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ORIGINAL ARTICLE

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Postprandial time in tight range with faster insulin aspart compared with standard insulin aspart in youth with type 1 diabetes using automated insulin delivery

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Abstract

Aims: The aim of this study was to assess postprandial glycaemic outcomes using automated insulin delivery with faster acting insulin aspart (FIA) or standard insulin aspart (SIA) over 4 weeks in youth (aged 10–18 years) with type 1 diabetes.

Materials and Methods: We undertook a secondary analysis of postprandial glycaemic outcomes from a double-blind, randomised, crossover study comparing FIA to SIA using an investigational version of MiniMed™ 780G. Endpoints included postprandial time in tight range (70–140 mg/dL; TITR), postprandial glucose excursions and peak glucose, and incremental area under curve (iAUC).

Results: The mean ± SD age of 30 included participants was 15.0 ± 1.7 years, 47% were male, mean HbA1c was 7.5% ± 0.9% (58 ± 9.8 mmol/mol) and the number of meals per day per participant was 3.2 ± 1.2 meals. Overall, the postprandial outcomes were improved with FIA compared with SIA. Mean glucose at the start of the meal was 151 mg/dL in the FIA group and reached a peak glucose of 194 mg/dL, compared with starting level of 151 mg/dL in the SIA group and a peak of 198 mg/dL (difference in excursion: −3.8 mg/dL; 95% confidence interval −5.8 to −1.7; p <0.001). FIA group also had a 1.9% increase in mean TITR ($p = 0.02$) and a 2.0-mg/dL decrease in mean iAUC ($p = 0.003$). Differences in outcomes were the most noticeable for breakfast, meals with a larger amount of carbohydrates (>45 g) and participants with lower insulin-to-carbohydrate ratios.

Conclusions: Faster insulin formulation with AID improved postprandial glycaemic outcomes and could be a useful therapeutical option in youth with type 1 diabetes that have challenges achieving glycaemic targets.

KEYWORDS
continuous glucose monitoring (CGM), glycaemic control, insulin therapy, type 1 diabetes

1 | INTRODUCTION

Automated insulin delivery (AID) is recommended as the treatment modality of choice for both children and adults with type 1 diabetes, improving glycaemic outcomes and quality of life.[1,2] Currently available AID systems are considered 'hybrid', as they require user input for carbohydrate intake and manual delivery of an insulin bolus for meals, as well as exercise announcements.[3,4]

Rapid-acting insulin analogues are commonly used, but their efficacy is limited due to slower absorption and delayed peak of action compared with physiological insulin secretion.[5] To overcome these challenges, considerable efforts have been made to develop ultrarapid insulins that mimic endogenous insulin secretion and have the potential to improve the efficacy of AID technology, principally to counteract postprandial glucose excursions.[6,7] There are limited data evaluating postprandial glycaemic outcomes with ultrarapid insulin use in AID,[8–13] especially in children and adolescents with type 1 diabetes in an unsupervised setting.

The aim of this study was to assess postprandial glycaemic outcomes including time in tight range (TITR 70–140 mg/dL) with faster acting insulin aspart (FIA) or standard insulin aspart (SIA) over 4 weeks in youth with type 1 diabetes using AID technology.

2 | METHODS

The Fast Advanced Closed-Loop Therapy (FACT) study was a multisite, double-blind, randomised crossover trial conducted at the University Children's Hospital Ljubljana in Slovenia and Department of Paediatrics and Adolescent Medicine, Medical University Graz, in Austria. The objective of the study was to evaluate glycaemic outcomes with FIA versus SIA in youth with type 1 diabetes using AID technology. The study is listed on clinicaltrials.gov under registration number NCT04853030 and has been described elsewhere.[14]

Briefly, inclusion criteria were age 10–18 years, diagnoses of type 1 diabetes for at least 6 months, use of an insulin pump for at least 3 months and HbA1c <11.0% (97 mmol/mol). Participants meeting the eligibility criteria were asked to complete two 4-week periods using the Medtronic MiniMed™ 670G 4.0 hybrid closed-loop (referred to as AID) system (investigational version of MiniMed™ 780G with equivalent algorithm) with one of the two insulin formulations, FIA or SIA, administered in each period and assigned in random order. Study participants and investigators were blinded to the treatment allocation.

