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Original Article

An early prediction of postprandial glycemia evolution using the MD001 algorithm: a muticentre prospective trial

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Abstract

To date, the closed-loop system represents the best commercialized management of type 1 diabetes. However, mealtimes still require carbohydrate estimation and are often associated with postprandial hyperglycemia which may contribute to poor metabolic control and long -term complications. A multicentre, prospective, non-interventional clinical trial was designed to determine the effectiveness of a novel algorithm to predict changes in blood glucose levels two hours after a usual meal. Forty patients were included, and 765 meals were analyzed of which 278 were followed by a postprandial hyperglycemic event i.e. value > 160 mg/dL two hours after the start of the meal. The developed algorithm correctly predicts the postprandial hyperglycemia risk or absence of risk in 87% of cases. The results suggest that early prediction of the glycemic evolution within a few minutes after the end of a meal can considerably improve the postprandial hyperglycemia management and thus reduce the associated emotional burden. The study was supported by M-DT1 SAS, France.

Keywords: Type 1 diabetes, Postprandial hyperglycemia, Algorithm.

1. Introduction

Type I diabetes (T1D) is an autoimmune disease caused by destruction of insulin-secreting cells of the pancreas [1]. Insulin deficiency is characterized by high hyperglycemia which can rapidly lead to massive glycosuria and ketoacidosis [2].

Maintaining glycemic control is the primary goal of diabetes management, but post-meal hyperglycemia (PPH) accounts for a large part of poor metabolic control. Such hyperglycemia phase often lasts several hours and represents a significant risk of chronic complications (e.g. micro and macro vascular, retinopathy, neuropathy, joint, dental, etc.) [3,4]. The specific postprandial period is however still little or not enough considered. Therefore, it is essential to propose solutions that drastically improve the postprandial blood glucose management especially because in most cases they account for poor glucose control and glycemic variability in patients with T1D. Consequently, any significant impact on their duration will result in reduction of complications [5-7].

We have developed an algorithm able to predict whether blood glucose levels will return to values below 160 mg/dL two hours after the start of the meal (i.e. international diabetes association's recommendations) [8]. Briefly, based on just two variables (time and glycemia respectively before and after meal), the algorithm determines what would normally be the time and the height of the post-prandial (PP) peak. We have previously demonstrated and patented that when the realization of such calculations effectively match with the future PP peak characteristics (that will be measure and shown by the Continuous Glucose Monitoring (CGM) System), blood glucose levels will then reach values below 160 mg/dL within the next two hours".

Therefore, the aim of this algorithm calculations consists in a sequential way:

i) to detect as early as possible (at the PP peak occurrence calculated by the algorithm), the risk of persistent values of blood glucose above 160 mg/dL two hours after the start of the meal

ii) to prevent or drastically reduce the PP hyperglycemic phase duration by allowing the patient with T1D to deliver a corrective insulin dose as soon as possible.

In this study, no modification of the patient's protocol for corrective insulin dose was proposed in case of hyper-

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glycemia. The purpose of this study is only to validate the algorithm effectiveness by predicting the risk or absence of risk of a hyperglycemic event following a usual meal (breakfast, lunch or dinner).

Closed loop systems or **"artificial pancreas"** are automated insulin delivery systems that use a continuous glucose monitor, an insulin pump, and a control algorithm to adjust insulin in real time, aiming to keep blood glucose levels within a target range. They a**re** now the trends for T1D management strategies and have significantly improved the patient quality of life. However, meal time still requires carbohydrate estimation and the time spent in PPH is often superior at two hours. While we do believe that the perfect T1D management in the future will indeed require synergistic actions of many different algorithms, the evolution of the above technology may pave the way to the full autonomy of diabetic patient during meal (with no need of carbohydrate counting).

2. Materials and methods

2.1. Trial design

The aim of this two-center (CHITS-Hôpital Sainte Musse, Toulon and APHM-Hôpital La Conception, Marseille), prospective, non-interventional study was to demonstrate the efficacy of a new algorithm (MD001) to anticipate the PP glycemic profile in T1D patients. The glycemic values calculated by the algorithm were retrospectively compared to those obtained using the continuous glucose monitoring systems.

2.2. Participants

Eligible patients were adult patients living with T1D and using a CGM System. The exclusion criteria were: i) patient not using a CGM system, ii) presence of a disease other than diabetes (i.e. bulimia, anorexia), iii) patient on dialysis, iv) known history of drug or alcohol abuse, v) patient under judicial protection, vi) person deprived of liberty, vii) patient in psychiatric care, viii) patient admitted to health or social institution for purposes other than research, ix) any reasons that might interfere with the study objectives evaluation.

