1 **Original Article**

2 **The hypoglycemia-prevention effect of sensor-augmented pump therapy with**

3 **predictive low glucose management in Japanese patients with type 1 diabetes**

4 **mellitus: a short-term study.**

5

6 Akihiro Katayama[1*], Atsuhito Tone[2], Mayu Watanabe[3], Sanae Teshigawara[2], Satoshi Miyamoto[4], Jun

7 Eguchi[5], Atsuko Nakatsuka[5], Kenichi Shikata[4] and Jun Wada[5]

8

9 [1] Diabetes center, Okayama University Hospital, Kita-ku, Okayama 700-8558, Japan

10 [2] Okayama Saiseikai General Hospital, Diabetes Center, Kita-ku, Okayama 700-8511, Japan

11 [3] Department of Primary Care and Medical Education, Okayama University Graduate School of

12 Medicine, Dentistry and Pharmaceutical Sciences, Kita-ku, Okayama 700-8558, Japan

13 [4] Center for Innovative Clinical Medicine, Okayama University Hospital, Kita-ku, Okayama 700-

14 8558, Japan

15 [5] Department of Nephrology, Rheumatology, Endocrinology and Metabolism,

16 Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Kita-

17 ku, Okayama 700-8558, Japan

18

19 **Correspondence**:

20 Akihiro Katayama, M.D., Ph.D.

21 Diabetes center, Okayama University Hospital

22 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

23 Phone +81-86-235-7235

24 FAX +81-86-222-5214

25 E-mail: katayama-akihiro@okayama-u.ac.jp

26

1 **Abstract**

2 **Aims/Introduction:** The predictive low glucose management (PLGM) system was introduced in

3 March 2018 in Japan. Although there are some reports demonstrating the benefit of PLGM in

4 preventing hypoglycemia, no data are currently available in Japanese patients with type 1 diabetes

5 mellitus (T1DM). The aim of the present study is to evaluate the effect of PLGM with sensor-

6 augmented pump therapy in the prevention of hypoglycemia in Japanese patients.

7

8 **Materials and Methods:** We included 16 patients with T1DM who used the MiniMed®640G system

9 after switching from the MiniMed®620G system. We retrospectively analysed the data of the

10 continuous glucose monitoring system in one month after switching to MiniMed®640G.

11

12 **Results:** The area under the curve (AUC) of hypoglycemia of <70 mg/dL was lowered from 0.42 ±

13 0.43 mg/dL· day to 0.18 ± 0.18 mg/dL· day (P=0.012). Correspondingly, the duration of severe

14 hypoglycemia (<54 mg/dL) was reduced significantly from 15.3 ± 21.7 min/day to 4.8 ± 6.9 min/day

15 (P=0.019). The duration of hypoglycemia were reduced, but the reduction was not significant.

16 Regarding the AUC for hyperglycemia >180 mg/dL and the duration of hyperglycemia did not change.

17 With the PLGM function, 79.3% of the predicted hypoglycemic events were avoided.

18

19 **Conclusions:** The hypoglycemic reduction rate was comparable to those in previous reports. In

20 addition, we demonstrated that PLGM can markedly suppress severe hypoglycemia without

21 deteriorating glycemic control in Japanese T1DM patients. It is necessary to further investigate the

22 more effective use of the PLGM feature such as establishing a lower limit and the timing of resumption.

23

24 **Key words**: Hypoglycemia, Predictive low glucose management (PLGM), Type 1 diabetes mellitus

25 (T1DM), Sensor-augmented pump therapy (SAP)

Introduction

Currently, insulin pump therapy is one of the important treatment methods for type 1 diabetes mellitus (T1DM). Since sensor-augmented pumps (SAP) equipped with real-time continuous glucose monitoring (CGM) were launched in recent years, the management of glycemic control for individuals with T1DM has greatly advanced. Although these new medical devices such as CGM and SAP have enabled the prevention of severe hypoglycemia [1-6], the preventive effects have still not been satisfactory, especially in cases aiming for strict glycemic control. For these circumstances, the MiniMed®640G system (Medtronic, Northridge, CA, USA) was made commercially available in Japan in March 2018. This system includes a predictive low glucose management (PLGM) algorithm, in which insulin delivery is suspended when the sensor glucose (SG) value is predicted to be 20 mg/dl above the pre-set limit in 30 min. Previous studies have shown preventive effects on hypoglycemia in which 75 to 83% of cases of predicted hypoglycemia can be avoided without deteriorating glycemic control by using the PLGM feature [7, 8], but the clinical utility of the device in Japan has remained unknown.

In this study, we investigated the hypoglycemia-preventive effect of switching from the MiniMed®620G (Medtronic, Northridge, CA, USA) system to the MiniMed®640G system in Japanese patients with T1DM. We analysed glycemic profiles with the use of CGM data before and after changing the equipment.

Materials and Methods

This study was a retrospective observational study that was approved by the ethics committee of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (approval no. ken1812-016, approval date. 14 December 2018). We switched from the MiniMed®620G system to the MiniMed®640G system between April 2018 and October 2018 for all 21 patients with T1DM who are on SAP therapy at Okayama University Hospital. We included only 16 of these patients (4 males and 12 females) because the inclusion criteria for this study was

1   patients who used CGM for 5 days/week or more. Baseline characteristics of the participants were

2   shown in Table 1.

