

## **Prolonged Nocturnal Hypoglycemia Is Common During 12 Months Of Continuous Glucose Monitoring In Children And Adults With Type 1 Diabetes**

**Running Title:** Nocturnal Hypoglycemia in Type 1 Diabetes

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group

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*Objective:* To characterize the amount of nocturnal hypoglycemia and evaluate factors associated with nocturnal hypoglycemia assessed with continuous glucose monitoring (CGM) in adults and children with type 1 diabetes who participated in the JDRF CGM Randomized Clinical Trial.

*Research Design and Methods:* The analysis included 36,467 nights with  $\geq 4$  hours of CGM glucose readings between 12 midnight and 6 a.m. from 176 subjects assigned to the trial's CGM group. The percentage of nights in which hypoglycemia occurred (2 consecutive CGM readings  $\leq 60$ mg/dL in 20 minutes) was computed for each subject. Associations with baseline characteristics and clinical factors were evaluated using a multivariate regression model.

*Results:* Hypoglycemic events occurred during 8.5% of nights, with the median percentage of nights with hypoglycemia per subject being 7.4% (interquartile range 3.7% to 12.1%). The duration of hypoglycemia was  $\geq 2$  hours on 23% of hypoglycemic nights. In a multivariate model, a higher incidence of nocturnal hypoglycemia was associated with (1) lower baseline HbA1c levels ( $P < 0.001$ ) and (2) the occurrence of hypoglycemia on one or more nights during baseline blinded CGM ( $P < 0.001$ ). The hypoglycemia frequency was not associated with age or with insulin modality (pump versus multiple daily injections).

*Conclusions:* Nocturnal hypoglycemia is frequent and often prolonged in adults and children with type 1 diabetes. Patients with low HbA1c levels are at an increased risk for its occurrence. One week of blinded CGM can identify patients who are at greater risk for nocturnal hypoglycemia.

Even with the use of insulin pumps and long-acting insulin analogs, severe hypoglycemia is common in patients with type 1 diabetes (T1D), especially during sleep at night. In the DCCT, more than half of severe hypoglycemic events occurred during sleep (1) and other studies have shown an even greater incidence of severe nocturnal hypoglycemic events in T1D (2). Moreover, Sovik reported that among patients under age 40 years who died over a 10-year period, 6% of the deaths were due to “dead-in-bed” syndrome (3), which in many cases likely was the result of severe nocturnal hypoglycemia. Delayed glucose-lowering effects of afternoon exercise (4), sleep-induced defects in counter regulatory hormone responses to hypoglycemia (5-7), and missed bedtime snacks (8) are among the contributing causes of severe nocturnal hypoglycemic events.

Studies that utilized retrospective and real-time continuous glucose monitoring (CGM) systems to assess glycemic control of T1D indicate that severe hypoglycemic events are only the tip of the iceberg regarding the risk of nocturnal hypoglycemia, since many more events are unrecognized and asymptomatic (8-14). Detection of such events is important; however, as recurrent episodes of mild hypoglycemia have been shown to contribute to the development of defective counter regulatory hormone responses to subsequent reductions in blood sugar, thus setting the stage for clinically important hypoglycemic events. Buckingham et al documented four episodes of seizures occurring during the night in patients wearing CGM devices which demonstrated that there were 2 ¼

to 4 hours of low sensor glucose values preceding each seizure (15).

Our Juvenile Diabetes Research Foundation CGM Study Group recently reported the results of a 6-month randomized clinical trial and 6-month extension study that evaluated the effectiveness of real-time CGM in intensively treated T1D subjects with baseline HbA1c levels  $\geq 7.0\%$  (n=322) and  $< 7.0\%$  (n=129) (16-18). These studies have provided a very large dataset of nighttime CGM profiles to evaluate the frequency of nocturnal hypoglycemia during 12 months of CGM use in the home environment and factors associated with greater risk.

