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ORIGINAL RESEARCH

Sensor-Augmented Insulin Pump with Predictive Low-Glucose Suspend (PLGS): Determining Optimal Settings of Pump and Sensor in a Multicenter Cohort of Patients with Type 1 Diabetes

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ABSTRACT

Introduction: The use of predictive low-glucose suspend (PLGS) sensor-augmented pumps has been shown to lead to a significant reduction in hypoglycemic episodes in patients with type 1 diabetes (T1D), but their effects on hyperglycemia exposure are heterogeneous. The aim of this study was to determine the settings of the Medtronic 640G system to obtain the optimal balance between occurrence of both hypoglycemia and hyperglycemia.

Methods: The hypo- and hyperglycemia area under the curve (AUC), as well as system settings [hypoglycemic threshold, mean insulin total daily dose (TDD), mean basal insulin percentage, and mean daily duration of PLGS] were collected between 2 and 12 times during 1 year in patients from four university hospital centers. Univariate/multivariate analyses and receiver operating characteristics (ROC) curves were performed to determine factors associated with hyper- and hypoglycemia AUC.

Results: A total of 864 observations were analyzed from 110 patients with T1D. Two preselected settings predictive of low hyperglycemia AUC were a basal insulin percentage $< 52.0\%$ [sensitivity (Se) = 0.66 and specificity (Sp) = 0.53] and a PLGS duration > 157.5 min/day (Se = 0.47 and Sp = 0.73). The preselected setting predictive of a low hypoglycemia AUC was a PLGS duration ≤ 174.4 min (Se = 0.83 and Sp = 0.51). Between-visit variation of PLGS and TDD was positively correlated ($r = 0.61$; $p < 0.0001$).

Conclusion: The most important Medtronic 640G setting was the mean daily PLGS duration, where a value between 157.5 and 174.4 min/day was associated with the best reduction in both hypo- and hyperglycemia AUC. In this study, we showed that PLGS duration could be indirectly modified through total daily insulin dose

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adaptation.**Trial Registration:** This study is registered in clinicaltrials.gov (NCT 03047486).

Keywords: Type 1 diabetes; Sensor-augmented pump; Predictive low-glucose suspend; Hypo-minimizer

Key Summary Points
Why carry out this study?
Effect of hypo-minimizer systems on overall glucose control is heterogeneous. This effect mostly relies on system settings.
The aim of this study was to determine optimal settings of the Minimed 640G hypo-minimizer system to reduce both hypo- and hyperglycemia exposure.
What was learned from the study?
Optimal settings were determined to optimize glucose control.
The most important parameter to adjust was total daily insulin dose in order to target a mean daily predictive low-glucose suspend duration between 157.5 and 174.5 min/day.

INTRODUCTION

The gold-standard treatment for patients with type 1 diabetes (T1D) is intensified insulin therapy, whether by multiple daily injections (MDI) or by continuous subcutaneous insulin injection (CSII), preferably using insulin analogs in order to reduce hypoglycemic events. Patients with T1D should also be trained to adapt prandial insulin doses according to carbohydrate intake, premeal blood glucose, and planned physical activity [1]. In addition, continuous glucose monitoring (CGM) has emerged in the past decade as a key device for lowering and/or maintaining hemoglobin A1C (HbA1C) levels and/or reducing hypoglycemia in adults and young subjects with T1D [2]. Combined insulin pump and CGM systems have also been developed in recent years, leading to sensor-augmented pumps with hybrid closed-loop algorithms (HCL) that increase and decrease insulin delivery on the basis of sensor-derived glucose levels [2]. Several studies have demonstrated that the use of these HCL systems is associated with an increased time in range (TIR) and a decrease in time below range (TBR), time above range (TAR), and HbA1c both in children and adults [3–5]. However, HCL systems are not widely available, mainly owing to their high cost and regulatory and reimbursement issues. Sensor-augmented pumps that suspend insulin when glucose is low (low-glucose suspend, LGS) or predicted to go low within the next 30 min (predictive low-glucose suspend, PLGS) are more readily available and are covered by healthcare authorities in some countries. The two principal PLGS systems routinely available in Europe are (1) Medtronic 640G pump + Medtronic Enlite sensors + embedded Medtronic "suspend before low" algorithm (referred to herein as "640G") and (2) Tandem T-slim X2 pump + Dexcom G6 sensor + embedded Basal-IQ algorithm (termed herein as "Basal-IQ"). Both systems have the same operating principle with cessation of basal insulin delivery 30 min before interstitial glucose reaches the threshold of 80 mg/dL for the Basal-IQ system, or a customizable threshold between 50 and 90 mg/dL for the 640G system, as predicted by the algorithm. Basal insulin suspension lasts for up to 2 h before restarting when conditions indicate that there is no longer risk of hypoglycemia. A few randomized studies have assessed efficacy and safety of these two systems in children, adolescents, and adults, and demonstrated a reduction of hypoglycemic exposure, even in the adult study, which included hypoglycemia-prone patients [6–9]. In this latter challenging population, the PLGS system reduced both nonsevere and severe hypoglycemic episodes [8]. Apart from this benefit of reducing risk of hypoglycemia, the effect of PLGS systems on exposure to hyperglycemia is variable, with some prospective or cohort studies showing an increase in time above range [6, 10–12], some showing no effect