From December 2021 to December 2022, 40 patients were included. The participants flow chart is presented in Figure 1.

2.3. Enrollment and patient follow-up

Eligible patients cared for T1D were informed of the study during a follow-up visit as part of daily practice. All enrolled patients provided informed consent to participate in the study. They were assigned a patient code and were asked to monitor their sensor glucose (SG) levels before and after each meal for 15 days (SG dataset), as well as provide their daily SG profiles from the associated app of their CGM system. The glucose dataset and daily SG profiles were collected at the end of the 15 days during a follow-up visit as part of routine practice.

2.4. Outcome

The primary endpoint was to assess the overall algorithm reliability in predicting the presence or the absence of PPH occurrence lasting more than 2 hours with values greater than 160 mg/dL. The matching of the of PP peak parameter's calculations (time (T1) and height (G1)) with the real PP peak time and heigh values (T2 and G2) occurring normally after the meal is associated with an absence of hyperglycemic risk.

Then, to test the reliability of the algorithm to predict risk or the absence of risk, the PP peak values calculated by the algorithm were compared to actual PP SG peak values. Actual PP peak values (T2 and G2) were collected manually from daily glucose profiles obtained from the continuous glucose monitoring systems.

Based on an accepted margin of error (ΔG and ΔT) (20% on the glycemia peak height (ΔG ± 20%) and 20 minutes on the peak time (ΔT± 20 min)), a correct prediction of the time and height of the peak were correlated with an absence of hyperglycemic risk (SG < 160 mg/dL two hours after the start of the meal). A false prediction of the height and time of the peak was thus associated with a risk of hyperglycemia (SG value greater than 160 mg/dl two hours after the start of the meal).

PPH presence or absence was assessed by manually checking SG changes two hours after the start of the meal on daily SG profiles. A SG level stabilized at values less than or equal to 160 mg/dL two hours after the start of the meal was considered to be an absence of hyperglycemia. A SG level greater than 160 mg/dL two hours after the start of the meal was considered as an hyperglycemic phase.

Some meals were excluded from the Per Protocol analysis in case of:

- SG values at the beginning of the meal were greater than or equal to the SG value at the end of the meal;
- SG values at the beginning of the meal and at the end of the meal were too close (difference of less than or equal to 10 mg/ml);
- The PP peak occurred before the end-of-meal SG measurements;
- The SG values were close to the detection limit values of SG sensors (< 45 mg/ml and > 280 mg/ml);
- The glucose profiles were missing or the measured values do not correspond to the values transcribed by the patient;
- Insulin correction was performed within two hours after PP blood glucose measurement;
- Food was consumed within two hours of PP SG measurements.

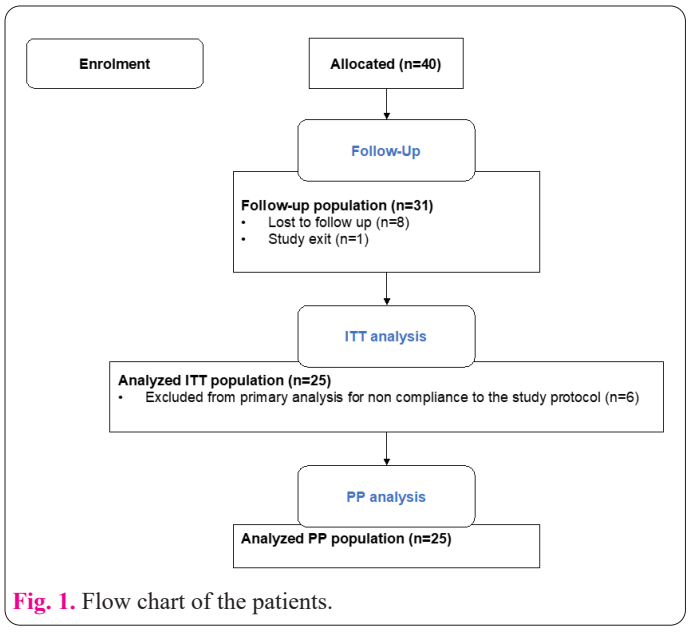

Fig. 1. Flow chart of the patients.

2.5. Statistical analyses

The intent-to-treat population (ITT) was defined as all the allocated meals (breakfast, lunch, and dinner) for which the full data set was available (pre- and post-meal SG values collected by the patient and associated daily glucose profile). It excluded all meals from 6 patients who did not collect PP SG correctly, as well as meals that lasted longer than two hours. The ITT population included the protocol violation listed above (e.g., SG values at the beginning of the meal greater than or equal to the SG value at the end of the meal).

The Per Protocol population included all meals for which the data set was available and the protocol was properly adhered to.

