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 percent-age 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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* 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. © 2010 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
midnight to 6:00 A.M. Only nights having

ents of minor subjects completed the Hy-

meters with hypoglycemia and number of nights

cause 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 com-
pared for each subject.

The associations between nocturnal
hypoglycemia rate, defined as the per-
centage of nights with hypoglycemia per
subject, and baseline demographic and clinical
factors (listed in Table 1) were
evaluated using regression models. Be-
cause 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 multi-
variate model and then a backward elim-
ation procedure was used to remove
variables with \( P > 0.05 \). A forward selec-
tion 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
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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.

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 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.
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- to 65-year-old, healthy, nonobese 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 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.

Acknowledgments — The writing committee members are as follows: Lead authors: Nelly Mauras, MD; Dongyuan Xing, MPH; Roy W. Beck, MD, PhD; and William V. Tamborlane, MD. Additional members (alphabetical): Rosanna Fiallo-Scharer, MD; Irl Hirsch, MD; Craig Kollman, PhD; Lori Lafel, MD, MPH; Joyce Lee, MD, MPH; Katrina J. Ruedy, MSPH; Eva Tsalikian, MD; and Darrell Wilson, MD.

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Table 2—Association of baseline factors and nocturnal hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>% Nights with hypoglycemia per subject</th>
<th>Unadjusted P value</th>
<th>Model 1*</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>176</td>
<td>7.4 (3.7, 12.1)</td>
<td>0.05</td>
<td>0.12</td>
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</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>8–14 years</td>
<td>64</td>
<td>6.3 (2.0, 11.4)</td>
<td>0.05</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>15–24 years</td>
<td>42</td>
<td>8.8 (3.9, 16.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥25 years</td>
<td>70</td>
<td>7.4 (4.6, 10.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>94</td>
<td>7.2 (3.7, 10.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>82</td>
<td>7.8 (3.7, 14.2)</td>
<td>0.36</td>
<td></td>
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<tr>
<td>Severe hypoglycemia events in 6 months before to study (self-reported)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>164</td>
<td>7.2 (3.7, 12.2)</td>
<td>0.63</td>
<td></td>
<td></td>
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<tr>
<td>≥1</td>
<td>12</td>
<td>8.3 (4.3, 10.5)</td>
<td>0.28</td>
<td></td>
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<tr>
<td>Nights with hypoglycemia during blinded use at baseline‡</td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>102</td>
<td>6.0 (2.8, 10.5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>≥1</td>
<td>68</td>
<td>9.4 (5.1, 15.9)</td>
<td>0.001</td>
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<tr>
<td>Home blood glucose meter measurements per day (self-reported at baseline)§</td>
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<tr>
<td>≤5</td>
<td>43</td>
<td>8.1 (4.1, 13.7)</td>
<td>0.63</td>
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<tr>
<td>6–8</td>
<td>78</td>
<td>8.8 (3.7, 12.2)</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>&gt;8</td>
<td>26</td>
<td>5.4 (3.2, 12.4)</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Insulin delivery</td>
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<tr>
<td>Pump</td>
<td>163</td>
<td>7.4 (3.9, 12.0)</td>
<td>0.11</td>
<td>0.22</td>
<td></td>
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<tr>
<td>Multiple daily injections</td>
<td>13</td>
<td>5.1 (1.8, 12.6)</td>
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<td></td>
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<tr>
<td>A1C§</td>
<td></td>
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<tr>
<td>&lt;7.0%</td>
<td>57</td>
<td>9.0 (5.3, 14.7)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>7.0–&lt;8.0%</td>
<td>72</td>
<td>8.2 (4.5, 12.0)</td>
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<tr>
<td>≥8.0%</td>
<td>47</td>
<td>3.9 (1.6, 8.7)</td>
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</tr>
<tr>
<td>Hypoglycemia Fear Scale score§¶</td>
<td></td>
<td>7.5 (3.3, 10.3)</td>
<td></td>
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<tr>
<td>&lt;20</td>
<td>65</td>
<td>7.7 (4.6, 11.0)</td>
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<tr>
<td>20–&lt;30</td>
<td>32</td>
<td>7.5 (3.3, 10.3)</td>
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<tr>
<td>≥30</td>
<td>78</td>
<td>7.0 (3.7, 13.5)</td>
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</table>

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.
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price from DexCom (San Diego, CA), Medtronic MiniMed (Northridge, CA), and Abbott Diabetes Care (Alameda, CA). Home glucose meters and test strips were provided to the study by LifeScan and Abbott Diabetes Care. A listing of relationships of the investigators with companies that make products relevant to the manuscript between 1 July 2006 and 4 November 2009 follows. Research funds listed below were provided to the legal entity that employs the individual and not directly to the individual. C.K. received consulting fees from Medtronic MiniMed. L.L. received consulting fees from LifeScan, consulting fees and speaker honorarium from Abbott Diabetes Care, and consulting fees and research funding from Medtronic MiniMed. N.M. received grant support from Medtronic MiniMed. W.V.T. received consulting fees from Abbott Diabetes Care and LifeScan and consulting fees, speaker honorarium, and research funding from Medtronic MiniMed. No other potential conflicts of interest relevant to this article were reported.

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.

Parts of this study were presented at the Diabetes Technology Society Meeting, San Francisco, California, 5–7 November 2009. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group recognizes the efforts of the subjects and their families and thanks them for their participation.

References