[7, 8, 13, 14], and only two demonstrating a reduction in this parameter [9, 15]. These discrepancies could be explained by the differences in populations, methods, and PLGS systems used, but also by the various and heterogeneous settings of these systems. Pump settings (total daily dose and basal/bolus ratio) and the hypo-threshold setting of the PLGS (for 640G only) were generally not specified precisely in the above-mentioned studies, but one can hypothesize that such adjustments may theoretically lead to different metabolic outcomes, some adjustments protecting more against hypoglycemia and others more effectively limiting hyperglycemia. The aim of this study was to determine, in a cohort of patients with T1D using the Medtronic 640G system, the settings of pump and sensor (PLGS) to obtain the optimal balance between occurrence of hypoglycemia and occurrence of hyperglycemia.

METHODS

Design and Study Population

A multicenter cohort study was conducted in four University Hospital Diabetes Care Units (centers) in France. Inclusion criteria were: (1) type 1 diabetes diagnosed for at least 1 year; (2) CSII $\geq$ 6 months; (3) previous education on flexible insulin therapy; (4) the patient being willing to use sensors and PLGS option for 1 year; (5) HbA1c $\geq$ 7.5% and/or severe hypoglycemia $\geq$ 2 episodes during the last 6 months and/or recurrent hypoglycemia and/or hypoglycemia unawareness and/or brittle diabetes; (6) use of 640G system implemented between January 2015 and December 2016; and (7) availability of at least two data downloads after the 640G system was turned on over a 12-month period. This multicenter non-interventional study was approved by the French regulatory agency (ANSM; number 2016-A02095-46) and by the national ethics committee (CPP-Sud Méditerranée III; number 2017.01.02 bis). The study was conducted within the framework of the French MR04 legislation, requiring only simple written information to the patient and signing of a non-opposition form. This study is registered at clinicaltrials.gov (NCT 03047486).

Data Collection

Baseline data collected included age, duration of diabetes, duration of pump use, weight, height, body mass index (BMI), and HbA1c at inclusion.

Downloads of 640G system data were performed using CareLink Pro 6.0A software (Medtronic Minimed, Northridge, CA, USA). For each download, a 14-day dataset was collected including: (1) device parameters that can be directly adjusted (hypoglycemic threshold (60–90 mg/dL); mean insulin total daily dose (TDD) (UI/kg); mean basal percentage (% basal); (2) mean daily PLGS (min); and (3) hypo- and hyperglycemia area under the curve (AUC) (mg/dL/min). The latter CGM parameters were chosen owing to the unavailability of consensus CGM criteria (TIR, TBR, TAR) in the CareLink Pro 6.0A software.

Endpoints

The hypo- and hyperglycemia AUC, as well as system settings, were collected between 2 and 12 times during 1 year of system use. All hypo- and hyperglycemia AUC were grouped for each center and adjusted by center to account for heterogeneity in the calculation of AUC within each center, prior to analysis. The values of hypo- and hyperglycemia AUC were grouped by center and then centered and reduced so that their mean value was 0 and their standard deviation was 1. This transformation was done prior to analysis to account for heterogeneity in the way the calculation of AUC was computed in each center.

