



Frequency of Morning Ketosis After Overnight Insulin Suspension Using an Automated Nocturnal Predictive Low Glucose Suspend System

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Roy W. Beck,¹ Dan Raghinaru,¹
R. Paul Wadwa,² H. Peter Chase,²
David M. Maahs,² and
Bruce A. Buckingham,³ for the In Home
Closed Loop Study Group*

OBJECTIVE

To assess the effect of overnight insulin pump suspension in an automated predictive low glucose suspend system on morning blood glucose and ketone levels in an attempt to determine whether routine measurement of ketone levels is useful when a closed-loop system that suspends insulin delivery overnight is being used.

RESEARCH DESIGN AND METHODS

Data from an in-home randomized trial of 45 individuals with type 1 diabetes (age range 15–45 years) were analyzed, evaluating an automated predictive low glucose pump suspension system in which blood glucose, blood ketone, and urine ketone levels were measured on 1,954 mornings.

RESULTS

One or more pump suspensions occurred during 744 of the 977 intervention nights (76%). The morning blood ketone level was ≥ 0.6 mmol/L after 11 of the 744 nights (1.5%) during which a pump suspension occurred and 2 of the 233 nights (0.9%) during which there was no suspension compared with 11 of 977 control nights (1.1%). The morning blood ketone level was ≥ 0.6 mmol/L after only 2 of 159 nights (1.3%) with a pump suspension exceeding 2 h. Morning fasting blood glucose level was not a good predictor of the presence of blood ketones.

CONCLUSIONS

Routine measurement of blood or urine ketones during use of an automated pump suspension system using continuous glucose monitoring, whether threshold based or predictive, is not necessary. Recommendations for checking ketone levels should be no different when a patient is using a system with automated insulin suspension than it is for conventional diabetes self-management.

A concern with the use of an insulin infusion pump in individuals with type 1 diabetes is that cessation of insulin delivery, such as with infusion set failure, could result in diabetic ketoacidosis (DKA). A number of studies have shown, under experimental conditions, that insulin delivery can be stopped for several hours before substantial ketosis develops (1–8). Despite concern that infusion set occlusion could result in an increased frequency of DKA in pump users compared with injection users, this possibility has not been supported by registry data (9,10).

¹Jaeb Center for Health Research, Tampa, FL
²Barbara Davis Center for Childhood Diabetes, Aurora, CO
³Stanford University, Stanford, CA

Corresponding author: Roy W. Beck, rbeck@jaeb.org.

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*A complete list of the In Home Closed Loop Study Group can be found in the Supplementary Data online.

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With automated systems that suspend insulin delivery in response to a hypoglycemic threshold or predicted hypoglycemia, a concern for the Food and Drug Administration is that ketosis may develop. We were able to assess the frequency of ketosis in the home setting after suspension of insulin infusion from a pump by analyzing data collected during and after 1,954 nights in 45 adolescents and adults in a randomized trial evaluating an automated nocturnal predictive low glucose suspend system. Each morning, blood glucose, blood ketone, and urine ketone levels were measured irrespective of the level of the blood glucose, providing the opportunity to determine the frequency of ketosis assessed by a standardized protocol. The trial results showed that the predictive low glucose suspend system reduced overnight hypoglycemia (median time below 60 mg/dL) by 70%, without increasing morning ketone levels (blood ketone levels >1.0 mmol/L 0.3 vs. 0.1%, urine ketone levels ≥ 15 mg/dL 2 vs. 3%, and blood glucose levels >250 mg/dL 6 vs. 6% on intervention and control nights, respectively) (11). In this article, we further explore the effect of overnight pump suspension on morning blood glucose and ketone levels in an attempt to determine whether routine measurement of ketone levels is useful when a closed-loop system that suspends insulin delivery overnight is being used.

RESEARCH DESIGN AND METHODS

The study protocol 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.

