A Randomized Trial of a Home System to Reduce Nocturnal Hypoglycemia in Type 1 Diabetes

OBJECTIVE

Overnight hypoglycemia occurs frequently in individuals with type 1 diabetes and can result in loss of consciousness, seizure, or even death. We conducted an in-home randomized trial to determine whether nocturnal hypoglycemia could be safely reduced by temporarily suspending pump insulin delivery when hypoglycemia was predicted by an algorithm based on continuous glucose monitoring (CGM) glucose levels.

RESEARCH DESIGN AND METHODS

Following an initial run-in phase, a 42-night trial was conducted in 45 individuals aged 15–45 years with type 1 diabetes in which each night was assigned randomly to either having the predictive low-glucose suspend system active (intervention night) or inactive (control night). The primary outcome was the proportion of nights in which \( \leq 60 \) mg/dL occurred.

RESULTS

Overnight hypoglycemia with at least one CGM value \( \leq 60 \) mg/dL occurred on 196 of 942 (21%) intervention nights versus 322 of 970 (33%) control nights (odds ratio 0.52 [95% CI 0.43–0.64]; \( P < 0.001 \)). Median hypoglycemia area under the curve was reduced by 81%, and hypoglycemia lasting >2 h was reduced by 74%. Overnight sensor glucose was >180 mg/dL during 57% of control nights and 59% of intervention nights (\( P = 0.17 \)), while morning blood glucose was >180 mg/dL following 21% and 27% of nights, respectively (\( P < 0.001 \)), and >250 mg/dL following 6% and 6%, respectively. Morning ketosis was present <1% of the time in each arm.

CONCLUSIONS

Use of a nocturnal low-glucose suspend system can substantially reduce overnight hypoglycemia without an increase in morning ketosis.
when a near-hypoglycemia glucose threshold is reached can reduce the frequency and duration of hypoglycemia without increasing hyperglycemia. The next logical step is to suspend insulin delivery earlier, when the glucose trend predicts hypoglycemia.

We developed such a hypoglycemia prediction algorithm and have tested it in a system in which a CGM device communicates with an insulin pump via a laptop computer on which the algorithm resides (4). Following demonstration of efficacy by reducing nocturnal hypoglycemia in an inpatient study (5) and an outpatient pilot study (6), the current randomized trial was designed to assess the efficacy and safety of home use of the automated nocturnal predictive low-glucose suspend system in a larger number of individuals with type 1 diabetes over a longer time period.

RESEARCH DESIGN AND METHODS

The study was conducted at three clinical centers. The protocol was approved by each institutional review board, and written informed consent was obtained from each participant or parent, with assent obtained as required. An independent data and safety monitoring board provided oversight. The study is listed on ClinicalTrials.gov (NCT01591681). Key aspects of the study protocol are described below.

Major eligibility criteria included ages 15–45 years; type 1 diabetes with use of daily insulin therapy for ≥1 year and an insulin infusion pump for ≥6 months; and glycated hemoglobin level measured with a point-of-care device ≤8.0%. Exclusion criteria are listed in Supplementary Table 1.

The pump suspension system consisted of a MiniMed Paradigm REAL-Time Veo System and Enlite glucose sensor (Medtronic Diabetes, Northridge, CA), in which the CGM and pump communicate with a bedside laptop computer that contained the hypoglycemia prediction algorithm (referred to as “the system”). The system used a Kalman filter to estimate the glucose level and rate of change and suspended basal insulin delivery if glucose was predicted to fall <80 mg/dL in the next 30 min (6). Additional suspension/restart rules included a threshold suspend override at 70 mg/dL, no suspension if CGM >230 mg/dL or if a pressure-induced sensor attenuation was suspected based on glucose rate of change, and restoration of basal insulin on the first CGM rise following a suspension. For safety reasons, pump suspension could not exceed 120 min in a 150-min window or a cumulative total of 180 min nightly. Audible alarms were set at 60 mg/dL on both intervention and control nights. Additional details about the system have been published (6).

A run-in phase preceded the randomized trial. During the initial part of the run-in phase, CGM was initiated and used for 10–15 days to verify that the participant could successfully use the CGM device and to document a minimum amount of nocturnal hypoglycemia (at least one night with a sensor glucose value ≤60 mg/dL or at least 3 different nights with a sensor glucose value ≤70 mg/dL). Successful participants then used the complete system at home for 5 nights to verify the ability to use it properly. Three participants did not successfully complete the first part of the run-in phase, and one additional participant did not successfully complete the second part (Supplementary Fig. 1).

