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Postprandial Glucose Excursions with Ultra-Rapid Insulin Analogues in Hybrid Closed-Loop Therapy for Adults with Type 1 Diabetes

Running title: Postprandial glucose control with faster acting insulins

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Abstract

Objective: To evaluate postprandial glucose control when applying (i)faster-acting insulin aspart (Fiasp) compared to insulin aspart, and (ii)ultra-rapid insulin lispro (Lyumjev) compared to insulin lispro using the CamAPS FX hybrid closed-loop algorithm.

Research Design and Methods: We undertook a secondary analysis of postprandial glucose excursions from two double-blind, randomized, crossover hybrid closed-loop studies contrasting Fiasp to standard insulin aspart, and Lyumjev to standard insulin lispro (NCT04055480, NCT05257460). Endpoints included incremental area under curve iAUC-2h, iAUC-4h, 4h postprandial time in target range, time above range, and time below range.

Results: Two trials with 8-weeks of data from 51 adults with type 1 diabetes were analysed and 7137 eligible meals were included. During Lyumjev compared with insulin lispro, iAUC-2h and iAUC-4h were significantly decreased following breakfast (mean difference 92 mmol/L per 2h (95%CI 56 to 127); p<0.001 and 151 mmol/L per 4h (95%CI 74 to 229); p<0.001, respectively) and evening (p<0.001 and p=0.011, respectively). Mean time in target range (3.9-10.0 mmol/L) for 4h postprandially significantly increased during Lyumjev with a mean difference of 6.7percentage points (95%CI 3.3 to 10) and 5.7percentage points (95%CI 1.4 to 9.9) for breakfast and evening, respectively. In contrast, there were no significant differences in iAUC-2h, iAUC-4h, and the other measures of postprandial glucose control between insulin aspart and Fiasp during breakfast, lunch, and evening meal (p>0.05).

Conclusion: The use of Lyumjev with CamAPS FX closed-loop system improved postprandial glucose excursions compared with insulin lispro, while the use of Fiasp did not provide any advantage compared with insulin aspart.

Introduction

Hybrid closed-loop systems have become increasingly prevalent in the routine care of individuals with type 1 diabetes, offering notable enhancements in glucose control and quality of life (1-3). However, these systems face limitations, due to the relatively slow absorption rate of subcutaneously administered rapid-acting insulin analogues (4, 5). To overcome these challenges and mitigate rapid glucose fluctuations, there has been a concerted effort to develop faster-acting insulins.

Fast acting insulin aspart (Fiasp) is the first faster-acting insulin analogue, which includes L-arginine and niacinamide as excipients to facilitate faster initial absorption of insulin aspart (6). Short-term studies have demonstrated that Fiasp improves postprandial glucose control compared to insulin aspart in open-loop and some hybrid closed-loop system (7-9). However, in other short-term closed-loop studies, Fiasp did not exhibit significant differences in postprandial glucose control when compared to insulin aspart (10, 11).

Ultra-rapid lispro (Lyumjev) is another faster-acting insulin and contains two excipients, treprostinil and citrate, that facilitate increased early absorption (12). In a double-blind hybrid closed-loop crossover study, Lyumjev demonstrated a reduction in early 0-2h postprandial glucose excursions (13). There were no significant differences in 4h postprandial glucose levels or other glucometric endpoints (13).

Previous studies evaluating postprandial glucose control during hybrid closed-loop use have certain limitations, such as controlled meal periods, open-label designs, or short-term study periods. The objective of the present study was to assess the postprandial glucose excursions of Fiasp and Lyumjev in comparison to insulin aspart and insulin lispro respectively, over a longer duration using the CamAPS FX hybrid closed-loop system.

Research Design and Methods

Study design and study population

We undertook a secondary analysis of 8 weeks of postprandial data from two double-blind, randomized, two-period, crossover studies (NCT04055480 and NCT05257460) that

evaluated the safety and efficacy of hybrid closed-loop insulin delivery with CamAPS FX using faster insulin aspart (Fiasp, Novo Nordisk, Bagsvaerd, Denmark) compared with insulin aspart (Novo Nordisk) (14) and ultra-rapid insulin lispro (Lyumjev**,** Eli Lilly, Indianapolis, IN, USA) compared with insulin lispro (Eli Lilly) in type 1 diabetes (15). Both studies were approved by independent research ethics committees and study participants signed informed consent prior to any study procedures.

