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Advanced hybrid closed loop (artificial pancreas) and carbohydrate count in type 1 diabetes

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Abstract.
BACKGROUND: Postprandial Glucose Excursion (PPGE) control is one of the goals of diabetes therapy. Patients should count meal carbohydrates but it is often inaccurate. Automated Advanced Hybrid Closed Loop (AHCL) systems may overcome carbohydrate count mistakes and aid to improve PPGE control.
OBJECTIVE: To evaluate the effect of switching from manual Sensor Augmented Pump (SAP) to AHCL on PPGE in Type 1 Diabetic (T1D) subjects.
METHODS: In 15 T1D patients using manual SAP, the Area Under the Curve (AUC) after breakfast, lunch and dinner was calculated for two weeks before (T0), immediately (T1) and 3 months (T2) after switching to 780 G AHCL system. Total Daily Dose (TDD), Time Above/Below/In Range (TAR, TBR, TIR), BMI, A1c, lipid profile and Treatment Satisfaction Questionnaire (DTSQ) were considered.
RESULTS: A significant reduction in AUC was observed for breakfast and dinner at T2 and for lunch and dinner at T1. TIR increased, while TAR and TBR reduced significantly from T0 to T1 and T2. For A1c, BMI and plasma lipids no statistically significant differences were observed, although A1c decreased from 7.2% to 6.8%. TDD increased significantly, due to the automatic correction boluses. DTSQ score at T2 was 33 (range 32–34, max 36).
CONCLUSIONS: After switching to AHCL, PPGE decreased rapidly by automatic correction boluses, without weight gain. Meal management simplification and glucose control improvement were associated with high satisfaction scores.

Keywords: Glucose metrics, insulin pump, postprandial glucose excursion, type 1 diabetes

1. Introduction

The increasing utilization of Continuous Glucose Monitoring (CGM) systems in the management of type 1 diabetes (T1D), have enabled the use of new glucose metrics based on continuous data. These metrics complement the traditional pillars of glycemic targets: Fasting Blood Glucose (FBG), Postprandial Glucose (PPG) and

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glycosylated hemoglobin (A1c). Though PPG contributes significantly to the overall glycemic load, especially in patients with relatively good glucose control, and is an independent cardiovascular (CV) risk factor [1–5], it was not included in the 2019 international expert consensus guide, in the ten most useful CGM derived parameters for use in routine clinical practice [6].

Postprandial Glucose Excursion (PPGE) can be calculated from CGM tracing as the Area Under the Curve (AUC) spanning from the time preceding the meal and ending 2 hours post the start of the meal. The calculated PPGE evaluates not only glucose peak intensity, but also amplitude and duration [7].

Advanced Hybrid Closed Loops (AHCL) systems are more efficient in improving glucose control than conventional insulin pumps [8–10]. This improvement is recognized very early after the start of the therapy [11, 12]. However, there is paucity of data on the effect of these automated insulin devices on PPGE control.

Aim of this study was to evaluate the effect of switching from manual mode of Sensor Augmented Pump (SAP) to the 780 G AHCL® system (automated "Smartguard"® model) on PPGE (represented by AUC) in T1D subjects.

The second endpoint was the evaluation of CGM metrics, metabolic and clinical parameters before and after switching of the therapies, as well as treatment satisfaction.

2. Materials and methods

2.1. Study design and population

This was a monocentric observational ("retrospective-prospective") study carried out at the Diabetes Unit of San Camillo – Forlanini Hospital in Rome, Italy, between March and November 2020. Consecutive people with T1D using open loop Continuous Subcutaneous Insulin Infusion (CSII) therapy for at least five years with automatic insulin suspension before low glucose (SAP therapy – Medtronic 670® predominantly in manual mode) who started 780 G AHCL system (MM780G®) were enrolled. The study data was accumulated during the routine follow up of these patients by a multidisciplinary diabetes care team consisting of diabetologists, nurses and certified nutritionists/dietitians.

The switch was a normal upgrade of technological systems at the end of the guarantee of the previous model, maintaining the same insulin analogue. The 670G® auto mode was used by patients discontinuously and, in any case, before switching to MM780G® a routine couple of weeks reset period in manual mode was required.

The inclusion criteria were: (i) aged $\geq$ 18 years, (ii) consumption of 3 main meals/day and (iii) able to sign the informed consent. The study was approved by the territorial ethical committee and a written informed consent was obtained from all participants.