During the randomized trial, the system was used until 42 nights with at least 4 h of sensor glucose data were completed. The laptop contained a randomization schedule that indicated whether the hypoglycemia prediction algorithm would be in operation that night (intervention night) or would not be activated (control night), to which the participant was blinded, with half of the nights being intervention nights and half control nights. A bedtime blood glucose level between 90 and 270 mg/dL was required to start the system. Participants were instructed to use the system on consecutive nights if possible but to avoid system use during periods of illness. The maximum allowable number of days to complete the 42 nights of the study was 70. Supplementary Fig. 2 shows a system schematic and example overnight data profile for an intervention night.

When the system was stopped in the morning, blood glucose (with OneTouch Ultra2 meter; LifeScan, Milpitas, CA), blood ketone (with Precision Xtra meter; Abbott Diabetes Care, Alameda, CA), and urine ketone (with Ketostix strips; Bayer, Pittsburgh, PA) levels were measured, and overnight carbohydrate intake was recorded. During the day, the participant used the CGM device and pump as it would be prescribed for usual diabetes management (without the algorithm being active). The threshold-based low-glucose suspend feature of the Veo pump was disabled while the pump was used in the study.

Adverse event reporting included severe hypoglycemia, diabetic ketoacidosis, and any study or device-related event.

Statistical Methods

Sample size was computed to be 45 participants using the system for 42 nights (21 nights with the system active and 21 control nights) for a total of 1,890 nights in order to have 90% power with a type 1 error rate of 5% to reject the null hypothesis of no difference in nocturnal hypoglycemia, assuming a true population rate of 30% of control nights and 15% of intervention nights with hypoglycemia after adjusting for the correlation from repeated nights and misclassification due to sensor inaccuracy (7).

The analysis followed the intent-to-treat principle with each night analyzed by the intervention arm assigned by randomization. The time period for outcome assessment each night was from the participant’s initiation of the system at bedtime until deactivation the following morning. All randomized nights were included in safety analyses; however, only randomized nights with ≥4 h of CGM glucose data were included in the efficacy analysis based on an a priori rule.

The primary outcome was the proportion of nights in which one or more CGM glucose value ≤60 mg/dL occurred. Numerous other overnight CGM-measured outcomes were assessed. Primary safety outcomes included morning blood glucose and ketone levels. For continuous variables, repeated-measures regression models were used to test the differences between the two treatment arms, accounting for correlated data from the same participant and for the overnight measures, adjusting for the bedtime blood glucose value. Ranked normal score transformations were used for continuous outcomes variables with a skewed distribution. For binary variables, repeated-measures logistic regression was used to test the differences between the two treatment arms using mixed-effects and a within-subject
autocorrelation structure to account for multiple nights from the same subject. Four clinicians, blinded to control versus intervention, reviewed each night with a hypoglycemic outcome to opine whether the drop in glucose level appeared to be physiologic. In a secondary analysis, only outcomes in which at least two of four expert reviewers believed the outcome to be valid were included. All P values are two-tailed, and analyses were performed using SAS 9.3 (SAS Institute).

RESULTS

The randomized trial included 45 individuals with type 1 diabetes (age range 15–45 years; 47% male; 93% Caucasian; median type 1 diabetes duration 15 years; median glycated hemoglobin level 6.8% (Supplementary Tables 2 and 3). Forty-one (91%) of the 45 participants completed the protocol-specified 42 nights of the study (30, 39, 41, and 41 nights completed in the other four participants). The median number of nights to complete the study was 60 (Supplementary Table 6). Overall, there were 1,912 nights in the analyses, with 942 being intervention nights and 970 control nights.

One or more pump suspensions occurred on 719 (76%) of the 942 intervention nights, with a median total duration of pump suspension of 71 (interquartile range [IQR] 29–115) minutes (Supplementary Table 4). On 10% of nights, there was a pump suspension lasting 120 min within a 150-min window, and on 3% of nights, cumulative suspension time was the maximum 3 h.