Adults aged 18 years or over with type 1 diabetes on insulin pump therapy for at least 6 months and with HbA1c of 10% (86 mmol/mol) or less were recruited. During the study periods, all participants used hybrid closed-loop insulin delivery with the CamAPS FX hybrid closed-loop system. Participants were advised to bolus 15 minutes before eating and carb-insulin ratio kept identical during both study periods.

Hybrid closed-loop system

The CamAPS FX closed-loop app (CamDiab Ltd, Cambridge, UK) was used with the Dana Diabecare insulin pump (Sooil, Seoul, South Korea) and Dexcom G6 continuous glucose monitor (Dexcom, San Diego, CA, USA). The CamAPS FX closed-loop system uses an adaptive model predictive control algorithm to direct insulin delivery every 8-12 minutes. The default glucose target value of 5.8 mmol/L (104 mg/dL) can be adjusted by participants as required between 4.4 mmol/L (80 mg/dL) and 11.0 mmol/L (198 mg/dL) (2).

Study endpoints and data analysis

The key endpoints were the net incremental area under curve (iAUC) of sensor glucose values during 2h and 4h postprandial periods post breakfast, lunch, and evening meal. Postprandial period was defined as 4 hours after at least 25g of carbohydrates entry (16). Other endpoints included time spent in glucose range 3.9 to 10.0 mmol/L (70-180 mg/dL), time above 10.0 mmol/L (180 mg/dL), time below 3.9 mmol/L (70 mg/dL), the maximum and minimum glucose concentration, time to maximum (peak) and time to minimum (nadir) glucose concentration during 4h postprandial period. The pre-prandial glucose concentration was calculated as the mean of sensor glucose values within 15 min before the carbohydrate entry.

Criteria for inclusion of a meal in the analysis included pre-prandial glucose level ≥3.9 mmol/L (70 mg/dL) and ≤10.0 mmol/L (180 mg/dL) to exclude the effect of hypoglycaemia treatment and significant hyperglycaemia due to set failure, and sensor glucose data availability of ≥80% during the 4h postprandial period. Postprandial periods that contained a secondary main meal (>25g) were excluded. Meal periods were classified as breakfast (05:00-10:59), lunch (11:00-16:59) and evening (17:00-22:59).

Mean endpoints for each meal period were calculated on a per participant basis over the 8 weeks. The per person mean values were compared using a linear mixed model. Outcomes were calculated using R studio (version 4.4.2, R Foundation for Statistical Computing, Vienna, Austria). Statistical analyses were performed using SPSS (version 27, IBM software). Data are presented as mean±standard deviation (SD) for normally distributed or median (interquartile range [IQR]) for non-normally distributed data. To compare non-normally distributed data, winsorisation at 10^{th} and 90^{th} percentile was performed prior to applying a linear mixed model. P values <0.05 were considered statistically significant.

Results

Fifty-one participants provided 7,317 eligible meals for analysis (breakfast 1,886; lunch 2,634; evening 2,797). Baseline demographics and glycaemic characteristics of study participants are shown in Table 1. The Aspart-Fiasp group included 25 adults aged 38 ± 9 years. Lispro-Lyumjev group included 26 adults aged 44 ± 11 years. Endpoints for each meal are presented in Table 2.

Lispro-Lyumjev group. Meal carbohydrate size was similar between study periods for each meal (Table 2). iAUC-2h was significantly decreased during the Lyumjev period when compared with insulin lispro period for breakfast (197 ± 122 vs. 103 ± 98 mmol/L per 2h for Lispro vs. Lyumjev; p <0.001) and evening (87 ± 91 vs. 38 ± 91 mmol/L per 2h for Lispro vs. Lyumjev; p <0.001). There was no significant difference for lunch (128 ± 90 vs. 99 ± 78 mmol/L per 2h for Lispro vs. Lyumjev; p=0.10). There was a significant reduction in iAUC-4h during breakfast and evening with Lyumjev intervention compared with insulin lispro

(347 ± 191 vs. 200 ± 175 mmol/L per 4h for Lispro vs. Lyumjev; p <0.001 and 298 ± 224 vs. 211 ± 183 mmol/L per 4h for Lispro vs. Lyumjev; p=0.011, respectively) (Figure 1).

