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[THELANCETDE-D-15-00149 0237
[S2213-8587(15)00141-2]
Embargo: June 9, 2015—00:01 (BST)

Outpatient overnight glucose control with dual-hormone artificial pancreas, single-hormone artificial pancreas, or conventional insulin pump therapy in children and adolescents with type 1 diabetes: an open-label, randomised controlled trial

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Summary

Background Additional benefits of the dual-hormone (insulin and glucagon) artificial pancreas compared with the single-hormone (insulin alone) artificial pancreas have not been assessed in young people in outpatient unrestricted conditions. We evaluated the efficacy of three systems for nocturnal glucose control in children and adolescents with type 1 diabetes.

Methods We did a randomised, three-way, crossover trial in children aged 9–17 years with type 1 diabetes attending a diabetes camp in Canada. With use of sealed envelopes, children were randomly assigned in a 1:1:1:1:1:1 ratio with blocks of six to different sequences of the three interventions (single-hormone artificial pancreas, dual-hormone artificial pancreas, and conventional continuous subcutaneous insulin pump therapy). Each intervention was applied for 3 consecutive nights. Participants, study staff, and endpoint assessors were not masked. The primary outcome was the percentage of time spent with glucose concentrations lower than 4·0 mmol/L from 2300 h to 0700 h. Analysis was by intention to treat. A p value of less than 0·0167 was regarded as significant. This study is registered with ClinicalTrials.gov, number NCT02189694.

Findings Between June 30, 2014, and Aug 9, 2014, we enrolled 33 children of mean age 13·3 years (SD 2·3; range 9–17). The time spent at a glucose concentration lower than 4·0 mmol/L was median 0% (IQR 0·0–2·4) during nights with the dual-hormone artificial pancreas, 3·1% (0·0–6·9) during nights with the single-hormone artificial pancreas (p=0·032), and 3·4% (0–11·0) during nights with conventional pump therapy (p=0·0048 compared with dual-hormone artificial pancreas and p=0·32 compared with single-hormone artificial pancreas). 15 hypoglycaemic events (<3·1 mmol/L for 20 min measured by sensor then confirmed with capillary glucose <4·0 mmol/L) were noted during nights with conventional pump therapy compared with four events with the single-hormone system and no events with the dual-hormone system. None of the assessed outcomes varied with the order in which children and young adults were assigned interventions.

Interpretation The dual-hormone artificial pancreas could improve nocturnal glucose control in children and adolescents with type 1 diabetes. Longer and larger outpatient studies are now needed.

Funding Canadian Diabetes Association, Fondation J A De Sève.

Lancet Diabetes Endocrinol 2015
Published Online
June 9, 2015
http://dx.doi.org/10.1016/S2213-8587(15)00141-2
See Online/Comment
http://dx.doi.org/10.1016/PII

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Introduction

Type 1 diabetes is one of the most common chronic diseases in young people and its incidence is increasing by 2–5% a year worldwide.[1] Children with type 1 diabetes are treated with intensive insulin therapy to tighten glucose control because a sustained increase in glucose concentration can lead to long-term complications.[2] However, the current HbA_{1c} average in children with type 1 diabetes is around 8·7% (71·6 mmol/mol)[3] and only 21% of patients aged 13–20 years achieve the HbA_{1c} target of lower than 7·5% (58·5 mmol/mol).[4]

Fear of hypoglycaemia, particularly nocturnal, is the major barrier to efforts to intensify treatment.[5] Moderate hypoglycaemia is very frequent during the night, with longer duration in children and adolescents than in adults.[6] 75% of hypoglycaemia seizures in children and adolescents happen at night-time,[5] and fear of these episodes is a major source of stress and anxiety for families and caregivers of children with type 1 diabetes.[7]

Development of glucose sensors provided unprecedented real-time continuous views of glucose concentrations and their trends, accompanied by alarms for hyperglycaemia and hypoglycaemia. Investigators found glucose sensors to be effective in adults, but not in children and adolescents, mostly because of poor adherence in this age group.[8] Even when combined with insulin pumps, glucose sensors are 60% less effective at reducing HbA_{1c} in children and adolescents than they are in adults,[9] and reduce hypoglycaemia only in a system in which they are linked to the pump to trigger automatic threshold-based suspensions.[10]

Research in context

Evidence before this study

We searched PubMed for articles published up to May 4, 2015, using search terms "glucagon" AND ("closed-loop" OR "artificial pancreas") AND ("randomized" OR "randomised") AND "type 1 diabetes", and identified two randomised trials in which dual-hormone (insulin and glucagon) artificial pancreas systems were assessed in children and young adults. In 2014, Russell et al reported the comparison of a dual-hormone artificial pancreas with conventional insulin pump therapy in 33 adolescents in a diabetes camp for 5 days and showed reduction in mean glucose and frequency of interventions for hypoglycaemia, but not in time spent in hypoglycaemia. In 2015, Haidar et al reported the comparison of a dual-hormone artificial pancreas, a single-hormone (insulin alone) artificial pancreas, and conventional insulin pump therapy in adult and paediatric patients for 24 h in inpatient settings, but this study was not powered to detect differences in the paediatric subgroup. No study, inpatient or outpatient, was identified that was designed to quantify the relative benefits that glucagon brings in children and adolescents to the artificial pancreas system.

Added value of this study

In this study, we undertook the first three-way comparison, in paediatric outpatient nocturnal camp settings, over multiple nights, between a dual-hormone artificial pancreas, a single-hormone artificial pancreas, and conventional pump therapy. The dual-hormone artificial pancreas reduced the time spent in nocturnal hypoglycaemia compared to the single-hormone artificial pancreas and conventional insulin pump therapy.

Implications of all the available evidence

The observed benefits of glucagon during the night in our study motivate the conduction of other clinical trials. Outpatient studies to quantify the benefits of glucagon during the day in children and adolescents are needed. Longer and larger outpatient studies that assess the benefits of glucagon in reducing severe hypoglycaemia are also needed. The benefits of adding glucagon to the artificial pancreas in other populations which might benefit most from the technology (eg, patients with hypoglycaemia unawareness) also need to be quantified.

