Prolonged Nocturnal Hypoglycemia Is Common During 12 Months of Continuous Glucose Monitoring in Children and Adults With Type 1 Diabetes

JUVENILE DIABETES RESEARCH FOUNDATION CONTINUOUS GLUCOSE MONITORING STUDY GROUP*

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 Juvenile Diabetes Research Foundation CGM randomized clinical trial.

RESEARCH DESIGN AND METHODS — The analysis included 36,467 nights with ≥4 h of CGM glucose readings between 12 midnight and 6:00 A.M. from 176 subjects assigned to the CGM group of the trial. The percentage of nights in which hypoglycemia occurred (two consecutive CGM readings ≤60 mg/dl in 20 min) 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 3.7–12.1%). The duration of hypoglycemia was ≥2 h on 23% of nights with hypoglycemia. In a multivariate model, a higher incidence of nocturnal hypoglycemia was associated with *1*) lower baseline A1C 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 A1C 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.

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Even with the use of insulin pumps and long-acting insulin analogs, severe hypoglycemia is common in patients with type 1 diabetes, especially during sleep at night. In the Diabetes Control and Complications Trial, 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 type 1 diabetes (2). Moreover, Sovik and Thordarson (3) 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 probably was the result of severe nocturnal hypoglycemia. Delayed glucose-lowering effects of afternoon exercise (4), sleep-induced defects in counterregulatory hormone responses to hypoglycemia (5–7), and missed bedtime snacks (8) are among the contributing causes of severe nocturnal hypoglycemic events.

Studies that used retrospective and real-time continuous glucose monitoring (CGM) systems to assess glycemic control of type 1 diabetes indicate that severe hypoglycemic events are only the tip of the iceberg regarding the risk of nocturnal hypoglycemia, because many more events are unrecognized and asymptomatic (8–14). Detection of such events is important, however, because recurrent episodes of mild hypoglycemia have been shown to contribute to the development of defective counterregulatory hormone responses to subsequent reductions in blood glucose, thus setting the stage for clinically important hypoglycemic events. Buckingham et al. (15) documented four episodes of seizures occurring during the night in patients wearing CGM devices, which demonstrated that there were 2¼–4 h of low sensor glucose values preceding each seizure.

Our Juvenile Diabetes Research Foundation (JDRF) 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 type 1 diabetic subjects with baseline A1C levels ≥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.

RESEARCH DESIGN AND METHODS

— The study protocol and clinical characteristics of enrolled subjects have been described in detail elsewhere (16,17,19). Major eligibility criteria included age ≥8 years, type 1 diabetes for at least 1 year, use of either an insulin pump or multiple (at least three) daily insulin injections, and A1C level <10.0%. The dataset used for the current analyses included 180 subjects assigned to the CGM group who used either the

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*A full listing of the members of the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group is available in the online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-2081/DC1.

Table 1—*Baseline characteristics*

	Overall	Age-group		
		8–14 years	15–24 years	≥25 years
n	176	64	42	70
Age (years)	25.6 ± 15.6	11.6 ± 2.0	19.6 ± 3.2	42.1 ± 11.4
Diabetes duration (years)	14.7 ± 12.5	6.1 ± 3.1	10.2 ± 5.1	25.4 ± 13.2
Sex				
Female	94 (53)	34 (53)	21 (50)	39 (56)
Male	82 (47)	30 (47)	21 (50)	31 (44)
Severe hypoglycemia events in 6 months before study (self-reported)				
0	164 (93)	61 (95)	39 (93)	64 (91)
≥1	12 (7)	3 (5)	3 (7)	6 (9)
Nights with hypoglycemia during blinded use at baseline*				
0	102 (60)	42 (67)	21 (51)	39 (59)
≥1	68 (40)	21 (33)	20 (49)	27 (41)
Home blood glucose meter measurements per day (self-reported at baseline)†	6.8 ± 2.3	6.8 ± 2.0	6.0 ± 2.1	7.1 ± 2.5
≤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)
Insulin delivery				
Pump	163 (93)	57 (89)	38 (90)	68 (97)
Multiple daily injections	13 (7)	7 (11)	4 (10)	2 (3)
A1C	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)
Hypoglycemia Fear Scale score‡	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)