## **METHODS**

The study protocol and clinical characteristics of enrolled subjects have been described in detail (16; 17; 19). Major eligibility criteria included age  $\geq 8$  years, T1D for at least one year, use of either an insulin pump or multiple (at least 3) daily insulin injections, and HbA1c level  $< 10.0\%$ . The dataset utilized for the current analyses included 180 subjects assigned to the CGM group who used either the FreeStyle Navigator™ (Abbott Diabetes Care, Inc., Alameda, CA) or the MiniMed Paradigm® REAL-Time Insulin Pump and Continuous Glucose Monitoring System (Medtronic MiniMed, Inc., Northridge, CA). At baseline, a blinded CGM device was used for one week. Thereafter, the goal was to use the unblinded CGM device on a daily basis if possible. CGM glucose data were downloaded at each visit over 12 months of follow up. Subjects and parents of minor subjects completed the Hypoglycemia Fear Survey (20) at baseline, 6 months, and 12 months.

The CGM data were evaluated from 12 midnight to 6 a.m. Only nights having at least 4 hours of glucose data were included in the analysis. Subjects needed to have at least 42 such nights to be included in the analysis (this restriction was placed since hypoglycemia rates were calculated per subject). Four subjects did not meet this criterion and were not included in the analysis. The dataset included 36,467 nights from 176 subjects with a median value of 217 nights per subject. Eighty-six percent of nights had the full 6 hours of data without any skips from 12 midnight to 6 a.m. A hypoglycemia event was defined as the occurrence of at least 2 CGM glucose values  $\leq 60$  mg/dL within a 20 minute period. The percentage of nights with at least one hypoglycemia event was computed for each subject.

The associations between nocturnal hypoglycemia rate, defined as the percentage of nights with hypoglycemia per subject, and baseline demographic and clinical factors (listed in table 1) were evaluated using regression models. Due to the skewed distribution of the hypoglycemia rate, a rank transformation (van der Waerden scores) was used in the models. Baseline demographic and clinical factors with a P-value  $< 0.20$  in the univariate model were included in an initial multivariate model and then a backward elimination procedure was used to remove variables with a P-value  $> 0.05$ . A forward selection process resulted in a similar model. Age was evaluated as a discrete factor in three pre-specified levels (8 to 14, 15 to 24, and  $\geq 25$  years). To avoid collinearity in the model building, the highly correlated baseline hypoglycemic measures (percentage of daytime, nighttime, or 24 hours with hypoglycemia and number of nights with hypoglycemia)

and other baseline glycemic measures (the percentage of blinded CGM values between 71 and 180 mg/dL, the percentage of values  $> 250$  mg/dL, and HbA1c) were included in the model one at a time. Subjects with missing values for covariates were excluded from the corresponding univariate models. For the multivariate models, missing was treated as a separate category for discrete covariates and an indicator for missing was added to the model for continuous covariates. The association of age and hypoglycemia duration during nights with a hypoglycemic event was evaluated using repeated measures regression with rank scores. The comparison of the hypoglycemia rate in the first 6 months and in the second 6 months was based on rank scores.

Analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC). All P-values are 2-sided. Due to the exploratory nature of these analyses and the multiple statistical tests, the threshold for statistical significance was adjusted to  $P < 0.01$ .

## **RESULTS**

The clinical characteristics of the 176 subjects who met the criteria for inclusion in these analyses are shown in Table 1. Hypoglycemic events occurred between 12 midnight and 6 a.m. during 3,083 (8.5%) of the 36,467 nights, with the median percentage of nights with hypoglycemia per subject being 7.4% (interquartile range 3.7% to 12.1%) which is approximately twice per month. The maximum percentage of hypoglycemic nights per subject was 27.8%; 6 (3%) of subjects had no hypoglycemic nights (number of nights for these subjects ranged from 55 to 235, their baseline HbA1c ranged from 7.7% to 8.9%,

supplemental table 1 on the journal website).