Artificial pancreas systems combine insulin pumps with glucose sensors via a dosing algorithm that titrates insulin delivery dynamically.[11] Outpatient randomised trials in children and adolescents show that the artificial pancreas can reduce both the overnight mean glucose concentration and the time spent in nocturnal hypoglycaemia compared with conventional pump therapy.[12–15] However, hypoglycaemia was not completely eliminated with the insulin-only artificial pancreas. The dual-hormone artificial pancreas delivers insulin and glucagon and has the potential to further reduce hypoglycaemia.[16–18] Only one outpatient study has tested the dual-hormone artificial pancreas in children and adolescents[18] in which it was compared with conventional pump therapy. Although overnight mean glucose reduction was effective, the time spent in nocturnal hypoglycaemia was not reduced in the paediatric population, contrary to findings in adult group.[18]

The benefits of adding glucagon to an artificial pancreas system must be assessed because the single-hormone artificial pancreas has a lower cost and less system-complexity and use-complexity than does the dual-hormone system. In a recent three-way crossover trial that compared dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional pump therapy in adults and children, the investigators reported that the addition of glucagon to the system can bring additional reduction in the time spent in hypoglycaemia compared with the single-hormone artificial pancreas.[19] However, each system was tested for only 24 h in an inpatient environment and was not powered to detect differences in the paediatric subgroup. In our study, we did the first three-way comparison in outpatient unrestricted conditions (a diabetes camp), over many nights, in children and adolescents with type 1 diabetes. We hypothesised that the dual-hormone artificial pancreas would reduce time spent in nocturnal hypoglycaemia compared with the single-hormone artificial pancreas, which in turn would reduce the time spent in nocturnal hypoglycaemia compared with conventional pump therapy.

For the **protocol** see http://www.ircm.qc.ca/LARECHERCHE/axes/Maladies/pancreas/Documents/ProtocolCLASS08_20140716.pdf

See Online for the appendix

Methods

Study design and participants

We did a randomised, open-label, three-way, controlled, crossover study to compare the dual-hormone artificial pancreas, the single-hormone artificial pancreas, and conventional pump therapy in children and adolescents with type 1 diabetes. Each intervention was applied for 3 nights consecutively (total 9 nights) in a diabetes camp with unrestricted food intake and physical activity. The protocol is available online.

We enrolled children and adolescents with type 1 diabetes at a specialised diabetes camp (Camp Carowanis, Sainte Agathe des Monts, QC, Canada). Registered campers were sent a letter by the camp administration describing the study and inviting them to participate, and interested campers were recruited by the study staff on the first day of the camp. Participants were required to be aged 8–17 years, on an insulin pump for at least 3 months, and diagnosed with type 1 diabetes for at least 1 year. We excluded patients with poorly controlled diabetes (HbA_{1c} >11% [96·7 mmol/mol]). Other exclusion criteria were applied (appendix). Participants provided written assent and their guardians provided written informed consent. The study was approved by the Institut de recherches cliniques de Montréal and Montreal Children's Hospital ethics committees.

Randomisation and masking

VM manually calculated blocked randomisation (block size of six) with a 1:1:1:1:1:1 ratio to generate allocation sequences of patients, which were placed in sealed opaque envelopes in the same order they were withdrawn and then opened by MD after the recruitment. Participants and investigators were not masked to allocation assignments. Participants were masked to sensor glucose readings during all intervention nights and to hormone infusions during nights with an artificial pancreas. For safety reasons, investigators had access to sensor glucose readings during study nights. Participants had access to their finger-stick glucose measurements during all interventions.

Procedures

The camp is composed of three sessions, each lasting for 11 days, and accommodates about 90 campers. During the day, study participants engaged in all social and physical activities, taking place over 150 acres of forested land on a lake shore. At night, all campers slept in tents, each tent housing six to eight campers of similar age and one older counsellor (appendix). Study participants were not separated from other campers.

On the first day of the camp, and before the participants enrolled in our study, the camp's health-care staff reduced all campers' basal rates of insulin by about 15% to account for the increased physical activity levels during the camp. Study participants wore a glucose sensor during the whole camp period (Dexcom G4 Platinum, Dexcom, San Diego, CA, USA). The sensor was calibrated two to three times a day using the scheduled pre-meal capillary finger-stick measurements, and was not recalibrated or replaced in the event of suboptimum accuracy. The sensor receiver was kept with the study team during the day and was used for the interventions during the night. A new sensor was installed after 6 days (sensor lifetime) or in case of sensor failure.

Campers aged 8–12 years ingested a snack at 2030 h and campers aged 13–17 years ingested a snack at 2130 h. The snack was unrestricted, varied between individuals and days, and the camp staff determined its bolus. After the snack, for nights with the single-hormone artificial pancreas, study participants replaced their pump with the study pump (Accu-Chek Combo system, Roche Diagnostics, Mannheim, Germany) filled by insulin aspart (Novorapid, Novo Nordisk, Mississauga, ON, Canada). For nights with the dual-hormone artificial pancreas, a second pump was installed with glucagon (Eli Lilly Canada, Toronto, ON, Canada). Fresh glucagon was reconstituted every night as per the manufacturer's recommendations. All campers went to their tent after the snack to sleep. Campers were allowed to eat at night and food intake was recorded by camp staff.

Artificial pancreas interventions started between 2200 h and 2300 h (based on bedtime) until 0700 h. The sensor receiver was placed outside the tent to collect data for glucose concentrations. Every 10 min, the sensor reading was entered manually by study staff into an electronic tablet computer, which runs a dosing algorithm that calculated basal insulin delivery during nights with the single-hormone artificial pancreas or basal insulin and glucagon delivery during nights with the dual-hormone artificial pancreas. The advice of the dosing algorithm was always adhered to, and insulin and glucagon were then delivered manually by study staff from outside the tent by a remote controller. Study participants were not approached during these 10 min cycles, and study staff did not enter the tent.

	Mean
Age (years)	13·3 (3·0; 9–17)
BMI (kg/m^2)	22·2 (3·9; 15·7–33·1)
HbA_{1c} (%)	8·3 (0·8; 7·2–10·4)
HbA_{1c} (mmol/mol)	67·2 (8·2; 55·2–90·2)
Duration of diabetes (years)	7·5 (4·0; 2–15)
Daily insulin dose (U/kg)	0·89 (0·2; 0·57–1·31)

Data are mean (SD; range).