Data are means ± SD or *n* (%). *From use of a blinded CGM device for 1 week at baseline, missing for 6 subjects. †Collected on randomization form, as assessed by clinic personnel over the last 7 days. A question was added to Case Report Form 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 0–100 range with higher scores indicating more fear of hypoglycemia; missing for 1 subject.

FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA) or the MiniMed Paradigm REAL-Time Insulin Pump and Continuous Glucose Monitoring System (Medtronic MiniMed, Northridge, CA). At baseline, a blinded CGM device was used for 1 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 midnight to 6:00 A.M. Only nights having at least 4 h 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 because 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. Of the nights, 86% had the full 6 h of data without any skips from midnight to 6:00 A.M. A hypoglycemia event was defined as the occurrence of at least two CGM glucose values ≤60 mg/dl within a 20-min 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. Because of 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 $P < 0.20$ in the univariate model were included in an initial multivariate model and then a backward elimination procedure was used to remove variables with $P > 0.05$. A forward selection process resulted in a similar model. Age was evaluated as a discrete factor in three prespecified levels (8–14, 15–24, and ≥25 years). To avoid collinearity in the model building, the highly correlated baseline hypoglycemic measures (percentage of daytime, nighttime, or 24 h 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 A1C) were included in the model one at a time. Subjects with miss-

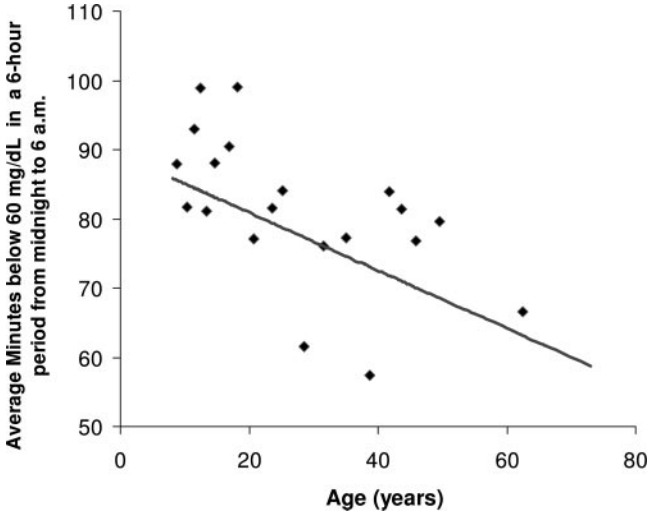

Figure 1—*Duration of hypoglycemia (≤60 mg/dl) vs. age. For presentation purposes, the hypoglycemic nights ordered by age were divided into 20 groups with an approximately equal number of nights per group. The average duration was then plotted against the average age for each group. The regression line, however, is based on all the data points, not the 20 groups.*

ing 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 two-sided. Because of 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 midnight and 6:00 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 3.7–12.1%), which is approximately twice per month. The maximum percentage of hypoglycemic nights per subject was 27.8%; six (3%) of subjects had no hypoglycemic nights (number of nights for these subjects ranged from 55 to 235, their baseline A1C ranged from 7.7 to 8.9%) (supplementary Table 1, available in an online appendix at http://care.diabetesjournals. org/cgi/content/full/dc09-2081/DC1).