Normally distributed quantitative variables were described using the mean or median ± standard deviation and compared between treatments using the Student Test t-test. The algorithm efficiency was characterized using accuracy and recall [9].

Precision is essentially defined as the ratio of correctly predicted positive classes to all predicted positive classes. It can be expressed mathematically as:

Precision = TP / (TP + FP) (where TP is True Positives and FP is False Positives)

Recall is simply defined as a ratio between correctly predicted positive classes and all actually existing positive classes. It can be expressed mathematically as:

Recall = TP / (TP + FN) (where FN is False Negative)

2.6. Ethics

The study protocol and any amendments were reviewed and approved by a French "Comité de Protection des Personnes (n°ID RCB: 2021-A02599-32- CPP 1-21-109 / 21.03503.000059. This study was conducted in accordance with applicable regulatory requirements (UE regulation n°2016/679 and MR003 CNIL n°2018-154). It was registered at www.clinicaltrials.gov under the number NCT0515770 and title “Type 1 Diabetic Post Prandial Glycemia Evaluation Using an Algorithm (EGHYA)”. All research procedures were carried out in accordance with the Declaration of Helsinki.

3. Results

3.1. Baseline data

No significant differences were observed between women and men characteristics (Table 1). In particular, age (45,57 ± 15,39 vs 48,00 ± 21,46), body mass index (23,61 ± 3,79 vs 25,99 ± 3,99), diabetes duration (18,29 ± 14,65 vs 20,36 ± 13,46), and HbA1c (7,11 ± 1,03% vs 7,17 ± 1,05%).

3.2. Meal flow

The meal flow chart is shown in Figure 2. Meals analyzed were then assigned according to the SG values

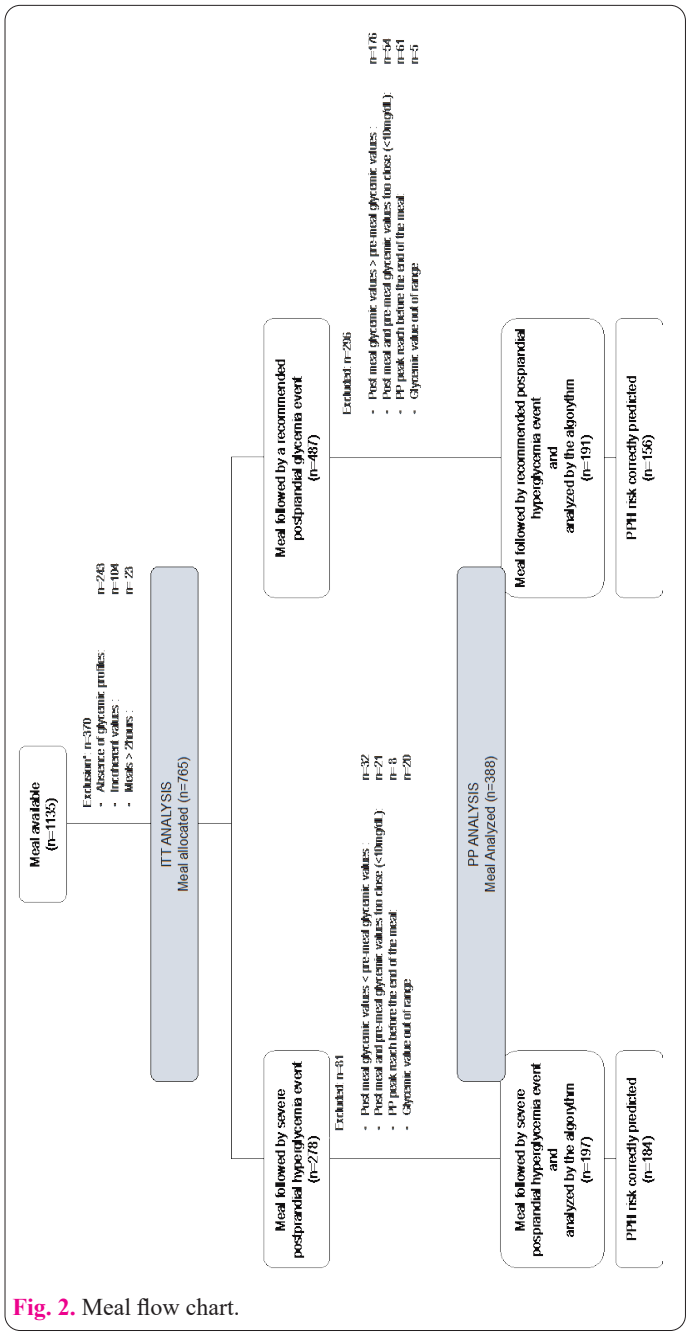

Fig. 2. Meal flow chart.

