Efficacy of Artificial Pancreas Use in Patients With Type 2 Diabetes Using Intensive Insulin Therapy: A Randomized Crossover Pilot Trial

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Artificial pancreas (AP) systems have proven efficacy and superiority in glucose control compared with other insulin delivery methods in patients with type 1 diabetes (1,2). Patients with type 2 diabetes (T2D) requiring intensive insulin therapy are difficult to treat and could potentially benefit from AP. Two published reports have addressed AP and T2D in hospitalized patients, with overall results favoring AP (2,3). We aimed to test the applicability of a single-hormone (SH) (insulin only) AP algorithm in patients with T2D who require multiple daily injections (MDI) of insulin.

We conducted an open-label, randomized, crossover study to compare glucose control under SH-AP and MDI in adults with T2D (≥55 years old, BMI >25 kg/m^2, on ≥3 insulin injections/day). Exclusion criteria were change in hypoglycemic agents within 6 weeks prior to or during the study, creatinine clearance <30 mL/min, macrovascular event within the past 6 months, infections and hospitalization within the past 2 months, severe hypoglycemia in the past 2 weeks, or morning basal insulin. Participants were recruited at diabetes clinics of three Canadian (Quebec) participating centers. Respective ethics committees approved the study with written informed consent. Dexcom G4 Platinum (Dexcom, San Diego, CA) was inserted 24 h before interventions and calibrated 2–3 times/day. In a crossover design, each participant underwent two 24-h intervention visits using SH-AP and MDI in randomized order (separated by at least 3 days). Schedules were identical between these interventions: arrival at the research center at 6:30 P.M. (dinner and insulin bolus prior to that at home), standardized evening snack, next day's breakfast at 8:00 A.M., lunch at 12:00 P.M., dinner at 5:00 P.M., 15-min walks at 10:00 A.M. and 3:00 P.M., and discharge at 9:00 P.M. Blood samples were collected every 20 min starting at 9:00 P.M. for 24 h. During MDI visits, patients decided their insulin basal and premeal doses without research team interference. For AP visits, glucose was controlled by algorithm only for both rapid insulin analog rate and announced premeal boluses using a subcutaneous pump (Accu-Chek Combo; Roche, Mannheim, Germany). AP, as previously reported (4), used a model predictive algorithm initiated with the participant's weight and 70% of usual basal and bolus insulin doses and was of a hybrid type that required meal announcement. A linear mixed-effects model suited for repeated observations was used for analysis (R software, version 3.4.1).

The study was completed by 15 patients (11 males, mean ± SD 63.6 ± 6.7 years old, BMI 33.4 ± 5.6 kg/m^2, HbA_{1c} 7.85 ± 0.6% [62.0 ± 4.9 mmol/mol]).

Over the 24-h period, a trend was observed for an improved median plasma glucose (PG) time in target range (72–180.0 mg/dL 2 h postmeal and 72–144 mg/dL otherwise), from 78.9% (interquartile range [IQR] 63.3–85.5%) with MDI to 86.2% (IQR 76.5–91.7%) with AP ($P = 0.057$) (mean values in Table 1). With AP, there was a trend for decrease of time in hyperglycemia and lower mean PG (not significant). No differences in time in hypoglycemia nor in number of participants with hypoglycemia events were observed between AP and MDI. Lower insulin doses (−31.7%, $P < 0.001$) were administered by the AP algorithm,

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Table 1—Comparison of AP and MDI