***Table* 1: Baseline characteristics of the total population (n=33)**

During the artificial pancreas interventions, insulin delivery was based on a proprietary dosing algorithm (appendix) that used model predictive control and adopted the compartmental approach to describe insulin-glucagon-glucose dynamics. Glucagon delivery was based on logical rules that used estimates of glucose concentrations and their trends. The algorithm used daily insulin requirements, which were recorded on the first day of the camp after the camp's health-care staff reduced the campers' basal rates (any further adjustment to basal rates by the camp's health-care staff were not provided to the algorithm). The algorithm did not use bodyweight. Insulin delivery algorithms were identical in both the single-hormone and the dual-hormone artificial pancreas systems, except that glucagon-on-board was taken into account by the insulin delivery algorithm of the dual-hormone artificial pancreas.

During nights with conventional pump therapy, participants continued with their regular pump therapy, and their glucose concentrations were collected by the glucose sensor placed outside the tent. In the morning, data from the previous night were provided to the camp's health-care staff, who adjusted subjects' basal rates night by night. These adjusted basal rates were not provided to the algorithm during nights with an artificial pancreas.

During all nights, if the sensor read glucose concentrations lower than 3·1 mmol/L or higher than 20 mmol/L for 20 min consecutively [three readings], the tent counsellor was woken, and camp protocols for hypoglycaemia or hyperglycaemia were applied by the

camp staff (appendix). The same protocols were applied for nights with conventional pump therapy or an artificial pancreas.

Outcomes

The primary outcome was the percentage of time during which glucose concentrations were lower than 4·0 mmol/L. Secondary outcomes included mean glucose concentrations; percentage time spent with glucose concentrations in target ranges 4·0–8·0 mmol/L and 4·0–10·0 mmol/L; percentage time spent and the area under the curve for glucose concentrations lower than 3·5 mmol/L, lower than 3·3 mmol/L, higher than 8·0 mmol/L, and higher than 10·0 mmol/L; total insulin delivery; SD of glucose; the number of participants who developed hypoglycaemic events (<3·1 mmol/L for 20 min consecutively measured by sensor then confirmed with capillary glucose <4·0 mmol/L); and the number of hypoglycaemic events. Study outcomes were calculated with sensor readings and were calculated from 2300 h to 0700 h.

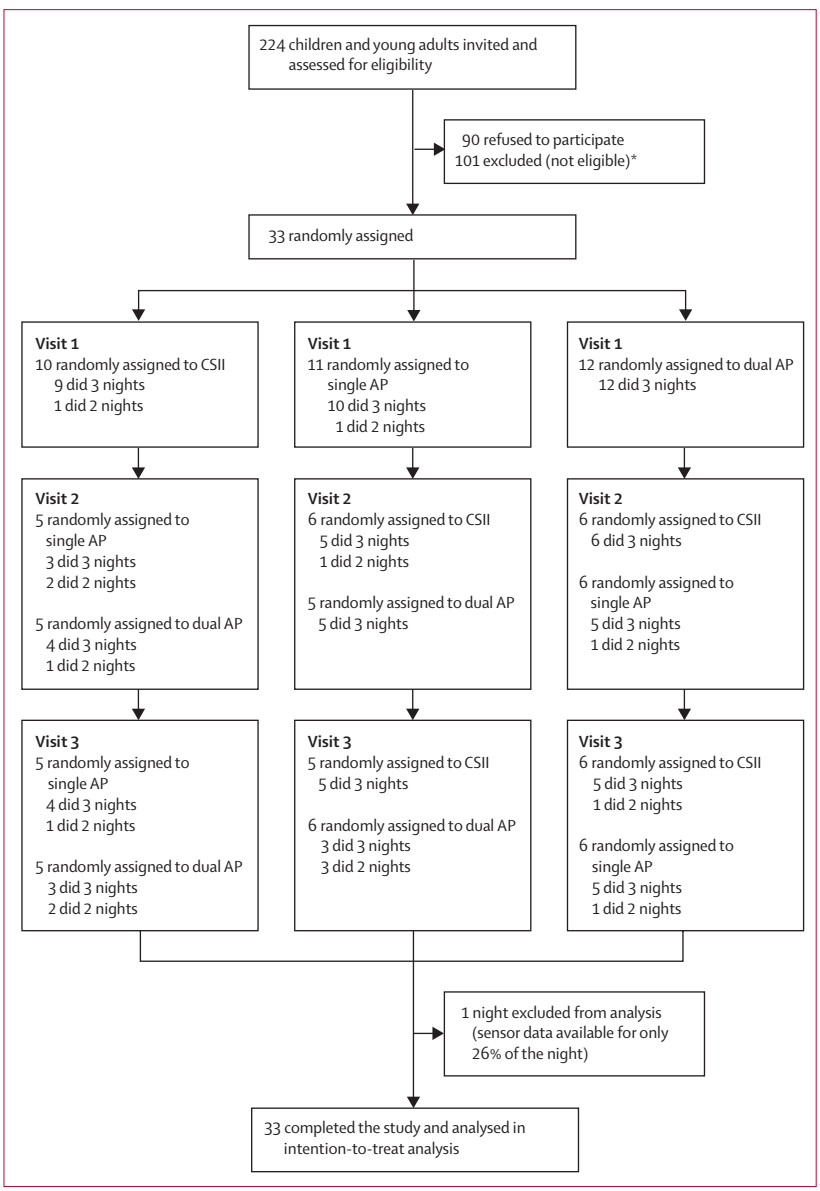

Figure 1: **Flow of participants through the study. CSII=continuous subcutaneous insulin infusion. Single AP=single-hormone artificial pancreas. Dual AP=dual-hormone artificial pancreas.**
*Not on an insulin pump.

Statistical analysis

We anticipated that the dual-hormone artificial pancreas would decrease the percentage of time during which glucose concentrations would be lower than 4·0 mmol/L by 2·4% (SD 3·0) compared with the single-hormone artificial pancreas. We also anticipated that the differences between both artificial pancreas systems and conventional pump therapy would be larger than 2·4% (SD 3). We consequently calculated, using that difference of 2·4%, that 22 participants would provide 80% power at the 5% significance level (corrected for multiple comparisons) to detect differences between the three interventions. Moreover, we anticipated that additional participants would be required to achieve enough power to detect differences in the secondary endpoint of percentage time spent with glucose concentration lower than 3·5 mmol/L. Therefore, we aimed to recruit a minimum of 22 participants with a maximum recruitment limit of 36 participants.