3   We retrospectively investigated the glycemic profile, insulin administration status and CGM data

4   before and 1 month after changing to the MiniMed®640G system using the CGM analysis software

5   (CareLink® Pro Therapy Management Software, Medtronic). Insulin administration status included

6   total daily insulin dose (TDD), total basal insulin dose (TBD), and the percentage of total basal

7   insulin dose to total daily insulin dose (%TBD); HbA1c and glycated albumin (GA) were used as the

8   glycemic profile. We analysed the mean SG value, the number of insulin suspensions by PLGM

9   (PLGM event), the duration of insulin suspension, severe hypoglycemia (< 54 mg/dL),

10   hypoglycemia (< 70 mg/dL) and hyperglycemia (> 180 mg/dL), the areas under the curve (AUCs)

11   for hypoglycemia and hyperglycemia and the carbohydrate values that the patients input for

12   automatic bolus calculation as the CGM data. In addition, we investigated the SG value at the time

13   of suspension initiation, the lowest SG value during suspension, the SG value at the resumption of

14   insulin infusion and the SG value 1 hour after initiating insulin infusion. All patients did not change

15   the basal insulin setting or carbohydrate-to-insulin ratio after the initiation of PLGM, and all patients

16   used the automatic bolus calculation function of the insulin pump. The preset lower limit value when

17   the PLGM feature was introduced was 70 mg/dL. Because previous report advocated that in case of

18   suspension, patients should monitor the trend and delay hypoglycemia treatment to ''let the pump do

19   the work'' [9], we recommended all patients not to resume insulin infusion manually during

20   suspension. However, we also advised them to resume insulin infusion manually at meals, even in

21   suspension mode, because they could not administer bolus insulin infusion while suspended. In

22   addition, we instructed patients not to perform preventive supplementation as much as possible

23   during suspension.

24

25   **Statistical Analysis**

1   All data are presented as the mean ± SD. Differences in HbA1c, GA, TDD, TBD, %TBD, and the

2   carbohydrate values measured before and after the change in treatment were analysed with the

3   Wilcoxon signed-rank test. Other statistical data were assessed with a Mann-Whitney U test. All

4   statistical analyses were performed with SPSS software version 20 (IBM SPSS statistics). A P value

5   of < 0.05 was considered statistically significant.

6

7   **Results**

8   **Glycemic control markers and insulin administration status**

9   Both the HbA1c and GA values were unchanged from before to after the PLGM feature was

10   introduced (HbA1c : $7.0 \pm 0.8\%$ vs. $7.0 \pm 0.9\%$, P=0.867, GA : $19.5 \pm 4.2\%$ vs. $20.1 \pm 3.5\%$, P=0.400).

11   TDD, TBD and %TBD all decreased after the PLGM feature was introduced, but this reduction was

12   not statistically significant (Table 2).

13   **CGM data**

14   There was no significant change in mean SG value, the duration of hyperglycemia or the AUC of

15   hyperglycemia >180 mg/dl from before to after the PLGM feature was introduced. No significant

16   decrease was observed in the duration (58.2 ± 49.4 min/day vs. 30.1 ± 25.9 min/day, P=0.067) of

17   hypoglycemia. In contrast, the duration of severe hypoglycemia (15.3 ± 21.7 min/day vs. 4.8 ± 6.9

18   min/day, P=0.019) and the AUC of hypoglycemia <70 mg/dL (0.42 ± 0.43 mg/dL· day vs. $0.18 \pm$

19   0.18 mg/dL· day, P=0.012) were both significantly reduced (Table 3). There were no episodes of

20   diabetic ketoacidosis (DKA) or serious device-related adverse events during the research period.

21   **PLGM operation status and hypoglycemia avoidance rate**

22   There were 1,345 PLGM events during the research period, for a rate of 3.0 ± 1.2 per subject per

23   day. In addition, the overall mean duration of suspension before hypoglycemic events was 156 ± 46

24   min/day. Moreover, 1,067 out of the 1,345 events did not reach the preset threshold; that is, 79.3% of

25   the predicted hypoglycemia was avoided (Fig. 1a). This hypoglycemia avoidance rate was similar in

26   the daytime (8:00 until 22:00) and night-time (22:00 until 8:00) (Fig. 1b).

The change in SG value during suspension and after resumption of insulin infusion

We further investigated the SG value at the time of suspension initiation (start), the lowest SG value during suspension (nadir), the SG value at the resumption (resumption) and the SG value 1 hour after resumption (resumption 1 hour). The mean SG value 1 hour after resumption increased to 136.7±16.7 mg/dL (Fig. 2a), and the mean suspension duration was 55.2 ± 10.6 min. In the comparison of daytime and night-time SG values, it was determined that the mean SG value at the start, nadir, resumption and resumption 1 hour were all higher in the daytime, but the differences were not significant (start: 102.8 ± 5.2 mg/dL vs. 100.5 ± 4.9 mg/dL, P=0.110, nadir: 84.6 ± 5.1 mg/dl vs 82.9 ± 6.1 mg/dl, P=0.323, resumption: 101.7 ± 6.5 mg/dL vs. 97.8 ± 6.2 mg/dL, P=0.094, resumption 1 hour: 140.1 ± 19.1 mg/dL vs. 128.5 ± 14.8 mg/dL, P=0.110) (Fig. 2b). In addition, the mean suspension time was significantly longer in the night-time than in the daytime (49.1 ± 10.2 min vs. 70.2 ± 16.0 min, P<0.0005).

Furthermore, we compared the SG value and the suspension time by 2-quantile groups such as BMI (high BMI group with BMI≥22, n=8; low BMI group with BMI<22, n=8), TDD (high TDD group with TDD≥38.7, n=8; low TDD group with TDD<38.7, n=8), TBD (high TBD group with TDD≥17.8, n=8; low TDD group with TDD<17.8, n=8) and %TBD (high %TBD group with %TBD>30, n=8; low %TBD group with %TBD≤30, n=8). We did not find a difference in SG value by BMI (Fig. 2c), TDD and TBD at any time point. Similarly, there was no difference in the mean suspension time. In contrast, the SG value at resumption 1 hour was significantly higher in the high %TBD group than in the low %TBD group (148.8 ± 12.9 mg/dl vs 124.6 ± 9.9 mg/dl, P=0.001) (Fig. 2d) without differences of the mean suspension time (57.2 ± 8.4 min vs. 53.2 ± 12.1 min, P=0.645).

Hyperglycemia after suspension

There were some cases in which the duration of hyperglycemia was increased by completely relying on the algorithm. Fig. 3a shows a case of hyperglycemia after 2 hours' suspension while sleeping. Fig. 3b shows a case of severe hyperglycemia after suspension of insulin infusion because PLGM started just after meal.

