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Research Article

Automated Insulin Delivery Systems Outperform Standard Care for High-Fat, High-Protein Meal Management in Adults with Type 1 Diabetes: A Crossover Trial

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Abstract

Background: Meal management represents a significant challenge for people with Type 1 Diabetes (T1D), particularly with High-Fat, High-Protein (HFHP) meals. While Automated Insulin Delivery (AID) systems reduce diabetes management burden, their effectiveness in handling complex meals remains unclear, with no established guidelines for HFHP meal management.

Objective: To evaluate AID system effectiveness in managing HFHP meals using two approaches: precise carbohydrate counting with single bolus, and simplified carbohydrate-free dosing, compared to standard Open-Loop (OL) therapy.

Methods: Open-label, single-center, repeated-measures crossover trial in adults with T1D. Participants consumed standardized pizza meals (60g carbohydrates, 38g protein, 41g fat) under three **conditions**: OL with dual-wave bolus and protein/fat adjustments, closed-loop (CL) with accurate carbohydrate counting, and simplified closed-loop (CLP) with predetermined dosing. Each approach was tested three times per participant. Primary outcome was 5-hour postprandial glucose Area Under Curve (AUC).

Results: Thirteen participants (mean age 46.8±12.8 years, HbA1c 6.7±1.2%) completed the study. No significant differences in 5-hour glucose AUC were observed between approaches. However, during 5-10 hours post-meal, both CL and CLP demonstrated superior time-in-range compared to OL (85.5±16.3% and 78.2±23.7% vs. 64.6±23.5%, p=0.004 and p=0.036, respectively). OL required frequent nocturnal corrections (73% of meals), while AID approaches required no manual interventions. Hypoglycemia rates were significantly lower with CL versus OL during the 10-hour period (p=0.03).

Conclusions: AID systems provide superior or comparable glycemic control for HFHP meals compared to complex OL management, with reduced hypoglycemia risk and eliminated nocturnal intervention requirements, substantially reducing patient burden.

Keywords: Type 1 Diabetes; Postprandial Blood Glucose; Insulin; AID; High Fat Meal; High Protein Complex Meal

Introduction

The importance of achieving adequate glycemic to prevent long-term complications has been clearly established in people with T1D [1]. However, achieving these recommended glycemic targets remains challenging. This is highlighted in a recently published data from the T1D Exchange consortium demonstrating that only 21% of adults achieve the desired HbA1c < 7%, without significant hypoglycemia [2], despite a widespread use of continuous glucose monitors. The inability to achieve optimal glycemic in diabetes is multifaceted, with challenging post meal glucose management, being a key contributing factor [3]. The complexity of meal management is related to the complexity of nutritional constituents' absorption, the interactive effect of meal components on the overall glycemic effect, poor reproducibility of meal absorption all leads to unpredictability of post meal glucose excursion. Physiological, 90% of dietary carbohydrates are absorbed within 1–2 hours after eating [4], the attempt to mimic this physiological response to meals with subcutaneous insulin injections using currently available insulins and delivery systems is sub-optimal causing disturbing and unpredictable post meal excursions and hypoglycemia.

Dietary fat and protein effect postprandial glycemia in patients with T1DM [5,6] by the attenuation of blood glucose elevation in the early postprandial phase (2-3 hours post-meal) with delayed peak and prolonged glycemic excursion later in the postprandial phase (>3 hours post- meal) [7]. Possible explanation for effects includes:

1. Transient insulin resistance attributed to dietary fat and Free Fatty Acids (FFAs) and altered response of other hormones involved in glucose regulation including glucagon, Glucagon Like Peptide 1(GLP1), ghrelin and Glucose-Dependent Insulinotropic Peptide (GIP) [8].