We did all analyses on an intention-to-treat basis. For continuous outcomes, a linear mixed model was fitted to do pairwise comparisons between the three treatments while adjusting for the period effect and the randomisation sequence. Bonferroni adjustment was made for multiple comparisons on the primary outcome, and p values lower than 0·0167 were regarded as significant. To ensure normality, data were transformed using the square root transformation before model fitting. For each individual, continuous outcomes were calculated as the average of the 3 nights. Missing glucose sensor data were interpolated. Fisher's exact test was used to compare hypoglycaemia rates. We did analysis with R software, version 3.1.2. This study is registered with ClinicalTrials.gov, number NCT02189694.

Role of the funding source

The funders of this study had no role in study design, data collection, data interpretation, or writing of the report. Study investigators had final responsibility for the decision to submit for publication. The first author has access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Results

Between June 30, 2014, and Aug 9, 2014, we enrolled 33 children of mean age 13·3 years (range 9–17) to the study (table 1, figure 1). 25 participants completed all nine planned nights, four completed 8 nights, four

	Conventional pump therapy (96 nights)	Paired difference (*vs* single-hormone; 95% CI; p value)*	Single-hormone artificial pancreas (93 nights)	Paired difference (*vs* dual-hormone; 95% CI; p value)†	Dual-hormone artificial pancreas (93 nights)	Paired difference (*vs* conventional; 95% CI; p value)‡
Time spent at glucose concentrations (%)						
<4·0 mmol/L§	3·4% (0–11·0)	0% (–8·0 to 5·8; p=0·32)	3·1% (0–6·9)	–2·0% (–4·5 to 0·0; p=0·032)	0% (0–2·4)	–1·7% (–5·7 to 0; p=0·0048)
<3·5 mmol/L	0% (0–5·7)	0% (–4·8 to 0; p=0·103)	0% (0–4·4)	0% (–2·1 to 0, p=0·061	0% (0–1·0)	0% (–4·5 to 0; p=0·0051)
<3·3 mmol/L	0% (0 to 3·8)	0% (–3·4 to 0; p=0·070)	0% (0 to 3·7)	0% (–2·8 to 0; p=0·071)	0% (0–0)	0% (–3·8 to 0·0; p=0·0062)
4·0–8·0 mmol/L	29% (20 to 47)	23% (5–44; p=0·0001)	55% (43–68)	17% (0–23; p=0·032)	63% (55–76)	34% (15–46; p<0·0001)
4·0–10·0 mmol/L	54% (33–70)	16% (4–34; p=0·00027)	77% (66–86)	8% (–2 to 23; p=0·016)	84% (79–94)	33% (10–44; p<0·0001)
>8·0 mmol/L	59% (45–78)	–19% (–43 to 9; p=0·0010)	42% (23–53)	–3% (–25 to 7; p=0·13)	35% (21–45)	–26% (–41 to –12; p<0·0001)
>10·0 mmol/L	38% (16–55)	–15% (–37 to 1; p=0·0016)	20% (6–32)	–5% (–23 to 4; p=0·074)	13% (2–19)	–27% (–39 to –5; p<0·0001)
Sensor glucose measurements						
Mean glucose (mmol/L)	9·3 (7·8–10·8)	–1·6 (–3·0 to 0·6; p=0·0093)	8·1 (6·4 to 9·7)	–0·3 (–2·2 to 0·7; p=0·066)	7·7 (6·7–8·1)	–1·6 (–3·3 to –0·5; p<0·001)
SD of glucose (mmol/L)	1·4 (1·0–1·8)	0·2 (–0·3 to 0·6; p=0·20)	1·7 (1·2–2·1)	0·2 (–0·4 to 0·4; p=0·14)	1·7 (1·5–2·1)	0·6 (0–0·7; p=0·72)
Area under the curve (mmol/L x min per h) for glucose concentrations						
<4·0 mmol/L	0·3 (0–4·7)	0 (-3·4 to 1·0; p=0·13)	0·2 (0 to 3·3)	–0·1 (–2·4 to 0; p=0·044)	0 (0–0·6)	–0·2 (–3·0 to 0; p=0·0038)
<3·5 mmol/L	0 (0–1·8)	0 (–1·6 to 0; p=0·11)	0 (0 to 1·3)	0 (–0·9 to 0; p=0·088)	0 (0–0·1)	0 (-1·5 to 0; p=0·0100)
<3·3 mmol/L	0 (0–1·1)	0 (–1·1 to 0; p=0·15)	0 (0–0·5)	0 (–0·5 to 0; p=0·12)	0	0 (–1·1 to 0; p=0·019)
>8·0 mmol/L	109 (43–215)	–50 (–124 to 10; p=0·0070)	69 (27–129)	–14 (–87 to 16; p=0·027)	40 (13–68)	-72 (–146 to –24; p<0·0001)
>10·0 mmol/L	46 (6–150)	–19 (–89 to 10; p=0·033)	30 (3 to 69)	–10 (–56 to 7; p=0·027)	12 (1–23)	–27 (–102 to 0; p=0·00024)
Insulin delivery (U/h)	0·7 (0·6–0·9)	0·2 (0·0–0·5; p<0·0001)	0·9 (0·8–1·3)	–0·1 (–0·3 to 0·1; p=0·24)	0·9 (0·8–1·1)	0·2 (0–0·3; p<0·0001)

Data in median (IQR), unless otherwise stated. P value of less than 0·0167 is regarded as significant for all comparisons. *Single-hormone system versus conventional therapy; paired difference is single-hormone system minus conventional therapy. †Dual-hormone system versus single-hormone system; paired difference is dual-hormone system minus single-hormone system. ‡Dual-hormone system versus conventional therapy, paired difference is dual-hormone system minus conventional therapy. §Primary outcome.

***Table* 2: Comparisons of dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional pump therapy**

completed 7 nights, and one completed 6 nights. All participants completed at least 2 nights per intervention (figure 1). For the uncompleted nights, one night was due to illness of a participant (not related to study drug) and all other nights were because the participants were not present on the camp site (eg, biking or canoeing trips). Data from 1 night (conventional pump therapy) were excluded from the analysis due to the unavailability of sensor readings (sensor data was available for only 26% of the night). 4·6% of sensor readings were missing on nights with conventional pump therapy, 4·1% were missing for nights with the single-hormone artificial pancreas, and 4·4% were missing for nights with the dual-hormone artificial pancreas. In total, out of the planned 99 nights per intervention, we had 96 nights of data for conventional pump therapy intervention, 93 nights of data for the single-hormone artificial pancreas intervention, and 93 nights of data for the dual-hormone artificial pancreas intervention (figure 1).