Discussion

1   Despite advances in medicine and medical devices, hypoglycemia remains a critical issue in the

2   treatment of T1DM. In recent years, the MiniMed®640G system equipped with a PLGM function

3   became available, and an improvement in the hypoglycemia avoidance rate is expected. We analysed

4   hypoglycemia prevention in Japanese T1DM patients using SAP therapy before and after switching

5   from the MiniMed®620G system to the MiniMed®640G system. In this study, there was a declining

6   trend in the duration of hypoglycemia, and the duration of severe hypoglycemia and the AUC of <70

7   mg/dL were both significantly reduced. The hypoglycemia avoidance rate was 79.3%, which was

8   almost the same in both the daytime and night-time. Moreover, the duration of hyperglycemia, the

9   AUC of >180 mg/dL, and the values of HbA1c and GA did not increase. From these results, it was

10   shown that the risk of hypoglycemia is lowered by using the PLGM feature without deteriorating

11   glycemic control, at least in the short-term.

12   Similar results have been reported in Western countries. Zhong A and colleagues retrospectively

13   examined the effect of PLGM, and they reported that both hypoglycemic (SG <70 mg/dL) and

14   hyperglycemic (SG >240 mg/dL) exposure time decreased in patients using PLGM [8]. Biester T et

15   al. reported that the frequency and duration of hypoglycemia and the AUC <70 mg/dL decreased

16   significantly in a prospective study of children with T1DM using PLGM for 6 weeks [9]. In addition,

17   Battelino T and colleagues carried out a randomized controlled trial of children with T1DM divided

18   into two groups with or without the use of PLGM for 14 days. They showed that the incidence of

19   hypoglycemic events with SG values <65 mg/dL was significantly reduced in the PLGM-treated group

20   during both the daytime and night-time, and there was no increase in hyperglycemic exposure time at

21   any level (SG value >140 mg/dL, >180 mg/dL and >250 mg /dL) [10]. However, their data

22   demonstrated that PLGM did not prevent severe hypoglycemia below 50 mg/dL, which is different

23   from our results. Battelino T and colleagues considered that the participants in their study were

24   relatively well-managed, the study period was too short, and the overall number of hypoglycemic

25   events below 50 mg/dL was too small to provide statistically significant results. More recently, the

26   results of a randomized controlled trial on the presence or absence of 6 months of PLGM use in 154

27   children and adolescent patients with T1DM were reported. This trial showed that the incidence of

1   hypoglycemic events with SG values <63 mg/dL decreased significantly in the PLGM group and that

2   the HbA1c value at 6 months was not significantly different between the two groups: 7.6 ± 1.0% in

3   the non-PLGM group and 7.8 ± 0.8% in the PLGM group. This result indicated that even when using

4   PLGM for a long time, glycemic control does not deteriorate [11]. Besides that, Maahs DM et al.

5   reported that the suspension system reduced nocturnal hypoglycemia (<60 mg/dl) by 12%, median

6   hypoglycemia area under the curve by 81% and hypoglycemia lasting >2hr by 74%. They also reported

7   overnight hyperglycemia (>180 mg/dl) was almost same level with or without suspension [12].

8   Regarding the hypoglycemia avoidance rate, Choudhary P et al. reported that 82.7% and 84.0% of

9   predicted hypoglycemia was avoidable in the daytime and the night-time, respectively, by using the

10   PLGM feature [7], while Zhong et al. reported that the avoidance rate was 73.9% and 77.4%,

11   respectively [8]. Since our study also showed a rate of hypoglycemia avoidance similar to those in

12   these reports, PLGM could be expected to suppress hypoglycemic events in Japanese patients with

13   T1DM.

14   Next, we investigated the change in the SG value during suspension and after resumption of insulin

15   infusion. We confirmed that the SG value increased 1 hour after resumption, which is the same as the

16   findings of previous reports [7, 9, 13-15]. When comparing daytime and night-time, the suspension

17   time was significantly longer at night, and the SG value at the start, resumption and resumption 1 hour

18   tended to be lower at night. Biester T et al. reported similar results in which the SG value 1 hour after

19   resumption was lower at night (174 mg/dL in the daytime vs. 137 mg/dL in the night-time), and the

20   suspension time during daytime was shorter than during night-time (54 min vs. 68 min) [9]. They

21   discussed that manual resumption was performed at approximately 46% after insulin suspension, and

22   as a result, the suspension time was shorter during the daytime, and the rise in SG value 1 hour after

23   resumption was noted in their article. Although we instructed the participants to avoid manual

24   resumption and preventive carbohydrate intake after suspension was initiated as much as possible after

25   the introduction of the PLGM feature, we obtained a similar result as those previously reported.

26   However, there was no significant difference in SG value after suspension between the daytime and

27   night-time, and it was considered that higher SG values in the daytime were prevented by instructing

1   the patients to follow the insulin pump algorithm. The reason the suspension time during the daytime

2   was longer than during the night-time is that it was necessary to resume insulin infusion manually at

3   the time of bolus administration at a meal. Moreover, since we could not confirm the manual

4   resumption rate, there is a possibility that manual resumption was carried out to the same extent as in

5   the previous report. These results suggested that better glycemic control could be obtained by

6   following the insulin pump algorithm rather than resuming the insulin infusion manually after PLGM

7   was initiated.

8   In addition, we speculated that the time-course changes in the SG value during and after suspension

9   might be influenced by BMI, TDD, TBD or %TBD, so we compared the SG value and the suspension

10   time classified with these parameters. Though there were no differences in the SG value and mean

11   suspension time when classified with BMI, TDD, and TBD, we found the differences of the SG value

12   at resumption 1 hour classified with %TBD. The reason for this is not clear, but in the low %TBD

13   group, relatively large amount of bolus insulin might overlay and mask the lack of basal insulin

14   supplement while basal insulin suspension, resulting in suppression of SG elevation after PLGM.

