

Prevention of Nocturnal Hypoglycemia Using Predictive Alarm Algorithms and Insulin Pump Suspension

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OBJECTIVE — The aim of this study was to develop a partial closed-loop system to safely prevent nocturnal hypoglycemia by suspending insulin delivery when hypoglycemia is predicted in type 1 diabetes.

RESEARCH DESIGN AND METHODS — Forty subjects with type 1 diabetes (age range 12–39 years) were studied overnight in the hospital. For the first 14 subjects, hypoglycemia (<60 mg/dl) was induced by gradually increasing the basal insulin infusion rate (without the use of pump shutoff algorithms). During the subsequent 26 patient studies, pump shutoff occurred when either three of five ($n = 10$) or two of five ($n = 16$) algorithms predicted hypoglycemia based on the glucose levels measured with the FreeStyle Navigator (Abbott Diabetes Care).

RESULTS — The standardized protocol induced hypoglycemia on 13 (93%) of the 14 nights. With use of a voting scheme that required three algorithms to trigger insulin pump suspension, nocturnal hypoglycemia was prevented during 6 (60%) of 10 nights. When the voting scheme was changed to require only two algorithms to predict hypoglycemia to trigger pump suspension, hypoglycemia was prevented during 12 (75%) of 16 nights. In the latter study, there were 25 predictions of hypoglycemia because some subjects had multiple hypoglycemic events during a night, and hypoglycemia was prevented for 84% of these events.

CONCLUSIONS — Using algorithms to shut off the insulin pump when hypoglycemia is predicted, it is possible to prevent hypoglycemia on 75% of nights (84% of events) when it would otherwise be predicted to occur.

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Continuous glucose monitoring (CGM) represents the “third era” in diabetes management after the eras of urine glucose testing and (self-monitoring) blood glucose testing. One of the important potential benefits of real-time CGM is the ability of these devices to alarm for hypoglycemia. However, a previous study showed that 71% of youth did not respond to hypoglycemia alarms dur-

ing the night (1). Moreover, the most severe hypoglycemic events in the Diabetes Control and Complications Trial occurred during sleep hours (2). Davis et al. (3) found that 75% of hypoglycemic seizures in children occurred during sleep. Sovik and Thordarson (4) reported that among patients aged <40 years who died over a 10-year period, 6% of the deaths were due to “dead-in-bed” syndrome,

which in many instances was probably the result of severe nocturnal hypoglycemia.

The availability of CGM systems has allowed determination of the incidence of nocturnal hypoglycemia in the home environment. In a randomized trial evaluating daily CGM use over a 6-month period in children and adults with type 1 diabetes, 216 subjects used a CGM device for a total of 25,473 nights (5). The glucose level was ≤ 70 mg/dl on 25% of nights, ≤ 60 mg/dl on 15% of nights, and ≤ 50 mg/dl on 8% of nights (5) (C. Kollman, unpublished data). Similar or even higher frequencies of nocturnal biochemical hypoglycemia have been found in other studies (6–9).

In a previous report, we prospectively studied the prevention of daytime hypoglycemia using CGM, hypoglycemia prediction algorithms, and temporary discontinuation of insulin via continuous subcutaneous insulin infusion (insulin pump) (10). Hypoglycemia was prevented using a 90-min pump suspension on 60–80% of days. Cengiz et al. (11) described automatic pump suspension using the proportional integral derivative algorithm during 34 h of closed-loop automated insulin delivery in 17 patients. They were successful in preventing hypoglycemia (glucose <60 mg/dl) in 14 of 18 (78%) suspension episodes. The purpose of the present study was to extend our original observations to evaluate the prevention of nocturnal hypoglycemia using hypoglycemia prediction algorithms.

RESEARCH DESIGN AND METHODS

Subjects for this study were recruited at the Barbara Davis Center (Aurora, CO) and the Stanford Medical Center (Stanford, CA). The protocol was approved by the local institutional review boards, and all subjects and parents or guardians signed an informed consent form and an assent form if necessary. Subjects in this study had had type 1 diabetes for at least 1 year and had used a downloadable insulin pump for at least 3 months.

Participants were trained on the use of the FreeStyle Navigator CGM system

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(Abbott Diabetes Care, Alameda, CA) and were instructed to wear two systems for each study. The two CGM systems were usually inserted 1–2 days before admission. Subjects arrived at the Clinical Translational Research Center (CTRC) at ~7:30 P.M. after a dinner consisting of known amounts of carbohydrate, protein, and fat.