Statistical Analyses

There was no a priori sample size computation. The baseline characteristics were described using the mean $\pm$ standard deviation (SD) or the median and interquartile range (IQR), according to their distribution for all populations and by center. These variables were

Table 1 Baseline characteristics of the entire population and for each center

Baseline characteristics	All (n = 110)	Center 1 (n = 26)	Center 2 (n = 42)	Center 3 (n = 21)	Center 4 (n = 21)	p
Age at inclusion (years), mean ± SD	46.9 ± 11.9	46.3 ± 13.3	48.4 ± 11.3	44.5 ± 10.4	47.2 ± 13.0	0.667
Duration of diabetes* (years) mean ± SD	28.2 ± 11.9	26.8 ± 12.6	31.4 ± 11.8	27.5 ± 11.9	24.5 ± 10.8	0.140
Duration of pump** (years), median (IQR)	10 (7–14)	9 (7–14)	11.5 (8–17)	8 (6–13)	8 (3–13)	0.058
Weight* (kg), mean ± SD	75.8 ± 15.7	74.2 ± 13.9	77.1 ± 16.3	76.3 ± 17.4	74.4 ± 15.4	0.867
Height* (cm), mean ± SD	170.5 ± 8.3	170.1 ± 8.5	171.4 ± 8.3	170.76 ± 9.6	169.0 ± 6.8	0.729
BMI* (kg/m^2), median (IQR)	25.1 (22.4–29.3)	24.8 (23–27.8)	25.6 (22.3–29.4)	25.6 (22.0–30.1)	24.8 (22.9–28.4)	0.984
HbA1c* (%), median (IQR)	7.6 (7.2–8.2)	7.3 (6.9–7.7)	7.5 (7.2–7.9)	8.1 (7.6–8.4)	7.8 (7.3–8.8)	**0.003**

Bold value indicates the significant results (with $p < 0.05$)

*One missing value; **three missing values. Comparison of means between centers was performed via ANOVA test (parametric test) or Kruskal–Wallis test (nonparametric test)

compared between centers using analysis of variance (ANOVA) or Kruskal–Wallis tests, depending on their distribution.

Regarding the primary endpoint, generalized linear models were calculated using a first-order autoregressive [AR(1)] correlation structure, taking into account several observations per patient over time. Univariate and multivariate analyses, including baseline characteristics and time-varying setting parameters of the pump, were performed to determine factors associated with hyper- and hypoglycemia AUC in two separate models.

The hypo- and hyperglycemia AUC were dichotomized according to their mean into two separate binary variables. Then, receiver operating characteristics (ROC) curves were calculated using logistic regression to assess the diagnostic value of each setting parameter and determine the cutoff using the Youden Index, derived from the associated sensitivity and specificity.

Between visits, evolution of PLGS and TDD was also analyzed using Pearson correlation coefficients.

Only complete-case datasets were analyzed, to exclude missing values. Threshold for statistical significance was set at the $p < 0.05$ level. Statistical analyses were performed with SAS software V9.4 (SAS Institute, Cary, NC, USA) and R statistical software version 4.0.5 (2021 The R Foundation for Statistical Computing).

RESULTS

In total, 110 patients were recruited from the four centers. Given the longitudinal nature of data collection for each patient, 864 observations were analyzed. Pump and sensor parameters could vary for the same patient during the different observations over the 12-month period. The main baseline characteristics of patients are presented in Table 1. All baseline characteristics were found to be similar between centers, except baseline HbA1c, which was lower in centers 1 and 2 (7.3% IQR 6.9–7.7 and 7.5% IQR 7.2–7.9, respectively) and higher in centers 3 and 4 (8.1% IQR 7.6–8.4 and 7.8% IQR 7.3–8.8, respectively) (p = 0.003) (Table 1).

Hypo- and hyperglycemia AUCs were plotted in four quadrants according to their mean (Fig. 1). Each dot represents both hypo- and