On the 3,083 nights during which hypoglycemia occurred, the median duration of hypoglycemia ( $\leq 60$  mg/dL) was 53 minutes (interquartile range 29 to 110 minutes) and the mean was  $81 \pm 75$  minutes, with 47% of nights having at least 1 hour of hypoglycemia, 23% at least 2 hours, and 11% at least 3 hours. An exploratory plot of the duration of hypoglycemia versus age suggested a shorter mean duration of the events in subjects  $\geq 25$  years old than in those  $< 25$  years old (Figure 1). In a statistical comparison of these two age groups, mean duration of hypoglycemia during the nights on which hypoglycemia occurred was 73 minutes in subjects  $\geq 25$  years and 88 minutes in subjects  $< 25$  years (median 50 versus 58 minutes,  $P=0.007$ ).

As shown in table 2, a higher incidence of nocturnal hypoglycemia over the 12 months of follow up was associated with (1) lower baseline HbA1c levels ( $P<0.001$ ) and (2) the occurrence of hypoglycemia on one or more nights during baseline blinded CGM use ( $P<0.001$ ) in a multivariate model. Similar results were obtained when the percentage of daytime, nighttime, or 24 hours with hypoglycemia during the baseline blinded CGM use was included in the model instead of the number of nights with hypoglycemia and when the percentage of blinded CGM values between 71 and 180 mg/dL or the percentage of values  $>250$  mg/dL was included in the model instead of HbA1c (see data in supplemental table 2 on the journal website).

There was a suggestion of an upside down U-shaped association between age and hypoglycemia rate. The median hypoglycemia rate was 6.3%

in the 8 to 14 age group, 8.8% in the 15-24 age group and 7.4% in the  $\geq 25$  age group (univariate  $P=0.05$ , multivariate  $P=0.12$ ). The frequency of nocturnal hypoglycemia was not statistically different between pump and MDI users ( $P=0.63$ ). Scores on the Hypoglycemia Fear Survey completed at baseline also were not predictive of the frequency of nocturnal hypoglycemia. The factors associated with hypoglycemia appeared similar in the three age groups (supplemental table 2 on journal website). The median hypoglycemia rate was 6.6% (25<sup>th</sup> and 75<sup>th</sup> interquartile range: 3.5%, 12.6%) in the first 6 months and 7.7% (3.7%, 13.6%) in the second 6 months ( $P=0.45$ ).

## **CONCLUSION**

The greater than 36,000 nights with 4 or more hours of sensor glucose readings, totaling  $>2.4$  million individual glucose values in 176 patients with T1D, aged 8-72 years, provided us with a unique opportunity to determine the frequency of nocturnal hypoglycemia. During treatment aimed at lowering HbA1c levels to 7.0% or less, as has been suggested in other smaller studies, the occurrence of nocturnal hypoglycemia in our intensively treated subjects was both frequent occurring on 8.5% of nights during the 12 months of CGM use, and prolonged. On 23% of hypoglycemic nights, sensor glucose levels  $\leq 60$  mg/dL were present for almost 2 hours and the duration of hypoglycemia was longer in those  $< 25$  years old. It seems unlikely that the observed incidence of nocturnal hypoglycemia is an overestimate since prior outpatient studies using CGM have reported even higher rates (8; 9; 11-13), as have inpatient studies using blood glucose measurements (10; 14). Although sensor inaccuracy could

produce misclassification of some nights as to whether hypoglycemia occurred, an inpatient accuracy study conducted by the Diabetes Research in Children Network using the Navigator found that the false positive and false negative rates for nocturnal hypoglycemia were approximately the same (21). Thus, the point estimate of nocturnal hypoglycemia from the current study is unlikely to be appreciably affected by sensor inaccuracy.

A sensor glucose level  $\leq 60$  mg/dL rather than  $\leq 70$  mg/dL was used to define hypoglycemia because there is considerably greater concern for serious sequelae for glucose levels  $\leq 60$  mg/dL than for levels between 61 and 70 mg/dL. Moreover, in our study of sensor glucose levels in 8-65 year old, healthy, non-obese subjects with normal fasting glucose and normal glucose tolerance, nighttime sensor glucose values  $\leq 60$  mg/dL were much less common than values between 61 and 70 mg/dL (median frequency 0.0 versus 1.0%, respectively,  $P < 0.001$ ) (22).