15   As shown in Figure 3, there were some cases of hyperglycemia after suspension. Zisser H examined

16   how much blood glucose would rise after interrupting insulin delivery. He demonstrated the rate of

17   rise in glucose concentration over 3 h was ~1 mg/dl for each minute insulin infusion was interrupted

18   [16]. Sherr JL et al. also reported the sensor glucose level rose by 18 ± 58 mg/dl by the end of the 2

19   h suspension, and by 55 ± 73 mg/dl 4 h after the suspension [17], and Fig. 3a follows their findings.

20   Fig. 3b shows a rebound hyperglycemia after suspension. In this case, PLGM started just after meal

21   and the participant ingested carbohydrates without resumption, resulting in rebound hyperglycemia.

22   Furthermore, this participant may have consumed excess amount of carbohydrate during

23   hypoglycemia. Collectively, we recognized that early insulin resumption was necessary to prevent

24   rebound hyperglycemia after carbohydrate intake for hypoglycemia, and we also need to inquire the

25   patient about amount of carbohydrate during hypoglycemia. Although the initial setting of the lower

26   limit was 70 mg/dL in this study, depending on the case, the timing of PLGM initiation was early or

1 the timing of the resumption of insulin infusion was late, and the subsequent increase in the SG value

2 was marked in some cases. Even though similar severe rebound hyperglycemia after PLGM has been

3 reported, such risk is believed to be very low [14,15,17,18]. Indeed, there were no cases with marked

4 hyperglycemia with ketoacidosis in our study.

5 This study had several limitations. First, this was a small retrospective observational study in a

6 single facility. Second, the participants were relatively well-managed patients with T1DM (mean

7 HbA1c 7.0%), so the frequency of hypoglycemia and hyperglycemia may be low. Third, the current

8 research period is short, only one month before and after PLGM introduction. Because of short

9 research period, we could not assess sustained effects on metabolic control and HbA1c. Most of the

10 published studies were limited to short-term evaluation for 2 to 6 weeks [7, 9, 10, 12]. Under longer

11 observation period for more than 2 months, other factors besides PLGM, such as a change in pump

12 settings and life-style. Therefore, we set 1 month to assess the real clinical picture of PLGM. In

13 addition, since we conducted thorough education for the patients before the introduction of

14 MiniMed®640G system to use the new system safely and effectively, we obtained such good results.

15 Besides these, we did not consider physical activity in this study. Recently, interesting results were

16 reported that assessed the optimal setting of the PLGM algorithm for preventing exercise-induced

17 hypoglycemia in adolescents with T1DM [19]. They concluded that setting a PLGM threshold to 90

18 mg/dL during the night in adolescents performing frequent physical exercise reduced time of

19 hypoglycemia; however, a threshold of 70 mg/dL seems to be safe during physical exercise.

20 It is necessary to further investigate the setting of the lower limit according to each case, time zone,

21 and the frequency of physical exercise; the timing of manual resumption; and the approach of

22 preventive carbohydrate intake against hypoglycemia. Finally, although PLGM is a very effective

23 mechanism, there are some points to be addressed, such as the fact that hypoglycemia cannot be

24 avoided completely and that there is a possibility of severe hyperglycemia after suspension of insulin

25 infusion. Therefore, when introducing PLGM, it is necessary to take sufficient time to explain the

26 features and precautions of this system to patients and to ensure that they use it with full understanding.

1

Conclusion

2

3   In this research, we demonstrated the short-term effects in which the PLGM feature can markedly

4   suppress hypoglycemia, particularly severe hypoglycemia, without deteriorating glycemic control in

5   Japanese patients with T1DM. Further examination is necessary to determine the longer-term effects

6   and to further improve of the hypoglycemia avoidance rate.

7

10

11   **Compliance with ethical standards**

18   **Ethical standards** All procedures followed were in accordance with the ethical standards of the

19   responsible committee on human experimentation (institutional and national) and with the Helsinki

20   Declaration of 1964 and later versions. This study was approved by the ethics committee of Okayama

21   University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (approval no.

22   ken1812-016, approval date. 14 December 2018). We did not receive the informed consent, but we

23   provided the participants with the opportunity to deny by publishing the Opt Out document.

24

References

1. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, Kollman C, Kruger D, McGill JB, Polonsky W, Toschi E, Wolpert H, Price D; DIAMOND Study Group. Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA 2017; 24; 317(4): 371-378.

2. Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, Hermanns N. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycemia awareness or severe hypoglycemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 2018; 7; 391(10128): 1367-1377.

3. Atsuko M, Yushi H, Shin U, Tetsushi H, Takehito T, Hiroshi M, Natsu S, Anna S, Tomoaki N, Hisako K, Yuko O, Kazuhiko S, Wataru O. Effect of switching from conventional continuous subcutaneous insulin infusion to sensor augmented pump therapy on glycemic profile in Japanese patients with type 1 diabetes. Diabetol Int 2018; 9(3): 201-207.

4. Battelino T, Conget I, Olsen B, Schütz-Fuhrmann I, Hommel E, Hoogma R, Schierloh U, Sulli N. Bolinder J; SWITCH Study Group. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomized controlled trial. Diabetologia 2012; Dec; 55(12): 3155-62.

5. Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, Joyce C, Peoples T, Perkins BA, Welsh JB, Willi SM, Wood MA, STAR 3 Study Group. Effectiveness of sensor augmented insulin-pump therapy in type 1 diabetes. N Engl J Med 2010; 22; 363(4): 311-20.

6. Bosi E, Choudhary P, de Valk HW, Lablanche S, Castañeda J, de Portu S, Da Silva J, Ré R, Vorrink-de Groot L, Shin J, Kaufman FR, Cohen O; SMILE Study Group. Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): an open-label randomised controlled trial. Lancet Diabetes Endocrinol; 2019; 7(6):462-472.

7. Choudhary P, Olsen BS, Conget I, Welsh JB, Vorrink L, Shin JJ. Hypoglycemia prevention and user acceptance of an insulin pump system with predictive low glucose management. Diabetes Technol Ther 2016; 18(5):288-291.