The single-hormone artificial pancreas started at median 2210 h (IQR 2200–2230) and was operational for 8·8 h (8·3–9·0) per night. The dual-hormone artificial pancreas started at 2210 h (2200–2230) and was operational for 8·8 h (8·3–8·8) per night. No difference was observed in the carbohydrate content of the evening snack between each of the interventions (mean 29 g [SD 17] per evening). Although the snack bolus was determined by the camp staff, who were masked to the interventions, it might have been affected by intervention of the previous night.[12] The bolus was median 2·2 U (IQR 1·4–3·0) before nights with conventional pump therapy, 2·4 U (1·7–2·9) before nights with the single-hormone artificial pancreas (p=0·38 *vs* conventional pump therapy), and 1·9 U (1·4–2·8) before nights with the dual-hormone artificial pancreas (p=0·027 *vs* single-hormone artificial pancreas, and p=0·41 *vs* conventional pump therapy). We observed no difference in sensor accuracy when assessed using capillary finger-stick measurements that were used for the calibration before the evening snack (ie, last calibration before the start of the interventions; appendix).

The median time participants spent with concentrations lower than 4·0 mmol/L was low but similar during nights with conventional pump therapy (3·4% [IQR 0–11·0]; median 16 min per night) and those on single-hormone artificial pancreas (3·1% [0–6·9]; median 14 min per night; paired difference for single-hormone artificial pancreas *vs* conventional pump therapy 0 [–8·0 to 5·8]; p=0·032; table 2, figure 2). The dual-hormone artificial pancreas reduced the median time to 0% (IQR 0–2·4; paired difference *vs* single-hormone artificial pancreas –2·0 [–4·5 to 0·0; p=0·032], paired difference *vs* conventional pump therapy –1·7 [–5·7 to 0; p=0·0048]), significantly reducing the median time compared with conventional pump therapy and single-hormone artificial pancreas. Median times spent with concentrations lower than 3·5 mmol/L and 3·3 mmol/L were zero for all interventions, but the third-quartile times were lowest

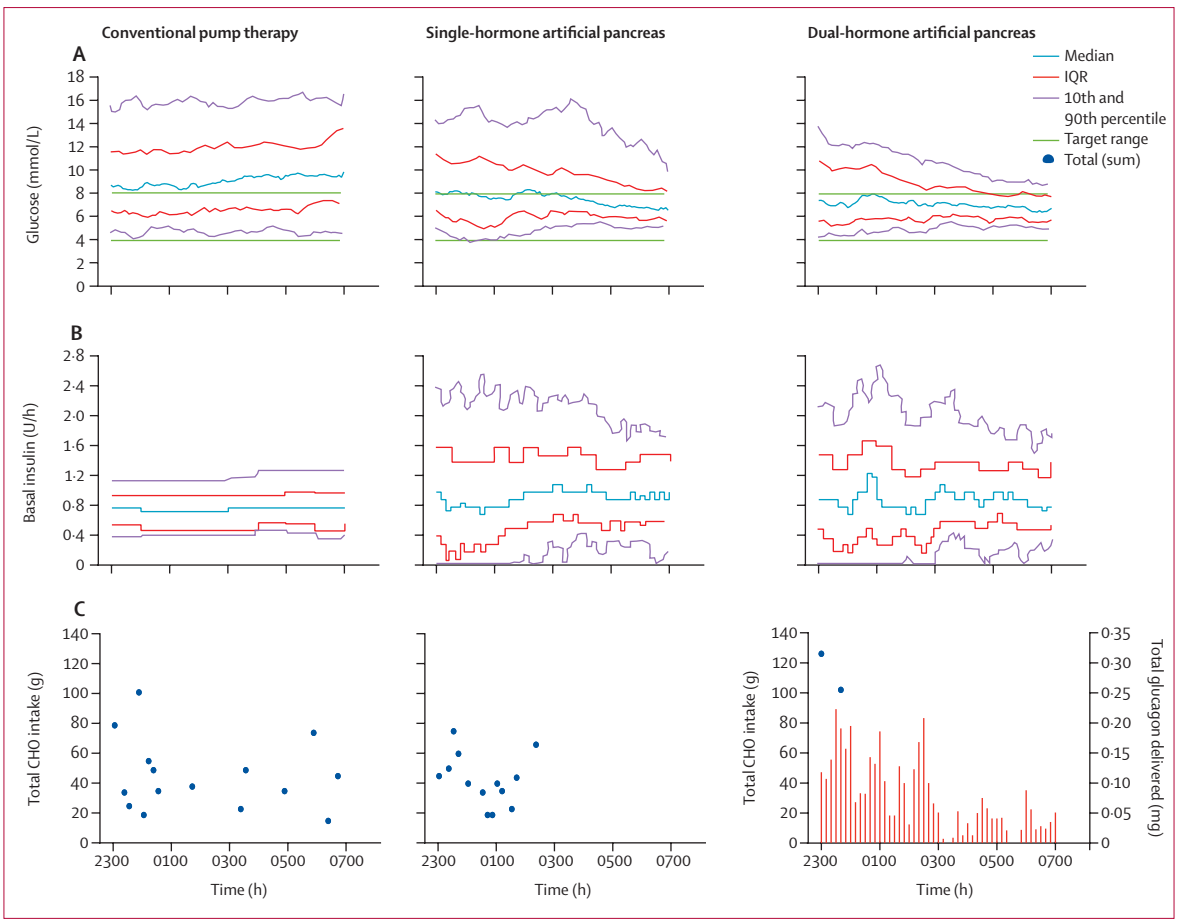

***Figure 2*: Profiles of glucose concentration (A), insulin delivery (B), and the total amount (sum across nights) of glucagon delivery and carbohydrate ingestion (C) for each of the three interventions.**
CHO=carbohydrate.

with the dual-hormone artificial pancreas and highest with conventional pump therapy (table 2). Outcomes of area under the curves for hypoglycaemia show similar results compared with times spent in hypoglycaemia (table 2). No differences in any of the study endpoints were observed due to the order of interventions (p=0·63 for the primary outcome).