Inducing nocturnal hypoglycemia

Fourteen subjects completed the control (hypoglycemia induction) visit at the CTRC with the intent to establish a consistent method for inducing nocturnal hypoglycemia using increases in basal insulin. After admission to the CTRC and stabilization, basal insulin was increased in 5–25% increments every 90 min, depending on the current blood glucose, the glucose rate of change, and the linearly predicted glucose value to be reached by 5:00 A.M. (aim <60 mg/dl). The subject's blood glucose was monitored every 15–30 min using the FreeStyle meter built into the Navigator (the only meter used in this study). Blood was also collected for YSI (Yellow Springs, OH) glucose analysis once the FreeStyle reading was <70 mg/dl. When the hypoglycemic threshold was reached (blood glucose value <60 mg/dl), oral carbohydrates were given to return glucose levels to >70 mg/dl.

Preventing hypoglycemia

The same consistent method for inducing hypoglycemia was used in the subsequent studies to assess whether hypoglycemia prediction and insulin pump suspension could prevent nocturnal hypoglycemia. The Navigator glucose alarms, including the built-in Projected Low Alarm, were not activated during the study. For the hypoglycemia prevention studies, one of the Navigator sensors was connected to a laptop computer containing the artificial pancreas system (12) and the hypoglycemia prediction algorithm (13) composed of five separate prediction algorithms and a voting schema, explained briefly in the following.

1. Modified linear prediction alarm. This alarm uses a 15-min linear extrapolation and an uncertainty threshold based on the SD of the glucose measurements in the previous 15 min.
2. Kalman filtering. A Kalman filter is used to obtain an estimate of glucose and its rate of change, which are then used to make predictions of future glucose levels. The filter is tuned to

Table 1—Demographic information

	Study to induce hypoglycemia	Pump shutoff requiring three predictions	Pump shutoff requiring two predictions
Age (years)	21.0 ± 7.5	22.5 ± 6.3	22.0 ± 8.9
Duration of type 1 diabetes (years)	12.1 ± 6.0	12.7 ± 5.5	11.5 ± 6.9
A1C (%)	7.8 ± 1.9	7.3 ± 0.8	7.3 ± 0.7
BMI (kg/m ²)	22.0 ± 3.1	24.6 ± 2.8	25.2 ± 3.9

Data are means ± SD.

choose between the probabilities that a measured glucose change is real versus the result of signal noise (14).

3. Adaptive hybrid infinite impulse response (HIIR) filter. An infinite impulse response filter updates parameters adaptively using the CGM signal. The HIIR filter considers a bandwidth of past data to update the filter parameters.
4. Statistical prediction. Multiple empirical, statistical models are used to estimate future glucose values and their error bounds. A probability of hypoglycemia is generated and thresholded to produce an alarm (15).
5. Numerical logical algorithm. The algorithm transmits a three-point calculated rate of change and the current value into logical expressions to detect impending hypoglycemia. The numerical logical algorithm provides insensitivity to sensor signal dropouts.

The algorithms for pump suspension were based on a 35-min prediction horizon (looking 35 min into the future) and a glucose threshold of 80 mg/dl. The glucose threshold and 35-min prediction horizon were chosen to allow time for the pump suspension to be effective in lowering insulin levels once the basal rate was suspended and was based on analysis of previous CGM data with nocturnal hypoglycemia. There is a sustained negative rate of change in glucose levels lasting a mean of 75 min after insulin pump suspension (10). In our initial 10 patient studies we required three of the hypoglycemia prediction algorithms to be simultaneously positive twice in a 10-min window before the pump was suspended. In the subsequent 16 studies we only required two alarms to be simultaneously positive twice in a 10-min window. When the hypoglycemia prediction algorithm alarmed (on a computer outside the subject's room), study staff manually suspended insulin delivery from the pump

using a 90-min suspend protocol. Serum ketone levels were measured at the pump suspension, after insulin restart, and each morning on completion of the study using the Precision Xtra meter (Abbott Diabetes Care).