Overnight hypoglycemia with at least one CGM value ≤60 mg/dL occurred on 196 of 942 (21%) intervention nights versus 322 of 970 (33%) control nights (odds ratio 0.52 [95% CI 0.43–0.64]; P < 0.001) (Table 1). Results were consistent for other hypoglycemia outcomes overall (Table 1) and within age groups 21–45 and 15–20 years (Supplementary Table 5). As shown in Fig. 1, the treatment arm difference in first overnight occurrence

Table 1—Efficacy and safety outcome measures

| Outcome Measure | Control arm (N = 45) | Intervention arm (N = 45) | P value |
|-----------------|----------------------|---------------------------|---------|
| Number of nights | 970                  | 942                       |         |
| Bedtime measures |                      |                           |         |
| Bedtime sensor glucose, mg/dL [median (IQR)] | 144 (109–192) | 143 (110–189) |         |
| Bedtime blood glucose, mg/dL [median (IQR)] | 152 (114–197) | 144 (115–195) |         |
| Overnight measures using CGM sensor |                      |                           |         |
| Number of measurements/night [median (IQR)] | 96 (84–110) | 96 (85–107) |         |
| Hypoglycemia outcomes |                      |                           |         |
| Percentage of nights with ≥1 value, mg/dL ≤50 | 19 | 10 | <0.001 |
| ≤60* | 33 | 21 | <0.001 |
| ≤70 | 45 | 32 | <0.001 |
| Percentage of nights with ≥2 consecutive values ≥60 mg/dL | 31 | 19 | <0.001 |
| Percentage of nights with ≥5 consecutive values ≥60 mg/dL | 25 | 14 | <0.001 |
| Participant time <60 mg/dL per 8 h, min [median (IQR)]† | 23 (11–45) | 7 (3–12) | <0.001 |
| Participant time <50 mg/dL per 8 h, min [median (IQR)]† | 10 (4–25) | 2 (0–4) | <0.001 |
| Participant overnight AUC 60 mg/dL per 8 h [median (IQR)]† | 215 (88–482) | 40 (18–96) | <0.001 |
| Participant LBGI [median (IQR)] | 2.28 (1.45–3.52) | 0.92 (0.69–1.63) | <0.001 |
| Hyperglycemia outcomes |                      |                           |         |
| Percentage of nights with ≥1 value, mg/dL >180 | 57 | 59 | 0.17 |
| >250 | 20 | 20 | 0.93 |
| >300 | 5 | 6 | 0.37 |
| >400 | 0 | 0 | — |
| Participant time >250 mg/dL per 8 h, min [median (IQR)]† | 12 (5–19) | 10 (4–19) | 0.78 |
| Participant overnight AUC 250 mg/dL per 8 h [median (IQR)]† | 236 (83–772) | 219 (72–666) | 0.98 |
| Participant HBGI [median (IQR)] | 4.17 (2.99–5.30) | 3.99 (2.50–5.73) | 0.95 |
| Overall control outcomes |                      |                           |         |
| Overnight mean glucose, mg/dL [median (IQR)] | 125 (98–163) | 132 (110–163) | <0.001 |
| Percentage of glucose values 71–180 mg/dL [median (IQR)] | 75 (46–93) | 82 (54–99) | <0.001 |
| Morning measures |                      |                           |         |
| Morning blood glucose, mg/dL [median (IQR)]‡ | 129 (96–173) | 144 (114–186) | <0.001 |
| Percentage of mornings with blood glucose, mg/dL ≤60 | 4 | <1 | <0.001 |
| ≤70 | 9 | 2 | <0.001 |
| 71–180 | 70 | 70 | 0.87 |
| >180 | 21 | 27 | <0.001 |
| >250 | 6 | 6 | 0.71 |
| Percentage of mornings with blood ketone >1.0 mmol/L§ | 0.3 | 0.1 | 0.62 |
| Percentage of mornings with urine ketones ≥15 mg/dL¶ | 2 | 3 | 0.10 |

*Boldface indicates prespecified primary outcome. †For each patient, time below and above a threshold and AUC was divided by total time and multiplied by 8 h. ‡One morning blood glucose measurement in the control arm was missing. §Nine blood ketone measurements in the control arm and 10 blood ketone measurements in the intervention arm were missing. ¶ value computed using permutation test because parametric analysis had convergence issue. ¶Twelve urine ketone measurements in the control arm and 12 urine ketone measurements in the intervention arm were missing.
of hypoglycemia was most prominent after the first 3 h. Results were similar when hypoglycemic outcomes were confirmed by the clinician-blinded review in which hypoglycemic glucose values were considered to be invalid (nonphysiologic) on 27 intervention nights and 30 control nights. Reclassifying these nights as "no hypoglycemia," overnight hypoglycemia with at least one CGM value \( \leq 60 \text{ mg/dL} \) occurred on 169 of 942 (18%) intervention nights versus 292 of 970 (30%) control nights (odds ratio 0.50 [95% CI 0.41–0.62]; \( P < 0.001 \)).