Not surprisingly, the frequency of nighttime hypoglycemia was greater in subjects with lower HbA1c values and in those who had the occurrence of nocturnal hypoglycemia during a week of blinded CGM use at baseline. The method of insulin administration was not a significant predictor but the number of patients using multiple daily injections was small, limiting the interpretation of this finding. It also is important to note that nocturnal hypoglycemia was frequent and prolonged in our subjects even though nighttime CGM profiles were being used to adjust overnight basal rates, and long-acting insulin analog doses and sensor alarms were used to limit the duration of nocturnal hypoglycemic events.

These results support the contention that overnight insulin replacement may never be optimal in patients with T1D until closed-loop systems that provide minute to minute feedback control of insulin delivery based on real-time sensor glucose sensor data are developed for home use.

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Below is a listing of relationships of the investigators with companies that make products relevant to the manuscript between July 1, 2006 and November 4, 2009. Research funds were listed below were provided to the legal entity that employs the individual and not directly to the individual.

Dr. Kollman reports having received consulting fees from Medtronic MiniMed, Inc.; Dr. Laffel reports having received consulting fees from Lifescan, Inc., consulting fees and a speaker honorarium from Abbott Diabetes Care, Inc., consulting fees and research funding from Medtronic MiniMed, Inc.; Dr. Mauras reports having received grant support from Medtronic MiniMed, Inc.; Dr. Tamborlane reports having received consulting fees from Abbott Diabetes Care, Inc. and Lifescan, Inc. and consulting fees, a speaker honorarium, and research funding from Medtronic MiniMed, Inc.

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**Figure 1. Duration of Hypoglycemia ( $\leq 60$ mg/dL) versus Age**

For presentation purposes, the hypoglycemic nights ordered by age were divided into 20 groups with approximately equal number of nights per group. The average duration was then plotted against the average age for each group. The regression line, however, is based on all the data points, not the 20 groups.

Table 1. Baseline Characteristics

	Overall	Age Group		
		8-14 Years	15-24 Years	≥25 Years
	N=176	N=64	N=42	N=70
<b>Age (years, Mean ± SD)</b>	25.6 ± 15.6	11.6 ± 2.0	19.6 ± 3.2	42.1 ± 11.4
<b>Diabetes duration (years, Mean ± SD)</b>	14.7 ± 12.5	6.1 ± 3.1	10.2 ± 5.1	25.4 ± 13.2
<b>Gender</b>				
Female	94 (53%)	34 (53%)	21 (50%)	39 (56%)
Male	82 (47%)	30 (47%)	21 (50%)	31 (44%)
<b># Severe hypoglycemia events in 6 months prior to study (self-reported)</b>				
0	164 (93%)	61 (95%)	39 (93%)	64 (91%)
≥ 1	12 (7%)	3 (5%)	3 (7%)	6 (9%)
<b>#Nights with hypoglycemia during blinded use at baseline*</b>				
0	102 (60%)	42 (67%)	21 (51%)	39 (59%)
≥ 1	68 (40%)	21 (33%)	20 (49%)	27 (41%)
<b>Home blood glucose meter measurements per day (self-reported at baseline) †</b>				
≤5	43 (29%)	12 (23%)	16 (52%)	15 (23%)
6-8	78 (53%)	31 (60%)	12 (39%)	35 (55%)
>8	26 (18%)	9 (17%)	3 (10%)	14 (22%)
<b>Insulin delivery</b>				
Pump	163 (93%)	57 (89%)	38 (90%)	68 (97%)
Multiple Daily Injections	13 (7%)	7 (11%)	4 (10%)	2 (3%)
<b>HbA1c (mean ± SD) (%)</b>				
N (%)	7.4 ± 0.9	7.6 ± 1.0	7.6 ± 0.8	7.1 ± 0.8
<7.0%	57 (32%)	17 (27%)	11 (26%)	29 (41%)
7.0%-<8.0%	72 (41%)	22 (34%)	16 (38%)	34 (49%)
≥ 8.0%	47 (27%)	25 (39%)	15 (36%)	7 (10%)
<b>Hypoglycemia Fear Scale Score ‡ (mean ± SD)</b>				
N (%)	28 ± 18	25 ± 17	29 ± 18	31 ± 18
<20	65 (37%)	27 (42%)	15 (36%)	23 (33%)
20-<30	32 (18%)	14 (22%)	8 (19%)	10 (14%)
30+	78 (45%)	22 (35%)	19 (45%)	37 (53%)