On the 3,083 nights during which hypoglycemia occurred, the median duration of hypoglycemia (≤60 mg/dl) was 53 min (interquartile range 29–110 min) and the mean was 81 ± 75 min, with 47% of nights having at least 1 h of hypoglycemia, 23% at least 2 h, and 11% at least 3 h. An exploratory plot of the duration of hypoglycemia versus age suggested a shorter mean duration of the events in subjects aged ≥25 years old than in those aged <25 years old (Fig. 1). In a statistical comparison of these two age-groups, mean duration of hypoglycemia during the nights on which hypoglycemia occurred was 73 min in subjects aged ≥25 years and 88 min in subjects aged <25 years (median 50 vs. 58 min, $P = 0.007$).

As shown in Table 2, a higher incidence of nocturnal hypoglycemia over the 12 months of follow up was associated with *1*) lower baseline A1C 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 h 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 A1C (supplementary Table 2).

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-year age-group, 8.8% in the 15- to 24-year age-group, and 7.4% in the ≥25-year age-group (univariate $P = 0.05$, multivariate $P = 0.12$). The frequency of nocturnal hypoglycemia was not statistically different between pump and multiple daily injection 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 to be similar in the three age-groups (supplementary Table 2). The median hypoglycemia rate was 6.6% (25th and 75th interquartile range 3.5, 12.6%) in the first 6 months and 7.7% (3.7, 13.6%) in the second 6 months ($P = 0.45$).

CONCLUSIONS — The >36,000 nights with ≥4 h of sensor glucose readings, totaling >2.4 million individual glucose values in 176 patients with type 1 diabetes, aged 8–72 years, provided us with a unique opportunity to determine the frequency of nocturnal hypoglycemia. During treatment aimed to lower A1C levels to ≤7.0%, 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 ≤60 mg/dl were present for almost 2 h and the duration of hypoglycemia was longer in those aged <25 years. It seems unlikely that the observed incidence of nocturnal hypoglycemia is an overestimate because 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 FreeStyle Navigator showed 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.

Table 2—*Association of baseline factors and nocturnal hypoglycemia*

	n	% Nights with hypoglycemia per subject	Unadjusted *P* value	Model 1*	Model 2†
Total	176	7.4 (3.7, 12.1)			
Age			0.05	0.12	
8–14 years	64	6.3 (2.0, 11.4)			
15–24 years	42	8.8 (3.9, 16.1)			
≥25 years	70	7.4 (4.6, 10.8)			
Sex	94	7.2 (3.7, 10.8)			
Female			0.36		
Male	82	7.8 (3.7, 14.2)			
Severe hypoglycemia events in 6 months before to study (self-reported)			0.87		
0	164	7.2 (3.7, 12.2)			
≥1	12	8.3 (4.3, 10.5)			
Nights with hypoglycemia during blinded use at baseline‡			<0.001	<0.001	<0.001
0	102	6.0 (2.8, 10.5)			
≥1	68	9.4 (5.1, 15.9)			
Home blood glucose meter measurements per day (self-reported at baseline)§‖			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)			
Insulin delivery					
Pump	163	7.4 (3.9, 12.0)	0.63		
Multiple daily injections	13	5.1 (1.8, 12.6)			
A1C§			<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)			
Hypoglycemia Fear Scale score§¶			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)			

Data are median (25th, 75th percentile). *The multivariate regression model included all variables with $P < 0.20$. †Multivariate regression model using backward selection keeping those variables with $P < 0.05$. ‡From use of a blinded CGM device for 1 week at baseline, missing for 6 subjects. §*P* value obtained by treating as continuous variable. ‖Collected on a randomization form, as assessed by clinic personnel over the last 7 days. A question was added to Case Report Form 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 1 subject.

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

Not surprisingly, the frequency of nighttime hypoglycemia was greater in subjects with lower A1C 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 type 1 diabetes 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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The study was designed and conducted by the investigators listed in the online appendix, who collectively wrote the manuscript and vouch for the data. The investigators had complete autonomy to analyze and report the trial results. There were no agreements concerning confidentiality of the data between the Juvenile Diabetes Research Foundation and the authors or their institutions. The Jaeb Center for Health Research had full access to all of 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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