The cumulative amount of hypoglycemia exposure was substantially less on intervention nights compared with control nights (Table 1). Median hypoglycemia area under the curve (AUC) was 81% lower on intervention nights compared with control nights, median time \( \leq 60 \text{ mg/dL} \) was 70% lower, and median time \( \leq 50 \text{ mg/dL} \) was 80% lower (Table 1). Results were unchanged when these analyses included the 95 nights with \( >4 \text{ h} \) of sensor glucose data. Sensor values were \( \leq 60 \text{ mg/dL} \) for \( >2 \text{ h} \) on 3% of intervention nights versus 11% of control nights (\( P < 0.001 \); Fig. 2, Supplementary Fig. 3, and Supplementary Table 8). Participants reported overnight carbohydrate intake on 75 (8%) intervention nights and 142 (15%) control nights.

Although overnight mean glucose was slightly higher on intervention than control nights (median 132 [IQR 110–163] vs. 125 [98–163] mg/dL, respectively; \( P < 0.001 \)) (Fig. 3), the percentages of nights with a glucose value \( >180 \text{ or } >250 \text{ mg/dL} \) were not (59 vs. 57% \( >180 \text{ mg/dL} \); \( P = 0.17 \); and 20 vs. 20% \( >250 \text{ mg/dL} \); \( P = 0.93 \)), and the median percentage of glucose values 71–180 mg/dL was higher on intervention nights compared with control nights (82 [IQR 54–99] vs. 75% [46–93%], respectively; \( P < 0.001 \) (Table 1).

Median morning blood glucose was 144 mg/dL (IQR 114–186 mg/dL) following intervention nights versus 129 mg/dL (IQR 96–173 mg/dL) following control nights (\( P < 0.001 \)). In each arm, 6% of nights had values \( >250 \text{ mg/dL} \). As seen in Table 1, the frequency of elevated morning urine or blood ketones was low and similar in the two treatment arms. Median glycated hemoglobin level of 6.8% at study completion was unchanged from baseline (Supplementary Table 7).

**CONCLUSIONS**

Several inpatient and closely monitored short-term outpatient studies in camps or other settings have shown reduction...
in overnight hypoglycemia using a predictive algorithm (8–12). In this randomized, controlled trial conducted during 1,912 nights, home use of a predictive low-glucose suspend system substantially reduced the frequency and duration of nocturnal hypoglycemia. Importantly, cumulative exposure to hypoglycemia as measured with the AUC was reduced by 81%, and episodes of prolonged overnight hypoglycemia (≤60 mg/dL for >2 h) were reduced more than threefold. This was accomplished without an increase in overnight hyperglycemia despite the fact that pump suspension occurred on 76% of intervention nights. Although morning blood glucose levels were higher following intervention nights, the frequency of levels >250 mg/dL (6 vs. 6%) and frequency of morning ketosis (0.1 vs. 0.3%) were similar. There were no serious adverse events in either arm.

The system was most effective as the night progressed. This likely reflects the inability of the system to effectively compensate during the initial part of the night for insulin given prior to the system being activated for the night. Given current insulin analog actions, the effect of insulin delivered prior to activation of the system will be a limitation of any artificial pancreas system used intermittently and is an important finding in these data. The potential tradeoff for reducing hypoglycemia with insulin suspension is an increase in hyperglycemia and theoretically an increased risk of ketoacidosis. Importantly, ketosis was no more likely after an intervention versus control night, alleviating potential concern that suspension of insulin delivery could increase the risk of ketoacidosis. Thus, as demonstrated in this study and others (3,6,13–22), insulin delivery from a pump can be safely stopped for several hours without developing substantial ketosis. Although the study was not long enough to see the full effect of hyperglycemia on glycated hemoglobin levels, it was reassuring to find that levels did not increase during the study.