The mean percentage of time in the target glucose range (3.9-10.0 mmol/L) (70-180 mg/dL) for the 4h postprandial period was significantly higher during the Lyumjev period than with insulin lispro (77.2 ± 11.4% vs. 83.6 ± 8.7% for breakfast and 73.4 ± 12.5% vs. 79.1 ± 9.0% for evening in Lispro vs. Lyumjev; p <0.001 and 0.011, respectively) with a mean difference of -6.7 percentage points (95% CI 3.3 to 10) and -5.7 percentage points (95% CI 1.4 to 9.9) for breakfast and evening, respectively. The time spent with sensor glucose ≥10.0 mmol/L (180 mg/dL) for the 4h postprandial period was reduced with Lyumjev compared with insulin lispro for breakfast and evening with a mean difference 7.5 percentage points (95% CI 4.0 to 10.9) and 5.6 percentage points (95% CI 1.2 to 10), respectively (Figure 1). There was no difference in the median percentage of time spent in hypoglycaemia (<3.9 mmol/L) (70 mg/dL) between the two study periods.

Aspart-Fiasp group. Meal carbohydrate content was comparable between study periods (Table 2). Similar iAUC-2h and iAUC-4h were observed between insulin aspart and Fiasp during breakfast, lunch, and evening (p=0.96 and 0.35 for breakfast, p=0.10 and 0.70 for lunch, p=0.08 and 0.46 for evening, respectively) (Table 2). There was no significant difference in the time spent with sensor glucose readings in range, above or below range for any meals with Fiasp when compared with insulin aspart (Table 2).

Conclusions

The present retrospective analysis of two double-blind, randomized, controlled studies demonstrate that using Lyumjev with the CamAPS FX hybrid closed-loop system improved postprandial glycaemia compared to insulin lispro. The use of Fiasp did not provide any advantage in terms of postprandial glucose levels compared to insulin aspart**.**

Previous hybrid closed-loop studies have yielded conflicting results regarding postprandial glucose excursions with Fiasp in individuals with type 1 diabetes (8-10). A 670G (Medtronic, CA, USA) hybrid closed-loop study reported a reduction in 1h postprandial glucose

increment with Fiasp compared with insulin aspart during mixed meal test (9), while another study using 670G pump found no difference in postprandial glucose after identical breakfast over 3 days (10). An open-label study conducted under free-living conditions showed slightly higher time in target glucose range (4h postprandial) with Fiasp compared to insulin aspart with 780G hybrid closed-loop system (Medtronic, CA, USA) (8). In an open-label study with the CamAPS FX hybrid closed-loop system that was performed with standardized meal types and times showed no significant difference during 4h postprandial period between Fiasp and insulin aspart (11).

In the present analysis utilising data from two double-blind randomized controlled studies and over a longer duration, we did not observe a difference in postprandial glucose excursions between Fiasp and insulin aspart in any meal period. Although open-label design and short-term studies have a risk of bias, these variations in outcomes observed in different studies may be attributed to the different hybrid closed-loop algorithms. The CamAPS FX algorithm adapts to day-to-day prandial and diurnal glucose patterns and automatically adjusts the duration of insulin action (3).

Only one trial has investigated the effect of Lyumjev on postprandial glucose in individuals with type 1 diabetes using hybrid closed-loop systems (13), enrolling participants with relatively good metabolic control in a double-blind, crossover (two periods of 4-week) study with 670G (Medtronic). The study reported significantly reduced glucose excursions and iAUCs during the 0-1h and 0-2h postprandial periods with Lyumjev compared to insulin lispro. There was no improvement in 4h iAUC or other glucometric parameters (13).

Our findings demonstrate significant improvements in iAUC-2h, iAUC-4h, and 4h postprandial time in range and time above range during breakfast and evening meal with Lyumjev. No significant difference in postmeal glycaemic excursions was observed at lunch, potentially due to variations in meal composition during that time. The observed improvement in postprandial hyperglycaemia was consistent with the 24h time in target and above range in the dataset analysed for the original study (15). Differences between our study and the 670G study may be attributed to the different hybrid closed-loop algorithms

as stated above. Bolus timing may also be a contributing factor, since the present study advised bolusing 15 minutes before meals and adjusting as needed, while the 670G study administered bolus doses immediately prior to meals (13).