2.2. Meal characteristics

Patients had a personalized meal plan, based on sex, age, weight, activity level and specific clinical needs. Energy intake was set to 25–30 kcal/kg/day; protein intake 1.0–1.1 g/kg/day with a particular recommendation to include plant-based food (legumes) 2–3 times a week; carbohydrates 40–50% of the total caloric intake; fiber intake $\geq$ 15 g/1000 kcal; fats aroud 30% of the total energy intake with a high polyunsaturated+monounsaturated/saturated fat ratio and the Mediterranean-style diet was encouraged [13]. A carbohydrate-counting retraining was performed during the visit to review the settings of the device.

2.3. Postprandial glucose excursion calculation

PPGE was calculated as AUC of the glucose variation between the beginning of the meal and the next two hours. The trapezoidal rule was applied [14]: for each curve 4 glucose sensor values were considered (at the

beginning of the meal, 30', 60' and 120' later). The breakfast, lunch and dinner AUC was calculated in each patient for 15 consecutive days before the switching to AHCL (T0), first two weeks after switching (T1) and two weeks after 3 months of use (T2). Average AUC for each daily meal was calculated per person. For comparison - the mean of the individual average values at T0, T1 and T2 were used.

2.4. Insulin daily dose calculation

Daily insulin dose was obtained from the Carelink TM ® platform at T0, T1 and T2. Total daily dose (TDD) included algorithm driven basal dose (BDD), automated delivered correction boluses (CDD) and user initiated prandial dose (PDD). For comparison - the mean of the individual averages values at T0, T1 and T2 were used.

2.5. Other parameters

Glucose metrics: Time In Range – TIR (70–180 mg/dL, %), Time Above Range – TAR (>180 mg/dL, %), Time Below Range – TBR (<70 mg/dL, %), Glucose Management Indicator – GMI (%) and Body Mass Index – BMI (calculated as a ratio between weight in kilograms and height in meters squared), A1c (% and mmol/mol, HPLC method), total cholesterol (mg/dL), HDL-cholesterol (mg/dL) and triglycerides (mg/dL) at T0 and T2 and were considered.

At the end of the study (T2) the Diabetes Treatment Satisfaction Questionnaire (DTSQ) was administered [15]. DTSQ assesses patient's satisfaction with the current diabetes treatment. It contains 6 questions, each of which ranges from 0 to 6 (total score 0 – 36): higher score indicates higher treatment satisfaction.

2.6. Statistical analysis

ANOVA One Way test was used for statistical analysis. Continuous variables were expressed as mean ± standard deviation. Significance was defined as p value < 0.05.

3. Results

3.1. Subject characteristics

15 subjects (80% males, mean age 51 ± 12.79 years) with disease duration of 24 ± 15.48 years and CSII duration of 9 ± 7.67 years were enrolled. The description of the sample including the medical history is summarized in Table 1.

3.2. Postprandial glucose excursion (PPGE)

The average AUC of the three meals at the three time points are reported in Table 2. No significant differences between the AUC at the three meals were noted at the individual time points. However, between the time points, significant reduction in AUC was observed for breakfast and dinner between T0 to T2 ($p < 0.05$) and for lunch and dinner between T0 to T1 for ($p < 0.05$) (Table 2).

3.3. CGM metrics

In Table 3 the CGM metrics at T0, T1 and T2 are reported. TIR increased significantly from T0 to T1 and T2 ($p < 0.005$). Similarly TAR and TBR reduced significantly from T0 to T1 and T2 ($p < 0.005$). GMI decreased from T0 to T1 and T2, but did not reach statistical significance.

Table 1
Description of the sample

Males /Females (%)	12/3 (80/20)
Age (years)	51 (±12.79)
Disease duration (years)	24 (±15.48)
CSII duration (years)	9 (±7.67)
Arterial Hypertension (%)	3/16 (18.75)
Cardiovascular events (%)	0/16 (0)
Non-proliferative retinopathy (%)	2/16 (12.5)
Microalbuminuria (%)	2/16 (12.5)
Neuropathy (%)	4/16 (25)
Foot ulcer (%)	0/16 (0)
Thyroiditis (%)	4/16 (25)
Previous malignancy (%)	2/16 (12.5)
Depression (%)	2/16 (12.5)

Table 2
Mean AUC of the three meals

	Breakfast	Lunch	Dinner
AUC T0	28023.3 ± 5676.7	26617 ± 4344	27904.6 ± 5354
AUC T1	22587.1 ± 3854	**22224 ± 3653***	**23145 ± 3271***
AUC T2	**22450 ± 4578****	23237 ± 5145	**23001.3 ± 4306****

Mean ± SD, $^{*}p < 0.05$ T0 vs. T1, $^{**}p < 0.05$ T0 vs. T2. Area Under the Curve (AUC).

