A Meal Detection Algorithm for the Artificial Pancreas: A Randomized Controlled Clinical Trial in Adolescents With Type 1 Diabetes

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OBJECTIVE

We developed a meal detection algorithm for the artificial pancreas (AP+MDA) that detects unannounced meals and delivers automatic insulin boluses.

RESEARCH DESIGN AND METHODS

We conducted a randomized crossover trial in 11 adolescents aged 12–18 years with HbA_{1c} ≥7.5% who missed one or more boluses in the past 6 months. We compared *1*) continuous subcutaneous insulin infusion (CSII), *2*) artificial pancreas (AP), and *3*) AP+MDA. Participants underwent three 9-h interventions involving breakfast with a bolus and lunch without a bolus.

RESULTS

In AP+MDA, the meal detection time was 40.0 (interquartile range 40.0–57.5) min. Compared with CSII, AP+MDA decreased the 4-h postlunch incremental area under the curve (iAUC) from 24.1 ± 9.5 to 15.4 ± 8.0 h · mmol/L ($P = 0.03$). iAUC did not differ between AP+MDA and AP (19.6 ± 10.4 h · mmol/L, $P = 0.21$) or between AP and CSII ($P = 0.33$). The AP+MDA reduced time >10 mmol/L (58.0 ± 26.6%) compared with CSII (79.6 ± 27.5%, $P = 0.02$) and AP (74.2 ± 20.6%, $P = 0.047$).

CONCLUSIONS

The AP+MDA improved glucose control after an unannounced meal.

A primary factor for poor glucose control in adolescents is the omission of insulin boluses at mealtimes (1), which has been associated with a higher HbA_{1c} (1,2). The success of the artificial pancreas (AP) at handling unannounced meals has yet to be shown and may benefit from the addition of an algorithm that automatically detects unannounced meals and delivers partial insulin boluses (3).

RESEARCH DESIGN AND METHODS

Study Design and Participants

We performed a randomized, three-way, crossover trial to compare the AP with a meal detection algorithm (AP+MDA), the AP alone, and conventional pump therapy (continuous subcutaneous insulin infusion [CSII]) in controlling glucose levels after a meal without a bolus. Adolescents underwent three 9-h interventions, with their order randomized, at our research facility or at home while accompanied by a member of our research staff. Each intervention included breakfast with a carbohydrate-matched bolus and lunch without a bolus.

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Adolescents with type 1 diabetes were recruited from the Montreal Children's Hospital. Inclusion criteria were 12–18 years old, use of an insulin pump, HbA_{1c} 7.5–12%, and at least one self-reported missed prandial bolus during the previous 6 months.

Intervention Procedures

Interventions occurred from 0800 to 1700 h or from 0900 to 1800 h. Participants installed a glucose sensor (Dexcom G5) before each intervention. Participants' at-home pumps were used with NovoRapid (insulin aspart) or Humalog (insulin lispro). Meals were self-selected and standardized between interventions for each participant. Breakfast (40–50 g carbohydrates) was served at the start of the intervention, and lunch (55–65 g carbohydrates) was served 4 h after the start of the intervention (see Supplementary Appendix for meal composition).

During CSII, participants' usual basal rates were delivered, and the breakfast boluses were calculated using the pump's bolus calculator. During AP and AP+MDA, study personnel programmed new basal rates every 10 min on the basis of the dosing algorithm's recommendation (model predictive controller). Breakfast boluses were calculated using the AP's bolus calculator. During the AP+MDA intervention, the algorithm detected the unannounced meal and computed a recommended bolus on the basis of *1*) the current glucose level and *2*) the estimated remaining carbohydrates on board (up to a maximum of 25 g) (3). Standardized hypoglycemia and hyperglycemia protocols were applied (see Supplementary Appendix).

Statistical Analysis

All outcomes were calculated from 0–4 hours postlunch. The study was powered to detect a minimum difference between the AP and CSII interventions in the incremental area under the curve (iAUC) of the postprandial (0–4 h) glucose excursions after lunch of 2.6 h · mmol/L. Other comparisons were designated as secondary. If an insulin correction bolus was delivered on the basis of the hyperglycemia criteria, the glucose data were analyzed as if the glucose would have stayed at the last glucose value before the correction bolus. See the Supplementary Appendix for details of the statistical analysis.