Before randomisation, participants completed a run-in period lasting at least 1 week using the study insulin pump without automated insulin delivery and using a Guardian™ sensor 3 continuous glucose monitoring (CGM) system. Each participant was trained to use the study pump (without AID mode) and CGM. Training was customized according to previous device experience. Capillary fingerstick blood glucose testing was performed using a Contour® Next Link 2.4 blood glucose meter (Ascensia Diabetes Care, Basel, Switzerland). Participants with at least 80% CGM wear time and an average of ≥3 blood glucose meter tests per day continued into the randomised clinical trial phase of the study.

Participants received training for the AID system at the beginning of each crossover period. Participants started the AID system with a glucose set point of 100 mg/dL but could change their glucose set point accordingly during the two 4-week periods of AID use. Participants also initialised their active insulin time setting, which determines how long the insulin is predicted to reduce glucose levels. There were two settings for the insulin activity time (IAT) utilised in this study: 120 min (recommended starting setting) or 180 min. For all other insulin pump settings (insulin to carbohydrates ratio, insulin correction factor, alarm settings), baseline settings were used. Participants were allowed to adjust their settings during the study period.

At the AID mode initiation contact, participants were reminded to obtain an overnight fingerstick blood glucose measurement (between 2 and 3 AM) for one night after AID initiation, and if blood glucose was <70 mg/dL, to treat with fast-acting carbohydrates, discontinue AID mode and notify the investigators the next day for advice to increase the glucose set point and/or active insulin time. Participants had telephone contacts with the study staff at 24 h, 3 days and 2 weeks after AID initiation and had clinic visits at 1, 3 and 4 weeks. Participants entered the amount of carbohydrates consumed to the AID system to manage postprandial excursions. We previously reported the results of this multinational randomised crossover trial comparing glycaemic outcomes during two unrestricted 4-week periods using hybrid AID with FIA and SIA in 30 physically active children and adolescents with type 1 diabetes (14). The primary outcome was the percentage of sensor glucose time above range (>180 mg/dL) between FIA compared with SIA, and there was no difference (19% vs. 20% respectively).[14]

The goal of the present study was to compare postprandial glycaemic outcomes with FIA versus SIA in youth with type 1 diabetes using AID. The postprandial period started when carbohydrates were entered into the pump and stopped either (a) 3 h after a meal, (b) when another carbohydrate amount was entered into the pump or (c) when exercise began. Postprandial periods were only analysed if the duration and amount of CGM data available were at least 2 h. The breakfast period was defined as 4:00 AM to 10:59 AM, the lunch period was defined as 11:00 AM to 3:59 PM and the dinner period was defined as 4:00 PM to 8:59 PM. All participants had a glucose set point of 100 mg/dL during the baseline period and FIA period (recommended setting). One participant raised their target set point to 120 mg/dL during the SIA period due to fear of hypoglycaemia.

2.1 | Statistical methods

The primary postprandial outcomes included TITR (70–140 mg/dL), postprandial excursions, incremental area under the curve (iAUC), peak glucose following carbohydrate intake and time to peak glucose. The TITR may be a more suitable metric when mean glucose values are approaching near-normoglycaemia.[15–18] The difference in glycaemic outcomes between the FIA and SIA groups were estimated using a repeated measures least squares regression model adjusting for the glucose value at start of meal, baseline HbA1c value and baseline

outcome value during run-in period using a compound symmetry covariance structure to handle the repeated meals for each participant. A sensitivity analysis considered using a spatial power covariance structure to account for the stronger correlation of meals closer together. The residuals were assessed for normality and, if violated, a generalised linear model was used instead using a shifted *t*-distribution with 10 degrees of freedom for the error distribution. Carryover effects for the primary postprandial outcomes were assessed by adding a period by treatment interaction term to the models. There was no evidence of carryover effects (p >0.10 for all).

The secondary postprandial outcomes included the number of hypoglycaemia and hyperglycaemia events. A hypoglycaemia event was defined as more than three consecutive readings or ≥15 consecutive minutes with a CGM glucose value <70 mg/dL. Hyperglycaemia events were defined as ≥15 consecutive minutes with a CGM glucose value >250 mg/dL. Extended hyperglycaemia events were defined as ≥90 cumulative minutes with a CGM sensor value >250 mg/dL within a 120-min period. The differences in the percentage of hypoglycaemia and hyperglycaemia events between the FIA and SIA groups were computed using a repeated measures logistic regression model adjusting for the glucose value at start of the meal and baseline HbA1c value using a compound symmetry covariance structure to handle the repeated meals for each participant. The 95% confidence intervals on the risk differences were obtained using a parametric bootstrapping procedure.