8. Zhong A, Choudhary P, McMahon C, Agrawal P, Welsh JB, Cordero TL, Kaufman FR. Effectiveness of automated insulin management features of the MiniMed® 640G sensor-augmented insulin pump. Diabetes Technol Ther 2016; 18(10): 657-663

9. Biester T, Kordonouri O, Holder M, Remus K, Kieninger-Baum D, Wadien T, Danne T. "Let the algorithm do the work": Reduction of hypoglycemia using sensor-augmented pump therapy with predictive insulin suspension (SmartGuard) in pediatric type 1 diabetes patients. Diabetes Technol Ther 2017; 9(3): 173-182

10. Battelino T, Nimri R, Dovc K, Phillip M, Bratina N. Prevention of hypoglycemia with predictive low glucose insulin suspension in children with type 1 diabetes: A randomized controlled trial. Diabetes Care 2017; 40(6): 764-770.

11. Abraham MB, Nicholas JA, Smith GJ, Fairchild JM, King BR, Ambler GR, Cameron FJ, Davis EA, Jones TW; PLGM Study Group. Reduction in hypoglycemia with the predictive low-glucose management system: A long-term randomized controlled trial in adolescents with type 1 diabetes. Diabetes Care 2018; 41(2): 303-310.

12. Maahs DM, Calhoun P, Buckingham BA, Chase HP, Hramiak I, Lum J, Cameron F, Bequette BW, Aye T, Paul T, Slover R, Wadwa RP, Wilson DM, Kollman C, Beck RW; In Home Closed Loop Study Group. A randomized trial of a home system to reduce nocturnal hypoglycemia in type 1 diabetes. Diabetes Care. 2014; Jul;37(7):1885-91

13. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, Ahmann AJ, Welsh JB, Lee SW, Kaufman FR; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013; 369(3): 224-232.

14. Agrawal P, Zhong A, Welsh JB, Shah R, Kaufman FR. Retrospective analysis of the real-world use of the threshold suspend feature of sensor-augmented insulin pumps. Diabetes Technol Ther 2015; 17(5): 316-319.

15. Buckingham BA, Cameron F, Calhoun P, Maahs DM, Wilson DM, Chase HP, Bequette BW, Lum J, Sibayan J, Beck RW, Kollman C. Outpatient safety assessment of an in-home predictive low-glucose suspend system with type 1 diabetes subjects at elevated risk of nocturnal hypoglycemia. Diabetes Technol Ther 2013; 15(8): 622-627

16. Zisser H, Quantifying the impact of a short-interval interruption of insulin-pump infusion sets on glycemic excursions. Diabetes Care. 2008; 31(2):238-9

17. Sherr JL, Palau Collazo M, Cengiz E, Michaud C, Carria L, Steffen AT, Weyman K, Zgorski M, Tichy E, Tamborlane WV, Weinzimer SA. Safety of nighttime 2-hour suspension of basal insulin in pump-treated type 1 diabetes even in the absence of low glucose. Diabetes Care 2014; 37(3): 773-779

18. Calhoun PM, Buckingham BA, Maahs DM, Hramiak I, Wilson DM, Aye T, Clinton P, Chase P, Messer L, Kollman C, Beck RW, Lum J; In Home Closed Loop Study Group. Efficacy of an overnight predictive low-glucose suspend system in relation to hypoglycemia risk factors in youth and adults with type 1 diabetes. J Diabetes Sci Technol 2016; 10(6): 1216-1221

19. Cherubini V, Gesuita R, Skrami E, Rabbone I, Bonfanti R, Arnaldi C, D'Annunzio G, Frongia A, Lombardo F, Piccinno E, Schiaffini R, Toni S, Tumini S, Tinti D, Cipriano P, Minuto N, Lenzi L, Ferrito L, Ventrici C, Ortolani F, Cohen O, Scaramuzza A. Optimal predictive low glucose management (PLGM) settings during physical exercise in adolescents with type 1 diabetes. Pediatr Diabetes 2019; 20(1): 107-112

1 **Figure Legends**

2

3 **Figure 1. The number of PLGM events and the hypoglycemia avoidance rate**

4 a: over 24 hours

5 b: during the daytime and night-time

6

7 **Figure 2. The change in the SG value during suspension and after resumption of insulin infusion**

8 a: All PLGM data

9 b: Classified by event starting time: daytime and night-time. The differences between day and night

10   are not significant.

11 c: Classified by BMI of patients. The differences between high BMI group and low BMI group are not

12   significant.

13 d: Classified by %TBD of patients. the SG value at resumption 1 hour was significantly higher in the

14   high %TBD group than in the low %TBD group

15 SG: sensor glucose, All data are presented as the mean ± standard deviation (SD).

16 * Statistically significant, $P < 0.05$

17

18 **Figure 3. The cases of hyperglycemia after suspension**

19 a: A case of hyperglycemia after 2 hours suspension at bedtime

20 b: A case of severe hyperglycemia after suspension of insulin infusion because PLGM started just