In the primary results of these two RCTs, the use of Lyumjev with CamAPS FX closed-loop increased 24h time in range and reduced mean glucose with no difference in hypoglycaemia (15), while Fiasp had no positive effect on 24h time in range and mean glucose, but a small reduction in time below range (14). It seems that 4h postprandial control of ultra-rapid insulin analogues reflects 24h glucose control in CamAPS FX closed-loop systems. Few studies have shown a slight reduction in time in below range (<3.9 mmol/L) (70 mg/dL) over 24h with ultra-rapid insulin analogues (13, 14). In the present study, the time spent in hypoglycaemia during 4h postprandial period for each meal was comparable in both the Aspart-Fiasp study and Lispro-Lyumjev study.

The strengths of the present study include obtaining data from two double-blind, crossover studies that, with each participant acting as their own control and a longer intervention duration compared to previous studies investigating postprandial glucose control of faster-acting insulins in hybrid closed-loop systems. Limitations include no adjustment for multiplicity although such an adjustment would not alter the conclusions, the lack of information regarding bolus timing in relation to meals, reliance on user provided information for carbohydrate counting, uncertainty regarding the optimization of carb-insulin ratio and the lack of ethnic diversity in the study population. However, the blinded and crossover study design minimizes potential bias from these factors.

In conclusion, the use of Lyumjev with the CamAPS FX closed-loop system reduces postprandial hyperglycaemia compared to insulin lispro in adults with type 1 diabetes. No such notable benefit was observed for Fiasp. Future studies evaluating hybrid closed-loop with faster-acting insulin analogues in populations with suboptimal metabolic control and in children are warranted.

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Author Contributions

BH and CKB co-designed the study. MN, RL, CKB, and SH were responsible for screening and enrolment of participants, arranged informed consent from the participants, and provided patient care. JW, JMA, HT, JKM, LB, LL and MLE supported study monitoring and randomization. RH designed and implemented the glucose controller. BH, RL, MEW undertook data analysis. BH, CKB, JW and RH contributed to the interpretation of the results. BH wrote the report. All authors critically reviewed the manuscript and approved the final version for publication. BH, CKB and RH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data and analyses.

Conflict of Interest

BH reports receiving speaker honoraria from Sanofi, CKB has received consultancy fees from CamDiab and speaker honoraria from Ypsomed. RL declares no duality of interest associated with the present manuscript. JW reports receiving speaker honoraria from Ypsomed and Novo Nordisk. MN has received travel grant support from Sanofi, Janssen and Eli Lilly and was previously chair of the Young Diabetologists' and Endocrinologists' Forum in the UK, which uses unrestricted sponsorship from industry partners to deliver educational programs for health care professionals. HT was on the advisory panels for Abbot and Roche, received consulting fees and speaker honoraria from Eli Lilly, and received research support from Dexcom Inc. JKM is a member of advisory boards of Abbott Diabetes Care, Becton-Dickinson, Boehringer Ingelheim, Eli Lilly, Embecta, Medtronic, NovoNordisk A/S, Roche Diabetes Care, Sanofi-Aventis, Viatris and received speaker honoraria from A. Menarini Diagnostics, Abbott Diabetes Care, AstraZeneca, Boehringer Ingelheim, Dexcom, Eli Lilly, Medtrust, MSD, NovoNordisk A/S, Roche Diabetes Care, Sanofi, Servier, Viatris and Ypsomed. She is

shareholder of decide Clinical Software GmbH and elyte Diagnostics and serves as CMO of elyte Diagnostics. LB reports having received speaker honoraria from Dexcom and Oviva. LL reports having received speaker honoraria from Animas, Abbott, Insulet, Medtronic, Novo Nordisk, Roche and Sanofi, was on advisory panels for Animas, Abbott, Novo Nordisk, Dexcom, Medtronic, Sanofi and Roche, and received research support from Abbott, Novo Nordisk and Dexcom. MEW reports receiving license fees from BBraun, patents related to closed-loop, and being a consultant at CamDiab. JMA reports training fees from CamDiab. SH reports speaker & advisory board fees from Dexcom, Medtronic, Sanofi & Ypsomed; being director at ASK Diabetes Ltd and receiving consulting / training fees from CamDiab. MLE has received speaker honoraria from Abbott, Medtronic, Novo Nordisk, and Eli Lilly, has been on advisory panels for Abbott, Medtronic, Novo Nordisk, Eli Lilly, Dexcom, Zucara and Pila Pharma and received research support from Abbott, Medtronic, Novo Nordisk and Eli Lilly. RH reports having received speaker honoraria from Eli Lilly, Dexcom and Novo Nordisk, receiving license fees from BBraun; patents related to closed-loop, and being director at CamDiab.