Table 1. Patient characteristics in intention to treat population.

	All patients		Women		Men		
	N	mean ± SD	N	mean ± SD	N	mean ± SD	p-value
Demographics							
Age (years)	25	46,64 ± 17,93	14	45,57 ± 15,29	11	48,00 ± 21,46	0,37
Height (cm)	25	169,40 ± 7,71	14	164,93 ± 5,95	11	175,09 ± 5,74	
Weight (kg)	25	71,00 ± 14,17	14	64,07 ± 9,73	11	79,82 ± 14,37	
BMI (kg/m2)	25	24,66 ± 3,98	14	23,61 ± 3,79	11	25,99 ± 3,99	0,07
Diabetes							
Age (years)	25	19,20 ± 13,89	14	18,29 ± 14,65	11	20,36 ± 13,46	0,36
HbA1c (%)	25	7,14 ± 1,02	14	7,11 ± 1,03	11	7,17 ± 1,05	0,44

reached two hours after the start of each meal.

- If SG levels were greater than 160 mg/dL, the meal was assigned as a meal followed by a severe PPH event.
- If SG levels were less than or equal to 160 mg/dL, the meal was classified as one followed by a **recommended postprandial (PP) glycemia event**, meaning that the postprandial glucose level remained within the target range **endorsed by the International Diabetes Federation (IDF), which defines acceptable PP glycemia as being below 160 mg/dL two hours after meal intake."**

Data were collected from 1135 meals available with globally a similar number of breakfasts, lunches and dinner (350, 401 and 384 respectively). A total of 370 meals were excluded from allocation (129 for breakfast, 85 for lunch and 156 for dinner) because of i) lack of SG values during the 2 hour-postprandial period (243 meals; 66%), ii) discordance between SG values reported by the patient and those collected from the daily SG profiles (104 meals; 28%), iii) meal duration superior to two hours (23 meals; 6%).

The ITT population consisted in 765 meals (278 were followed by a severe PPH event (36%) and 487 were followed by a recommended PP SG value (64%). A wide variability between patients with respect to the occurrence of severe PPH event was observed. Indeed, some patients have shown up to 70% of meals followed by a severe PPH event while other had few (median 33%) (data not shown)

The Per Protocol population consisted of 388 meals (197 were followed by a severe PPH event (51%) and 191 were followed by a recommended PP glycemia event (49%). A total of 377 meals were excluded from the Per Protocol population mainly due to a post-meal SG value similar to or lower than the pre-meal value (76%). Most meals excluded from the Per Protocol population were meals followed by recommended PPH (78%).

3.3. Outcomes

3.3.1. Prediction of the PPH risk

Severe PP hyperglycemia events were defined as events where blood glucose was greater than 160 mg/dL two hours after the start of a meal. Of the 278 meals followed by a severe PP hyperglycemia event, 197 could be analyzed by the MD001 algorithm. Meals excluded from the Per Protocol analysis (81) were mainly due to (i) blood glucose values measured after the meal too close to or lower than those measured at the start of the meal (65%) and (ii) SG values out of range (25%) (Figure 2). Of the 197 meals analyzed, MD001 correctly anticipated the PPH risk for 184 meals.

Regarding the ITT analysis, 66% of meals followed by a severe PPH event were correctly anticipated within minutes of the meal ending. However, as shown in Figure 3, there was a wide variability between patients, with patients having up to 100% of meals where the severe PPH event was correctly predicted by MD001 (median of 67%).

For the Per Protocol analysis of meals followed by a severe PPH event, the algorithm's efficiency demonstrated a mean of 84% precision and 93% recall in determining the risk of a PP event >160 mg/mL two hours after a meal (median 83% and 100%, respectively) (Figure 4).

There is also high interpatient variability when it comes to precision and recall. Precision is greater than 90% for 38% of patients and recall is greater than 90% for 80% of patients (Table 2).

3.3.2. Prediction of the absence of PPH risk (recommended PP glycemia event)

Recommended PP SG events were defined as events where SG was less than 160 mg/dL two hours after the start of a meal. The results showed high interpatient variability with a range of 8 to 71% of meals followed by a recommended PP glycemia event (data not shown). Of the

