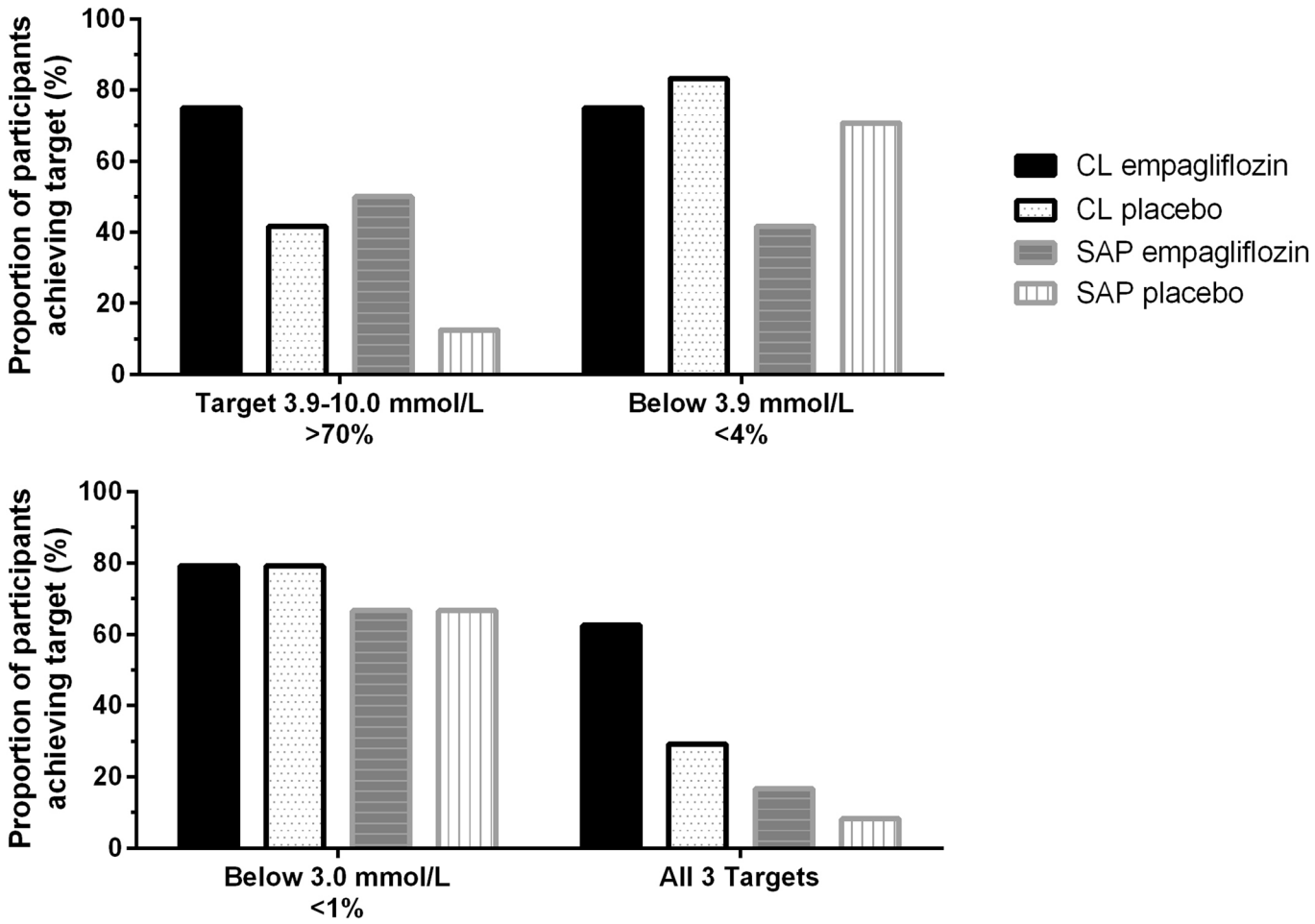
Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-022-01805-3.