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Table 1: Baseline characteristics of study participants

	Lispro:Lyumjev group (n=26)	Aspart:Fiasp group (n=25)
Age (n)	44 ± 11	38 ± 9
Gender – male, n (%)	18 (64)	12 (48)
Race/ethnicity, n (%)		
White	28 (100)	23 (92)
Other	0 (0)	2 (8)
BMI (kg/m^2)	28.3 ± 3.9	27.1 ± 4.9
Duration of diabetes (yrs)	29 ± 12	22 ± 12
HbA1c (%)	7.1 ± 0.9	7.4 ± 0.8
HbA1c (mmol/mol)	54 ± 10	57 ± 8
Percentage of time with glucose		
3.9 to 10.0 mmol/L (70-180 mg/dL)	63 ± 17	61 ± 13
>10.0 mmol/L (>180 mg/dL)	33 ± 18	35 ± 15
<3.9 mmol/L (70 mg/dL)	2.7 (1.1, 4.9)	2.4 (0.9, 4.6)
Mean glucose (mmol/L) (mg/dL)	9.1 ± 1.9 (164 ± 34)	9.1 ± 1.3 (164 ± 23)
Glucose CV (%)	35.6 ± 5.1	36.6 ± 5.3
Total daily insulin (units/day)	44 ± 19	46 ± 13
Total daily basal insulin (units/day)	21 ± 7	21 ± 7
Total daily bolus insulin (units/day)	24 ± 13	25 ± 8

BMI – body mass index, CV – coefficient of variation.

Data are shown as mean ± SD for normally distributed values, or median (IQR) for non-normally distributed values.

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Table 2: Postprandial endpoints calculated over 8 weeks of (i) closed-loop with ultra-rapid insulin lispro (Lyumjev) and (ii) closed-loop with insulin lispro (Lispro).

	Lispro	Lyumjev	p-value**	Mean difference (95% CI)**
Breakfast*				
Participants (n)	21	22		
Meals (n)	489	500		
Meals per participant (n)	23 ± 12	23 ± 15		
Meal size (g CHO)	35 (31, 40)	33 (31, 44)	0.86	-0.5 (-6.2, 5.2)
iAUC-2h (mmol/L per 2h)	197 ± 122	103 ± 98	< 0.001	92 (56, 127)
iAUC-4h (mmol/L per 4h)	347 ± 191	200 ± 175	< 0.001	151 (74, 229)
Percentage of time with glucose				
3.9 to 10.0 mmol/L (70-180 mg/dL)	77.2 ± 11.4	83.6 ± 8.7	< 0.001	-6.7 (-10.0, -3.3)
>10.0 mmol/L (180 mg/dL)	20.5 ± 11.6	13.3 ± 8.7	< 0.001	7.5 (4.0, 10.9)
<3.9 mmol/L (70 mg/dL)	2.0 (1.5, 2.4)	2.6 (1.3, 4.1)	0.14	-0.5 (-1.2, 0.2)
c_{max} (mmol/L) (mg/dL)	11.0 ± 1.5 (198 ± 27)	10.3 ± 1.0 (185 ± 18)	< 0.001	0.8 (0.4, 1.2)
c_{min} (mmol/L) (mg/dL)	4.8 ± 0.4 (86 ± 7)	4.7 ± 0.3 (85 ± 5)	0.15	0.2 (-0.0, 0.3)
t_{max} (min)	109 ± 19	118 ± 28	0.20	-8.7 (-22.7, 5.7)
t_{min} (min)	125 ± 23	126 ± 30	0.90	-9.5 (-16.4, 14.5)
Lunch*				
Participants (n)	23	24		
Meals (n)	643	677		
Meals per participant (n)	28 ± 9	28 ± 12		
Meal size (g CHO)	40 (30, 56)	43 (32, 55)	0.92	0.3 (-6.4, 7.1)
iAUC-2h (mmol/L per 2h)	128 ± 90	99 ± 78	0.10	30 (-6, 67)
iAUC-4h (mmol/L per 4h)	312 ± 193	283 ± 148	0.51	26 (-56, 109)
Percentage of time with glucose				
3.9 to 10.0 mmol/L (70-180 mg/dL)	75.2 ± 9.9	76.1 ± 9.4	0.44	-1.1 (-4.3, -1.9)
>10.0 mmol/L (180 mg/dL)	22.2 ± 10.9	20.9 ± 9.7	0.41	1.5 (-2.1, 5.0)
<3.9 mmol/L (70 mg/dL)	2.3 (0.7, 3.6)	2.4 (1.2, 4.3)	0.46	-0.3 (-1.2, 0.6)

