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ORIGINAL ARTICLE

Effect of real-life insulin pump with predictive low-glucose management use for 3 months: Analysis of the patients treated in a Japanese center

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ABSTRACT

Aims/Introduction: In Japan, an insulin pump with predictive low-glucose management (PLGM) was launched in 2018. It automatically suspends insulin delivery when the sensor detects or predicts low glucose values. The aim of this study was to analyze the safety and efficacy of PLGM in patients treated in a Japanese center.

Materials and Methods: We carried out a retrospective observational analysis of 16 patients with type 1 diabetes mellitus and one patient after pancreatectomy. They switched from the MiniMed 620G device to the 640G device with PLGM. The primary outcome was the change in the percentage of time in hypoglycemia. The secondary outcome was the change in HbA1c (%) over a period of 3 months. We also explored the presence of "post-suspend hyperglycemia" with the 640G device.

Results: After changing to the 640G device, the percentage of time in hypoglycemia (glucose <50 mg/dL) significantly decreased from 0.39% (0–1.51%) to 0% (0–0.44%; $P = 0.0407$). The percentage of time in hyperglycemia (glucose >180 mg/dL) significantly increased from 25.53% (15.78–44.14%) to 32.9% (24.71–45.49%; $P = 0.0373$). HbA1c significantly increased from 7.6 ± 1.0% to 7.8 ± 1.1% ($P = 0.0161$). From 1.5 to 4.5 h after the resumption of insulin delivery, the percentage of time in hyperglycemia was 32.23% (24.2–53.75%), but it was significantly lower, 2.78% (0–21.6%), when patients manually restarted the pump within 30 min compared with automatic resumption 31.2% (20–61.66%; $P = 0.0063$).

Conclusions: Predictive low-glucose management is an effective tool for reducing hypoglycemia, but possibly elicits "post-suspend hyperglycemia." This information is useful for achieving better blood glucose control in the patients treated with PLGM.

INTRODUCTION

Severe hypoglycemia that might cause loss of consciousness, seizures, abnormal behavior, trauma and sudden cardiac death is generally defined as an event requiring assistance of another person[1]. It has been reported in approximately 40% of patients with type 1 diabetes mellitus in 1 year[2]. In addition, 10% of deaths among adults with type 1 diabetes mellitus aged <40 years are estimated to be due to severe hypoglycemia[2–8]. Advances in insulin pump technology have further decreased the incidence of severe hypoglycemia. The usefulness of sensor-augmented pump technology with continuous glucose monitoring (CGM) was shown in a clinical trial in which 95 patients with type 1 diabetes mellitus were randomized to insulin pump only or pump with automated insulin suspension for 6 months. This trial showed that the adjusted hypoglycemia rate was 34.2 episodes per 100 patient-months (95% confidence interval [CI]

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22.0–53.3) for the pump-only group versus 9.5 episodes per 100 patient-months (95% CI 5.2–17.4) for the low-glucose suspension group[9], suggesting that use of a sensor-augmented pump with CGM is beneficial.

The number of Japanese patients with type 1 diabetes mellitus is estimated to be 100,000–140,000, corresponding to 0.09–0.1% of the overall population[10]. Among Japanese patients with type 1 diabetes mellitus, the number of insulin pump users is estimated at approximately 10,000, suggesting that the insulin pump has not permeated Japan yet.

Reflecting the small number of pump users in Japan, the MiniMed 620G device (Medtronic, Northridge, CA, USA) with sensor-augmented pump therapy was launched in February 2015, and the MiniMed 640G device was launched in March 2018, several years after the launch of each device in European countries. The predictive low-glucose management (PLGM) component of the MiniMed 640G device automatically suspends insulin delivery when the sensor detects low glucose values or glucose values are predicted to reach 20 mg/dL (1.1 mmol/L) above a preset low-glucose limit within 30 min. It resumes insulin delivery when the sensor detects glucose values at least 20 mg/dL (1.1 mmol/L) above the preset lower limit, and predicts that glucose values will be 40 mg/dL (2.2 mmol/L) higher than the preset lower limit within 30 min. It also resumes insulin delivery after it has been suspended for 2 h or when it is restarted manually by the patient[11].