The study used a novel design in which random assignment to intervention or control was made each night when the system was activated, and the participant was blinded to that night’s assignment. This design minimized bias due to awareness of treatment assignment, which could occur with either a parallel group or a two-period crossover design. The primary outcome of a single glucose value ≤60 mg/dL was chosen for simplicity and because prior studies had shown a high correlation between this outcome and numerous other hypoglycemia outcomes (14). However, the secondary outcomes related to prolonged hypoglycemia are more clinically relevant. The profound reduction seen in duration of hypoglycemia is important since prolonged very low glucose levels can produce loss of consciousness, seizure, or even death (23–26). To account for sensor inaccuracy, the sample size (number of nights) was increased by a factor of 6 to account for anticipated false-positive and false-negative hypoglycemia outcomes, estimated from prior study data (14). The observed 33% frequency of nocturnal hypoglycemia ≤60 mg/dL on the control nights was similar to the 30% projection used in the sample size estimation based on data from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Trial for participants with glycated hemoglobin levels ≤8.0% (27,28). Use of the system’s sensor for outcome assessment would not affect the probability of a type 1 error.

Figure 3—Sensor glucose levels overnight. The top portion of the figure shows the median glucose level across all nights in each treatment arm. The bottom portion of the figure shows the frequency of glucose level ≤60 mg/dL across all nights in each treatment arm.
but could produce a slight overestimate of the true treatment effect (7).

The study cohort was limited to individuals with type 1 diabetes and a glycated hemoglobin level ≤8.0% who demonstrated at least a minimum amount of nocturnal hypoglycemia during a run-in phase. These restrictions were placed since a prior study showed that the frequency of nocturnal hypoglycemia with higher glycated hemoglobin levels was low, which would impair the ability to compare intervention and control nights (29). Thus, although the predictive low-glucose suspend system would work irrespective of glycated hemoglobin level, the benefit-to-risk ratio might differ in those with very infrequent nocturnal hypoglycemia. The study included individuals 15–45 years old, and the results may not be generalizable to younger and older ages. We will be conducting a trial using this predictive low-glucose suspend system in 3–14 year olds. Although our study was of short duration, we expect the benefit and low risk would be similar with longer duration of use outside of a clinical trial.

The development of a closed-loop system to control glucose levels will be an incremental process, with safety being the foremost criterion for progression from one stage to the next (30). The first step in the progression toward a fully closed-loop system is suspending insulin when the sensor glucose level is in the hypoglycemic range and the patient does not respond to an alarm or suspending insulin when hypoglycemia is predicted. Threshold suspension, available on the Veo pump outside the U.S. since 2009, was shown in a study by Ly et al. (18) to reduce the frequency of moderate or severe hypoglycemic events compared with pump use alone. In the ASPIRE study (3), the Veo system was shown to be effective in reducing biochemical hypoglycemia without increasing hyperglycemia. Although our results using a predictive hypoglycemia algorithm to suspend insulin delivery showed an 81% relative reduction in the hypoglycemia AUC compared with the 37.5% relative reduction found in the ASPIRE study, substantial differences in study design preclude a conclusion that predictive suspension is better than threshold suspension. Full nocturnal closed loop has the potential to mitigate both hypoglycemia and hyperglycemia, and early inpatient and outpatient studies are promising (8,11,31,32).

In conclusion, we have demonstrated that in 15–45 year olds with type 1 diabetes and frequent nocturnal hypoglycemia, use of our nocturnal low-glucose suspend system can substantially reduce overnight hypoglycemia without a meaningful increase in hyperglycemia and no increase in ketoadosis. Use of a nocturnal low-glucose suspend system has the potential to not only reduce nocturnal hypoglycemia but also to reduce fear of hypoglycemia, which can be a significant deterrent to achieving blood glucose targets.