RESULTS

Thirteen adolescents were admitted to the study. Eleven participants were included in the analysis (Supplementary Appendix), with a mean baseline age of 14.9 ± 1.3 years, HbA_{1c} 8.3 ± 0.6%, duration of diabetes 8.2 ± 3.3 years, BMI 22.5 ± 3.7 kg/m^2, and daily insulin dose 0.9 ± 0.2 units/kg; 91% (n = 10) were female.

AP+MDA decreased the iAUC from 0 to 4 h postlunch compared with CSII (AP+MDA 15.4 ± 8.0 h · mmol/L vs. CSII 24.1 ± 9.5 h · mmol/L, P = 0.03) (Fig. 1). This improvement was not observed between AP (19.6 ± 10.4 h · mmol/L) and CSII (P = 0.33) or between AP+MDA and AP (P = 0.21). The AP+MDA increased the time in target (3.9–10 mmol/L) compared with CSII (AP+MDA 40.9 ± 27.9% vs. CSII 20.5 ± 27.5%, P = 0.03). There was no difference in time in target between AP (25.0 ± 19.7%) and CSII (P = 0.61) or between AP+MDA and AP alone (P = 0.07) (Supplementary Appendix).

The AP+MDA reduced time >10 mmol/L after lunch compared with CSII (AP+MDA 58.0 ± 26.6% vs. CSII 79.6 ± 27.5%, P = 0.02) and compared with AP alone (74.2 ± 20.6%, P = 0.047) (Supplementary Appendix). Sensor glucose 4 h after lunch was lower in AP+MDA (8.5 [interquartile range 6.9–10.5] mmol/L) compared with CSII (14.4 [12.9–17.2] mmol/L, P = 0.01).

The time <3.9 mmol/L was 0% (interquartile range 0–0) in all three arms, and there was a total of one hypoglycemic event, which occurred in the AP arm. There were five hyperglycemia events requiring correction boluses in the CSII arm, four events in the AP arm, and one event in the AP+MDA arm.

The median meal detection time was 40.0 [40.0–57.5] min after consumption of the meal. Total insulin delivery was larger in the AP+MDA arm (8.6 ± 1.8 units [63 ± 17% basal, 37 ± 17% bolus]) compared with CSII (4.2 ± 1.0 units [100% basal], P < 0.01) and AP alone (7.6 ± 1.5 units [100% basal], P < 0.01) (Fig. 1). Basal insulin in the AP arm (7.6 ± 1.5 units) was greater than CSII (4.2 ± 1.0 units, P < 0.01) and AP+MDA (5.4 ± 1.6 units, P < 0.01), while CSII and AP+MDA basal delivery did not differ (P = 0.07) (Supplementary Appendix). In the AP+MDA arm, the total amount of additional basal (above the programmed basal rate) and bolus insulin delivered by the AP after meal detection to 4 h postlunch was 4.5 ± 1.7 units, which represented, on average, 55% of the bolus that would have been delivered at mealtime.

CONCLUSIONS

People with type 1 diabetes, particularly adolescents, often forget to deliver their insulin boluses on time or even at all (4,5). However, missed bolus alarms only demonstrated short-term success (6). A safe MDA that delivers a bolus after an unbolused meal may improve postprandial glycemia and ultimately improve overall glycemic control.

The rate of glucose appearance in the blood is determined by the rate at which glucose is emptied from the stomach and absorbed in the intestine, the extraction by the splanchnic tissues, followed by the glucose entering the circulation (7). Pennant et al. (7) showed that in people with type 1 diabetes who missed a prandial insulin bolus, the rate of glucose appearance in the blood of 25% of a mixed meal was 31.7 ± 3.5 min, and 50% of the meal appeared after 54.1 ± 4.7 min. Our MDA detected the meal in between these times, after 40.0 [40.0–57.5] min.

The benefits of AP alone over CSII were not apparent in the study. The significant increase in basal insulin by the AP was still not sufficient to improve time in hyperglycemia, iAUC, or time in target. Other studies illustrated the superiority of the AP over CSII in handling snacks without a bolus (8,9) or meals with partial boluses (8,10), but its success in handling a full meal without a bolus has not been shown. This suggests that the AP's basal insulin delivery increase may be sufficient in controlling glycemia following a small amount of unannounced carbohydrates, but the bolus delivered by an MDA is necessary following a large meal.