Data from clinical trials in Western countries have already shown the safety and efficacy of the PLGM system[11–16]. However, there have been no precise reports about the effect of PLGM on Japanese patients with diabetes mellitus, especially for a short time. Thus, the present retrospective observational study was carried out to evaluate the safety and efficacy of the MiniMed 640G device with PLGM use for 3 months in the patients of Juntendo University Hospital, Tokyo, Japan, who switched from the MiniMed 620G device.

METHODS

Study design

We recruited patients who switched from the MiniMed 620G pump (Medtronic) to the MiniMed 640G pump from the outpatient clinic of Juntendo University Hospital with available CGM data on glucose profile for >120 h per week at the time of pump change and at 3 months after pump change. The patients were educated about appropriate use of the new 640G pump at the outpatient clinic from the certified nurses in diabetes for >30 min. The data on insulin pumps were collected at the outpatient clinic every month as an uploaded file.

The primary outcome was the change in the percentage of time in hypoglycemia (%TIHypo) <70 mg/dL and the percentage of time in hypoglycemia <50 mg/dL. The secondary outcome was the change in HbA1c (%) at 3 months after pump change. We also investigated whether "post-suspend hyperglycemia"[12,16] occurred after changing to the MiniMed 640G device. In our preliminary analysis, we found conspicuous hyperglycemia after resumption in some patients, and the average peak time of the sensor glucose after the resumption was 3.07 h and the time interval of 1.5–4.5 h could cover the post-suspend hyperglycemia. Thus, in this study, we analyzed the time in post-suspend hyperglycemia, defined as glucose >180 mg/dL, (%TIHyper >180mg/dL) from 1.5 to 4.5 h after pump resumption. In addition to automatic pump resumptions, patients manually restarted pump function for some reasons. We also analyzed whether "post-suspend hyperglycemia" could be decreased depending on whether pump function was automatically or manually resumed within 30 min of suspension. In cases of manual resumption, there might be the possibilities of the risk of hypoglycemia. Thus, we also analyzed whether hypoglycemia occurred during 3 h from pump suspension. The protocol for this research project was approved by the ethics committee of Juntendo University Hospital (Approval No. 18-197). The study conformed to the provisions of the Declaration of Helsinki. All study participants provided informed consent.

Study participants

Among patients in the outpatient clinic of Juntendo University Hospital, 47 patients with type 1 diabetes mellitus and one patient having no endogenous insulin secretion because of total pancreatectomy were being treated with the MiniMed 620G device in March 2018. After March 2018, the MiniMed 640G device was launched in Japan. All the patients were asked to change the pump to avoid hypoglycemia more effectively with the PLGM component of 640G, and 36 patients intended to switch. The data on insulin pumps and sensors from 4 June in 2018 to 13 June in 2019 were collected.

Of these 36 patients, five patients were excluded from the study because of pregnancy during the study period, and one patient was excluded because of lack of consensus. Thus, we collected CGM and pump data from 30 patients. However, in 12 patients, we were not able to collect enough sensor glucose data to meet the inclusion criteria. In addition, one patient was excluded because of inappropriate pump use. We analyzed the data from the remaining 17 patients.

Statistical analysis

Data are expressed as the mean ± standard deviation for normally distributed data, and medians (interquartile range) for data with skewed distributions. The Mann-Whitney *U*-test and Wilcoxon signed-rank test were used for data analysis. A *P*-value <0.05 denoted the presence of a statistically significant difference. All statistical analyses were carried out using the JMP statistical software package, version 10.0.2 (SAS Institute, Cary, NC, USA).

RESULTS

The baseline characteristics of the study participants are presented in Table 1. At 3 months after pump change, HbA1c increased significantly from 7.6 ± 1.0% to 7.8 ± 1.1% ($P = 0.0161$). Total daily insulin dose before and after pump

Table 1 | Characteristics of study patients and continuous glucose monitoring data of more than consecutive 120 h per week at the time of the pump change and 3 months after the pump change