Analyses were performed overall and stratified by meal type, carbohydrate intake, insulin-to-carbohydrate ratio (ICR), body mass index (BMI) and insulin activity time setting. All p-values are two-sided. Adjustment for multiple comparisons was done using the two-stage Benjamini–Hochberg adaptive false discovery rate procedure. Analyses were performed using the SAS software, version 9.4 (SAS Institute).

3 | RESULTS

All 30 participants completed both periods with no missing data. The mean ± SD age was 15.0 ± 1.7 years, 47% were male, all were non-Hispanic White and the mean diabetes duration was 7.8 ± 3.8 years. The mean HbA1c was 7.5% ± 0.9% (58 ± 9.8 mmol/mol), and mean BMI was 20 ± 3 kg/m^2 (Table S1). The mean number of meals per day per participant was 3.2 ± 1.2 meals. The mean number of calibrations per week was 20.6 ± 7.4 calibrations with less than 10% of calibrations being a manual entry. Participants' characteristics were balanced between the two sequences of the insulin type assignment.

Overall, the postprandial outcomes were improved with FIA compared with SIA. Specifically, mean glucose at the start of the meal was 151 mg/dL in the FIA group and reached a peak glucose of 194 mg/dL, while the glucose at the start of the meal was 151 mg/dL in the SIA group and reached a peak of 198 mg/dL (difference in excursion: −3.8 mg/dL; 95% CI −5.8 to −1.7; p <0.001). Compared with the SIA group, the FIA group also had a 1.9% increase in mean TITR (95% CI 0.3–3.5; $p = 0.02$), a 2.0-mg/dL decrease in mean iAUC (95% CI −3.4 to −0.7; $p = 0.003$) and a 3.6-min longer mean time to peak glucose (95% CI 0.7–6.6; $p = 0.01$; Table 1). A sensitivity analysis that considered a spatial power covariance structure yielded similar results (data not shown). An envelope plot of the mean and 95% confidence interval of mean glucose over time after meals with FIA versus SIA is reported in Figure 1. The figure shows the average glucose is lower with FIA compared with SIA and is useful for understanding the typical glucose

TABLE 1 Overall postprandial glycaemic outcomes.[a]

	Baseline *Mean* ± *SD*	FIA *Mean* ± SD	SIA *Mean* ± SD	Adjusted difference FIA minus SIA (95% CI) [*p*-value][b]
Overall	$N = 738$ meals from 30 participants	$N = 2505$ meals from 30 participants	$N = 2478$ meals from 30 participants	
Glucose at start of meal (mg/dL)	173 ± 64	151 ± 55	151 ± 56	
TITR[c]	41% ± 36%	46% ± 35%	44% ± 34%	1.9% (0.3%, 3.5%) [0.02]
Postprandial excursion (mg/dL)	35 ± 39	46 ± 42	50 ± 46	−3.8 (−5.8, −1.7) [<0.001]
Peak glucose (mg/dL)	205 ± 61	194 ± 51	198 ± 53	−3.8 (−5.8, −1.7) [<0.001]
iAUC (mg/dL)[c]	14 ± 21	20 ± 26	22 ± 29	−2.0 (−3.4, −0.7) [0.003]
Time to peak glucose (min)[c]	54 ± 60	72 ± 64	68 ± 61	3.6 (0.7, 6.6) [0.01]

Abbreviations: CI, confidence interval; FIA, faster acting insulin aspart; iAUC, incremental area under curve; SD, standard deviation; SIA, standard insulin aspart; TITR, time in tight range.

[a]Metrics calculated for each meal, and then averaged across all meals for each participant.

[b]*p*-values and 95% CIs were computed from a repeated measures least squares regression model with a compound symmetric covariance structure adjusting for period, starting glucose, baseline outcome and HbA1c at randomisation as fixed effects. Multiple comparisons were adjusted using the two-stage Benjamini-Hochberg adaptive false discovery rate procedure.

[c]Residuals were skewed so the mean and SD were estimated via maximum likelihood and the *p*-values computed using a shifted-*t* generalized linear mixed model.

reading after the start of the meal but does not sufficiently depict the postprandial outcomes which are referred to in the tables. Figure S1 shows the median and quartiles of the mean glucose over time in the postprandial period. There was no evidence of a treatment effect by period carryover effect for any of the postprandial outcomes (p >0.10).