21 after

22   a meal

23 Arrows show the degree of SG value increase, and squares indicate the time during which PLGM
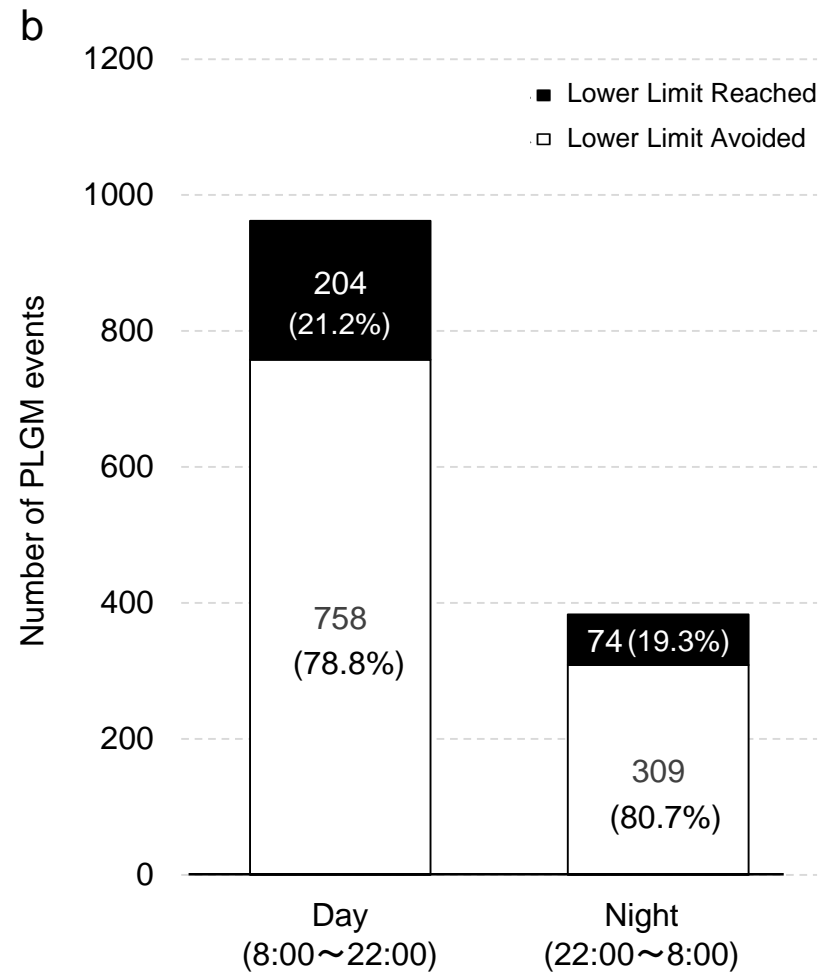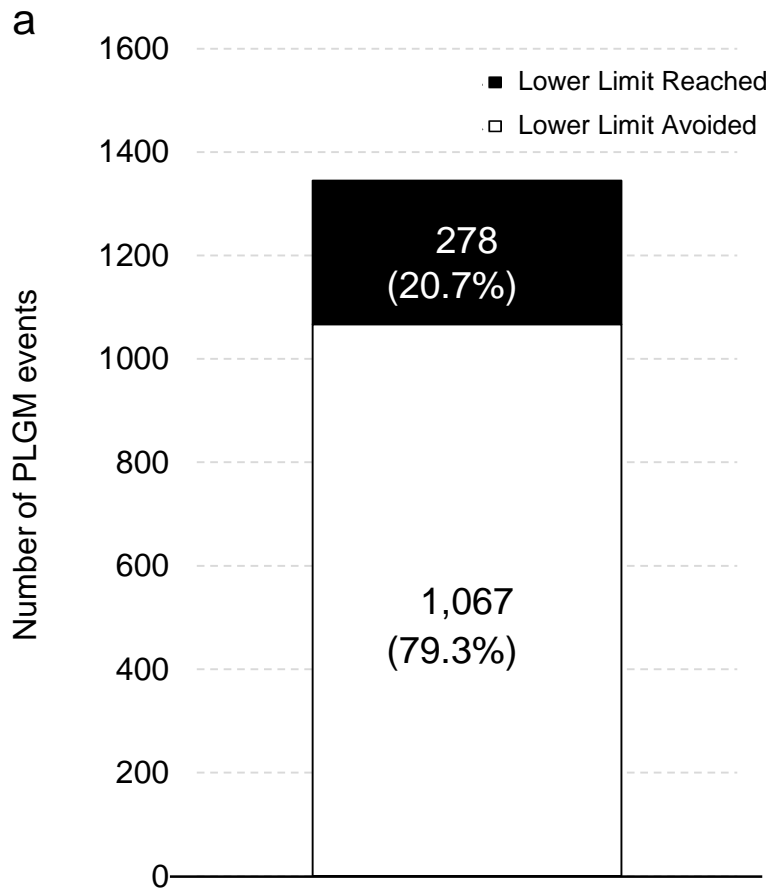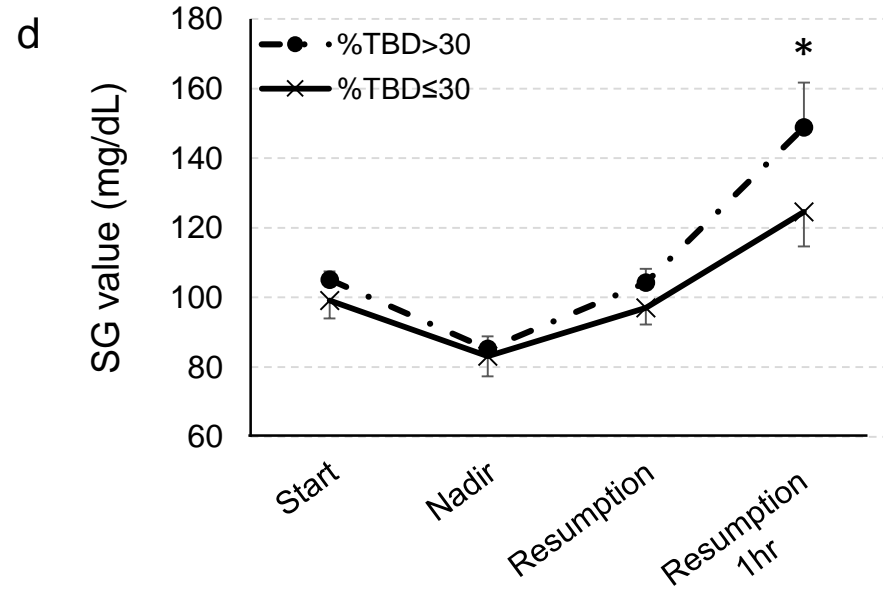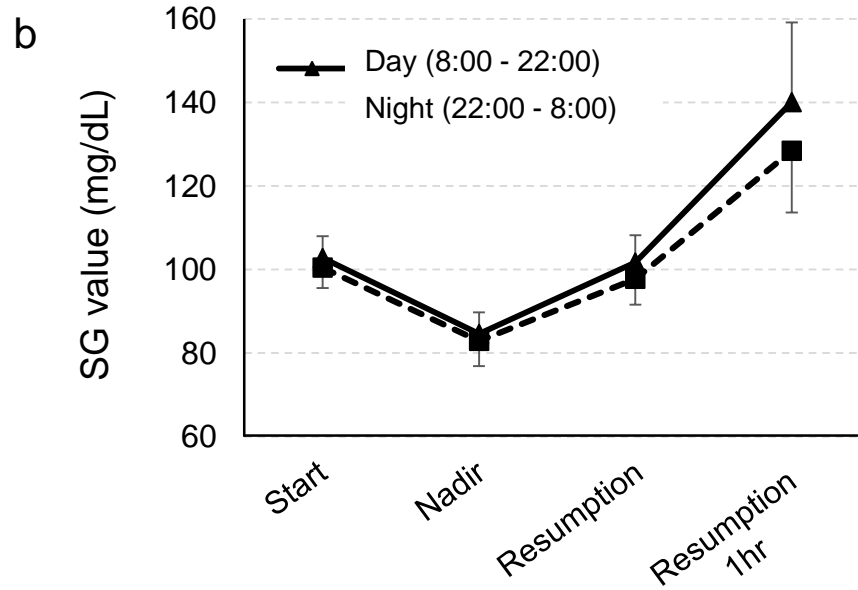
   was operating.