	At the time of the pump change	3 months after the pump change	*P*
Age (years)	51.6 ± 16.8		
Sex (male : female)	4:13		
Height (cm)	160.8 ± 8.2		
Bodyweight (kg)	58.5 ± 10.4		
Body mass index (kg/m^2)	22.5 ± 2.5		
Duration of T1DM (years)	21 (9–29.5)		
Duration of pump use, years (n = 15)	2.5 (2–12)		
HbA1c, % (n = 15)	7.6 ± 1.0	7.8 ± 1.1	0.0161*
Total daily insulin dose (units)	37.4 (26.91–43.28)	38.11 (28.24–43.92)	0.6950
Basal : bolus insulin (%)	40:60	40:60	0.9045
Duration of CGM data (days)	6.75 (5.8–6.88)	6.75 (6.42–6.79)	0.5537
Duration of pump suspension per day (min)	3 (1–14)	78 (37–137.75)	0.0006*
	1 month before the pump change	3 months after the pump change	
Average sensor glucose level (mg/dL)	147.67 (129.91–173.01)	159.88 (148.86–178.66)	0.0617
% Glucose <70 mg/dL	1.3 (0.42–5.92)	1.23 (0.26–2.66)	0.1203
% Glucose <50 mg/dL	0.39 (0–1.51)	0 (0–0.44)	0.0407*
% Glucose >180 mg/dL	25.53 (15.78–44.14)	32.9 (24.71–45.49)	0.0373*
% Glucose 70–180 mg/dL	69.31 (55.74–80.96)	61.66 (53.22–70.26)	0.0588

Total n = 17. Data were expressed as the mean ± standard deviation for normally distributed data, and medians (interquartile range) for data with skewed distributions. CGM, continuous glucose monitoring; T1DM, type 1 diabetes. *A P-value < 0.05 denoted the presence of a statistically significant difference.

change was comparable. No episodes of diabetic ketoacidosis or severe hypoglycemia were reported during the study period.

Although the average sensor glucose value did not change significantly, %TIHypo <50 mg/dL significantly decreased from 0.39% (0–1.51%) to 0% (0–0.44%; P = 0.0407) over the 3-month period. TIHypo <70 mg/dL decreased from 1.3% (0.42–5.92%) to 1.23% (0.26–2.66%), but this change was not statistically significant. In contrast, %TIHyper >180 mg/dL significantly increased from 25.53% (15.78–44.14%) to 32.9% (24.71–45.49%) at 3 months after pump change. Of note, %TIHyper >180 mg/dL from 1.5 h to 4.5 h after pump resumption was 32.23% (24.2–53.75%).

Besides automatic pump resumption, patients sometimes manually restarted the pump for reasons such as meals or fear of hyperglycemia. The number of automatic and manual resumptions, and the average duration until manual resumption are summarized in Table 2. It is obvious that patient 10 manually restarted the pump more frequently (10 times per week) and quickly (average of 3.1 min after suspension) than other patients. In contrast, five patients (patients 5, 6, 13, 14 and 16) did not manually restart the pump at all. PLGM settings are also summarized in Table 2. A total of 10 patients used PLGM with the "Before Low" setting, six patients used the "On Low" setting and one patient used both settings. Four patients changed the setting at daytime and at night while sleeping. Surprisingly, four patients set the sensor glucose level at a very low level, 50 mg/dL, for the "Before Low" or "On Low" alarm.

We compared the percentage of time in hyperglycemia from 1.5 h to 4.5 h after pump resumption by resumption type. % TIHyper >180 mg/dL during these 3 h was significantly lower when patients manually restarted the pump within 30 min compared with auto resumption (2.78% [0–21.6%] vs 31.2% [20–61.66%]; P = 0.0063). We also analyzed the percentage of time in hypoglycemia during 3 h after resumption. %TIHypo <50 mg/dL was 0% (0–8.03%) with manual resumption within 30 min from pump suspension and 0% (0–0.225%) with automatic resumption. There were no significant differences between the groups.

Different from other patients, the basic disease of patient 17 is after total pancreatectomy. He started MiniMed 620G soon after the operation of total pancreatectomy due to cancer in March 2017 and changed to 640G in March 2018. Before the switch, he manipulated the pump very well, and there were no episodes of hypoglycemia with glucose under 50 mg/dL. After pump change, %TIHypo <70 mg/dL decreased from 0.15% to 0.05%; however, his HbA1c increased from 7% to 7.4%. This is the case with successful prevention of hypoglycemia in the patients after total pancreatectomy by the use of PLGM.