	24 h (9:00 P.M.–9:00 P.M.)			Overnight (11:00 P.M.–7:00 A.M.)		
Outcome	AP	MDI	Paired difference; *P* value	AP	MDI	Paired difference; *P* value
Time spent at PG (%)						
In target*	84.2 (11.5)	74.0 (17.0)	10.2; $P = 0.057$	92.5 (11.6)	70.9 (27.1)	21.6; $P = 0.010$
72–180 mg/dL	92.3 (7.2)	85.2 (11.8)	7.1; $P = 0.046$	97.3 (7.6)	84.8 (11.7)	12.5; $P = 0.001$
Below 72 mg/dL	0 (0–0)	0 (0–6.2)	0; $P = 0.217$	0 (0–0)	0 (0–2.0)	0; $P = 0.450$
Below 63 mg/dL	0 (0–0)	0 (0–0.5)	0; $P = 0.685$	0 (0–0)	0 (0–0)	0; $P = 0.923$
Above 144 mg/dL	21.8 (13.5–29.9)	26.9 (12.8–47.9)	−5.1; $P = 0.111$	0 (0–0.5)	4.6 (0–49.4)	−4.6; $P = 0.024$
Above 180 mg/dL	4.2 (0–9.1)	7.4 (1.6–18.6)	−3.2; $P = 0.109$	0 (0–0)	0 (0–17.8)	0; $P = 0.012$
Total insulin daily dose (units)	84.0 (40.9)	115.7 (51.6)	−31.7; $P < 0.001$			
Insulin concentration (mU/L)	459.7 (296.5)	567.4 (294.4)	−107.7; $P = 0.010$			
PG (mg/dL)	120.6 (14.4)	127.8 (19.8)	−7.2; $P = 0.137$	100.8 (16.2)	120.6 (30.6)	−19.8; $P = 0.021$
SD of PG (mg/dL)	28.8 (5.4)	32.4 (9.0)	−3.6; $P = 0.260$	12.6 (7.2)	19.8 (10.8)	−7.2; $P = 0.058$
Coefficient of variation in PG (%)	24.0 (4.1)	25.0 (5.8)	−1.0; $P = 0.535$	13.0 (5.9)	16.0 (7.4)	−3.0; $P = 0.203$
AUC (mg/dL × min/h)						
AUC of PG <72 mg/dL	0 (0–0)	0 (0–18.0)	0; $P = 0.450$	0 (0–0)	0 (0–676.8)	0; $P = 0.441$
AUC of PG <63 mg/dL	0 (0–0)	0 (0–0)	0; $P = 0.923$	0 (0–0)	0 (0–0)	0; $P = 0.908$
AUC of PG >144 mg/dL	0 (0–9.0)	82.8 (0–889.2)	−82.8; $P = 0.024$	0 (0–36.6)	82.8 (0–1,780.8)	−82.2; $P = 0.050$
AUC of PG >180 mg/dL	0 (0–0)	0 (0–320.4)	0; $P = 0.012$	0 (0–0)	0 (0–6,166.8)	0; $P = 0.036$
Hypoglycemic events <63 mg/dL						
Participants with at least one event requiring treatment, *n* (%)**	3 (20.0)	5 (33.3)	−2; $P = 0.253$	1 (6.7)	3 (20.0)	−2; $P = 0.253$
Total events, *n*	4	6	–	2	3	–
Results according to sensor readings and parameters as defined in AP consensus guidelines***						
Time spent at sensor glucose (%)						
Below 70 mg/dL	0 (0–0.7)	0 (0–4.3)	0; $P = 0.45$	0 (0–0.70)	0 (0–1.4)	0; $P = 0.50$
70–140 mg/dL	68.3 (14.5)	58.8 (16.7)	9.5; $P = 0.05$	87.8 (14.4)	55.5 (29.6)	32.3; $P = 0.002$
70–180 mg/dL	90.4 (8.1)	84.2 (13.2)	6.2; $P = 0.11$	95.2 (8.2)	84.3 (25.5)	10.9; $P = 0.13$
Above 180 mg/dL	4.5 (0.7–10.7)	8.2 (1.2–17.9)	−3.7; $P = 0.25$	0 (0–0)	0 (0–0)	0; $P = 0.22$
Mean glucose (mg/dL)	126.0 (16.2)	133.2 (21.6)	−7.2; $P = 0.23$	102.6 (18.0)	127.8 (34.2)	−25.2; $P = 0.01$

Data are presented as median (IQR) or mean (SD) unless otherwise indicated. Paired difference is AP vs. MDI value. AUC, area under the curve. *Primary end point: time in target range is defined as PG 72–144 mg/dL at all times except in the 2 h postmeal, when the range is set at 72–180 mg/dL. **Hypoglycemia treated with 16-g glucose tablets. ***Study design and outcomes were set before the publication of AP consensus guidelines, but we calculated these values at study conclusion (4).

which resulted in lower plasma insulin levels in comparison with MDI.

For overnight control (11:00 P.M.–7:00 A.M.), AP resulted in higher time in target range at 100% (IQR 85.6–100%) vs. 78.0% (IQR 50.6–95.7%) ($P = 0.01$), lower mean PG (100.8 ± 16.2 vs. 120.6 ± 30.6 mg/dL, $P = 0.02$), and a trend toward lower glucose variability (SD).

Our findings confirm AP applicability under a controlled setting in patients with T2D on intensive insulin. Glucose control was significantly improved overnight (+21.6% for median time in target range) with a similar trend over 24 h (+7.3%). Overnight, tighter control was achieved without increasing hypoglycemia risk with AP (1 vs. 3 patients). In comparison with published results in hospitalized patients, which also favored AP, percentages of time in target range in our study were higher in both AP and control arms (2). This could be attributed to the compromised health status, absence of meal boluses, and sensor reporting (versus PG) in the hospitalized patients' trials. As seen in patients with type 1 diabetes, AP systems have better overnight performances due to persistent challenges of postprandial glucose control with available devices and insulin analogs (5). The observed improvement in glucose time in target range could have important clinical implications in the light of accumulating evidence linking time in target range to complications such as the prevalence and severity of retinopathy and microalbuminuria in patients with T2D (6). Interestingly, less insulin was needed with AP, but this could partly be due to the continuous infusion approach and not solely explained by algorithm dosing. These data could allow fine-tuning of the SH-AP algorithm in this population.

This first pilot trial testing an AP algorithm in MDI-treated patients with T2D had some limitations: a small number of participants, short duration, and no prior treatment optimization. Whether AP would outperform optimized T2D treatment with multiple alternative options (glucagon-like peptide 1 agonists, sodium–glucose cotransporter 2 inhibitors, ultralong-acting basal insulins, continuous or flash glucose monitoring, etc.) is worth investigating

for this population in larger and longer trials under free-living conditions. The potential clinical benefits of this technology in patients with advanced T2D will have to be weighed against complexity and costs of AP systems.

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