\* From use of a blinded CGM device for one week at baseline, missing for 6 subjects.

† Collected on randomization form, as assessed by clinic personnel over the last 7 days. Question was added to CRF after study initialization and data were missing for 29 subjects.

‡ The Hypoglycemia Fear Scale consists of 15 5-point Likert scale items, with scores scaled to a 0 to 100 range with higher scores indicating more fear of hypoglycemia; missing for one subject

**Table 2. Association of Baseline Factors and Nocturnal Hypoglycemia**

	%Nights with hypoglycemia per subject			Unadjusted P-value	Model 1*	Model 2†
	N	Median	(25 <sup>th</sup> 75 <sup>th</sup> percentile)			
<b>Total</b>	176	7.4%	(3.7%, 12.1%)			
<b>Age</b>				0.05	0.12	
8-14	64	6.3%	(2.0%, 11.4%)			
15-24	42	8.8%	(3.9%, 16.1%)			
≥ 25	70	7.4%	(4.6%, 10.8%)			
<b>Gender</b>						
Female	94	7.2%	(3.7%, 10.8%)	0.36		
Male	82	7.8%	(3.7%, 14.2%)			
<b># Severe hypoglycemia events in 6 months prior to study (self-reported)</b>				0.87		
0	164	7.2%	(3.7%, 12.2%)			
≥ 1	12	8.3%	(4.3%, 10.5%)			
<b>#Nights with hypoglycemia during blinded use at baseline §</b>				<0.001	<0.001	<0.001
0	102	6.0%	(2.8%, 10.5%)			
≥ 1	68	9.4%	(5.1%, 15.9%)			
<b>Home blood glucose meter measurements per day (self-reported at baseline) ‡,  </b>				0.28		
≤5	43	8.1%	(4.1%, 13.7%)			
6-8	78	8.8%	(3.7%, 12.2%)			
>8	26	5.4%	(3.2%, 12.4%)			
<b>Insulin delivery</b>				0.63		
Pump	163	7.4%	(3.9%, 12.0%)			
Multiple Daily Injections	13	5.1%	(1.8%, 12.6%)			
<b>HbA1c‡</b>				<0.001	<0.001	<0.001
<7.0%	57	9.0%	(5.3%, 14.7%)			
7.0%-<8.0%	72	8.2%	(4.5%, 12.0%)			
≥ 8.0%	47	3.9%	(1.6%, 8.7%)			
<b>Hypoglycemia Fear Scale Score ‡,¶</b>				0.11	0.22	
<20	65	7.5%	(3.3%, 10.3%)			
20-<30	32	7.7%	(4.6%, 11.0%)			
30+	78	7.0%	(3.7%, 13.5%)			

\* The multivariate regression model included all variables with P-value < 0.20

† Multivariate regression model using backward selection keeping those variables with P-value < 0.05

‡ P-value obtained by treating as continuous variable

§ From use of a blinded CGM device for one week at baseline, missing for 6 subjects.

|| Collected on randomization form, as assessed by clinic personnel over the last 7 days. Question was added to CRF after study initialization and data were missing for 29 subjects.

¶ The Hypoglycemia Fear Scale consists of 15 5-point Likert scale items, with scores scaled to a 0 to 100 range with higher scores indicating more fear of hypoglycemia; missing for one subject.

Figure 1.