DISCUSSION

From the Diabetes Control and Complications Trial dataset, biochemical hypoglycemia with glucose <70 mg/dL or <54 mg/dL is associated with an increased risk of severe hypoglycemia[17]. In the present study, we found that PLGM

Table 2 | List of study patients with the information of the device resumptions and their predictive low-glucose management setting

Patient	No. automatic and manual resumptions per week (automatic/manual)	Average duration until manual resumption (min)	PLGM setting, mg/dL (0 months)‡	PLGM setting, mg/dL (3 months from the pump change)‡
1	15/1	19	Before Low, 60	Before Low, 60
2	11/2	12.5	Before Low, 50	Before Low, 50
3	5/4	13.5	Before Low, 60	Before Low, 60
4	16/1	18	Before Low, 60	Before Low, 60
5	4/0	Did not manually restart	Before Low, 60	Before Low, 60
6	14/0	Did not manually restart	Before Low, 60	Before Low, 60
7	9/6	22.5	On Low, 80	On Low, 80
8	7/1	5	Daytime: On Low, 75 Night: On Low, 85	Daytime: On Low, 75 Night: On Low, 85
9	3/1	18	Daytime: On Low, 50 Night: On Low, 60	Daytime: On Low, 50 Night: On Low, 60
10	0/10	3.1	Daytime: On Low, 55 Night: On Low, 60	Daytime: On Low, 55 Night: On Low, 60
11	3/1	13	Daytime: On Low, 50 Night: Before Low, 50	Daytime: On Low, 50 Night: Before Low, 50
12	2/5	8	On Low, 50	On Low, 50
13	9/0	Did not manually restart	Before , 60	Before Low, 80
14	7/0	Did not manually restart	Before Low, 60	Before Low, 60
15	10/1	18	Before Low, 85	Before Low, 85
16	15/0	Did not manually restart	Before Low, 70	Before Low, 70
17†	20/4	25	On Low, 70	Before Low, 70

On Low: Set the predictive low-glucose management (PLGM) to alarm when the sensor glucose reaches the setting glucose level. Before Low: Set the PLGM to alarm before the sensor glucose reaches the setting glucose level. The number at PLGM setting is the setting glucose level. Some patients change the setting while sleeping at night. †Patient 17: After the total pancreatectomy. ‡PLGM setting. The PLGM component of the MiniMed 640G device automatically suspends insulin delivery when the sensor detects low glucose values or glucose values are predicted to reach 20 mg/dL above a preset low-glucose limit within 30 min.

significantly decreased the time in glucose <50 mg/dL, but significantly increased the time in hyperglycemia (glucose >180 mg/dL) and HbA1c at 3 months. We noticed the presence of conspicuous hyperglycemia after pump resumption, probably because the timing of resumption did not match glucose movement. This "post-suspend hyperglycemia"[12,16] would not have occurred without PLGM. We report for the first time that "post-suspend hyperglycemia" is frequently observed in adult patients undergoing PGLM pump therapy in a Japanese hospital. Our data suggest that this could be a major reason for worsening of HbA1c after pump change.

The previous studies[11,13–16] presented that an insulin pump with PLGM is an effective tool for reducing the time in hypoglycemia. For example, the Study of MiniMed 640G Insulin Pump with SmartGuard in Prevention of Low Glucose Events in Adults with Type (SMILE) study[11] is an open-label randomized controlled trial to investigate the effect of blood glucose control of MiniMed 640G pump with PLGM compared with that without PLGM for 6 months. This study showed that MiniMed 640G pump with PLGM is more effective for the reduction of %TIHypo <70 mg/dL and %TIHypo <55 mg/dL. Another 6-week randomized cross-over study, Prolog Trial also reported that PLGM is effective for reducing %TIHypo <70 mg/dL and TIHypo <50 mg/dL[15]. Compared with these previous studies, the data about time in hypoglycemia and hyperglycemia of the patients recruited here were comparable. In contrast, the amount of time with glucose >180 mg/dL was higher in the patients recruited in these studies, suggesting that glucose control should be more strictly managed without increasing hypoglycemia as much as possible.

To avoid "post-suspend hyperglycemia," some patients manually restarted the pump within 30 min after suspension. If the timing of pump resumption were effective, it could be helpful for glucose stabilization. %TIHyper >180 mg/dL over a period of 3 h was significantly lower when the patients manually restarted the pump within 30 min compared with automatic resumption. In contrast, if the timing of pump resumption were inappropriate, severe hypoglycemia can occur. However, in the present study, we did not observe any episodes of severe hypoglycemia. In addition, we did not find any differences in hypoglycemia during 3 h after resumption by resumption type. Thus, in the present study, the patients properly managed glucose control after pump suspension through manual resumption of pump function.