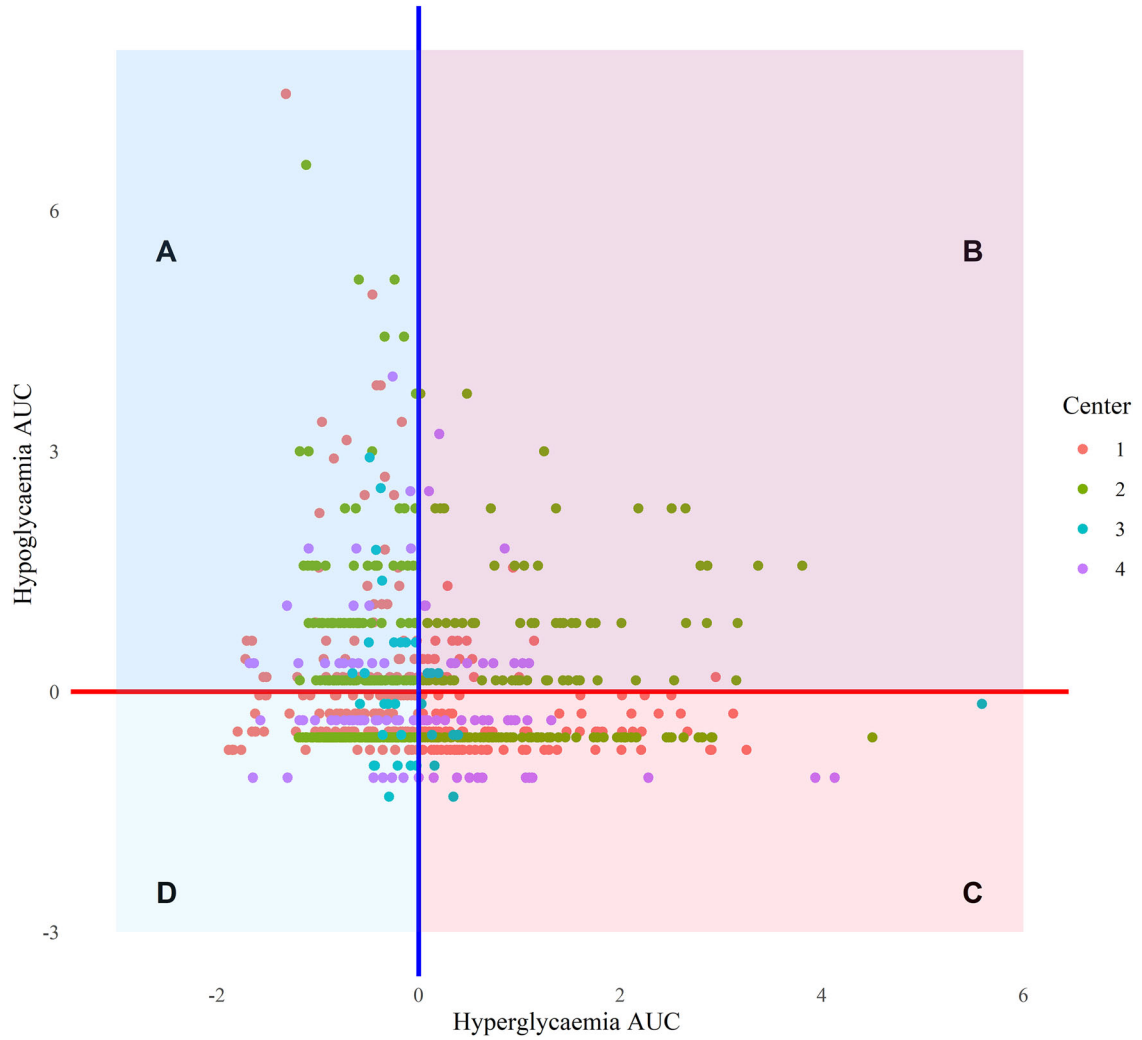

Fig. 1 Hyper- and hypoglycemia AUC centered and reduced in each participating center

hyperglycemia AUC values measured in a patient at one timepoint. Dots in quadrants A and D (blue) correspond to hyperglycemia AUC below mean, and dots in quadrants B and C (red) correspond to hyperglycemia AUC above mean. Dots in quadrants C and D (light colors) correspond to hypoglycemia AUC below mean, and dots in quadrants A and B (dark colors) correspond to hypoglycemia AUC above mean. From these quantitative variables, two binary variables were created to identify those patients with an AUC pattern showing protection from hyperglycemia (blue quadrants) and those patients with an AUC showing pattern protection from hypoglycemia (light quadrants).

Hyperglycemia AUC (Red Axis in Fig. 1)

In a univariate model, factors significantly associated with hyperglycemia AUC were age at inclusion ($\beta = -0.022$, 95% confidence interval (CI) [− 0.039; − 0.005], $p = 0.014$), baseline HbA1c ($\beta = 0.456$, 95% CI [0.221; 0.691], $p < 0.001$), % basal ($\beta = -0.018$, 95% CI [− 0.026; − 0.011], $p < 0.001$), PLGS duration ($\beta = -0.004$, 95% CI [− 0.006; − 0.003], $p < 0.001$) and TDD ($\beta = 1.139$, 95% CI [0.225; 2.053], $p = 0.015$) (Table 2).