Table 3
CGM metrics

	TIR (%)	TAR (%)	TBR (%)	GMI (%)
T0	66.8 ± 15.0	28.0 ± 15.0	6.3 ± 11.4	7.0 ± 0.006
T1	**79.1 ± 9.3***	**18.4 ± 10.0***	**2.3 ± 2.7***	6.6 ± 0.0031
T2	**79.0 ± 9.5****	**18.1 ± 8.4****	**2.5 ± 2.5****	6.6 ± 0.0033

Mean±SD, $^{*}p < 0.005$ T0 vs. T1, $^{**}p < 0.005$ T0 vs. T2. Contiunous Glucose Monitoring (CGM), Glucose Management Indicator (GMI), Time Above Range (TAR), Time Below Range (TBR), Time In Range (TIR).

3.4. Total insulin daily dose

A significant increase of TDD was observed at T2 (from 39.81 u/day at T0 to 46.04 u/day at T2; $p < 0.05$). The significant change was in the increase of automated delivered correction boluses (CDD) from T0 to T1 ($p < 0.005$) and from T0 to T2 ($p < 0.0001$) (Table 4). There were no significant differences between insulin delivered as basal (BDD) or prandial (PDD) daily dose from T0 to T1 and T2.

Table 4
Total insulin daily dose

	TDD	BDD	PDD	CDD
T0	39.81 ± 8.11	19.24 ± 4.76	20.60 ± 4.70	0 ± 0
T1	42.45 ± 10.47	19.33 ± 3.48	23.67 ± 8.67	**3.10 ± 2.91**°
T2	**46.04 ± 11.96***	18.38 ± 7.39	24.29 ± 10.45	**4.92 ± 3.92**°°

Mean ± SD, *$p < 0.05$ T0 vs. T2,° $p < 0.005$ T0 vs. T1, °°$p < 0.0001$ T0 vs. T2. Total insulin (TDD), Basal (BDD), Prandial (PDD) and Correctional (CDD) Daily Dose.

3.5. Other parameters

A1c level was reduced from 7.2% (55.2 mmol/mol)±0.9 (10) at T0 to 6.8% (50.8 mmol/mol)±0.7 (8) at T2, without reaching the statistical significance. Also for BMI, total cholesterol, HDL-cholesterol and triglycerides we did not observe statistically significant differences (data not shown).

DTSQ score at T2 was close to the maximum value of 36: median value 33, interquartile range 32–34.

4. Discussion

PPG control is one of diabetes treatment goals [16]. The control of PPG is important as postprandial hyperglycemia triggers a metabolic and haemodynamic event cascade increasing CV risk [17–20].

Evidence from epidemiologic studies has demonstrated the association between PPG and CV risk, independently from A1c levels.

However there are some limitations and gaps in knowledge when implies to T1D, as most of these studies concern Type 2 Diabetes (T2D), and based on oral glucose challenge [4, 5, 21] or mixed meal models [22, 23] and not based on continuous glucose data as measured by CGM systems. It is plausible that the epidemiological and clinical data about PPG control and CV risk in T2D may be extrapolated also to T1D, particularly in long-term older patients. The progressive diffusion of CGM and FGM (Flash Glucose Monitoring) among T2D subjects, not necessary treated with intensive insulin therapy or CSII, has given more complete information and consciousness about dietary and therapeutic choices which is associated with better outcomes in terms of reduced A1c levels, glucose metrics [24–26] as well as hospital admissions [27].

Indeed, the primary measure of PPG control is the glucose measurement at 2 h after the beginning of the meal, with a goal of capillary plasma glucose of < 180 mg/dL (<10.0 mmol/L), although an ideal target is mentioned to < 140 mg/dL (<7.8 mmol/L) does not represent the full scope of the PPGE.

The main treatment goals in TID are to achieve a good glucose control, represented by A1c, to reduce glucose variability and to limit hypoglycemia: the technology (CGM, CSII, SAP and AHCL) helps to achieve these goals significantly and has allowed to establish the current glucose metrics [6]. A higher attention to PPGE is aligned with the evaluation of the educational intervention efficacy, in particular with a nutrient count and meal management patient's skills.

Although the PPGE is not included among the current glucose metrics, patients are educated to manage it by counting carbohydrates and considering the impact of other nutrients according to their own experience [28]. The study conducted aimed to shed light on the ability of Automated Insulin Delivery (AID) systems to control PPGE and compare to open loop systems. The two types of therapy differ in the approach to meal handling to prevent high PPGE. In open loop systems the user calculates the carbohydrates content of the meal and it is also recommended to take into account the carbohydrate equivalence of the fat and protein constituents of the

meal and to provide extended or dual wave boluses if slow absorbing meals are consumed. All this contributes to the complexity and burden of meal management. On the contrary, the 780G® AID system, requires the announcement of only an approximated carbohydrate content of the meal and the bolus is administered as a simple bolus, relying on the automated adjusted basal rates and automated correction boluses to mitigate the rise in PPG [29]. In addition, a safe meal module is part of the algorithm which reduces a calculated meal bolus if it is predicted (by model simulation) to reach a level lower than 70 mg in a 4 hour window. These measures simplify meal management and prevent late postprandial hypoglycemia. We aimed to assess the outcome of the automated approach to meal handling with the MM780G® system.