2. High dietary fat-mediated delayed gastric emptying leading to late post-prandial glycemic response [6].

3. Directly conversion of amino acids to glucose (gluconeogenesis) increases blood glucose levels [8].

CHO counting with early, pre-meal insulin injections is one of the recommendations to mitigate some of these variabilities [9]. Indeed, the Diabetes Control and Complications Trial (DCCT) found that CHO counting is effective in meeting outcome goals and allows flexibility in food choices [1]. In addition, different conversion algorithms for fat and protein were also described. For example, the Pankowska Equation and Food Insulin index has demonstrated a reduction in postprandial glucose [10]. However, these measures of CHO counting and conversions, and meal bolus timing emerged as a major source of burden to PWD. Patients related factors such as fear of hypoglycemia also challenges meal glycemia [11]. Injecting before a meal, when the glucose levels might be normal, frighten some patients that are not certain if and what meal they will eventually consume, leading to late bolusing in relation to food consumption, and/or intentional underestimation of CHO intake, skipping meal bolus, leading to a mismatch between meal absorption and exogenous insulin action [12].

Beyond addressing the nutritional content of meals, different strategies of meal blousing were devised to address the delayed gastric emptying, such as splitting the meal bolus, in various ways, [13] adding to the complexity meal handling.

AID systems, such as the MM780G system, combine a closed-loop algorithm controller with continuous subcutaneous insulin infusion and continuous glucose monitor (CGM) to provide automated basal insulin delivery and an automated correction every five minutes. Meal boluses follow CHO announcement that effectively targets postprandial hyperglycemia by mitigating different factors that might affect the post meal glucose glycemia [14]. The concepts governing the development of the MM780G algorithm were reducing patient burden while significantly increasing the efficacy of the therapy, this included announcing only carb content of meals, with a single premeal bolus while the algorithm-driven controller autonomously manage all other parameters associated with meal variability. (Grossman B. et al manuscript accepted for publication DT&T).

This study was aimed at providing proof of the above algorithm design concepts by comparing the management of HPHF meals by the most elaborate non algorithmic driven therapy versus the use of MM780G system either in its intended use mode with accurate CHO counting or with a modified and simplified approach that precludes CHO counting. Identifying simplified approaches for complex meal management will aid in reducing the burden associated with meal management, while maintaining effectiveness and safety of insulin delivery [14].

Research Design and Methods

Methods: This was an open label, single-center, repeated-measures prospective meal trial.

Participants were included if they were 20 to 70 years of age, had body weight of 45-120 kg, had a clinical diagnosis of T1D for a minimum of 36 months prior to enrollment, used the MiniMed™ 780G insulin pump with real time continuous glucose monitoring (Medtronic GS3) for at least 6 months with the use of a rapid-acting insulin analogue, a minimum daily insulin requirement (total daily dose; TDD) equals to or greater than 8 units and had an HbA1c ≤ 10.0% measured at screening visit. Participants were

excluded if they had unresolved adverse skin condition, a history of hypoglycemic seizure or hypoglycemic coma within the past 12 months, a history of seizure disorder unrelated to diabetes within the past 12 months, had any condition, including screening lab values that in the opinion of the investigator may preclude them from participating in the study and completing study related procedures, and pregnant or lactating women. All participants provided written informed consent and were willing to comply with all study procedures and were proficient in the English language. Trial was registered at clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT04901143).

Study protocol

Run-in period: Subjects using AID, who met inclusion and exclusion criteria, were enrolled after providing a written informed consent. Demographics, anthropometric measures, medical history, and blood samples for HbA1c were collected. Subjects were trained on meal challenges procedures, and optimal pump settings were verified (glucose target=100 mg/dL and active insulin time=2 hours). During this period overnight OL settings were optimized by requiring the subjects to spend one night on OL after consuming a low fat, low protein, and low fiber meal with a regular bolus and setting the OL setting, to meet optimal glucose targets of 70-180 mg/mL.

Study period: Identical test meals were consumed during three treatment phases; Open loop (OL), Closed Loop (CL) and simplified CL with a predefined bolus (CLP), as following: (1) consume the meal test on the same day at supper; (2) no food consumption within 4 hours prior to, and during at least 6 h after the test meal (overnight); (4) consume the test meal 10 min after delivery of the insulin bolus; (5) avoid exercise for 24 h before the test meal and for 12 h following the meal. Participants were contacted daily by a member of the research team to ensure the protocol was being followed correctly. In addition, daily study diary was filled. Each meal test was repeated 3 times under each treatment phase for a total of 9 meals. Figure 1 depicts the study design.