Criteria for restarting insulin infusion

The initial protocol involved a 90-min pump suspension when hypoglycemia was predicted. Because there were often multiple hypoglycemia events predicted each night, it was desired to limit the time insulin was suspended once the glucose was past the nadir. Thus, for the final 11 subjects, the criteria for restarting a pump suspension included 1) a minimum of 30 min of pump suspension, 2) a positive rate of change on the FreeStyle Navigator system of >0.5 mg/dl-min, and 3) a FreeStyle Navigator glucose value >80 mg/dl. When basal insulin was restarted, it was at the subject's usual rate for that time of night.

RESULTS

Inducing nocturnal hypoglycemia

Fourteen subjects, aged 12–39 years, were initially studied for the induction of nocturnal hypoglycemia in the CTRC. Many of these same subjects participated in the subsequent two hypoglycemia prevention protocols. The demographic information for subjects participating in each of the three studies is shown in Table 1. The first study was designed to develop a reliable method of producing nocturnal hypoglycemia (>80% success) and the second and third studies were designed to study the possibility of preventing nocturnal hypoglycemia using predictive algorithms and temporary insulin suspension.

With use of the protocol to generate nocturnal hypoglycemia, 13 of the 14 subjects (93%) reached glucose levels ≤60 mg/dl; 9 of 14 had levels <55 mg/dl.

Table 2—Results of the three-alarm and two-alarm voting systems

No. predictive algorithms needed to trigger pump suspension	n	Subjects without hypoglycemia	No. events*	Events without hypoglycemia
3 of 5	10	60	15	71
2 of 5	16	75	25	84

Data are % unless indicated otherwise. *An event is an episode of predicted hypoglycemia resulting in a pump suspension.

The mean increase in basal rate was 180%. There were no seizures or loss of consciousness.

Preventing hypoglycemia

Twenty-six subjects participated in this phase of the study. A hypoglycemia threshold of 80 mg/dl and a prediction horizon (the time the algorithm is looking into the future to predict hypoglycemia) of 35 min was used for this study. For the first 10 patient studies, the insulin pump shutoff occurred when three algorithms predicted hypoglycemia and for the last 16 patient studies only two of five prediction algorithms were required to shut off the pump. During the study with the first 10 subjects, hypoglycemia was prevented on 6 (60%) of the 10 nights. There were a total of 15 hypoglycemic events predicted during these 10 nights (three subjects having two events and one subject having three events), and hypoglycemia was prevented for 71% of the events (Table 2).

When we assessed the time between

two hypoglycemia prediction algorithms voting to turn off the pump and three algorithms voting to turn off the pump, there was a mean difference of 12 min. To provide more time for the pump shutoff to be effective, we therefore conducted our next set of studies with the requirement of only two of the five algorithms to predict hypoglycemia to trigger pump suspension. This resulted in hypoglycemia being prevented on 12 of 16 nights (75%) (Table 2). Four subjects had two events during the night, one subject had three events, and one subject had four events. For the 25 hypoglycemic events, hypoglycemia was prevented 84% of the time. Figure 1 illustrates successful prevention of hypoglycemia using two insulin suspensions during the night.

We also evaluated which alarms were contributing to the first, second, and third votes to turn the pump off (Table 3). The linear prediction algorithm was the least likely to predict hypoglycemia. Other-

Table 3—Distribution of algorithms that were the first, second, or third to predict hypoglycemia

Alarm	First alarms	Second alarms	Third alarms
Statistical prediction	60	28	6
Numerical logical	30	28	24
HIIR	3	10	49
Kalman	7	31	21
Linear prediction	0	3	0

Data are %.

wise, all of the algorithms played a significant role in contributing to the vote.

Factors relating to successful hypoglycemia prevention

A comparison was done between several factors that may play a role in the success of the system. These included the accuracy of the FreeStyle Navigator system (a comparison of the FreeStyle Navigator system value with the YSI blood glucose value), the rate of change in the glucose readings at the time of pump suspension, and the YSI blood glucose value at the time of pump suspension. The difference between the FreeStyle Navigator system and the YSI glucose values at the time of pump suspension was 4 ± 9 mg/dl (mean \pm SD) for successful events, and the Navigator was always reading higher than the YSI when the predictive pump shutoff failed (mean of 18 ± 10 mg/dl for failures) ($P = 0.001$). The other factors, such as rate of glucose change and YSI glucose value at the time of pump shutoff, were not significantly different between successful and unsuccessful events. The first episode of pump suspension was successful 75% of the time, and subsequent episodes were successful 80% of the time. The glucose rate of change was less with subsequent pump suspensions, because the basal rate was returned to the usual infusion rate for that time of night (mean \pm SD rate of change -0.72 ± 0.42 mg/dl-min on first shutoff and -0.24 ± 0.13 mg/dl-min on subsequent shutoffs).