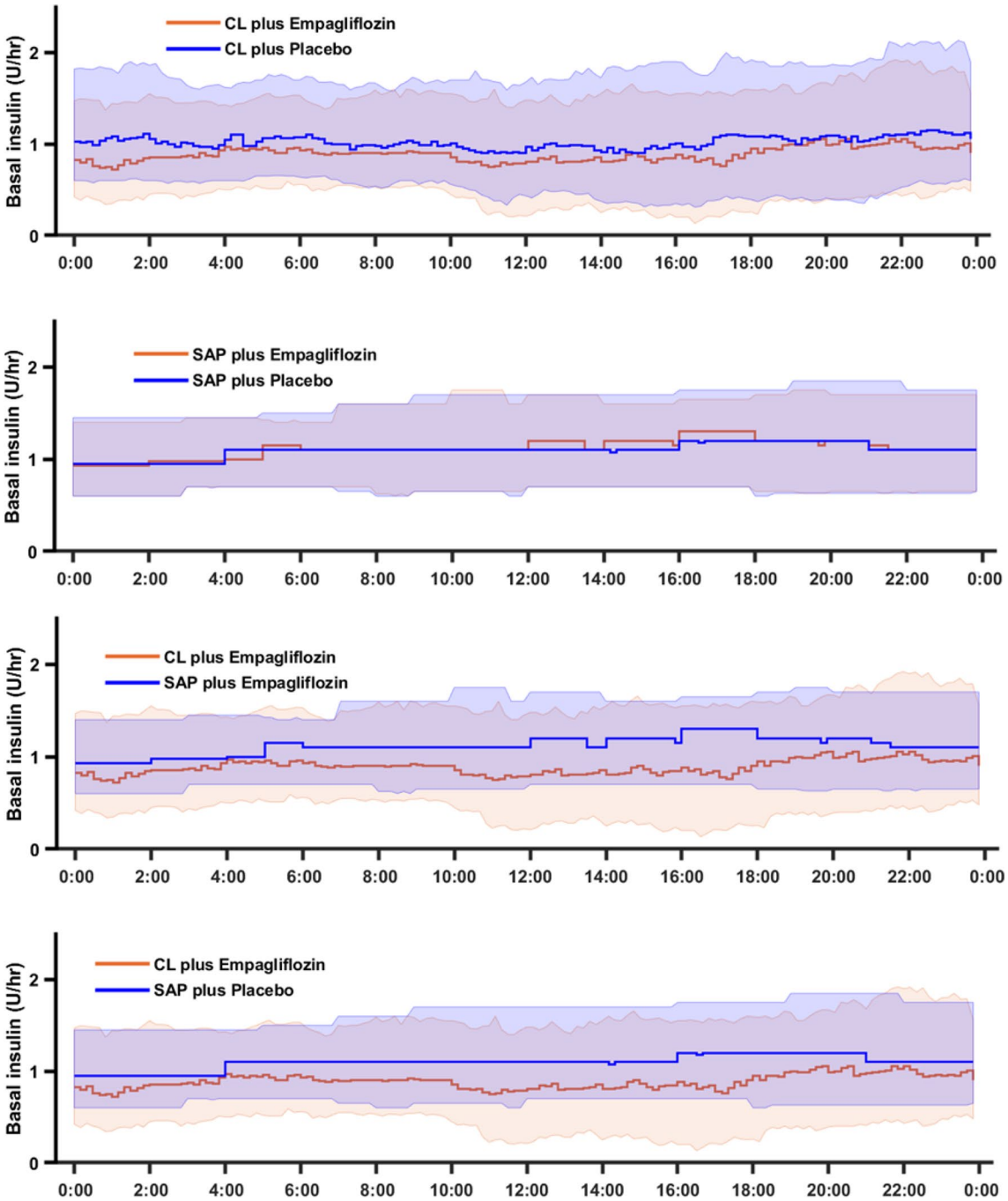
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-022-01805-3.

Correspondence and requests for materials should be addressed to Bruce A. Perkins.