The randomized trial included 45 individuals with type 1 diabetes (47% male, 93% Caucasian) using an insulin infusion pump, who ranged in age from 15 to 45 years, had median type 1 diabetes duration of 15 years, and median glycosylated hemoglobin level of 6.8% (interquartile range 6.4–7.6%). The pump suspension system consisted of a MiniMed Paradigm REAL-Time Veo

System and Enlite glucose sensor (Medtronic Diabetes, Northridge, CA), in which the continuous glucose monitor (CGM) and pump communicated with a bedside laptop computer which contained a Kalman filter–based hypoglycemia prediction algorithm (referred to as “the system”). Insulin delivery was suspended when the glucose level was predicted to be <80 mg/dL in the next 30 min. The maximum pump suspension time was 120 min within a 150-min window and a maximum nightly cumulative total suspension time of 180 min. A bedside laptop computer contained a randomization schedule that determined 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 42 nights being intervention nights and half being control nights. When the system was stopped each morning, blood glucose (OneTouch Ultra2; LifeScan, Milpitas, CA), blood ketone (Precision Xtra meter; Abbott Diabetes Care, Alameda, CA), and urine ketone (Ketostix strips; Bayer, Pittsburgh, PA) levels were measured. 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).

Statistical Methods

Analyses used the data from the 977 intervention nights (pump suspension system active) and the 977 control nights (standard pump and CGM use without automated suspension system active) for which morning measurements of blood glucose, blood ketone, and urine ketone levels were available.

Frequencies of morning blood ketone and urine ketone measurements were tabulated according to duration of overnight pump suspension and morning fasting blood glucose level. Separate repeated-measures regression models were used to 1) compare morning blood ketone levels between control and intervention nights, to 2) evaluate associations between morning urine and blood ketone levels, and to 3) model the probability of a morning blood ketone level ≥ 0.6 mmol/L based on the morning fasting blood glucose value (logistic regression). All models included random subject effects to account for

correlated data due to multiple mornings from the same participant. All reported *P* values are two-sided. Statistical analyses were conducted using SAS version 9.3 software (SAS Institute, Inc., Cary, NC).

RESULTS

One or more pump suspensions occurred on 744 of the 977 intervention nights (76%). Among these 744 nights, median total duration of overnight pump suspension was 70 min (interquartile range 28–114 min): ≤ 30 min on 201 nights (27%); 31–60 min on 120 nights (16%); 61–120 min on 264 nights (35%); and >120 min on 159 nights (21%).

After the 977 intervention nights, morning blood ketone levels were zero on 141 mornings (14%); 0.1–0.2 mmol/L on 766 mornings (78%); 0.3–0.5 mmol/L on 57 mornings (6%); 0.6–0.9 mmol/L on 10 mornings (1%); and ≥ 1.0 mmol/L on 3 mornings (0.3%), with a similar distribution after the 977 control nights (*P* = 0.94) (Table 1). There were no cases of ketoacidosis.

The morning blood ketone level was ≥ 0.6 mmol/L after 11 of 744 nights (1.5%) during which a pump suspension occurred and 2 of 233 nights (0.9%) during which there was no suspension. Even with a prolonged overnight pump suspension, the frequency of a morning blood ketone level ≥ 0.6 mmol/L or a moderate/large urine ketone level was very low (Table 2). After 159 nights in which pump suspension exceeded 2 cumulative hours, the morning blood ketone level was ≥ 0.6 mmol/L on only two occasions (1.3%), and there were no cases in which urine ketone levels were moderate or large. Among the 11 nights (1 night in seven participants and 4 nights in one participant) with a pump suspension and a morning blood ketone level ≥ 0.6 mmol/L, the duration of pump suspension was <1 h on 3 nights, between 1 and 2 h on 6 nights, and >2 h on 2 nights (Supplementary Table 1).

The morning fasting blood glucose level was not a good predictor of the presence of blood ketones (Table 2). The fasting blood glucose level was ≥ 300 mg/dL on only 9 of the 977 intervention mornings (0.9%), and on only 2 of the 9 mornings (22%) was the blood ketone level ≥ 0.6 mmol/L (blood glucose level 334 mg/dL, small urine ketone

Table 1—Distribution of morning blood and urine ketone levels according to whether insulin pump suspension occurred during the preceding night