Early restart of basal insulin

In the last 11 patient studies, an early restart of basal insulin was permitted once the glucose was past the nadir (see RESEARCH DESIGN AND METHODS). There were 19 hypoglycemic events on these 11 nights, and the early pump restart occurred on 5 occasions. The mean peak glucose after restart of an insulin infusion in the cohort

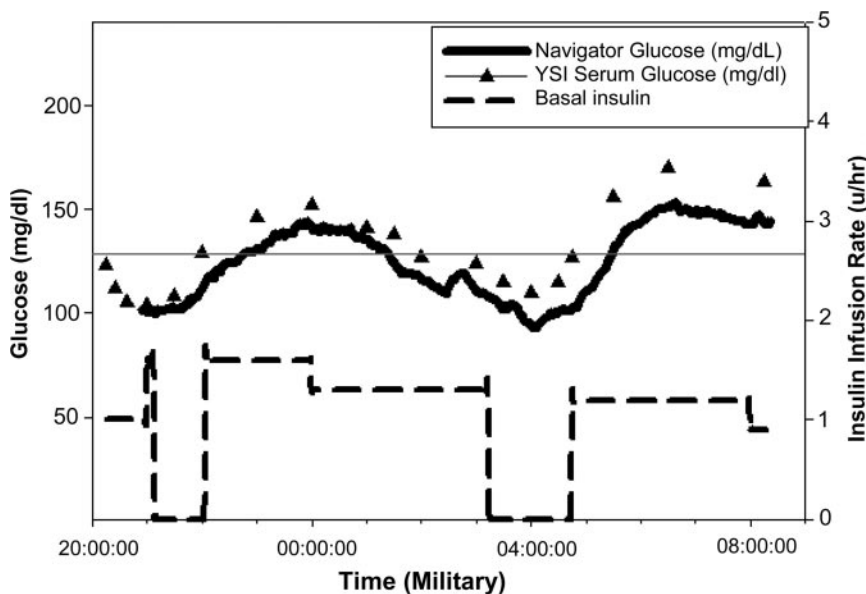


Figure 1—Successful prevention of hypoglycemia (glucose levels by CGM or venous blood <60 mg/dl) as a result of two 90-min periods of insulin pump suspension. The hypoglycemia prediction algorithm required two (of five) alarms for pump suspension and was based on a 35-min prediction horizon and a CGM glucose threshold of 80 mg/dl.

of 11 subjects using an early restart was 149 ± 32 mg/dl, and the maximum glucose was 210 mg/dl. In the nights in which an early restart of insulin was not permitted, the mean peak glucose after pump suspension was 158 ± 50 mg/dl and the highest glucose was 275 mg/dl. These differences were not statistically significant.

Occurrence of ketonemia

Four subjects developed ketone levels >0.3 mmol \cdot l⁻¹ \cdot l⁻¹ (range 0.4–1.5 mmol \cdot l⁻¹ \cdot l⁻¹). In each instance, when the serum ketone levels were checked several hours later, they were <0.3 mmol \cdot l⁻¹ \cdot l⁻¹. In two instances, the pump had been suspended for 90 min (final glucose levels 146 and 155 mg/dl), and in two instances (with more than one suspension), the pump had been suspended for a total of 180 min (final glucose levels 202 and 261 mg/dl). In each case the serum ketone levels were <0.3 mmol \cdot l⁻¹ \cdot l⁻¹ after the first suspension. There were no clinical symptoms such as upset stomach, nausea, or Kussmaul respirations, and no specific treatment was given.