The largest glycaemic differences between FIA and SIA occurred for breakfast. For breakfast, the FIA group had a 10.8-mg/dL lower mean postprandial excursion (95% CI −16.0 to −5.6; p <0.001), a 7.3% higher mean TITR (95% CI 3.5–11.0; p <0.001) and a 6.3-mg/dL lower mean iAUC (95% CI −9.9 to −2.7; p <0.001) compared with the SIA group. In contrast, the mean postprandial excursion in the FIA group was 1.4 mg/dL lower for lunch ($p = 0.46$), and 3.2 lower for dinner ($p = 0.10$) compared with the SIA group, but the differences in mean excursion for lunch and dinner did not reach statistical significance (Table 2). Time to peak glucose was 11.0 min longer in the FIA group compared with the SIA group (95% CI 4.8–17.2; p <0.001) for lunch meals. Box plots showing the treatment differences overall and by meal type are reported in Figure 2.

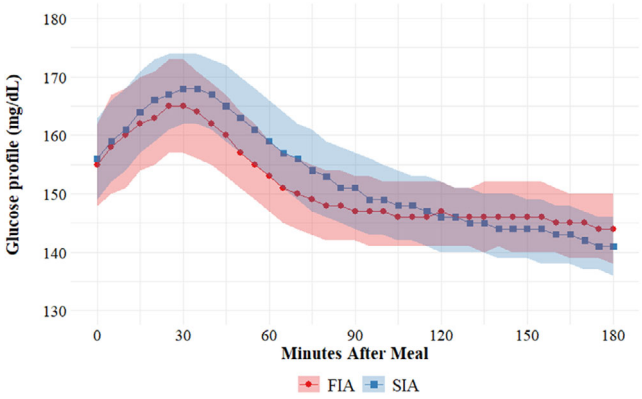

FIGURE 1 Mean glucose by hour after the meal averaged over all participants. Mean glucose values averaged over the participants by period every 5 min after the meal. The bands represent the 95% confidence interval of mean glucose. FIA, faster acting insulin aspart; SIA, standard insulin aspart.

Glycaemic differences between FIA and SIA were also larger for meals with higher grams of carbohydrates and participants with a lower ICR (i.e. gave larger meal boluses for a given amount of carbohydrates). For meals with at least 45 g of carbohydrates, the mean postprandial excursions in the FIA group were 6.7 mg/dL lower (95% CI −10.9 to −2.6; $p = 0.002$), TITR was 3.7% higher (95% CI 0.6–6.7; $p = 0.02$) and iAUC was 3.8 mg/dL lower (95% CI −6.5 to −1.2; $p = 0.004$) compared with the SIA group. For meals with less than 30 g of carbohydrates, the mean postprandial excursion, TITR and iAUC were similar for FIA and SIA groups, while for meals with 30–45 g of carbohydrates, mean excursions were 7.1 mg/dL lower ($p = 0.003$), TITR was 2.9% higher ($p = 0.10$) and iAUC was 3.0 mg/dL lower ($p = 0.06$) for FIA compared with SIA (Table S2). For participants with low ICR (<10 g/U), the mean postprandial excursion in the FIA group was 5.4 mg/dL lower (95% CI −9.7 to −1.0; $p = 0.005$),

TABLE 2 Postprandial outcomes by meal type.