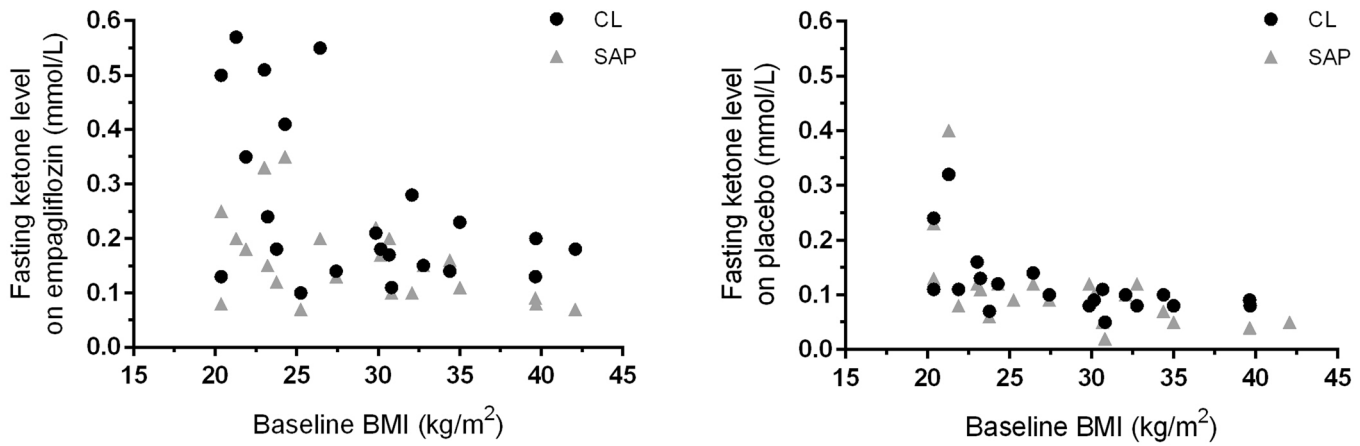
Peer review information *Nature Medicine* thanks Tadej Battelino, Victor Volovici and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Riikka Jokinen and Jennifer Sargent were the primary editors on this article and managed its editorial process and peer review in collaboration with the rest of the editorial team.



Extended Data Fig. 1 | The proportion of participants achieving glycemic targets in each arm. $n = 24$ independent participants in each of the four settings.



Extended Data Fig. 2 | The median (IQR) profiles of basal insulin delivery during the interventions. $n = 24$ independent participants in each of the four settings.



Extended Data Fig. 3 | The relationship between individual mean fasting ketone level and BMI in each intervention arm.

Sick Day Guidelines

Instructions for Patients

If you are ill, particularly if you become dehydrated (e.g. if you have vomiting or diarrhea), some medications can cause your kidney function to worsen or result in side effects.

If you become sick and are unable to drink enough fluid to keep hydrated, you should **STOP** the following medications:

S Sulfonylureas
(e.g.: Diamicron, Amaryl)

A ACE-inhibitors (e.g.: Altace, Coversyl)

D Diuretics, direct renin inhibitors
(eg: Hydrochlorhiazide, Lasix)

M Metformin
(e.g.: Glucophage, Glumetza)

A Angiotensin receptor blockers
(e.g.: Atacand, Olmetec)

N Non-steroidal anti-inflammatory drugs
(e.g.: Advil, Aleve)

S SGLT2 inhibitors
(e.g.: Invokana, Jardiance, Forxiga)

Please increase the number of times you check your blood glucose and ketones levels. If they are high or low, please contact your health care professional.

If you have any concerns or become pregnant/breastfeeding, please contact your healthcare provider:

_____

For more info on Sick Day Guidelines visit:
www.diabetes.ca/guidelines

SGLT2 Inhibitors Approved in Canada:

Invokana (canagliflozin)

Forxiga (dapagliflozin)

Jardiance (empagliflozin)

References:
Diabetes Canada 2018. Sick Day Guidelines
https://www.abbottdiabetescare.ca/diabetes-care-and-support/freestyle-precision-neo-support
http://www.gazetadopovo.com.br/viver-bem/saude-e-bem-estar/anvisa-suspende-venda-e-uso-de-lotes-do-paracetamol-e-antibiotico-amoxicilina/
https://www.mrsupplement.com.au/freestyle-optium-neo-machine
https://hcp.jardiance.com/moa.php
http://www.diabetesincontrol.com/diabetes-therapies/sglt-2/

Handout for Patients on Sodium Glucose Linked Transporter (SGLT2) Inhibitors

Mount Sinai Hospital
Sinai Health System
Joseph & Wolf Lebovic Health Complex

Nov2018. N.Cardinez NP, M.Falappa CRC, A.DelAmeida, B.Perkins MD

Extended Data Fig. 4 | Brochure provided to participants for the management of ketone levels while on empagliflozin, page 1 of 2.