All but one parameter, TDD, remained significantly associated with hyperglycemia AUC in multivariate analysis (Table 2).

Table 2 Factors associated with hyper- and hypoglycemia AUC in univariate and multivariate models

Risk factors	Hyperglycemia AUC						Hypoglycemia AUC					
	Univariate			Multivariate (n = 106)			Univariate			Multivariate (n = 108)		
	β	95% CI	p	β	95% CI	p	β	95% CI	p	β	95% CI	p
Baseline characteristics												
Age at inclusion	− 0.022	[− 0.039; − 0.005]	**0.014**	− 0.028	[− 0.045; − 0.012]	**< 0.001**	− 0.012	[− 0.025; 0.002]	0.091	− 0.013	[− 0.025; − 0.001]	**0.035**
Duration of diabetes	− 0.009	[− 0.023; 0.006]	0.230				− 0.005	[− 0.017; 0.007]	0.448			
Duration of pump	− 0.022	[− 0.048; 0.005]	0.107	− 0.005	[− 0.031; 0.020]	0.687	0.007	[− 0.019; 0.033]	0.612			
BMI	− 0.003	[− 0.044; 0.037]	0.874				− 0.049	[− 0.074; − 0.024]	**< 0.001**	− 0.027	[− 0.051; − 0.003]	**0.027**
Baseline HbA1c	0.456	[0.221; 0.691]	**< 0.001**	0.359	[0.122; 0.597]	**0.003**	− 0.221	[− 0.457; 0.014]	0.066	− 0.040	[− 0.249; 0.168]	0.703
Center												
2	1						1					
1	− 0.071	[− 0.480; 0.338]	0.734				− 0.038	[− 0.458; 0.383]	0.861			
3	0.100	[− 0.467; 0.667]	0.730				− 0.046	[− 0.521; 0.430]	0.851			
4	− 0.024	[− 0.524; 0.476]	0.925				− 0.063	[− 0.436; 0.309]	0.739			
Pump parameters												
Hypoglycemia threshold	0.005	[− 0.011; 0.022]	0.536				− 0.004	[− 0.021; 0.013]	0.623			
% basal	− 0.018	[− 0.026; − 0.011]	**< 0.001**	− 0.017	[− 0.023; − 0.012]	**< 0.001**	− 0.006	[− 0.014; 0.002]	0.113	− 0.006	[− 0.013; 0.001]	0.077
PLGS	− 0.004	[− 0.006; − 0.003]	**< 0.001**	− 0.004	[− 0.005; − 0.003]	**< 0.001**	0.004	[0.003; 0.006]	**< 0.001**	0.004	[0.003; 0.006]	**< 0.001**
TDD	1.139	[0.225; 2.053]	**0.015**	0.514	[− 0.243; 1.271]	0.184	− 0.133	[− 0.563; 0.298]	0.546			
Time	− 0.009	[− 0.027; 0.009]	0.333				− 0.013	[− 0.032; 0.006]	0.190			

Bold values indicate the significant results (with $p < 0.05$)

n, number of patients

p value of univariate and multivariate generalized linear regression with repeated data

Hypoglycemia AUC (Blue Axis in Fig. 1)

In a univariate model, factors significantly associated with hypoglycemia AUC were BMI at inclusion ($\beta = -0.049$, 95% CI [− 0.074; − 0.024], $p < 0.001$) and PLGS duration ($\beta = 0.004$, 95% CI [0.003; 0.006], $p < 0.001$) (Table 2). On multivariate analysis, all of the above-described factors remained significantly associated with hypoglycemia AUC, while age also became significant ($\beta = -0.013$, 95% CI [− 0.025; − 0.001], $p = 0.035$) (Table 2).

Prediction Model

The predictive value of setting parameters to minimize hyper- and hypoglycemia were analyzed only for those that were significantly associated with AUC in multivariate analysis (Table 3).

Avoidance of Hyperglycemia (Avoidance Shown in Red in Fig. 1)

The two preselected settings predictive of low hyperglycemia AUC were a % basal insulin < 52.0% [AUC 0.62, 95% CI [0.58–0.66], $p < 0.001$, sensitivity (Se) = 0.66 and specificity (Sp) = 0.53] and a PLGS duration > 157.5 min/day (AUC 0.60, 95% CI [0.56–0.64, Se = 0.47 and Sp = 0.73) (Fig. 2).