In our sample, the MM780G® system improved postprandial glucose early in the course of use, as demonstrated by the AUC decrease at T1, that was sustained for 3 months. The improvement was evident at lunch and dinner already in the first two weeks of use (T0 to T1; $p < 0.05$), and at breakfast and at dinner after 3 months (T0 to T2; $p < 0.05$). It has taken a longer time to reach the significant AUC decrease at breakfast. It may be due to the different insulin sensitivity in the morning observed in T1D patients [30] and due to the higher carbohydrate load with lower glycemic index of breakfast according to the Italian eating habits (milk, biscuits, oven-baked food) which may require a longer adaptation period of the system and specific patients skills (e.g. optimal timing of bolus delivery before eating).

TIR increased significantly from 67% to 80% already in the first two weeks of utilization; at the same time TAR reduced from 28% to 18.4 % at T1 and to 18.1% at T2; TBR from 6.3% to 2.3% and to 2.5% at T1 and T2 respectively. GMI was decreases from 7.0% to 6.6% (n.s.). Severe hypoglycemia was not reported. The results confirm the safety and efficacy of the meal handling approach of the MM780G® AID system, confirming previous studies [29].

BMI and plasma lipids changes did not reach the statistical significance confirming no negative effects on body weight, but it may be due to a short duration of the study.

The slight TDD increase after 3 months of AHCL start is not related to the body weight gain: the TDD increase has been observed also in children and adolescents after 6 months [31] or 1 year [32] of AHCL use: in these subjects it seems to be due to the puberal physiological increase. In a previous study, adults transitioning from SAP with low glucose suspend system (LGS) or predictive low glucose suspend system (PLGS) to AHCL, were observed having a decrease in basal insulin with a simultaneous increase in bolus insulin, which is most likely due to self-correction [33].

In our sample the TDD increase was mostly due to the increase in automated correction doses. We thereby hypothesize that the automated insulin delivery of basal insulin and the automated correction dosages where superior to the practice of prolonging and splitting meal boluses as it provides the amount of insulin required every 5 minutes in real time. It is also likely that this system is more efficient in PPGE control as it can overcome carbohydrate (CHO) counting mistakes, the inability to fully recognize glycemic index, food processing and other mixed meal nutrients (fat, protein, fiber). It is of crucial importance to understand if the TDD increase can lead to long-term negative effects, such as weight gain or insulin resistance.

We were interested to assess the users' attitude toward the algorithm "taking over" decisions on their therapy and the lack of features such as prolonged and dual boluses. The DTSQ average value documented a high level of satisfaction with treatment (median score was 33 with the maximum score of 36 [15]). Satisfaction with treatment is an important mediator of patient adherence and achievement of targets. The increase in satisfaction can, in fact, be due to the simplification of the meal bolus calculation which is laborious and not always effective to control PPGE. It is important to mention that these patients received the support of the multidisciplinary team and education for CHO counting which are necessary to manage the meal properly and to limit PPGE beyond the algorithm properties.

The strength of this real-life observational study is the inclusion of consecutive patients under regular clinical follow up at our center. Key limitations are the short duration, the low sample size, the lack of a control group and the single center nature of the study which is limiting the generalizability of the results.

5. Conclusions

Switching to an AID-MM780G® system decreased PPGE rapidly and in a sustainable way. This was achieved by increasing the automated insulin correction dose. Automation was effective in providing insulin in a way that compensated for miscalculation of meal constituents, utilizing simple premeal bolus. The simplification of meal management and the improved glycemic control, was associated with high user satisfaction scores.

Our data suggest also to consider AUC as a PPGE related independent glucose metric, specifically useful to underline the impact of dietary choices on glucose profile, and to verify the efficacy of multidisciplinary nutritional educational therapy and the implementation of healthy dietary habits.

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Ethic statement

The study was approved by the territorial ethical committee of Lazio, Area 4, protocol number 46-2024 of 22 May 2024.

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Conflict of interest statement

The authors have no conflict of interest to report.

Author contributions

All authors contributed equally to the writing of this manuscript. All authors have read and agreed to the published version of the manuscript.

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