	Baseline *Mean ± SD*	FIA *Mean ± SD*	SIA *Mean ± SD*	Adjusted difference FIA minus SIA (95% CI) [*p*-value][a]
Breakfast	*N* = 201 meals from 30 participants	*N* = 657 meals from 30 participants	*N* = 658 meals from 30 participants	
Glucose at start of meal (mg/dL)	173 ± 64	134 ± 45	136 ± 47	
TITR[b]	37% ± 36%	50% ± 35%	43% ± 33%	7.3% (3.5%, 11.0%) [<0.001]
Postprandial excursion (mg/dL)	40 ± 46	55 ± 46	64 ± 49	−10.8 (−16.0, −5.6) [<0.001]
Peak glucose (mg/dL)	213 ± 62	190 ± 50	200 ± 52	−10.8 (−16.0, −5.6) [<0.001]
iAUC (mg/dL)[b]	17 ± 27	27 ± 30	32 ± 34	−6.3 (−9.9, −2.7) [<0.001]
Time to peak glucose (min)[b]	49 ± 52	73 ± 57	76 ± 54	−2.0 (−7.7, 3.7) [0.46]
Lunch	*N* = 187 meals from 30 participants	*N* = 749 meals from 30 participants	*N* = 770 meals from 30 participants	
Glucose at start of meal (mg/dL)	160 ± 60	148 ± 55	154 ± 58	
TITR[b]	45% ± 36%	45% ± 34%	43% ± 33%	−0.5% (−3.6%, 2.7%) [0.75]
Postprandial excursion (mg/dL)	44 ± 39	51 ± 42	50 ± 46	−1.4 (−5.6, 2.7) [0.46]
Peak glucose (mg/dL)	204 ± 61	198 ± 49	204 ± 53	−1.4 (−5.6, 2.7) [0.46]
iAUC (mg/dL)[b]	18 ± 23	21 ± 26	22 ± 28	−0.9 (−3.6, 1.8) [0.48]
Time to peak glucose (min)[b]	70 ± 64	81 ± 66	66 ± 61	11.0 (4.8, 17.2) [<0.001]
Dinner	*N* = 206 meals from 30 participants	N = 749 meals from 30 participants	*N* = 683 meals from 30 participants	
Glucose at start of meal (mg/dL)	172 ± 66	159 ± 56	154 ± 54	
TITR[b]	43% ± 35%	45% ± 34%	44% ± 33%	1.8% (−1.5%, 5.0%) [0.28]
Postprandial excursion (mg/dL)	34 ± 34	40 ± 38	45 ± 42	−3.2 (−7.0, 0.7) [0.10]

TABLE 2 (Continued)

	Baseline *Mean ± SD*	FIA *Mean ± SD*	SIA *Mean ± SD*	Adjusted difference FIA minus SIA (95% CI) [*p*-value][a]
Peak glucose (mg/dL)	206 ± 60	200 ± 50	199 ± 50	−3.2 (−7.0, 0.7) [0.10]
iAUC (mg/dL)[b]	13 ± 17	15 ± 22	19 ± 26	−2.3 (−4.7, 0.1) [0.07]
Time to peak glucose (min)[b]	57 ± 61	71 ± 68	72 ± 66	1.9 (−4.6, 8.4) [0.53]

Abbreviations: CI, confidence interval; FIA, faster acting insulin aspart; iAUC, incremental area under curve; SD, standard deviation; SIA, standard insulin aspart; TITR, time in tight range.

[a]*p*-values and 95% CIs were computed from a repeated measures least squares regression model with a compound symmetric covariance structure adjusting for period, starting glucose, baseline outcome, and HbA1c at randomisation as fixed effects. Multiple comparisons were adjusted using the two-stage Benjamini–Hochberg adaptive false discovery rate procedure.

[b]Residuals were skewed so the mean and SD were estimated via maximum likelihood and the *p*-values computed using a shifted-*t* generalized linear mixed model.