SODIUM GLUCOSE LINKED TRANSPORTER 2 (SGLT2) INHIBITORS

These medications are approved for use in type 2 diabetes; these are not yet approved for use in type 1 diabetes however these drugs are currently being studied in research studies.
How it works: These drugs help to remove excess sugar from the blood and excrete it into the urine via the kidneys thereby lowering blood sugar levels. This helps to improve HbA1c results.

BEING SICK CAN RAISE YOUR BLOOD SUGAR AND CAUSE DANGEROUS KETONE ELEVATION

High blood sugar levels can lead to Diabetic Ketoacidosis (DKA). DKA can occur:

- If you are unwell, have a fever, flu, diarrhea, vomiting or infection
- If you insulin delivery has been interrupted/stopped or decreased
- If you have high ketone and/or glucose levels

Signs & symptoms of DKA can include weakness, fatigue, stomach pain, feeling unwell, rapid breathing, nausea & vomiting, and in severe stages lead to coma and death. Usually if someone has DKA the blood sugar level is very high. However due to the SGLT2 inhibitor mechanism of action, your blood sugar levels might be at target (normal) while ketones can be elevated.

We advise that you monitor for DKA very seriously by following these steps AND adjust your insulin as follows:

1. *We suggest that you check a daily morning blood ketone level and more frequently if unwell, see next step*), notify your team if levels are 0.6 or above.
2. If you have unexpected blood sugar levels more than 11 mmol/L or if you feel unwell and/or have nausea/vomiting at any level of blood sugar, check your blood ketone levels. If you are unwell, exercising, drinking alcohol and/or have missed insulin doses - test your blood sugar & blood ketone levels:

If blood ketones are less than 0.6 mmol/L	*If blood ketones are between 0.6- 1.5 mmol/L*	*If blood ketones are more than 1.5 mmol/L*
Take your correction bolus; recheck blood glucose and blood ketone level in 1 -2 hours.	Take 1.5 times your correction bolus; contact your health care provider; recheck blood sugar and ketones levels in 1-2 hours	Take 1.5 times our correction bolus; contact your healthcare provider: _____

*** If your blood glucose level is within normal range (4-7mmol/L) and ketones are more than or equal to 0.6; then have something to eat and take a food bolus. Retest blood glucose & ketones in 1-2hrs.**

COMMON SGLT2i SIDE EFFECTS

Mild side effects include:

- Increased thirst
- Frequent urination
- Hypoglycemia
- Weight loss
- Genital and urinary tract infections

Serious side effects may include:

- Low blood pressure and dehydration
- Diabetic ketoacidosis (DKA) symptoms include vomiting, stomach pain, nausea, confusion, unusual tiredness, and increased blood ketones (blood sugar levels may not be markedly high). Talk to your healthcare provider if you have a prior history of DKA
- Severe urinary infections (urosepsis)

*this is not a complete list of side effects, please refer the drug monograph for more information

Extended Data Fig. 5 | Brochure provided to participants for the management of ketone levels while on empagliflozin, page 2 of 2.