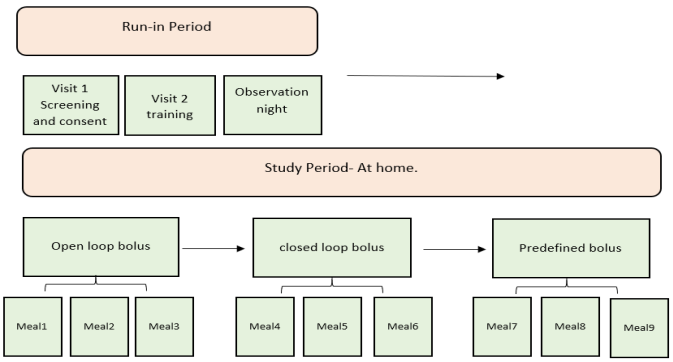

Figure 1: Study overview.

Test Meals:

A standardized HPHF test meal of pre-made frozen pizza was provided to subjects by the study team at the beginning of the study. The meal contained 41 g fat, 38 g protein and 60 g carbohydrates, with a total energy content of 761 kCal. The macronutrient content of the meal tests was analyzed by a certified chemical laboratory (Bactochem Ltd. Israel)

In the OL phase, insulin delivery was used with the PLGM feature switched on, meal bolus dose was based on common practice and recommendations (10), i.e. Participants were instructed to enter the accurate amount of CHO (60g) through "bolus wizard" feature, to increase the recommended amount of insulin units by 30% to account for the protein content of the meal and to use a combination bolus (dual wave bolus) with a 50/50% split over 2.5 h. Insulin was delivered 10 minutes prior to consuming the meal. The participants were required not to give a correction bolus within 3 hours post meal unless glucose level meet the pre-defined safety criteria as described below. Following 3 hours of meal initiation and throughout the night, participants could correct high glucose level by using the "Bolus Wizard" feature.

In the CL phase, bolus was given with an accurate CHO content of the meal (60 g) entered to the "Bolus Wizard" calculator. Mealtime insulin was delivered 10 minutes prior to consuming the meal. Participants were instructed not to interact with the insulin delivery during the hours post meal and throughout the night.

In the CLP phase, a predefined carbohydrate meal estimation was delivered 10 minutes prior to each meal. This estimation was individually calculated for each participant by first determining their fixed insulin dose, which was derived by dividing their TDD by 6 (representing 50% of TDD allocated to bolus insulin, further divided by 3 main meals). This insulin dose was then converted to a carbohydrate value by multiplying by an insulin-to-carb ratio of 7. For safety purposes, the calculated carbohydrate value was capped at 60g to prevent potential excessive insulin delivery and minimize the risk of hypoglycemia.

The universal meal dose per participant is presented in Table 1). As in the CL phase, participants were instructed not to interact with the insulin delivery during the hours post meal and throughout the night.

Participant ID number	TDD (units)	Aprox units per meal	Carbs announced
1	46	7.6	53
2	22	3.6	25
3	40	6.6	46
4	43	7.1	50
5	50	8.3	58
6	55	9.1	60
7	24	4	28
8	31	5.1	36
9	28	4.7	32
10	23	3.8	26
11	93	8.5	60
12	81	8.5	60
13	45	7.5	52
14	23	3.8	26
15	55	8.5	60

Table 1: Optimal priming dose.

Safety measures:

Hypoglycemia- In the event of grade 2 hypoglycemia, defined as blood glucose level < 54 mg/mL confirmed by a glucose meter, subjects were instructed to consume approximately 15 grams of carbohydrates and if self-monitoring of blood glucose shows continued hypoglycemia fifteen minutes following treatment, CHO consumption should be repeated.

Hyperglycemia- In the event of hyperglycemia, defined as glucose values that remain above 250 mg/dL (13.9 mmol/L) for more than 3 hours, a correction bolus was given using the "Bolus Wizard" feature recommendation. Blood beta hydroxybutyrate concentration was measured using a handheld meter and if blood ketones > 3.8mmole/L the subjects were to be treated as if there is a concern of diabetic keto-acidosis per investigator discretion.