Single-hormone and dual-hormone artificial pancreas systems both significantly reduced the time spent with a glucose concentration higher than 8·0 mmol/L compared with conventional pump therapy (from 59% with conventional pump therapy, to 42% [p=0·001] and 35% [p<0·0001], respectively; table 2). Similarly, time spent with a glucose concentration higher than 10·0 mmol/L was reduced from 38% during nights with conventional pump therapy to 20% with the single-hormone system and 13% with the dual hormone system. Although differences between the dual-hormone and the single-hormone pancreas systems in time spent higher than 8·0 mmol/L and 10·0 mmol/L are probably clinically significant, comparisons between the two did not reach statistical significance (p=0·13 and p=0·074, respectively, table 2). However, differences between the dual-hormone and the single hormone artificial pancreas systems were more remarkable in the area under the curve for time spent with concentrations higher than 8·0 mmol/L and 10·0 mmol/L (table 2).

The differences in times spent in hypoglycaemia and hyperglycaemia resulted in differences in times spent in target ranges between the three interventions. The time spent between 4·0 and 8·0 mmol/L was 63% during nights with the dual-hormone artificial pancreas, 55% during nights with the single-hormone artificial pancreas, and 29% during nights with conventional pump therapy (p=0·032 for single-hormone *vs* dual-hormone artificial pancreas systems, and p≤0·0001 otherwise). Similarly, the time spent between 4·0 and 10·0 mmol/L was 84% during nights with the dual-hormone artificial pancreas, 77% during with the single-hormone artificial pancreas, and 54% during nights with conventional pump therapy (table 2).

During nights with conventional pump therapy, mean glucose concentration was high at 9·3 mmol/L (7·8 to 10·8). The single-hormone artificial pancreas

significantly decreased mean glucose to 8·1 mmol/L (6·4–9·7) (p=0·0093), whereas the dual-hormone artificial pancreas decreased it to 7·7 mmol/L (6·7–8·1; p<0·0001 *vs* conventional pump therapy; p=0·066 *vs* the single-hormone artificial pancreas; table 2). This decrease in glucose was due to a 29% increase in mean insulin delivery during nights with either type of artificial pancreas compared with nights with conventional pump therapy (table 2). Moreover, study participants ingested carbohydrate during 19% of nights with conventional pump therapy compared with 15% of nights with the single-hormone artificial pancreas and 6% of nights with dual-hormone artificial pancreas, possibly contributing to differences in mean glucose concentrations between the interventions. On the nights during which participants ingested carbohydrate, the ingested amount did not differ between therapies (mean 39 g [SD 15] per night).

During nights with the single-hormone or dual-hormone artificial pancreas, incidence of hypoglycaemia was highest in the early night hours, between 2300 h and 0200 h (figure 3), which coincided with higher variability in insulin delivery, higher glucagon delivery, and higher carbohydrate intake (figure 2). There was no temporal pattern in the incidence of hypoglycaemia during nights with conventional pump therapy (figure 3), in line with a dispersion of carbohydrate intake throughout the night with this intervention (figure 2). In the second half of the night, between 0300 h and 0700 h, both artificial pancreas systems reduced the incidence of hypoglycaemia compared with conventional pump therapy. The dual-hormone artificial pancreas eliminated almost all glucose readings of less than 3·5 mmol/L from 0120 h onward and almost all glucose readings below 4·0 mmol/L from 0300 h onward, preventing hypoglycaemia more effectively than both the single-hormone artificial pancreas and conventional pump therapy.

Similarly, the incidence of hyperglycaemia during nights with the single-hormone or dual-hormone artificial pancreas was highest during the early night hours and decreased gradually throughout the night (figure 3). By contrast, during nights with conventional pump therapy, the incidence of hyperglycaemia increased slightly but gradually during the night until 0600 h.

During nights with conventional pump therapy, 11 (33%) participants had 15 hypoglycaemic events between them that required team intervention (<3·1 mmol/L for 20 min consecutively measured by sensor then confirmed with capillary glucose <4·0 mmol/L; table 3), compared with four (12%) participants having four events during nights with the single-hormone artificial pancreas (p=0·078) and no events during nights with the dual-hormone artificial pancreas (p=0·00096 *vs* conventional pump therapy; p=0·12 *vs* the single-hormone artificial pancreas). Hypoglycaemia occurred in the early night hours during nights with the single-hormone artificial pancreas (median 0025 h, IQR 0010–0047) whereas events were spread out during nights with conventional pump therapy (median