Variables	Intervention nights (pump suspension)			Control nights (N = 977)
	No (N = 233)	Yes (N = 744)	All (N = 977)	
Morning blood ketone level (mmol/L)				
0	44 (19)	97 (13)	141 (14)	140 (14)
0.1	149 (64)	462 (62)	611 (63)	624 (64)
0.2	26 (11)	129 (17)	155 (16)	145 (15)
0.3	10 (4)	31 (4)	41 (4)	41 (4)
0.4	2 (<1)	12 (2)	14 (1)	15 (2)
0.5	—	2 (<1)	2 (<1)	1 (<1)
0.6	2 (<1)	4 (<1)	6 (<1)	5 (<1)
0.7	—	2 (<1)	2 (<1)	2 (<1)
0.8	—	1 (<1)	1 (<1)	1 (<1)
0.9	—	1 (<1)	1 (<1)	1 (<1)
1.0	—	2 (<1)	2 (<1)	1 (<1)
1.1	—	1 (<1)	1 (<1)	1 (<1)
Morning urine ketone level				
Negative	219 (94)	656 (88)	875 (90)	901 (92)
Trace	11 (5)	64 (9)	75 (8)	57 (6)
Small	3 (1)	22 (3)	25 (3)	12 (1)
Moderate	—	2 (<1)	2 (<1)	6 (<1)
Large	—	—	—	1 (<1)

Values are given as n (%).

levels and blood glucose 348 mg/dL, moderate urine ketone levels on the two mornings). Similarly, among the 977 control mornings, the fasting blood glucose level was ≥ 300 mg/dL on 17 mornings (1.7%), and on only 3 of 17

mornings (18%) was the blood ketone level ≥ 0.6 mmol/L (blood glucose 307 mg/dL, moderate urine ketone levels; blood glucose level 323 mg/dL, small urine ketone levels; and blood glucose level 359 mg/dL, large urine ketone

levels on the 3 mornings). As can be seen in Fig. 1, after both intervention and control nights the probability of a blood ketone level ≥ 0.6 mmol/L was low even with elevated fasting blood glucose levels.

With respect to the association between blood and urine ketone measurements, mean (\pm SD) blood ketone levels were 0.11 ± 0.08 , 0.23 ± 0.18 , and 0.31 ± 0.25 mmol/L, respectively, on mornings where the urine ketone level was negative, trace, and small after intervention nights ($P < 0.001$), and 0.11 ± 0.08 , 0.19 ± 0.13 , and 0.39 ± 0.32 mmol/L, respectively ($P < 0.001$), after control nights. As seen in Supplementary Table 2, 91% of 977 intervention mornings (Supplementary Table 2A) and 93% of 977 control mornings (Supplementary Table 2B) had negative or trace urine ketone levels and blood ketone levels of ≤ 0.2 mmol/L. There was only one instance after an intervention night and two instances after a control night where urine ketone levels were moderate or large and serum ketone levels were < 0.3 mmol/L.

CONCLUSIONS

As part of an in-home randomized trial assessing an automated nocturnal predictive low glucose suspend system,

Table 2—Percentage of mornings with blood ketone level ≥ 0.6 mmol/L or moderate/large urine ketone levels according to morning fasting blood glucose level and duration of insulin pump suspension during the preceding night

Variables	Morning blood glucose levels													
	All		<100 mg/dL		100–149 mg/dL		150–199 mg/dL		200–249 mg/dL		250–299 mg/dL		≥ 300 mg/dL	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Mornings with blood ketone level ≥ 0.6 (mmol/L)														
Pump suspension duration														
0 min	233	2 (1)	18	0	68	0	72	1 (1)	51	0	22	1 (5)	2	0
1–30 min	201	2 (1)	34	0	72	1 (1)	56	0	27	0	12	1 (8)	—	—
31–60 min	120	1 (1)	13	0	61	0	26	0	16	1 (6)	4	0	—	—
61–120 min	264	6 (2)	46	1 (2)	113	3 (3)	65	0	25	0	9	0	6	2 (33)
>120 min	159	2 (1)	35	0	67	0	34	0	17	2 (12)	5	0	1	0
Total intervention nights	977	13 (1)	146	1 (1)	381	4 (1)	253	1 (<1)	136	3 (2)	52	2 (4)	9	2 (22)
Control nights	977	11 (1)	265	2 (1)	353	2 (1)	208	2 (1)	92	0	42	2 (5)	17	3 (18)
Mornings with moderate or large urine ketones														
Pump suspension duration														
0 min	233	0	18	0	68	0	72	0	51	0	22	0	2	0
1 to ≤ 30 min	201	0	34	0	72	0	56	0	27	0	12	0	—	—
31 to ≤ 60 min	120	0	13	0	61	0	26	0	16	0	4	0	—	—
61 to ≤ 120 min	264	2 (1)	46	0	113	0	65	1 (2)	25	0	9	0	6	1 (17)
>120 min	159	0	35	0	67	0	34	0	17	0	5	0	1	0
Total intervention nights	977	2 (<1)	146	0	381	0	253	1 (<1)	136	0	52	0	9	1 (11)
Control nights	977	7 (1)	265	0	353	1 (<1)	208	1 (<1)	92	1 (1)	42	1 (2)	17	3 (18)