Statistical Analysis

The mean ± standard deviation is reported for continuous variables. Outcomes were calculated with IBM SPSS Statistics, using the paired-sample t-test. Statistical significance was defined as $p < 0.05$. Endpoints were the average of the 3 repeated meals per subject and compared between OL and CL, OL and CLP and CL and CLP. The primary outcome measure was mean postprandial glucose excursion from baseline to 5.0 h post-meal using the 5.0 h area under the glucose curve (AU glucose).. Other endpoints included percent of SG values in various glucose ranges (i.e., 180 mg/dL, and >250 mg/dL), insulin delivered (i.e., total meal dose, and precent of. auto correction and auto basal of total meal dose).

Sample size: Sample size was determined using WINPEPI sample size calculator program based on the following assumptions: 1) Primary outcome: AUC glucose 300 minutes post meal mean difference on open loop therapy using standard of care bolus vs. AID system. 2) Comparison will be conducted using the paired-T statistic. 3) In a previous study of 19 individuals with type 1 diabetes an AUC glucose 300 minutes of 51.2 (mmol/l/min) with a SE of 5.3(mmol/l.) was found [15]. SD =SE (5.3) * $\sqrt{n}(\sqrt{19})$=23.1022. Therefore, a sample size of 12 is estimated to provide 80% power at 5% significant level, to detect a potential mean difference in glucose AUC of at least 20 (mmol/l/min).

Results

Participant characteristics

A total of 15 participants were recruited, of whom 13 (11 men) completed the protocol. Two participants withdrew consent and data was excluded due to failure to complete the protocol. Incomplete data due to lost sensor signal or other technical issues were excluded. Baseline characteristics are presented in Table 2. Participants had a mean age of 46.8 ±12.8 years, a diabetes duration of 20.1± 12.3 years, HbA1c of 6.7±1.2% and a BMI of 25.5 ±3.6 Kg/m^2. The mean duration of insulin pump therapy was 12.8 ±7.0 years. Figures 2&2b demonstrate the mean postprandial glucose for 5.0 h and for the overnight period after the meal tests (0 to 10 hours postprandial).

Characteristics (n=13)		
Sex	Male	11 (84.7%)
	Female	2 (15.3%)
Duration of diabetes, (years)		20.1±12.3
Duration of insulin pump therapy, (years)		12.8 ±7.0
Age, (years)		46.8 ±12.8
HbA1c, (%)		6.7±1.2
BMI, (kg/m^2)		25.5 ±3.6
Data are presented as n (%) or mean ± SD		

Table 2: Summary of clinical participant characteristics.

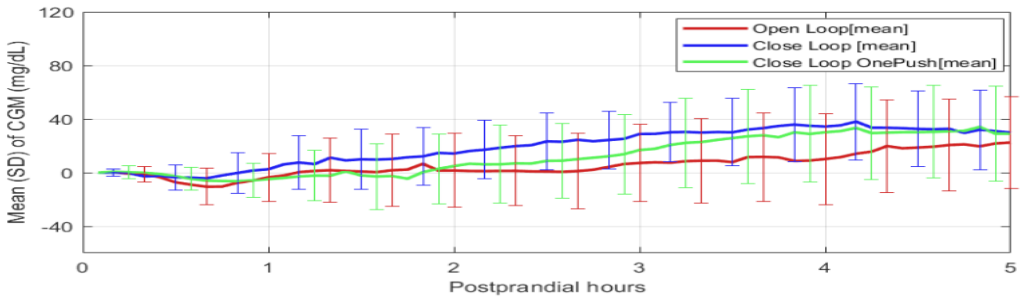

Figure 2: Postprandial glucose profiles (mg/dL) from 0-300 min for 3 different meal handling approaches for a HFHP meals in adults with T1DM.