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c_{max} (mmol/L) (mg/dL)	11.1 ± 1.2 (200 ± 22)	11.1 ± 1.2 (200 ± 22)	0.86	0.0 (-0.4, 0.4)
c_{min} (mmol/L) (mg/dL)	4.9 ± 0.5 (88 ± 9)	4.8 ± 0.5 (86 ± 9)	0.76	0.3 (-0.1, 0.2)
t_{max} (min)	129 ± 25	133 ± 22	0.45	-3.5 (-13.1, 6.1)
t_{min} (min)	107 ± 22	106 ± 27	0.71	1.9 (-8.8, 12.6)
Evening*				
Participants (n)	24	24		
Meals (n)	719	769		
Meals per participant (n)	30 ± 11	32 ± 10		
Meal size (g CHO)	48 (37, 55)	45 (36, 57)	0.82	0.8 (-5.9, 7.5)
iAUC-2h (mmol/L per 2h)	87 ± 91	38 ± 91	< 0.001	48 (24, 73)
iAUC-4h (mmol/L per 4h)	298 ± 224	211 ± 183	0.011	86 (22, 151)
Percentage of time with glucose				
3.9 to 10.0 mmol/L (70-180 mg/dL)	73.4 ± 12.5	79.1 ± 9.0	0.011	-5.7 (-9.9, -1.4)
>10.0 mmol/L (180 mg/dL)	23.6 ± 13.4	18.0 ± 10.0	0.016	5.6 (1.2, 10.0)
<3.9 mmol/L (70 mg/dL)	2.7 (0.9, 4.0)	3.0 (2.1, 4.6)	0.25	-0.4 (-1.2, 0.3)
c_{max} (mmol/L) (mg/dL)	11.1 ± 1.3 (200 ± 23)	10.8 ± 1.2 (194 ± 22)	0.13	0.3 (-0.1, 0.7)
c_{min} (mmol/L) (mg/dL)	5.1 ± 0.6 (92 ± 11)	4.9 ± 0.4 (88 ± 7)	0.75	0.2 (-0.0, 0.4)
t_{max} (min)	141 ± 19	139 ± 19	0.65	2.0 (-7.4, 11.5)
t_{min} (min)	86.4 ± 23	86 ± 14	0.90	-0.5 (-9.8, 8.6)

iAUC – incremental area under the curve, c_{max} – maximum concentration of glucose, c_{min} – minimum concentration of glucose, t_{max} – time to maximum glucose, t_{min} – time to minimum glucose.

Data are shown as mean ± SD for normally distributed values, or median (IQR) for non-normally distributed values. Transformation (winsorisation) was applied to highly skewed endpoints prior to statistical analysis.

*Breakfast 5:00am to 10:59am, lunch 11:00am to 16:59pm, and evening 17:00pm to 22:59pm.

**Based on a linear mixed model with insulin as a fixed effect and participant as a random effect.

Table 3: Postprandial endpoints calculated over 8 weeks of (i) closed-loop with fast-acting insulin aspart (Fiasp) and (ii) closed-loop with insulin aspart (Aspart).