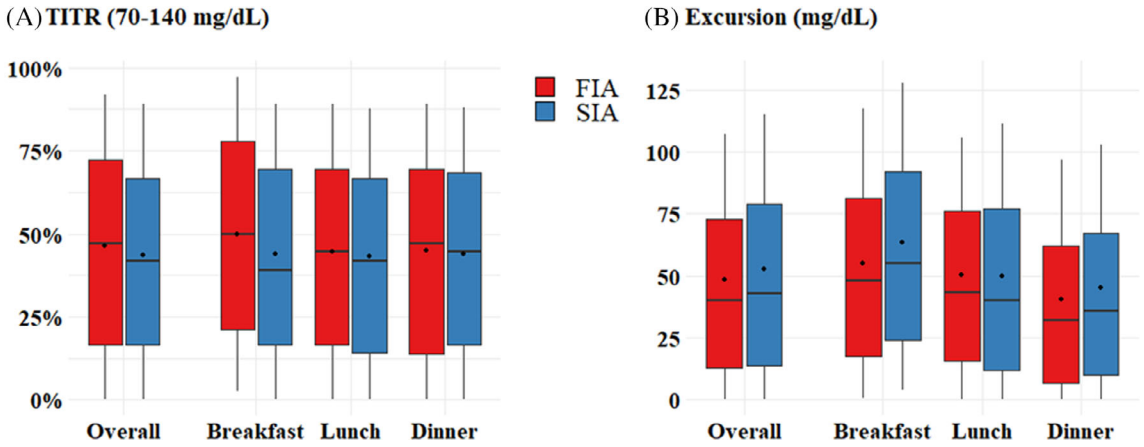

FIGURE 2 Outcomes by treatment overall and by meal type. Boxplots of (A) % time in 70–140 and (B) excursion (mg/dL) for each treatment period overall and by meal type. The dot inside the box represents the mean, and the line inside the box represents the median. The bottom and top of the box represent the first and third quartiles respectively, while the bottom and top ends of the whiskers represent the 10th and 90th percentiles respectively. TITR, time in tight range.

TITR was 1.9% higher ($p = 0.25$) and iAUC was 2.6 mg/dL lower ($p = 0.051$) compared with the SIA group, although some of the glycaemic differences did not reach statistical significance. The glycaemic differences for participants with higher ICR showed similar trends, but the magnitude of the difference was often less pronounced as shown in Table S3. Taken together, the FIA group had the greatest improvement for large breakfast meals handled with a large insulin bolus. Specifically, for breakfasts with at least 45 g of carbohydrates, the FIA group reduced mean postprandial excursion by 18.5 mg/dL (95% CI −26.5 to −10.6; p <0.001) and TITR increased by 9.6% (95% CI 4.3–14.9; p <0.001) compared with the SIA group. For breakfast meals with less than 45 g of carbohydrates, the excursion was decreased by 5.8 mg/dL (95% CI −11.3 to −0.3; $p = 0.04$) and the TITR was increased by 6.1% (95% CI 1.9%–10.3%; $p = 0.004$) (Table S4). Participants with a body mass index (BMI) between the 15th and 80th percentiles experienced better postprandial outcomes with the FIA (Table S5).

Most meals used an insulin active time (IAT) setting of 120 min ($N = 4662$ meals for 120 min; $N = 893$ meals for 180 min), and there was no difference in the distribution of IAT between FIA and SIA groups. For meals with an IAT setting of 120 min, the FIA group had a 3.3-mg/dL lower mean postprandial excursion (95% CI −5.5 to −1.1; $p = 0.006$), a 2.0% higher mean TITR (95% CI 0.3–3.7; $p = 0.02$), a 2.1-mg/dL lower iAUC (95% CI −3.6 to −0.6; $p = 0.006$) and 4.7 min longer time to peak (95% CI 1.6–7.8; $p = 0.006$) compared with the SIA group.

For meals with an IAT setting of 180 min, the FIA group had a 1.3-mg/dL higher mean postprandial excursion ($p = 0.81$), but a 1.1% decrease in mean TITR ($p = 0.79$) compared with the SIA group; these postprandial outcomes did not reach statistical significance perhaps in part due to the smaller sample sizes with this setting ($N = 893$ meals for 180 min vs. $N = 4662$ meals for 120 min). However, the estimates suggest FIA may perform better than SIA when the insulin activity curve setting was 120 min.

The postprandial hypoglycaemia and hyperglycaemia event rates were similar for treatment groups. Specifically, the percentage of meals with a hypoglycaemia event was 12% in the FIA group and 13% in the SIA group ($p = 0.97$; Table S6). Similarly, the percentage of meals with a hyperglycaemia event were 11% versus 12% respectively ($p = 0.73$) and the percentage of meals with an extended

hyperglycaemia event were 2.0% in FIA versus 1.8% in SIA ($p = 0.97$; Table S7).

4 | CONCLUSIONS

This secondary analysis of a double-blind, multinational, randomised, controlled trial demonstrated that using FIA versus SIA with AID improved postprandial TITR by 1.9%. Additionally, FIA use resulted in lowering postprandial glucose excursions (by 3.8 mg/dL), peak glucose levels (3.8 mg/dL) and reducing iAUC (2.0 mg/dL).

Previous clinical trials evaluating postprandial glycaemic outcomes comparing FIA and SIA using AID systems in adults with type 1 diabetes,[12,19,20] including two double-blind clinical trials,[9,10] demonstrate divergent results. A recent secondary analysis of double-blind randomised clinical trials evaluating postprandial glycaemic excursions comparing FIA to SIA with the CamAPS FX closed-loop system in an unrestricted living setting showed no additional benefit with the use of FIA compared with SIA.[9] Similar results were obtained by Hsu et al. in their randomised, double-blind, crossover study comparing FIA to SIA using the MiniMed 670G system in an outpatient setting.[10] Conversely, an open-label study by Lee et al.[19] in 25 adults with type 1 diabetes during a 17-week period demonstrated a greater 4-h postprandial time in range in the FIA arm compared with the SIA arm with a significant difference of 3.5%.