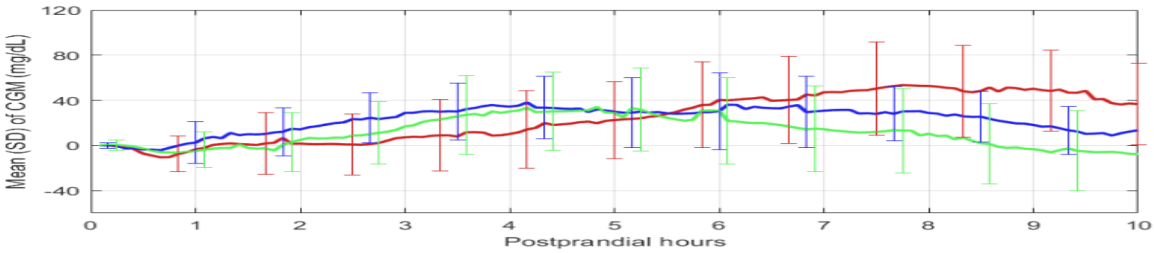

Figure 2b: Overnight postprandial glucose profiles (mg/dL) for 3 different meal handling approaches for a HFHP meals in adults with T1DM.

OL Versus CL

No significant differences in the 5.0 h AUC glucose were observed between the groups (6801.1.3±7750.6 mg/dL/min, and 7890.9.6±7210.8 mg/dL/min for OL and CL, respectively; p=0.435). When using OL, there was a tendency for increased time in hypoglycemia (defined as SG <70 mg/dL, % time) at 5.0 h (10±15.3 % vs.4.7±6.2 %; for OL vs, CL, respectively, p=0.098). A similar post-prandial insulin delivery at 2.0 h post-meal was observed between groups (8.1±4.3 units vs.7.4±2.5 units, P=0.15), while significantly higher amount of insulin was delivered using CL between 2.0 to 5.0 h post-meal (2.5±1.5 units vs. 4.8±4.3 units; p=0.015). Time in target range (70-180 mg/dL, %) was comparable for OL and CL (76.2±22.7 % vs.83.6±20 %, p=0.26). (Tables 3)

When using CL, participants spent more time in the desired glucose range for the entire 10 hours post prandial, as reflected by a higher TIR (70-180 mg/dL, %) compared with OL (85.5±16.3% vs. 64.6±23.5 %; p=0.004), and with better mean SG (128.5±20.9 vs. 143.7±35.2 mg/dL; p=0.05). Delivering insulin using OL increased time in hyperglycemia and in extreme hyperglycemia (defined as SG>180 mg/dL and SG>250 mg/dL, respectively). In addition, incidence of hypoglycemia during 10 hours postprandial was increased using OL compared to CL ((6.9±7.5 % vs.3.3±4 %; p=0.029) while insulin delivery was similar (14±6.7 units vs.16.2±9.6 units for OL vs. CL, respectively; p=0.161). Moreover, the standard deviation of glucose and the coefficient of variation were significantly lower with CL as compared with OL (p=0.0095 and p=0.0235; respectively). (Table 4, Figure 3)

Dosing approach, parameter	OL	CL	CLP	P value		
				OL-CL	OL-CLP	CL-CLP
Mean SG, mg/dL	124 (34.2)	125.4 (26.4)	142 (34.4)	0.50495	0.08101	**0.02841**
<54 mg/dL, %	1.4 (2.9)	1 (2.2)	0.1 (0.5)	0.42188	0.21114	0.19788
<70 mg/dL, %	10 (15.3)	4.7 (6.2)	4.9 (11.6)	0.09807	0.43488	0.94163
70-180 mg/dL, %	76.2 (22.7)	83.6 (20)	74.6 (24.8)	0.26002	0.88914	0.05822
>180 mg/dL, %	13.8 (21.9)	11.7 (19.8)	20.6 (25.2)	0.88923	0.52323	0.08088
>250 mg/dL, %	1.2 (4.4)	0 (0)	2.8 (7)	0.14794	0.4837	0.13349
PP peak, mg/dL	175.9 (43.7)	170.2 (37.9)	192.9 (53.9)	0.6247	0.61233	0.05667
PP peak from baseline , mg/dL	56.3 (42.2)	64.3 (46.2)	63.9 (51.8)	0.61558	0.64053	0.91508
Post 1hr from baseline, mg/dL	-2.3 (37.7)	2.4 (37)	-4 (28.9)	0.5199	0.6425	0.79184
Post 2hr from baseline, mg/dL	2.4 (55.5)	14.9 (43.4)	6.4 (55.5)	0.99088	0.44166	0.6492
Post 3hr from baseline , mg/dL	5 (57.2)	28.7 (44.6)	19.8 (64.9)	0.10252	0.27735	0.69175
Post 4hr from baseline, mg/dL	8.5 (66.1)	34.9 (56.4)	34.4 (74.9)	0.1929	0.0313	0.92768
Post 5hr from baseline, mg/dL	18 (74.2)	27 (70)	19.9 (54.1)	0.99031	0.97274	0.97731
PP AUC from baseline, min x mg/dL	6801.1 (7750.6)	7890 (7210.8)	6804.8 (7202)	0.69336	0.97764	0.81966
Total Insulin 0-2 h, U	8.1 (4.3)	7.4 (2.5)	8.1 (3.4)	0.15244	0.9074	0.64778
Total Insulin 2-5 h, U	2.5 (1.5)	4.8 (4.3)	5.6 (2.8)	**0.01534**	**0.00052**	0.48132
Pct. auto corr. bolus, %: 0-2 h	NA	11.7 (12.4)	13.6 (9.8)	NA	NA	0.9927