Figure 1

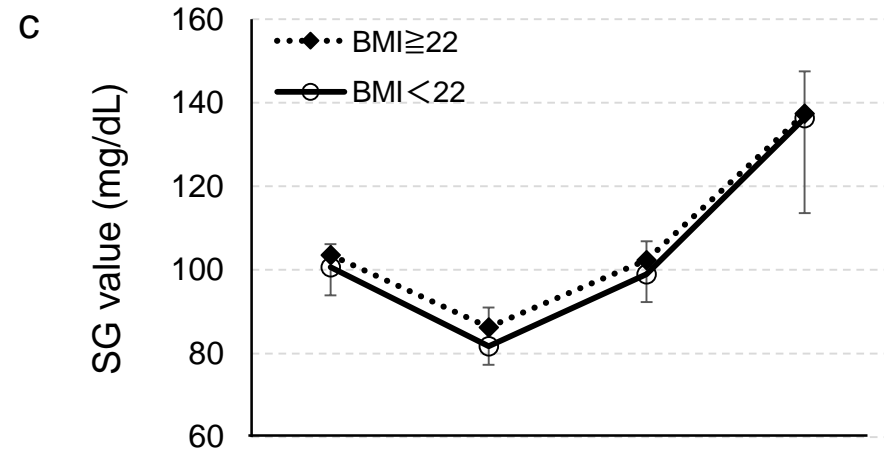Figure 2

Figure 3

a

SG
(mg/dl)

Insulin
(U/hr)

2.0

Time

b

1.5

10.0

Time
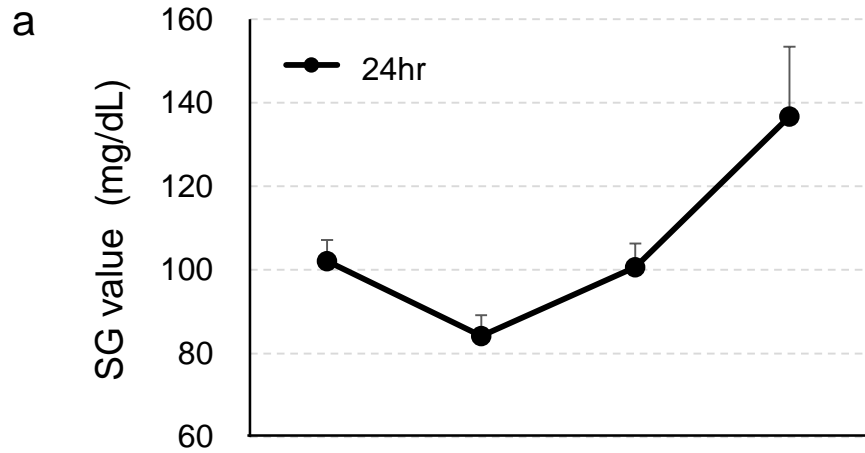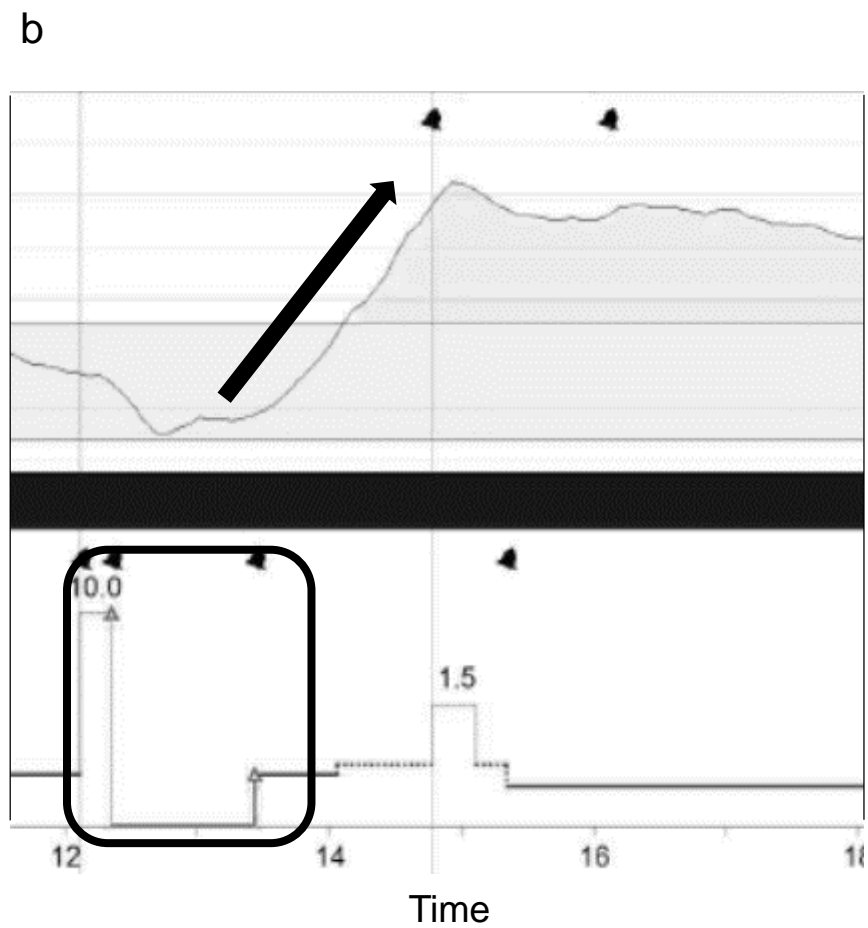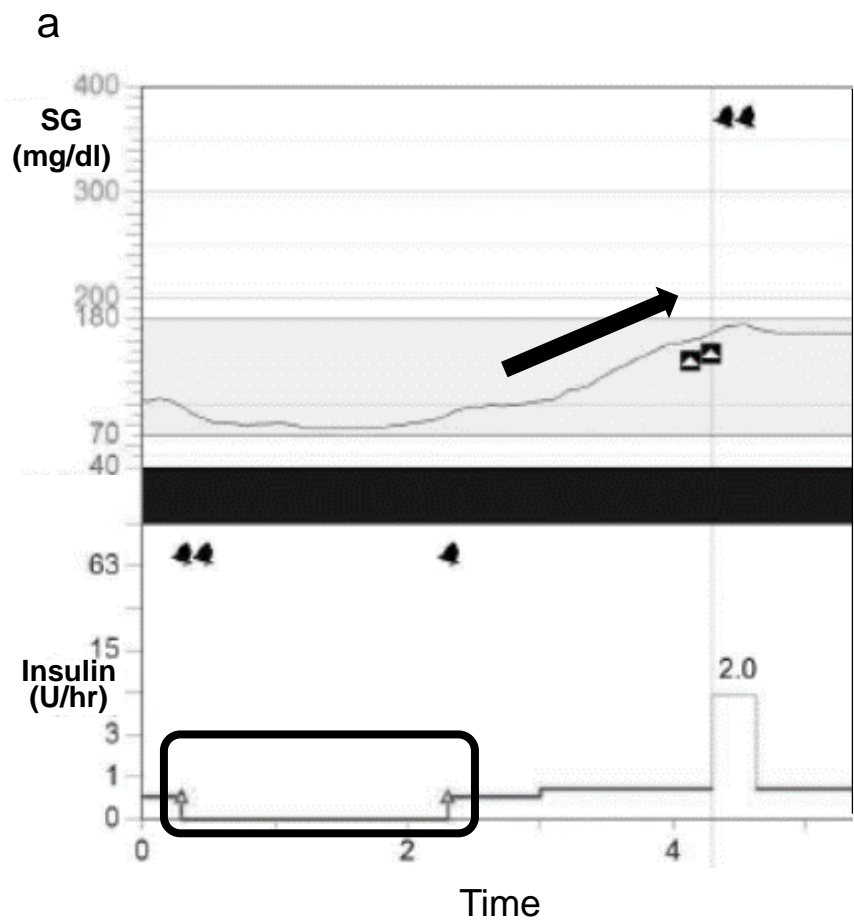
Table 1. Baseline characteristics of the participants