CONCLUSIONS — Prevention of severe nocturnal hypoglycemic events remains one of the most challenging goals in the treatment of diabetes. With the prevention of severe hypoglycemia, it is likely that more people would be able to move toward optimal glycemic control. Because of the decrease in counterregulatory hormone secretion during sleep, even in people without diabetes (16), and the frequent loss of counterregulatory hormone secretion in people with diabetes (17,18), prevention will probably require the use of a closed-loop system. In this initial step toward a closed-loop system, we tested the use of a subcutaneous sensor signal to predict impending hypoglycemia and to trigger pump suspension. It was not possible to eliminate nocturnal hypoglycemia completely. However, hypoglycemia was prevented during 75% of the nights and for 84% of predicted events. Presumably, a hypoglycemia prediction algorithm, as used in the present study, will be combined with discontinuation of continuous subcutaneous insulin infusion at a specific glucose level. The latter currently occurs in the Medtronic MiniMed Paradigm Veo Real-Time System in Europe. The two working together may be very effective in preventing severe hypoglycemia.

In some cases for which hypoglyce-

mia was not successfully prevented, the subjects' sensor glucose values were consistently running higher than the blood glucose values. This may have been due to CGM inaccuracy or due to the known lag time of ~ 8 –10 min between the two compartments (19). Future investigators may be able to use a forced CGM calibration at bedtime if there is a significant discrepancy between a discrete bedtime glucose value and the sensor glucose to minimize this effect. We initially hypothesized that the rate of fall of the glucose values before a hypoglycemic event would also be a major factor in determining the success or failure of hypoglycemia prevention. However, this did not prove to be true.

To achieve a high rate of nocturnal hypoglycemia, we systematically increased nocturnal basal infusion rates until there was a $>80\%$ risk of hypoglycemia. Because of receiving higher basal insulin infusion rates than on a typical night, subjects probably experienced a more rapid rate of fall in glucose levels with a longer residual insulin effect. This may have made it more difficult for the pump suspension algorithms to prevent impending hypoglycemia. Unfortunately, even when the basal rate was at the usual infusion rate for that subject (after the first pump suspension), we still failed to prevent hypoglycemia 20% of the time.

It is known that once a person has had one hypoglycemic event, a second event is more likely (17). Thus, overall these results seem promising.

Although a rigid blood glucose cutoff of <60 mg/dl was used to define failure of prevention of hypoglycemia, it is possible that we were overly cautious. The shortest known time of prolonged hypoglycemia (<40 mg/dl while using the Medtronic Paradigm CGM system) before a seizure is currently 2.25 h (20). There were no severe hypoglycemic events in the current study. It would also be unlikely using the current protocol that the duration of hypoglycemia would be long enough to result in a severe hypoglycemic episode. Previous studies have shown that suspension of insulin delivery for up to 2 h has not resulted in significant ketosis (10,21–25). In our studies, there was mild ketosis on four occasions when the pump was suspended for 90–180 min, and in each instance serum ketone levels returned to normal with the reinstatement of basal insulin therapy.

Studies in the home setting are now needed. The initial aim will be to prevent-

ing nocturnal hypoglycemia, and studies will be randomized to include nights when the prevention system is in place and to include control nights when the system is not in use. The bedside mini-computer will randomize the nights and will also act as an intermediary (containing the prevention algorithms) between the insulin pump and the CGM. Studies will begin with adults but will then be extended to children. It is our belief that most episodes of severe nocturnal hypoglycemia will be preventable, using either this or a similar system.

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References

1. Buckingham B, Block J, Burdick J, Kalajian A, Kollman C, Choy M, Wilson DM, Chase P, Diabetes Research in Children Network. Response to nocturnal alarms using a real-time glucose sensor. *Diabetes Technol Ther* 2005;7:440–447
2. The DCCT Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med* 1991;90:450–459
3. 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
4. Sovik O, Thordarson H. Dead-in-bed syndrome in young diabetic patients. *Diabetes Care* 1999;22(Suppl. 2):B40–B42
5. Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Hirsch IB, Huang ES, Kollman C, Kowalski