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References

1. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Prolonged nocturnal hypoglycemia is common during 12 months of continuous glucose monitoring in children and adults with type 1 diabetes. Diabetes Care 2010;33:1004–1008.
2. Buckingham B, Wilson DM, Lecher T, Hansa R, Kaiserman K, Cameron F. Duration of nocturnal hypoglycemia before seizures. Diabetes Care 2008;31:2110–2112.
3. Bergenstal RM, Klonoff DC, Garg SK, et al. ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–232.
4. Buckingham B, Chase HP, Dassau E, et al. Prevention of nocturnal hypoglycemia using predictive alarm algorithms and insulin pump suspension. Diabetes Care 2010;33:1013–1017.
5. Cameron F, Wilson DM, Buckingham BA, et al. Inpatient studies of a Kalman-filter-based predictive pump shutoff algorithm. J Diabetes Sci Tech 2012;6:1142–1147.
6. Buckingham BA, Cameron F, Calhoun P, et al. 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;15:622–627.
7. Beck RW, Calhoun PM, Kollman C. Use of continuous glucose monitoring as an outcome measure in clinical trials. Diabetes Technol Ther 2012;14:877–882.
8. Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet 2010;375:743–751.
9. Kovatchev BP, Erenard E, Cobelli C, et al. Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. Diabetes Care 2013;36:1851–1858.
10. O’Grady MJ, Rettherath AJ, Keenan DB, et al. The use of an automated, portable glucose control system for overnight glucose control in adolescents and young adults with type 1 diabetes. Diabetes Care 2012;35:2182–2187.
11. Phillips M, Battelino T, Atlas E, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med 2013;368:824–833.
12. Russell SJ, El-Khatib FH, Nathan DM, Magyar KL, Jiang J, Damiano ER. Blood glucose control in type 1 diabetes with a biphasmic bionic endocrine pancreas. Diabetes Care 2012;35:2148–2155.
13. Attia N, Jones TW, Holcombe J, Tamborlane WV. Comparison of human regular and isprol insulin after interruption of continuous subcutaneous insulin infusion and in the treatment of acutely decompensated IDDM. Diabetes Care 1998;21:817–821.
14. Beck RW, Kollman C, Xing D, Buckingham BA, Chase HP. Outcome measures for outpatient hypoglycemia prevention studies. J Diabetes Sci Tech 2011;5:999–1004

15. Castillo MJ, Scheen AJ, Lefebvre PJ. The degree/rapidity of the metabolic deterioration following interruption of a continuous subcutaneous insulin infusion is influenced by the prevailing blood glucose level. J Clin Endocrinol Metab 1996;81:1975–1978

16. Krzentowski G, Scheen A, Castillo M, Luyckx AS, Lefebvre PJ. A 6-hour nocturnal interruption of a continuous subcutaneous insulin infusion: 1. Metabolic and hormonal consequences and scheme for a prompt return to adequate control. Diabetologia 1983;24:314–318

17. Ly TT, Nicholas JA, Retterath A, Davis EA, Jones TW. Analysis of glucose responses to automated insulin suspension with sensor-augmented pump therapy. Diabetes Care 2012;35:1462–1465

18. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension versus standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. JAMA 2013;310:1240–1247

19. Orsini-Federici M, Akwi JA, Canonico V, et al. Early detection of insulin deprivation in continuous subcutaneous insulin infusion-treated patients with type 1 diabetes. Diabetes Technol Ther 2006;8:67–75

20. Pickup JC, Viberti GC, Bilous RW, et al. Safety of continuous subcutaneous insulin infusion: metabolic deterioration and glycaemic autoregulation after deliberate cessation of infusion. Diabetologia 1982;22:175–179

21. Sherr JL, Collazo MP, Cengiz E, et al. 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;37:773–779

22. Elleri D, Allen JM, Nodale M, et al. Suspended insulin infusion during overnight closed-loop glucose control in children and adolescents with Type 1 diabetes. Diabet Med 2010;27:480–484

23. Buckingham B, Block J, Burdick J, et al. Diabetes Research in Children Network. Response to nocturnal alarms using a real-time glucose sensor. Diabetes Technol Ther 2005;7:440–447

24. Davis EA, Keating B, Byrne GC, Russell M, Jones TW. Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. Diabetes Care 1997;20:22–25

25. Sovik O, Thordarson H. Dead-in-bed syndrome in young diabetic patients. Diabetes Care 1999;22(Suppl. 2):B40–B42

26. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the diabetes control and complications trial. Diabetes 1997;46:271–286

27. Tamborlane WV, Beck RW, Bode BW, et al. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–1476

28. Beck RW, Hirsch IB, Laffel L, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care 2009;32:1378–1383

29. Fiallo-Scharer R, Cheng J, Beck RW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Factors predictive of severe hypoglycemia in type 1 diabetes: analysis from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized control trial dataset. Diabetes Care 2011;34:586–590

30. Kowalski AJ. Can we really close the loop and how soon? Accelerating the availability of an artificial pancreas: a roadmap to better diabetes outcomes. Diabetes Technol Ther 2009;11(Suppl. 1):S113–S119

31. Nimri R, Danne T, Kordonouri O, et al. The "Glucositter" overnight automated closed loop system for type 1 diabetes: a randomized crossover trial. Pediatr Diabetes 2013;14:159–167

32. Nimri R, Müller I, Atlas E, et al. Night glucose control with MD-Logic artificial pancreas in home setting: a single blind, randomized crossover trial-interim analysis. Pediatr Diabetes 2014;15:91–99