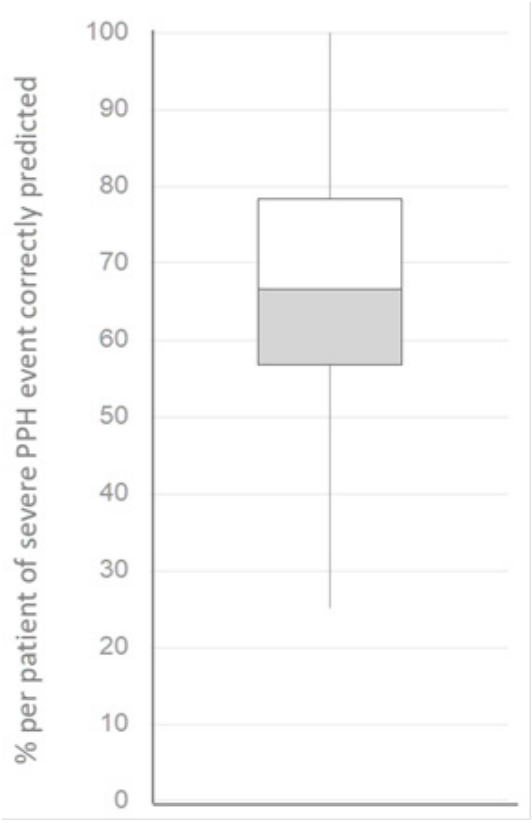

Fig. 3. Boxplot of per patient postprandial event correctly predicted (Intention to treat analysis. For the lines in a box and whisker plot: error bars are the 100% confidence interval, the bottom and top of the box are the 25th and 75th percentiles, the line inside the box is the 50th percentile (median).

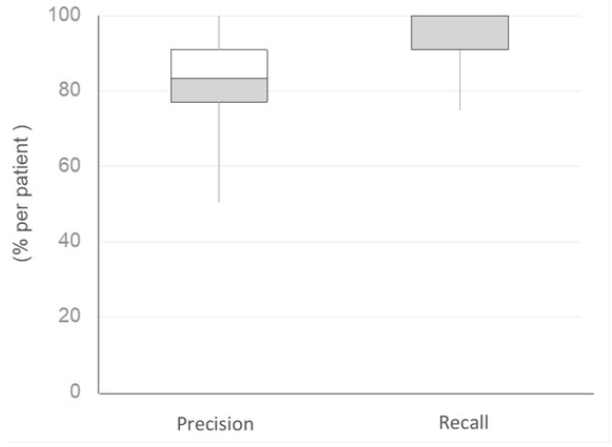

Fig. 4. Boxplot of per patient precision and recall of postprandial event correctly predicted (PP analysis. For the lines in a box and whisker plot: error bars are the 100% confidence interval, the bottom and top of the box are the 25th and 75th percentiles, the line inside the box is the 50th percentile (median).

Table 2. Precision and Recall, patient variability in predicting the risk of a postprandial hyperglycemia event (PP analysis).

Precision (PP analysis)	Proportion of patients concerned
> 90%	38%
> 75%	80%
83%	Median
Recall (PP analysis)	**Proportion of patients concerned**
> 90%	80%
> 80%	92%
100%	Median

487 meals followed by a severe PPH event, only 191 could be analyzed by the algorithm. Meals excluded from the Per Protocol analysis (296) were mainly due to SG values measured after the meal too close to or lower than those measured at the beginning of the meal (80%) (Figure 2). However, 60% of patients had more than 40% of meals followed by a recommended PP event analyzed by the algorithm, median of 45% (data not shown). Of the 197 meals analyzed, the algorithm correctly anticipated the absence of risk of a severe PPH event occurring for 156 meals.

Regarding the ITT analysis, 32% of meals followed by a recommended PP glycemia event were correctly anticipated as early as a few minutes after the end of the meal. The results also showed a large inter-patient variability in the recommended PP meals, correctly anticipated by the algorithm, ranging from 7 to 77% (data not shown).

For the Per Protocol analysis of meals followed by a recommended PP glycemia event, the algorithm's efficiency demonstrated a mean of 92% for precision and 82% for recall in determining no risk of a PP event <160 mg/mL two hours after a meal. There is also high interpatient variability when it comes to precision and recall (median 100 and 82%, respectively) (Figure 5).

Precision is also greater than 90% for 76% of patients and recall is greater than 75% for 72% of patients (Table 3).

3.3.3. Breakfast, lunch and dinner analysis for meals followed by severe PPH event

A total of 83, 109 and 86 meals could be allocated and the data processed by the MD001 algorithm for breakfast, lunch and dinner respectively (Table 4). The number of meals allocated (median) per patient was 2, 4 and 3 (mean 3.32 ± 2.91; 4.36 ± 2.43 and 3.44 ± 2.43) for breakfast, lunch and dinner respectively. Meals included in the ITT analysis were higher for lunches (77%) compared to 67% and 66% for breakfasts and dinners. The number of meals able to be analyzed by the MD001 algorithm (median) per patient was 2, 3 and 2 (mean 2.24 ± 2.40; 3.36 ± 2.18 and 2.28 ± 2.11) for breakfast, lunch and dinner, respectively.