Avoidance of Hypoglycemia (Avoidance Shown in Dark Color in Fig. 1)

The preselected setting predictive of a low hypoglycemia AUC was a PLGS duration ≤ 174.4 min (AUC 0.71, 95% CI [0.67–0.75], $p < 0.001$, Se = 0.83 and Sp = 0.51) (Fig. 2).

PLGS and TDD Correlation

Between-visit variation of PLGS (ΔPLGS) and TDD (ΔTDD) were positively correlated ($r = 0.6075$; $p < 0.0001$), allowing the regression equation to be derived (Fig. 3):

Table 3 Diagnostic values of setting parameters

Pump parameters	Hyperglycemia**					Hypoglycemia**				
	Cutoff	AUC [95% CI]	Sensitivity [95% CI]	Specificity [95% CI]	*p* value*	Cutoff	AUC [95% CI]	Sensitivity [95% CI]	Specificity [95% CI]	*p* value*
% basal (%)	≤ 52.0	0.62 [0.58–0.66]	0.66 [0.61–0.70]	0.53 [0.48–0.59]	< 0.001					
PLGS (min)	> 157.5	0.60 [0.56–0.64]	0.47 [0.43–0.52]	0.73 [0.68–0.78]	**< 0.001**	≤ 174.4	0.71 [0.67–0.75]	0.83 [0.79–0.86]	0.51 [0.46–0.57]	**< 0.001**

Bold values indicate the significant results (with $p < 0.05$)

*p value of logistic regression

**We modeled the probability of no event (avoidance of hyper- or hypoglycemia)

Cutoff for avoidance of hyper- or hypoglycemia

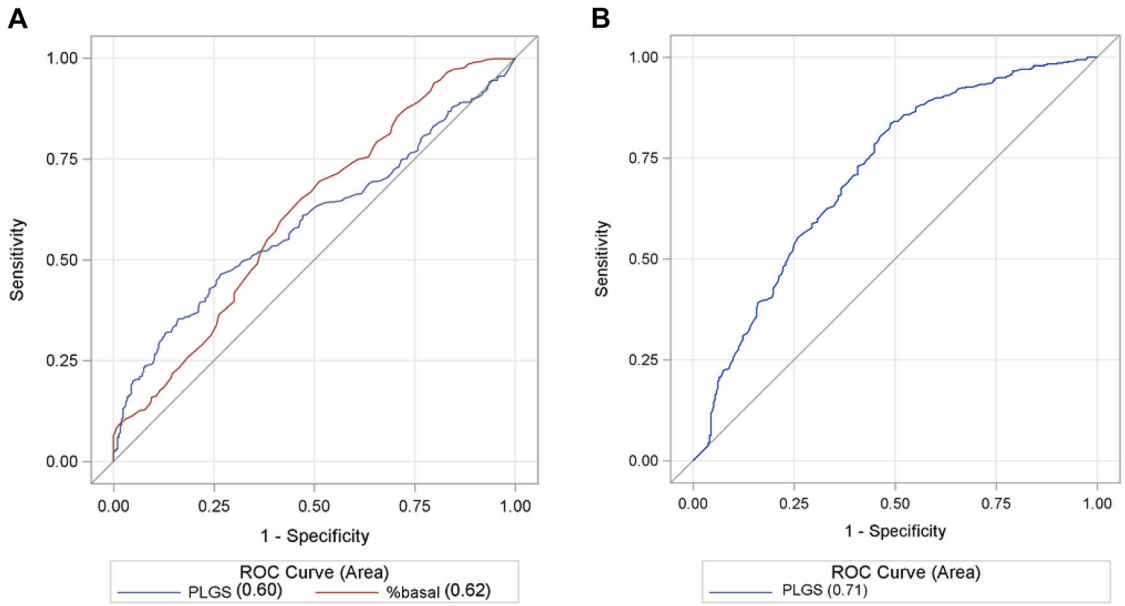

Fig. 2 ROC curves of setting parameters to protect from hyperglycemia (**A**) and hypoglycemia (**B**)

$$\Delta\text{PLGS(min)} = 5.4 + (153 \times \Delta\text{TDD(UI/kg)}).$$

DISCUSSION

In this multicenter cohort study, we explored for the first time, to our knowledge, the association between the system settings of Medtronic 640G PLGS and glycemic outcomes, to determine the most effective settings that would minimize occurrence of both hypoglycemia and hyperglycemia.