Regarding the etiology "post-suspend hyperglycemia," previous studies suggest it might be due to excessive carbohydrate consumption to prevent hypoglycemia when CGM alerts patients to falling glucose levels[12]. The present retrospective study did not include precise information about the timing of carbohydrate consumption. However, it might be elicited not only by pump suspension itself, but also by excessive carbohydrate consumption.

The Advanced Technologies & Treatments for Diabetes Congress identified time-in-range metrics for glycemic control that provide more actionable information than HbA1c alone, in February 2019[18]. As the present study started before the recommendations were released, our time below range (TBR; <50 mg/dL) was much stricter than 54 mg/dL, but the idea is almost the same. According to the guidance on targets for glycemic control in adults with type 1 or type 2 diabetes, the percentage of time-in-range (70–180 mg/dL) should be >70%, TBR (<54 mg/dL) should be <1%, TBR (<70 mg/dL) should be <4%, and time above range (TAR; >180 mg/dL) should be <25%. As Table 1 showed, compared with the recommendations, the percentage of TBR was lower with and without PLGM. However, the percentage of TAR was above the target with and without PLGM. The main purpose of changing to a pump with PLGM for the patients in this observational study was to avoid severe hypoglycemia. This was accomplished, as evidenced by the fact that %TIHypo <50 mg/dL decreased significantly at 3 months. However, it was obvious that the amount of time with glucose >180 mg/dL tended to be higher during real-world pump use. More strict management of hyperglycemia could be important for achieving the above target.

The present study had several limitations. First, the number of patients was small, mainly because we only recruited patients whose glucose profiles based on CGM data were available for >120 h per week for each period. The high percentage of patients that we could not include in this study suggests that not many patients continuously use CGM or cannot continue to wear it for a long time in the real world. A previous study showed that "time commitment, technical challenges, sensor alerts, sensor efficacy, sensor life and skin irritation" are some of the barriers[12] to continuous wearing. Second, this was a short-term study. Third, food and physical activity levels were not specifically reported in this retrospective study.

In the present study, we found that an insulin pump with PLGM is an effective tool for reducing the time in hypoglycemia in Japanese adult patients. At the same time, we also found more "post-suspend hyperglycemia[12,16]," which could be a cause of the increase in HbA1c. To prevent "post-suspend hyperglycemia," restarting the pump manually and properly before a meal could be useful. Indeed, in the present study, the patients properly managed after pump suspension through manual resumption of pump function. Thus, our data suggest that the patients who can manipulate pumps properly by accepting the guidance from health care professional would be good candidates to obtain benefits from 640G pump with PLGM.

DISCLOSURE

Junko Sato has received lecture fees from Sanofi-Aventis, Ono Pharmaceutical Co., Novo Nordisk Pharma, Novartis Pharmaceuticals, Daiichi Sankyo Inc., Mitsubishi Tanabe Pharma, Takeda Pharmaceutical Co., MSD, Terumo, Medtronic Japan Co. and Dainippon Sumitomo Pharma, and research funds from Sanofi-Aventis. Hirotaka Watada has received lecture fees from Boehringer Ingelheim, Sanofi-Aventis, Ono Pharmaceutical Co., Novo Nordisk Pharma, Novartis Pharmaceuticals, Eli Lilly, Sanwa Kagaku Kenkyusho, Daiichi Sankyo Inc., Takeda Pharmaceutical Co., MSD, Dainippon Sumitomo Pharma, and Kowa Co., and research funds from Boehringer Ingelheim, Pfizer, Mochida Pharmaceutical Co., Sanofi-Aventis, Novo Nordisk Pharma, Novartis Pharmaceuticals, Sanwa Kagaku Kenkyusho, Terumo Corp., Eli Lilly, Mitsubishi Tanabe Pharma, Daiichi Sankyo Inc., Takeda Pharmaceutical Co., MSD, Shionogi Pharma, Dainippon Sumitomo Pharma, Kissei Pharma and AstraZeneca. The other authors declare no conflict of interest.

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