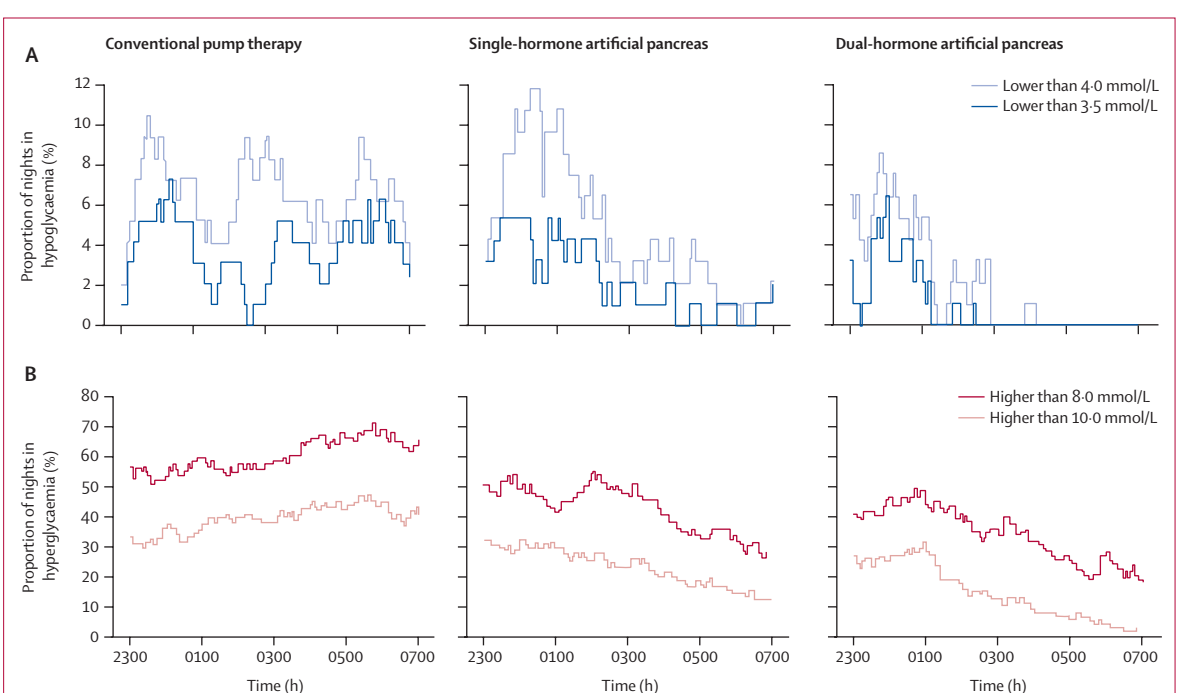

***Figure 3*: Proportion of nights in hypoglycaemia and hyperglycaemia**
For every 5 min interval between 2300 h and 0700 h, we calculated the proportion of nights in hyperglycaemia or hypoglycaemia as the number of nights in which glucose concentrations were in hyperglycaemia or hypoglycaemia at that specific 5 min interval divided by the total number of nights for which the intervention was applied.

	Conventional pump therapy (96 nights)	Single-hormone artificial pancreas (93 nights)	Dual-hormone artificial pancreas (93 nights)
Number of hypoglycaemic events	15	4	0
Patients with at least one hypoglycaemia event*	11 (33%)	4 (12%)	0
Median time of hypoglycaemia events (h)	0145 (0000–0520)	0025 (0010–0047)	..
Mean total insulin delivery 1 hour before hypoglycaemia events†	1	0·04 (0·06)	..
Mean total insulin delivery 2 h before hypoglycaemia events†	1	0·24 (0·20)	..
Number of hyperglycaemia events	2	2	0
Number of hyperglycaemia events accompanied with ketones	0	0	0
Time of hyperglycaemia events (h)	0340 and 0400	0130 and 0350	..

Data are n (%), median (IQR), or mean (SD), unless otherwise stated. Hypoglycaemia events are defined as 20 min consecutively with a sensor glucose concentration lower than 3·1 mmol/L confirmed by a capillary glucose concentration lower than 4 mmol/L. Hyperglycaemia events are defined as 20 min consecutively with a sensor glucose concentration higher than 20 mmol/L confirmed by a capillary glucose concentration higher than 18 mmol/L. p values of less than 0·0167 are regarded as significant for all comparisons.*p=0·078 for single-hormone system versus conventional therapy, p=0·00096 for dual-hormone system versus conventional therapy, p=0·12 for dual-hormone system versus single-hormone system. †Relative to regular basal rates.

Table 3: **Hypoglycaemia and hyperglycaemia events**

0145 h, 0000–0520). During nights with the single-hormone artificial pancreas, the amount of insulin delivery was reduced by a mean of 96% compared with each participant's regular basal rates in the 1 h preceding hypoglycaemia events, and by 76% in the 2 h preceding hypoglycaemia events (table 3).

Mean glucagon delivery during dual-hormone artificial pancreas nights was 0·04 mg (SD 0·06) or 0·7 µg/kg (SD 1·0) per night. Glucagon was delivered intermittently, with a mean of 2·5 (SD 3·2) boluses per night. Glucagon boluses were small, with an average bolus size of 0·017 mg (SD 0·011) or 0·31 µg/kg (0·16). 50% of the glucagon was delivered before 0100 h, 80% before 0300 h, and 90% before 0500 h. No participant reported any symptoms after glucagon boluses, There was no pump failure in glucagon delivery.

Discussion

We did the first outpatient head-to-head-to-head comparison between dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional pump therapy in children and adolescents with type 1 diabetes over multiple nights. No participants using the dual-hormone artificial pancreas had a nocturnal hypoglycaemia event requiring treatment, and this system intervention reduced the time spent in hypoglycaemia (<4·0 mmol/L) compared with the other two systems, with a significant effect versus conventional pump therapy.

Our recent three-way 24 h inpatient study in adults and children compared the same three systems as this study and showed that the addition of glucagon in the artificial pancreas can bring additional reduction in hypoglycaemia compared with the single-hormone artificial pancreas, but this reduction was only notable during the day and was marginal during the night.[19] This finding was due to the efficacy of the single-hormone artificial pancreas in eliminating nocturnal hypoglycaemia, making glucagon addition mostly irrelevant at night. However, the data presented here indicate that glucagon can be beneficial overnight in children and adolescents in an outpatient setting.

Hypoglycaemic events occurred on 16% of nights with conventional pump therapy, whereas the single-hormone artificial pancreas reduced the incidence to just 4% of nights (table 3). During single-hormone artificial pancreas nights, the times spent in hypoglycaemia were highest during early night hours (figure 3), and all hypoglycaemia events requiring treatment also occurred early and were preceded by little insulin delivery (table 3). This indicates that prandial boluses accompanying the bedtime snacks were probably the major contributor to these events. Better management of bedtime snack boluses[20] or using ultra-fast-acting insulin[21] might potentially eliminate these residual hypoglycaemic events without the need for glucagon.

We designed our single-hormone artificial pancreas to improve glucose control as much as possible, and then, without increasing the aggressiveness of insulin delivery, we added glucagon to eliminate residual hypoglycaemia. Hence, the amount of insulin delivery was similar during the two artificial pancreas interventions. However, mean glucose was higher during nights with the single-hormone artificial pancreas than during nights with the dual-hormone artificial pancreas (not significant, p=0·066; table 2). This is contrary to results of a recent inpatient comparison,[19] in which the dual-hormone artificial pancreas led to higher mean glucose. A key difference between the two studies is that food intake was unrestricted in this study and not interfered with by the research team, whereas the inpatient study restricted carbohydrate intake to the treatment of hypoglycaemia events (<3·3 mmol/L with symptoms, <3·0 mmol/L irrespective of symptoms).[19] When food intake was unrestricted, we observed an increase in frequency of carbohydrate ingestion during nights with the single-hormone artificial pancreas compared with nights with the dual-hormone artificial pancreas (figure 2), which thereby affected mean glucose. Campers often ingested extra carbohydrate as per their standard practice, likely based on capillary finger-stick glucose measurements and potential perception of hypoglycaemia. Whether use of glucagon in the artificial pancreas does or does not induce behavioural changes in dietary intake warrants further investigation in longer day and night outpatient studies.