Firstly, we found that the setting of the hypoglycemic threshold was not associated with hypo- or hyperglycemia exposure. This result was surprising, since it might be expected that an increased hypoglycemic exposure would be observed with a low hypoglycemia threshold, and an increased hyperglycemic risk with a high hypoglycemia threshold. Indeed, we intuitively thought that setting a lower hypoglycemia threshold would put patients at greater risk of hypoglycemia because the system would suspend insulin too late. In our experience, the choice of the hypoglycemia threshold may be guided by the patient's fear of hypoglycemia and can be chosen as a shared decision between the patient and their physician.

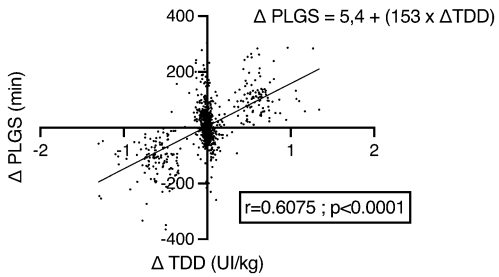

Fig. 3 Plot of between-visit PLGS evolution (ΔPLGS) (min) versus TDD evolution (ΔTDD) (UI/kg). The computed regression equation between these two parameters is indicated on the graph

The second important result of this analysis concerns the PLGS mean daily duration required to optimize avoidance of exposure to both hypoglycemia and hyperglycemia. It should be noted that the ROC curves for this parameter indicated low sensitivity and specificity, leading us to consider these thresholds with caution. However, we observed that a PLGS duration of between 157.5 and 174.4 min/day (i.e., between 2 h 37 min and 2 h 54 min) resulted in optimal reduction of both hypoglycemia and hyperglycemia exposure. To explain this finding, it could be hypothesized that a PLGS duration less than 157.5 min/day

reflects under-utilization of the basal suspension system for preventing hypoglycemia and is associated with frequent hyperglycemic excursions. Conversely, PLGS duration of more than 174.4 min/day may represent over-utilization of the basal suspension system, suggested by a high rate of hypoglycemic excursions. It should be underlined that PLGS duration is not directly adjustable but rather depends on adjustment of the total daily insulin dose. The computed regression equation that we derived, linking PLGS and TDD variations, could be translated as follows: an increase in TDD of 0.1 UI/kg/day leads to an increase in PLGS activation of about 20 min/day. This implies that, if a physician wanted to increase or decrease PLGS, they could increase or decrease TDD to indirectly modulate this parameter.

Regarding the ratio between basal and bolus insulin, we found that the percentage of basal insulin should not exceed 52% in order to minimize the risk of hyperglycemia, with no threshold identified to reduce the hypoglycemic risk.

These results lead us to propose default optimal settings for the use of a 640G system in order to optimize glucose control: (1) the hypoglycemia threshold should be defined in discussion with the patient according to their fear of hypoglycemia; (2) the percentage of basal insulin should be set to approximately 50%; (3) TDD should be secondary adjusted to target a mean daily PLGS duration between 157.5 and 174.5 min/day (2 h 37 min and 2 h 54 min).

We remind that there are no preset settings in the 640G hypo-minimizer system. Hypoglycemia threshold is determined by HCP when the hypo-minimizer system is started. For PLGS duration, the main parameter associated with hypoglycemia/hyperglycemia exposure, there is also no "preset" value as this parameter is not directly adjustable but indirectly reflects the total daily insulin dose which is adjusted for each patient. The settings suggested in this study are from statistical analysis of the present cohort and thus may not be suitable for all patients. However, they serve as a guide or supportive material in understanding how this particular system works. Some patients may require very different settings owing to their individual characteristics, and physicians will need to finely adjust these parameters for each patient.