nature research

Corresponding author(s): Bruce A. Perkins

Last updated by author(s): Mar 17, 2022

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	The closed-loop predictive control algortihm was the McGill dosing algorithm, version Lucie-3.9.0. The control algorithm cannot be made publicly available because it is proprietary intellectual property. The control algorithm cannot be used in routine practice in the outpatient setting as regulatory approval has not yet been granted.
Data analysis	SAS software version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The raw data (i.e., insulin delivery, glucose levels, and individual participant data) and informed consent form will be shared by the corresponding author, for academic purposes, subject to Material Transfer Agreement and approval of the Mount Sinai Hospital Research Ethics Board and McGill University Health Center's Research Ethics Board. All data shared will be deidentified. The code used for analysis is available from the corresponding author.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We aimed to recruit 28 participants (14 per site), a reduction from an initial planned recruitment owing to funding decisions prior to and during the pandemic. Assuming a standard deviation in time spent in target range of 13% and 15% for the empagliflozin arms and a correlation between arms of 0.50, 28 participants would give 73% and 60% power to detect 8% and 7% differences in time in range, respectively, at a significance level of 2.5%. Following the filing of the protocol, preliminary data became available that indicated that we had overestimated the standard deviation in time in range during exposure to empagliflozin and we felt confident that power was substantially higher.
Data exclusions	One participant withdrew prior to randomization due to circumstances surrounding COVID-19. Two (7%) participants withdrew from the study due to symptomatic ketosis (without acidosis); both within the first few days of their first interventions which were CL plus empagliflozin and CL plus placebo. The data of one participant were excluded from the analysis due to a pharmacy error that prevented accurate unblinding. Final analysis sample size was 24.
Replication	The findings were not replicated as this was a randomized controlled trial and replication would require a second trial.
Randomization	We used blocked randomization with equal ratios of size eight (separate blocks for each site) to generate allocation sequences. Sequences were generated by the Mount Sinai Hospital pharmacy and were placed in opaque envelopes,, which were disclosed distributed to both sites and opened by study coordinators after the therapy optimization period. The order of drug interventions (empagliflozin and placebo) was randomized, as well as the order of the insulin delivery method (CL and SAP) within each drug intervention.
Blinding	Empagliflozin and placebo doses were placed in identical capsules. Participants and investigators were blinded to the allocation of the drug. Participants and investigators were not blinded to the allocation of the insulin delivery method, due to the hardware used.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	Participants' characteristics were: 56% were female, age was 38±15 years, weight was 83±19 kg, BMI was 29.5±6.6 kg/m2, HbA1c was 7.7±0.9% (61±10 mmol/mol), duration of diabetes was 24±15 years, and total daily insulin was 0.63±0.21 U/kg.
Recruitment	Participants were recruited at the Leadership Sinai Centre for Diabetes at Mount Sinai Hospital (Toronto, Ontario, Canada) and the McGill University Health Centre Adult Diabetes Clinic (Montréal, Quebec, Canada). Participants of our past studies were contacted if they previously provided written consent. Participants who showed interest in participation had the study fully explained to them and were offered the opportunity to ask questions. Interested participants that met basic eligibility criteria were scheduled for the admission visit. We did not anticipate major effects of self-selection bias or other forms of selection bias to substantially affect applicability of the primary effect measure to type 1 diabetes source populations.
Ethics oversight	The two sites local boards approved the study (the Mount Sinai Hospital Research Ethics Board and the Ethics Committee of

Ethics oversight	the Research Institute of the McGill University Health Centre). Health Canada approved the study.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT03979352
Study protocol	The protocol is included in the supplemental materials.
Data collection	All data was collected at Mount Sinai Hospital and McGill University Health Centre from August 2019 to January 2021.
Outcomes	The primary comparisons aimed at assessing the benefits of empagliflozin as an adjunct therapy to both closed-loop therapy (CL) and senor-augmented pump therapy (SAP). Therefore, the two primary comparisons were the percent of times that the sensor glucose readings were in the target range (3.9–10.0 mmol/L) between (i) CL plus empagliflozin versus CL plus placebo and (ii) SAP plus empagliflozin versus SAP plus placebo. If the primary comparisons were achieved, then we aimed to assess (i) whether the use of empagliflozin with SAP could overcome the need for CL system and (ii) the benefits of combining both CL and empagliflozin. Therefore, the two conditional comparisons were the percent of times that the sensor glucose readings were in the target range between CL plus empagliflozin versus SAP plus (i) empagliflozin and (ii) placebo. Secondary outcomes included times spent below and above target range, glucose variability, and insulin delivery. Analysis was by intention to treat. Outcomes were calculated for the entire 4-week study period. For the CL arms, outcomes included all available data including when the system was in open loop mode. 5-min glucose sensor data were used in the calculations. If glucose sensor values were missing for less than 2 hours, then missing values were interpolated.