	Aspart	Fiasp	p-value**	Mean difference (95% CI)**
Breakfast*				
Participants (n)	21	22		
Meals (n)	439	458		
Meals per participant (n)	21 ± 12	21 ± 11		
Meal size (g CHO)	40 (36, 46)	41 (37, 49)	0.61	-1.1 (-5.6, 3.3)
iAUC-2h (mmol/L per 2h)	197 ± 128	193 ± 141	0.96	-1 (-44, 42)
iAUC-4h (mmol/L per 4h)	343 ± 201	367 ± 197	0.35	-29 (-94, 35)
Percentage of time with glucose				
3.9 to 10.0 mmol/L (70-180 mg/dL)	75.5 ± 10.9	76.0 ± 13.1	0.94	-1.6 (-4.7, 4.3)
>10.0 mmol/L (180 mg/dL)	20.9 ± 11.5	21.8 ± 13.9	0.53	-1.4 (-5.9, 3.1)
<3.9 mmol/L (70 mg/dL)	3.0 (1.5, 5.3)	2.2 (0.9, 4.4)	0.29	0.4 (-0.4, 1.2)
c_{max} (mmol/L) (mg/dL)	10.9 ± 1.3 (196 ± 23)	10.9 ± 1.3 (196 ± 23)	0.85	-0.0 (-0.4, 0.3)
c_{min} (mmol/L) (mg/dL)	4.8 ± 0.5 (86 ± 9)	4.8 ± 0.5 (86 ± 9)	0.82	-0.0 (-0.2, 0.2)
t_{max} (min)	112 ± 23	117 ± 29	0.23	-5.9 (-15.9, 4.0)
t_{min} (min)	114 ± 33	110 ± 26	0.66	3.5 (-7.5, 14.5)
Lunch*				
Participants (n)	24	25		
Meals (n)	675	639		
Meals per participant (n)	28 ± 8	26 ± 8		
Meal size (g CHO)	45 (37, 53)	47 (41, 55)	0.30	-1.4 (-6.7, 4.0)
iAUC-2h (mmol/L per 2h)	165 ± 96	133 ± 128	0.10	30 (-7, 68)
iAUC-4h (mmol/L per 4h)	352 ± 189	334 ± 224	0.70	14 (-65, 95)
Percentage of time with glucose				
3.9 to 10.0 mmol/L (70-180 mg/dL)	71.2 ± 8.1	72.1 ± 11.4	0.68	-0.6 (-4.0, 2.7)
>10.0 mmol/L (180 mg/dL)	26.1 ± 8.9	24.7 ± 13.0	0.50	1.3 (-2.5, 5.0)
<3.9 mmol/L (70 mg/dL)	2.1 (0.9, 3.5)	2.8 (0.8, 5.0)	0.10	-0.7 (-1.5, 0.1)

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c_{max} (mmol/L) (mg/dL)	11.5 ± 1.0 (207 ± 18)	11.3 ± 1.4 (203 ± 25)	0.30	0.2 (-0.2, 0.5)
c_{min} (mmol/L) (mg/dL)	4.9 ± 0.3 (88 ± 5)	5.0 ± 0.6 (90 ± 11)	0.67	-0.0 (-0.2, 0.1)
t_{max} (min)	125 ± 14	132 ± 21	0.11	-7.0 (-15.9, 1.8)
t_{min} (min)	109 ± 23	95 ± 27	0.03	14.0 (0.9, 27.0)
Evening*				
Participants (n)	25	25		
Meals (n)	658	651		
Meals per participant (n)	26 ± 10	26 ± 8		
Meal size (g CHO)	44 (38, 56)	47 (38, 57)	0.76	-0.9 (-6.5, 4.7)
iAUC-2h (mmol/L per 2h)	100 ± 115	96 ± 135	0.82	-23 (-89, 42)
iAUC-4h (mmol/L per 4h)	293 ± 226	317 ± 241	0.46	3 (-27, 34)
Percentage of time with glucose				
3.9 to 10.0 mmol/L (70-180 mg/dL)	74.5 ± 10.7	72.2 ± 10.0	0.10	2.2 (-0.5, 5.0)
>10.0 mmol/L (180 mg/dL)	21.7 ± 11.6	24.4 ± 11.8	0.11	-2.6 (-5.9, 0.6)
<3.9 mmol/L (70 mg/dL)	3.6 (1.3, 5.7)	2.6 (0.9, 5.5)	0.16	0.5 (-0.2, 1.2)
c_{max} (mmol/L) (mg/dL)	11.1 ± 1.2 (200 ± 22)	11.4 ± 1.3 (205 ± 23)	0.19	-0.2 (-0.5, 0.1)
c_{min} (mmol/L) (mg/dL)	4.9 ± 0.6 (88 ± 11)	5.0 ± 0.5 (90 ± 9)	0.08	-0.2 (-0.3, 0.0)
t_{max} (min)	136 ± 21	137 ± 17	0.91	-0.6 (-11.0, 9.9)
t_{min} (min)	93 ± 23	86 ± 18	0.18	7.0 (-3.5, 17.7)

iAUC – incremental area under the curve, c_{max} – maximum concentration of glucose, c_{min} – minimum concentration of glucose, t_{max} – time to maximum glucose, t_{min} – time to minimum glucose.