Other studies have reported consistent results regarding the association between mean daily PLGS duration and glucose control. A retrospective analysis by Beato-Vibora et al. of children and adults with T1D treated with Medtronic 640G PLGS, reported a reduction of TBR < 70 mg/dL from $10 \pm 7\%$ to $6 \pm 5\%$ ($p = 0.001$) after using the PLGS system over a few months [13]. Apart from the reduction in hypoglycemic risk, the effect on overall glucose control was heterogeneous among the 162 patients analyzed, prompting the authors to compare a group of patients with TIR 70–180 mg/dL in the higher quartile with a group in the lowest quartile. Among the differences found between these two subgroups, the authors highlighted the mean daily PLGS duration, which was higher (204 min/day) in the highest TIR quartile and lower (114 min/day) in the lowest TIR quartile [13]. Similar to our results, these findings suggest that a low PLGS duration is associated with a greater exposure to high glucose levels. Choudhary et al. also performed a retrospective analysis of 920 patients with T1D using a sensor-augmented pump (SAP) or an LGS or PLGS system [10]. In the latter group ($n = 316$ adults), the authors reported that the TBR was only 23 min/day compared with 58 min/day in the SAP group ($n = 58$). On the other hand, the TIR was greater in the SAP group (70%) than the PLGS group (64%). Such excessive hyperglycemia observed in the PLGS group may be explained by a low mean daily PLGS duration of 59 min/day, possibly reflecting a relative lack of insulin delivery [10]. A Japanese study by Tsunemi et al. also reported an increase in TAR > 180 mg/dL from 25.5% to 32.9% ($p < 0.05$) in patients with T1D after 3 months using the Medtronic 640G PLGS system, with a mean daily PLGS time of only 78 min/day [12]. Conversely, Forlenza et al. found significant reduction of AUC hyperglycemia with the Basal-IQ PLGS system compared with a control group with SAP, but the mean daily PLGS duration was 104 ± 83 min/day, higher than

reported in the other studies discussed, and in 25% of patients was even higher than 155 min/day. Not surprisingly, in this study as in other PLGS system studies, TBR was significantly reduced by the Basal-IQ system (primary outcome) [9].

Overall, these results are consistent with there being an association between mean daily PLGS duration and glucose control. As described above, the main explanation for this finding is that a lower mean daily PLGS duration reflects an insufficient total daily dose of insulin, leading to a trend toward higher glucose values. A higher PLGS duration probably reflects a better adjustment of insulin total daily dose, driving the whole glucose profile down. A limitation is that a longer PLGS duration, probably driven by a total daily dose that is too high, may prompt the occurrence of hypoglycemic episodes, despite activation of the hypo-minimizer system.

However, another possible explanation is that a reduced mean daily PLGS duration can be observed when insulin delivery is manually resumed and/or carbohydrates are ingested after a predictive low-glucose suspend. Although it is recommended to allow the system to work in the case of predictive suspend before hypoglycemia, some patients manually restart insulin delivery and/or eat carbohydrates even though they did not reach the hypoglycemic threshold. These behaviors may lead to hyperglycemic rebound that could explain a deterioration in glycemic control with a reduced mean daily PLGS duration [16]. In our study, we cannot rule out this possibility, as data regarding manually restart of insulin delivery and/or carbohydrate ingestion to correct/avoid hypoglycemia were not available. In the same vein, it would have been interesting to collect the correction boluses performed by the patients given their potential impact on hyperglycemia exposure.

Our study presents several limitations. Our analysis relies solely on CGM data to assess hypoglycemic risk, thus not taking into account the clinical hypoglycemic events experienced by patients, especially since their long diabetes duration exposes them to impaired glucose awareness. We had no data on physical activity and dietary habits, two parameters that are associated with hypo- and hyperglycemia exposure. Had they been available, it would have been more relevant to analyze validated CGM metrics (TIR, TAR, TBR), rather than AUC hypo- and hyperglycemia that are not standardized and for which there are no reference values. The Medtronic Enlite sensor belongs to an old sensor generation with a lower accuracy (mean absolute relative difference of 13.9%) than newer sensors as the Medtronic Guardian sensor 3 (mean absolute relative difference of 9.6%) [17, 18]; thus, the results of our study should be observed with caution and would not necessarily apply to more recent sensors. Finally, it should be noted that hypo-minimizer technology is disappearing in favor of hybrid closed loops, although these systems are still used in some indications and depending on the availability of newer technologies.

CONCLUSIONS

In this multicentric cohort study, we determined which system settings showed the greatest association with better glucose control. Among our findings, the most important parameter appeared to be the mean daily PLGS duration, for which a value between 157.5 and 174.4 min/day was associated with the best reduction of both hypo- and hyperglycemia AUC. Although this parameter cannot be directly set on the system, we showed that it could be indirectly modified through adaptation of total daily insulin dose (with increase/decrease of total daily insulin dose resulting in longer/shorter mean daily PLGS duration, respectively). This target PLGS duration should be considered as a "default" recommendation that needs to be customized for each situation, according to the individual characteristics and observed glucose profiles of the patient.

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Data Availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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