For our conclusions to be generalised to other single-hormone artificial pancreas systems, the performance of our single-hormone system needs to be similar to that of others tested in the paediatric population. Compared with the system of Hovorka and colleagues[12] that was tested

overnight at home for 3 weeks compared to sensor-augmented pump-therapy, our single-hormone system reduced mean glucose by a higher margin (1·6 mmol/L *vs* 0·8 mmol/L), but our participants had a higher mean glucose on control nights than did participants in their study (9·3 mmol/L *vs* 8·4 mmol/L). Both systems did not reduce time spent in hypoglycaemia, which was rare on nights with the control intervention (median times spent with glucose <3·9 mmol/L were 1·7% in our study and 1·4% in the study by Hovorka and colleagues[12]–ie, less than 10 min per night in both studies). Compared with the single-hormone artificial pancreas system of Nimri and colleagues[13] that was tested overnight at home for 6 weeks and compared with sensor-augmented pump-therapy, our system reduced mean glucose by a higher margin (1·6 mmol/L *vs* 0·8 mmol/L), with mean glucose on control nights higher in our study than in theirs (9·3 mmol/L *vs* 8·9 mmol/L). However, unlike our study and that of Hovorka and colleagues,[12] the system of Nimri and colleagues[13] reduced the time spent in hypoglycaemia compared with sensor-augmented pump therapy, but their participants had a substantially higher time spent with glucose lower than 3·9 mmol/L on control nights compared with our participants and those of Hovorka and colleagues (median 5·2% *vs* 1·7% *vs* 1·4%, respectively). Two other outpatient studies that tested the system by Nimri and colleagues[14,22] also showed reduced time spent in hypoglycaemia compared with sensor-augmented pump therapy, but these two studies also reported that participants spent a high percentage of time in hypoglycaemia on control nights (ie, 10%), and no difference was observed in mean glucose between interventions. Ly and colleagues[15] tested their single-hormone artificial pancreas system overnight in a diabetes camp and showed no difference in mean glucose compared with sensor-augmented pump therapy, and hypoglycaemia was reduced in the per-protocol analysis (intention-to-treat analysis for time spent in hypoglycaemia was not reported).

We tested artificial pancreas systems during the night only. Hypoglycaemia is very common during the night, especially in children and adolescents,[6] and night-time accounts for most of their hypoglycaemia seizures.[5] Fear of severe nocturnal hypoglycaemia is a major source of anxiety for patients and their families.[7] This made night control a plausible first application of artificial pancreas systems, and the first long-term (eg, several weeks) outpatient studies focused on night-time control.[12,13,23] However, if the artificial pancreas only operates during the night, then the early part of the night might be affected by the patient's decisions before the operation of the artificial pancreas. Whether applying the artificial pancreas during the day and night, as opposed to the night only, further improves overnight glucose control warrants further investigation.

Our study has several limitations. First, we used manual control rather than an automated system, but this is not likely to have affected the clinical conclusions. The sensor receiver, the pump remote controller, and the algorithm tablet were all placed outside the tent, and study staff operated the artificial pancreas systems without entering the tent or interacting with study participants. Moreover, manual control resulted in robust data transmission and avoided technical problems experienced by other investigators,[12,15,18] mimicking the performance of a future integrated system. Second, we used a crossover study design, which has an intrinsic limitation since the order of the interventions may affect the outcomes. However, in our study, we observed no difference in the results due to the order of the interventions. Third, camp settings are different than usual home settings, and our participants were engaged in more physical activities than they would likely do outside the camp setting. Single-hormone artificial pancreas systems might still be sufficient for overnight control for most nights[19] and glucagon benefits might only be observed on nights preceded by higher-than-usual levels of physical activity. Fourth, our study lacked allocation blinding, and we cannot rule out the possibility of treatment bias. Blinding participants to the interventions was practically challenging due to the nature of the interventions.

Whether it is justifiable to add glucagon to the artificial pancreas is a challenging question to answer and needs further research. First, the single-hormone and the dual-hormone systems are yet to be compared in larger and longer studies with important endpoints such as the incidence of severe hypoglycaemia and HbA_{1c} concentrations. Second, psychosocial outcomes should be compared between the two artificial pancreas systems. The dual-hormone system will likely produce reduced hypoglycaemia, potentially improving quality of life, but it also necessitates an additional catheter and additional drug manipulation. To predict future adherence to dual-hormone therapy, we should assess, from patients' perspectives, whether the clinical benefits outweigh the increased complexity. Third, cost-effectiveness should be analysed and compared between the two artificial pancreas systems. Finally, all these questions should be addressed and compared between different age groups and populations. Dual-hormone artificial pancreas might only be justifiable in certain populations, such as patients with hypoglycaemia unawareness, young children, those with long duration of diabetes, and physically active patients, among others.

Contributors

AH, RR-L, and LL coordinated and supervised the study. AH, RR-L, LL, VM, and MD designed the study. AH, LM-P, MD, and VM conducted the study. LM-P, ML, and VM carried out the data processing, graphs preparations, and the statistical analyses. AH designed and implemented the dosing algorithm. All authors approved the final version of the manuscript.

Declaration of interests

AH received consultant and speaker honoraria from SNELL Medical Communication and the Diabetic Children's Foundation. RR-L reports grants, consulting fees, and speaker fees from AstraZeneca; consulting

fees from Boehringer; grants, consulting fees, and speaker fees from Eli Lilly; grants, consulting fees, and speaker fees from Merck; grants, consulting fees, and speaker fees from Novo-Nordisk; grants, consulting fees, and speaker fees from Sanofi-Aventis; speaker fees from Medtronic; consulting fees from Takeda; consulting fees and speaker fees from Janssen; consulting fees and speaker fees from Neomed; consulting fees and speaker fees from Novartis; consulting fees from Valeant; consulting fees from Roche; consulting fees and speaker fees from Becton Dickinson; grant from Immunotec; and consulting fees and speaker fees from Lifescan. AH, RR-L, and LL own intellectual properties in the area of the artificial pancreas. LM-P, VM, MD, and ML declare no competing interests.

Acknowledgments

This study was supported by funding from the Canadian Diabetes Association (OG-3-14-4500-RR) and J-A De Sève Chair held by RRL. AH holds Canadian Banting postdoctoral fellowship, RR-L is a senior FRQS (Fonds de recherches du Québec en santé) researcher, and LM-P held a Quebec Diabetes Association summer scholarship. We thank the Camp Carowanis administration and its staff for their precious collaboration. We thank Claire Deprez for helping with data processing.

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