The n is a combination of duration of pump suspension and morning fasting blood glucose level, and (%) refers to a blood ketone level ≥ 0.6 mmol/L and a moderate or large urine ketone level.

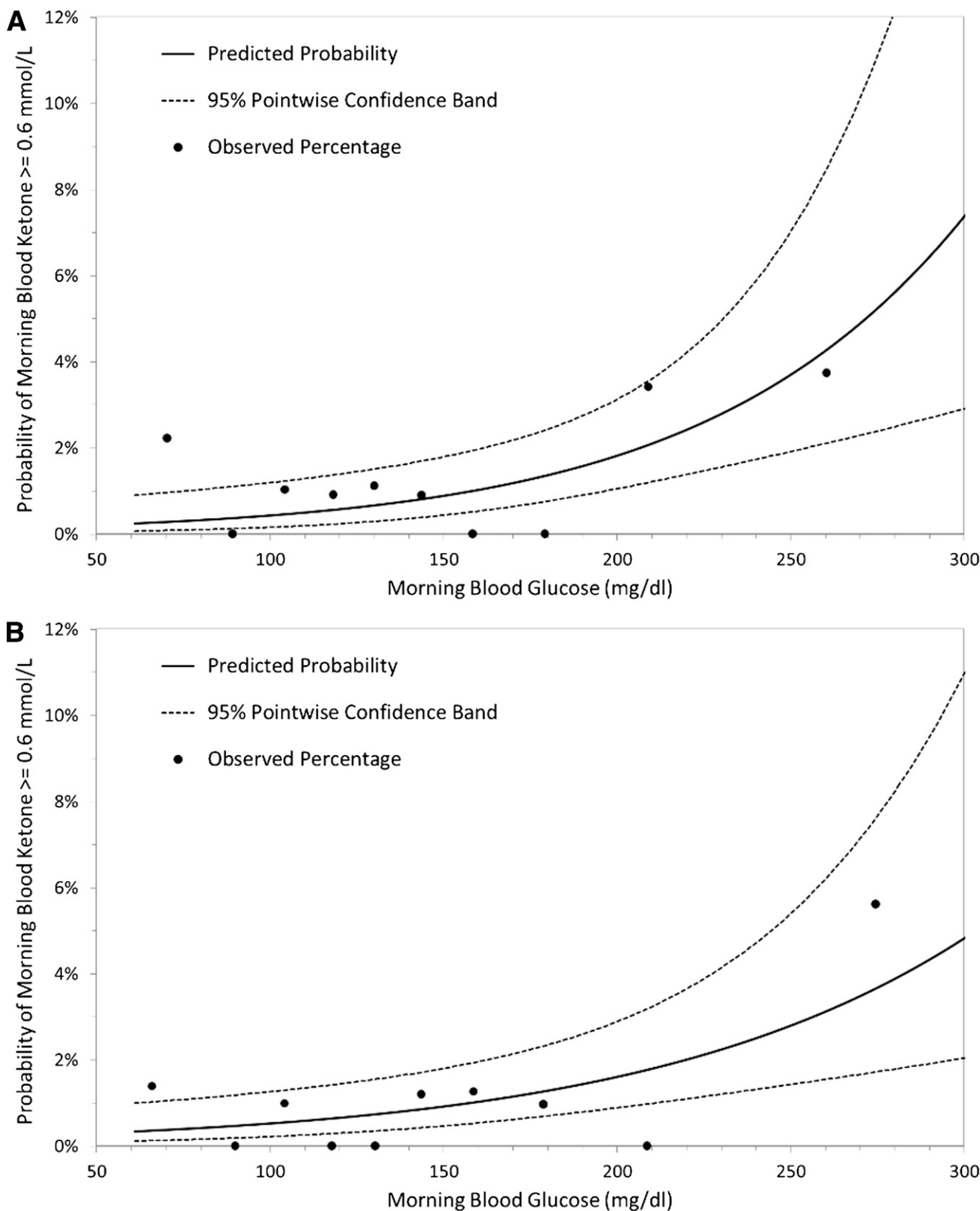


Figure 1—Probability of a morning blood ketone level ≥ 0.6 mmol/L predicted by morning blood glucose level, along with 95% pointwise confidence bands after intervention nights (A) and after control nights (B).

blood and urine ketone levels were measured each morning, irrespective of the blood glucose level, in individuals with type 1 diabetes who were between

15 and 45 years of age. This provided a large data set with standardized data collection for assessing the frequency of morning blood and urine ketone

levels and their relationship to the blood glucose level. The measurements from the control mornings provide a relatively unique opportunity to determine

the frequency of elevated ketone levels according to the blood glucose level, which can be useful for informing patients as well as for serving as a benchmark for studies involving automated suspension of insulin delivery. Overall, the frequency of elevated ketone levels was similar after intervention and control nights. Even after ≥ 2 h of overnight suspension of insulin delivery, the presence of blood ketone levels ≥ 0.6 mmol/L, or moderate or large urine ketone levels was very uncommon ($\sim 1\%$) and was no higher than it was after intervention nights with no pump suspension or control nights. Moderate elevation of the morning fasting blood glucose level (200–300 mg/dL) increased the likelihood that ketones would be present only slightly and, thus, was not a good predictor of the presence of ketones. There were too few mornings (7 of 977 mornings [0.7%]) with a fasting glucose level >300 mg/dL and a prolonged pump suspension to assess with reasonable precision the association of these factors with elevated ketone levels.