Data are shown as mean ± SD for normally distributed values, or median (IQR) for non-normally distributed values. Transformation (winsorisation) was applied to highly skewed endpoints prior to statistical analysis.

*Breakfast 5:00am to 10:59am, lunch 11:00am to 16:59pm, and evening 17:00pm to 22:59pm.

**Based on a linear mixed model with insulin as a fixed effect and participant as a random effect.

Figure Legend

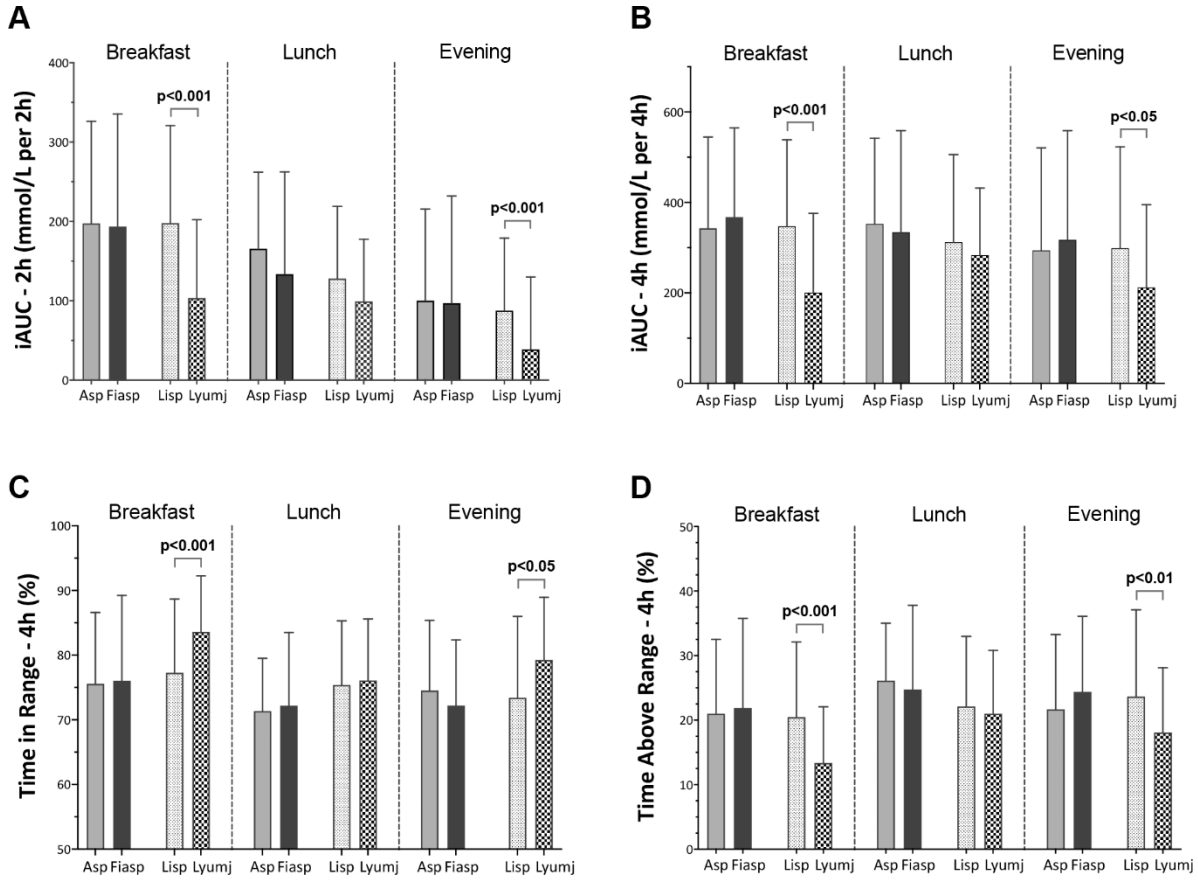

Figure 1: Comparison of key endpoints. Plots include data of insulin aspart (Asp), fast-acting insulin aspart (Fiasp), insulin lispro (Lispro) and ultra-rapid insulin lispro (Lyumjev) for breakfast, lunch, and evening for (A) iAUC-2h (B) iAUC-4h (C) percentage of time spent in target glucose range, and (D) percentage of time spent above glucose range. Data are mean±SD.