Looking at the ITT analysis, the percentage of meals followed by a correctly anticipated severe PPH event was found to be higher for lunches (73%) than for breakfasts and dinners (60% and 63%, respectively) (median values were 67% for breakfast and dinner, 73% for lunches). Considering the Per Protocol analysis of meals followed by a severe PPH event, the algorithm gave a correct prediction

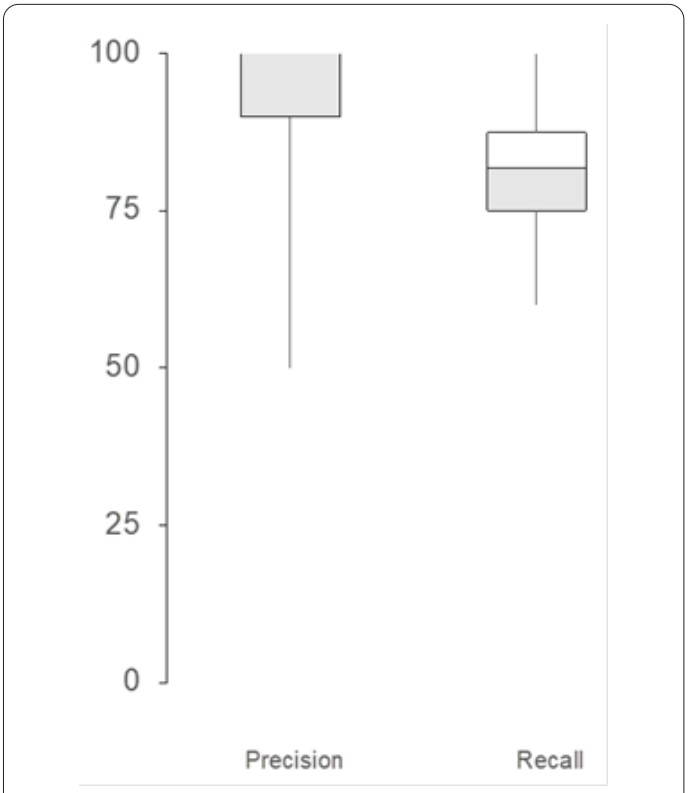

Fig. 5. Boxplot of per patient precision and recall recommended postprandial event analyzed by the algorithm (Per Protocol analysis). For the lines in a box and whisker plot error bars are the 100% confidence interval, the bottom and top of the box are the 25th and 75th percentiles, the line inside the box is the 50th percentile (median).

Table 3. Precision and Recall, patient variability in predicting the risk of a postprandial hyperglycemia event (PP analysis).

Precision (PP analysis)	Proportion of patients concerned
100%	64%
> 90%	76%
>80%	84%
> 75%	92%
100%	Median
Recall (PP analysis)	**Proportion of patients concerned**
> 90%	20%
>85%	40%
> 80%	60%
>75%	72%
82%	Median

for 89.3% of breakfasts and around 95% of lunches and dinners (mean of patients 88.28 ± 26.58; 95.45 ± 10.20 and 95.08 ± 13.53 for breakfasts, lunches and dinners respectively) (Table 4).

3.3.4. Breakfast, lunch and dinner analysis for meals followed by recommended PPH

A total of 138, 207 and 142 meals could be allocated and the data processed by the MD001 algorithm for breakfast, lunch and dinner respectively (Table 5). The number of meals (median) per patient was 6, 8 and 5 (mean 5.52 ± 3.62; 8.28 ± 3.26 and 5.68 ± 4.03) for breakfast, lunch

Table 3. Precision and Recall, patient variability in predicting the risk of a postprandial hyperglycemia event (PP analysis).

Precision (PP analysis)	Proportion of patients concerned
100%	64%
> 90%	76%
>80%	84%
> 75%	92%
100%	Median
Recall (PP analysis)	**Proportion of patients concerned**
> 90%	20%
>85%	40%
> 80%	60%
>75%	72%
82%	Median

and dinner respectively. Meals included in the ITT analysis were higher for breakfasts, 48% compared to 41% and 28% for lunches and dinners. The number of meals able to be analyzed (median) per patient was 2, 3 and 1 (mean 2.64 ± 2.33; 3.40 ± 2.12 and 1.60 ± 1.68) for breakfast, lunch and dinner respectively. Considering the Per Protocol analysis of meals followed by a recommended PP glycemia event, the algorithm gave a correct prediction for 75.8% of breakfasts, 82.4% of lunches, and 90% of dinners (patient mean 74.21 ± 32.06; 83.46 ± 25.59 and 92.78 ± 15.71 for breakfasts, lunches, and dinners respectively) (Table 5).