- AJ, Laffel L, Lawrence JM, Lee J, Mauras N, O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer S, Wilson DM, Wolpert H, Wysocki T, Xing D. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464–1476
6. Boland EA, DeLucia M, Brandt CA, Grey M, Tamborlane WV. Limitations of conventional methods of self blood glucose monitoring: lessons learned from three days of continuous glucose monitoring (CGMS) in pediatric patients with type 1 diabetes (Abstract). *Diabetes* 2000;49 (Suppl. 1):A98
 7. Kaufman FR, Austin J, Neinstein A, Jeng L, Halvorson M, Devoe DJ, Pitukcheewanont P. Nocturnal hypoglycemia detected with the continuous glucose monitoring system in pediatric patients with type 1 diabetes. *J Pediatr* 2002;141:625–630
 8. Ludvigsson J, Hanas R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. *Pediatrics* 2003;111:933–938
 9. Jeha GS, Karaviti LP, Anderson B, Smith EO, Donaldson S, McGirk TS, Haymond MW. Continuous glucose monitoring and the reality of metabolic control in preschool children with type 1 diabetes. *Diabetes Care* 2004;27:2881–2886
 10. Buckingham B, Cobry E, Clinton P, Gage V, Caswell K, Kunselman E, Cameron F, Chase HP. Preventing hypoglycemia using predictive alarm algorithms and insulin pump suspension. *Diabetes Technol Ther* 2009;11:93–97
 11. Cengiz E, Swan KL, Tamborlane WV, Steil GM, Steffen AT, Weinzimer SA. Is an automatic pump suspension feature safe for children with type 1 diabetes? An exploratory analysis with a closed-loop system. *Diabetes Technol Ther* 2009;11:207–210
 12. Dassau E, Zisser H, C Palerm C, A Buckingham B, Jovanovic L, J Doyle F 3rd. Modular artificial β -cell system: a prototype for clinical research. *J Diabetes Sci Technol* 2008;2:863–872
 13. Dassau E, Cameron F, Lee H, Bequette BW, Doyle FJ, Niemeyer G, Chase HP, Buckingham B. Real-time hypoglycemia prediction using continuous glucose monitoring (CGM): a safety net to the artificial pancreas. *Diabetes* 2008;57 (Suppl. 1):A13
 14. Palerm CC, Bequette BW. Hypoglycemia detection and prediction using continuous glucose monitoring—a study on hypoglycemic clamp data. *J Diabetes Sci Technol* 2007;1:624–629
 15. Cameron F, Niemeyer G, Gundy-Burlet K, Buckingham B. Statistical hypoglycemia prediction. *J Diabetes Sci Technol* 2008;2:612–621
 16. Jones TW, Porter P, Sherwin RS, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV. Decreased epinephrine responses to hypoglycemia during sleep. *N Engl J Med* 1998;338:1657–1662
 17. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care* 2003;26:1902–1912
 18. Diabetes Research in Children Network (DirecNet) Study Group, Tsalikian E, Tamborlane W, Xing D, Becker DM, Mauras N, Fiallo-Scharer R, Buckingham B, Weinzimer S, Steffes M, Singh R, Beck R, Ruedy K, Kollman C. Blunted counterregulatory hormone responses to hypoglycemia in young children and adolescents with well-controlled type 1 diabetes. *Diabetes Care* 2009;32:1954–1959
 19. Cengiz E, Tamborlane WV. A tale of two compartments: interstitial versus blood glucose monitoring. *Diabetes Technol Ther* 2009;11(Suppl. 1):S11–S16
 20. Buckingham B, Wilson DM, Lecher T, Hanas R, Kaiserman K, Cameron F. Duration of nocturnal hypoglycemia before seizures. *Diabetes Care* 2008;31:2110–2112
 21. Diabetes Research in Children Network (DirecNet) Study Group, Tsalikian E, Kollman C, Tamborlane WB, Beck RW, Fiallo-Scharer R, Fox L, Janz KF, Ruedy KJ, Wilson D, Xing D, Weinzimer SA. Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. *Diabetes Care* 2006;29:2200–2204
 22. Orsini-Federici M, Akwi JA, Canonico V, Celleno R, Ferolla P, Pippi R, Tassi C, Timi A, Benedetti MM. Early detection of insulin deprivation in continuous subcutaneous insulin infusion-treated patients with type 1 diabetes. *Diabetes Technol Ther* 2006;8:67–75
 23. Castillo MJ, Scheen AJ, Lefèbvre 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
 24. Scheen A, Castillo M, Jandrain B, Krzentowski G, Henrivaux P, Luyckx AS, Lefèbvre PJ. Metabolic alterations after a two-hour nocturnal interruption of a continuous subcutaneous insulin infusion. *Diabetes Care* 1984;7:338–342
 25. Scheen AJ, Krzentowski G, Castillo M, Lefèbvre PJ, Luyckx AS. A 6-hour nocturnal interruption of a continuous subcutaneous insulin infusion: 2. Marked attenuation of the metabolic deterioration by somatostatin. *Diabetologia* 1983;24:319–325