In our study, the differences in postprandial glycaemic outcomes for the overall postprandial period were driven by the breakfast period, where the improvement of TITR was the greatest (50% in FIA compared with 43% in SIA, adjusted difference 7.3%), and when the highest postprandial glycaemic excursions were observed. Additionally, greater improvements in TITR were observed when more carbohydrates (≥45 g) were consumed. The benefit of faster insulin action during mornings and with bigger meals could be more pronounced due to a greater insulin dose needed, which could be associated reduced insulin sensitivity during mornings and the amount of simple carbohydrates consumed commonly during breakfast.[21] This might have direct clinical implications as hyperglycaemia has both acute and chronical effects on cognitive function, including spatial working memory, which could have a detrimental impact on school performance of youth with type 1 diabetes.[22,23] As these alterations to the developing brain in type 1 diabetes might be preventable or reversible with precise glucose control, it is crucial that the best possible therapy is equally available for all youth with type 1 diabetes,[24] Focused long-term research is needed to verify these assumptions.

In the primary results of two recent double-blind randomised controlled studies involving children with type 1 diabetes, the use of FIA with AID did not result in improvement of overall time in range or time in hyperglycaemia.[13,14] As time in range approached recommended time in range target >70% also in the control arm, it was possible a more sensitive metric, such as TITR, might be needed when AID systems are evaluated and especially when efficacy of different medications with AID are assessed.[15]

There were limitations in our study. These include the lack of ethnical diversity in our study cohort, leading to limited generalisability to the general population, and the reliance of self-reported data regarding carbohydrate counting and inputting carbohydrate data into the AID system. Additionally, the relatively short study duration and small sample size of participants made it difficult to fully explore when FIA was most effective with an AID system, although there appeared to be strong evidence that FIA was most beneficial following large breakfast meals with large insulin boluses. The primary analyses showed significant postprandial improvements with FIA, but some of the subgroup analyses may lack adequate power due to the smaller sample sizes and multiple hypotheses testing adjustment. Strengths of this study included obtaining data from a rigorous double-blind, crossover multinational study design, including an active population of youth with type 1 diabetes, as well as including a large number of meals (more than 5000 meals combined) in the analysis.

In summary, our results demonstrate that FIA versus SIA with AID technology improved postprandial glycaemic outcomes including TITR that might be a useful therapeutical option especially in youth with type 1 diabetes that have challenges achieving postprandial glycaemic targets. Future larger and longer studies evaluating both hybrid and full AID technology with even faster ultrarapid insulin analogues are warranted.

AUTHOR CONTRIBUTIONS

K.D., C.S., E.C. and T.B. drafted/wrote the article. C.S. and P.C. did the statistical analysis and verified the underlying data. K.D., C.S., E.C., E.F.-R., D.P.Z., N.P., T.H., P.C., M.F., N.B. and T.B. reviewed and edited the article. All contributing authors approved the final version of the article. T.B. is the guarantor of this study 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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CONFLICT OF INTEREST STATEMENT

KD has received honoraria for speaking engagements from Abbott, Eli Lilly, Medtronic, Novo Nordisk and Pfizer and is on an advisory board for Medtronic and Novo Nordisk. EFR has received honoraria for speaking engagements and advisory boards from Medtronic, Eli Lilly, Sanofi, Merck and Sandoz. DPZ has received honoraria for speaking engagements from Ascensia Diabetes, Insulet Canada, Dexcom Canada and Medtronic and is on an advisory board for Dexcom and has received an ISPAD-JDRF Research Fellowship and research

support from Insulet and the Leona M, and Harry B. Helmsley Charitable Trust. TB received honoraria for participating on the speaker's bureaux of Eli Lilly, Novo Nordisk, Medtronic, Abbott, Sanofi, Dexcom, Aventis, Astra Zeneca and Roche. TB's institution received research grant support from Abbott, Medtronic, Novo Nordisk, Sanofi, Novartis, Sandoz, Zealand Pharma, Slovenian Research Agency, the National Institutes of Health and the European Union. Other authors report no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16211.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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