Parameter	Mean ± standard deviation	Range
N (F)	16 (12)	-
Age (years)	46.1 ± 16.9	17 – 78
BMI (kg/m^2)	22.2 ± 2.6	17.7 – 27.4
Duration of diabetes (years)	15.8 ± 12.6	2 – 44
Experience with CSII (years)	5.4 ± 2.7	1.3 – 7.8
Experience with SAP (years)	2.2 ± 1.0	0.8 – 3.9
HbA1c (%)	7.0 ± 0.8	5.8 – 8.6
GA (%)	19.5 ± 4.2	13.0 – 27.5
TDD (u/day)	40.9 ± 13.0	22.2 – 64.9
TBD (u/day)	12.2 ± 5.2	5.1 – 22.4
%TBD (%)	30.9 ± 14.4	17 – 46
Carbohydrate input value (g/day)	177 ± 64	91 –251

BMI; body mass index, CSII; continuous subcutaneous insulin infusion, SAP;

sensor-augmented pump, GA; glycated albumin, TDD; total daily insulin dose; TBD;

total basal insulin dose, %TBD; the percentage of the total basal insulin dose out of the

total daily insulin dose.

Table 2. Comparison of glycemic control markers and insulin administration

status before and after PLGM was introduced

	Baseline	PLGM	*P*
HbA1c (%)	7.0 ± 0.8	7.0 ± 0.9	0.867
GA (%)	19.5 ± 4.2	20.1 ± 3.5	0.400
TDD (u/day)	40.9 ± 13.0	38.1 ± 11.4	0.564
TBD (u/day)	12.2 ± 5.2	11.0 ± 5.2	0.402
%TBD (%)	30.9 ± 14.4	29.3 ± 13.2	0.616
Carbohydrate input value (g/day)	177 ± 64	189 ± 73	0.696

GA; glycated albumin, TDD; total daily insulin dose, TBD; total basal insulin

dose, %TBD: the percentage of the total basal insulin dose out of the total daily insulin

dose. All data are presented as the mean ± standard deviation (SD).

Table 3. Comparison of the CGM data before and after PLGM was introduced

	Baseline	PLGM	*P*
SG value (mg/dl)	155.3 ± 34.0	152.9 ± 44.2	0.669
Time >180 mg/dL (min/day)	421.3 ± 262.0	440.4 ± 290.1	0.926
AUC >180 (mg/dL/day)	17.8 ±19.2	16.1 ± 14.0	0.926
Time <70 mg/dL (min/day)	58.2 ± 49.4	30.1 ± 25.9	0.067
Time <54 mg/dL (min/day)	15.3 ± 21.7	4.8 ± 6.9	0.019*
AUC <70 (mg/dL/day)	0.42 ±0.43	0.18 ± 0.18	0.012*

SG, sensor glucose; AUC, area under the curve. All data are presented as the mean ±

standard deviation (SD), * P <0.05.