4. Discussion

Blood glucose levels are physiologically highly variable and can be influenced by many different factors (carbohydrate absorption (which also depends on both the glycemic index and meal composition), hormones that stimulate glucose release and/or absorption by cells and organs), but also by many external factors such as stress, medications, physical activity, behavior or the environment [10-12]. Physiological insulin secretion is normally permanent throughout the day and constantly controls blood glucose levels [13]. Because carbohydrate absorption is the main contributor to rising blood sugar levels, pronounced secretory insulin spikes occur after meals while weaker secretions occur during the rest of the day [14]. In people without diabetes, plasma glucose concentrations peak on average 60 minutes after the start of a meal and rarely exceed 140 mg/dl. The return to preprandial levels (80-120 mg/dL) then occurs within 2-3 hours [11]. In patients with T1D, this blood glucose management can only be done by sub cutaneous injection of insulin using pens or pumps

Table 4. Sub-meal analysis for meals followed by a severe postprandial hyperglycemic event.

		BREAKFAST	LUNCH	DINNER
Meal followed by a postprandial hyperglycemia event allocated				
N (total)		83	109	86
N (patient median)		2	4	3
N (patient mean)		3,32 ± 2,91	4,36 ± 2,43	3,44 ± 2,43
Meal followed by a postprandial hyperglycemia event analyzed				
N (total)		56	84	57
N (patient median)		2	3	2
N (patient mean)		2,24 ± 2,40	3,36 ± 2,18	2,28 ± 2,11
% analyzed vs allocated		67,47	77,06	66,28
	% (patient median)	75*	77,5**	66,7***
	% (patient mean)	65,50 ± 35,20*	77,26 ± 21,84**	61,59 ± 34,54***
Meal followed by a postprandial hyperglycemia correctly predicted				
N (total)		50	80	54
N (patient median)		2	3	1
N (patient mean)		2,00 ± 2,12	3,20 ± 2,14	2,16 ± 2,08
% correct prediction ITT		60,24	73,39	62,79
	% (patient median)	66,67*	73,21**	66,67***
	% (patient mean)	59,59 ± 38,19*	73,20 ± 21,08**	57,50 ± 32,83***
% correct prediction PP		89,29	95,24	94,74
	% (patient median)	100#	100##	100###
	% (patient mean)	88,28 ± 26,58#	95,45 ± 10,20##	95,08 ± 13,53###

* value calculated based on 19 patients because 6 patients had zero HPP event allocated. ** value calculated based on 22 patients because 3 patients had zero HPP event allocated. *** value calculated based on 24 patients because 1 patient had zero HPP event allocated. # value calculated based on 17 patients because 8 patients had zero HPP event analyzed. ## value calculated based on 22 patients because 3 patients had zero HPP event analyzed. ### value calculated based on 21 patients because 4 patients had zero HPP event analyzed.

Table 5. Sub-meal analysis for meals followed by a recommended postprandial hyperglycemic event.

	BREAKFAST	LUNCH	DINNER
Meal followed by a recommended postprandial hyperglycemia event allocated			
N (total)	138	207	142
N (patient median)	6	8	5
N (patient mean)	5,52 ± 3,62	8,28 ± 3,26	5,68 ± 4,03
Meal followed by a recommended postprandial hyperglycemia event analyzed			
N (total)	66	85	40
N (patient median)	2	3	1
N (patient mean)	2,64 ± 2,33	3,40 ± 2,12	1,60 ± 1,68
% analyzed vs allocated	47,8	41,06	28,17
% (patient median)	50*	48,1	33,3**
% (patient mean)	46,85 ± 29,15*	41,67 ± 23,52	29,83 ± 28,28**
Meal followed by a recommended postprandial hyperglycemia correctly predicted			
N (total)	50	70	36
N (patient median)	2	3	1
N (patient mean)	2,00 ± 1,89	2,80 ± 1,89	1,44 ± 1,53
% correct prediction ITT	36,23	33,8	25,35
% (patient median)	30*	38,75	27,5**
% (patient mean)	32,22 ± 24,98*	33,86 ± 21,63	28,30 ± 28,43**
% correct prediction PP	75,76	82,4	90
% (patient median)	83,3	100##	100###
% (patient mean)	74,21 ± 32,06#	83,46 ± 25,59##	92,78 ± 15,71###

value calculated based on 21 patients because 4 patients had zero HPP event analyzed. * value calculated based on 19 patients because 6 patients had zero HPP event allocated. ** value calculated based on 22 patients because 3 patients had zero HPP event allocated. # value calculated based on 17 patients because 8 patients had zero HPP event analyzed. ## value calculated based on 22 patients because 3 patients had zero HPP event analyzed