Our results are consistent with a number of prior studies in which insulin delivery was experimentally suspended for varying lengths of time to assess the effect on blood glucose and ketone levels (Table 2) (1–8). In these mostly inpatient studies, ketonemia and/or ketonuria occurred if insulin delivery was suspended for a long enough period of time, but ketosis declined rapidly once insulin delivery was restored. Our results also are consistent with those of studies conducted using the low glucose suspend feature of the Paradigm Veo pump (12–17), which have demonstrated that a 2-h suspension of insulin delivery when a hypoglycemic threshold is reached is safe and does not increase the risk of ketoacidosis. Our study differs from the prior reports in having almost 2,000 at-home blood and urine ketone measurements obtained in a standardized manner irrespective of the blood glucose level, and provides valuable data with respect to the expected frequency of blood and urine ketone levels with and without pump suspension.

In summary, our results indicate that routine measurement of blood or urine ketone levels during the use of an automated pump suspension system using CGM, whether threshold-based or

predictive, is not necessary. The measurement of urine ketone levels provided no significant clinical information that was not provided by the measurement of serum ketone levels. The risk of development of morning ketosis and DKA using these systems to suspend insulin delivery overnight is not increased in individuals who are 15–45 years old, even when insulin delivery is suspended for up to 2–3 h. Recommendations for checking ketone levels should be no different when a patient is using a system with automated insulin suspension than it is for conventional diabetes self-management. The conventional recommendations are to check serum ketone levels if the fasting glucose level is >250 mg/dL, or if the blood glucose level is >300 mg/dL at any time during the day, when there is illness (especially with nausea or emesis), or when an insulin infusion site failure is suspected.

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algorithm. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. R.W.B. wrote and edited the manuscript. D.R., R.P.W., H.P.C., D.M.M., and B.A.B. researched the data, contributed to the discussion, and reviewed and edited the manuscript. The writing group collectively produced the manuscript. R.W.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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