Pct. auto corr. bolus, %: 2-5 h	NA	33.9 (18.7)	37.6 (19.1)	NA	NA	0.68305
Pct. auto basal, %: 0-2 h	NA	10.5 (8)	12.3 (7.9)	NA	NA	0.39335
Pct. auto basal, %: 2-5 h	NA	61.3 (28.7)	53.1 (28.8)	NA	NA	0.21443
Patient derived boluses (bolus insulin-auto corrections=)	7.2 (3.2)	6.1 (2)	6.4 (2.2)	**0.02091**	**0.03876**	0.80044
PP insulin of TDD (%)	27.3 (8.8)	27.4 (6.4)	28.3 (7.1)	0.22833	0.16402	0.30747

Table 3: 5.0-hr post prandial Glycemic outcomes following a high protein and a high fat meal.

Dosing approach, parameter	**OL**	**CL**	**CLP**	**P value**		
				OL-CL	**OL-CLP**	**CL-CLP**
Mean SG, mg/dL	143.7 (35.2)	128.5 (20.9)	141.4 (26.7)	**0.04933**	0.14455	**0.04035**
SD	43.6 (19)	31.1 (13.4)	34.4 (16.3)	**0.00951**	**0.048**	0.32224
Coefficient of variation	0.3 (0.1)	0.2 (0.1)	0.2 (0.1)	**0.02351**	0.11067	0.98045
<54 mg/dL, %	0.9 (1.6)	0.6 (1.3)	0.1 (0.3)	0.88628	0.23744	0.20051
<70 mg/dL, %	6.9 (7.5)	3.3 (4)	2.6 (5.8)	**0.02906**	0.13534	0.56599
70-180 mg/dL, %	64.6 (23.5)	85.5 (16.3)	78.2 (23.7)	**0.00433**	**0.03684**	0.11472
>180 mg/dL, %	28.6 (24.1)	11.3 (15.6)	19.1 (24.1)	**0.00967**	0.07658	0.11074
>250 mg/dL, %	5 (9.5)	0 (0)	2.4 (6.7)	**0.01326**	0.05468	0.13824
PP AUC from baseline, min x mg/dL	36497 (21553)	21839.7 (181)	13321.6 (10472.1)	0.44421	0.0609	0.76821
Total Insulin, U	14 (6.7)	16.2 (9.6)	16.8 (8.7)	0.16163	0.34522	0.9429
Pct. auto corr. bolus, %: 5-10 h	NA	27.9 (15.1)	29.5 (22.9)	NA	NA	0.90762
Pct. auto basal, %: 5-10 h	NA	63.8 (29.5)	63.9 (28.4)	NA	NA	0.67061
Patient derived boluses (bolus insulin-auto corrections=)	7.6 (3.6)	6.8 (2.5)	7 (3.1)	0.20119	0.18099	0.76602
PP insulin of TDD (%)	34.2 (12.7)	35.3 (10.4)	34 (10.1)	0.29413	0.58572	0.81583

Table 4- 10.0-hr post prandial Glycemic outcomes following a high protein and a high fat meal.