several times a day. To avoid the long-term complications associated with chronic hyperglycemia [15], keeping blood glucose levels as close as possible to the normal range (70-120 mg/dL) is the main goal and challenge of diabetes management [16]. PPH accounts for most of the overall blood glucose control in diabetic patients [17]. Effective control of PPH is one of the most complicated challenges for diabetic patients, as PP glycemic spikes are influenced by many factors despite insulin administration [10-12]. They can be extremely variable in height and duration from meal to meal, day to day, and individual to individual. Daily analysis of PPH shows that despite the administration mode of a correct insulin amount (pens, insulin pumps or closed-loop systems), the PP peak is often prolonged by more than two hours at high blood glucose values (> 160 mg/day). As shown by the EGHYA study, the occurrence of PPH is highly variable from patient to patient and can account for up to 70% of all meals followed by a PP hyperglycemic event.

Secondly, for a better management of PPH and indirectly of long-term average blood glucose, patients with T1D must quickly anticipate their blood glycemic values evolution. We developed a method to predict the range of blood glucose values two hours after meals. The mathematical algorithm is based on two glucose values and gives an accurate prediction of the PP glycemic peak characteristic, value and time of onset (without any need for meal carbohydrate content or insulin delivery data). Interestingly, we have previously demonstrated that prediction accuracy is strongly correlated with a decrease of 2 hours or less in PPH in a range below 160 mg/dL corresponding to the International Diabetes Federation recommendations.

Then, the main objective of the EGHYA study was to evaluate the algorithm effectiveness in predicting blood glucose fate two hours after the start of a full meal. The time of onset and the value of the PP peak were measured from the daily SG profiles of the CGM system and compared to those calculated by the algorithm. The presence or absence of PPH was also manually recorded from the daily glucose profiles provided by the patient. To avoid bias in data analysis, each patient also provided their meals composition during the study period to demonstrate that the algorithm's results were not related to similar eating habits. Each meal was analyzed according to its composition of sugars, carbohydrates, fibres, fats and proteins and demonstrated a high degree of heterogeneity in meals composition and therefore in eating habits between the different patients (data not shown).

The Per Protocol analysis shows a very high efficiency of the algorithm both in predicting the PPH risk and the absence of this risk. However, the study showed several limitations. Once is not directly related to the algorithm itself but results from the lack of available data in 30% of cases (problems with CGM systems operation or discor-

dance between values recorded by the patient and those reported on the daily glucose profile). The ITT population represented 67% of all meals. On the other hand, the Per Protocol population accounted for 34% of all meals and 51% of the ITT population. However, most of the exclusions defining the Per Protocol population occurred for meals followed by recommended PP events (79%), a meal category that theoretically does not require special attention from the patient. Regarding meals followed by a PP hyperglycemic event, the algorithm was able to process 7 out of 10 meals with an accuracy and recall of 83 and 100% respectively (184 meals with a correctly predicted risk out of 194). The greatest limitation in this study was the number of meals excluded from the Per Protocol analysis, mainly concerning meals followed by recommended PPH. Interestingly, the Per Protocol exclusions were due to meals with blood glucose levels that were higher or substantially equal to those taken after the meal (76%). However, the EGHYA study shows that when these conditions are met, the proportion of chance that the meal will be followed by a recommended PP event increases to 80%. In addition, for meals followed by a recommended PP event that could be analyzed by the algorithm, the PP analysis showed an accuracy and recall of 100% and 82% respectively.

In conclusion, the PP blood glucose management remains largely unsatisfactory and represents a heavy mental burden for the patient, thus reducing the quality of life [18-19]. Meals always require carbohydrates estimate and are often associated with PPH (PPH constitutes the majority of daily hyperglycemia and is linked to many chronic complications (retinopathy, vascular disease, nephropathy...).

Although the closed-loop system represents the best commercially available management of T1D to date, it is still necessary to inform the algorithm about the amount of carbohydrate ingested. These approximative estimates made by the patient often lead to errors which are subsequently followed by hyperglycemia after meals [20].

We have developed a new algorithm capable of predicting the glycemic profile fate two hours after a meal. The results of such prediction can be available a few minutes after the end the meal. The EGHYA study demonstrated that such technology could be able to anticipate PPH for nearly 7 out of 10 meals. Its future full integration into closed-loop systems, insulin pumps or continuous glucose monitoring systems could bring more autonomy to diabetic patients, thus reducing the enormous emotional burden of managing PPH. In addition, integration into current or future closed-loop systems may represent a step forward towards a fully closed-loop system that represents the holy grail in diabetes management.

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