There are currently no recommendations regarding postprandial insulin bolusing (e.g., if a patient only remembers to bolus >30 min after a meal). The amount of additional basal and bolus insulin delivered by the AP+MDA after meal detection to 4 h postlunch represented 55% of the bolus that would have been delivered at mealtime. This AP+MDA brought sensor values to 8.5 (6.9–10.5) mmol/L 4 h postmeal. Therefore, ~40 min postmeal, it appears that

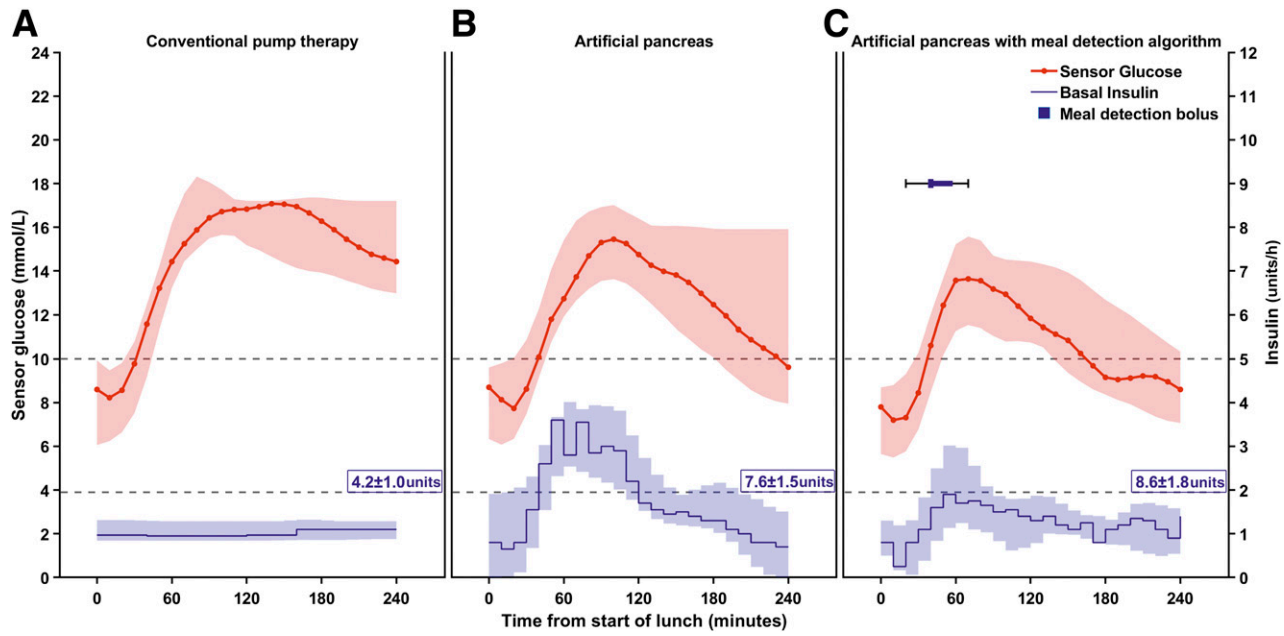

Figure 1—Glucose and insulin profiles from the start of lunch without a bolus (time = 0 min) to 4 h postlunch (time = 240 min) among all three interventions ($n = 11$). *A*: CSII. *B*: AP. *C*: AP+MDA. Red lines and their shaded areas indicate median sensor glucose profiles and IQR. Blue lines and their shaded areas indicate median basal insulin delivery and IQR. Total insulin delivery is shown in the blue boxes. Meal detection boluses are indicated as a boxplot of the time of the meal detection and insulin bolus delivery.

delivering ~65% of the full bolus that one would have received at mealtime may be an effective recommendation for bringing glucose back into the target range without inducing hypoglycemia.

In conclusion, the MDA successfully detected unannounced meals and delivered boluses, reducing postprandial glucose excursions compared with CSII. Longer and larger outpatient free-living clinical trials are warranted.

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Duality of Interest. A.H. received research support/consulting fees from Eli Lilly, Medtronic, AgaMatrix, Tandem, and Dexcom and has pending patents in the AP area. L.L. has pending patents in the field of AP, has received consulting fees from Dexcom and Eli Lilly, and has received support for clinical trials from Merck, AstraZeneca, and Sanofi. A.E.F. has a pending patent in the AP area. E.P. owns intellectual property in the field of AP. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. E.P. wrote the first draft of the manuscript. E.P., A.E.F., J.E.v.O., and L.L. conducted the study. E.P., A.E.F., A.H., and L.L. designed the study. A.E.F. designed the MDA. A.E.F. performed the statistical analysis. J.E.v.O., A.H., and L.L. supervised the study. All authors interpreted the data and read/edited and approved the final version of the manuscript. A.H. and L.L. are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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