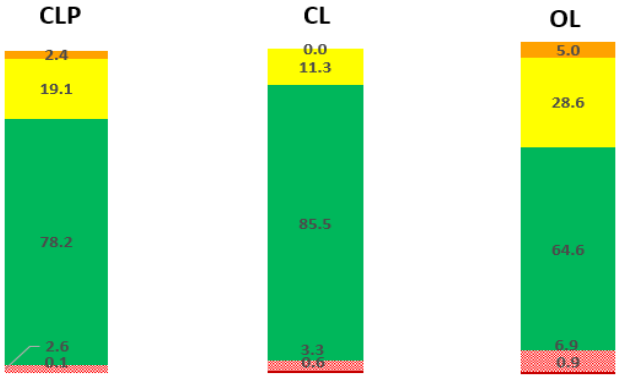

Figure 3: Overnight TIR (%) for 3 different meal handling approaches for a HFHP meals in adults with T1DM.

OL Versus CLP

No significant differences in 5.0 h AUC glucose were observed for the two approaches (6801.1.3±7750.6 mg/dL/min and 6804.8±7202.0 mg/dL/min for OL and CLP, respectively; p=0.977). Significant differences were observed in total insulin delivery at 2.0-5.0 h post-meal (2.5±1.5 units vs. 5.6±2.8 units for OL and CLP respectively; =p<0.001) yet with similar rates of hypoglycemia (define as SG<70) (p=0.434) (Table 3)

When the 10-hour postprandial period was analyzed, using a CLP approach resulted in increased TIR^{70-180} (78.2±23.7 % vs. 64.6±23.5 % for CLP and OL, respectively; p=0.036). while mean SG, was comparable (141.4±26.7 mg/dL vs.143.7±35.2 mg/dL, respectively; p=0.144). Similarly, insulin doses were not significantly different between the two groups (p=0.345).

CL Versus CLP

When comparing CL and CLP , mean SG were significantly lower with CL (127±17.7 mg/dL vs. 138±23.3 mg/dL, p=0.028), and with approximately 9% more time spent in target glucose (TIR^{70-180} of 83.6± 20 % vs. 74.6±24.8 % for CL and CLP respectively; p=0.058). No significant differences were observed in hyperglycemia (SG >180) and extreme hyperglycemia (SG> 250) (p=0.08 and p=0.13). The participants received a comparable amount of autocorrection both at 0.0-2.0 h (p=0.99) and 2.0-5.0 h post meal(p=0.683). (Table 3)

During the 10.0-hour postprandial period, CL presented superiority in mean SG compared to CLP (128.5±20.9 mg/dL vs. 141.4±26.7 mg/dL; p=0.04). There were no significant differences in any other glucose metrics as presented in Table 4.

OL Correction boluses:

Out of a total of 41 meals on OL, 30 manual corrections were given throughout the night (73% of meals). As per protocol, no correction boluses were given using the CL or CLP approach.

Discussion

To the best of our knowledge, this is the first study to compare the current standard of care for meal management using open loop SAP+PLGM with an advanced hybrid closed loop system for complex meals, rich in fat and protein. This study highlights three important findings: first, it demonstrates that OL utilizing dual wave boluses and carbohydrate adjustment for fat and proteins has no advantage in the early (5 hours) postprandial period. However, in the extended observation time of 10 hours, the use of CL system with precise carbohydrate counting was significantly superior for controlling delayed hyperglycemia associated with HPHF meals compared with OL, with significantly better mean SG, and with less tendency to hyperglycemia and hypoglycemia. Secondly, simplified, carbohydrate counting-free approach, provides better glycemia compared with current standard of care.

Automated insulin delivery systems have been demonstrated to improve glycemia for people with T1D [14]. While the burden associated with diabetes management is significantly reduced using these advanced technologies, users continue to struggle with meal announcement, which is considered one of the major burdens for PWD [16]. Complex meals consisting of HPHF are the most challenging to manage in both early and late postprandial periods. Several strategies have been implemented to address this issue including various timing and patterns of blousing, such as dual bolus, split bolus, or extended bolus, as well as different partitioning schemes between early and late phases of the meal (usually 70/30% or 50/50%). Others, recommend on different protocols for conversion of protein and fat content to carbohydrate equivalents, and modifications of the carbohydrate to insulin ratio [17]. While such approaches may result in improved post-prandial glycemia, they often impose additional layers of complexity for many PWD. The AID system M780G is geared toward burden reduction while safety improving glycemic outcomes. The burden reduction is exemplified by requiring only carb estimation and announcement prior to a meal, with no other requirement as bolus type decisions. This study provided the proof that indeed, with these minimal requirements, the AID MM780G system provides superior glycemia following complex meal consumption in comparison it to the best current practice in an open loop mode. We further provide evidence that even a simpler approach, that entirely excludes the need for carbohydrate assessment was favorable to OL and only slightly less effective than CL with precise carb estimates. Furthermore, the results support that CL therapy with a single bolus prior to a HPHF meal initiation provides comparable glycemia to complex bloused as dual wave, split boluses etc.

Our results have important implication for patient education and suggest that patients can be recommended to bolus before HPHF meals accounting only for the amount of carbohydrates, without the need for burdensome calculations of additional insulin to account for the protein and fat content, and without the need to provide an additional late bolus for the delayed absorbed carbohydrates. Safety is well demonstrated in the study as, during the CL phases, the patients should not be concerned about night-time hyperglycemia or hypoglycemia, and that an AID system can adequately address the varying insulin requirements over night without the need for manual corrections.

This study provides the mechanistic explanation for the advantages of the AID system in addressing the postprandial glycemia of HPHF meals. With the AID algorithm used in this study, we found that CL provides similar total insulin delivered during the 10.0 h post HPHF meal in comparison with OL but with significantly reduced risk of hypoglycemia as it controlled the rate of delivery based on real-time glucose response thus controlling for the substantial intraindividual variability in insulin requirements.

Our results are in line with expectations of PWD as reflected in an online survey where 63% of the participants reported they would either strongly or extremely like to be liberated from counting carbohydrates. Furthermore, 62% reported they find it difficult to calculate the right amount of insulin to certain types of meals like protein- or fat-rich meals [18].

In this study, we asked the participants to consume a pizza, a very common and readily available meal option, consumed by children, adolescents, and adults all over the world. Yet, this meal represents a significant challenge for PWD, as it required the integration of all the above-mentioned skills to achieve an adequate post glycemia. The ability of CL systems to automatically adjust the insulin doses according to the glucose levels can be the substitute for accurate carbohydrate counting, fat and protein assessment and modifications of insulin delivery pattern and thus allow more people with T1D to eat a wider variety of foods with greater freedom and significantly less burden.

The limitation of the study is that all test meals were consumed at dinner time, to minimize the possible confounding factors that could diminish the power to detect a difference in glucose excursions, thus limiting the generalizability of the results to other periods of the day. In addition, while no sex-dependent differences in meal absorption were previously reported, most of our participants were men, which limits our ability to conclude regarding the glycemic response among women. Furthermore, we studied only adult's participants and did not examine the potential interaction with physical activity, alcohol consumption among other factors that may affect glycemic response.

The advantage of the study is the repeated measures to overcome the mark intraindividual variability in glucose meal responses that challenge studies of this sort. All identical meals were consumed under identical conditions and repeated 3 times in each treatment modality, controlling for pre and post meal potential confounders with a precise assessment of meal composition using a gold standard chemical method. The study examined both short (5 hours) and long (overnight) glycemic effects extending up to 10.0-h post meal, given the prolonged effects on glycemia of such meals. Another advantage is the tightly monitored, daily verification of compliance and adherence with protocol.

In conclusion, the study provides evidence that the use of the AID system MM780G can successfully and safely control complex HPHF meals with simplified meal management approach. This, in turn, may lead to the development of new dietary recommendations that are compatible with AID systems, with an emphasis on simplicity, broader selection of foods with more complex composition, decrease disease burden and improvement of patient satisfaction and quality of life. Such an approach may also allow providers to offer AID to PWD who have traditionally considered to be challenging candidates for advanced diabetes technologies due to inability to count carbohydrates or who were overwhelmed by meal management requirements.

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